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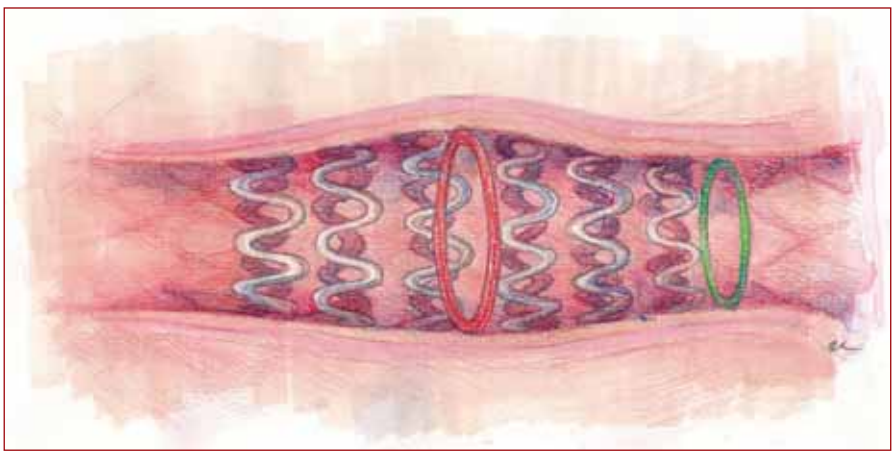

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Polish Heart Journal

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Hyperviscosity and high thrombus burden: Is it time to re-evaluate an old but still gold pathophysiological concept?

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Related article
by Çınar et al.

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The existence of an association between hyperviscosity and acute myocardial infarction (AMI) has been previously analyzed and reported, in particular in young patients, either in the acute phase [1] and during follow-up [1, 2].

In AMI patients, thrombotic lesions are a common finding on angiography and can increase the rate of procedural complications and the incidence of in-hospital major adverse cardiac events, thus affecting short- and long-term outcomes [3]. The prediction of high thrombus burden (HTB) in the infarct-related artery could help to improve procedural success and related clinical outcomes in these patients.

The article by Çınar et al. [4] reports an association between high values of whole blood viscosity (WBV) at both high and low shear rates and HTB on angiography in non-ST elevation myocardial infarction (NSTEMI) patients. Moreover, patients with HTB also exhibited higher values of hematocrit, triglycerides, baseline cardiac troponin I, and total protein. These results are consistent with a previous study performed in our Institution in which, among the hemorheological variables analyzed (WBV at high and low shear rates, plasma viscosity, and the erythrocyte deformability index), higher values of hematocrit and of WBV at low shear rate were found in patients with ST-elevation myocardial infarction (STEMI) with respect to NSTEMI and unstable angina. This suggests a role of these parameters in favoring STEMI occurrence during acute coronary syndromes (ACS) [5]. Our results and those by Çınar et al. [4] strengthen the concept that hemorheological variables play an important role in the pathogenesis of ACS. Moreover, these results are also supported by previous histologic findings showing that transmural AMI was frequently associated with the presence of reddish thrombi, rich in erythrocytes and fibrin, while unstable angina was characterized more often by whitish or greyish thrombi, rich in platelets [6], which suggests a role of high hematocrit values in the formation of complete thrombotic occlusions.

The need for a simple and reliable tool in everyday clinical practice to predict the amount of thrombus on angiography is a heartfelt theme for cardiologists and is also confirmed by the validation of the CHA_2DS_2-VASc score for predicting HTB in patients with either STEMI [7] or NSTEMI [8], regardless of the presence of atrial fibrillation.

In particular, in NSTEMI patients, receiver-operating characteristics analysis revealed the cut-off value of CHA_2DS_2-VASc score >2 as a predictor of HTB with a sensitivity of 74% and a specificity of 61% with an area under curve of 0.71. In that study, increased baseline serum C-reactive protein levels, lower serum albumin levels (representing the counterpart of increased values of acute phase proteins) and decreased lymphocyte counts (indicating the left shift of the formula due to the increase

in neutrophils) were also additional independent predictors of HTB [8].

Another interesting finding of the study by Çınar et al. [4] is that, in patients with HTB, hyperviscosity is not only a determinant factor in thrombus pathogenesis but can also affect microvascular perfusion. In fact, in that study HTB was associated with an increased risk of distal embolization, no-reflow phenomenon, and a lower percentage of postprocedural thrombolysis in myocardial infarction (TIMI) flow >II and of TIMI Myocardial Blush Grade >II. This suggests that hemorheological variables can contribute to the occurrence of the no-reflow phenomenon after successful restoration of epicardial coronary blood flow, possibly causing greater myocardial damage. These results are in line with another study performed by our group, in which we demonstrated, in STEMI patients, a correlation between blood viscosity and infarct size, expressed by the peak values of 2 cardiac biomarkers, creatine kinase, and cardiac troponin I [9]. In this latter study, we also hypothesized that increased neutrophils in response to myocardial necrosis could cause further myocardial damage also by contributing to the no-reperfusion phenomenon, as previously demonstrated [10, 11] and recently confirmed in a cardiac magnetic resonance study conducted in STEMI patients [12]. Furthermore, in agreement with data reported by Çınar et al. [4] we also demonstrated that alterations of hemorheological variables were found in relation to the achievement of a final TIMI flow less than 3, which in turn was associated with an increased infarct size [5].

In conclusion, the study by Çınar et al. [4] reinforces previous evidence on the role of hemorheological variables in ACS patients and underlies the possible impact of an alteration of blood viscosity in patients with NSTEMI and, in particular, the importance of pre-operative evaluation in these patients.

Moreover, the article by Çınar et al. [4] together with those performed in our Institution could also have an important impact on primary prevention during cardiological evaluations, guiding the search for primary or secondary causes of polycythemia, and their possible treatment. Finally, it may also aid the search for other determinants of blood viscosity in order to reduce the risk of STEMI or at least of procedural complications in case of ACS.

Article information

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All that glitters is not gold

J Scott Rankin

Heart and Vascular Institute, West Virginia University, Morgantown, WV, United States

Related article
by Deja et al.

"All that glisters is not gold —
Often have you heard that told.
Many a man his life hath sold
But my outside to behold.
Gilded tombs do worms enfold.
Had you been as wise as bold,
Young in limbs, in judgment old,
Your answer had not been inscrolled
Fare you well. Your suit is cold"

William Shakespeare,
Merchant of Venice, Act II Scene 7

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Mister Hugh H Bentall was an innovative cardiothoracic surgeon, participating in the first cardiopulmonary bypass cases in Europe [1] and inventing potassium cardioplegia [2]. He also was an expert on 18th century English tall-case clocks (Figure 1) and an excellent educator at the Royal Postgraduate Medical School, Hammersmith Hospital, London. But it was his invention of composite aortic valve-root conduit replacement [3] that sustains his name in current clinical practice almost 60 years later. Most of us learned about his operation in the 1970s, and it has been a mainstay of cardiac surgery for the past half-century. The procedure, however, is limited by its inclusion of a valve prosthesis in the aortic position, with consequent valve-related complications. One might argue that the Bentall procedure should no longer be considered the "gold standard" treatment for aortic root aneurysms. The excellent follow-up data presented in the current issue by the Katowice group would support this view.

In assessing outcomes in 204 patients with aortic root aneurysms managed surgically over a 10-year period, Gocol and associates [4] have contributed importantly to current knowledge. It is appropriate to start with a comment about the biostatistics used in this study. Single-center series have advantages, primarily related to detailed understanding by the authors of every aspect of each patient's course. The disadvantage, of course, is a small sample size. With only 23 deaths, 6 reoperations, and 30 other events in the entire study, any multivariable analysis could only support 2–3 variables — an inadequate number for proper risk adjustment (and the full multivariable model is never presented). However, a descriptive review of the data always is valuable, and several concepts are evident in this series. First, selection bias is present with older patients being selected for bio-Bentall procedures, which is standard. Without a proper multivariable analysis, much of the inferior survival associated with bio-Bentall operations could have been related to older age at baseline. However, tissue valves tend to deteriorate faster beyond 10 years, so even more significant decrements in bio-Bentall outcomes are likely past the duration of this study.

The most striking finding of this analysis is the dearth of valve-related complications after aortic valve repair (valve-sparing root replacement). This observation is consistent with other reports [5, 6], and if a composite major adverse cardiac event (MACE) outcome

Figure 1. London tall-case clock from 1770 selected by Mr. Bentall for the author in 1986 — still gracing the author's entry hall almost 40 years later while keeping perfect time

were to be analyzed [7], valve repair likely would win hands down. Moreover, the mechanical Bentall group was younger, so proper risk adjustment might have lowered associated survival, and especially with longer follow-up, accumulating valve-related complications might have compromised survival [8]. So, the data clearly suggest the superiority of valve repair for aortic root aneurysms, as compared to Bentall procedures employing either type of prosthetic valve. The Katowice group should be complemented on achieving an approximately 50% repair rate in their series. Even in experienced centers, the rule is 27% repair for aortic insufficiency [9, 10] in recent years. However, the goal of cardiac surgical practice now should be to increase repair rates for all patients with aortic insufficiency toward 90%, as in the case of mitral repair [11]. The advent of aortic ring annuloplasty could help in that regard [12, 13], but expanding aortic valve repair clearly is an appealing next developmental step. In summary, one must conclude that Mister Bentall's reputation and contributions may still "glitter", but his operation no longer is the "gold standard" for management of aortic root aneurysms.

Article information

Conflict of interest: None declared.

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REVIEW

Low levels of vitamin D and coronary artery disease: Is it time for therapy?

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ABSTRACT

The association between vitamin D and the prevalence and severity of coronary artery disease (CAD), major established cardiovascular risk factors, and acute ischemic events has been consistently demonstrated in large-scale observational studies and meta-analyses, with relevant prognostic implications. The rise in prevalence of hypovitaminosis D in recent years, reaching pandemic proportions, has pointed to the importance of the identification and optimization of the indications and strategies for the therapeutic use of vitamin D, with particular relevance for cardiovascular health. However, vitamin D supplementation has provided so far inconsistent results in primary prevention, with even fewer data reported in patients with established CAD. The present review aims to provide an updated overview of the available evidence and potential therapeutic applications of vitamin D in patients with CAD.

Key words: vitamin D, atherosclerosis, inflammation, thrombosis, pharmacological therapy

INTRODUCTION

Vitamin D is a secosteroid mainly involved in the homeostasis of calcium and bone tissue but also displaying a broad spectrum of systemic hormonal effects, including both the modulation of the expression of about 3% of the human genome, and "acute", non-genomic-dependent effects, mediated by the regulation of intracellular calcium [1].

Several large-scale studies have previously demonstrated that vitamin D deficiency is associated with the development of atherosclerosis and its thrombotic complications, which increases the risk of cardiovascular events and mortality [2–5].

Inadequate levels of vitamin D deficiency or insufficiency, defined as <20 ng/ml, have reached dramatic prevalence in the last years, exceeding 50% in certain areas and subsets of population, and especially among elderly and more frail subjects, with chronic comorbidities, renal failure, diabetes, and inflammatory disease [6, 7]. This has attracted attention to the consequences of vitamin D deficiency in the pathogenesis of coronary artery disease (CAD) and potential benefits of vitamin D supplementation.

However, there is still much uncertainty about the underlying pathophysiological mechanisms. The results of the studies conducted so far to assess the cardioprotective benefits of vitamin D are still unclear and make it impossible to reach a general consensus, develop consistent guidelines, and use vitamin D on a large scale as a pharmacological therapy.

The present review provides an update on the existing evidence and the current indications for the supplementation with vitamin D in patients with CAD, focusing on potential future perspectives.

VITAMIN D DEFICIENCY: A PANDEMIC DISORDER

Severe vitamin D deficiency can cause rickets and osteomalacia, which are rarely observed in developed countries. However, less severe

Table 1. Derivates of vitamin D with clinical indications

Compound	Clinical indication
Calcidiol 3,25(OH)D3	Renal osteodystrophy
Calcitriol 4,1,25(OH)	Renal osteodystrophy
Calcipotriol 5, 22-ene-26, 27-dehydro-1,25(OH)2D3	Psoriasis
Doxercalciferol 6, 1α(OH)D2	Secondary hyperparathyroidism
Alfacalcidol 7,1α(OH)D3	Osteoporosis
Tacalcitol 8, 1α, 24(OH)2D3	Psoriasis
Oxacalcitriol 10, 22-oxa-1, 25(OH)2D3	Psoriasis
Falecalcitriol 11, 1,25(OH)2-26, 27-F6-D3	Secondary hyperparathyroidism

deficiency is more frequent and associated with osteoporosis and the risk of bone fractures [8]. Vitamin D deficiency is currently considered a global health problem [9, 10], especially in low- and middle-income countries, where it affects about 50% of adults and 90% of infants. In the USA, up to 37% of adults and up to 46% of dark-skinned infants suffer from this condition [9]. A recent analysis considering mostly Nordic and western European populations found significant variability between countries [10]. In fact, when restricted to the adult population, Nordic countries appear to have a lower incidence of vitamin D deficiency, most probably due to increased vitamin supplementation or food fortification compared to lower-latitude countries.

VITAMIN D METABOLIC PATHWAY

Cholecalciferol, the form of vitamin D named D3, is synthetized in the skin from 7-dehydrocholesterol upon irradiation with ultraviolet waves (ultraviolet B light [UV-B]) (Figure 1) [11]. 7-dehydrocholesterol is part of the metabolic pathway that controls the synthesis of cholesterol in human cells. By absorbing ultraviolet radiation, 7-dehydrocholesterol turns into pre-vitamin D3, which, because of its molecular instability, subsequently converts to cholecalciferol that is expelled in the extracellular space, binding to a carrier (vitamin D-binding protein). Although production of vitamin D3 in the skin is its primary source in humans, it can be derived from food, such as fish oil or mushrooms, in the form of ergocalciferol (Figure 2) [12]. Skin synthesis of vitamin D3 rises proportionally with the intensity of the UV radiation. It also reduces proportionally with sunblock usage or the quantity of melanin encountered in the skin, i.e., in higher-latitude-living populations, during months with reduced sun exposure, or in patients with darker skin [11, 13, 14]. However, cholecalciferol is not biologically active; thus, vitamin D is hydroxylated in the liver cells to form 25(OH)D followed by 1α-hydroxylation [11]. The active hormonal form is produced in this last step of 1α-hydroxylation mainly in the kidneys and at other extrarenal sites, resulting in a compound named 1,25(OH)2D3 [15–17].

Table 2. Vitamin D and atherosclerosis: mechanistic links

Lipid profile	• Reduces total cholesterol • Reduces LDL-C • Reduces triglycerides • Increases HDL-C
Endothelial adhesion and activation	• Reduces vascular cell adhesion molecule 1 • Reduces E-selectin
Vascular tone and endothelial function	• Increases the level of nitric oxide • Reduces the level of reactive oxygen species released
Inflammation and atherosclerosis	• Reduces proinflammatory type 1 cytokines: IL-12, IL-6, IL-8, IFN-gamma, TNF-alpha • Increase anti-inflammatory type 2 cytokines: IL-4, IL-5, and IL-10 • Reduces oxidative stress through reducing cathepsin, IL-6 and adiponectin
Coagulation and platelet aggregation	• Increases trombomodulin expression • Reduces tissue factor expression • Reduces PAI-1 expression • Reduces thrombospondin expression • Increases the level of nitric oxide • Decreases ADP-induced aggregation
Arterial smooth muscle cells	• Decreases production of angiotensin II • Decreases oxidative stress • Inhibits cellular senescence • Reduces tissue factor expression

Abbreviations: ADP, adenosine diphosphate; HDL-C, high density lipoprotein cholesterol; IFN, interferon; IL, interleukin; LDL-C, low density lipoprotein cholesterol; PAI-1, plasminogen activator inhibitor-1; TNF, tumor necrosis factor

MECHANISMS OF ACTION AND ITS IMPLICATIONS IN THE PATHOPHYSIOLOGY OF ATHEROSCLEROSIS

The hormonal form of vitamin D, which is a lipid-soluble molecule, is transported in the blood bound to a serum protein named vitamin D-binding protein (DBP) [18]. At molecular level, vitamin D in the form of 1,25(OH)2D3 exerts its actions by binding to a membrane-bound and cytoplasmic receptor, the vitamin D receptor (VDR), which can be found in almost all human tissue, including the cardiovascular system [11, 19]. Binding of vitamin D to its VDR is critical for its action because 1.25 dihydroxy vitamin D, the active form, penetrates the cell membrane and binds to VDR [20]. This vitamin D-VDR complex acts with the retinoic acid receptor and forms important heterodimers that activate elements of vitamin D response elements by initiation of the cascade of molecular interactions regulating the suppression and transcription of specific genes [21]. In total, VDR has a direct action on the expression of more than 1000 genes [22], approximately 3% of the genome [12]. Ways in which vitamin D acts non-genomically have also been identified, such as through intracellular signaling molecules, generation of second messengers, and activation of specific protein kinases [23]. The change in the chemical structure of cholecalciferol leads to the emergence of new molecules, which, surprisingly, can bind to VDR.

Vitamin D deficiency has been consistently associated with the prevalence and severity of CAD and acute ischemic events.

In fact, vitamin D has been shown to promote endothelial function and to counteract inflammation and oxidative stress, thus preventing the development of atherosclerosis and its thrombotic complications [24–27].

In the ARIC study, vitamin D levels were measured in 11 945 participants, and an association with the incidence of coronary heart disease among white-skinned participants was reported [28].

In the LURIC Study, in a large cohort of subjects (n = 1801) referred for coronary angiography, 92% of individuals had suboptimal levels of vitamin D, which was associated with an increased all-cause mortality and cardiovascular mortality [29]. The Framingham Offspring Study found that individuals with 25(OH)D <37.5 nmol/l had a hazard ratio of 1.62 for the development of cardiovascular disease (CVD) compared to those with a level of ≥37.5 nmol/l [30].

In a large cohort study enclosing over 1400 patients undergoing coronary angiography, Verdoia et al. showed that lower circulating 25(OH)D was independently related with the prevalence and extent of CAD, especially for patients with values <10 ng/ml [3].

Furthermore, calcitriol levels have been inversely associated with coronary artery calcifications, thus serving as an early marker of coronary atherosclerosis [2].

In fact, vitamin D can directly improve the endothelial health and function, promoting the production of nitric oxide and reducing the exposure of proteins responsible for the adhesion of leukocytes and platelets. This prevents the inflammatory response and thrombotic phenomena. In addition, the inhibition of the extravasation and activation of macrophages and the antioxidant properties can prevent lipid oxidation and the production of foam cells, which contribute to plaque progression and instability [1, 24]. Indeed, levels of 25(OH)D in healthy volunteers are independently associated with various measures of endothelial function, arterial stiffness, and coronary flow reserve. In a subgroup of participants with vitamin D deficiency, normalization of 25(OH)D levels at 6 months was associated with a significant increase in reactive hyperemia indices, and in other studies, treatment with vitamin D improved arterial stiffness [2].

Moreover, vitamin D has been shown to lower tissue factor, downregulate the pro-thrombotic plasminogen activator inhibitor-1 and thrombospondin-1 mRNA expression, and upregulate thrombomodulin, thus accounting for its antithrombotic properties [31].

Additionally, the vitamin D receptor has been also identified in platelets, which suggests a direct regulatory effect. In effect, platelet activation is a calcium-dependent process, and calcitriol has been shown to display also a "rapid" non genomic action, mediated by the modulation of intracellular calcium. In fact, hypovitaminosis D has been previously linked to an enhanced platelet reactivity and a reduced effectiveness of antiplatelet drugs [25].

VITAMIN D AND CARDIOVASCULAR RISK FACTORS

Vitamin D has displayed a positive interaction with major cardiovascular risk factors and was related to the levels of blood pressure and a "healthier" metabolic profile [5, 32, 33].

A Mendelian randomization study suggested a link between vitamin D deficiency and hypertension risk [34], which was further confirmed by experimental evidence in animal studies [35]. In effect, vitamin D promotes the production of nitric oxide, a potent vasodilator, and downregulates the activity of the renin-angiotensin system, thus lowering the blood pressure and positively interacting with anti-hypertensive drugs [36].

Moreover, vitamin D has been shown to lower the glycemia levels in patients with diabetes and to protect against diabetes through the regulation of insulin synthesis and secretion or through direct action on pancreatic beta-cells function [37].

The levels of 25(OH)D have also been shown to condition the lipid asset, which is associated with lower levels of circulating cholesterol and a less atherogenic lipid profile and prevents the formation of foam cells with potentiating the effectiveness of statins [38–40],

Furthermore, vitamin D deficiency could be even more frequent among subjects at increased cardiovascular risk, due to comorbidities, aging or renal failure, or unhealthy lifestyle. In fact, low 25(OH)D concentrations can be enhanced by obesity, air pollution, or limited outdoors activity, which are associated with worse cardiovascular outcomes [41].

VITAMIN D SUPPLEMENTATION IN CAD: CURRENT EVIDENCE

Although several studies have linked lower levels of vitamin D with more severe cardiovascular disease and increased mortality [42–44], controversies still exist about using vitamin D supplementation in cardiovascular prevention [45, 46].

The ViDA (Vitamin D Assessment) study in New Zealand, which randomized over 5 000 subjects, showed an increase in serum 25(OH)D concentrations with the supplementation, although it was ineffective in reducing the primary outcome of incident CVD and death [47].

In the recent VITAL trial [48], which randomized over 25 000 healthy subjects to two groups with either n–3 fatty acid or vitamin D3 supplementation, no prognostic difference was observed at a 5-year follow-up.

However, heterogeneity in these strategies, with inadequate dosing and duration of the treatment and the failure to achieve optimal levels of vitamin D, as summarized in Table 3, could have determined the negative findings of most of the trials.

Moreover, increased benefits could be expected when focusing on higher-risk populations, such as patients with

Table 3. Vitamin D supplementation in primary and secondary prevention

Study name	Patients (n)	Inclusion criteria	Vitamin D dosing	Follow-up duration	Study outcome and results
Secondary prevention					
Sokol et al. [49]	90	CAD (angiographic) and vitamin D <30 ng/ml	ergocalciferol (50 000 IU/week)	12 weeks	No difference in blood pressure and all markers of endothelial function
Bahrami et al. [50]	80	CAD (angiographic) and vitamin D <30 ng/ml	Vitamin D 50 000 IU/ week	8 weeks	Decreased systolic and diastolic blood pressure, waist circumference and fat percentage
Aslanabadi et al. [51]	99	Patients undergoing elective PCI	300 000 IU dose of cholecalciferol given before PCI	In-hospital	Periprocedural myocardial injury: no difference
Wu et al. [29]	90	CAD (angiographic)	Calcitriol (0.5 µg/day)	6 months	CAD (SYNTAX score) and C-reactive protein significantly decreased
Shaseb et al. [52]	95	T2DM with ischemic heart disease	Single dose of chole-calciferol (300 000 IU, i.m.)	8 weeks	Glycemic status: HbA1c was reduced by 0.48%
Witham et al. [53]	75	Patients with a prior history of MI	Two high-doses of orally administered cholecalciferol (100 000 IU)	6 months	Vascular function (reactive hyperemia index, systolic BP, diastolic BP) and cholesterol levels: no difference. C-reactive protein: reduced significantly
Farrokhian et al. [54]	60	T2DM patients with coronary artery disease.	50 000 IU cholecalciferol every second week	6 months	Significant attenuation in vascular inflammation and improved glycemic status
Schleithoff et al. [55]	123	Participants with heart failure	Vitamin D3, 2000 IU/d	Average 1.3 years	Reduced the inflammatory milieu
Primary prevention					
Aloia et al. [56]	27	Postmenopausal women	Vitamin D3, 400 IU/d	2 years	No difference in MACE
Ott et al. [57]	86	Postmenopausal women	Vitamin D3, 1000 mg/d	2 years	No difference in MACE
Komulainen et al. [58]	227	Women in early postmenopause who were non-osteoporotic	Vitamin D3, 300 and 100 IU/d	5 years	No difference in MACE
STOP IT/Gallagher et al. [59]	489	Women aged 65-77 years with femoral neck density in normal range (SD, ≤2) for their age	Calcitriol, 0.25 µg twice daily	3 years	No difference in MACE
Trivedi et al. [60]	2686	Participants aged 65–85 years	Vitamin D3, 100 000 IU/4 months	5 years	No difference in MACE
RECORD/Grant et al. [26]	5292	Participants aged ≥70 years who had had a low trauma, osteoporotic fracture in the previous 10 years	Vitamin D3, 800 IU daily	Median (IQR), 3.8 (3.1–4.3) years	No difference in MACE
Brazier et al. [61]	172	Ambulatory women aged >65 years	Vitamin D3, 400 IU twice daily	1 years	No difference in MACE
WHI/Jackson et al. [62]	36282	Women aged 50–79 years with no evidence of a medical condition	Vitamin D3, 400 IU/d	12 years	No difference in MACE, improvement in hip bone density
Berggren et al. [63]	199	Participants aged ≥70 years who had femoral neck fractures	Vitamin D3, 800 IU/d	1 year	No difference in MACE
Zhu et al. [64]	120	Women aged 70–80 years	Vitamin D3, 1000 IU/d	5 years	No difference in MACE
Prince et al. [65]	302	Women aged 70–90 years	Vitamin D3, 1000 IU/d	1 year	No difference in MACE, reduction in falls
Vital D/Sanders et al. [66]	2256	Women aged ≥70 years at high risk of fracture	Vitamin D3, 500 000 IU/year	Median (IQR), 2.96 (2.92–3.00)	Increased falls, no difference in MACE
Lehouck et al. [67]	182	Current of former smokers with COPD	Vitamin D, 100 000 IU/ month	1 year	Reduced COPD exacerbations in vitamin D deficient patients
VITDISH/Witham et al. [68]	159	Participants aged ≥70 years with isolated systolic hypertension	Vitamin D, 100 000 IU/month	1 year	MACE, blood pressure, arterial stiffness, endothelial function, cholesterol level, glucose level, and walking distance: no difference
OPERA/Wang et al. [69]	60	Stages 3–5 chronic kidney disease and left ventricle hypertrophy	Paricalcitol, 1 µg/d	1 year	No impact of left ventricular mass, improved secondary hyperparathyroidism
Baron et al. [70]	2259	Participants aged 45–75 years who had ≥1 colorectal adenoma	Vitamin D3, 1000 IU\d	3 years	Adverse events: no difference
EVITA/Zitterman et al. [71]	400	Participants aged 18–79 years who were classified as having New York Heart Association functional class ≥II	Vitamin D3, 4000 IU/d	3 years	No difference in mortality
VIDA/Scragg et al. [47]	5110	Vitamin D insuficient patients	Cholecalciferol (100 000 IU/month)	Median follow-up = 3.3 years	No beneficial effects of cholecalciferol supplementation on CVD risk or mortality

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Table 3 (cont.). Vitamin D supplementation in primary and secondary prevention

Study name	Patients (n)	Inclusion criteria	Vitamin D dosing	Follow-up duration	Study outcome and results
J-DAVID/Shoji et al. [72]	954	Patients on hemodialysis	Alfacalcidol, 0.5 μg/d	Median (IQR), Vitamin D: 4.0 (2.6–4.0)a; Placebo: 4.0 (3.5–4.0)	no difference in selected cardiovascular events
VITAL/Manson et al. [25]	754	All women	Calcium (1000 mg/day) + cholecalciferol (400 IU/day)	Average of seven years	No significant changes in CAC score
Gulseth et al. [73]	62	Subjects with T2DM	Single dose of 400,000 IU oral vitamin D3	4 weeks	No change in insulin sensitivity or insulin secretion
Jorde et al. [74]	438	Overweight or obese subjects	Vitamin D (3) 40 000 IU per week (DD group), vitamin D 20 000 IU per week (DP group)	12 months	Glucose tolerance, blood pressure or serum lipids: no change
BEST-D trial /Clarke et al. [75]	305	Elderly	cholecalciferol (4000 IU or 2000 IU)	12 months	No significant changes in CVD risk factors
Seibert et al. [76]	106	Healthy subjects	cholecalciferol (2000 IU/day)	12 weeks	No difference in mortality, major cardiovascular events and invasive cancer
Forouhi et al. [77]	340	Patients with high risk of diabetes type 2	Ergocalciferol (100,000 IU/month) or cholecalciferol (100 000 IU/month)	4 months	Improvements in pulse wave velocity, no difference in other cardiometabolic parameters

Abbreviations: CVD, cardiovascular disease; IQR, interquartile range; IU, international units; MACE, major adverse cardiovascular events; PCI, percutaneous coronary intervention; S, supplementary; T2DM, type 2 diabetes mellitus

Endothelial adhesion and activation # reduces vascular cell adhesion molecule 1 (VCAM-1) # reduces E-selectin Vascular tone and endothelial function • increases the level of nitric oxide • reduces the level of reactive oxygen species released Inflammation and atherosclerosis # reduces proinflammatory type 1 cytokines: IL-12, IL-6, IL-8, IFN-gamma, TNF-alpha # increase anti-inflammatory type 2 cytokines: IL-4, IL-5, and IL-10 # reduces oxidative stress through reducing cathepsin, IL-6 and adiponectin Arterial smooth muscle cells • decreases production of angiotensin II • decreases oxidative stress • inhibits cellular senescence • reduces tissue factor expression

established cardiovascular disease. In the randomized controlled trial: the Randomised Evaluation of Calcium Or vitamin D (RECORD), treatment with cholecalciferol prevented cardiac failure among 5292 older people but did not appear to protect against myocardial infarction or stroke [78].

In addition, Le et al. [79] explored the effects of vitamin D on cardiac function in mice with post-myocardial infarction, showing a significant reduction in the fibrotic scar area and wall thinning in the animals receiving calcitriol supplementation, mediated by a reduction of fibrosis and enhanced myocytes differentiation. Thus, these data could further reinforce the incoming evidence of the potential benefits of using vitamin D in patients with left ventricular dysfunction and heart failure [80].

In a study in which calcitriol was administered over 6 months (0.5 mg/day) in patients with stable CAD, improvements were noted in the SYNTAX score and cardiometabolic variables [81].

Moreover, Bonakdaran et al. [82] reported that calcitriol supplementation could improve metabolic parameters and the control of cardiovascular risk factors among 119 patients with diabetes, suggesting that inadequate activation of vitamin D to its active metabolite, calcitriol, could represent a cause of the failure of major trials.

In fact, Saghir Afifeh et al. [83] previously reported a prevalence of calcitriol deficiency of about 10% in the patients with CAD, even despite adequate levels of vitamin D.

FUTURE PERSPECTIVES

Thus, future trials specific for subsets of higher-risk patients are certainly warranted to define whether a more tailored approach with vitamin D supplementation could be beneficial. Nevertheless, considering the positive effects on reducing overall mortality, cancer and functional status, consistently demonstrated in different trials and meta-analyses, and the safety, tolerability and low cost of vitamin D supplementation, such a strategy should certainly be considered, in particular in subjects at higher risk of deficiency [46, 84].

Such strategy should certainly be further reinforced in the context of the ongoing COVID-19 pandemic. In fact, the role of vitamin D in the modulation of the immune system and inflammation, and the prevention of thrombotic events, has been suggested. Vitamin D was reported to lower the rate of complications and improve the outcomes for infected patients [85]. Moreover, in addition to empowering the immune defense, vitamin D could prevent of contagion, by lowering the expression of the ACE-2 enzyme [86], thus leading the scientific societies to recommend the maintenance of adequate levels of vitamin D, and especially among subjects with increased risk for complications, as in patients with CAD [87, 88].

Moreover, the exact definition of the optimal vitamin D levels to reduce the cardiovascular risk and the appropriate dosing of pharmacological therapy, still need to be settled by experts' agreement. Possibly, the achievement of levels higher than expected is required to observe the cardioprotective effects of vitamin D, especially in those severely deficient subjects [89].

Finally, a tailored approach to vitamin D supplementation, accounting for the differential mechanisms of deficiency and comorbidities conditioning its effectiveness [90], certainly represents a promising option, which should be further assessed in future randomized trials.

Supplementary material

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

Article information

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REVIEW

Percutaneous coronary intervention to treat unprotected left main: Common (un-answered) challenges

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ABSTRACT

Percutaneous coronary intervention (PCI) with drug-eluting stent (DES) implantation is a widely adopted strategy to obtain myocardial revascularization in patients with unprotected left main (LM) disease. Although thoroughly investigated across scientific literature, LM PCI offers patient-specific technical options and poses many operative challenges that cannot be fully addressed by the published studies. Therefore, we have summarized and discussed in this review possible options related to PCI in LM patients. First, functional and imaging assessment for LM is still evolving and requires increased dedication to identify patients requiring revascularization and to enhance the results in the case of PCI performance. Second, specific coronary atherosclerosis patterns of LM involvement (like an isolated ostial disease of one of its bifurcation branches, extensive disease jeopardizing both branches, etc.) pose specific challenges for DES implantation so that careful selection of technical options (stepwise provisional single stent, upfront 2-stent strategy, when and how apply "kissing ballooning") is required. Third, despite improvement of techniques, PCI-related ischemia might not be tolerated by some patients with LM disease so mechanical circulatory support devices may come into play.

Key words: left main bifurcation, PCI, ostial disease, and stenting techniques

INTRODUCTION

To date, unprotected left main (LM) percutaneous coronary intervention (PCI) is strongly recommended only in patients with a low (≤22) Synergy Between PCI With Taxus and Cardiac Surgery (SYNTAX) score (class I recommendation) [1]. Yet, progress in PCI techniques is continuously ongoing and, in real-world practice, PCI is offered to many LM patients with a wide spectrum of anatomic complexities. Many specific issues related to LM PCI are not standardized and are heterogeneously approached by different centers and operators. In this paper, we discuss the main unanswered questions that pose challenges in the everyday clinical practice of PCI in patients with ULM.

WHAT ROLE SHOULD FUNCTIONAL AND IMAGING PLAY IN THE ASSESSMENT IN LM DISEASE

According to the current guidelines for myocardial revascularization, angiographic LM stenosis with a cut-off value of ≥50% should be scheduled for revascularization [1]. However, two-dimensional coronary angiography often poorly correlates with actual anatomic (morphological) and functional status [2, 3]. Therefore, supporting imaging and functional assessment in LM treatment should be done more frequently than in any other coronary bed, also due to the amount of supplied myocardium by LM. Various forms of clinical presentation may be crucial in selecting one or both of them. While imaging techniques can

be applied in both chronic and acute coronary syndromes, a functional assessment is mainly oriented to chronic coronary syndrome.

When facing problems in the assessment of LM stenosis significance by angiography, functional evaluation with hyperemic or non-hyperemic tests [4] aims to find eligible patients for safe PCI deferral. Thus, in patients with chronic coronary syndrome (CCS), a fractional flow reserve (FFR) value of >0.8 and instantaneous wave-free ratio (iFR) value of >0.89 are considered to be cut-off values for safe revascularization deferral [5–7]. The same FFR cut-off value could be also used in the estimation of LM severity in patients with NSTEMI [8], while ST elevated acute coronary syndrome should be the reason not to perform a functional assessment. When performing FFR, it is important to highlight that equalization of guiding catheter and wire pressures should be done with a disengaged guiding catheter and that adenosine should be administered as a continuous intravenous infusion with a disengaged guiding catheter throughout all measurements [5]. Furthermore, estimation of LM significance should be done by measuring FFR towards both, left anterior descending (LAD) and left circumflex (LCX), given that FFR or iFR values could be confounded by the concomitant presence of downstream disease, especially LAD [5]. Except to evaluate LM significance, functional assessment tools can be used to navigate intervention and valuate final results [9].

On the other hand, intravascular imaging techniques can be used not only for the assessment of stenosis significance but also for morphological plaque evaluation, particularly in the setting of acute coronary syndrome, and for PCI result optimization as well.

Intravascular ultrasound (IVUS) is used for evaluation of complete LM, from the ostium, across the trunk, and toward distal LM bifurcation, having class IIa recommendation for use in LM PCI [1]. According to IVUS measurement of the LM minimal lumen area (MLA), revascularization may be safely deferred if MLA is >6 mm^2 while treatment is recommended if MLA is <4.5 mm^2 [6, 10]. Of course, MLA may differ and should be tailored by ethnicity and body mass index [11]. A recently published study of IVUS guidance in LM PCI provides prognostic benefits concerning angiography guidance, particularly when following a detailed protocol with predefined optimization criteria (stent expansion and apposition, proximal stent deformation, plaque burden, and dissection at stent edges) [12].

Optical coherence tomography (OCT) as a junior imaging technique has higher axial resolution compared to IVUS, allowing higher image quality and plaque morphology assessment, better distinguishing fine details including residual thrombus, minor edge dissections, and tissue prolapse, which usually have a benign course [13, 14]. Due to the inability to achieve complete blood clearance even with a disengaged guiding catheter and reduced penetration rate, accurate vessel sizing could be limited, thus OCT is discouraged in ostial LM disease. Conversely, OCT assessment is feasible in distal LM lesions [15]. A small study recently reported the feasibility of OCT guidance to support the decision to defer revascularization in low-risk patients with angiographically-intermediate distal LM lesions [16]. Notably, despite the adoption of very conservative OCT parameters prompting revascularization, very few events occurred in deferred patients.

When moving from lesion assessment to PCI optimization, OCT potential is increasingly recognized. Due to the ability of 3D reconstruction, OCT has an advantage in the visualization of struts hanging over the side branch ostium, in the estimation of wire position and wire recrossing point. OCT is accepted as a feasible and safe imaging tool in the distal LM PCI setting, particularly for the detection and correction of acute stent underexpansion and malapposition [17]. The recently published LEft Main Oct-guided iNterventions (LEMON) study, showed that OCT-derived information regarding stent optimization changed procedural strategy in 26% of the studied LM PCI patients [18]. Furthermore, a large retrospective multicenter study comparing OCT with IVUS and angiography in patients who underwent distal LM stenting allowed researchers to document that intravascular imaging was superior to angiography for distal LM stenting, with no difference between OCT and IVUS [19].

Figures 1 and 2 describes the main features of LM functional and imaging assessment.

HOW TO MANAGE ISOLATED OSTIAL LEFT ANTERIOR OR LEFT CIRCUMFLEX ARTERY DISEASE?

One of the most challenging atherosclerotic plaque distribution patterns in LMB is certainly ostial disease of one of its branches. Although described and defined as apparently simple Medina 0.1.0 or Medina 0.0.1 by angiography, the involvement of distal LM disease in these circumstances is often not easy to estimate. According to an IVUS study, isolated ostial LAD and ostial LCX disease were far less common than when appreciated by simple angiography [20]. Similar observations have been collected more recently by OCT [15]. In other words, any time isolated LAD or LCX stenosis is encountered, the main concern to guide therapy is related to the proper assessment of distal LM anatomy.

Concerning the stenting technique, the common choice is between the ostial branch stenting and crossover stenting from LM to the diseased branch (according to either provisional or inverted provisional).

Ostial stenting can pose difficulties with stent positioning, which can lead to the longitudinal geographical miss. If positioned too distal, there is a concern of missing the diseased ostium, and if placed too proximal, it can produce free-floating struts in front of the side branch (SB) ostium, inducing a higher risk for thrombosis and restenosis.

Furthermore, even when properly done, "nailing" the LAD ostium can cause damage to LCX ostium, mostly by shifting/displacement of the carina although the snow-

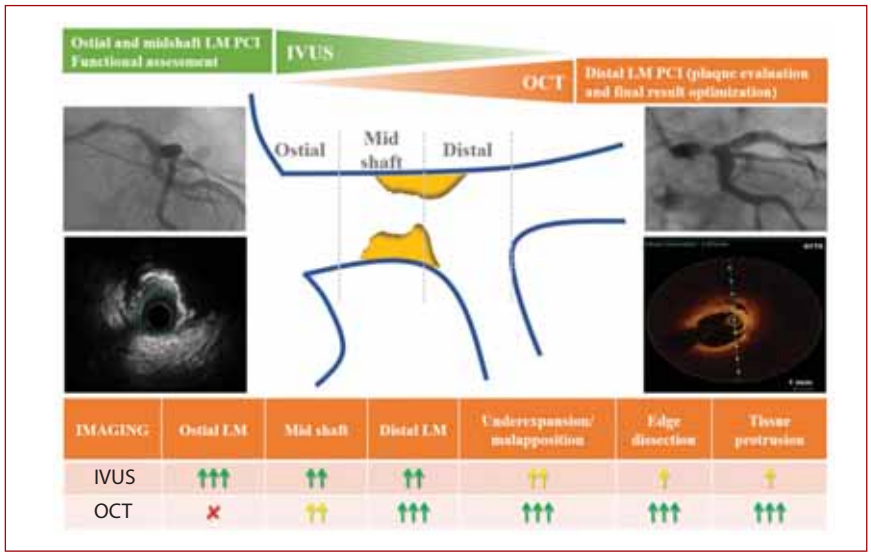
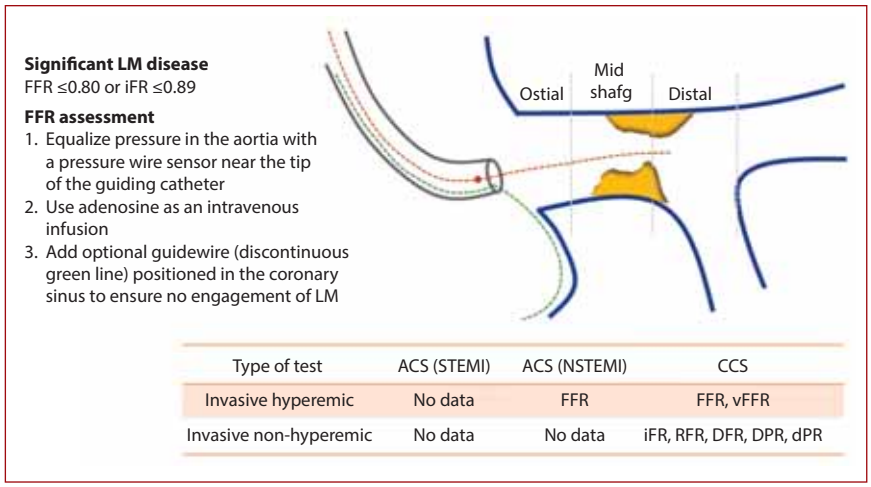


Figure 1. The main features of the left main imaging assessment

Abbreviations: IVUS, intravascular ultrasound; LM, left main; OCT, optical coherence tomography; PCI, percutaneous coronary intervention



Type of test	ACS (STEMI)	ACS (NSTEMI)	CCS
Invasive hyperemic	No data	FFR	FFR, vFFR
Invasive non-hyperemic	No data	No data	iFR, RFR, DFR, DPR, dPR

Figure 2. The main features of the left main functional assessment

Abbreviations: ACS, acute coronary syndrome; CCS, chronic coronary syndrome; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; other — see Figure 1

plow phenomenon (plaque shifting), spasm, and dissection could be seen as well. According to Medina et al. [21], among all features, the presence of the vulnerable carina, spiky carina, morphology described as an "eyebrow" sign on IVUS, was recognized as the only independent predictor of the LCX damage after ostial LAD stenting. Unexpectedly, although the mean stent protrusion in front of the LCX ostium was 2.48 mm (2.8 mm in the group with LCX damage and 2.3 mm in the group without LCX damage), it was not recognized as an independent predictor of LCX damage [21].

However, if the longitudinal geographical miss is recognized, it can be solved either by crossover stenting or with a 2-stent technique, depending on the level and the degree of longitudinal geographical miss. Otherwise, when not recognized immediately, it can cause obliteration of LCX ostium due to fenestrated restenosis. Converting to the 2-stent technique seems to be the best solution as it is shown in Figure 3.

The prevalence of vulnerable carina or "eyebrow" sign is described to be higher in bifurcation lesions with smaller bifurcation angles (LAD-D for example), compared to LMB [22]. Not only in ostial LAD stenting but also in crossover bifurcation stenting, the presence of the "eyebrow" sign is a powerful predictor of SB damage [22].

When all the prerequisites for ostial stenting are met, including proper distal guidewire position and guiding catheter engagement, 3 additional techniques can help to avoid the longitudinal geographical miss.

One of them is the very well-known Szabo technique [23], which was used for aorto-ostial lesions at first and then modified to use for ostial bifurcation lesion stenting. This technique requires a second anchor guidewire which will pass through the last proximal stent strut. The stent is

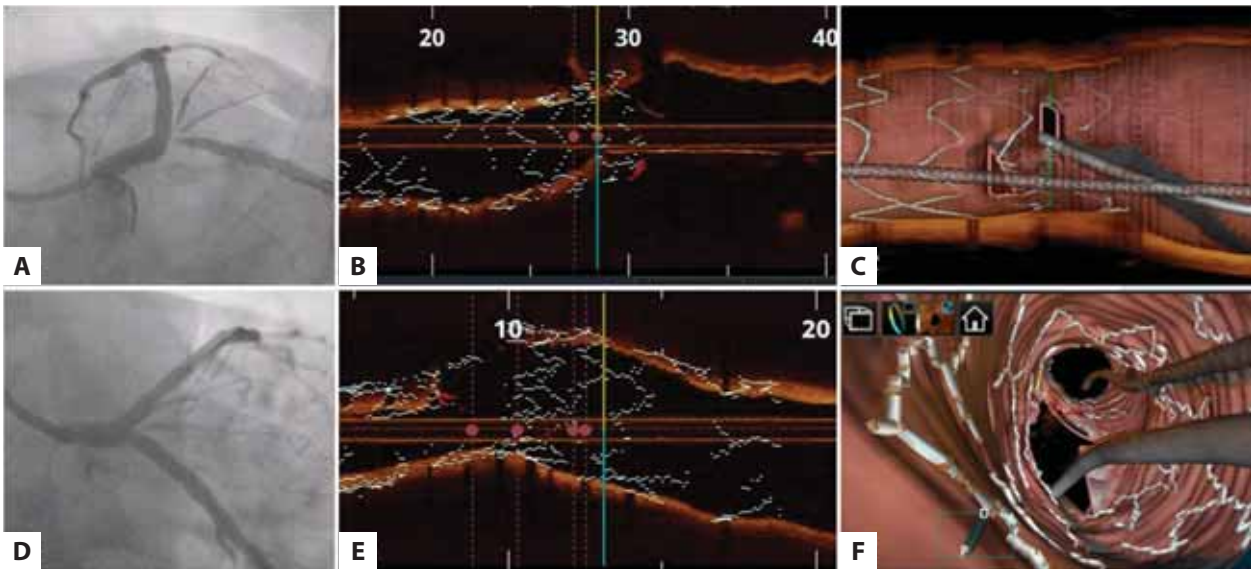


Figure 3. Tight ostial LCX stenosis caused by fenestrated restenosis after ostial LAD stenting with stent struts protruding into the LM. Successful treatment with the mini-Culotte technique. **A.** Ostial LCX stenosis after ostial LAD stenting; **B.** OCT run from LAD showing stent struts protruding into the LM in front of LCX ostium; **C.** Fenestrated restenosis at the LCX ostium; **D.** Final angiography result after PCI (DES 4.0 × 28 mm from LM toward the LCX-mini Culotte technique with a previously implanted stent in LAD); **E–F.** Final OCT run from LAD, showing good stent apposition, short stent overlap in LM (mini Culotte), widely open both SBs and centered carina

Abbreviations: DES, drug-eluting stent; LAD, left anterior descending; LCX, left circumflex; SB, side branch; other — see Figure 1

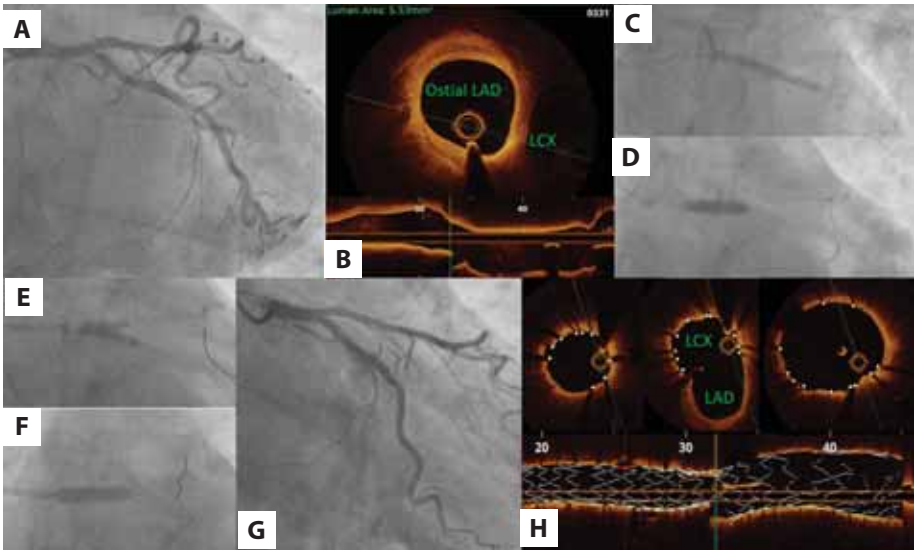


Figure 4. Crossover stenting in isolated ostial LCX disease. **A.** LM bifurcation Medina 0.0.1 (AP-CAU view); **B.** OCT run from LAD before PCI showing tight lesion at the level of LCX and no significant stenosis of ostial LAD and distal LM; **C.** Crossover stenting (DES 3.5 × 38 mm) from LM toward LCX (AP-CRA view); **D.** POT with 4.5 × 12 mm (AP-CAU view); **E.** Kissing with NC balloons 3.25 × 15 mm (LCX) and 2.75 × 12 mm (LAD) balloons; **F.** Repeated POT with 4.5 × 12 mm; **G.** Final angiography result (AP-CAU view); **H.** Final OCT run showing widely open SB (LAD) and perfect stent apposition in LCX and LM

Abbreviations: POT, proximal optimization technique; other — see Figures 1 and 3

advanced over both the primary and the anchor guidewire which is placed in the SB and used to stop the advancement of the stent just at the ostium of the target vessel.

When high mobility of the stent is noticed (due to bobbing or to-and-fro motion of the stent caused by cardiac contraction), other alternatives like the buddy balloon technique [24] or rapid transcoronary pacing [25] have been proposed to increase the chance to deliver the stent in the appropriate location.

In conclusion, despite experience and tricks, precise ostial stenting (notwithstanding its apparent simplicity) should be regarded as a technique associated with a good final result that is difficult to achieve. Accordingly, crossover stenting is often adopted not only in ostial LAD but also in ostial LCX disease as it is shown in Figure 4. According to a small study comparing ostial versus crossover stenting in ostial LAD disease, crossover stenting was associated with numerically lower MACE rates (10.1 vs. 21%; $P = 0.2$) and target vessel revascularization (TVR) rates (5.6% vs. 21%; $P = 0.04$) in comparison to ostial stenting [26]. Another retrospective study confirmed those results and showed that PCI strategy (ostial stenting) was an independent predictor of 1-year MACE (HR 2.561; 95% CI, 1.041–6.299; $P = 0.021$) [27].

Figure 5 summarizes the options to be considered for ostial LAD and LCX treatment.

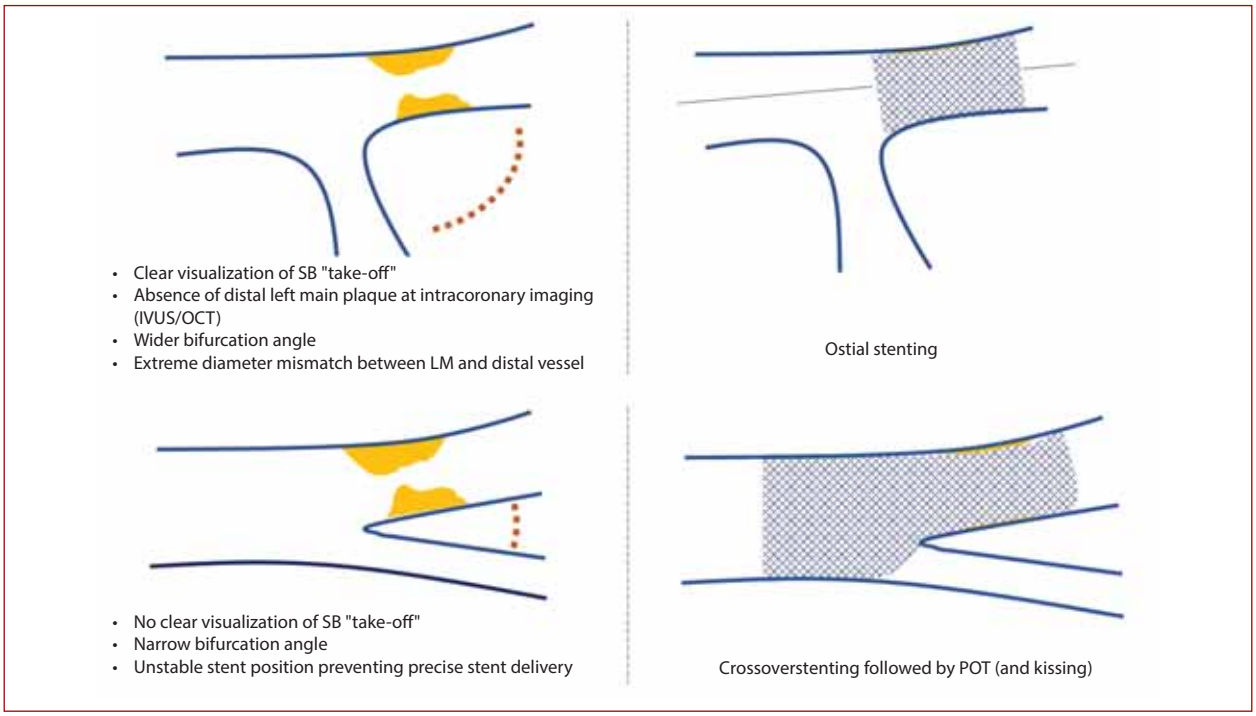


Figure 5. Ostial side branch disease — choosing between ostial versus crossover stenting
Abbreviations: see Figures 1, 3 and 4

WHEN TREATING LEFT MAIN WITH A SINGLE STENT, IS "KISSING" MANDATORY?

The most commonly adopted technique in LM stenting is the stepwise provisional single stent technique. According to this approach, recommended by the European Bifurcation Club (EBC) [28], a stent is implanted in the main vessel (with the size selected according to the distal reference) and appropriate postdilation of the proximal stent segment (lying in the left main) is done with a properly sized balloon according to the proximal optimization technique (POT) technique. These simple steps might imply some challenges in the specific setting of LM where differences in the size of proximal and distal references might be major (so that the stent expansion limits might be reached) and balloons needed might be large (beyond 5 mm). If properly done, with a balloon positioned exactly at the level of the carina, reaching, but not exceeding the proximal stent edge in the absence of ostial coverage [29], POT is known to expand the stent's side cells so that further interventions (like wire and balloon advancement) on the side branch are facilitated. For instance, such partial removal of stent struts from the side branch ostium is sometimes so effective (Figure 6) that the question about the real need to dilate the side branch in the presence of good angiographic results does exist.

While kissing balloon inflation (KBI) is considered to be an obligatory step in the 2-stent strategy, in the provisional single stent strategy, there is conflicting evidence about its usefulness, not only in non-LM but also in LMB (Table 1). Although it is shown that KBI can reduce the incidence of SB restenosis, it does not influence clinical outcomes and is not recommended to be used systematically [30, 31]. Furthermore, the benefit of KBI in terms of MACE reduction has not been confirmed in the recently published sub-analysis of the EXCEL trial [32] investigating the influence of final KBI in the distal LMB.

Notably, there is some evidence that only POT can be considered a protective factor for TLF while both KBI and the joint action of POT and KBI do not affect TLF reduction [34]. However, the lack of randomized trials that investigate the synergism of POT and KBI, as well as a low rate of POT and not reported rate of POT in a majority of trials, may influence the heterogenicity of results (Table 1).

Importantly, although the advantages of systematic KBI in provisional single stenting are not recognized, there was no penalty in the clinical outcome either (Table 1).

However, not only kissing but also the quality of kissing might influence its efficacy and SB opening [35]. More recently, a large registry on ULM PCI with last-generation stents looking at the technique for KBI showed that only short overlap KBI (<3 mm) was associated with a lower rate of target lesion revascularization compared with no KBI (2.6% vs. 5.4%; $P = 0.034$), while long overlap was not (6.8% vs. 5.4%; $P = 0.567$) [36].

Longer proximal balloons overlap, and the use of SC balloons can cause overstretching of proximal MB that becomes oval, which should be fixed with repeated POT. With this re-POT, we aim to restore the round shape of proximal MB, to achieve better stent expansion, to fix malapposition and a "bottleneck" effect if present, thus regaining the fractal geometry of LM [37].

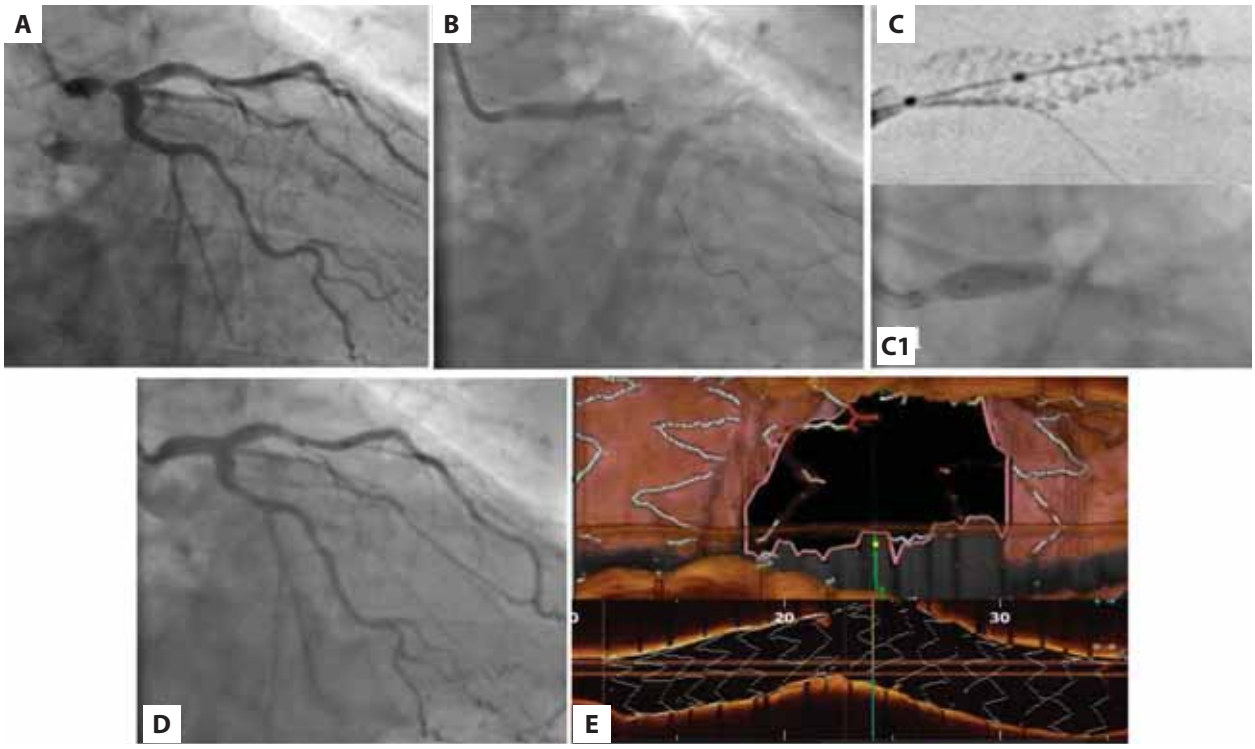


Figure 6. Feasibility of SB opening with properly done POT after crossover stenting in distal LM (Medina 1.1.0). **A.** LMB Medina 1.1.0; **B.** Implantation of DES 4.0 × 24 mm in LM-LAD; **C.** Stent boost for precise POT balloon positioning; **C1.** POT with NC balloon 5.0 × 15 mm; **D.** Final angiography result; **E.** Final OCT showing wide SB opening (upper picture) and perfect adaptation of the stent of the 2 diameters of LM and LAD (bottom picture)

Abbreviations: see Figures 1, 3, 4

Table 1. Effect of KBI vs. no KBI in provisional single stent technique in the trials that included LMB

Study/first author	Study design	No. of patients	% LM	KBI (N)	POT (%)	Follow-up, months	% MI KBI vs. no KBI	% Cardiac death KBI vs. no KBI	% TLR KBI vs. no KBI	% MACEb KBI vs. no KBI
COBIS II [61]	Registry	1901	25.9	620	NA	36	0.6 vs. 1.8	0.6 vs. 1.2	5.8 vs. 6.6	6.8 vs. 8.6[a]
NORDIC III [62]	RCT	477	8.0	238	NA	6	0.4 vs. 1.3	0.8 vs. 0.0	1.3 vs. 1.7	2.1 vs. 2.5
AOI-LMCA [63]	Registry	738	100	578[d]	NA	48	2.6 vs. 6.4	6.3 vs. 9.1	10.7 vs. 14.3	17.0 vs. 21.3
SMART-STRATEGY [64]	RCT	258	44.1	130	NA	12	0 vs. 0	0.8 vs. 0.0	5.4 vs. 7.8	9.2 vs. 9.4
CORPAL [65]	RCT	244	8.2	124	31	12	0.8 vs. 0.8	1.6 vs. 0.8	4 vs. 1.7	9.0 vs. 6.0
ASAN-MAIN [66]	Retrospective	413	100	95	NA	24	0 vs. 0.7	4.6 vs. 3.9	8.1 vs. 4.8	12.5 vs. 8.5
Gao [67]	Retrospective	790	100	230	NA	48	5.7 vs. 7.5	3.5 vs. 3.0	3.5 vs. 5.0	7.8 vs. 10
I-BIGIS [68]	Retrospective	2849	13.1	1176	NA	22.4	4.9 vs. 3.4	2.9 vs. 2.7	10.7 vs. 8.9	14.5 vs. 12.7
Hariki [69]	Retrospective	76	7.9	33	NA	25.9	NA	NA	9.1 vs. 12.8	6.1 vs. 2.6
RAIN-CARDIOGROUP VII [36]	Registry	2099	NA[e]	755	NA	16	7.3 vs. 5.3	6.1 vs. 6.6[f]	5.3 vs. 3.2	15 vs. 12.4
EXCEL [32]	RCT	430	100	175	NA	48	8.4 vs. 5.6	4.8 vs. 3.6 10 vs. 9.3[f]	9.5 vs. 9.5	17.5 vs. 15.9[c]
COBIS III [33]	Retrospective	2194	31.1	509[d]	28.7	60	2.4 vs. 1.5	2.8 vs. 3.0	3.5 vs. 4.0	6.7 vs. 7.0
Chevalier et al. [34]	Registry	4180	13.6	1517	37.7	12	1.0 vs. 1.9	1.8 vs. 1.6	2.4 vs. 2.7%	4.5 vs. 4.7

[a]*P* <0.05. [b]MACE-Target lesion failure (defined as a composite of cardiac death, target vessel MI, or target lesion revascularization). [c]Primary endpoint (death, MI, stroke); [d]SB opening; [e]26.7% in the overall RAIN-GROUP VII population that included 2742 patients. [f]All-cause death

Abbreviations: KBI, kissing balloon inflation; LM, left main; MACE, major adverse cardiac events; MI, myocardial infarction; NA, not applicable; POT, proximal optimization technique; RCT, randomized clinical trial; SB, side branch; TLR, target lesion revascularization

Another technique for SB opening in crossover stenting is POT-side-rePOT [38, 39]. This technique consists in single balloon dilatation of SB ostium after the first POT and properly done distal rewiring, followed by repeated POT. Although simple and feasible, with a reduction of SB obstruction from 26% to 3.3% in the experimental model [38], it can distort the stent, usually on the opposite wall, especially if the SB is of a bigger diameter; the larger the balloon, the larger the stent deformation.

However, in LMB, especially in true LMB, with a large amount of jeopardized myocardium in the SB territory, the only acceptable SB opening technique would be kissing, practiced in a refined way, in a joint action of POT, distal SB rewiring, and done with short proximal overlap and followed with re-POT. Only in this way, complete struts clearance in front of SB ostium and relocation of carina in the center can be obtained, thus improving wall shear stress [40].

Nevertheless, when dealing with LM trifurcation disease, which is distinct due to the presence of 2 SBs, 2 carinas, at least four angles, in provisional single stent technique, after essential POT, two-step kissing or triple balloon kissing ("trissing") is advisable for side branches opening and relocation of both carinas [41].

WHICH TECHNIQUE FOR LEFT MAIN BIFURCATION WITH EXTENSIVE DISEASE IN BOTH BRANCHES?

One of the most frequently asked questions in LM PCI, especially in the presence of extensive disease in both branches, defined as true LM bifurcation (Medina 1.1.1, Medina 1.0.1, or Medina 0.1.1), is whether to select upfront the two stent technique or to downgrade it to a single stent technique and in what circumstances.

A recently conducted meta-analysis of nine randomized controlled trials with 3265 patients, evaluating long-term outcomes (≥1 year) according to treatment strategy for coronary bifurcation lesions concluded that provisional single stenting was associated with lower all-cause mortality (2.94% vs. 4.23%; risk ratio: 0.69; 95% CI, 0.48–1.00; $P = 0.049$) [42].

However, when focusing on LM bifurcation lesions only, the first and until recently the only randomized trial conducted in these subgroup of patients, DKCRUSH-V showed superior results with the double kissing (DK) crush technique over the provisional single stent technique [43], therefore DK crush is considered as preferred option to treat true LMB (Class of recommendation IIb, level of evidence B) [1].

On the other hand, the recently published EBC MAIN trial [44] compared the stepwise provisional single stent strategy, which could convert into two stents as a bailout (patients with <TIMI 3 flow in SB, >90% of ostial pinching of SB, threatened SB closure or dissection > type A), with the upfront 2-stent technique in true distal LMB. It showed that there was no difference in the primary composite endpoint at 1 year (14.7% in stepwise provisional single stent vs. 17.7% in the upfront 2 stent group). There was no significant difference in any of the individual components of the primary endpoint.

Comparing those 2 trials (Table 2), the DK CRUSH-V population had a higher mean SYNTAX score in comparison to the EBC MAIN trial (31 vs. 23), with a higher SB lesion length (16 vs 7 mm), which is why almost half of the patients in DK CRUSH-V were converted from a single to 2-stent technique (47.1% of patients). By comparison, in the EBC MAIN trial, only 22 % of patients randomized to a single stent strategy converted to two stent strategy (Culotte or T/TAP equally).

The contradictory results of the ten RCTs evaluating outcomes between 1 versus 2 stents in bifurcation lesions that included LMB (Table 2), may be explained by the diversity of the study population, which not only presented true LMB lesions but also by disease complexity and the extent, presence of calcium, and unfavorable angles which can influence the outcome [45–48], as well as heterogenicity of double stenting techniques.

Furthermore, when it comes to stenting optimization techniques, although there are also conflicting results (Table 3), it is important to underline that unlike in the provisional single stent technique, where kissing is optional, in two stent strategy, it is shown that final KBI can influence outcomes and should be considered mandatory [36]. In the 2-stent subgroup of patients included in the large RAIN-CARDIOGROUP VII registry, final KBI was associated with lower rates of TVR (7.8% vs. 15.9%; $P = 0.030$) and target lesion revascularization (7.3% vs. 15.2%; $P = 0.032$), thus demonstrating the necessity of applying KBI in 2 stent techniques [36]. Importantly, KBI is done in a specific manner (sequential kissing with non-compliant balloons with short proximal overlap [40]).

Consequently, the stepwise provisional single stent strategy may be a reasonable option to treat the majority of true LMB lesions, of course, bearing in mind the complexity and the extent of the disease, discrepancy in SB diameters, and presence of unfavorable angles, which can make operators convert to two stent strategy if needed. Thus, in complex LMB with diffusely diseased, calcified SB and particularly with unfavorable SB take-off, when SB damage could be expected after MB stenting or SB needed to be treated first, we should start with an upfront 2 stent technique. In all other circumstances, and when there is no damage of SB after MB stenting, we should continue with a single stent strategy. However, if the result in SB is not satisfactory (dissection >type A, impaired flow), then proceeding to a 2-stent technique is mandatory (either Culotte or T/TAP, mainly based on bifurcation angle), followed by obligatory sequences of POT, kissing and re-POT.

Table 2. Trials on single stent vs. 2-stents in bifurcation lesions

Study/year	No of pts	1[c] end--point	True bif. % (1 vs. 2 stents)	LMB, %	2-stent technique, %	SB lesion length, mm	SB stenosis diameter % (1 vs. 2 stents)	% of pts with B angle < 70[c] (or avg degree)	Cross--over from 1 to 2 stents, %	KBI 1 vs. 2 stents	Follow--up, years	MI 1 vs. 2 stents, %	Death 1 vs. 2 stents, %	TLR 1 vs. 2 stents, %	Primary end-point 1 vs. 2 stents, %
NORDIC 2013 [70]	413	MACE (CD, NPMI, TVR, ST)	72 (77 vs. 67)[a]	0.7	Crush (50) Culotte (21) Other (29)	5	NA	63 vs. 66	4.4	32 vs. 74	5	4.0 vs. 7.9	5.9 vs. 10.4	11.3 vs. 15.3	15.1 vs. 21.8
BBK 1 2015 [71, 72]	202	All-cause de-ath, MI or TLR	68.3	0	T stent	10.2	53.8	(49.9 vs. 47.6)	18.8	100 vs. 100	5	NA	7.9 vs. 10.0	16.2 vs. 16.3	22.8 vs. 22.9
PERFECT 2015 [73]	419	CD, MI or TVR	86.6	0	Crush (99)	9.3	55.2	NA	28.2	79 vs. 96	1	14.1 vs. 14.1	1.0 vs. 1.4	3.4 vs. 1.9	18.5 vs. 17.8
NORDIC BALTIC Bifurcation IV 2015 [74]	446	MACE (CD, NPMI, TLR and def ST)	100	2	Culotte (67) T-stent (7) Other (26)	5.8	45.8	49.3 vs. 48.9	3.7	36.1 vs 91.2	2	5.1 vs. 3.1	2.3 vs. 2.2	9.2 vs. 6.2	12.8 vs. 8.4
BBC1 2016 [75, 76]	500	Death	83.2 (81 vs. 84)	0	Crush (68) Culotte (30) Other (2)	NA	NA	85 vs. 87[d]	2.8	29 vsc 76	5	3.6 vsc 11.2[a]	0.4 vsc 0.8	5.6 vsc 7.2[e]	8.0 vs 15.2[a]
EBC TWO 2016 [77]	202	Death, MI or TVR	100	0	Culotte	10.3	54.5	NA	16	94 vs. 96	1	4.9 vs. 10.3	2.0 vs. 1.1	2.9 vs. 1.0[f]	7.7 vs. 10.3
SMART STRATEGY 2016 [78]	258	TVF (CD, spont. MI or TVR)	66.3	44.2	TAP	NA	NA	NA	7	26 vs. 69	3	0 vs. 3.1	0.8 vs. 3.1[b]	8.6 vs. 11.5	11.7 vs. 20.8[a]
DK CRUSH II 2017 [79]	370	CD, MI or TVR	100	16.7	DK Crush	15	NA	NA	29	79.2 vs. 100	5	3.2 vs. 3.8	3.2 vs. 2.2[b]	16.2 vs. 8.6[a]	23.8 vs. 15.7
DK CRUSH-V 2017 [43]	482	CD, TVMI, or TLR	100	100	DK Crush	16	65.6 (65.3 vs. 65.8)	(79.7 vs. 76.3)	47.1	78.9 vs. 99.6[a]	1	2.9 vs. 0.4[a,c]	2.1 vs. 1.2[b]	7.9 vs. 3.8	10.7 vs. 5.0[a]
EBC MAIN 2021 [44]	467	Death MI TLR	100	100	Culotte (53) T/TAP (32) DK crush (5)	7	53.6 (51.9 vs. 55.4)	(80.4 vs. 82.3)	22	89 vs. 93	1	10 vs. 10.1	3.0 vs. 4.2	6.1 vs. 9.3	14.7 vs. 17.7

[a]*P* <0.05. [b]Cardiac death. [c]Target vessel MI. [d]Bifurcation angle <60%. [e]Target vessel failure (TVR with PCI or CABG or postprocedural TIMI<3 in either MB or SB). [f]Target vessel revascularization

Abbreviations: CABG, coronary artery bypass grafting; CD, cardiac death; LMB, left main bifurcation; NPMI, non-procedural MI; ST, stent thrombosis; TVMI, target vessel MI; TVR, target vessel revascularization; other — see Table 1

Table 3. Effect of KBI vs. no KBI in the 2-stent technique in the studies that included the left main bifurcation

Study/first author	Study design	Number of patients	% left main	KBI, n	POT, %	Follow-up months	% MI KBI vs. no KBI	%Cardiac death KBI vs. no KBI	% TLR KBI vs. no KBI	% MACE KBI vs. no KBI
Ge et al. [80]	Observational	181	26.5	116	NA	9	10.3 vs. 13.9	1.7 vs. 0.0	9.5 vs. 24.6[a]	19.8 vs. 38.5[a,d]
Grundeken et al. [81]	Registry	745	5.6	624	NA	6	5.0 vs 4.6	1.7 vs 4.6[a]	4.7 vs 2.9	9.2 vs 10.1[e]
RAIN-CARDIOGROUP VII [36]	Registry	439	NA[b]	321	NA	16	vs 6.0	6.6 vs. 3.9[c]	7.3 vs 15.2[a]	16.6 vs 24.9[f]
EXCELsubstudy [32]	Substudy from RCT	329	100	235	NA	48	13.5 vs 14.4	7.4 vs 10 8.6 vs. 17.4[a,c]	17.3 vs 14.1	19.8 vs 25.8[g]

[a]*P* <0.05. [b]26.7% in the overall RAIN-GROUP VII population that included 2742 patients. [c]All-cause death. [d]MACE-cardiac death, MI and TVR. [e]Target vessel failure (TVF) — cardiac death, any MI and TVR; [f]MACE — all-cause death, MI, TLR, and stent thrombosis. [g]MACE — death, MI, or stroke

Abbreviations: see Tables 1 and 2

WHAT ABOUT HEMODYNAMIC STABILITY DURING LM PCI?

One of the most challenging situations in terms of possible hemodynamic compromise and poor clinical outcome is, for sure, LM PCI in the setting of absent right coronary artery (RCA) support. The definition of absent RCA support varies throughout the published data, with chronic total occlusion (CTO) being the most common. Although the majority of patients with LM disease and RCA CTO are scheduled for coronary artery bypass grafting (CABG) [49], it is not an infrequent situation to deal with LM PCI in this particular setting. The current data support the fact that patients with concomitant RCA CTO have a worse outcome and a higher mortality rate in comparison to patients without RCA CTO [50–52], with RCA CTO as an independent predictor of 3-year cardiac mortality in LM PCI (HR 2.15 [1.02–4.05]; $P = 0.043$) [51]. Furthermore, it is shown that the recanalization of RCA CTO significantly improves long-term survival [52].

Contrary to previous retrospective trials and registries, the recently published data by Skorupski et al. [53] failed to demonstrate the impact of RCA support on prognosis in patients undergoing LM PCI and exhibited a low risk of both acute hemodynamic compromise and late adverse outcome. However, the study population enrolled by Skorupski et al. [53] was characterized by the broad definition of absent RCA support, including patients not only with RCA CTO (only 14.3% of patients) but also with significant stenosis or recessive (non-dominant) RCA. Furthermore, the average SYNTAX score of 21, EuroSCORE II of 1.45%, and preserved ejection fraction (mean value around 55%) definitely influenced the results in this trial.

When faced with significant RCA stenosis in patients selected for LM PCI, it has also been shown that PCI on significant (>70%) RCA stenosis during the same hospitalization might reduce the rate of 30-day cardiovascular death [54].

Altogether, these data imply that the relevance of RCA support is strongly predisposed and influenced by the clinical condition of the patients (acute vs. chronic coronary syndrome), left ventricular ejection fraction, and complexity of LM PCI (Figure 7).

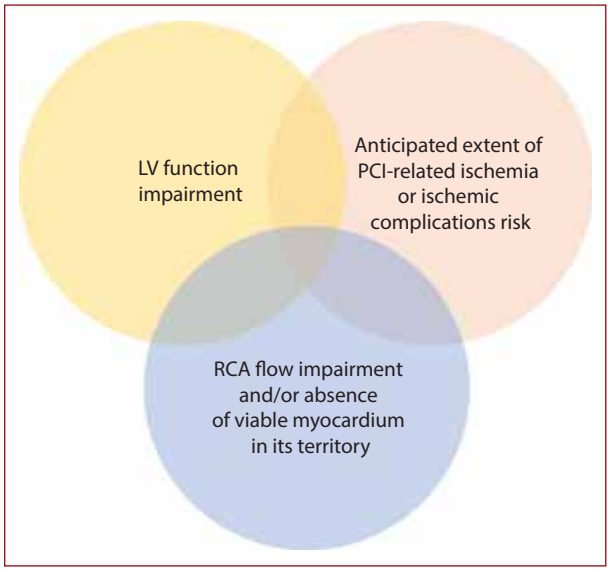


Figure 7. Factors that might be assessed when considering hemodynamic support during left main PCI planning

Abbreviations: LV, left ventricle; RCA, right coronary artery; other — see Figure 1

Thus, in the case of complex LM PCI in the setting of poor/absent RCA support (RCA stenosis or CTO), an individual approach to each patient is recommended. In complex, diffusely diseased LM PCI with reduced EF, which is considered a "high-risk PCI", the use of short-term mechanical circulatory support ("protected" PCI) is advisable to increase procedural safety [55, 56]. Furthermore, in patients with a large area of jeopardized myocardium due to RCA disease (significant stenosis of dominant proximal RCA) undergoing LM PCI, it is recommended not to leave untreated, since it is shown that it may result in impaired late outcome despite successful protected PCI [56, 57]. Despite the conflicting result of the use of MCS in high-risk PCI, except in the prevention of hemodynamic collapse, short-term MCS (preferably "axial flow pump" as Impella,

HeartMate PHP, iVAC2l) should provide adequate time to achieve optimal and complete revascularization (or a reasonable level of revascularization completeness) [58, 59].

CONCLUSIONS

According to the current evidence about the most challenging issues in LM PCI summarized in this review and concerning the amount of myocardium at risk and possible consequences, it is important to highlight several crucial points:

- pragmatic use of functional assessment and imaging techniques in LM evaluation, guidance, and final result assessment;
- if weighing between stenting techniques, the stepwise provisional single stent is preferable over the two stent technique;
- different techniques can be used for SB opening, but POT cannot be omitted;
- in ostial SB disease, do not hesitate to perform crossover stenting.

Concerning all the mentioned above points, it is obvious that LM PCI should be done only by an experienced intervention cardiologist [60] familiar with all bifurcation techniques, intracoronary imaging, and mechanical circulatory support devices.

Article information

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The association between whole blood viscosity and high thrombus burden in patients with non-ST elevation myocardial infarction

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ABSTRACT

Background: Prior studies showed that patients with elevated whole blood viscosity (WBV) had a higher risk of arterial thrombosis, acute stent thrombosis, and left ventricular apical thrombus presence after acute coronary syndrome. This investigation aimed to determine the association between WBV and high thrombus burden (HTB) in non-ST elevation myocardial infarction (NSTEMI) patients treated with percutaneous coronary intervention (PCI).

Methods: This retrospective cohort investigation included data from consecutive 290 NSTEMI patients who received PCI at a tertiary institution. Patients with grade 1–3 thrombus burden were categorized as having low thrombus burden (LTB) (n = 178), whereas those with grade 4–5 thrombus burden were classified as having HTB (n = 112). WBV at high shear rate (HSR) and low shear rate (LSR) were estimated using hematocrit (HTC) and total protein levels.

Results: Patients with HTB had higher WBV at both LSR and HSR. In HTB patients, the frequency of infarct-related artery (IRA) reference vessel diameter, distal embolization, and no-reflow was also higher. Multivariable logistic regression models indicated that WBV at LSR (odds ratio [OR], 1.028; 95% confidence interval [CI], 1.014–1.043; $P < 0.001$) and HSR (OR, 1.606; 95% CI, 1.334–1.953; $P < 0.001$) were independent predictors of HTB in NSTEMI patients. Notably, the area under the curve value of WBV at both shear rates was greater than that of its components, including total protein and HTC.

Conclusion: This is the first study showing that WBV at both shear rates is a significant predictor of HTB in NSTEMI patients.

Key words: whole blood viscosity, thrombus burden, high, non-ST elevation myocardial infarction

INTRODUCTION

The main underlying cause of acute coronary syndrome (ACS) is atherosclerotic plaque erosion or injury, which leads to thrombus formation due to the exposure of thrombogenic plaque components to cellular constituents of the blood flow [1]. Notably, excessive thrombus development is a strong predictor of poor outcomes in individuals with ACS [2]. High thrombus burden (HTB) is commonly detected in ST-elevation myocardial infarction (STEMI) patients [2]. Besides that, the presence of HTB is also related to worse clinical outcomes, such as an increased risk of myocardial infarction, no-reflow, and stent thrombosis, in patients with non-ST elevation myocardial infarction (NSTEMI) [3]. Thus, predicting HTB in the infarct-related artery (IRA) before the interventional procedure may assist physicians in improving short- and long-term outcomes of NSTEMI patients.

Whole blood viscosity (WBV) is termed as internal resistance of blood flow that is closely associated with endothelial shear stress (ESS) [4]. It had long been noted that both higher ESS and blood viscosity might trigger the thrombus formation [5]. WBV is also a crucial element of Virchow's triad, which is the primary mechanism for thrombi. Since it is believed to be an appropriate indicator of blood flow,

WHAT'S NEW?

Patients with high whole blood viscosity (WBV) were more likely to develop arterial thrombosis or acute stent thrombosis. In this research, WBV at low shear rate (LSR) and high shear rate (HSR) were found to be independent predictors of high thrombus burden (HTB) in non-ST elevation myocardial infarction (NSTEMI) patients. Notably, the area under the curve value of WBV was greater at both shear rates than that of its components, including total protein and hematocrit. This is the first study to indicate that WBV at both shear rates is a significant predictor of HTB in patients with NSTEMI.

WBV has been evaluated in several cohort settings. It has been demonstrated that patients with elevated WBV have a higher risk of arterial thrombosis, acute stent thrombosis, and left ventricular apical thrombus presence after ACS [6–8]. However, to the best of our knowledge, no data suggest that WBV is also associated with HTB in patients with NSTEMI undergoing percutaneous coronary intervention (PCI). As a result, this investigation aimed to determine the association between WBV and HTB in NSTEMI patients treated with PCI.

METHODS

Data collection

The NSTEMI was accepted as persistent angina pectoris for more than 20 minutes with a rise in cardiac troponin I level beyond the upper normal limit in the context of non-ST segment elevation on a surface electrocardiogram [9]. The current study was related to the data from consecutive NSTEMI patients who had PCI at a tertiary hospital. Initially, the medical records of consecutive NSTEMI cases who were treated with PCI were screened retrospectively. Patients who had an acute infection, end-stage chronic liver disease, autoimmune illness, and those who underwent hemodialysis or peritoneal dialysis were not included. Additionally, patients with moderate to severe cardiac valvular disease and cardiac valve surgery were excluded. Lastly, to calculate WBV, hematocrit (HTC) levels should be between 32% and 53%, and plasma protein levels should be between 54 g/l and 95 g/l; thus, those who were not in the range of specified limits were excluded from the study (Figure 1). All patients' baseline characteristics, comorbidities, and previous medications were obtained from the hospital database. Our study design was evaluated and approved by the Local Ethics Commission (no. 2021/21).

Laboratory examination

Following admission to our center, all blood samples were obtained from the antecubital vein. All hematologic parameters, including white blood cell count, HTC, and hemoglobin, were determined using a hematology analyzer (Beckman Coulter, FL, US). All biochemical parameters,

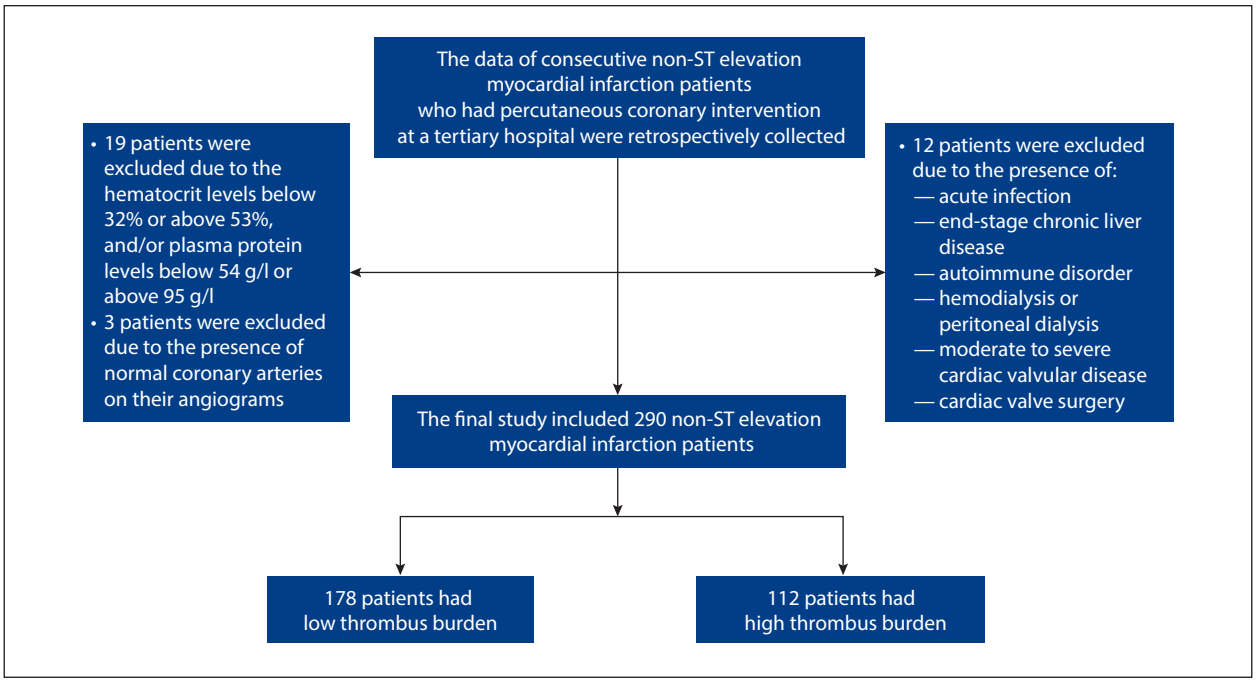

Figure 1. Flow chart of the study participants

including total protein levels, were determined using the conventional methods.

Calculation of WBV

As suggested by De Simone et al. [10], WBV at a high shear rate (HSR) (208 sec^{-1}) and a low shear rate (LSR) (0.5 sec^{-1}) were determined using HTC (percent) and total protein (g/l) levels; WBV at HSR (208 sec^{-1}) = (0.12 × HTC) + (0.17 × [total protein-2.07]) and WBV at LSR (0.5 sec^{-1}) = (1.89 × HTC) + (3.76 × [total protein-78.42]).

Coronary angiography and PCI

Conventional coronary angiography (CAG) was performed by an experienced operator utilizing either a trans-radial or a trans-femoral approach. In very high-risk NSTEMI patients, an urgent CAG (within 2 hours) was performed to accomplish revascularization [9]. CAG was performed within 24 hours of hospital admission in high-risk NSTEMI patients [9]. Before the CAG procedure, all patients were treated with 300 mg of acetylsalicylic acid and a loading dose of P_2Y_{12} inhibitors. The choice to use a glycoprotein IIb/IIIa receptor inhibitor was left to the discretion of the attending cardiologist as per hospital protocol. The PCI technique was carried out in accordance with the current European Society of Cardiology NSTEMI guidelines [9]. Two experienced operators who were blinded to the clinical data meticulously evaluated the angiographic scans of all patients. In this investigation, angiographic thrombus burden was graded as the followings: grade 0: no thrombus, grade 1: possible thrombus (reduced contrast density, haziness, irregular lesion contour), grade 2: the greatest dimension of thrombus was less than 1/2 vessel diameter, grade 3: the greatest dimension of thrombus was more than 1/2 but less than <2 vessel diameter, grade 4: the greatest dimension of thrombus was more than 2 vessel diameter, and grade 5: total vessel occlusion by a thrombus [11]. Grade 5 angiographic thrombus burden was reclassified after restoring antegrade flow through guidewire or small balloon dilatation. Based on the final thrombus burden, the patients who had grade 1–3 thrombus burden were classified as low thrombus burden (LTB) and those who had grade 4–5 thrombus burden were classified as HTB, as suggested in prior studies [11, 12]. The thrombolysis in myocardial infarction (TIMI) flow grade classification was used to determine the TIMI flow after PCI [13]. Patients were divided into four categories according to the final TIMI myocardial blush grade (TMBG) as follows: grade 0: no myocardial blush, grade 1: minimum myocardial blush, grade 2: moderate myocardial blush, and grade 3: normal myocardial blush. The TIMI flows 0, I, and II were regarded as no-reflow [14].

Statistical analysis

All statistical analyses were performed using R-software v. 3.6.3 (R statistical software, Institute for Statistics and Mathematics, Vienna, Austria). The Kolmogorov-Smirnov test was used to determine normality. Continuous variables with a normal distribution were presented as the arithmetical mean (SD), whereas those without a normal distribution were given as the median (interquartile range [IQR]). Categorical variables were presented as numbers and percentages. The independent Student's t-test and Mann-Whitney U tests were used to compare continuous variables between the groups. The χ^2 test or Fisher's exact test was performed to compare categorical variables, as appropriate. The Kruskal-Wallis test was employed to compare WBV at both shear rates based on the thrombus burden grade. For *post-hoc* comparisons between the subgroups, the Dunn's procedure with Bonferroni correction was used. Univariable logistic regression analysis was used to detect the association of variables with HTB. A multivariable logistic regression analysis was performed with clinically relevant variables that had a *P*-value <0.1 in univariable logistic regression analysis. To avoid multicollinearity, WBV at LSR and HSR were entered into two different multivariable models separately with the same cofounders. Since multicollinearity was detected between HTC, total protein, and WBV (variance inflation factor >3, tolerance <0.1), we did not enter HTC and total protein in the multivariable models. Receiver operating characteristic (ROC) curve analysis was used to calculate the best cutoff values of WBV at HSR and LSR for detecting patients with HTB. ROC curve comparisons were calculated using the DeLong test between variables to compare the discrimination ability for HTB. A 2-sided *P* <0.05 was considered significant.

RESULTS

The final study comprised 290 NSTEMI cases. In all, 231 patients (73.4%) were male with a mean age (SD) of 63.4 (12.4) years. Patients were divided into two groups based on the thrombus burden; those with HTB (n = 112 cases) and those with LTB (n = 178 cases). The total in-hospital mortality rate was 5.5% (n = 16 cases).

Table 1 displays baseline properties, previous medications, and laboratory results of all patients. There was only one significant difference between the groups with respect to family history of coronary artery disease (CAD) and Killip class >2 on admission. Other baseline characteristics were comparable between groups. The previous medications between the groups were not different. In terms of laboratory results, patients with HTB exhibited greater HTC, triglyceride, baseline cardiac troponin I, total protein, WBV at LSR and HSR. Furthermore, the lymphocyte and high-density lipoprotein (HDL) cholesterol levels in these individuals were lower. Other laboratory results did not differ between the groups.

When we compared WBV at HSR and LSR according to the grades of thrombus burden, there were statistically significant differences in WBV at both shear rates from grade 1 thrombus burden through grade 5 thrombus burden (*P* <0.001, for all comparisons) (Table 2). In *post-hoc* comparisons, patients with grade 4 and 5 thrombus burden

Table 1. Baseline features and laboratory results of all patients according to high and low thrombus burden

	High thrombus burden (n = 112)	Low thrombus burden (n = 178)	*P*-value
Age, years	63.2 (12.6)	65.2 (16.8)	0.28
Male sex, n (%)	86 (76.8)	127 (71.3)	0.38
Body mass index, kg/m^2	25.6 (2.2)	25.4 (2.6)	0.63
Risk factors, n (%)			
Diabetes mellitus	15 (13.4)	29 (16.3)	0.62
Hypertension	66 (58.9)	115 (64.6)	0.40
Hyperlipidemia	31 (27.7)	68 (38.2)	0.09
Smoking	70 (62.5)	106 (59.6)	0.71
Previous history of CAD	43 (38.4)	79 (44.4)	0.38
Family history of CAD	30 (26.8)	28 (15.7)	0.03
Congestive heart failure	27 (24.1)	50 (28.1)	0.54
Cerebrovascular event	5 (4.5)	5 (2.8)	0.52
LV ejection fraction, %	48.6 (7.2)	47.6 (6.9)	0.19
Killip class >2	22 (19.6)	17 (9.6)	0.02
Previous medications, n (%)			
Acetylsalicylic acid	42 (37.5)	72 (40.4)	0.71
P_2Y_{12} inhibitors	21 (18.8)	38 (21.3)	0.70
Beta-blockers	42 (37.5)	74 (41.6)	0.57
ACE inh/ARBs	62 (55.4)	94 (52.8)	0.76
Statin	17 (15.2)	45 (25.3)	0.06
Laboratory data			
White blood cell count, 10^3/µl	9.6 (8.1–11.7)	9.7 (7.2–11.6)	0.32
Hemoglobin, g/dl	13.6 (1.9)	13.8 (2.4)	0.65
Hematocrit, %	44.5 (4.3)	39.7 (6.3)	<0.001
Neutrophil, 10^3/µl	7.1 (4.9–9.3)	6.3 (5–8.8)	0.47
Lymphocyte, 10^3/µl	1.7 (1.2–2.1)	2 (1.4–2.5)	0.01
Platelet, 10^3/µl	246 (93)	242 (76)	0.62
Serum creatinine, mg/dl	0.9 (0.8–1)	0.9 (0.8–1.1)	0.13
LDL cholesterol, mg/dl	104 (38)	110 (44)	0.16
HDL cholesterol, mg/dl	35 (31–42)	39 (35–46)	<0.001
Triglycerides, mg/dl	119 (75–179)	104 (77–123)	0.03
Baseline troponin I, ng/ml	8 (2.4–14)	5 (2.3–6.5)	0.01
Total protein, g/l	72 (6)	69 (8)	0.01
Albumin, mg/dl	4.4 (4.1–4.6)	4.2 (3.8–4.5)	0.01
WBV at LSR	62 (46–75)	45 (38–61)	<0.001
WBV at HSR	17.2 (1.2)	16.3 (1.5)	<0.001
In-hospital mortality, n (%)	11 (9.8)	5 (2.8)	0.02

Continuous variables are presented as median (IQR) or mean (SD), nominal variables presented as frequency (%)

Abbreviations: ACE inh/ARBs, angiotensin converting enzyme/angiotensin receptor blockers; CAD, coronary artery disease; HDL, high-density lipoprotein; HSR, high shear rate; IQR, interquartile range; LV, left ventricle; LDL, low-density lipoprotein; LSR, low shear rate; SD, standard deviation; WBV, whole blood viscosity

Table 2. Whole blood viscosity at both shear rates according to the thrombus burden grade

	Thrombus burden grade					*P*-value
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	
WBV at HSR	14.4 (1.2)	15.9 (1.6)	16.5 (1.4)	17.1 (1)	19.3 (0.5)	<0.001
WBV at LSR	41.4 (32.6–42.3)	43 (35.5–54.6)	46.9 (39.3–64)	59.2 (44.5–72.4)	84.1 (79.9–86.8)	<0.001

Continuous variables are presented as median (IQR) or mean (SD)

Abbreviations: see Table 1

had higher WBV at both shear rates than those with grade 3, 2, and 1 thrombus burden (P <0.05, for all comparisons).

Table 3 presents the angiographic data for all patients based on thrombus burden. In HTB patients, the frequency of IRA reference vessel diameter, distal embolization, and no-reflow was greater. These patients also showed lower postprocedural TIMI flow >II and TMBG >II. There was no difference between the groups with respect to the use of glycoprotein IIb/IIIa receptor inhibitors and P_2Y_{12} treatments. Other angiographic results were also comparable between the groups.

Table 4 shows the results of univariable and multivariable logistic regression analyses for independent predictors of HTB. According to univariable logistic regression analysis, HTB was related to family history of CAD, HTC, Killip class >II, HDL cholesterol, triglyceride, baseline troponin I, total

Table 3. Angiographic findings and medications of all patients according to high and low thro`mbus burden

	High thrombus burden (n = 112)	Low thrombus burden (n = 178)	*P*–value
Culprit lesion location, n (%)			
LAD	49 (43.8)	95 (53.4)	
Cx	32 (28.6)	41 (23)	0.45
RCA	30 (26.8)	41 (23)	
LMCA	1 (0.9)	1 (0.6)	
CTO, n (%)	14 (12.5)	14 (7.9)	0.27
Multivessel disease, n (%)	41 (36.6)	46 (25.8)	0.07
IRA reference vessel diameter >4 mm	18 (16.1)	19 (10.7)	0.25
IRA lesion length, mm	32 (24–38)	25 (21–36)	0.01
Procedure, n (%)			
Direct stenting	0 (0)	8 (4.5)	
PTCA+stenting	108 (96.4)	167 (93.8)	0.06
Only PTCA	3 (2.7)	1 (0.6)	
CABG	1 (0.9)	2 (1.1)	
Glycoprotein IIb/IIIa inhibitors, n (%)	95 (85)	139 (78)	0.16
P_2Y_{12} inhibitors, n (%)			
Clopidogrel	94 (84)	143 (80)	
Ticagrelor	15 (13)	33 (19)	0.34
Prasugrel	3 (3)	2 (1)	
Postprocedural TIMI flow >2, n (%)	77 (69.8)	157 (88.2)	<0.001
TMBG >2, n (%)	54 (48.2)	116 (65.2)	0.01
Distal embolization, n (%)	8 (7.1)	3 (1.7)	0.03
No-reflow, n (%)	35 (31.2)	21 (11.8)	<0.001

Continuous variables are presented as median (IQR) or mean (SD), nominal variables are presented as frequency (%).

Abbreviations: CABG, coronary aorta bypass grafting; CTO, chronic total occlusion; Cx, circumflex artery; IRA, infarct-related artery; LAD, left anterior descending artery; LMCA, left main coronary artery; PTCA, percutaneous transluminal coronary angioplasty; RCA, right coronary artery; TIMI, thrombolysis in myocardial infarction; TMBG, TIMI myocardial blush grade; other — see Table 1

Table 4. Multivariable models for independent predictors of high thrombus burden

	Multivariable model[1]		Multivariable model[2]	
	OR (95 %CI)	*P*-value	OR (95 %CI)	*P*-value
Family history of CAD	2.386 (1.351–4.253)	0.012	2.411 (1.377–4.257)	0.01
Lymphocyte	0.622 (0.472–0.805)	0.003	0.663 (0.508–0.853)	0.01
Triglyceride	1.004 (1.002–1.008)	0.016	1.005 (1.002–1.008)	0.01
Baseline troponin I	1.071 (1.022–1.121)	0.015	1.080 (1.033–1.131)	0.01
WBV at LSR	—	—	1.028 (1.014–1.043)	<0.001
WBV at HSR	1.606 (1.334–1.953)	<0.001	—	—

Model[1]: WBV at HSR was an independent variable with covariates in this model; Model[2]: WBV at LSR was an independent variable with covariates in this model

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

protein, IRA lesion length, WBV at LSR, and WBV at HSR. We constructed two separate multivariable models to determine whether WBV at LSR and HSR was an independent predictor of HTB. Multivariable logistic regression models indicated that family history of CAD, lymphocyte, triglyceride, baseline troponin I, WBV at LSR (odds ratio [OR], 1.028; 95% confidence interval [CI], 1.014–1.043; *P* <0.001), and WBV at HSR (OR, 1.606; 95% CI, 1.334–1.953; *P* <0.001) were independent predictors of HTB in NSTEMI patients. The use of glycoprotein IIb/IIIa receptor inhibitors and P_2Y_{12} inhibitors were not associated with HTB in the logistic regression analysis (*P*-values = 0.152 and 0.338, respectively).

The area under the curve (AUC) values of WBV at LSR and HSR in a ROC analysis were 0.716 (95% CI, 0.659–0.771) and 0.767 (95% CI, 0.713–0.823), respectively (Figure 2). Notably, the AUC value of WBV at both shear rates was greater than that of its components, including total protein (AUC, 0.605) and HTC (AUC, 0.615). To predict HTB in NSTEMI patients, the optimum value of WBV at LSR was >45.5 with 85% sensitivity and 52% specificity, while the ideal value of WBV at HSR was >16.7 with 82% sensitivity and 64% specificity.

DISCUSSION

This is the first report to suggest that WBV at both shear rates seems to be a significant determinant of HTB in NSTEMI individuals.

HTB is a clinical entity that can adversely affect both short- and long-term outcomes of NSTEMI patients with an increased risk for occurrence of no-reflow phenomenon, stent thrombosis, and intraventricular thrombus formation [7, 15, 16]. Additionally, a final TMBG after PCI was lower in coro-

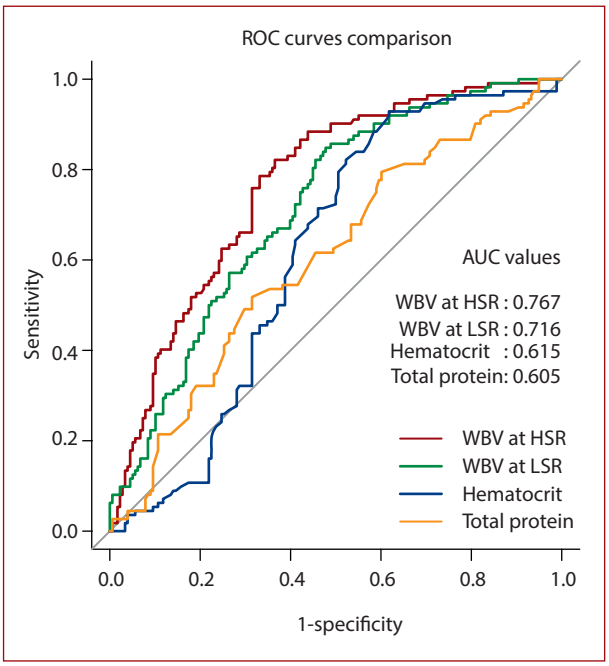

Figure 2. Receiver operating characteristic (ROC) curve analyses of whole blood viscosity (WBV) at high shear rate (HSR) and low shear rate (LSR), hematocrit, and total protein

naries with HTB, leading to the observation that even after successful reperfusion with PCI, residual ischemia may persist in such patients [17]. This was consistent with our findings, as the final TMBG >2 and TIMI flow >2 were lower, and the NR phenomenon was more prevalent in patients with HTB.

ACS is typically characterized by rupture of atherosclerotic plaque, and the aggregation of blood components on top of the rupture site, impeding flow to the segments distal to the occlusion. NSTEMI differs little in this context from STEMI, as it arises from incomplete obstruction of the coronary artery. The rupture of the atherosclerotic plaque is aggravated by localized elevation of shear stress and could be further demonstrated by the fact that nearly all plaque ruptures occur on the proximal "hill" of the plaque, where wall shear stress (WSS) is highest [18]. The WSS is calculated as shear rate multiplied by WBV, and shear rate is calculated as flow velocity divided by lumen diameter [19]. As shear rate, by definition, is a fixed value, WSS can only be increased by an increase in WBV. Due to the non-Newtonian nature of blood as a fluid, which is because it contains blood cells, its viscosity depends on shear stress. In our study, we found that elevated WBV in both shear stress settings was associated with an increased risk of HTB. This could be due to the tendency of red blood cells to aggregate in LSR areas, such as ruptured plaques, and persist in HSR areas distal to the lesion, causing slowing down blood flow and increasing thrombus burden [20].

Ideally, WBV can be measured using a "viscometer", which is expensive and proprietary laboratory equipment. However, most laboratory settings do not have access to these resources. Thus, de Simone and colleagues reported an equation for calculating WBV in an adequate accuracy relative to direct viscometer measurements, utilizing HTC and total protein levels [21]. This formula has been also investigated and validated in a variety of cohort settings [10, 22]. Specifically, changes in HTC and plasma protein levels were in most close relation to actual changes in mechanically measured WBV.

The importance of WBV had been investigated in prior studies. For example, it was demonstrated that high WBV at both shear rates was associated with worse outcomes for ACS patients undergoing PCI with an elevated risk for the no-reflow phenomenon, stent thrombosis, and the presence of apical thrombus [7, 23, 24]. It could also adversely affect the prognosis of acute pulmonary embolism and stroke patients [25, 26]. However, the association between WBV and HTB presence in NSTEMI patients has been unknown. In the present study, we showed that high WBV at HSR and LSR was independently associated with HTB in NSTEMI patients undergoing PCI. In our analysis of the data, we also clearly showed that the AUC of WBV was greater than HTC and total protein alone for predicting HTB, which could further demonstrate the value of WBV as a derived parameter.

The prediction of HTB is crucial in NSTEMI patients to increase procedure success rate and related clinical outcomes. Based on our results, patients with high WBV can be considered to have a high risk for HTB. Thus, some preventive measures, such as using glycoprotein IIb/IIIa inhibitors before PCI, can be applied to decrease the potential thrombus burden [27]. Furthermore, early stent implantation in a highly thrombotic environment may result in a greater risk of complications, such as distal embolization and peri-procedural MI. WBV may thus be estimated before invasive treatment of NSTEMI patients, and it may help us to determine the ideal time of the invasive procedure in such patients.

Limitations

There are a few limitations to our study. First, since only NSTEMI patients were included, the results might not be expanded to all ACS patients. Second, our study was conducted at a single tertiary care center. Therefore, the results might not be expanded universally. Third, although the extrapolation method we used in this study had been validated in previous investigations, a direct comparison of estimated and measured WBV in this specific patient group may strengthen our findings. Fourth, there might be some residual confounding factors even after multivariable analysis. Finally, prospective studies with a larger population are needed to confirm our findings.

CONCLUSION

The present study showed that WBV at both shear rates was an independent predictor of HTB in NSTEMI patients planned to undergo invasive treatment.

Article information

Conflict of interest: None declared.

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Outcome comparison of different approaches to aortic root aneurysm

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ABSTRACT

Background: The treatment of aortic root aneurysm remains challenging for both cardiac surgeons and cardiologists.

Aims: This study aimed to assess and compare the long-term outcomes of different approaches to aortic root replacement (ARR).

Methods: All elective patients operated for aortic root aneurysm with or without aortic regurgitation at our institution over a 10-year period were included. We excluded patients with any degree of aortic stenosis and with active endocarditis. We assessed mortality, freedom from reoperation, freedom from aortic valve regurgitation, and the rate of hemorrhagic and thromboembolic complications.

Results: Two hundred and four patients underwent elective aortic root replacement: 107 (53%) valve-sparing aortic root replacement (VSARR), 35 (17%) mechanical Bentall procedure (MB), and 62 (30%) Bio-Bentall procedure (BB). Early mortality for VSARR, BB, and MB group was 2.8%, 4.8%, and 0%, respectively ($P = 0.40$). Estimated 5-year survival was: 90.2% vs. 78.4% vs. 94.2%, respectively ($P = 0.12$), 5-year freedom from reoperation: 97.8%, 96.6%, and 96.8%, respectively ($P = 0.99$). Estimated 5-year freedom from complications was: 94.2%, 83.1% and 57.3% in the VSARR, BB and MB group, respectively ($P < 0.001$). On last follow-up echocardiography, 90.5%, 98.4%, and 97.1% ($P = 0.08$) of patients were free from aortic regurgitation grade 2 or higher. The median (IQR) aortic valve peak gradient was 9 (6–12) mm Hg, 12 (10–18) mm Hg and 16 (14–22) mm Hg, respectively ($P < 0.001$). Complications were predicted by mechanical Bentall (hazard ratio, 6.70 [2.54–17.63]; $P < 0.001$).

Conclusion: With the same mortality, freedom from reoperation, and a minimal late complication rate in comparison with mechanical Bentall and Bio-Bentall, VSARR might be the preferred approach to aortic root aneurysm.

Key words: aortic root aneurysm, aortic root replacement, Bio-Bentall, mechanical Bentall, valve-sparing

INTRODUCTION

The only effective treatment method for aortic root aneurysm is aortic root replacement (ARR) [1]. Currently, the „gold standard" for ARR is represented by the procedure proposed in 1968 by Bentall, which consists of the replacement of both the aortic root and the aortic valve with the use of a composite mechanical valved conduit [2]. In older patients, the available alternatives to the classical Bentall procedure include the ARR with the homograft [3], xenograft [4], or bio-conduit [5]. However, in younger patients who want to avoid the adverse effects of mechanical or biological aortic valve prostheses, the procedure of valve-sparing aortic root replacement (VSARR) has been proposed. This approach enables the replacement of the enlarged aortic root, with the preservation of the native aortic valve. Two main techniques of

WHAT'S NEW?

This analysis of long-term outcomes of different surgical approaches to aortic root aneurysm is the largest performed to date in Poland (and one of the largest in Europe). The analysis of mortality, freedom from reoperation, aortic valve regurgitation, and hemorrhagic and thromboembolic complications identified valve-sparing aortic root replacement as a surgical approach associated with low early morbidity and a very low rate of late hemorrhagic and thromboembolic complications.

VSARR are currently available in clinical practice: the aortic valve re-implantation introduced by David and Feindel in 1992 [6] and aortic root remodeling proposed by Sarsam and Yacoub in 1993 [7].

The selection of an approach to ARR is important both for patients, whose expectations it has to meet, and for their cardiologist.

Several studies on late outcomes of different approaches to ARR have been published recently; however, only a few include the direct comparison of these approaches [8, 9].

This study aimed to assess and compare the long-term outcomes of different approaches to ARR.

METHODS

The local Institutional Review Board did not consider the study to be a medical experiment. Therefore, approval was not required (no. KNW/0022/KB/284/17 dated December 12, 2017).

Study population

The study included patients who underwent an elective ARR with or without co-existing aortic valve regurgitation at our institution from January 2010 to December 2020 but excluded those with aortic valve stenosis. Patients with acute aortic dissection or active endocarditis were also excluded. However, we included patients requiring additional surgical procedures (Figure 1).

The study group was divided into 3 subgroups, depending on the approach to ARR: VSARR, Bentall procedure with mechanical aortic valve prosthesis (MB), and Bentall procedure with biological aortic valve prosthesis (BB).

Clinical outcomes

We assessed mortality, freedom from reoperation, recurrence of aortic valve regurgitation, rate of hemorrhagic and thromboembolic complications, and infective endocarditis. The functional status was determined according to the New York Heart Association (NYHA) class. Aortic regurgitation was assessed by transthoracic echocardiography (TTE) and was classified according to the 4-grade scale: 0 — none or trivial, 1 — mild, 2 — moderate, 3 — moderately severe, 4–severe [10, 11]. Freedom from aortic valve regurgitation was defined as grade <2. Definitions of complications followed the guidelines for reporting morbidity and mortality [12]. Only major thromboembolic and hemorrhagic

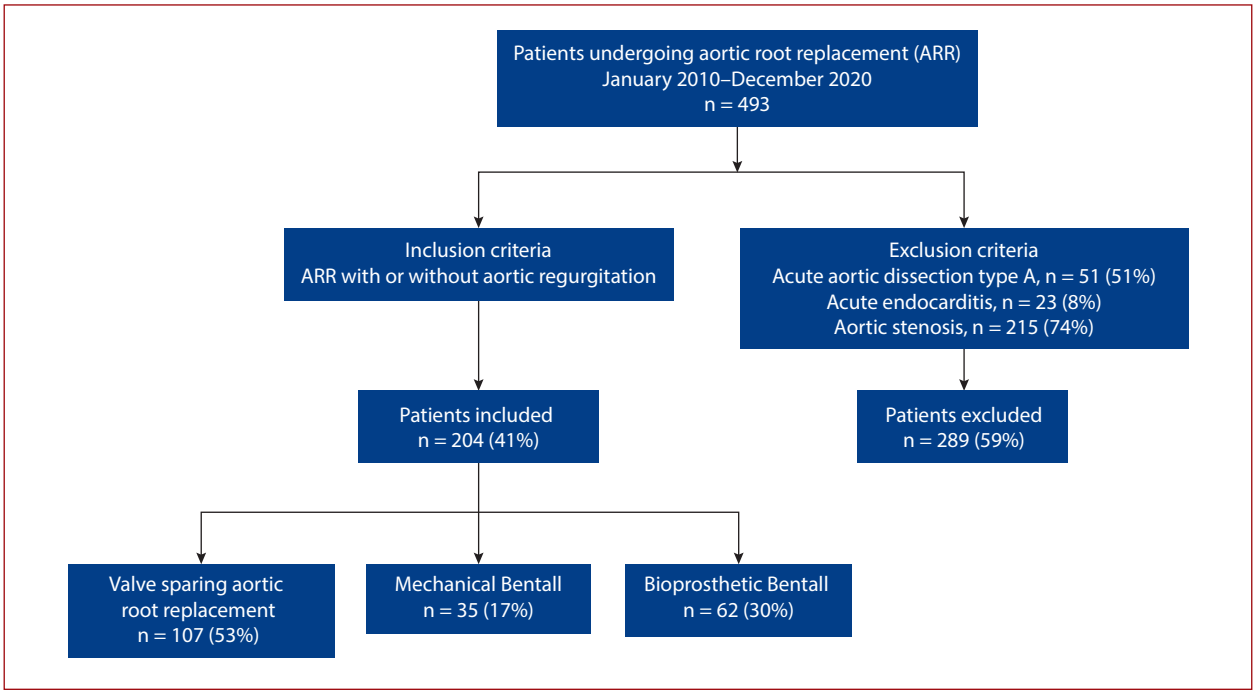

Figure 1. Study cohort flow chart

complications requiring hospitalization were analyzed. Thromboembolic complications were defined as stroke, peripheral organ ischemia, or dysfunction of the prosthetic valve leaflet, whereas hemorrhagic complications as cardiac tamponade or any bleeding from the upper or lower gastrointestinal tract, intracranial bleeding, or hemarthrosis. Freedom from complications defined as freedom from reoperation, endocarditis, and thromboembolic, or hemorrhagic events was analyzed. Death was considered early when it occurred within 30 days of surgery.

Follow-up

Mortality, the occurrence of complications, and freedom from reoperation status were ascertained from one or more of the following: the patient's visit in the outpatient clinic, telephone contact with the patient or patient's relatives, National Registry of Cardiac Surgical Procedures (www.krok.csioz.gov.pl). This registry contains the mortality data obtained from the National Health Fund. Death from all causes and only reoperations due to aortic valve dysfunction were included in the analysis. Freedom from aortic valve regurgitation was assessed in the TTE performed during the follow-up visit or ascertained based on the latest TTE report available from the outpatient clinic.

Surgical technique

Before surgery, the TTE was performed to evaluate left ventricular ejection fraction (LVEF), end-diastolic (LVEDV), and end-systolic (LVESV) volumes, the diameters of the left ventricular outflow tract (LVOT), aortic annulus, aortic root, and ascending aorta. Computed tomography was performed to plan accordingly the surgery on the aorta.

The decision about the type of ARR (valve-sparing vs. mechanical vs. biological Bentall) was made by the operating surgeon and the patient.

For aortic valve reimplantation, two types of vascular conduits were used: Vascutec Gelweave Valsalva (Vascutek, Renfrewshire, UK) and Hemashield (Maquet, Rastatt, Germany). For aortic root remodeling, two types of vascular conduits were used: Hemashield (Maquet, Rastatt, Germany) and Bioseal (Jotec Inc., Hechingen, Germany). For MB procedures we used 2 types of mechanical valved conduits: St. Jude Medical (SJM, St. Paul, MN, US) and Carbomedics Carbo-Seal (Sorin, Milano, Italy) and 2 types of bio-conduits (BB subgroup): Freestyle (Medtronic, Minneapolis, MN, US) and Biovalsalva biological valved conduit (Vascutek, Renfrewshire, UK) (Supplementary material, *Video S1*).

Statistical analysis

Data are presented as median (interquartile range [IQR]). Categorical data are expressed as a percentage. χ^2 or Fisher's exact tests were used where appropriate to compare proportions with *post hoc* comparisons using the z test. *P*-values were adjusted for multiple comparisons using the Bonferroni correction. To compare the groups, the Kruskal-Wallis H test for the independent sample with Bonferroni adjusted pairwise comparisons was used. Kaplan-Meier time to event curves were generated, and the 5-year event probability estimate with the standard error was reported. The groups were compared with the log-rank (Mantel-Cox) test. A *P*-value of less than 0.05 was considered significant. The predictors of mortality and complications were identified by the parsimonious multivariable Cox regression. The backward conditional method was used for variables selection with variables with score statistics below <0.1 retained in the model. In the case the final model did not include the variable of interest (i.e. Root replacement method), this variable was entered into the final model manually to assess its impact on the outcome.

IBM SPSS Statistics, version 27 (IBM Corp. Armonk, NY, US) was used for all statistical analysis except Kaplan-Meier analysis which was done using GraphPad Prism 9.1 (GraphPad Software, San Diego, CA, US).

RESULTS

Study cohort

Of the 493 patients who underwent the ARR procedure, only 204 patients (41.4%) met the inclusion criteria (Figure 1). The numbers of patients in particular study subgroups were: VSARR — 107 (52.5%), MB — 35 (17.1%), BB — 62 (30.4%) (Figure 2).

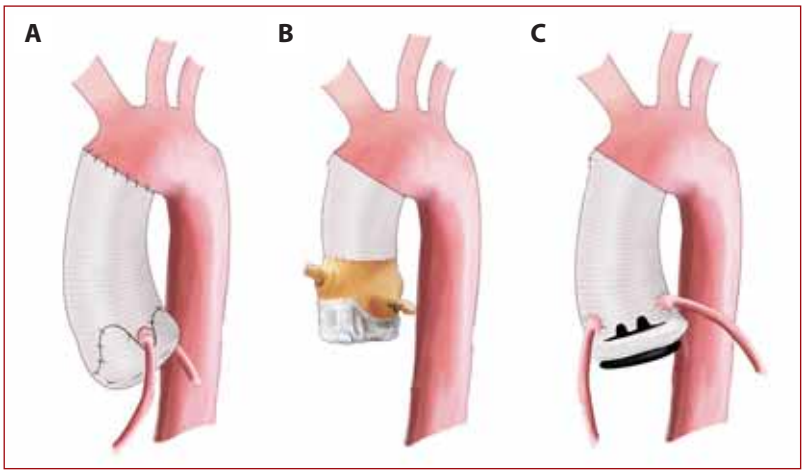

Figure 2. Surgical techniques of aortic root replacement. **A.** Valve-sparing aortic root replacement. **B.** Biological Bentall. **C.** Mechanical Bentall

Table 1. Clinical and echocardiographic characteristics.

Variable	All (n = 204)	VSARR (n = 107)	MB (n = 35)	BB (n = 62)	*P*-value
Clinical data					
Male gender, n (%)	181 (88.7)	94 (87.9)	32 (91.4)	55 (88.7)	0.85
Age, years, median (IQR)	55 (39–64)	52 (36–64)[a]	50 (39–59)[b]	60.5 (46.7–69)	0.02
BMI, kg/m^2, median (IQR)	27 (24–30)	27.0 (24–30)	28 (24–31)	27.5 (25–31)	0.56
NYHA, median (IQR)	2 (1–2)	2 (1–2)[a]	2 (1–3)	2 (2–3)	0.004
NYHA class, n (%)					0.02
I	70 (34.3)	44 (41.1)[a]	12 (34.3)	14 (22.6)	
II	97 (47.5)	53 (49.5)	14 (40.0)	30 (48.4)	
III	31 (15.2)	8 (7.5)[a]	7 (20)	16 (25.8)	
IV	6 (2.9)	2 (1.9)	2 (5.7)	2 (3.2)	
BAV, n (%)	91 (44.6)	43 (40.2)	18 (51.4)	30 (48.4)	0.39
Marfan syndrome, n (%)	26 (12.7)	17 (15.9)	4 (11.4)	5 (8.1)	0.33
Coronary artery disease, n (%)	30 (14.7)	14 (13.1)	8 (22.9)	8 (12.9)	0.33
Reoperation, n (%)	15 (7.4)	4 (3.7)[c]	6 (17.1)	5 (8.1)	0.03
At least moderate mitral regurgitation, n (%)	30 (14.7)	12 (19.4)	6 (17.1)	12 (11.2)	0.32
At least moderate tricuspid regurgitation, n (%)	17 (8.3)	12 (11.2)	2 (5.7)	3 (4.8)	0.29
Arterial hypertension, n (%)	150 (73.5)	76 (71.0)	25 (71.4)	49 (79.0)	0.50
Atrial fibrillation, n (%)	27 (13.2)	11 (10.3)	5 (14.3)	11 (17.7)	0.38
Diabetes mellitus, n (%)	19 (9.3)	7 (6.5)	3 (8.6)	9 (14.5)	0.23
Chronic renal failure, GFR <50 ml/min, n (%)	9 (4.4)	4 (3.7)	1 (2.9)	4 (6.5)	0.63
EuroSCORE II, median (IQR)	3.38 (2.48–6.22)	3.41 (2.48–5.06)	4.8 (2.76–9.46)	2.89 (1.83–6.53)	0.08
Echocardiographic data					
Aortic regurgitation grade, median (IQR)	3.5 (3.0–4.0)	3.0 (2.0–4.0)[c,a]	4.0 (3.0–4.0)	4.0 (3.0–4.0)	<0.001
Aortic regurgitation grade, n (%)					0.001
0	12 (5.9)	11 (5.4)[a]	0	1 (1.6)	
1	10 (4.9)	9 (8.4)	1 (2.9)	0	
2	18 (8.8)	14 (13.1)	1 (2.9)	3 (4.8)	
3	62 (30.4)	32 (29.9)	13 (37.1)	17 (27.4)	
4	102 (50)	41 (38.3)[a]	20 (57.1)	41 (66.1)	
LVOT, mm, median (IQR)	n = 145 24 (22–26)	n = 53 25 (22.5–27.0)[a]	n = 35 25 (23–27)	n = 57 23 (21–25)	0.02
Aortic annulus, mm, median (IQR)	n = 185 28 (26–30)	n = 93 27 (26–20)	n = 35 28 (26–31)	n = 57 28 (26–30)	0.54
Aortic root, mm, median (IQR)	50 (46–54)	50 (46–55)[a]	50 (47–55)	48 (44–52)	0.04
Ascending aorta, mm, median (IQR)	49 (40–55)	51 (46–56)[a]	51 (44–56)[b]	41.5 (36–50)	<0.001
LVEF, n (%)	55 (50–60)	55 (50–60)	53 (43–57)	55 (49.5–60)	0.13
LVEDV, ml, median (IQR)	n = 169 200 (160–253)	n = 81 195 (156–245)	n = 33 220 (162–310)	n = 55 198 (162–241)	0.23
LVESV, ml, median (IQR)	n = 169 94 (73–123)	n = 81 85 (65–123)	n = 33 100 (80–154)	n = 55 97 (75–123)	0.07

[a]*P* <0.05 VSARR vs. BB. [b]*P* <0.05 MB vs. BB. [c]*P* <0.05 VSARR vs. MB

Abbreviations: BAV, bicuspid aortic valve; BB, Bio-Bentall; BMI, body mass index; LVEDV, end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, end-systolic volume; LVOT, left ventricular outflow tract; MB, mechanical Bentall; NYHA, New York Heart Association; TAV, tricuspid aortic valve; VSARR, valve-sparing aortic root replacement

Patient characteristics

Detailed demographic and echocardiographic data are presented in Table 1. Patients in the MB subgroup were the youngest — median (IQR) age 50 (39–59) years, and those in the BB subgroup were the oldest — median (IQR) age 60.5 (46.7–69) years. All 3 groups did not differ with regard to co-morbidities. In the MB subgroup, a significantly higher rate of reoperations was noted — 6 patients (17.1%) vs. 4 patients (3.7%) in the VSARR subgroup and 5 patients (8.1%) in the BB subgroup ($P = 0.03$).

The echocardiographic data revealed a significantly lower grade of aortic valve regurgitation in the VSARR subgroup — median 3 (2–4) vs. the MB subgroup — median 4 (3–4) and the BB subgroup — median 4 (3–4) ($P < 0.001$). Patients in the VSARR and MB subgroups had statistically larger diameters of LVOT, aortic root, and ascending aorta (Table 1).

Operative details

Detailed operative data are presented in Supplementary material, *Table S1*. In the VSARR subgroup, the remodeling procedure was performed in 53 (49.5%) patients and the reimplantation procedure in 54 (50.5%) patients. In the BB subgroup, the Freestyle xenograft was implanted in 59 (95.2%) patients and the BioValsalva biological valved conduit in 3 (4.8%) patients. In the MB subgroup, the

St. Jude Medical conduit was implanted in 13 (37.1%) patients and the Carbomedics Carbo-Seal conduit in 22 (62.9%) patients. There were fewer formal ascending aorta replacements in the BB subgroup — 31 patients (50%) vs. the VSARR subgroup — 97 (90.7%) patients and the MB subgroup — 35 (100%) patients (P <0.001). The shortest cardiopulmonary bypass and cross-clamp times were recorded in the BB subgroup, and the longest in the VSARR subgroup (Supplementary material, *Table S1*).

Early outcomes

Early mortality in the whole study population was 2.9% (6 patients). The numbers for subgroups VSARR, BB, and MB were 2.8% (3 patients), 4.8% (3 patients), and 0%, respectively (P = 0.40). There were no significant differences between the subgroups as to the rate of postoperative bleeding, tamponade, stroke, renal failure, pneumonia, wound infection, and permanent pacemaker implantation (Supplementary material, *Table S1*). The shortest stay in the intensive care unit and the cardiac surgical ward was recorded in the VSARR subgroup — 2 (2–3) days and 8 (7–10) days, respectively (P = 0.003).

Late outcomes

Median follow-up was 52.4 (27.4–5.4) months.

Mortality: Twenty-three (11.6%) patients died during the follow-up period. Kaplan-Meier estimated 5-year survival with standard error (SE) was: 90.2 (3.2) % in the VSARR, 78.4 (5.6) % in the BB, and 94.2 (4) % in the MB subgroup (P = 0.12, log-rank test) (Figure 3A).

Reoperations: A reoperation was performed in 6 patients (2.9%) during the follow-up period. The number of reoperations was: VSARR–3 patients (2.8%) due to severe aortic valve regurgitation, BB — 2 patients (3.2%) due to endocarditis and MB — 1 patient (2.9%) due to endocarditis (P = 0.99). Kaplan-Meier estimated 5-year freedom from reoperation (SE) was: 97.8 (1.5) % in the VSARR, 96.6 (2.4) % in the BB subgroup, and 96.8 (3.2) % in the MB subgroup (P = 0.99, log-rank test) (Figure 3B, Table 2).

Complications: Kaplan-Meier estimated 5-year freedom from complication was: 94.2 (2.6) % in the VSARR, 83.1 (5.6) % in the BB, and 57.3 (9.7) % in the MB subgroup (P <0.001, log-rank test) (Figure 3C, Table 2).

Hemorrhagic complications occurred in 13 patients (7.3%): nose bleeding in 8 (61.5%), cardiac tamponade in 3 (23.1%), hemarthrosis in 1 (7.7%), and hemorrhoids bleeding in 1 (7.7%). The hemorrhagic complication rate in particular subgroups was: VSARR — 1 patient (1%), BB — 3 patients (6.4%), and MB — 9 patients (27.3%) (P <0.001). Kaplan-Meier estimated 5-year freedom from hemorrhagic complications (SE) was: 99 (1)% in the VSARR, 92.2 (4.4) % in the BB, and 71.1 (8.9) % in the MB subgroup (P <0.001, log-rank test) (Figure 4A, Table 2).

Thromboembolic complications were recorded in 9 patients (5.1%): stroke in 8 (88.8%) and popliteal artery embolism in 1 (11.2%) (P <0.001). The thromboembolic complication rate was: VSARR — none, BB — 3 patients (6.4%), and MB — 6 patients (18.2%) (P <0.001). Kaplan–Meier estimated 5-year freedom from thromboembolic complications (SE) was: 100% in the VSARR, 94.1 (4.2) % in the BB, and 78.2 (10) % in the MB subgroup (P <0.001, log-rank test) (Figure 4B, Table 2).

The multivariable analysis showed that none of the approaches to ARR is a predictor of mortality: MB (hazard ratio [HR], 0.13; 95% confidence interval [CI], 0.09–1.36; P <0.13) and BB (HR, 1.35; 95% CI, 0.56–3.26; P <0.51). However, it revealed the following predictors of death: New York Heart Association (NYHA) functional class, LVEF, reoperation, and concomitant TV repair. Following predictors of complications were identified: the mechanical Bentall procedure (HR, 6.70; 95% CI, 2.54–17.63; P <0.001) and atrial fibrillation (HR, 2.83; 95% CI, 1.25–6.42; P <0.013) (Table 3).

Echocardiographic follow-up: Follow-up echocardiography for the assessment of the aortic valve regurgitation was performed in 93.8% of patients at the median of 46.8 (20.8–74.7) months after surgery. On last echocardiography, 98.1%, 98.4%, and 97.1% (P = 0.91) patients were free from ≥grade 3 aortic valve regurgitation in VSARR, BB and MB subgroups respectively. Freedom from ≥grade 2 aortic regurgitation was 90.5%, 98.4%, and 97.1% (P = 0.08).

Additionally, the echocardiographic follow-up revealed, that patients in the VSARR subgroup had the lowest median (IQR) aortic valve peak gradient of 9 (6–12) mm Hg, whereas in the BB and MB subgroups these medians of gradients were 12 (10–18) mm Hg and 16 (14–22) mm Hg, respectively (P <0.001) (Figure 5).

Discussion

The classic Bentall procedure currently represents the gold standard approach to ARR, particularly in younger patients, for whom it seems to be a lifelong solution [13]. In elderly patients, to avoid the need for oral anticoagulation, the BB procedure can be performed alternatively [13]. With a growing number of reports reporting a considerable ratio of thromboembolic complications after MB [14, 15], new stentless valves have been proposed for younger patients [16]. Moreover, VSARR procedures have been introduced to clinical practice [6, 7], which not only obviate the need for oral anticoagulation but also enable the preservation of the patient's native valve, thus ensuring a better hemodynamic profile in comparison to MB and BB. There is no consensus in the literature, whether during the ARR procedure the aortic valve should be repaired or replaced, and in the case of replacement, whether a mechanical or biological prosthesis should be preferred [17, 18]. Our analysis provides some guidance as to which approach to ARR yields the best outcomes and is associated with the lowest complication rate. Even though we have performed almost 500 ARR procedures during 10 years at our institution, we had to exclude patients with aortic valve stenosis to directly compare different approaches to ARR as in this group a VSARR procedure is usually not feasible and the

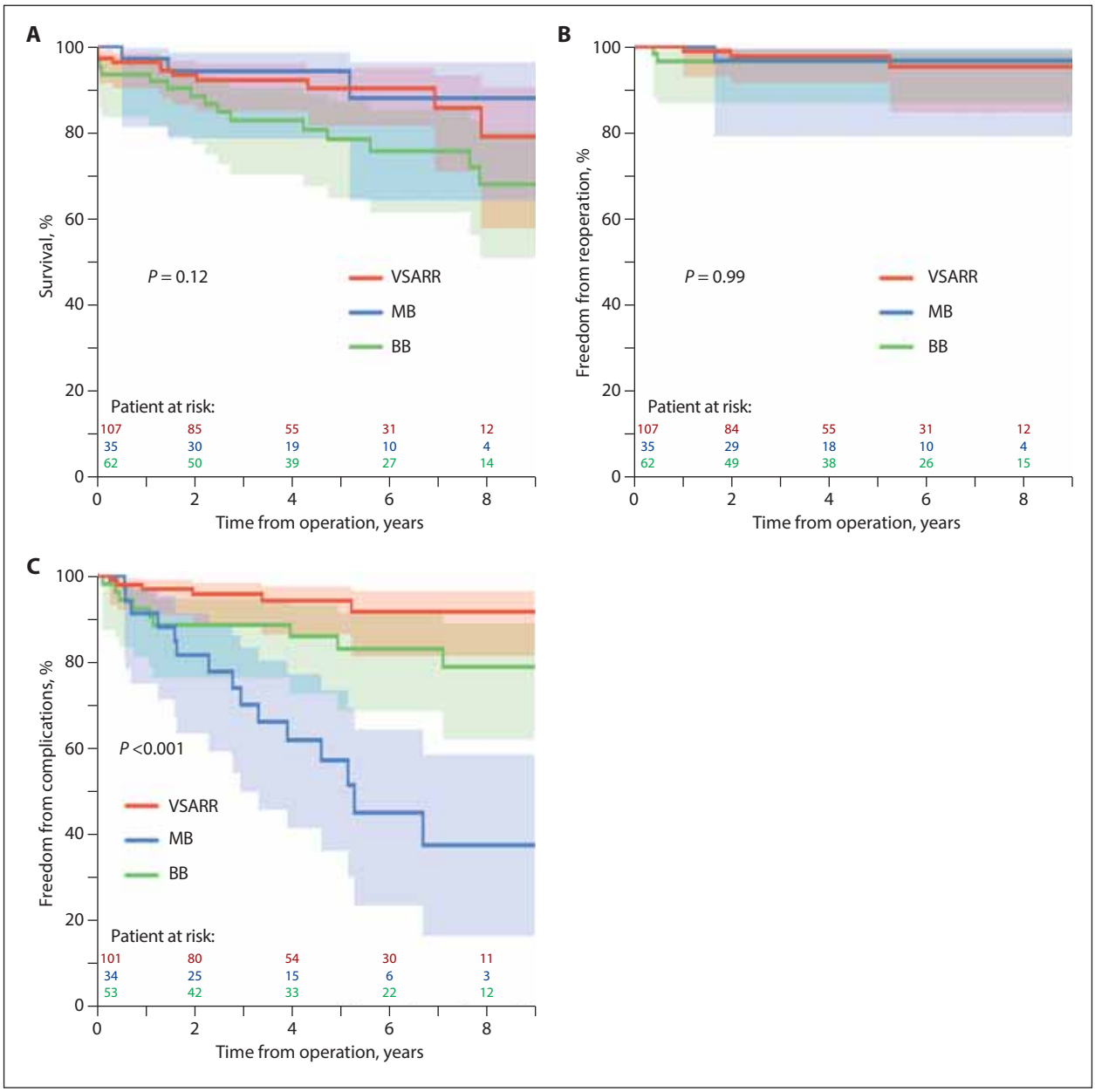

Figure 3. Kaplan-Meier curves after root replacement according to the surgical procedure. **A.** Survival. **B.** Freedom from reoperation. **C.** Freedom from complications (reoperation, endocarditis, hemorrhagic complications, and thromboembolic complications). Kaplan-Meier curves with 95% confidence interval. *P* from the log-rank (Mantel-Cox) test

Abbreviations: see Table 1

Table 2. Complications during the follow-up period

Variable	All (n = 204)	VSARR (n = 107)	MB (n = 35)	BB (n = 62)	*P*-value
Aortic valve reoperation	6 (2.9)	3 (2.8)	1 (2.9)	2 (3.2)	0.99
Thromboembolic complications	9 (5.1)	0	6 (18.2)	3 (6.4)	<0.001
Hemorrhagic complications	13 (7.3)	1 (1.0)[a]	9 (27.3)[b]	3 (6.4)	<0.001
Infective endocarditis	2 (1.0)	0	1 (2.9)	1 (1.6)	0.27

Data are presented as n (%); [a]*P* <0.05 VSARR vs. MB. [b]*P*<0.05 MB vs. BB

Abbreviations: see Table 1

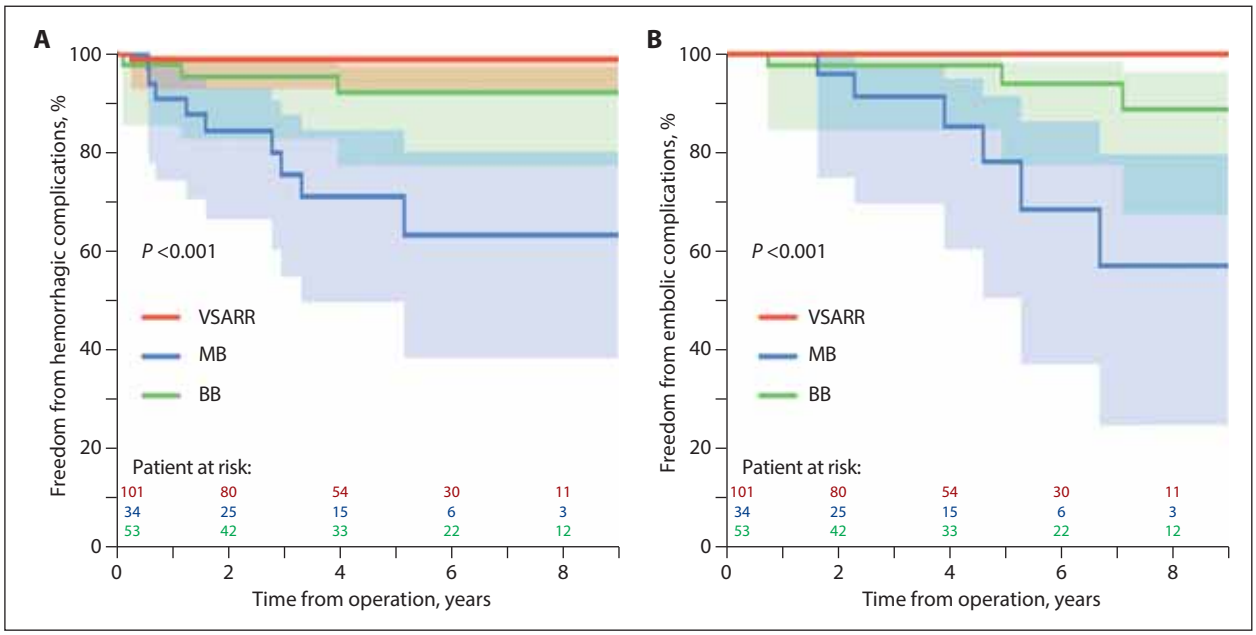

Figure 4. Freedom from complications after root replacement according to the surgical procedure. **A.** Hemorrhagic complications. **B.** Thromboembolic complications; Kaplan-Meier curves with 95% confidence interval. *P* from the log-rank (Mantel-Cox) test

Abbreviations: see Table 1

Table 3. Multivariable analysis of risk factors for mortality and complications.

Risk factors	Multivariable analysis	
	HR (95% CI)	*P*-value
Predictors of mortality		
Root replacement method (vs. VSARR)	0.13 (0.09–1.36)	0.13
Mechanical Bentall	1.35 (0.56–3.26)	0.51
Biological Bentall		
NYHA class (vs. NYHA I)		
NYHA II	5.88 (1.25–27.63)	0.03
NYHA III	8.62 (1.742–42.59)	0.008
NYHA IV	73.58 (13.49–401.27)	<0.001
LVEF	0.96 (0.92–1.0)	0.03
Concomitant tricuspid valve annuloplasty	7.02 (1.28–38.55)	0.03
Redo surgery	2.97 (0.98–9.07)	0.055
Predictors of complications		
Root replacement method (vs. VSARR)	6.70 (2.54–17.63)	<0.001
Mechanical Bentall	2.19 (0.77–6.21)	0.14
Biological Bentall		
Atrial fibrillation	2.83 (1.25–6.42)	0.01
NYHA class III–IV	2.07 (0.96–4.50)	0.07

Abbreviations: CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; VSARR, valve-sparing aortic root replacement

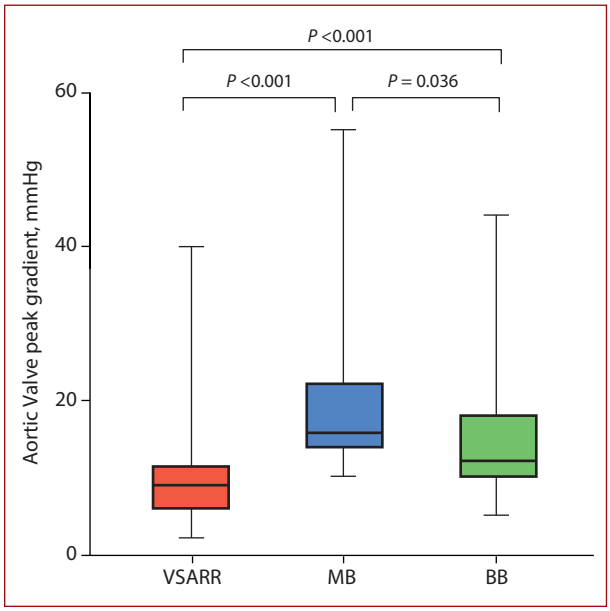

Figure 5. Aortic valve peak gradient at follow-up. Data are presented as median (IQR)

Abbreviations: see Table 1

pathology of the left ventricular wall muscle is different. All exclusions narrowed the study group to 204 patients; however, the selected study subgroups did not differ significantly as to baseline characteristics. The only difference was age, and it seems obvious, as the oldest patients were in subgroup BB and the youngest in subgroup MB. The baseline age heterogeneity seems to be inseparably associated with the analysis of different approaches to ARR and is present in several investigations published to date [17–19]. This is the consequence of age being one of the major factors impacting the choice of the valve prosthesis (biological vs. mechanical).

The assessment of early mortality did not reveal significant differences between the 3 subgroups ($P = 0.40$), and the overall mortality in the entire study group of 2.9% does not significantly differ from the early mortality of

1.9% reported by Yamabe et al. [20], who analyzed a large cohort of 371 patients.

Similarly, the estimated survival did not differ between the subgroups ($P = 0.12$, log-rank test). The best 5-year survival was noted in the MB subgroup, while the worst was in the BB subgroup (94.2% and 78.4%, respectively). Conversely, Bilkhu et al. [21], who analyzed 344 patients, reported the best 5-year survival in the VSARR group (100%) and the worst in the BB group (87%).

Interestingly, our analysis of freedom from reoperation also failed to reveal a significant difference between the subgroups ($P = 0.99$, log-rank test), and the proportion of patients who underwent reoperation during the follow-up period was rather low at 2.9%. In this regard, particularly good outcomes were noted in the VSARR subgroup where the 5-year freedom from reoperation (97.8%) was better in comparison to the 5-year freedom from reoperation of 87.9% reported by Badiu et al. [17].

This is the consequence of the small proportion of patients (1.9%) who developed severe aortic valve regurgitation during the follow-up. Notably, all 3 reoperations in the VSARR group were elective procedures performed due to severe aortic valve regurgitation, and all patients survived the surgery. In contrast, the reoperations in MB (1 patient) and BB subgroup (2 patients) were urgent procedures performed due to endocarditis with high operative risk, and 1 patient did not survive the surgery.

Considering that the comparison of early and late mortality, freedom from reoperation, and freedom from aortic valve regurgitation failed to demonstrate the advantage of any particular approach, it seems that the outcome which differs across the analyzed approaches is the rate of complications, both hemorrhagic and thrombo-embolic.

It is universally accepted that these complications not only substantially compromise the quality of life but also affect prognosis. Therefore, they should be taken into account while planning ARR surgery.

The analysis of complications that occurred during follow-up, revealed major differences between the assessed approaches. The VSARR procedures are associated with a very low risk of late complications both thromboembolic (0 patients) and hemorrhagic (1 patient, 1%), which translates into 99% estimated 5-year freedom from hemorrhagic complications and 100% estimated 5-year freedom from thromboembolic complications. Our results are in line with those published by Badiu et al. [17] who report in the VSARR group the 5-year freedom from hemorrhagic complications at 99.3%.

In our study, the highest rate of the above-mentioned complications was noted in the MB subgroup, where thromboembolic complications occurred in 18.2% of patients and hemorrhagic complications in 27.3%. This results in low estimated 5-year freedom from hemorrhagic and thromboembolic complications of 71.1% and 78.2%, respectively.

Similar low 7-year freedom from hemorrhagic and thromboembolic complications of 74.3% and 87.7%, respectively in the MB group was reported by Radu et al. [15].

The multivariable analysis confirmed that MB is an independent risk factor for complications (HR, 6.70; 95% CI, 2.54–17.63; $P < 0.001$).

In conclusion, based on our findings it seems that VSARR procedures represent the best option for patients undergoing ARR surgery. This approach is associated with low mortality, a low reoperation rate, and a very low rate of late complications. Among the analyzed approaches, VSARR is also favored by the lowest follow-up NYHA class and the lowest aortic valve peak gradient.

Study limitations

The major limitation of our study is its retrospective design and non-randomized assignment to the analyzed subgroups. This is a single-center study, and the selection of the approach to ARR was left at the discretion of the operating surgeon.

Conclusions

With the same mortality, freedom from reoperation, and a small complication rate in comparison with mechanical Bentall and Bio-Bentall, VSARR might be the preferred approach to aortic root aneurysm.

Supplementary material

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

Article information

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Influence of a long-term proctoring process on the effectiveness of chronic total occlusion percutaneous coronary interventions

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ABSTRACT

Background: Despite the complexity of the chronic total occlusion (CTO) percutaneous coronary intervention (PCI) procedures and unsatisfactory results in centers with low volume experience, the practice of training and certifying operators is not a routine.

Aims: The study aimed to identify factors influencing the effectiveness and complications of PCI CTOs during a proctoring program.

Methods: The study group consisted of 194 consecutive patients (226 PCI CTOs) as part of the proctoring program. The relationships between clinical and treatment parameters and the experience gained along with the duration of the proctoring program on the effectiveness and safety of the procedure were assessed.

Results: The multivariable analysis showed an independent effect of CTO morphology (odds ratio [OR], 0.38; 95% confidence interval [CI], 0.21–0.71; P <0.01) and an independent effect of increasing operator's experience (OR, 2.62; 95% CI, 1.24–5.60; P = 0.01) on the effectiveness of the procedure. The increase in the efficiency of the PCI CTO, related to the treatment experience gained during the program, was observed especially in the first 50 procedures, treatment effectiveness increased from 55% to 72% (P <0.05). The success of procedures was higher in months when ≥3 procedures were performed (75% vs. 52%; P <0.001). Periprocedural complications occurred in 11 patients (4.9%). In the multivariable analysis, no independent factors influencing the risk of complications were identified.

Conclusions: The effectiveness of PCI CTO depended on lesion complexity and broadening operator's experience. No independent factors affecting the risk of complications were identified. The number of >50 procedures under the proctor's supervision should be considered in designing teaching programs.

Key words: chronic total occlusion, experience, percutaneous coronary intervention, proctoring, success

INTRODUCTION

The chronic total occlusion (CTO) percutaneous coronary intervention (PCI) is the most complex percutaneous coronary procedure [1, 2]. PCI CTO requires skills of a highly specialized operator and has high costs resulting from the need to use expensive, technologically advanced equipment. Technical complexity determines the higher complication rate (1.6% vs. 0.8%) and lower efficiency of PCI CTO (70% vs. 97%) compared to routine PCI [2–5]. As a result of the technological advancement made in recent years, these differences gradually disappear in the clinical

WHAT'S NEW?

In our study, we investigated whether lesion complexity and operator's experience gained during educational program under the proctor's supervision were independent factors influencing the success of percutaneous coronary intervention for chronic total occlusion (PCI CTO) determined in multivariable analysis. The supervision of a proctor significantly increased the effectiveness of training in a low-experienced center compared to the self-acquired experience presented in other studies. The increase in effectiveness was greatest during the first 50 procedures of the proctoring process, which may be a factor to consider in designing training programs. The success of PCI CTO procedures was higher in months when ≥3 procedures were performed. Any independent factors affecting the risk of complications were not identified.

centers with the highest level experience, nonetheless, they remain in the centers with limited experience (91% vs. 54%) [1–3, 6–10].

Significant differences between centers concerning the effectiveness of treatments do not constitute a formal premise for the introduction of PCI CTO accreditation. The process of implementation of the PCI CTO procedure along with educating the operators is not standardized and not subject to routine evaluation. This remains in contradiction with the invasive cardiology practice in introducing complex interventions. For example, the left atrial appendage occluder implantation or the percutaneous implantation of aortic valve prostheses are not recommended in non-accredited centers [11, 12]. The process of training operators remains under strict supervision. It covers the theory, exercises on simulators, and a clinical phase under the proctor's supervision. Granting approval by the Food and Drug Association for the therapeutic use of new devices in the United States depends, among others, on the documentation of the training process effectiveness. Each of the training phases is assessed, and its completion is mandatory to obtain the operator's certificate. Otherwise, it is not possible to purchase equipment for procedures from the manufacturer [13–15].

Despite the complexity of PCI CTOs and unsatisfactory outcomes in centers with little experience, the practice of certifying centers and operators is not routine. The "CTO Club" indicates in their recommendations the key importance of the educational process [1, 2]. Among educational models, the practical hands-on training conducted with an experienced operator (proctor) is characterized by the highest efficiency. Initial experience shows that the effectiveness of the procedure obtained during the training is significantly higher and achieved much faster than in the case of independent education [16–18]. So far, the duration of such designed programs has not been determined. Therefore, this study aimed to assess the impact of the duration and other potential factors related to the proctor's training program on the effectiveness and complications of the PCI CTO.

METHODS

Study group

The study group consisted of consecutive patients who underwent PCI CTO in 2012–2017 at the Military Institute of Medicine in Warsaw as part of a proctored training program. A CTOs were defined as a total obstruction of the artery of at least 3 months duration with preserved but impaired native flow through the microchannels or bridging blood flow, and complete occlusion with retrograde filling of the peripheral artery from the collateral circulation. Data relating to the characteristics of the study group and endpoints were obtained from medical records, procedure descriptions, and angiographic films. The morphological characteristics of the occlusion were determined using the Japanese Chronic Total Occlusion (J-CTO) score. The J-CTO scale is a five-point scale consisting of entry shape, calcifications, bending >45%, occlusion length, and re-try lesion (one point for each) [19, 20]. Inclusion criteria were angina symptoms caused by exercise or ≥10% induction of ischemia in the vascular area of the occluded coronary artery confirmed by imaging examinations. The exclusion criteria were the patient's refusal, uncorrected anemia, hemodynamic instability, respiratory failure, or other causes that prevented the patient from undergoing a potentially long endovascular procedure.

Design of the proctoring program

Four interventional cardiologists employed at the Department of Cardiology with ≥15 years of procedural experience in percutaneous coronary interventions but with a limited experience in the PCI CTO participated in the proctor's training program. The process of qualifying patients, planning the treatment strategy, the educational process of the operators, and the team participating in the procedures, were managed by the proctor who is a well-known and respected operator in the field of CTO PCI and the head of one of the leading in this field cardiology centers in Europe.

The assumptions of the proctoring program included the proctor's supervision over each of the procedures. The proctor supervised all stages of the treatment, from patient qualification to the procedure, through comprehensive angiographic evaluation, and the selection of the appropriate treatment technique in all cases. The treatment strategy implemented during the program assumed the routine usage of the "antegrade wire escalation, antegrade dissection, re-entry" technique, and in the event of failure, the "retrograde, CART (controlled antegrade and retrograde subintimal tracking) and reverse CART" technique using guidewires and microcatheters tailored to perform PCI CTO. Contralateral injections were routinely used. We used quintiles of the number of treatments for subsequent periods assessing the effectiveness and complications of the procedure during the training program.

Informed consent was obtained from each patient. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee (Bioethics Committee of the Military Institute of Medicine No. 56/WIM/2017).

Aim of the study

The endpoint of the study was the success of the procedure, defined as the artery recanalization accompanied by a flow to the peripheral section (TIMI 3), completed with stent implantation.

The complex endpoint assessing the safety of the procedures included the occurrence of acute periprocedural complications. Death, resuscitated sudden cardiac arrest, myocardial infarction (MI), aortic dissection, tamponade, significant bleeding, and stroke were taken into consideration.

Statistical analysis

The study protocol assumed the separation, in the multivariable analysis, of clinical and periprocedural parameters and operators' experience gained as a result of the implementation of the program, independent factors affecting the endpoint of the study, and a complex endpoint assessing the safety of the procedures.

Continuous variables are presented as mean with standard deviation (SD) or median with interquartile range (IQR) and compared between the groups using Student's t-test or the Wilcoxon rank-sum test, respectively. Categorical variables were reported as frequency in a given group by number and percentage, and differences in frequencies were compared between successful and unsuccessful procedures using Fisher's exact test (for binary variables) or the χ^2 independence test (for variables having more than two levels, we used a simulated *P*-value). To identify independent factors predicting the effectiveness and complications of the procedure, the logistic regression model was used. The reported estimation results present models estimated including all variables that were hypothesized to be clinically significant (patient age, chronic kidney disease, previous coronary artery bypass grafting [CABG], previous PCI, ejection fraction [EF] <35%, J-CTO and the impact of the experience) — a single model was estimated, no statistical selection of variables was performed to avoid bias in the estimates of the reported p-values that could be introduced by model selection procedures. The statistical significance of parameters was used to analyze the estimation results, assuming the significance level of 0.05. Statistical analysis was performed with R 4.1.0 and Julia 1.6.2 software and their compliance was verified.

RESULTS

Clinical characteristics

The study group consisted of 194 patients aged mean (SD) 65 (10) years (75% men). More than half of the patients have had a previous myocardial infarction (50%) or angioplasty (PCI) (57%) and 13% had a history of CABG. The mean (SD) value of the EF was 51% (9%). The low ejection fraction (<35%) patients constituted 2.7% of the study group. Patients with diabetes mellitus constituted 42% and patients with chronic kidney disease 21% of the study group. A total of 226 coronary arteries underwent the procedure; 156 (69%) were effectively recanalized. The proctor performed the procedure in 81 out of 226 cases (35.8%) throughout the whole educational program. Four operators participating in the program were engaged in all performed procedures, either actively (in 145 procedures) or passively as assistants and observers. The distribution of the main risk factors did not differ between the groups of patients with successful and unsuccessful revascularization (Table 1).

Treatment characteristics

The CTO recanalization procedure was most often performed in the right coronary artery (RCA) (n = 128; 57%). The percentage of complex procedures (J-CTO ≥2) was 37%. Out of all 226 procedures performed, the "antegrade" technique was used in 205 (90%), including the wire escalation technique in 156 cases (67%) (Table 1). The median (IQR) radiation dose was 2286 (1340–3496) mGy, the median (IQR) volume of contrast administered was 280 (200–400) ml. The morphological complexity of the occlusion (J-CTO ≥2), the presence of calcifications, and the occlusion angle >45° occurred statistically significantly more often in the group of ineffective procedures. The effectiveness of the procedure in the J-CTO <2 group was significantly higher than in the J-CTO ≥2 group (71% vs. 30%; *P* <0.01).

The endpoint of the study — the impact of clinical, angiographic, and periprocedural parameters, as well as growth in operators' experience, on the effectiveness of CTO recanalization procedures

An independent, statistically significant effect on success of the procedure was demonstrated for morphological com-

Table 1. Clinical and procedural characteristics in relation to the effectiveness of the procedure

Variable	All procedures	Successful procedure	Unsuccessful procedure	*P*-value
Number of procedures, n (%)	226 (100)	156 (100)	70 (100)	<0.01
Age, years, mean (SD)	65.29 (9.9)	64.93 (9.78)	66.09 (10.29)	0.43
Male gender, n (%)	169 (74.78)	114 (73.08)	55 (78.57)	0.48
Hypertension, n (%)	187 (82.74)	127 (81.41)	60 (85.71)	0.55
Diabetes mellitus, n (%)	95 (42)	65 (41.67)	30 (42.86)	0.14
Smoking, n (%)	78 (34.51)	53 (33.97)	25 (35.71)	0.92
Dyslipidemia, n (%)	138 (61.06)	91 (58.33)	47 (67.14)	0.27
CKD, n (%)	48 (21.23)	36 (23.08)	12 (17.14)	0.41
Hemodialysis, n (%)	6 (3.09)	5 (3.21)	1 (1.42)	0.18
Previous MI, n (%)	114 (50.44)	73 (46.79)	41 (58.57)	0.14
Previous PCI, n (%)	128 (56.64)	86 (55.13)	42 (60)	0.59
Previous CABG, n (%)	30 (13.27)	19 (12.18)	11 (15.71)	0.61
Previous stroke, n (%)	16 (7.08)	11 (7.05)	5 (7.14)	1.00
EF, %, mean (SD)	51.39 (8.99)	51.53 (9.19)	51.1 (8.55)	0.2
CCS, n (%)				
0	2 (0.88)	0 (0)	2 (2.86)	0.11
1	63 (27.88)	44 (28.21)	19 (27.14)	
2	95 (42.04)	66 (39.10)	29 (41.43)	
3	36 (15.93)	27 (17.31)	9 (12.86)	
4	1 (0.44)	0 (0)	1 (1.43)	
CTO target vessel				
Right coronary artery, n (%)	128 (56.6)	80 (51.28)	48 (68.57)	0.1
Left anterior descending artery, n (%)	34 (15.04)	24 (15.38)	10 (14.29)	
Left circumflex artery, n (%)	62 (27.43)	50 (32.05)	12 (17.14)	
Intermediate branch, n (%)	1 (0.44)	1 (0.64)	0 (0)	
Venous graft, n (%)	1 (0.44)	1 (0.64)	0 (0)	
Procedural technique				
Antegrade, n (%)	205 (90.7)	152 (97.44)	53 (75.71)	<0.01
Wire escalation, n (%)	151 (66.8)			
Dual injection, n (%)	78 (34.5)			
Retrograde, n (%)	21 (9.3)	4 (2.56)	17 (24.29)	
Anatomical factors				
J-CTO, n (%)				
0	75 (33.2)	56 (35.9)	19 (27.14)	<0.01
1	68 (30.09)	54 (34.62)	14 (20)	
2	40 (17.7)	25 (16.03)	15 (21.43)	
3	25 (11.06)	15 (9.62)	10 (14.29)	
4	13 (5.75)	4 (2.56)	9 (12.86)	
5	5 (2.21)	2 (1.28)	3 (4.29)	
J-CTO ≥2, n (%)	83 (36.73)	46 (29.49)	37 (52.86)	<0.01
J-CTO <2, n (%)	143 (63.27)	110 (70.51)	33 (47.14)	
Occlusion length, n (%)	94 (41.59)	59 (37.82)	35 (50)	0.11
Blunt stump/entry, n (%)	53 (23.45)	33 (21.15)	20 (28.57)	0.24
Calcifications, n (%)	73 (32.3)	43 (27.56)	30 (42.86)	0.03
Bending >45°, n (%)	58 (25.66)	26 (16.67)	32 (45.71)	<0.001
Exposure factors				
Radiation dose, mGy, median (IQR)	2286 (1340–3496)	2183 (1253–3287)	2869 (1628–4090)	0.04
Radiation dose, mGy, in J-CTO <2, median (IQR)	1877 (981.5–3134.5)	1957 (1013–3185)	1678 (931–3064)	0.72
Radiation dose, mGy, in J-CTO ≥2, median (IQR)	3047 (1895–4328)	2482 (1880–3880)	3404 (2263–4697)	0.03
Contrast volume, ml, median (IQR)	280 (200–400)	300 (200–400)	250 (165–400)	0.56
Contrast volume, ml, in J-CTO <2, median (IQR)	225 (160–350)	230 (150–350)	200 (160–300)	0.4
Contrast volume, ml, in J-CTO ≥2, median (IQR)	350 (225–500)	354.5 (280–457.5)	350 (200–500)	0.28

Abbreviations: CABG, coronary artery by-pass graft; CCS, Canadian Cardiovascular Society; CKD, Chronic kidney disease; CTO, chronic total occlusion; IQR, interquartile range; J-CTO, Japanese Chronic Total Occlusion score; EF, ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; SD, standard deviation

Table 2. Multivariable analysis of the influence of selected variables on the effectiveness of the treatment

	OR (95% CI)	*P*-value
Age	0.98 (0.94–1.01)	0.16
CKD	1.75 (0.78–4.16)	0.19
Previous CABG	0.88 (0.37–2.17)	0.78
EF <35%	1.01 (0.97–1.04)	0.74
J-CTO ≥2	0.38 (0.21–0.71)	0.002
Previous PCI	0.69 (0.37–1.29)	0.25
Operator experience	2.62 (1.24–5.60)	0.012

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

Table 3. Multivariable analysis of the influence of selected variables on the occurrence of complications

	OR (95% CI)	*P*-value
Age	1.02 (0.98–1.06)	0.32
CKD	1.09(0.43–2.64)	0.84
Previous CABG	0.52 (0.12–1.63)	0.32
EF <35%	1.00 (0.96–1.04)	0.92
J-CTO ≥2	0.83 (0.38–1.77)	0.64
Previous PCI	0.97 (0.47–2.02)	0.93
Operator experience	0.99 (0.41–2.68)	0.99

Abbreviations: see Table 1 and Table 2

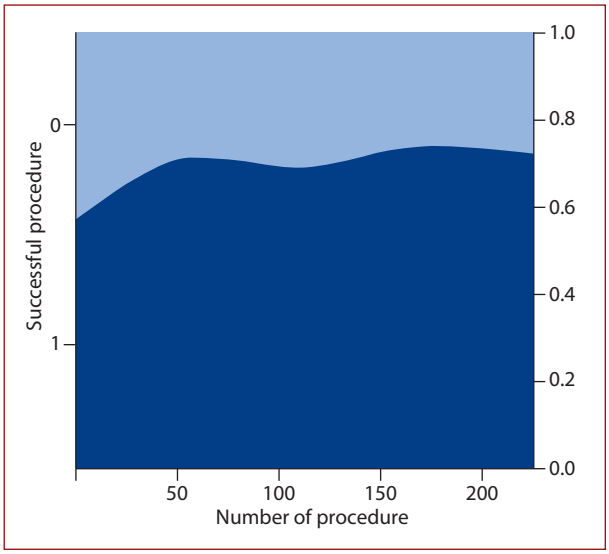

Figure 1. Plot of the conditional probability of successful procedure as a function of the number of procedures

plexity of the lesion (J-CTO≥2) (odds ratio [OR], 0.38; 95% confidence interval [CI], 0.21–0.71; *P* <0.01) and operator's experience (OR, 2.62; 95% CI, 1.24–5.60; *P* = 0.01) (Table 2). A higher J-CTO score resulted in decreased success of CTO PCI, and experience gained during the proctoring program increased the effectiveness of the procedure. The remaining variables did not affect the success. The increase in the efficiency of CTO recanalization, related to the acquired procedural experience, was observed especially during the first 50 procedures (Figure 1). The treatment effectiveness increased between the first and the remaining quintiles of the program from 55% to 72% (*P* <0.05). In the months with more than 3 PCI CTOs performed, a higher percentage of successful recanalization was achieved compared to the months with less than 3 procedures (75% vs. 52%; *P* <0.001).

A composite endpoint assessing safety

Periprocedural complications occurred in the case of 11 patients (4.9%). One patient died, 3 patients experienced myocardial infarctions, 3 patients had tamponade, one patient had aortic dissections, and 3 patients were successfully resuscitated from sudden cardiac arrest. No patients experienced significant bleeding or stroke. No independent factors affecting the risk of complications were identified in the multivariable analysis (Table 3). The absorbed median (IQR) radiation dose was significantly higher in complex occlusions (J-CTO <2 vs. J-CTO ≥2: 3047 (1895–4328) mGy vs. 1877 (981.5–3134.5) mGy; *P* <0.01). The median (IQR) volume of the administered contrast also was significantly higher in the case of complex procedures (350 [225–500] ml vs. 225 [160–350] ml; *P* <0.01).

In this study, the influence of the volume of contrast and radiation dose on the occurrence of complications was not assessed.

DISCUSSION

The complexity of CTO procedures and their complications require using proven educational programs and professional supervision at the implementation stage [1]. The recommendations of the "CTO Club" lead operators to "online" didactic programs that enable learning. These online programs start from the correct interpretation of angiographic images in the context of the use of appropriate treatment techniques, discuss differences regarding the technical properties of the angioplasty equipment and the principles of its selection depending on the angiographic image and the course of the procedure [2].

The measurable effect of the experience gained is the increase in operator effectiveness. For example, in a meta-analysis of 65 studies published in 2013, Patel et al. [21] showed an 11-year upward trend in the effectiveness of CTO recanalization from 68% to 79%. The similar dependence between the effectiveness and the number of recanalizations performed was documented in a seven-year registry of 94 000 procedures; their effectiveness in groups of operators performing 1–10, 11–50, >50 treatments per year was 58.4%, 65.6%, and 72.7%, respectively [18].

Theoretical knowledge of PCI CTO is not sufficient to obtain satisfactory treatment results even among experienced operators who do not have practical experience in CTO recanalization. An expert opinion of the Association of Cardiovascular Interventions of the Polish Cardiac Society emphasizes the role of experience in obtaining high efficiency of CTO PCI procedures, indicating the number of 50 procedures per year as the minimum that allows achieving sufficient effectiveness [22]. Due to the

awareness of this fact, it was necessary to base the practical education process on direct consultations and substantive supervision at the operating table by operators-teachers experienced in performing such procedures. In 2017, Yamamoto et al. [16] published data on the impact of proctoring on the effects of CTO recanalization procedures in 2009–2016, demonstrating comparable effectiveness of recanalization among experienced and inexperienced operators after the completion of the proctor's program (96.9% vs. 90.5%; $P = 0.12$) [16]. The impact of the proctoring process on the increase in the effectiveness of PCI CTO was also documented by Sharma et al. [17] who reported on the effects of 232 procedures performed before proctoring and 355 procedures performed after the implementation of the proctoring program, showing an increase in the percentage of effective recanalizations from 62.1 to 77.5% ($P < 0.001$). In particular, the effectiveness of procedures that were technically difficult due to the complex morphology of the occlusion increased (J-CTO ≥2 from 49.5% to 70.7%; $P < 0.001$) [17].

PCI CTO proctoring programs find many enthusiasts. However, the framework of such programs, their form and duration, have not yet been defined. In this context, the results of the presented study provide new information. Over the course of the 6-year program, an effective increase in the efficiency of recanalization from 56% to 73% was documented in the first 18 months of the program. After the first 50 procedures, the impact of the proctoring process was not noticeable, and the effectiveness of the procedures remained unchanged for the next 4.5 years of the study. However, there is a noticeable dynamic increase in efficiency, which allowed for higher efficiency than in the already-discussed seven-year registry of 94 000 non-proctored procedures performed by inexperienced operators, where after 7 years the effectiveness of recanalization was 61.4% [18]. The results of the analysis by Brilakis et al. [3] from 2015, which documented the dynamics of the increase in the effectiveness of CTO recanalization procedures in the non-proctored program, indicated the decisive role of the first 20 procedures, at the same time flagging the importance of the number of procedures performed by operators (<5 = 53.1%, 5–1 = 62.1%, and >10 = 74.6%; $P < 0.001$). The results of the research of Brilakis et al. [3] correspond with the results obtained in our study. The lowest efficiency of recanalizations was recorded in the months when the number of procedures performed fell below three.

As far as we know, the results obtained in our study show for the first time the independent impact of the proctoring program on the success of CTO recanalization procedures. The study determined prognostic factors such as the timeframe of the program and the number of procedures that may influence the achievement of the best possible educational results. Among the analyzed parameters, only the morphological characteristics of the occlusion (J-CTO score) and the proctor's support during the first 50 procedures, were independent factors influencing the effectiveness of recanalizations. Contrary to the results of the PROGRESS-CTO, RECHARGE, and CASTLE studies, in this analysis, clinical factors did not influence the effectiveness of the procedure. The criterion of the patient's age >65 years, considered prognostically unfavorable for the success and safety of the procedure, and the history of coronary revascularization, which are included in the scales determining the effectiveness of CTO recanalization, lost their importance, perhaps due to the importance of gaining experience in the proctoring program [23–26].

This is particularly important given that the population included in this analysis was clinically more burdened than the populations presented in the meta-analysis; it was older (65 vs. 60), with a more common history of hypertension (83% vs. 54%), diabetes (42% vs. 22%), dyslipidemia (61% vs. 52%), previous MI (50% vs. 40%), PCI (56% vs. 21%), and CABG (13% vs. 10%) [27]. On the other hand, our analysis of the significance of individual components of the J-CTO score was consistent with the results of the PROGRESS, RECHARGE, and CASTLE studies, indicating the strongest impact of the presence of massive calcifications and occlusion within the tortuous segment of the vessel [23–26].

The relatively low percentage of procedures on anatomically complex occlusions (J-CTO score ≥2) and procedures using the retrograde technique are unquestionable limitations of this study. Nevertheless, this characteristic of the studied group reflects the actual population of our center that begins the systematic introduction of this treatment technique.

Article information

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Feasibility and safety of left bundle branch area pacing in very elderly patients (≥80 years)

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ABSTRACT

Background: Left bundle branch area pacing (LBBAP) has emerged as a promising physiologic pacing strategy. Though many clinical studies have established the feasibility and safety of LBBAP, the data for very elderly patients are lacking.

Aims: This study aimed to assess the feasibility and safety of LBBAP in very elderly patients (≥80 years).

Methods: Two hundred and forty consecutive patients who received LBBAP implantation were retrospectively enrolled in the present study. Inclusion criteria were patients with atrioventricular block, atrial fibrillation with a slow ventricular response, and heart failure with bundle branch block. The patients were divided into two groups: those aged ≥80 years and those aged <80 years. LBBAP implantation was successfully performed in 48 of 53 (90.6%) very elderly patients and 162 of 187 (86.5%) counterparts. In the very elderly group, the mean (standard deviation [SD]) age was 84 (3) years, mean (SD) paced QRS duration was 112.4 (9.0), and the mean (SD) stimulus to R wave peak time was 82.0 (14.2) ms. Mean (SD) pacing thresholds and mean (SD) R wave sensing were 0.61(0.21) V and 12.1 (4.7) mV at implant. Pacing parameters in very elderly patients were similar to those in their counterparts. During a median follow-up of 6 months, pacing parameters remained stable. Five patients in the very elderly group developed complications (1 with septal perforation during the procedure, 1 with pocket hematoma, 1 with pacing threshold increase, and 2 with micro lead dislodgement during follow-up).

Conclusion: LBBAP is safe and effective in patients ≥80 years old. LBBAP can be considered as an alternative method for delivering physiological pacing in this special population.

Key words: feasibility, left bundle branch area pacing, physiological pacing, very elderly patients, safety

INTRODUCTION

The proportion of very elderly patients requiring permanent pacemaker implantation (PPM) has increased due to improved therapeutic options for heart disease and augmented life expectancy [1]. It is also related to the pathomorphological changes that occur in the cardiac conduction system with advancing age and the coexistence of hypertension or ischemic heart disease [2]. In a recent study, severe complication rates and life prognosis after traditional PPM were reported to be similar between patients aged ≥ and <85 years [3]. However, controversy over PPM in very elderly patients still occurs since they are burdened with many cardiovascular risk factors [4].

Left bundle branch area pacing (LBBAP) has emerged as an alternative method for delivering physiological pacing to achieve electrical synchrony of the left ventricle [5]. According to the experience in our center, since the target is much broader and the left bundle branch has fibers fanning on the subendocardial aspect of the left side of the interventricular septum, LBBAP is easier to perform than His bundle pacing (HBP). Though many

WHAT'S NEW?

The study demonstrates that left bundle branch area pacing (LBBAP) is safe and effective in patients ≥80 years old. Pacing thresholds and R wave sensing were similar to those in the control group and remained stable during follow-up. The complication rate was not higher than the in counterparts. LBBAP can be considered as an alternative method for delivering physiological pacing in this special population.

clinical studies have established the feasibility and safety of LBBAP [5–8], the data for very elderly patients are lacking. In this study, we explored the feasibility and safety of LBBAP in patients ≥80 years old.

METHODS

Study population

Consecutive patients with a PPM indication who underwent LBBAP were retrospectively evaluated from April 2018 to December 2020. Inclusion criteria were patients with AVB, atrial fibrillation with a slow ventricular response, and heart failure with left bundle branch block (LBBB). Patients diagnosed with LBBB should meet the Strauss criteria: QRSd ≥130 ms in women, ≥140 in men, QS or rS in leads V1 and V2, and mid-QRS notching or slurring in 2 of leads V1, V2, V5, V6, I, and aVL. Then patients were divided into two groups: those aged ≥80 years and those aged <80 years as a control group (Supplementary material, *Figure S1*). The study protocol was approved by the Institutional Review Board of the 1st Affiliated Hospital of Nanjing Medical University, and all patients gave written informed consent.

LBBAP implantation procedure

The detailed implantation procedure was the same as those we have previously reported [9]. The custom ventricular pacing electrode (Minneapolis, MN 3830 electrode) was introduced transvenously into the right ventricle using a 7-Fr guiding catheter (Model C315-S10; Medtronic Inc., Dublin, Ireland). After positioning against the basal or middle ventricular septum, the ventricular lead was driven through the interventricular septum to catch the left bundle branch. Pre-implantation echocardiography was performed routinely to evaluate the thickness of the septum. During lead fixation, the paced QRS morphology and the impedance were carefully monitored. Sheath angiography is a useful way to avoid septum perforation. The penetration depth was assessed by injecting small amounts of contrast medium through the guiding catheter under fluoroscopy in left anterior oblique (LAO) 40-degree view (Supplementary material, *Figure S2*). An estimation of penetration depth was provided in combination with earlier knowledge of the lead tip dimension (10.8 mm from tip to ring) and the IVS wall thickness. Successful LBBAP was defined as unipolar paced QRS with RBBB-like morphology and with at least one of the following three conditions fulfilled: (1) LBB potentials; (2) selective LBB capture; (3) short and constant stimulus to R wave peak time in surface leads V5–6 (RWPT) at high- and low-output pacing or RWPT abruptly shortening more than 10 ms at high-output pacing.

Data collection

Baseline patient characteristics (especially the comorbidities, such as hypertension, coronary artery disease, and diabetes mellitus) and indications for PPM were documented. Baseline QRSd and the presence of BBB were also recorded. Paced QRSd (without the pacing artifact and the initial latency) and RWPT were recorded. According to the novel criterion described by Jastrzębski et al. [10], which suggested different optimal cut-off values of RWPT for LBB capture, the diagnosis was 83 ms in patients with narrow QRS and RBBB and 101 ms in patients with LBBB and non-specific intraventricular conduction disturbance; we differentiated between LBB pacing and LV septal pacing. Pacing threshold, R wave sensing, impedance, and pacing percentages were documented at implant, at 1-week follow-up, and at 1-, 6- and 12-month follow-up. Total fluoroscopy doses for LBBAP lead placement and procedure duration were also documented. Transthoracic echocardiography was performed at baseline and 6-month follow-up. Left ventricular ejection fraction (LVEF), left ventricular end-systolic diameter (LVESD), and left ventricular end-diastolic dimension (LVEDD) were measured. Complications during the procedure such as pneumothorax, pericardial effusion, and septum perforation were recorded. Device-related infection, pocket hematoma, postoperative septum perforation, macro lead dislodgment, or micro lead dislodgement at any time during follow-up were recorded. Micro lead dislodgment was defined as failing to capture the left-sided conduction system resulting in a QS pattern in V1.

Statistical analysis

Continuous variables were expressed as mean (standard deviation [SD]) and compared by independent t-test if the data were normally distributed. Nonnormally distributed variables were expressed as the median with interquartile range (IQR) and compared by Mann-Whitney U-tests. Categorical variables were expressed as observed number and percentage values. Pearson's χ^2 test and Fisher's exact test were used to compare categorical variables. A linear mixed-effect model was used to analyze the repeated measurement data. All *P*-values were two-tailed, and *P*-values of <0.05 were considered significant. Statistical

Table 1. Patient characteristics

	Age <80 years (n = 187)	Age ≥80 years (n = 53)	*P*-value
Age, years, mean (SD)	66 (10)	84 (3)	<0.001[a]
Male gender, n (%)	111 (59.4)	33 (62.3)	0.703
Hypertension, n (%)	96 (51.3)	41 (77.4)	0.001[a]
Diabetes mellitus, n (%)	56 (29.9)	24 (45.3)	0.037[a]
Coronary artery disease, n (%)	40 (21.4)	12 (22.6)	0.845
AF, n (%)	57 (30.5)	21 (39.6)	0.210
Renal failure, n (%)	13 (7.0)	2 (3.8)	0.532
Syncope, n (%)	29 (17.0)	9 (15.5)	0.795
NT-proBNP, pg/ml, median (IQR)	679.4 (199.1–2078.0)	804.2 (308.1–2033.0)	0.577
Baseline QRSd, ms, mean (SD)	130.1 (37.7)	121.5 (32.3)	0.106
LVEF, %, mean (SD)			
≥50%	62.8 (3.2)	63.1 (4.0)	0.601
<50%	34.3 (8.3)	41.9 (2.2)	<0.001[a]
LVEDD, mm, mean (SD)	53 (9)	48 (5)	<0.001[a]
IVS, mm, mean (SD)	10.1 (1.5)	10.5 (1.4)	0.089
Pacemaker indication			0.111
Atrioventricular block, n (%)	124 (66.3)	41 (77.4)	
AF with slow ventricular response, n (%)	26 (13.9)	8 (15.1)	
Heart failure with LBBB, n (%)	37 (19.8)	4 (7.5)	
LBBB, n (%)	44 (23.5)	8 (15.1)	0.188
RBBB, n (%)	22 (11.8)	14 (26.4)	0.008[a]

[a]*P* <0.05

Abbreviations: AF, atrial fibrillation; IVS, interventricular septum; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; NT-proBNP, amino-terminal pro-brain natriuretic peptide; RBBB, right bundle branch block

analysis was performed using SPSS 24.0 (IBMCorp, Armonk, NY, US).

RESULTS

Baseline characteristics

Finally, 240 patients in total were enrolled in the present study and divided into 2 groups: those aged ≥80 years (n = 53) and those aged <80 years (n = 187). Basic clinical details are demonstrated in Table 1. In the very elderly group, the mean (SD) age was 84 (3) years. The most common pacemaker indications were AVB (41 patients) followed by atrial fibrillation with a slow ventricular response (8 patients) and heart failure with LBBB (4 patients). Twenty-two patients had BBB (8 left BBB and 14 right BBB). The prevalence of diabetes mellitus, hypertension and RBBB in the very elderly group was higher than in counterparts (diabetes mellitus: 45.3% vs. 29.9%; *P* = 0.037; hypertension: 77.4% vs. 51.3%, *P* = 0.001; RBBB, 26.4% vs. 11.8%; *P* = 0.008). Other baseline demographics did not differ significantly between the two groups.

Procedural and pacing parameters

LBBAP implantation was successfully performed in 48 of 53 (90.6%) very elderly patients and 162 of 187 (86.5%) counterparts. No difference was observed between the two groups (86.5% vs. 90.6%; *P* = 0.445). Left ventricular septum pacing resulting in a relatively narrower QRSd was performed in those patients who failed LBBAP. The mean (SD) paced QRSd and mean (SD) RWPT were 112.4 (9.0) ms and 82.0 (14.2) ms in the very elderly group. There were also no significant differences between the two groups. Fluoroscopy doses for LBBAP lead placement, procedure duration, and the depth of lead implantation were the same between the two groups (Table 2). Capture thresholds, R wave sensing, and lead impedance tested at implant showed no significant difference between the two groups (Table 3). According to the criterion described by Jastrzębski et al. [10], the success rate of LBBP, paced QRSd and RWPT were also summarized in Table 2. No significant difference was observed between the two groups.

For patients with BBB, the details of electrocardiographic characteristics were summarized in Table 4. In the very elderly group, LBBAP resulted in LBBB correction in 5 of 8 (62.5%) patients, and mean (SD) QRSd decreased from 144.6 (12.6) ms to 109.2 (7.9) ms (*P* <0.001). In the aged <80 years group, LBBAP resulted in LBBB correction in 35 of 44 (79.5%) patients, and mean (SD) QRSd decreased from 170.0 (16.1) ms to 116.3 (9.1) ms (*P* <0.001). No difference was observed in the LBBB correction rate (*P* = 0.366) between the two groups.

Follow-up

For the very elderly patients, all patients completed pre-discharge follow-up, and 27 patients completed 6-month follow-up. The median (interquartile range [IQR]), follow-up duration was 6 (4–12) months in the very elderly group and 6 (1–12) months in the counterparts. Capture thresholds, R wave sensing, impedance, and pacing percentage are summarized in Table 4 and Figure 3. Supplementary material, *Table S1* contains the test results of fixed effects. There

Table 2. Pacing parameters

	Age <80 years (n = 187)	Age ≥80 years (n = 53)	*P*-value
Successful LBBAP, n (%)	162 (86.5)	48 (90.6)	0.445
Paced QRSd, ms, mean (SD)	114.3 (10.0)	112.4 (9.0)	0.240
RWPT, ms, mean (SD)	81.3 (12.0)	82.0 (14.2)	0.750
Depth of lead, mm, mean (SD)	11.3 (1.9)	12.1 (2.0)	0.123
Implantation duration, min, mean (SD)	118 (41)	93 (49)	0.099
X ray exposure dose, mGy, median (IQR)	18 (5–33)	27 (5–62)	0.601
Successful LBBP, n (%)	108 (57.8)	29 (54.7)	0.693
Narrow QRS/RBBB	75 (54.3)	24 (53.3)	0.869
Paced QRSd, ms, mean (SD)	111.8 (10.8)	110.9 (8.9)	0.709
RWPT, ms, mean (SD)	72.6 (7.0)	73.4 (6.4)	0.614
LBBB/NIVCD	33 (67.3)	5 (62.5)	1.000
Paced QRSd, ms, mean (SD)	116.9 (11.2)	109.2 (7.9)	0.148
RWPT, ms, mean (SD)	80.6 (9.3)	71.4 (13.8)	0.062

Abbreviations: NIVCD, non-specific intraventricular conduction disturbance; RWPT, R wave peak time; other — see Table 1

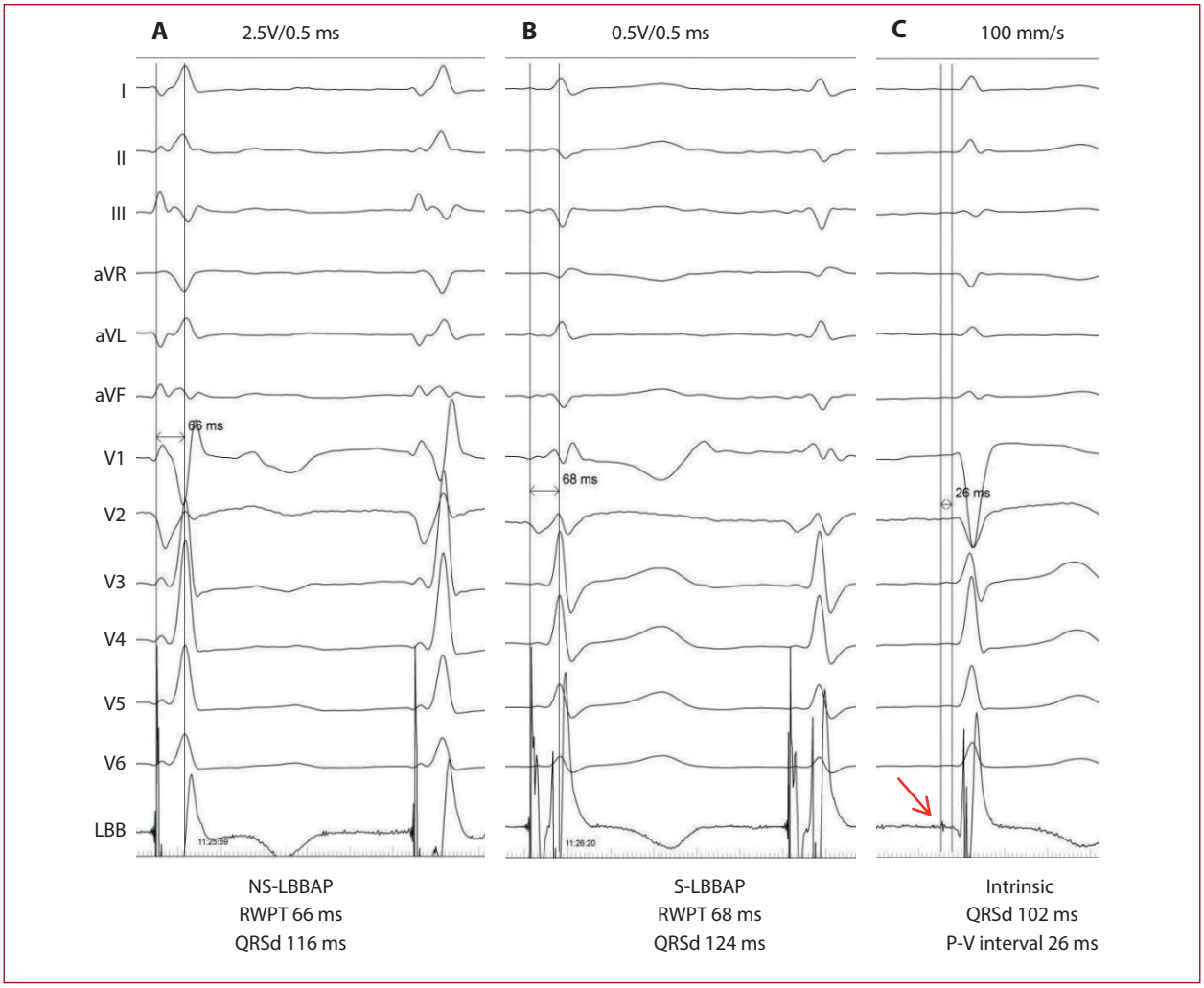

Figure 1. Nonselective to selective left bundle branch area pacing and left bundle branch potential

Abbreviation: LBBAP, left bundle branch area pacing

was no interaction between grouping factors and time factors (Threshold: F = 0.356; *P* = 0.839; Sensing: F = 0.970; *P* = 0.424; Impedance: F = 2.225; *P* = 0.065), which indicated the mean pacing parameters of the two groups were close and followed similar trends over time. There was no significant difference between groups (Threshold: F = 0.645; *P* = 0.424; Sensing: F = 1.480; *P* = 0.225; Impedance: F = 0.319; *P* = 0.573). Time factors had an effect and the mean pacing parameters were statistically different over the time points (Threshold: F = 11.837; *P* <0.001; Sensing: F = 13.617; *P* <0.001; Impedance: F = 286.229; *P* <0.001). Multiple pairwise comparisons were made, and the *P*-value

Table 3. Pacing parameters at implant and follow-up in two groups

	N (%)	Threshold, V/0.4 ms, mean (SD)	Sensing, mV, mean (SD)	Impedance, Ω, mean (SD)	Pacing percentage, %, median (IQR)
Age ≥80 years					
At implant	48 (100.0)	0.61 (0.21)	12.1 (4.7)	803 (147)	—
1 week	48 (100.0)	0.51 (0.12)	14.6 (4.1)	518 (131)	99.8 (88.6–100.0)
1 month	31 (64.6)	0.55 (0.11)	15.9 (3.4)	455 (57)	100.0 (73.9–100.0)
6 months	27 (56.3)	0.60 (0.13)	15.6 (5.3)	444 (51)	99.9 (97.8–100.0)
12 months	14 (29.2)	0.64 (0.13)	14.2 (2.7)	430 (39)	99.9 (78.4–100.0)
Age <80 years					
At implant	162 (100.0)	0.59 (0.18)	12.4 (6.5)	780 (166)	—
1 week	144 (88.9)	0.51 (0.13)	14.4 (4.0)	497 (102)	99.9 (96.1–100.0)
1 month	103 (63.6)	0.57 (0.12)	17.2 (6.3)	468 (79)	99.9 (93.9–100.0)
6 months	87 (53.7)	0.66 (0.17)	16.0 (5.1)	476 (88)	99.7 (84.6–100.0)
12 months	58 (35.8)	0.68 (0.18)	16.5 (5.6)	460 (68)	99.8 (87.4–100.0)

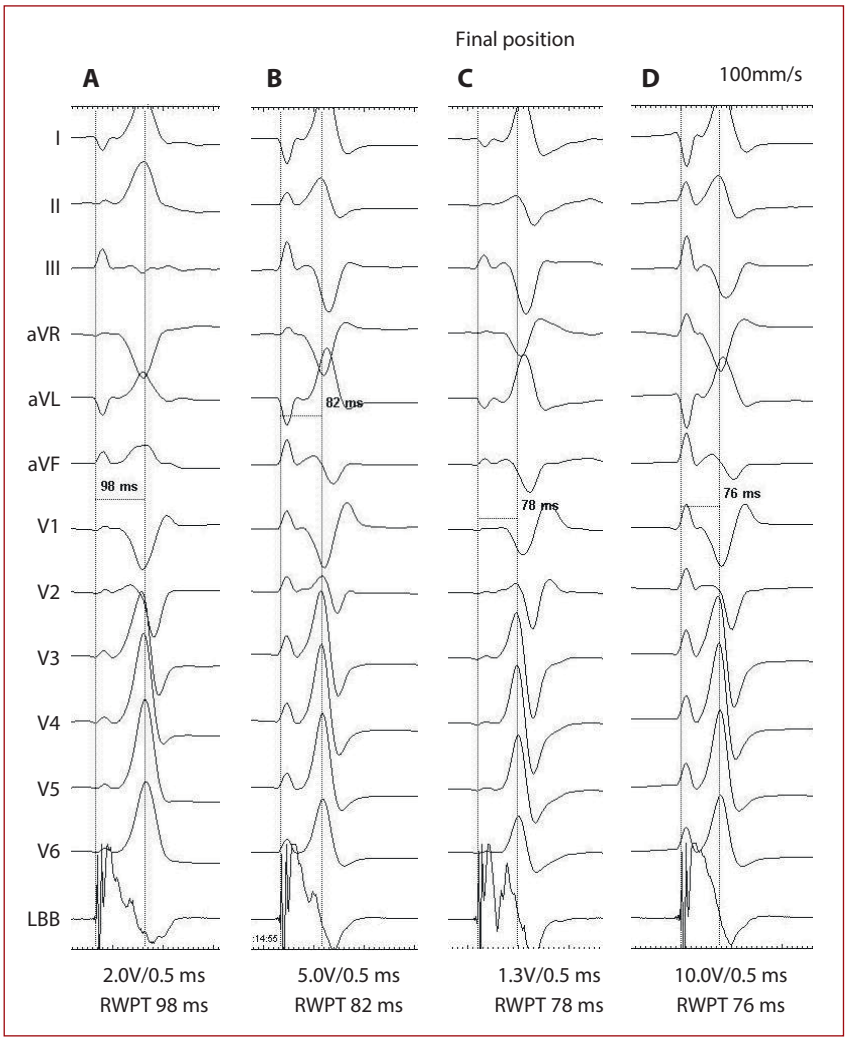

Figure 2. Dynamic changes of R wave peak time in surface leads V5–6 during left bundle branch area pacing procedure

were displayed in Supplementary material, *Tables S2–S4*. In the very elderly group, compared to baseline data, pacing thresholds and impedance decreased (mean [SD], 0.61 [0.21] V/0.4 ms vs. 0.51 [0.12] V/0.4 ms; P = 0.004; mean [SD], 803 [147] Ω vs. 518 [131] Ω; P <0.001), while R wave sensing increased (mean [SD], 12.1 [4.7] mV vs. 14.6 [4.1] mV; P = 0.005) in 1 week after implantation. Thereafter, pacing parameters remained stable over the follow-up period.

The echocardiographic parameters were presented in Supplementary material, *Table S5*. Eighteen patients in the very elderly group had echocardiography at 6-month follow-up. Compared to baseline, LVEF, LVEDD, and LVESD remained unchanged (mean [SD], LVEF: 62.2 [5.1] % vs. 62.3 [2.8] %; P = 0.941; mean [SD], LVEDD: 47.0 [4.5] mm vs. 46.1 [2.5] mm; P = 0.484; mean [SD], LVESD: 31.1 [4.2] mm vs. 31.0 [3.2] mm; P = 0.888) in 16 patients and 2 heart

Table 4. Electrocardiogram characteristics of patients with bundle branch block

	Age <80 years	Age ≥80 years	*P*-value
ALL (n)	66	22	
Successful LBBAP, n (%)	56 (84.8)	18 (81.8)	0.743
Baseline QRSd, ms, mean (SD)	162.1 (19.9)	145.9 (14.5)	0.002
Paced QRSd, ms, mean (SD)	117.4 (8.6)	110.6 (7.7)	0.004
RWPT, ms, mean (SD)	81.9 (11.4)	81.6 (15.4)	0.912
LBBB (n)	44	8	
Successful LBBAP, n (%)	35 (79.5)	5 (62.5)	0.366
Baseline QRSd, ms, mean (SD)	170.0 (16.1)	144.6 (12.6)	0.002
Paced QRSd, ms, mean (SD)	116.3 (9.1)	109.2 (7.9)	0.106
RWPT, ms, mean (SD)	83.0 (12.0)	71.4 (13.8)	0.054
RBBB (n)	22	14	
Successful LBBAP, n (%)	21 (95.5)	13 (92.9)	1.000
Baseline QRSd, ms, mean (SD)	148.5 (18.5)	146.5 (15.6)	0.740
Paced QRSd, ms, mean (SD)	119.3 (7.6)	111.2 (7.9)	0.005
RWPT, ms, mean (SD)	80.1 (10.3)	85.5 (14.6)	0.218

Abbreviations: see Table 2

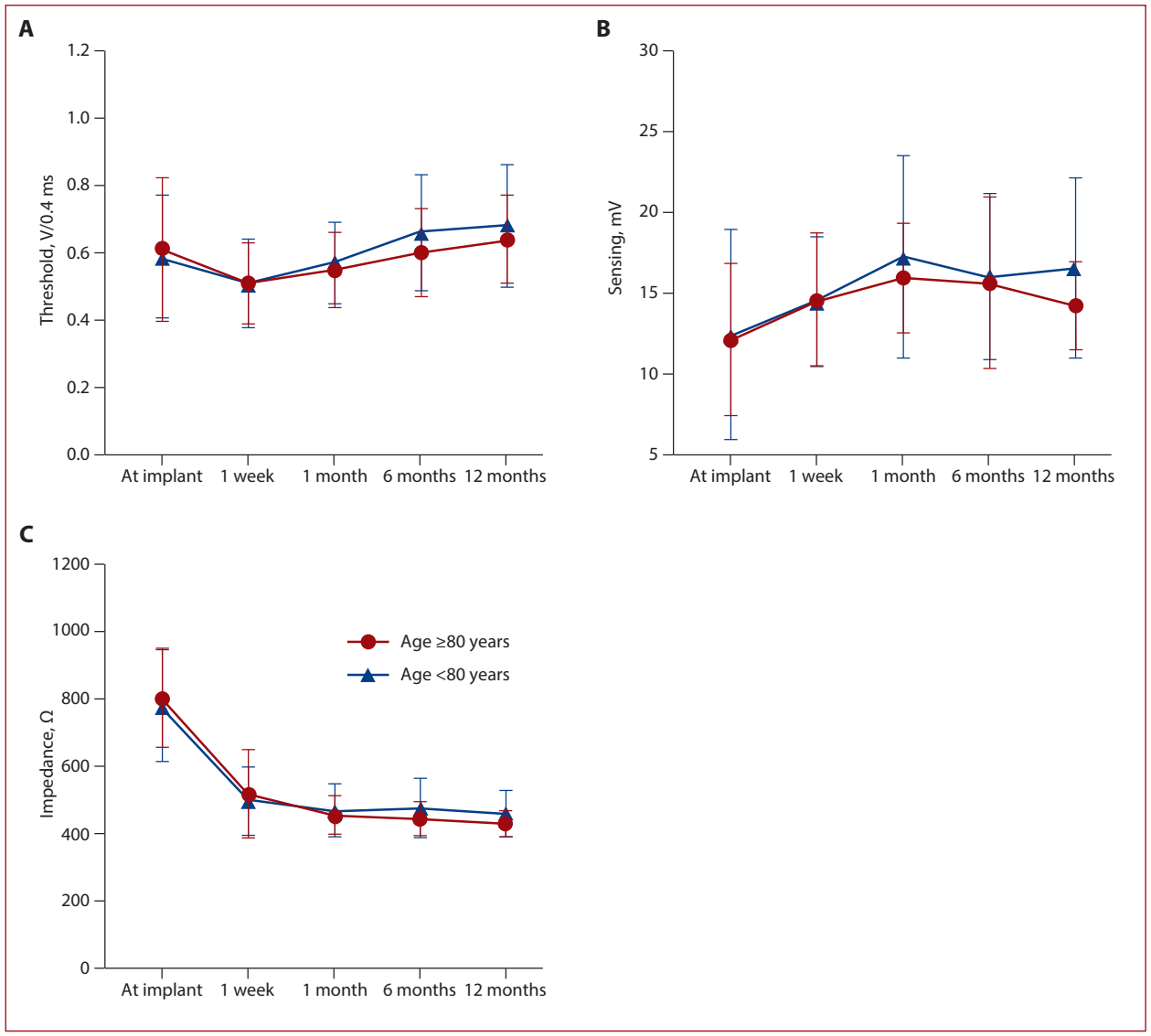

Figure 3. Pacing parameters at implant and during follow-up

Table 5. Complications

	Age <80 years (n = 162)	Age ≥80 years (n = 48)	*P*-value
Complications during procedure			1.000
Septal perforation, n (%)	4 (2.5)	1 (2.1)	
Complications during follow-up			0.483
Pocket hematoma, n (%)	2 (1.2)	1 (2.1)	
Macro lead dislodgement, n (%)	1 (0.6)	0	
Micro lead dislodgement, n (%)	5 (3.1)	2 (4.2)	
Increase of pacing threshold, n (%)	1 (0.6)	1 (2.1)	

failure patients with LBBB had improvements in LVEF of ≥5%. In the <80-year-old group, fifty-seven patients with normal cardiac function had echocardiography at 6-month follow-up and parameters remained unchanged (mean [SD], LVEF: 61.8 [7.3] % vs. 62.3 [5.0] %; $P = 0.452$; mean [SD], LVEDD: 49.6 [4.9] mm vs. 48.7 [4.0] mm; $P = 0.096$; mean [SD], LVESD: 33.1 [5.3] mm vs. 32.4 [4.0] mm; $P = 0.092$). Seventeen heart failure patients with LBBB had echocardiography at 6-month follow-up. Compared to baseline, LVEF improved from 35.9 (9.5) % to 45.3 (13.1) % (mean [SD]; $P = 0.006$), LVEDD decreased from 61.0 (8.4) mm to 55.9 (8.8) mm (mean [SD]; $P = 0.013$), and LVESD decreased from 50.1 (9.3) mm to 43.4 (11.0) mm (mean [SD]; $P = 0.010$). Five patients had improvements in LVEF of ≥5%, and eight patients had improvements in LVEF of ≥10%.

Complications

No significant difference was observed in complications between the two groups (Table 5). In the very elderly group, one septal perforation occurred during the procedure confirmed by contrast medium leaking into the LV cavity, and the lead was repositioned slightly away from the initial site. No pneumothorax or pericardial effusion was observed. During follow-up, one patient on oral anticoagulation developed pocket hematoma 2-weeks after discharge and recovered after discontinuing anticoagulant therapy. One patient had an increase in pacing threshold (>1V) to 2.75 V /0.4 ms at 24-month follow-up. Two patients had micro lead dislodgement (Supplementary material, *Figure S3*). Pacing parameters remained stable in both patients during follow-up, no lead revision was attempted. Other device-related complications such as device-related infection and postoperative septum perforation were not observed during follow-up.

DISCUSSION

Around 25% of clinical trials investigating the effects of new methods of treatment for cardiovascular diseases still overlook very elderly patients, and recommendations for management derived from younger patients frequently lack evidence-based support for these patients. Although clinical results tend to confirm the positive effect of physiological cardiac pacing on echocardiographic and hemodynamic parameters, as well as on exercise capacity and quality of life of these patients, a prevalence of right ventricular apex pacing in very elderly patients can still be observed [11, 12]. In this study, we demonstrated that LBBAP can be safely and effectively used in very elderly patients.

The ideal physiological approach to ventricular pacing should engage the normal conduction through the His-Purkinje conduction system. Based on a systematic review of the available published literature, HBP is recommended as a class IIa indication in patients requiring ventricular pacing who have an LVEF of 36% to 50% and as a class IIb indication in patients with AVB at the level of the AV node [13]. LBBAP can effectively overcome some limitations of HBP, such as high pacing thresholds and low sensing. In the 2021 ESC guidelines [14], LBBAP is mentioned as a very promising technique. However, recommendations for using LBBAP cannot be formulated for lack of solid evidence. Special pathomorphological changes in very elderly patients are usually related to the changes that occur in the cardiac conduction system with advancing age and the coexistence of hypertension or ischemic heart diseases [4]. In the present study, the very elderly patients showed a higher prevalence of hypertension, diabetes mellitus, and RBBB. These baseline characteristic differences are consistent with a more advanced pathophysiological state.

In the first case of LBBAP reported by Huang et al. [15], the patient was a 72-year-old female who had heart failure with dilated cardiomyopathy. In the following studies, the feasibility and safety of LBBAP were demonstrated in patients with normal QRS complex and symptomatic bradycardia such as SND (age, 63.8 [11.4] years) or AVB (age, 55.1 [18.5] years) [16]. In the study of Vijayaraman et al. [5], the age was 75 (13.1) years. In a recent study, the researchers reported successful application of LBBAP in a 10-year-old child with LBBB and enlarged heart size [17]. In our study, the average age of the very elderly group was 84 (3) years. Paced QRSd, RWPT, pacing parameters, and procedure parameters were the same as those in the group of patients aged <80 years. Pacing parameters remained stable over follow-up.

In this vulnerable population, complications are worthy of attention. Physicians usually prejudge those elderly patients who may have higher complication rates due to their comorbidities. According to the published LBBAP studies, the overall incidence of lead dislodgments (1%) and septal perforations (1.7%) was low. In a single-center experience

reported by Chen et al. [18], the procedure-related complications rate of LBBAP was only 1.63% (10/612) including 2 postoperative septum perforations, 2 postoperative lead dislodgements, 4 intraoperative septum injuries, and 2 intraoperative lead fractures. The incidence of micro lead dislodgement described by Ravi et al. [19] was relatively high, which was noted in 4 patients (7.0%). In a recent study, the novel continuous pace mapping technique described by Jastrzębski et al. [20] enabled real-time monitoring of lead behavior and depth, facilitated reaching the LBB capture area, and had the potential to limit the risk of septal perforation. In the current study, the complication rate in very elderly patients was not higher than in their counterparts. One patient in the very elderly group developed septum perforation during the procedure, and the lead was successfully revised. One patient's pacing threshold increased by more than 1V at 24-month follow-up, and in two patients micro lead dislodgement occurred, no lead revision was attempted.

Beyond the traditional use of LBBAP for symptomatic bradycardia, another potential application in the very elderly patients is HF with LBBB, which is a cardiac resynchronization therapy (CRT) indication according to the guidelines. The traditional cardiac venous CRT procedure is complicated and time-consuming. Additionally, about 10% of patients remain untreated owing to an unsuitable coronary sinus venous branch. In a recent report by Huang et al. [8], LBBAP was successfully performed in 61 of 63 patients with nonischemic cardiomyopathy (97%, mean age 68 [11] years, LVEF 33 [7.4]%), and QRSd narrowed significantly from 169 (16) ms to 118 (12) ms. In the present study, 2 of 4 heart failure patients with LBBB in the very elderly group achieved successful LBBAP and had improvements in LVEF of ≥5% at 6-month follow-up.

In the study of Jastrzębski et al. [10], the authors used dynamic electrocardiogram maneuvers with output-dependent and refractoriness-dependent QRS morphological changes as the "gold standard" and found optimal V6 RWPT cut-off for LBB capture diagnosis. This criterion was relatively strict, and the cut-off value might be changed due to differences in population and implantation techniques. They measured the stimulus to RWPT in V6, but we measured stimulus to the RWPT in V5 or V6, decided by which was longer. It might also affect the results. In the present study, the success rate of LBBP was low diagnosed by the novel criterion in both groups. We were focused on the effectiveness and safety of LBBAP in elderly patients and attached more importance to minimizing its duration. Such an approach might increase the risk of complications, like septum perforation, in pursuit of the perfect LBBP for this vulnerable population.

Limitations

First, the sample size of heart failure patients with LBBB was small. This was a preliminary, single-center, and retrospective study, and further trials should be conducted in such patients. Second, the safety of LBBAP, compared between our two groups, might be better if using the Kaplan-Meier method. Uni and multivariate analysis may reveal the impact of age on the risk of LBBAP. However, the multivariate analysis could not be estimated owing to few patients with complications. Third, in this <1-year follow-up study the LBBAP appears safe in the very elderly, but complications that can be significant persist. Long-term data are needed to determine which elderly population subsets may benefit.

CONCLUSION

LBBAP is safe and effective in patients ≥80 years old. Therefore, LBBAP can be considered an alternative method for delivering physiological pacing in this special population.

Supplementary material

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

Article information

Conflict of interest: None declared.

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Adherence to the 4S-AF Scheme in the Balkan region: Insights from the BALKAN-AF survey

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ABSTRACT

Background: The 4S-AF scheme includes stroke risk, symptoms, severity of burden, and substrate severity domain.

Aim: We aimed to assess the adherence to the 4S-AF scheme in patients classified according to stroke risk in *post hoc* analysis of the BALKAN-AF dataset.

Methods: A 14-week prospective enrolment of consecutive patients with electrocardiographically documented atrial fibrillation (AF) was performed in seven Balkan countries from 2014 to 2015.

Results: Low stroke risk (CHA_2DS_2-VASc score, 0 in males or 1 in females) was present in 162 (6.0%) patients. 2 099 (77.4%) patients had CHA_2DS_2-VASc score ≥3 in females or ≥2 in males (high stroke risk), and 613 (22.6%) had CHA_2DS_2-VASc score <3 in females or <2 in males. Seventy-five (46.3%) patients with low stroke risk and 1555 (74.1%) patients with high stroke risk were prescribed oral anticoagulants (OAC). Two thousand six hundred and seventy-seven (98.6%) had data on European Heart Rhythm Association (EHRA) class. Among 2099 patients with high stroke risk, 703 (33.4%) had EHRA class ≥3. Two hundred and seven (29.4%) patients with EHRA class ≥3 and high stroke risk were offered rhythm control; 620 (55.2%) of individuals with first-diagnosed or paroxysmal AF with high stroke risk were offered rhythm control. Two or more comorbidities occurred in 1927 (91.8%) patients with high stroke risk.

Conclusions: OAC overuse was observed in patients with low stroke risk, whilst OAC underuse was evident in those with high risk of stroke. The percentage of highly symptomatic patients with high risk of stroke who were offered a rhythm control strategy was low.

Key words: atrial fibrillation, oral anticoagulants, rhythm control, risk of stroke

WHAT'S NEW?

Data on the use of the 4S-AF scheme in clinical practice are scarce. This study, therefore, provides a novel insight into the adherence to the 4S-AF scheme in real-world atrial fibrillation (AF) patients. Unfortunately, treatment decision-making was not based on the 4S-AF structured scheme in the BALKAN-AF cohort. Using the 4S-AF scheme may facilitate treatment decision-making associated with the management of patients with AF in clinical practice.

INTRODUCTION

Atrial fibrillation (AF) is a substantial source of morbidity and mortality, with a major economic burden for countries worldwide [1]. Moreover, AF is often asymptomatic (but still confers a poor prognosis) [2], and the complexity of AF needs a holistic approach with multidisciplinary, integrated management with active involvement of AF patients [3–5]. This integrated approach to patient evaluation and management is associated with improved outcomes in AF [6] and is also increasingly advocated in various other clinical settings with chronic long-term conditions [7–8].

Currently, the AF guidelines propose a structured characterization of AF including domains with management and prognostic implications to facilitate the evaluation of AF patients by healthcare professionals [9]. The 4S-AF structured scheme includes four domains: Stroke risk, Symptoms, Severity of AF burden, and Substrate severity [9].

The Stroke risk domain with stroke risk assessment is based on the CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥75 years, diabetes, stroke/transient ischemic attack [TIA], vascular disease, age 65-74 years, sex category [female]). The indications for oral anticoagulants (OAC) use are based on the European Society of Cardiology guidelines or other international documents [3, 10].

The Symptom severity domain is associated with the EHRA symptom score and facilitates patient-centered, symptom-directed AF management [4]. The Severity of the AF burden domain describes the density of AF episodes in time and the proportion of time of AF. The Substrate for the AF domain relates to the complexity of AF pathophysiology including characteristics such as age, cardiovascular risk factors, and underlying comorbid conditions, as well as parameters of the left atrium (enlargement, function, and fibrosis of its myocardium) [11].

This *post hoc* analysis aimed to evaluate the adherence to the 4S-AF scheme in the BALKAN-AF cohort in patients classified according to their stroke risk.

METHODS

The design of the BALKAN-AF study has been described previously [12]. This 14-week prospective, multicenter "snapshot" registry of consecutive patients with electrocardiographically documented AF was designed and conducted by the Serbian Atrial Fibrillation Association (SAFA). Consecutive AF patients were enrolled in the survey from December 2014 to February 2015 in cooperation with individual National Cardiology Societies and Associations or Working Groups in Albania, Bosnia & Herzegovina, Bulgaria, Croatia, Montenegro, Romania, and Serbia. Universities, non-university hospitals, and outpatient health centers (a total of 49 centers) were sites involved in the BALKAN-AF study. The respective National Coordinator selected the sites. The registry was approved by the local/national institutional review board in participating countries. The study received ethical approval. A signed patient informed consent form was obligatory in the enrolment process. The study protocol was concordant with the Declaration of Helsinki.

Exclusion criteria included those aged <18 years or patients with prosthetic mechanical heart valves or significant valvular disease with indications for surgical repair.

Data on patient presentation, patient characteristics, healthcare setting, and diagnostic procedures within the last 12 months and at enrolment and AF management at enrolment and discharge were collected and stored using the electronic case report forms (eCRFs). Stroke risk was evaluated using the CHA_2DS_2-VASc score [10]. Truly low risk of stroke was defined as a CHA_2DS_2-VASc score of 0 in males, and 1 in females, whilst the intermediate risk of stroke included male patients with a CHA_2DS_2-VASc score of 1 or females with a CHA_2DS_2-VASc score of 2. High risk of stroke was defined as CHA_2DS_2-VASc score ≥3 in females or ≥2 in males.

Bleeding risk was assessed according to the HAS-BLED score (hypertension, abnormal renal /liver function, stroke, bleeding history or predisposition, labile International Normalized Ratio [INR], elderly [>65 years], drugs or alcohol concomitantly) [13]. The included cardiovascular risk factors, risk scores, and diseases were defined using the individual European Society of Cardiology guidelines, other international guidelines, scientific statements, and textbooks as described previously [14].

Regular monitoring of centers and follow-up visits were not performed due to the relatively short period of the survey. National coordinators and investigators were responsible for validation of the consecutiveness of enrolled patients and correctness and completeness of entered data.

Available domains of the 4S-AF scheme were identified and assessed using data from the baseline visit.

Statistical analysis

Categorical variables were presented as absolute frequencies and percentages. Numerical variables were presented

as mean (standard deviation [SD]) or median with interquartile range (IQR) and compared between groups by Student's t-test or Mann-Whitney's test where appropriate. Comparative analysis between groups was performed using Chi^2 for dichotomous parameters. The descriptive analysis involved stroke prevention, quality of life, management strategies, severity of AF burden, and the Substrate for AF domain in the BALKAN-AF cohort. A two-sided *P*-value of less than 0.05 was considered statistically significant. All analyses were performed using SAS software version 9.4 (SAS Institute, Inc., Cary, NC, US).

RESULTS

The Stroke risk domain

Patients with high risk of stroke were older, more likely to be female, and more likely to have concomitant diseases than those with low or intermediate risk of stroke (all P <0.05), Table 1. Congestive heart failure, hypertension, and coronary artery disease were the most frequent concomitant diseases in individuals with high, low, and intermediate stroke risk. The baseline characteristics of patients are summarized in Table 1.

Of 2712 enrolled patients, 2712 (100.0%) had data on CHA_2DS_2-VASc score. One hundred and sixty-two (6.0%) individuals had a truly low risk; 2550 (94.0%) patients had CHA_2DS_2-VASc score ≥1 in males or ≥2 in females; 2099 (77.4%) patients had high risk of stroke, and 613 (22.6%) individuals had low or intermediate risk of stroke, Table 1.

Patients with high risk of stroke had a higher mean HAS-BLED score than those with intermediate or low risk of stroke (P <0.001), Table 1.

Patients with high risk of stroke were less likely to receive no antithrombotic therapy, warfarin, and dabigatran than those with low or intermediate risk of stroke (all P <0.05), Table 1. Among patients with truly low risk of stroke, 75 (46.3%) patients were medicated with OAC, Table 1.

The Symptom severity domain

Of 2712 patients, 2 677 (98.6%) had data on the European Heart Rhythm Association (EHRA) symptom score: (1) 571 (21.0%) patients had EHRA symptom score of 1; (2) 1254 (46.2%) of individuals had EHRA symptom score of 2; (3) 712 (26.2%) patients had EHRA symptom score of 3; and (4) 140 (5.2%) patients had EHRA symptom score of 4. Among 2 099 patients with CHA_2DS_2-VASc score ≥3 in females or ≥2 in males, 703 (33.4%) individuals had EHRA symptom score of 3 or 4.

Patients with high risk of stroke were more likely to have shortness of breath, chest pain, dizziness, and fatigue than those with low or intermediate risk of stroke (all P <0.001), Table 2.

A rhythm control strategy was implemented in 207 (29.4%) patients with high risk of stroke and EHRA symptom score of 3 or 4. Notably, 620 (55.2%) of patients with high risk of stroke and paroxysmal AF or first diagnosed AF were assigned to rhythm control strategy, while 646 (57.5%) individuals with high risk of stroke and paroxysmal AF or first diagnosed AF were medicated with amiodarone, Table 3. Amiodarone was the most commonly prescribed drug in individuals with high risk of stroke, and EHRA symptom score of 3 or 4.

The Severity of AF burden domain

Patients with low or intermediate risk of stroke were more likely to have first diagnosed AF, paroxysmal AF, or persistent AF than those with high risk of stroke (all P <0.05), Table 4.

The Substrate for AF domain

Patients with high risk of stroke were more likely to have a higher median number of comorbid diseases than those with low or intermediate risk of stroke (P <0.05).

The mean diameter of the left atrium (LA) was higher in individuals with high risk of stroke than in those with low or intermediate risk of stroke (P <0.001), Table 5.

DISCUSSION

The main findings of this study were as follows: (1) OAC overuse was seen in patients with truly low stroke risk, whilst OAC underuse was evident in patients with high risk of stroke; (2) the proportion of highly symptomatic patients (EHRA 3 or 4) with high risk of stroke who were offered rhythm control strategy was low; (3) the proportion of patients with first diagnosed AF or paroxysmal AF with high risk of stroke who received rhythm control was small; and (4) the majority of AF patients with high risk of stroke had ≥2 comorbidities.

Data on the use of the 4S-AF scheme in everyday clinical practice are scarce. This study, therefore, provides a novel insight into the adherence to the 4S-AF scheme in real-world AF patients. The 4S-AF scheme facilitates our evaluation and characterization of the AF patient during the clinical consultation. Moreover, this structured characterization of AF patients provides prognostic information, and this study validates the 4S-AF scheme in the Balkan region. We found that OAC overuse in patients with low risk of stroke and OAC underuse in those with high risk of stroke was common, and seen also in recent European reports [15–17]. Efforts to improve the prescription of OACs in AF patients are, therefore, needed [18], and the availability of NOACs has improved such efforts [19, 20].

The use of NOACs has increased over time in Europe. This finding has been shown in other studies [19–24]. The risk of stroke is closely linked with bleeding risk, and thromboembolic factors such as older age, hypertension, or history of stroke have also been bleeding risk factors [25]. Thus, patients with high risk of stroke have higher bleeding risk than those with low or intermediate risk of stroke.

The EHRA symptom score expresses how physicians weigh the symptoms of AF patients, but in the BALKAN-AF

Table 1. Stroke prevention in patients according to stroke risk

Variable	CHA_2DS_2-VASc score of 0 in males or 1 in females n = 162 (6.0%)	CHA_2DS_2-VASc score ≥1 in males or ≥2 in females n = 2550 (94.0%)	*P*-value	CHA_2DS_2-VASc score ≥3 in females or ≥2 in males n = 2099 (77.4%)	CHA_2DS_2-VASc score <3 in females or <2 in males n = 613 (22.6%)	*P*-value
Age, years, mean (SD)	49.9 (11.4)	70.1 (9.9)	<0.001	72.5 (8.6)	56.7 (9.2)	<0.001
Female gender, n (%)	41 (25.3)	1151 (45.1)	<0.001	953 (45.4)	239 (39.0)	<0.001
BMI, kg/m^2, mean (SD)	26.4 (3.3)	27.8 (4.4)	<0.001	27.8 (4.5)	27.7 (4.0)	0.848
Alcohol abuse, ≥8 units/week, n (%)	7 (4.3)	103 (4.0)	0.860	81 (3.9)	29 (4.7)	0.336
First diagnosed AF, n (%)	52 (32.1)	580 (22.7)	<0.001	455 (21.7)	177 (28.9)	<0.001
Paroxysmal AF, n (%)	79 (48.8)	881 (34.5)	<0.001	668 (31.8)	292 (47.6)	<0.001
Permanent AF, n (%)	17 (10.5)	1071 (42.0)	<0.001	973 (46.4)	115 (18.8)	<0.001
Concomitant diseases, n (%)						
Congestive HF	0 (0.0)	1336 (52.4)	n/a	1240 (59.1)	103 (16.8)	<0.001
Hypertension	0 (0.0)	2121 (83.2)	n/a	1800 (85.8)	321 (52.4)	<0.001
CAD	0 (0.0)	819 (32.1)	n/a	764 (36.4)	57 (9.3)	<0.001
Prior MI	0 (0.0)	369 (14.5)	n/a	359 (17.1)	10 (1.6)	<0.001
PAD	0 (0.0)	122 (4.8)	n/a	120 (5.7)	2 (0.3)	<0.001
Diabetes	0 (0.0)	668 (26.2)	n/a	636 (30.3)	32 (5.2)	<0.001
Prior stroke	0 (0.0)	281 (11.0)	n/a	280 (13.3)	1 (0.2)	<0.001
Prior TIA	0 (0.0)	83 (3.3)	n/a	83 (4.0)	0 (0.0)	n/a
Anemia	7 (4.3)	366 (14.4)	<0.001	337 (16.1)	36 (5.9)	<0.001
Chronic kidney disease	1 (0.6)	410 (16.1)	<0.001	391 (18.6)	20 (3.3)	<0.001
Previous bleeding event	1 (0.6)	132 (5.2)	<0.001	121 (5.8)	12 (2.0)	<0.001
COPD	3 (1.9)	339 (13.3)	<0.001	305 (14.5)	37 (6.0)	<0.001
Cancer	2 (1.2)	117 (4.6)	0.096	106 (5.1)	13 (2.1)	0.004
HAS-BLED score, mean (SD)	0.31 (0.6)	2.1 (1.2)	<0.001	2.3 (1.1)	0.8 (0.8)	<0.001
No antithrombotic therapy, n (%)	44 (27.2)	221 (8.7)	<0.001	174 (8.3)	91 (14.8)	<0.001
Overall OAC, n (%)	75 (46.3)	1890 (74.1)	<0.001	1555 (74.1)	410 (66.9)	0.105
OAC alone, n (%)	70 (43.2)	1571 (61.6)	<0.001	1265 (60.3)	376 (61.3)	0.633
VKA, n (%)	62 (38.3)	1565 (61.4)	<0.001	1301 (62.0)	326 (53.2)	0.012
Warfarin, n (%)	35 (21.6)	520 (20.4)	0.128	408 (19.4)	147 (24.0)	0.002
Acenocoumarol, n (%)	27 (16.7)	1044 (40.9)	<0.001	892 (42.5)	179 (29.2)	<0.001
NOAC, n (%)	13 (8.0)	325 (12.7)	0.320	254 (12.1)	84 (13.7)	0.125
Dabigatran, n (%)	9 (5.6)	166 (6.5)	0.917	125 (6.0)	50 (8.2)	0.022
Rivaroxaban, n (%)	4 (2.5)	111 (4.4)	0.459	89 (4.2)	26 (4.2)	0.797
Apixaban, n (%)	1 (0.6)	48 (1.9)	0.344	40 (1.9)	9 (1.5)	0.575
Single antiplatelet therapy alone, n (%)	12 (7.4)	309 (12.1)	0.289	257 (12.2)	64 (10.4)	0.430
DAPT alone, n (%)	1 (0.6)	119 (4.7)	0.034	107 (5.1)	13 (2.1)	0.003
Dual antithrombotic therapy, n (%)	5 (3.1)	236 (9.3)	0.031	210 (10.0)	31 (5.1)	0.001
Triple antithrombotic therapy, n (%)	0 (0.0)	83 (3.3)	0.035	80 (3.8)	3 (0.5)	<0.001

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes, stroke/transient ischemic attack (TIA), vascular disease, age 65-74 years, sex category (female); DAPT, dual antiplatelet therapy; HF, heart failure; MI, myocardial infarction; NOAC, non-vitamin K oral antagonist; OAC, oral anticoagulants; PAD, peripheral artery disease; SD, standard deviation; TIA, transient ischemic attack; VKA, vitamin K antagonists

Single antiplatelet therapy alone was defined as aspirin

Table 2. Quality of life in patients according to stroke risk

Variable	CHA_2DS_2-VASc score ≥3 in females or ≥2 in males n = 2099 (77.4%)	CHA_2DS_2-VASc score <3 in females or <2 in males n = 613 (22.6%)	*P*-value
Palpitations, n (%)	904 (43.1)	325 (53.0)	<0.001
Syncope, n (%)	99 (4.7)	21 (3.4)	0.253
Shortness of breath, n (%)	1089 (51.9)	189 (30.8)	<0.001
Chest pain, n (%)	452 (25.8)	102 (16.6)	<0.001
Dizziness, n (%)	376 (17.9)	59 (9.6)	<0.001
Fatigue, n (%)	905 (43.1)	169 (27.6)	<0.001
General not-well-being, n (%)	499 (23.8)	116 (18.9)	0.051
Fear, anxiety, n (%)	209 (10.0)	58 (9.5)	0.994

Abbreviations: see Table 1

Table 3. Management strategies in patients according to the EHRA symptom score

Variable	Patients with CHA_2DS_2-VASc score ≥3 in females or ≥2 in males with EHRA 3 or 4 n = 703	Patients with CHA_2DS_2-VASc score ≥3 in females or ≥2 in males with first diagnosed or paroxysmal AF n = 1123
Rhythm control, n (%)	207 (29.4)	620 (55.2)
Amiodarone, n (%)	199 (28.3)	646 (57.5)
Propafenone, n (%)	40 (5.7)	121 (10.8)
Flecainide, n (%)	1 (0.1)	1 (0.00
ECV, n (%)	14 (2.0)	7 (0.0)
AF ablation, n (%)	8 (1.1)	15 (0.0)

Abbreviations: ECV, electric cardioversion, EHRA, European Heart Rhythm Association; see Table 1

Table 4. Severity of AF burden domain

AF pattern	CHA_2DS_2-VASc score ≥3 in females or ≥2 in males n = 2099 (77.4%)	CHA_2DS_2-VASc score <3 in females or <2 in males n = 613 (22.6%)	*P*-value
First diagnosed, n (%)	455 (21.7)	177 (28.9)	<0.001
Paroxysmal, n (%)	668 (31.8)	292 (47.6)	<0.001
Persistent, n (%)	219 (10.4)	100 (16.3)	<0.001
Long-standing persistent, n (%)	49 (2.3)	15 (2.4)	0.872
Permanent, n (%)	973 (46.4)	115 (18.8)	<0.001

Abbreviations: see Table 1

Table 5. The substrate for AF domain in the BALKAN-AF cohort

Variable	CHA_2DS_2-VASc score ≥3 in females or ≥2 in males n = 2099 (77.4%)	CHA_2DS_2-VASc score <3 in females or <2 in males n = 613 (22.6%)	*P*-value	CHA_2DS_2-VASc score of 0 in males or 1 in females n = 162 (6.0%)	CHA_2DS_2-VASc score ≥1 in males or ≥2 in females n = 2550 (94.0%)	*P*-value
Number of comorbid diseases, median (IQR)	4.7 (3.0–6.0)	2.1 (1.0–3.0)	<0.001	0.9 (0.0–1.0)	4.3 (2.0–6.0)	<0.001
Age ≥75 years	946 (45.1)	112 (18.3)	<0.001	0 (0.0)	947 (37.1)	NA
Obesity	511 (24.3)	160 (26.1)	0.256	38 (23.5)	633 (24.8)	0.536
Active smoker	228 (10.9)	112 (18.3)	<0.001	32 (19.8)	308 (12.1)	<0.001
Alcohol abuse	81 (3.9)	29 (4.7)	0.336	7 (4.3)	103 (4.0)	0.860
LA diameter, mm, mean (SD)	46.5 (7.8)	43.3 (7.4)	<0.001	40.4 (7.5)	46.0 (7.8)	<0.001

Abbreviations: LA, left atrium, IQR, interquartile range, SD, standard deviation; other — see Table 1

cohort, only one-third of patients with EHRA symptom score of 3 or 4 and high risk of stroke received a rhythm control strategy. Half of the patients with first diagnosed AF or paroxysmal AF were offered the strategy. Underuse of the rhythm control strategy in highly symptomatic patients was also been reported previously [26]. However, the EHRA symptom score may not adequately differentiate between AF-related and concomitant chronic conditions-related symptoms. Thus, the assessment of quality of life could be useful in the assessment of the symptom severity domain [9].

Our study used the temporal-pattern based classification of AF based on guideline recommendations. Notably, the above-mentioned classification may be imprecise in distinguishing between paroxysmal and persistent AF. Nonetheless, the utility of the 4S-AF scheme in selecting the AF patients who would be managed by rhythm or rate control strategy has been proposed [27].

Multimorbidity is common in AF, and the majority of the patients from the BALKAN-AF registry with high risk of stroke had ≥2 comorbidities. Approximately half of the individuals with high risk of stroke were ≥75 years old. Cardiovascular risk factors, patient age, and concomitant chronic conditions all play a role in the development and progression of AF [11]. In the Substrate for AF domain, identification and management of cardiovascular risk factors and multimorbidity should be emphasized in the AF-related treatment decisions process, as part of the holistic approach to AF care (based on the Atrial fibrillation Better Care [ABC] pathway) given that this has been associated with improved clinical outcomes [28]. Unfortunately, treatment decision-making in the BALKAN-AF cohort was not based on the 4S-AF scheme, and the introduction of the 4S-AF scheme may help facilitate AF management.

From a Polish perspective, AF management strategies in Poland may differ from those applied in other European countries [29]. The rhythm control strategy in individuals with AF with the use of ablation in cardiology wards seems more frequent in Poland than in other European countries. The limited use of AF ablation in the Balkans may be

associated with limited access to this management option in this region [30]. Similar to patients from the BALKAN-AF registry, undertreatment was observed in a significant proportion of Polish patients at high risk of stroke, while many low-risk patients are overtreated [29–31]. The BALKAN-AF study indicates a high prevalence of co-morbidities among patients with AF, which was also reflected in another Polish registry (RecordAF) [32].

Limitations

Our study has a limitation that should be noted. Since no follow-up was planned, there was no assessment of patient outcomes. Some descriptors, risk stratification scores, and imaging tools were not available in the BALKAN-AF cohort. The 4S-AF system does not include data about bleeding risk, repeated cardioversions or AF ablations, prior and current antiarrhythmic drug therapy, etc. so the above-mentioned data were not incorporated. Data on duration of AF, density of episodes, LA dysfunction/enlargement, LA fibrosis, and data on spontaneous termination of AF were not available.

CONCLUSION

Overall, decision-making was not based on the 4S-AF scheme. OAC overuse was seen in patients with truly low stroke risk, whist OAC underuse was evident in those with high risk of stroke. The proportion of highly symptomatic patients with high risk of stroke who were offered the rhythm control strategy was low. A more widespread introduction of the 4S-AF scheme may help facilitate AF management.

Article information

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Conflicts of interest: Milan Nedeljkovic has been a speaker for Bayer Serbia. Gregory YH Lip has been a consultant and speaker for BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo (no personal fees). Tatjana S Potpara has been a consultant for Bayer/Jansen and BMS/Pfizer (no fees). Other authors declare no conflict of interest.

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Management and predictors of clinical events in 75 686 patients with acute myocardial infarction

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ABSTRACT

Background: Although mortality in patients with acute myocardial infarction (MI) has decreased substantially over the last few decades in many countries, MI remains a major threat to public health.

Aims: To assess the number and outcomes of patients hospitalized for acute MI in Poland in 2018 as well as proportions of patients participating in cardiac rehabilitation and undergoing invasive cardiac procedures following discharge.

Methods: We used public databases. We included all patients hospitalized for acute MI in Poland in 2018 and assessed event-free survival along with uptake of invasive cardiac procedures, cardiac rehabilitation, and consultations with cardiologists.

Results: A total of 75868 patients (mean age, 68.8 years) were hospitalized for acute MI in Poland in 2018 (the admission rate, 197.0 per 100000 inhabitants). In-hospital mortality was 8.4%, while one-year mortality was 17.3% (one-year post-discharge mortality was 9.8%). Approximately 75% and 96% of discharged patients consulted a general practitioner, whereas 12% and 62% consulted a cardiologist, 5% and 19% underwent percutaneous coronary intervention, 0.6% and 2.9% underwent coronary artery bypass grafting, while 0.04% and 1.9% had an implantable cardioverter defibrillator implanted within 30 days and 365 days following discharge. The participation rate in cardiac rehabilitation within the first 14 days following discharge was 11%, within the first 30 days was 19%, and within 365 days was 35%.

Conclusions: In-hospital and post-discharge mortality is still high in Poland. The access to cardiac consultations and cardiac rehabilitation following MI is insufficient. There is considerable potential for a further decrease in mortality in patients suffering from MI in Poland.

Key words: cardiac rehabilitation, cardiovascular events, coronary artery disease, mortality, myocardial infarction

WHAT'S NEW?

We found that in 2018, 75 868 patients were hospitalized for acute myocardial infarction (MI) in Poland. This means a decrease compared to previously published estimates for 2012. The admission rate was 197.0 per 100 000 inhabitants: 255.2/100 000 among men and 142.5/100 000 among women. Among patients hospitalized for acute myocardial infarction in 2018, in-hospital mortality was 8.4%, while one-year mortality (counted starting from the admission to the hospital) was 17.3%, and one-year post-discharge mortality was 9.8%. These estimates are considerably lower compared to 2009–2010. Approximately 75% of discharged patients consulted a general practitioner, and 12% consulted a cardiologist within 30 days (37% within 90 days) following discharge. About 16% of MI survivors underwent percutaneous coronary intervention and 2.5% underwent coronary artery bypass grafting within the first 180 days, while 1.4% had an implantable cardioverter defibrillator implanted.

INTRODUCTION

Although mortality in patients with acute myocardial infarction (MI) has decreased substantially over the last few decades in many countries, MI remains the most serious complication of coronary artery disease [1, 2]. Several countries, including France, Japan, Korea, Poland, Sweden, and the United Kingdom have presented nationwide population-based studies [3–4]. The recent report from a countrywide population-based study analyzed the data of patients hospitalized for MI from 2009 to 2012 [3]. In addition, several reports analyzing subgroups of MI patients have also been published [2, 5–6]. Recently, an analysis of long-term outcomes of acute MI survivors was published [7]. There is convincing evidence of temporal changes in risk factor control as well in the invasive and non-invasive management of patients with MI in Poland since 2012 [8–9]. Therefore, the present study aimed to assess the number of patients hospitalized for acute MI in 2018 in Poland, in-hospital mortality, event-free survival following discharge, predictors of clinical events, and proportions of patients participating in cardiac rehabilitation programs and undergoing invasive cardiac procedures following discharge.

METHODS

We included all adult patients hospitalized for acute MI in Poland between January 1, 2018 and December 31, 2018 and reported to the National Health Fund database. We included all patients with reported ST-elevation MI, non-ST-elevation MI, and unspecified MI (see Supplementary material, *Table S1*). The study population consisted of patients who experienced acute MI for the first time during the study period, irrespective of a history of MI in the past. We analyzed only records of patients with Polish personal identification numbers (PESEL).

A patients' history was determined using data from the National Health Fund. A patient was coded as having a disease (e.g. diabetes or heart failure) if the disease was reported by any hospital or outpatient clinic to the National Health Fund database. The department classifications were based on the Polish Ministry of Health data. Survival was determined according to the national database of deaths (Central Statistical Office). Consultations with cardiologists and general practitioners and recurrent hospitalizations, including hospitalizations for acute MI, stroke, and invasive cardiac procedures, were determined using the National Health Fund database. Hospitalization was defined as admission to a health care facility lasting >24 hours unless the patient died within 24 hours. The index hospitalization for MI was defined as a continuous hospital stay, including all possible transfers between wards or hospitals for any reason until a patient's discharge home or death. If the time delay between hospital discharge and the subsequent admission for MI was ≤1 day, both admissions were considered due to the same MI.

Ethics committee approval was not needed as the authors analyzed the national database. Informed consent was not required.

Endpoints

The primary endpoint was defined as death from any cause, whereas secondary endpoints were (1) all-cause death or myocardial infarction or stroke; and (2) all-cause death or hospitalization for any cardiovascular disease.

Statistical analysis

Continuous variables are presented as means (standard deviations [SD]) or medians (interquartile ranges [IQRs]), while categorical values are presented as percentages with 95% confidence intervals (CI) when appropriate. The Shapiro-Wilk test was used to assess the normality. Normally distributed continuous variables were compared using Student's t-test. The Mann-Whitney U test was used in the case of variables without normal distribution. The Pearson $\chi 2$ test was applied to all categorical variables. A *P*-value of less than 0.05 was considered statistically significant. To calculate the admission rate for MI (number of admissions per 100 000 inhabitants) we used data provided by the Polish Central Statistical Office [10].

Multivariable, stepwise logistic analysis was used to assess factors independently related to in-hospital mortality. Kaplan-Meier methods were used to construct unadjusted survival curves for each outcome. Cox proportional hazard regression analysis was used to assess the independent predictors of the endpoints. Beginning with all the variables presented in Table 1, stepwise analysis was conducted

Table 1. Characteristics of the analyzed groups.

Variable	Number (%)
Age, years, mean (SD)	68.8 (12.0)
Sex	
Males, n (%)	47420 (62.7)
Females, n (%)	28266 (37.3)
Patients' history	
Hypertension, n (%)	55735 (73.6)
Diabetes, n (%)	23510 (31.1)
Atrial fibrillation, n (%)	9807 (12.6)
Previous stroke, n (%)	2358 (3.1)
Previous myocardial infarction, n (%)	5062 (6.7)
Previous PCI, n (%)	7982 (10.4)
Previous CABG, n (%)	640 (0.8)
Heart failure, n (%)	16675 (22.0)
Chronic kidney disease, n (%)	6345 (8.4)
Neoplasm in the history, n (%)	17058 (22.5)
Chronic obstructive pulmonary disease, n (%)	8283 (10.9)
Index hospitalization	
Coronary angiography, n (%)	66943 (87.9)
PCI, n (%)	54767 (72.4)
CABG, n (%)	3016 (4.0)
Department	
Cardiology, n (%)	65336 (86.3)
Internal medicine, n (%)	7437 (9.8)
Other, n (%)	2913 (3.8)

Values are presented as mean (standard deviation [SD]) or n (%)

Abbreviations: CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention

using the probability value <0.05. The statistics were calculated with STATISTICA 13 software (TIBCO Software, Palo Alto, CA, US).

RESULTS

A total of 75 868 patients (mean age, 68.8 [12.0] years) were hospitalized for acute MI from January 1, 2018 to December 31, 2018 in Poland, including 47420 men (mean age, 66.3 [11.6] years) and 28266 women (mean age, 73.1 [11.5] years). Admission rates due to myocardial infarction in Poland in 2018 in relation to age and sex are presented in Figure 1. In total, the admission rate was 197.0 per 100 000 inhabitants (255.2/100 000 among men and 142.5/100 000 among women). Overall, 86.3% of patients were hospitalized in a department of cardiology (Table 1).

Most patients were hospitalized in only one hospital (82.6%), while 14.8%, 2.4%, 0.3%, and 0.05% patients were hospitalized consecutively in two, three, four, and at least five hospitals. The median length of hospitalization was 6 (4–9) days, while the mean duration of hospitalization was 8.0 (8.8) days (median 6 [4–9] days). Invasive management (at least coronary angiography) was introduced in 87.9% of patients, percutaneous coronary intervention (PCI) in 72.4%, and coronary artery bypass grafting (CABG) in 4.0% of patients (Table 1).

In-hospital mortality was 8.4% (95% CI, 8.2%–8.6%) and 69 310 patients were discharged alive from the hospital. Figure 2 presents in-hospital mortality by age group. Mortality among patients hospitalized in a department of cardiology was 7.0 (6.8–7.2)%, among those hospitalized in departments of internal medicine the corresponding rate was 15.0 (14.2–15.8)%, and among patients hospitalized in other departments 22.9 (21.3–24.4)%; P <0.001. Among patients hospitalized in one hospital only, mortality was 8.1 (7.9–8.3)%, while among patients hospitalized consecutively in two, three, four, and at least five hospitals mortality was 9.1 (8.5–9.6)%, 14.4 (12.8–16.0)%, 13.7 (9.0–18.5)%, and 28.9 (13.8–44.1)%, respectively. Mortality was 6.4 (6.2–6.6)% in patients managed invasively and 22.9 (22.0–23.7)% in patients managed non-invasively (P <0.001), 6.6 (6.4–6.8)% in patients who underwent PCI, 6.8 (5.9–7.7)% in those who underwent CABG, and 5.7 (5.3–6.2)% in patients who

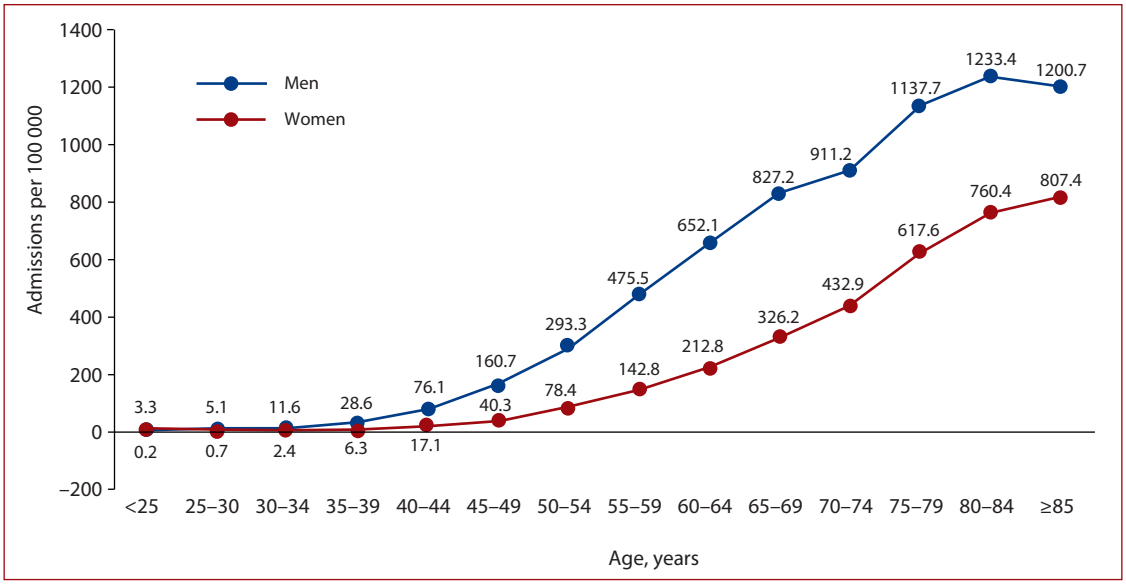

Figure 1. Crude admission rates due to myocardial infarction in Poland in 2018 in relation to age and sex

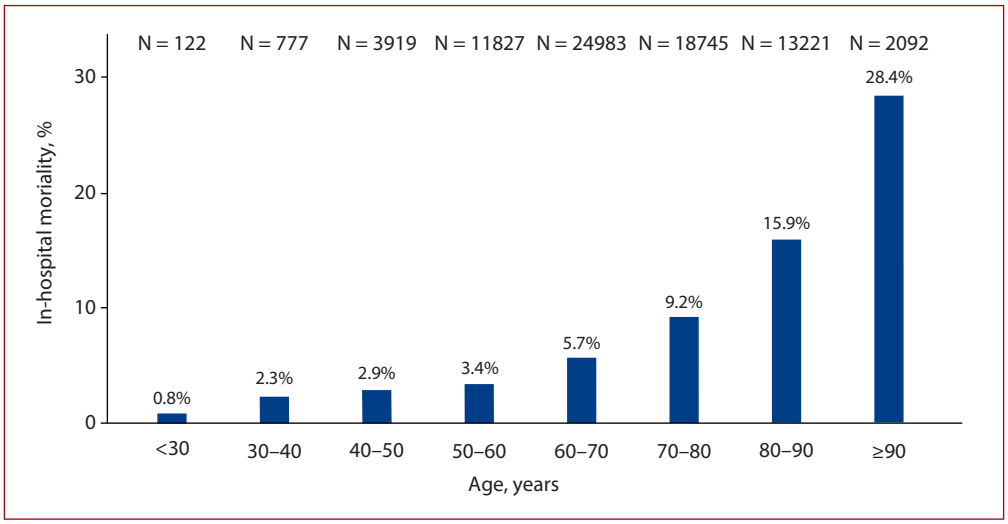

Figure 2. In-hospital mortality by age groups

Table 2. Factors independently related to in-hospital death (n = 75686)

Variable	OR (95% CI)
Age per 10 years	1.61 (1.57–1.65)
Hypertension	0.70 (0.66–0.75)
Diabetes	1.21 (1.14–1.28)
Previous stroke	1.43 (1.27–1.62)
Heart failure	1.24 (1.16–1.32)
Chronic kidney disease	1.31 (1.21–1.42)
Neoplasm in the history	0.78 (0.73–0.83)
Invasive management (at least coronary angiography)	0.40 (0.37–0.43)
Department	
Cardiology	0.37 (0.33–0.41)
Internal medicine	0.44 (0.39–0.49)
Other	1.00

Abbreviations: CI, confidence interval; OR, odds ratio

underwent coronary angiography only (without revascularization procedures). Supplementary material, *Figures S1* and *S2* present in-hospital mortality in patients managed invasively and non-invasively by age groups. Table 2 presents variables independently related to in-hospital mortality.

Overall, 5810 died during the observation period. In addition, the endpoint consisting of all-cause death, MI, or stroke occurred in 9253 patients, while the endpoint consisting of all-cause death or hospitalization for cardiovascular reasons occurred in 27100 patients. One-year all-cause mortality among patients hospitalized for MI (including in-hospital and post-discharge events) was 17.3 (17.0–17.6)%. Figure 3 presents the estimated event-free survival probability following discharge. The proportion of patients suffering from recurrent myocardial infarction within one year following discharge was 7.0 (6.8–7.2)%, the proportion of patients suffering from a stroke was 1.6 (1.5–1.7)%, and the proportion of patients hospitalized at least once for cardiovascular reasons was 40.4 (40.0–40.8)%. One-year death probability following discharge from hospital was 2.2 (1.9–2.6)% among patients aged <55 years, 5.0 (4.6–5.3)% among patients aged 55–65 years, 8.5 (8.1–9.0)% among patients aged 65–75 years, 15.5 (14.8–16.2)% among patients aged 75–85 years, and 27.4 (26.0–28.7)% among those aged ≥85 years. The corresponding proportions for endpoint consisting of all-cause death or MI or stroke were 6.6 (6.0–7.2)%, 10.6 (10.0–11.1)%, 15.0 (14.4–15.5)%, 21.9 (21.1–22.7)%, and 31.3 (29.8–32.7)%, respectively, while for endpoint consisting of all-cause death or hospitalization for any cardiovascular cause: 32.8 (31.7–34.0)%, 39.1 (38.3–40.0)%, 45.8 (45.0–46.6)%, 51.5 (50.5–52.5)%, and 53.3 (51.7–54.9)%. Supplementary material, *Figures S3–S5* present proportions of patients with MI, stroke, and patients hospitalized for cardiovascular reasons by age groups.

The independent predictors of the endpoints are presented in Table 3. About half of discharged patients consulted their general practitioners within 14 days following discharge, while 12% of patients consulted a cardiologist within 30 days following discharge (Figure 4). Overall, 0.06%, 0.14%, 0.27%, 0.33%, and 0.34% of the patients began telerehabilitation within 14, 30, 90, 180, and 365 days of discharge, respectively. The participation rate in any form of cardiac rehabilitation within first the 14 days following discharge was 11% and within the first 30 ways was 19% (Figure 4). In addition, 13% of MI survivors underwent PCI within the first 90 days following discharge, 2.5% underwent CABG within 180 days, and 1.9% had an implantable cardioverter-defibrillator implanted within 365 days following discharge (Figure 5).

DISCUSSION

This countrywide analysis included data on all patients hospitalized for acute MI in Poland in 2018. The main strength of our study is the fact that we analyzed all patients who had the Polish personal identification number and whose hospitalization for MI had been reported to the National

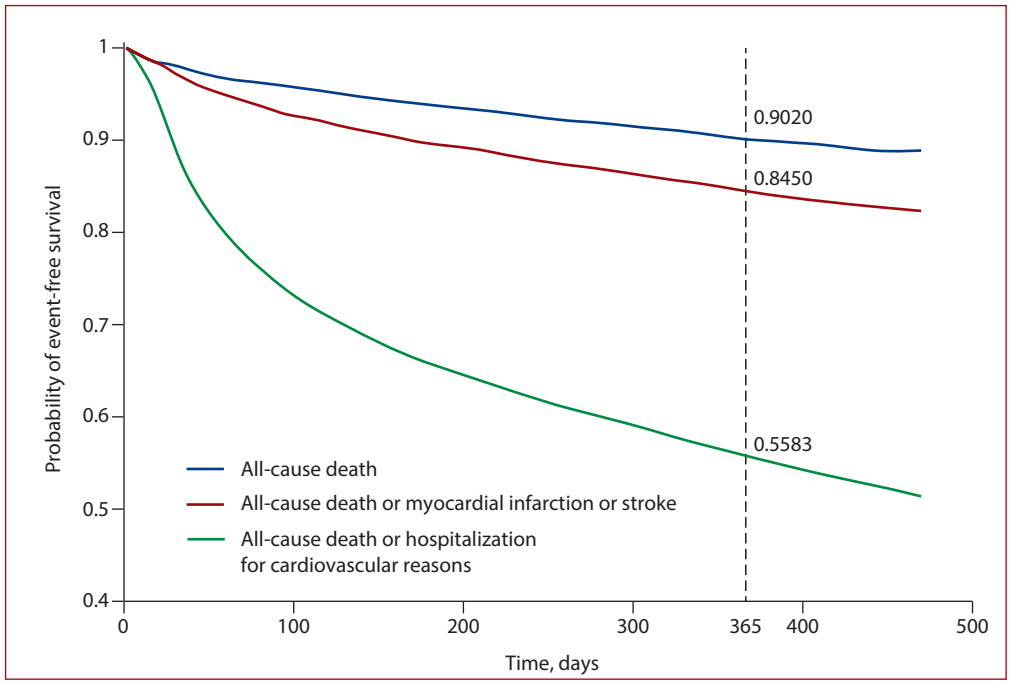

Figure 3. Kaplan-Meier curves displaying the estimated event-free survival probability

Table 3. Independent predictors of all-cause death, all-cause death or myocardial infarction or stroke, and all-cause death or hospitalization for cardiovascular reasons following discharge (n = 69310)

Variable	HR (95% CI)		
	All-cause death	All-cause death or myocardial infarction or stroke	All-cause death or hospitalization for cardiovascular reasons
Age per 10 years	1.62 (1.57–1.66)	1.34 (1.31–1.37)	1.13 (1.12–1.14)
Sex			
Female	1.0	1.0	1.0
Male	1.21 (1.14–1.28)	1.19 (1.14–1.25)	1.18 (1.15–1.21)
Hypertension	0.82 (0.76–0.88)	—	—
Diabetes	1.22 (1.15–1.29)	1.22 (1.17–1.28)	1.09 (1.06–1.12)
Atrial fibrillation	1.08 (1.01–1.15)	—	1.07 (1.03–1.11)
Previous stroke	1.61 (1.45–1.79)	1.60 (1.47–1.75)	1.15 (1.08–1.23)
Previous myocardial infarction	—	1.19 (1.09–1.29)	—
Previous PCI	—	1.15 (1.06–1.23)	1.08 (1.04–1.12)
Previous CABG	0.73 (0.55–0.97)	—	—
Heart failure	1.59 (1.49–1.69)	1.46 (1.39–1.53)	1.20 (1.17–1.24)
Chronic kidney disease	1.41 (1.32–1.52)	1.30 (1.23–1.38)	1.19 (1.14–1.24)
Neoplasm in the history	1.15 (1.09–1.22)	1.11 (1.06–1.16)	—
Chronic obstructive pulmonary disease	1.28 (1.19–1.37)	1.10 (1.04–1.17)	1.07 (1.03–1.11)
Invasive management (at least coronary angiography) during index hospitalization	0.60 (0.56–0.65)	0.65 (0.61–0.69)	0.82 (0.78–0.85)
PCI during index hospitalization	0.68 (0.64–0.73)	0.87 (0.83–0.92)	1.08 (1.05–1.12)
CABG during index hospitalization	0.51 (0.42–0.61)	0.58 (0.50–0.67)	0.79 (0.74–0.85)
Hospitalization in a department of cardiology	0.52 (0.48–0.59)	0.67 (0.61–0.73)	0.85 (0.82–0.88)
Hospitalization in a department of internal medicine	0.68 (0.61–0.76)	0.84 (0.76–0.93)	—

Abbreviations: CABG, coronary artery bypass grafting; HR, hazard ratio; PCI, percutaneous coronary intervention; other — see Tables 1 and 2

Health Fund database. We found that in 2018, 75 868 patients were hospitalized for acute MI in Poland. This means a decrease in the number of patients hospitalized for MI by 3532 (about 4.4%) compared to 2012 [3]. Several possible factors may have led to a reduction in the number of patients admitted for MI: the revised definition of MI, changed habits of physicians in diagnosing and reporting MI, an increase in the prescription rate of cardiovascular drugs in patients with established coronary artery disease, as well as improvements in the control of main cardiovascular risk factors in the general Polish population [11–15]. A gradual decrease in the admission rates for MI in Poland from 2009 to 2012 was shown previously [3]. We could not analyze patients who died outside the hospital due to MI,

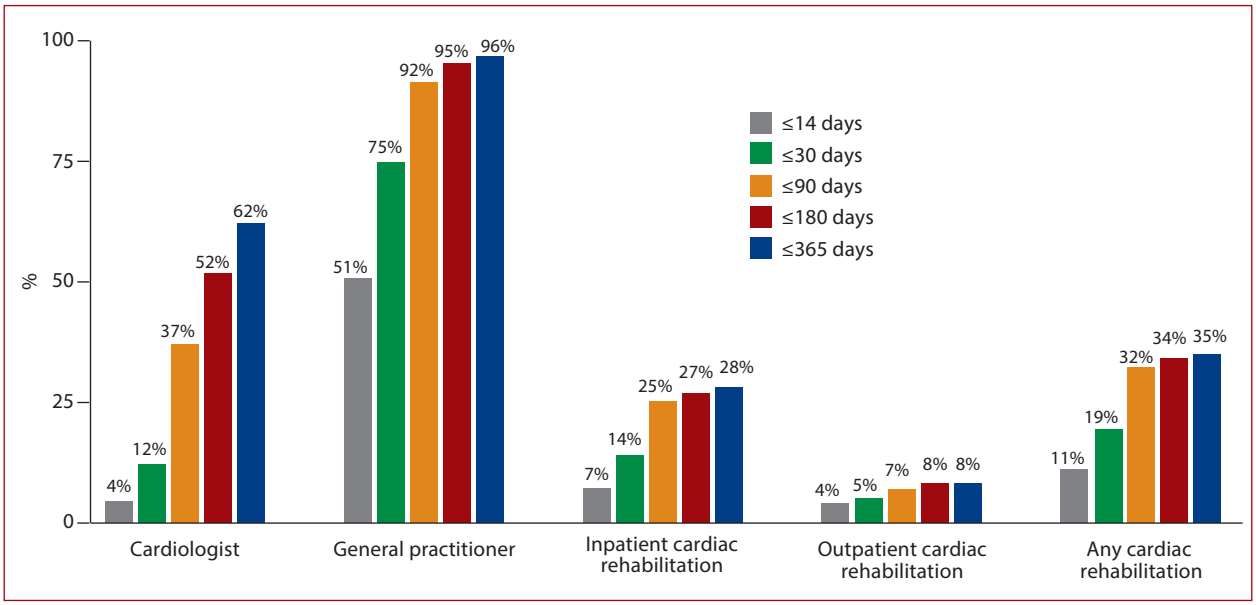

Figure 4. Cumulative proportions of patients consulted by a cardiologist, a general practitioner, and starting a cardiac rehabilitation programme by number of days following discharge

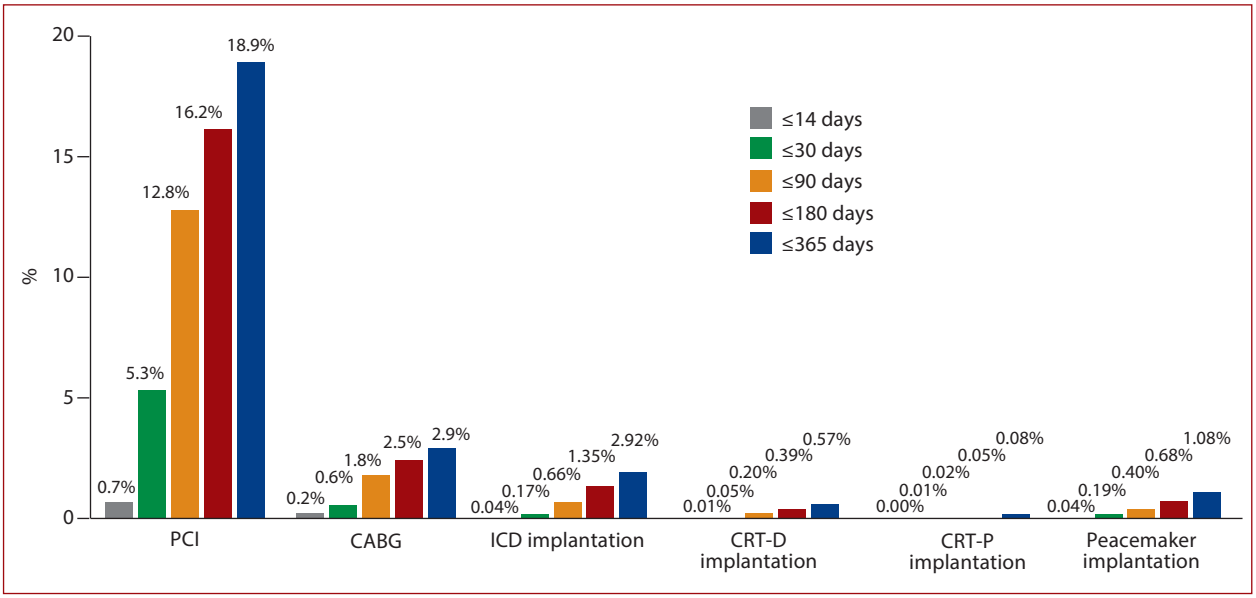

Figure 5. Cumulative proportions of patients undergoing selected invasive procedures by number of days following discharge

Abbreviations: CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; ICD, implantable cardioverter defibrillator; CABG, coronary artery bypass grafting; PCI, Percutaneous coronary intervention

before their admission to the hospital. The proportion of patients who died outside the hospital due to MI among all cases of MI in 2012 was estimated to be 6.6% [3]. If we apply this figure to our data, we could estimate the number of patients suffering from MI in 2018 to be about 81250. The admission rates increase with age in men and women, but the increase was steeper in women, although the admission rate was higher among men in every age group. These relations agree with the previous findings [3].

In-hospital mortality among patients hospitalized for MI was 8.4% in 2018. This estimate is considerably lower compared to 2009–2010 [3, 13]. This reduction may be due to improvements in the management of patients with acute MI, including an increase in the proportion of patients undergoing coronary angiography (from 72.5% in 2009 to 87.9% in 2018), percutaneous coronary intervention (from 59.1% to 72.4%), and coronary artery bypass grafting (from 1.9% to 4.0%) [3]. Other factors, such as progress in the pharmacotherapy of MI patients or better organizational standards of pre-hospital and in-hospital medical care, may also have played a significant role [12, 13].

The diagnosis of hypertension was not related to increased mortality in our analysis. The previous scientific evidence is contradictory: some studies show increased

risk among postinfarction patients with hypertension, some show no significant association between hypertension and mortality, while some analyses show even higher mortality among patients with low blood pressure [14–15]. It is possible that in some cases the lack of diagnosis of hypertension may be a marker of heart failure or other systemic, severe disease. Age, sex, diabetes, atrial fibrillation, stroke, heart failure, chronic kidney disease, chronic obstructive pulmonary disease, management in the acute phase of MI, and hospitalization in cardiology and general medicine departments were all independently related to the risk of the endpoints.

The estimate for 2009 suggested one-year mortality following discharge at a level of 10.1% [3]. We found one-year all-cause mortality to be slightly lower, although the cohort of MI survivors in 2018 was approximately 1.4 years older compared to patients discharged in 2009 and 2010 [13]. Although the prescription rate for cardiovascular drugs in patients with established coronary artery disease increased a high proportion of patients following MI still have cardiovascular risk factors uncontrolled [15, 16]. Indeed, only 2.3% of patients with coronary artery disease, including those after MI, had all the main risk factors well-controlled [24]. Furthermore, a significant increase has been observed in the proportion of coronary patients with obesity and diabetes in Poland [17]. Moreover, most patients still do not participate in cardiac rehabilitation programs, and only 37% of MI survivors consulted a cardiologist within 90 days of their discharge. It has been shown that patients who consulted a cardiologist have a lower risk of death compared to those consulted by a general practitioner alone [18].

The main healthcare payer in Poland is the National Health Fund. In the case of hospitalizations and procedures related to acute MI treatment, the National Health Fund is virtually the only payer that signs contracts with public and private healthcare providers. Therefore, the underestimation of the number of patients hospitalized for MI is not probable. On the other hand, some post-infarction patients could consult cardiologists omitting the National Health Fund system. Indeed, every tenth patient hospitalized for coronary artery disease consulted a cardiologist after discharge from the hospital [19].

Importantly, the recently launched MAnaged Care for Acute Myocardial Infarction Survivors (MACAMIS) system has been accompanied by increased access to early cardiac rehabilitation (odds ratio of starting cardiac rehabilitation within the first 14 days following discharge was 16.89), cardiac consultations (odds ratio of cardiac consultation within first 6 weeks following discharge was 7.28), and a lower risk of death and cardiovascular events [20, 21]. The improved concordance could also improve the MI survivors' prognosis. Our results suggest considerable potential for a further decrease in mortality in patients suffering from MI in Poland.

Limitations

The present analysis has some limitations. Firstly, this is a cohort study. Hence, only a statistical association rather than any causal relationships could be confirmed. Secondly, we were unable to analyze patients' lifestyles or the prescription rates for cardioprotective drugs. The inclusion of such data in the present analysis could have increased the impact of our results. Thirdly, we had no access to data on the utilization of fibrinolysis in the acute phase of myocardial infarction. However, the proportion of patients with acute MI administered fibrinolysis in 2009 in Poland was 1% [3]. One could expect an even lower proportion in 2018 as the utilization of invasive management increased significantly. Finally, the present results are based on the robustness of the public databases we used. Moreover, the database used in this study was an administrative registry, created mainly to reimburse medical procedures, which provided a limited number of clinical variables available for analysis. The diagnoses of MI and co-morbidities were not externally verified. In addition, we had no access to data on migration. Some patients may have emigrated from Poland and were lost to follow-up. On the other hand, a major advantage of the present study is the analysis of a large, nationwide database covering virtually all patients hospitalized for MI in 2018 in Poland. Thus, the data regarding therapy, readmissions, and deaths provide a summary of current everyday clinical practice and its outcomes.

CONCLUSION

The in-hospital and post-discharge mortality in patients suffering from MI in Poland, though lower than in the first decade of the 21st century, is still high. Access to cardiac consultations and cardiac rehabilitation following myocardial infarction is insufficient. There is considerable potential for a further decrease in mortality in this population of patients.

Supplementary material

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

Article information

Conflict of interest: None declared.

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Comparison of fusion imaging and two-dimensional angiography to guide percutaneous pulmonary vein interventions

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INTRODUCTION

Primary and acquired pulmonary vein (PV) stenoses comprise a group of complex conditions often requiring numerous interventions in early childhood [1]. Despite advancements in surgical techniques, often repeated transcatheter interventions are common in this patient population [2]. Balloon dilation has demonstrated limited long-term efficacy, whereas stent implantation requires repeat dilations to match somatic growth or in-stent restenosis [3].

Modern angiographic imaging platforms allow three-dimensional (3D) guidance with a fusion of transesophageal echocardiography or pre-operative datasets like computed tomography (CT) and magnetic resonance imaging [4–6]. Early experiences showed promising reductions in contrast and radiation dose, fluoroscopy, and study times [7, 8].

We report our initial experience with fusion imaging (FI) to guide percutaneous PV interventions, and we compare FI and PV interventions that use traditional 2D angiography.

METHODS

A retrospective review of the institutional database was performed to identify all patients who underwent percutaneous PV interventions. The study protocol was approved by the institutional review board (no. 19-2892) and patients' guardians provided written informed consent to participate in the study. Patient demographics including catheterization risk score for pediatrics (CRISP) and the risk for severe adverse events, pre-procedural cross-sectional imaging, and catheterization data were collected.

Computed tomography scans were performed as a routine diagnostic workup according to the standard institutional protocol for the visualization of PV. Therefore, radiation and contrast dose-related to CT imaging were not included in this analysis as patients would have been exposed to it regardless of whether scans were reutilized during cardiac catheterization.

The application of fusion software (VesselNavigator, Philips Healthcare, Eindhoven, The Netherlands) was described in detail elsewhere [9]. Briefly, it includes 4 steps: (1) segmentation of a previously obtained 3D dataset; (2) labeling key anatomy with marking rings/points, taking measurements, and saving optimal angulations; (3) registration of fluoroscopy with the labeled 3D reconstruction, and finally (4) guidance of the procedure with the 3D roadmap overlaid in the anterior-posterior plane (monoplane) and presented in one of several rendering modes.

Patients who underwent fusion of pre-catheter CT scans (available for the last 9 months of the studied period) for procedural guidance were matched (1:1) to those with standard 2D angiography. The following parameters were used for matching: the body surface area, a type of intervention (balloon dilation ± stent implantation), the number of treated veins. All matched patients had inter-atrial communication, hence there was

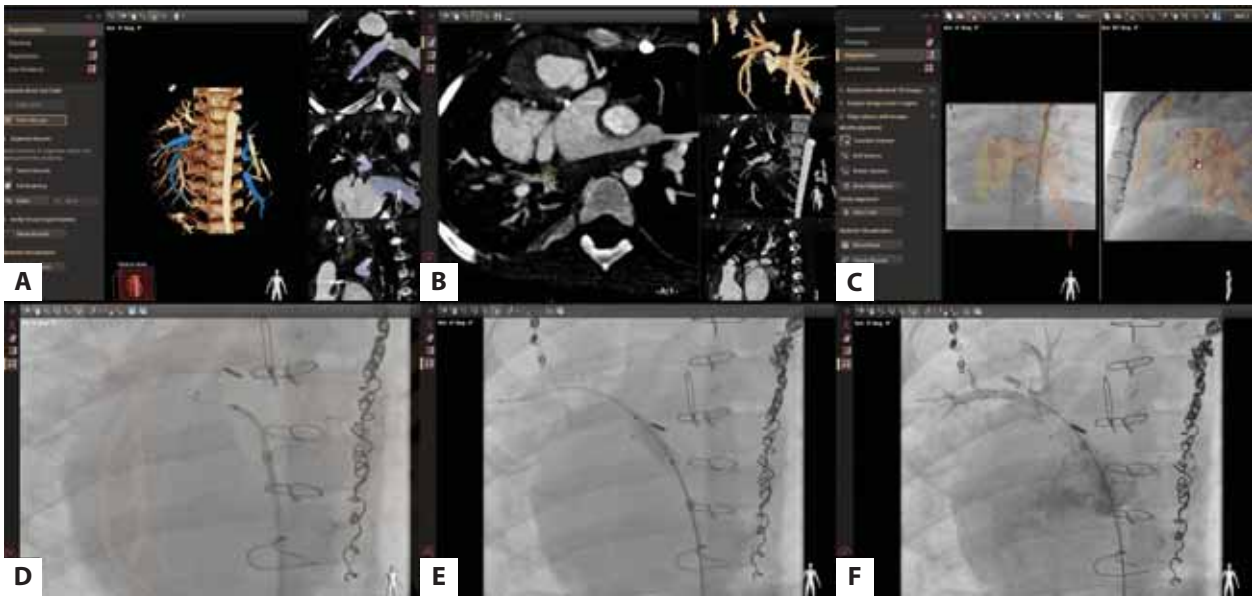

Figure 1. Fusion imaging for percutaneous pulmonary vein recanalization and stenting. VesselNavigator (Philips Healthcare, Eindhoven, The Netherlands) assisted the segmentation of contrast computed tomography scan (**A**). Pink and green marking points were placed to highlight the track between the left atrium and the right upper pulmonary vein (**B**). Previously placed coils were used for the registration of the 3D volume with stored fluoroscopy in two perpendicular projections (**C**). Three-dimensional reconstruction with marking points was used to guide pulmonary vein perforation and subsequent stent implantation (**D–F**)

no need for trans-septal puncture. The procedural time was calculated from the moment of vessel cannulation to sheath removal. Registration of fluoroscopy and 3D roadmap was performed after obtaining vessel access, during the setting up of the isocenter.

Statistical analysis

Analyses were performed using JMP Pro 13.0 (SAS Institute, Cary, NC, US). Data are reported as number and percentage for qualitative values and median (interquartile range) for quantitative values. All comparisons were performed using the Wilcoxon-matched pairs signed-rank test. The *P*-value <0.05 was considered significant.

RESULTS AND DISCUSSION

Over a period of 18 months, 24 patients with PV stenosis underwent 64 catheterizations: 8 diagnostic and 56 interventional. Fusion imaging was utilized during 7 interventional catheterizations (Figure 1). One case of radiofrequency PV perforation with FI was excluded from further analysis due to the lack of a matching example in the 2D group. There were no significant differences between those with 2D guidance (n = 6) and FI (n = 6) in terms of body surface area (median 0.38 vs. 0.4 m^2; *P* = 0.81), weight (7.5 vs. 7.8 kg; *P* = 0.99), or age (13.5 vs. 19 months; *P* = 0.625) (Supplementary material, *Table S1*). There were no differences in the CRISP score (11 vs. 10 points; *P* = 0.56) or the risk for severe adverse events (14.4 vs. 14.4 %; *P* = 0.99). All patients in each group underwent balloon dilation, with 3 patients in each group having additional stent implantation. Using FI resulted in lower contrast utilization (3.7 vs. 2.4 ml/kg, decrease of 31.5%; *P* = 0.22) and radiation exposure (Air kerma: 288 vs. 53 mGy, decrease of 82%; *P* = 0.22; Dose area product: 8852 vs. 1020 mGy × cm^2, decrease of 88.5%; *P* = 0.31). Fluoroscopy (71 vs. 52 min, decrease of 27%; *P* = 0.44) and total study times (256 vs. 165 min, decrease of 35.5%; *P* = 0.22) were also shorter in the cases guided with FI. However, the obtained differences were not statistically significant.

Percutaneous treatment of PV remains a challenging task requiring repeated anesthesia, contrast, and radiation exposure in the most vulnerable early stages of life [2, 3]. In addition to evolving transcatheter techniques and the availability of improved equipment, efforts have been made to improve non-invasive imaging for diagnosis and follow-up of PV stenosis [1]. Computed tomography provides precise information for diagnosis and procedural planning of PV interventions; however, it comes at a cost of exposing patients to radiation and contrast. Re-utilization of CT 3D data sets might allow reduction of the number of diagnostic 2D angiographies and, consequently, lower radiation and contrast usage during cardiac catheterization.

Until recently 2D imaging was the gold standard for the guidance of PV interventions. We have applied our experience in 3D guidance for cardiac catheterization in various congenital heart defects to PV interventions to reduce the catheterization burden to the patients [8–10]. Our initial, limited experience shows a possibility for lower contrast utilization and radiation exposure and shorter fluoroscopy and study times with the FI guidance compared to 2D angiography. Larger patient groups may allow us to determine if these differences are statistically significant.

Supplementary material

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

Article information

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The use of remote monitoring of patients with cardiac implantable electronic devices in Poland

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INTRODUCTION

Remote monitoring (RM) of patients with cardiac implantable electronic devices (CIED) allows physicians to regularly gather detailed information concerning the functioning of the devices, without the necessity for patients to present for an in-person examination (IPE) [1]. With the use of RM, vital parameters, such as the arrhythmia burden, pacing percentage, or thoracic congestion indicators, already proven to predict heart failure decompensation and worsen the patient's prognosis, can be routinely measured, and an appropriately timed response can be initiated. The recent guidelines of the European Society of Cardiology on cardiac pacing and resynchronization have introduced three recommendations regarding the use of RM in patients with CIEDs, including, for the first time, the possibility of increasing the periods between IPEs up to 24 months if the patient is monitored remotely [2]. Despite such recommendations, RM of patients with CIEDs in Poland is used in the minority of facilities, although exact data regarding this issue are not available. The purpose of this analysis was to investigate the implementation of RM in patients with CIEDs in Poland at the beginning of the third decade of the 21st century.

METHODS

The survey consisting of six brief either single- or multiple-choice questions was dispatched with the support of the Biotronik Polska (Poznań, Poland) among all electrotherapy centers which were on the correspondence list of the company in Poland between July and August 2021. The questions were designed to assess the utilization of RM, causes for the lack of its implementation, and perspectives of its initiation. The detailed survey can be found in the Supplementary material. Fifty centers sent their responses from 50. Approval of an ethics committee was not required for this analysis.

Statistical analysis

The data have been summarized and presented as absolute and relative frequencies.

RESULTS AND DISCUSSION

Of 50 centers that answered the questionnaire, 48% performed more than 300 procedures per year, while 36% between 100 and 300, as presented in Table 1. Among the 50 centers, 14 (28%) used RM; 57.1% used it for more than 5 years, while 28.6% introduced RM in the last 1–5 years. The primary form of RM utilization was as an addition to the conventional approach, as 50% of centers maintained the routine schedule of IPEs, and 42.9% of centers prolonged the periods between the consecutive IPEs if the patient was monitored remotely. Only in one center, RM was used as an equivalent of the conventional approach, and patients did not present for routine IPEs. In 72% of centers, RM was not used. The primary reasons for not implementing RM were the feasible generation of additional workload (94.4%) and lack of RM reimbursement (88.9%), while other reasons that were chosen much less frequently included legal uncertainties or no scientific evidence of RM effectiveness. Finally, 58.1% of respondents declared that their centers would introduce RM when its reimbursement was introduced, while 25.8% declared no such intention.

Although the IN-TIME randomized trial, as well as the TRUECOIN meta-analysis, which included IN-TIME and two other large ran-

Table 1. The answers to the survey regarding the use of RM in patients with CIEDs

Question		Number, n (%) of total (n = 50), if not indicated differently
Use of RM of CIEDs within the facility	Yes	14 (28)
	No	36 (72)
Duration of using RM	More than 5 years	8/14 (57.1)
	1–5 years	4/14 (28.6)
	Less than 1 year	2/14 (14.3)
The form in which RM is used	Patients attending IPEs as often as without RM	7/14 (50)
	Patients attending IPEs visits less frequently than without RM	6/14 (42.9)
	Patients not attending FU visits	1/14 (7.1)
Reasons for not using RM (may be more than one)	Lack of reimbursement	32/36 (88.9)
	Uncertainties from the legal point of view	3/36 (8.3)
	Generation of additional workload	34/36 (94.4)
	Unawareness of RM possibility	1/36 (2.8)
	Lack of sufficient evidence supporting RM	1/36 (2.8)
Number of electrotherapy procedures (implantations/replacements/lead extractions) performed per year	More than 300	24 (48)
	From 100 to 300	18 (36)
	Less than 100	8 (16)
If reimbursement is introduced in Poland will RM be implemented in your center (for centers not using RM)?	Yes	18/31 (58.1)
	No	8/31 (25.8)
	Maybe	5/31 (16.1)

Abbreviations: CIED, cardiac implantable electronic device; IPE, in-person examination; RM, remote monitoring

domized trials, demonstrated the survival benefit of daily RM transmissions over conventional IPEs, the data on the improvement of outcomes with RM are conflicting [3, 4]. In Poland, the randomized trials demonstrated a reduction in the combined endpoint of all-cause mortality and hospitalization for cardiovascular reasons in patients with implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy-defibrillator (CRT-D) monitored remotely [5], while in another single-center trial, the number of hospitalizations for progression of HF and all-cause death in patients with CRT was reduced with the use of multiparameter RM [6]. Therefore, it can be assumed that with the introduction of more advanced algorithms and technologies, including synchronising devices with patients' smartphones instead of the presently used transmitters, the number of patients monitored remotely might increase.

Nonetheless, the results of the European Heart Rhythm Association (EHRA) survey conducted in 2015 demonstrated that in 43 centers that responded to the questionnaire, RM was available in 74% of patients with ICD, 69% of patients with CRT, and only 22% of patients with a pacemaker [7]. In our survey, which did not assess the type of devices, RM was not used in 72% of centers, with the most frequent causes being concern about generating additional workload and the lack of RM reimbursement. It has been demonstrated that the mean (standard deviation [SD]) annual workload for every patient monitored remotely is approximately 1.1 (0.15) hours, and in the recent analysis of the large cohort, more than 50% of patients transmitted at least 1 alert during one year [8, 9]. Therefore, with no doubt, in the case of RM introduction, there is a great need to create dedicated facilities with established workflows to effectively monitor patients and properly identify those in the greatest need of a rapid clinical reaction.

In 2018, the Polish Agency for Health Technology Assessment and Tariff System (AOTMiT) positively recommended the reimbursement of RM in patients with ICD or CRT-D, giving the green light for wider adoption of RM in the Polish electrotherapy facilities [10]. However, since then, no reimbursement has been introduced, which according to our survey, is one of the most important obstacles for RM implementation. The results from the SILCARD registry demonstrated that during the three-year follow-up, the RM of patients with ICD and CRT-D resulted in a median cost reduction of 33.5%, which was more prominent in patients with a CRT-D (P <0.001) [11]. In the Health Technology Assessment report of the Health Quality Ontario, the estimated cost reduction achieved with RM could be approximately $14 million during the first five years of its use [12]. Therefore, apart from a probable improvement in patients' outcomes, reimbursement and wide adoption of RM could result in large savings for the national healthcare provider.

The primary limitation of our study is that it reflects the experiences of a fraction of electrotherapy facilities in Poland, as only 50 centers responded to the survey. Moreover, the lack of differentiation between types of devices prohibits generalizing the data to different device types. Such differentiation is important as the frequency of remote transmissions and the contents of the alert transmissions could vary depending on the type of the device, therefore generating different workloads for monitoring centers. Finally, the article describes the overall utilization of RM in the Polish electrotherapy facilities; however, the detailed

characteristics of the motivation for RM introduction were not evaluated. For instance, in some facilities RM could have been introduced as a result of a device recall. That means that the decision to introduce RM was not prompted by the facility's interest in RM but by the necessity to monitor the possibly malfunctioning device more closely.

In conclusion, our study demonstrates that only a minority of centers in Poland use RM of patients with CIEDs, and the primary barriers for its wider implementation are concerns about additional workload and lack of RM reimbursement.

Supplementary material

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

Article information

Conflict of interest: MT: scientific consultations for Boston Scientific, Biotronik, Abbott, Medtronic. MD: lecture honoraria from Biotronik. MG: lecture and consultations honoraria from Biotronik, Medtronic, Abbott, Boston Scientific. JK: educational support (course fees) from Biotronik. MN is an employee of Biotronik Polska; MG: none declared.

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Genotype-phenotype correlations in Polish patients with hypertrophic cardiomyopathy: Preliminary report

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INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is commonly defined by the presence of increased left ventricular (LV) wall thickness which cannot be explained by abnormal loading conditions such as arterial hypertension and/or aortic valve stenosis. The prevalence of HCM is 1:500, which makes it one of the most common genetic cardiological diseases [1]. According to the literature, the isolated form of HCM is most often caused by the occurrence of pathogenic variants in genes encoding sarcomere proteins. Until now around 1500 pathogenic variants in 11 genes encoding sarcomere proteins were identified [2]. In this report, we present the clinical characteristics and the results of genetic testing of HCM patients diagnosed and treated in the 3rd Department and Clinical Department of Cardiology, the Silesian Center for Heart Diseases.

METHODS

Forty-eight consecutive patients with HCM were recruited during their routine follow-up visit in the 3rd Department of Cardiology, the Silesian Center for Heart Diseases in Zabrze. Blood for biochemical analyses was collected after 8–10 hours of fasting; additionally, blood for genetic analyses was secured and stored in –80°C. The family history of each patient was collected in detail. Two patients were excluded because the diagnosis of HCM was negatively verified. The HCM sudden cardiac death risk score (HCM SCD risk score) was calculated for all patients [1]. Information regarding genetic and bioinformatics analysis is presented in Supplementary material.

Statistical analyses

Fisher's exact test was used for detection of differences between categorical variables, whilst the Kruskal-Wallis test was used for detection of differences between continuous variables. The Dunn test was used as a *post hoc* test for the Kruskal-Wallis test. Two-sided *P*-value <0.05 was considered statistically significant for all comparisons, except for the *post-hoc* test where the Bonferroni correction was used. Continuous variables were reported as medians and interquartile ranges, categorical variables were reported as counts and percentages. Statistical analyses were carried out in R software [3].

RESULTS AND DISCUSSION

We were able to identify the pathogenic/likely pathogenic variants associated with the occurrence of HCM in 15 (32.6%) patients. We have also found 16 additional variants that were classified as VUS (variant of uncertain significance). Interestingly 7 (44%) of those variants were predicted to have a significant damaging effect on coded protein by both SIFT and PolyPhen-2 prediction algorithms (PolyPhen-2 score ≥0.74 and Sift score ≤0.04).

Table 1. Clinical characteristics of the study population, and variants identified as disease-causing in the studied population

	Pathogenic/likely pathogenic variant positive (n = 15)	Variant of uncertain significance (n = 16)	No identified pathogenic/VUS variant (n = 15)	*P*-value
Age, years, median (IQR)	51 (37–59)	58 (46–68)	55 (40–65)	0.15
Male gender, n (%)	9 (60)	8 (50)	9 (60)	0.81
Heart failure, n (%)	9 (60)	9 (56)	7 (47)	0.81
Alcohol ablation or myectomy of IVS, n (%)	1 (7)	3 (19)	2 (13)	0.86
Implantable cardioverter defibrillation, n (%)	6 (40)	5 (33)	5 (33)	0.93
Atrial fibrillation, n (%)	6 (40)	6 (38)	2 (13)	0.23
Ventricular tachycardia, n (%)	7 (47)	5 (31)	4 (27)	0.54
HCM-SCD risk score, median (IQR)	5.7 (4.5–9.4)	3.4 (2.1–7.1)	3.7 (2.3–5.4)	0.15
NT-proBNP, pg/ml, median (IQR)	906 (177–1651)	657 (404–1025)	349 (139– 959)	0.25
Max. thickness of LV, mm, median (IQR)	20 (17.5–21)	19.5 (16–21.3)	18.0 (15.5–21)	0.55
LVOT Vmax (Valsalva), mm Hg, median (IQR)	9 (5–68)	15 (6–63)	22 (10–43)	0.73
Identified pathogenic/likely pathogenic variants (n = 15)				
Gene symbol	**Gene name**	**Identified variants**		
MYBPC3	Myosin-binding protein C	Transcript: NM_000256.3 c.3490+1G>T[a] (2), c.3697C>T[a], c.821+1G>A[a], c.3040delC[a], c.3407_3409delACT[b], c.2449C>T[b] (2×)		
MYH7	Myosin 7	Transcript: NM_000257.3 c.2555T>C[1], c.5135G>A[a], c.2011C>T[b]		
MYL3	Essential myosin light chain 3	Transcript: NM_000258.2 c.170C>G[b],		
TNNI3	Troponin I3	Transcript: NM_000363.5 c.407G>A[a]		
TNNT2	Troponin T	Transcript: NM_000364.3 c.311G>T[a]		
RYR2	Ryanodine receptor 2	Transcript: NM_001035.2 c.1069G>A[c]		

[a]Reported as pathogenic and/or likely pathogenic by multiple sources; [b]Reported as pathogenic and/or likely pathogenic and as VUS with *in-silico* analyses predicting damaging effect and/or functional studies; [c]Variant pathogenic for CPVT, we cannot exclude that this is not a causative variant of HCM. Dichotomous variables are presented as counts and percentages. Values are presented as the median and interquartile range (IQR)

Abbreviations: HCM, hypertrophic cardiomyopathy; IVS, interventricular septum; LVOT, left ventricular outflow tract; LVOTO, left ventricular outflow tract obstruction, VUS, variant of uncertain significance

There were no significant differences in clinical characteristics between the groups. There was, however, a trend toward a higher HCM SCD risk score in patients with pathogenic/likely pathogenic variants (Table 1).

HCM is one of the most common cardiomyopathies. Despite this, only in 40%–60% of patients, it is possible to identify the variant responsible for the disease [1]. The reason why it is not possible to identify causative variants in a large proportion of patients may be due to the involvement of other genes not yet identified as associated with HCM. Oligo- or even polygenic inheritance may be another cause. In rare cases, copy number variations, microdeletions, as well as incorrect classification of myocardial hypertrophy as HCM, may be the reason [4, 5].

The most common pathogenic/likely pathogenic variants responsible for the occurrence of HCM in our population were identified in genes encoding proteins of the sarcomere, in particular, *MYBPC3* and *MYH7*. This is consistent with the results of genetic testing of HCM patients in other populations [2, 4]. Our data suggested a possible relationship between a higher risk of SCD assessed using the HCM SCD risk score [1, 6] in patients with a confirmed pathogenic variant. This may reflect observations from other cohorts that in patients with identified causative variant the disease tends to have a more aggressive course [5]. The frequency of alcohol ablation or surgical myectomy was similar in both groups. Similar results were reported by Loar et al. [5]. In general, genotype-phenotype correlations in patients with HCM are modest [7, 8]. Interestingly in one case, we found a variant in the *RYR2* gene pathogenic for catecholaminergic ventricular tachycardia (CPVT) and not HCM. We did not find any other variants in this patient in genes typically associated with HCM. This patient was burdened with recurrent ventricular arrhythmias and his HCM-SCD risk score was calculated to be 24.7. In literature, *RYR2* variants were reported as a possible rare cause of HCM [9, 10]. The pathogenic variant in this gene was also proved to be associated with the HCM phenotype in animal studies [11]. Nonetheless, this variant will be subjected to segregation analysis, and we will try to carry out whole-exome sequencing in this patient.

CONCLUSIONS

In the studied population, we identified variants that might be responsible for the phenotype in 33% of patients. Fur-

ther analysis is required to assess the potential pathogenicity of identified VUS found in 35% of cases.

Supplementary material

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

Article information

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Conflict of interest: None declared.

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Psychological burden of the COVID-19 pandemic 6 months after the outbreak — the voice of the young doctors' generation: An international survey

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INTRODUCTION

Young doctors have made up a substantial part of the healthcare workforce during the COVID-19 pandemic [1–3]. Given their lower level of professional experience, redeployment, frequent exposure to COVID-19 patients, and unpredictable course of the infection in this age group, young doctors seem to be particularly vulnerable to psychological disorders in this context [1–3]. Despite actual threats and potential long-term consequences on their future clinical practice, the emotional impact of COVID-19 on young doctors has not been investigated.

The main aim of the study was to assess the rate and level of anxiety, depression, and stress among young doctors working clinically during the pandemic and to define the risk factors for this psychological distress.

METHODS

This was an international, cross-sectional cohort study performed as a survey between September and November 2020. The survey was dedicated to young doctors, at or below the age of 40. For detailed information about participating countries and numbers of participants see Supplementary material,

Figure S1. The survey was structured in 5 domains. See Supplementary material, *Table S1* for the full list of questions.

Potential risk factors for psychological suffering included demographics, direct contact with COVID patients, redeployment, change in salary or work hours, work organization, prior training in protective measures, and the chance to influence the work organization (Supplementary material, *Tables S2–S3*).

Psychological distress was assessed with the Hospital Anxiety and Depression Scale (HADS) and Perceived Stress Scale 10 (PSS-10) [4, 5]. The cut-off values were >13 for HADS and >14 for PSS-10 based on the previous literature [4–7].

All data were entered into a SurveyMonkey platform, a secure data capture web-based application. Participation in the survey was voluntary. Access to questions was only granted if informed consent was completed and no sensitive information was requested. The data were anonymized at the level of the questionnaire.

Statistical analysis

Categorical variables were expressed as numbers and percentages. Continuous variables were presented as mean and standard deviations or median and interquartile range (IQR) for Gaussian and non-Gaussian distribution, respectively. Comparative analyzes between prespecified subgroups of the study population were performed with the U Mann-Whitney, Kruskal-Wallis ANOVA, and the Fisher exact tests or the χ^2 test. Logistic regression analyzes were performed to define predictors of depression/anxiety, and stress. Variables significantly associated with outcomes in univariable analyzes entered multivariable logistic models with stepwise backward elimination. The *P*-value <0.05 was considered statistically significant. Statistica 13.1 (TIBICO Software Inc., 2016) was used for analyses.

The study was approved by the National Healthcare Service Health Research Authority (NHS HRA) and Care Research Wales (HCRW) (IRAS ID 287542, REC reference:20/HRA/3845). The study was performed in accordance with the Declaration of Helsinki for research with humans.

RESULTS AND DISCUSSION

A total of 1186 young doctors from 62 countries participated in the survey (Supplementary material, *Figure S1*). The median age of these respondents was 32 (28–39) years; with 675 (44.5%) being females.

Among the respondents, 73.47% managed COVID-19 patients; however, only 59.1% of young doctors reported being provided with full personal protective equipment (PPE). Training in donning and doffing of PPE was provided to only 53.04% of young doctors and only 48.5% had daily briefings to plan work on COVID units. Importantly, 52.78% of young doctors were redeployed. Work hours increased for 61.32% of the respondents, including more night shifts. Despite the increased workload, the salaries did not change for 71.6% and even decreased for 16% of those who managed COVID-19 patients (Supplementary material, *Table S2*).

The median level of HADS among young doctors was 20 (18–23) years, with 96% of the respondents having values above 13, indicating a high level of psychological distress (Supplementary material, *Figure S2*). The median value of the PSS-10 score was 25 (22–28), with 97% of the respondents reporting values >14 and being predominantly moderately and severely stressed (Supplementary material, *Figure S3*).

Results of comparative analysis for the level of anxiety/depression and stress among the specific subgroups of respondents are presented in Supplementary material, *Table S3*.

Multivariable logistic regression analysis proved that increased work hours and loss of pay were associated with significantly higher scores for anxiety/depression, while reduced work hours, increased salaries, good teamwork, and full PPE were associated with lower scores. In the case of stress, being more advanced in specialty training, having reduced salaries due to the pandemic, and living with a partner were significantly associated with a higher level of stress (Table 1).

Our study is the first worldwide analysis of COVID-19 related mental suffering among the population of young doctors. Based on our findings, high levels of anxiety, depression, and stress affected nearly all of the respondents. These numbers exceeded twofold the rate and cut-off value identified for the general and clinical population before the COVID-19 era, as well as for all healthcare workers during the pandemic [5–8]. Our results are consistent with the limited evidence in the field, which revealed that the combination of age, profession, and the range of the pandemic put more than half of young doctors in high psychological distress that substantially outweighed the levels noted during the previous outbreaks [1–3, 9–13]. Surprisingly, the enormously high frequency of relevant mental disorders was reported more than 6 months after the initial outbreak. This confirms the previous observation that high-risk healthcare workers may present not only sustained but growing levels of mental disorders that persist beyond the health care emergency [12, 13]. Similarly to our outcomes, the adverse impact of increasing work hours and reduced salaries, as well as the beneficial effect of efficient organizational support, infection control measures, and adequate training were previously identified as relevant modifying factors of psychological wellbeing among healthcare workers during the pandemic [10, 11, 14, 15]. Importantly, the recent workload of young doctors has been considerable with the working pattern of a quarter of junior doctors being associated with a doubled risk of common mental health problems and suicidal ideation [15].

In conclusion, our findings reflect the lack of support and loss of control in young doctors' personal and professional lives. Healthcare leaders should be aware of

Table 1. Risk factors for psychological disorders in the population of young doctors

Variables	HADS >13			
	Univariable analysis OR (95% CI)	*P*-value	Multivariable analysis OR (95% CI)	*P*-value
Opinion on effectiveness of COVID-19 training	0.99 (0.990–0.999)	0.016	0.99 (0.993 –1.003)	0.002
Opinion on teamwork during the pandemic	0.98 (0.983–0.994)	0.0001	0.99 (0.987–0.999)	0.003
Opinion on effectiveness of briefings to plan teamwork	0.98 (0.99–1.00)	0.03	1.00 (0.996–1.006)	0.66
Debriefings after emergencies	0.67 (0.49–0.89)	0.006	0.73 (0.52–1.01)	0.06
Increase in work hours, including night shifts	1.62 (1.14–2.3)	0.006	1.61 (1.116–2.341)	0.01
Decrease in work hours	0.71 (0.51–0.99)	0.04	0.687 (0.484–0.976)	0.03
Loss of pay during the pandemic	5.36 (1.55–18.53)	0.008	5.53 (1.575- 19.468)	0.008
Increase in salaries during the pandemic	0.56 (0.36–0.83)	0.008	0.54 (0.345 –0.846)	0.003
Full PPE[a]	0.70 (0.510–0.963)	0.02	0.81 (0.578–1.152)	0.24
Variables	**PSS-10 score >14**			
	Univariable analysis OR (95% CI)	***P*-value**	**Multivariable analysis OR (95% CI)**	***P*-value**
Year of training	1.078 (1.019 –1.141)	0.008	1.05 (0.992–1.117)	0.09
Loss of pay during the pandemic	1.74 (1.007–2.916)	0.04	1.54 (0.887–2.722)	0.13
Living with partner	1.536 (1.087–2.171)	0.01	1.39 (0.976 –2.002)	0.06
Living with flat mates[a]	0.50 (0.257- 0.995)	0.04	0.68 (0.435–1.034)	0.05

[a]Doctors directly managing COVID-19 patients

Abbreviations: CI, confidence interval; HADS, Hospital Anxiety and Depression Scale; PPE, personal protective equipment; PSS-10, Perceived Stress Scale 10; OR, odds ratio

a potential mental health crisis amongst young doctors that might evolve as a direct result of their involvement in clinical care during the pandemic. Improvements in work organization, including safe work hours and conditions, as well as protected salaries, are essential to prevent further psychological suffering among young doctors worldwide.

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Supplementary material

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

Article information

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Intravascular lithotripsy for ostial left main coronary artery disease

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Heavily calcified coronary lesions pose a challenge in adequate percutaneous treatment. Proper plaque preparation is crucial to ensure successful stent implantation without increasing the risk of stent thrombosis or restenosis [1, 2]. Left main (LM) coronary artery interventions carry a higher risk, compared to other coronary territories. Due to the large diameter of the vessel, the usefulness of well-recognized calcified plaque modification techniques, such as rotational atherectomy, may be limited.

Intravascular lithotripsy (IVL) is a method of plaque modification that uses sonic waves to selectively fracture intimal and medial calcium deposits without any damage to soft vascular tissue. The Shockwave C2 IVL catheter (Shockwave Medical, Santa Clara, CA, US) is a device based on a semi-compliant rapid exchange coronary balloon catheter, advanced over any 0.014" guidewire. The catheter contains two-wave emitters and the sonic energy is transferred after low-pressure (4–6 atm) balloon inflation. The Shockwave C2 IVL usage results in both circumferential and longitudinal calcium fracture thanks to its construction. The recent data from clinical trials and registries are encouraging [3, 4], and evidence on the successful usage of the device in LM disease has already been published [5].

We present a case of an 85-year-old female hospitalized for non-ST-elevation myocardial infarction. Coronary angiography revealed a severely calcified unprotected ostial LM stenosis. The Heart Team chose percutaneous treatment. A Judkins left (JL) 3.5 6-Fr catheter (Launcher, Medtronic, Minneapolis, MS, US) was used to engage LM. Left anterior descending (LAD) and circumflex (Cx) arteries were wired (Sion blue, Asahi Intecc, Japan). Baseline intravascular ultrasonography (IVUS) was not available as the catheter did not cross the lesion. A predilation with 2.0 × 10 mm and 3.5 × 10 mm semi-compliant balloon catheters (Solarice, Medtronic, Minneapolis, MS, US) was done without complete expansion of the latter catheter (a "dogbone" image). To avoid dissection and compromised flow, which might result in hemodynamic instability, an IVL device was chosen to modify the plaque instead of further predilation with non-compliant, cutting, or scoring balloon catheters. A Shockwave C2 IVL 3.5 × 12 mm catheter was introduced without complications (the crossing profile of the device before inflation is 0.044–0.047 inch) and inflated to 4 atm. Since the patient tolerated each inflation and shockwave energy application without any signs of hemodynamic instability or ischemia worsening, a total number of 80 applications (8 series × 10 applications) were done followed by a complete expansion of a non-compliant 3.5 × 12 mm balloon catheter (NC Solarice, Medtronic) at 12 atm. A 3.5 × 12 mm zotarolimus-eluting coronary stent (Resolute Onyx, Medtronic) was deployed and fully expanded at 14 atm. A postdilation with a 3.75 × 8 mm non-compliant balloon catheter (NC Solarice, Medtronic) at 18 atm was done.

Final angiography and IVUS (Opticross, Boston Scientific, Marlborough, MA, US) confirmed proper stent apposition and expansion. The patient made an uneventful recovery and was discharged home two days after the procedure (Figure 1).

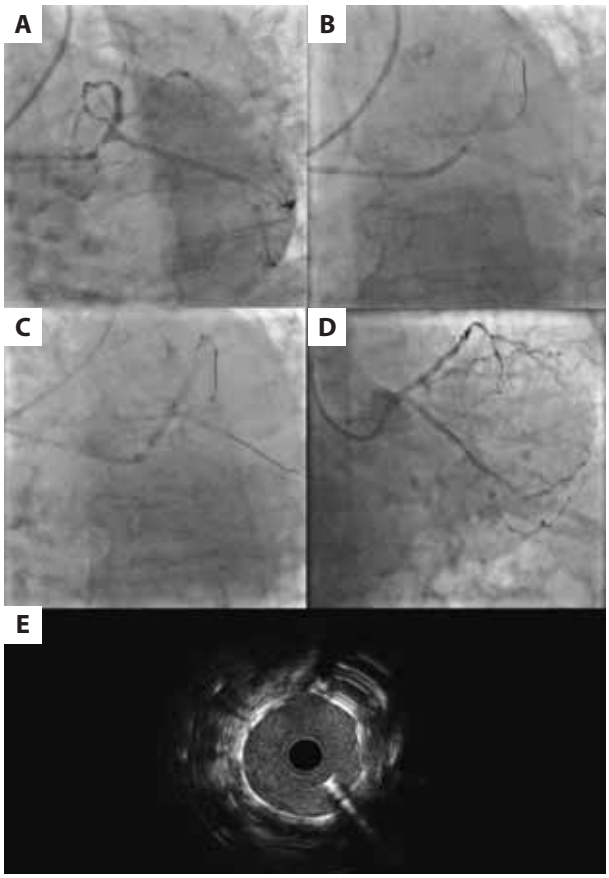

Figure 1. A. Baseline angiography. **B.** Shockwave C2 IVL catheter inflation. **C.** Stent deployment. **D.** Final angiogram. **E.** Final IVUS result

Abbreviations: IVL, intravascular lithotripsy; IVUS, intravascular ultrasonography

Article information

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High-risk percutaneous coronary angioplasty with rotational atherectomy and left ventricular assist device of chronically occluded left ascending artery in an obese patient with very low ejection fraction

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Successful percutaneous coronary intervention (PCI) of chronic total occlusion (CTO) remains one of the most challenging procedures in interventional cardiology. Combining various percutaneous techniques allows procedural and clinical success in the most severe cases.

A 58-year-old male patient was admitted to the cardiology department having a history of progressive exertional dyspnea with exercise capacity of functional class III/IV according to the New York Heart Association (NYHA). He was treated with maximally tolerated doses of an angiotensin-converting enzyme inhibitor and aldosterone antagonist. The β-blocker was not administered due to bradycardia. Echocardiography showed severely decreased left ventricular ejection fraction (LVEF) of 15% with akinesia of the inferior wall and post-myocardial infarction scar characteristics. Coronary angiography revealed diffused atherosclerosis with occlusions in the left descending artery (LAD) and right coronary artery (RCA) (Figure 1). Stress echocardiography with dobutamine confirmed the viability of the myocardium territory supplied by the LAD and an increase of LVEF from 15% to 37%. Nonetheless, the RCA territory remained acinetic. The patient was referred to PCI LAD CTO with a percutaneous left ventricle support device (pLVAD) and rotational atherectomy under the control of intravascular ultrasound (IVUS).

After obtaining left femoral access, the angiography was performed to confirm proper conditions for insertion of the pLVAD. Then, the Perclose ProGlide System (Abbott Vascular, Santa Clara, CA, US) was partially deployed and large bore access was used to deliver the Impella System (Abiomed, Danvers, MA, US) to the left ventricle. The right femoral artery was used to introduce the 7-French extra backup guide catheter to the LAD ostium. The Gaia Second guidewire was swapped to the Sion Blue S after crossing the lesion. During pre-dilation, the balloon stuck to calcifications and eventually ruptured. Consequently, rotational atherectomy was conducted. The Rotawire was used to cross the lesion with the assistance of the Caravelle microcatheter. Subsequently, couple pecking motions with a 1.5 burr were carried out, allowing pre-dilatation with 2.5 × 20 mm and 3.0 × 20 mm non-compliant balloons. Afterwards, the OCT probe was used to assess the anatomy and dimensions of the LAD. Three drug-eluting stents: 2.5 × 33 mm, 3.0 × 48 mm, and 3.0 × 12 mm were implanted consecutively, from the distal end to the ostium of the vessel. After post-dilation, optimal stent apposition was confirmed via OCT. The pLVAD was withdrawn and the large bore access was sealed with PP System deployment and the 6-French Angioseal (AS; St. Jude Medical, St. Paul, MN, US).

During ambulatory observation, the patient showed improvement on the NYHA functional scale, from class III to class II. Moreover, his LVEF raised by 5%, which is a result comparable to observational data indicating an increase in LVEF by 6.4% [4, 5]. The pharmacological treatment was optimized by the implementation of a beta-blocker and nepri-

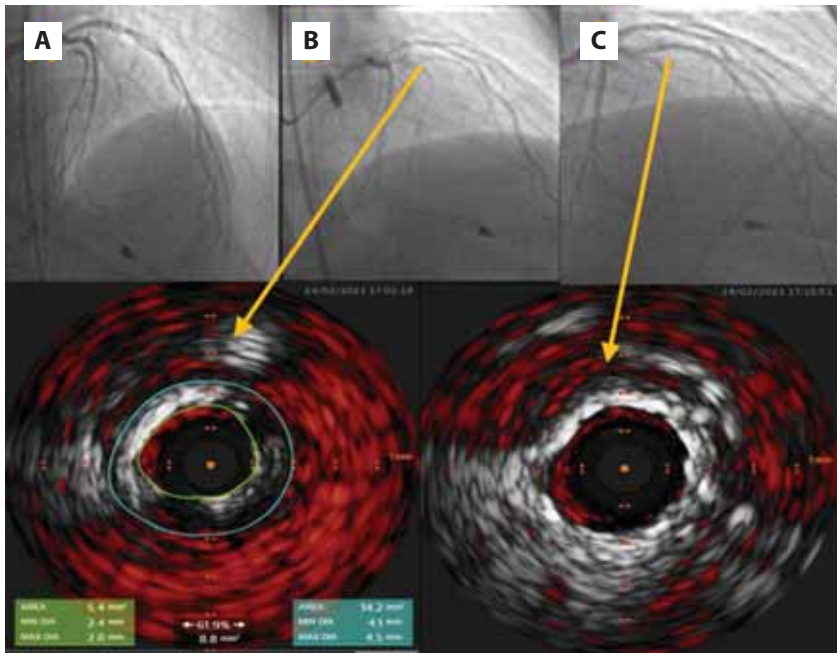

Figure 1. A. Initial left descending artery (LAD) arteriography. **B**. LAD arteriography after recanalization with intravascular ultrasonography (IVUS) showing significant stenosis in the medial segment of LAD. **C.** Final effect with proper stent apposition confirmed via IVUS

lysin inhibitor. After 3 months of optimal medical treatment, the patient will be re-assessed for cardioverter-defibrillator implantation.

Despite some studies showing no benefits of PCI CTO in comparison with optimal medical therapy, there is a growing body of evidence from randomized controlled trials indicating that PCI CTO may improve quality of life due to less residual angina, better exercise tolerance, and even improvement in depression [1–3]. Moreover, there are some studies in which improvement in long-term outcomes is suggested following successful CTO revascularization [4, 5]. Therefore, we assume that such technically challenging procedures are worth trying after careful clinical evaluation, assessment of myocardial viability, and comprehensive discussion with a patient about the procedure.

Article information

Conflict of interest: None declared.

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Ultrasound diagnostics of dilated thoracic lymphatic vessels in a newborn with PIEZO-1 defect

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Lymphangiectasia represents lymphatic vessels dilation following infections, radiation therapy, mastectomy, or Fontan operation when damaged lymphatic vessels or increased central venous pressure impair lymph drainage.

Congenital lymphedema is a condition in which lymph vessels dysfunction leads to hydrops fetalis. Generalized lymphatic dysplasia (GLD) is a rare form of primary lymphoedema. There are several disorders with lymphangiectasias including cystic hygroma, nonimmune hydrops, tumors (e.g. teratoma), genetic syndromes (e.g. Turner, Noonan, Prader-Willi, Angelman), Milroy disease, congenital pulmonary lymphangiectasia, or neurofibromatosis [1, 2]. The abnormal development of lymphatic structures may be due to PIEZO-1 mechanosensory transduction protein mutation [3], which was found in patients with GLD and hereditary hemolytic anemia — xerocytosis [4]. The autosomal recessive mutation is responsible for GLD with hydrops fetalis, childhood-onset lymphedema, and less pronounced hemolytic anemia. The signs of lymph congestion are peripheral edema, pleural or pericardial effusion, ascites, or protein-losing enteropathy. Postnatal edema may resolve spontaneously within the weeks but, in severe cases, may cause neonate demise. All patients present with abnormal lymphoscintigraphy [3].

Case presentation: We present a case of a 3-week-old baby boy with chronic generalized edema and respiratory failure referred for cardiological evaluation. In medical history, the prenatal course was complicated due to hydrops fetalis requiring multiple cordocenteses with blood and albumin transfusions and pleura drainage with pleuro-amniotic shunts. The prenatal microarray assessment was normal.

A preterm newborn (35 weeks of gestation) was born by urgent Caesarean section with a bodyweight of 3000 g. Physical examination revealed prominent nuchal fold, dysmorphia, peripheral edema, and symptoms of dyspnea.

Ultrasonography showed bilateral interstitial syndrome with multiple B lines and left pleural effusion. Postnatal screening transthoracic echocardiography (TTE) revealed normal heart anatomy, myocardial contractility, patent foramen ovale, and persistent arterial duct. The child presented signs of pulmonary distress requiring respiratory support, oxygen supply, and left pleural drainage.

In a 3-week cardiological follow-up, the condition was moderate with dyspnea, tachycardia 160/min without any heart murmur. Blood pressure was 76/47 mm Hg with mean arterial pressure of 57 mm Hg and SaO_2 95% on oxygen delivery. Peripheral edema in the lower extremities was prominent.

TTE revealed features of arterial pulmonary hypertension with an abnormal profile of pulse wave Doppler pulmonary flow with decreased acceleration time (Act) and the ratio of Act to pulmonary ejection time <0.3. On two-dimensional echocardiography, as well as color Doppler flow (Figure 1A–C) in suprasternal view, dilated lymphatic vessels were visual-

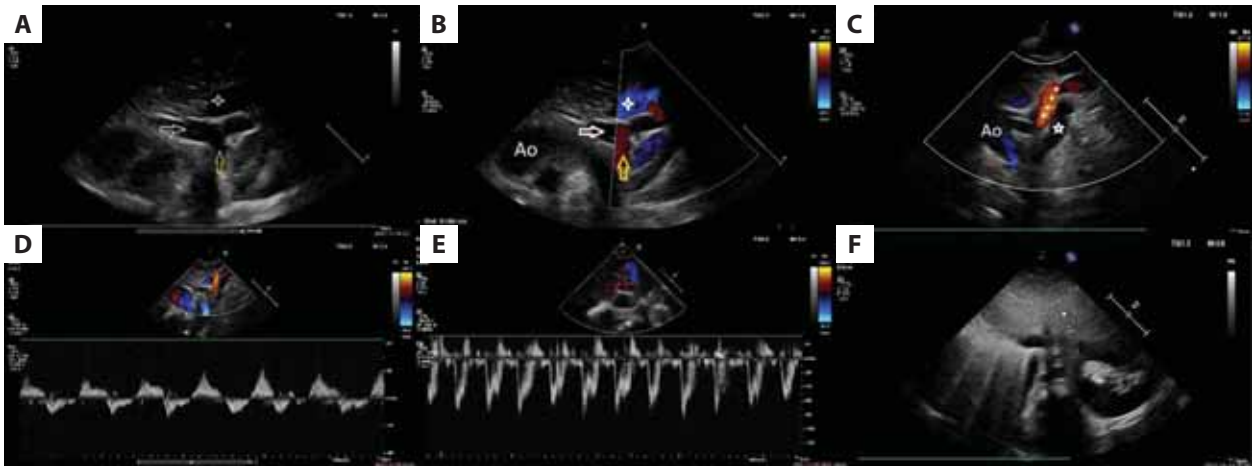

Figure 1. A, B. Suprasternal notch view, 2DE and color Doppler flow: dilated lymphatic vessels draining from lower (the yellow arrow) and right (the white arrow) side of the body *via* the thoracic duct into the innominate vein (the star). **C.** Dilated lymphatic vessel (the white star) below the left subclavian artery (the white dots) draining from the left side of the body. **D.** Pulse wave Doppler flow in a lymphatic vessel. **E.** Pulse wave Doppler pulmonary flow with features of pulmonary hypertension. **F.** Subcostal view, left pleural effusion

ized (Supplementary material, *Video S1–S4*). The presented figure suggested the diagnosis of persistent arterial duct or systemic — pulmonary — anastomoses. However, the color and wave Doppler flow indicated dilated lymphatic vessels with drainage via the thoracic duct into the innominate vein. The medical history of hydrops fetalis and lymphorrhea was crucial in the final diagnosis. Postnatal genetic consultation indicated PIEZO-1 lymphatic dysplasia with autosomal recessive inheritance. Progressive pulmonary and multiorgan failure caused the neonate's demise before heart catheterization and lymphoscintigraphy. The autopsy was not acceptable to the parents, and the diagnosis of generalized lymphatic vessels dysplasia was not confirmed.

Ultrasonography is a highly valuable tool in the differential diagnosis of congenital lymphedema with the possibility of abnormal lymphatic vessels visualization.

Supplementary material

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

Article information

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Edge-to-edge mitral repair with the Pascal system in a patient with corrected tetralogy of Fallot and bilateral hip joint contractures due to poliomyelitis

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A 62-year-old male with a medical history of anatomical correction of tetralogy of Fallot and simultaneous tricuspid and aortic valve replacement at the age of 52 was admitted to our hospital with progressive dyspnea and fatigue that had gradually worsened during the last few months. As the sequence of poliomyelitis that the patient had suffered in early childhood, he developed hip joint contractures. Transthoracic echocardiography (TTE) revealed significant functional mitral regurgitation (MR) with posterior leaflet restriction (effective regurgitant orifice 0.4 cm^2, regurgitant volume 52 ml), systolic dysfunction of the dilated left ventricle (ejection fraction, 42%; left ventricular end-diastolic diameter, 62 mm), hypokinetic right ventricle (S' 9 cm/s; tricuspid annular plane systolic excursion [TAPSE], 12 mm) and biatrial enlargement. The function of the previously replaced tricuspid and aortic valves was fine. Coronary angiography did not show any significant coronary lesions. The patient was on optimal guideline-driven pharmacotherapy over the past few months and was not a candidate for a heart transplant. Given the high surgical risk, the patient was qualified for MR transcatheter edge-to-edge repair (TEER) with the MitraClip system (Abbott Vascular, Santa Clara, CA, US) [1]. However, the pre-procedural checkup revealed that the stand stabilizing the MitraClip delivery catheter could not be placed over the patient's lower extremity because of severe hip contractures; positioning the MitraClip stand in between the patient's legs was unmanageable. Nevertheless, it was possible to place the smaller stand for the PASCAL (Edwards Lifesciences, Irvine, CA, US) TEER system in an unusual fashion between the patient's legs (Figure 1A), and the successful procedure was then performed in a standard manner. A Single PASCAL ACE device was implanted with good immediate echocardiographic results (Figure 1B–E). The patient

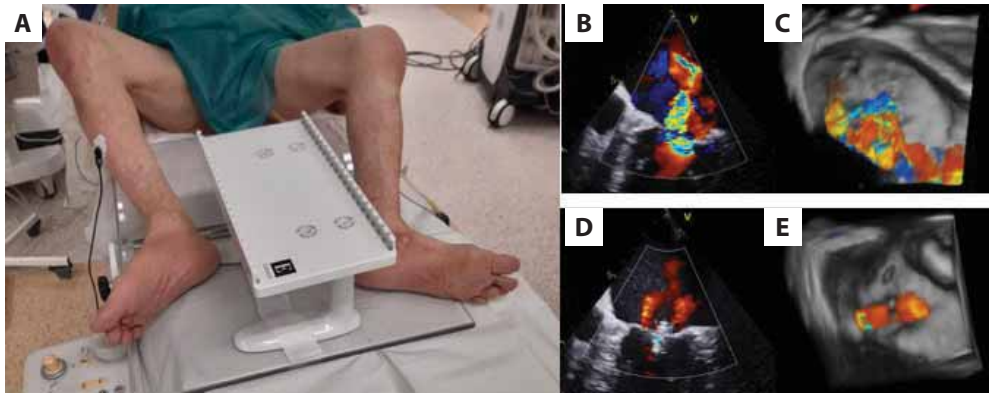

Figure 1. Patient's positioning and Pascal delivery stand (**A**). Baseline, severe mitral regurgitation demonstrated on 2-dimensional transesophageal echocardiography (TEE) (**B**) and 3-dimensional TEE (**C**). Reduction in mitral regurgitation to mild with two separate, small residual jets after implantation of the device demonstrated on 2-dimensional TEE (**D**) and 3-dimensional TEE (**E**)

was discharged home uneventfully in the New York Heart Association functional class II. TTE performed at 30-day follow-up documented stable and good procedural results.

To the best of our knowledge, this is the first case report of the PASCAL device implantation in a patient with congenital heart disease. The progression of left ventricular heart failure and functional MR occurs in patients after tetralogy of Fallot correction [2, 3] and the TEER procedure may be a viable therapeutic option for those patients. Moreover, we described a practical solution for the unusual procedural obstacle related to the hip joint contractures.

Article information

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Atrioventricular sequential pacemaker implantation in an adult patient with a Fontan circulation

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A 29-year-old female was referred to our hospital with recurrent syncope and heart failure symptoms. She had been born with tricuspid atresia, right ventricular hypoplasia, an atrial septal defect, ventricular septal defect, pulmonary valve stenosis, right retroesophageal subclavian artery, and persistent left superior vena cava. The patient had undergone Blalock-Taussig (BT) shunt in infancy, hemi-Fontan operation at five years of age, and fenestrated Fontan completion one year later. Electrocardiographic (ECG) monitoring showed episodes of sino-atrial dissociation and chronotropic incompetence (Figure 1A). The patient was listed for dual-chamber pacemaker implantation. Pre-procedural planning included a heart catheterization with a detailed hemodynamic and angiographic evaluation (Figure 1B, Supplementary material, *Figure S1*) and ECG-gated cardiac contrast computed tomography (CT). For a precise evaluation of intracardiac anatomy, we created a computed tomography reconstruction and printed a three-dimensional model of the Fontan circulation, heart chambers, and coronary sinus with its tributaries (Supplementary material, *Figure S2*). Pacemaker implantation was carried out under light analgosedation in a hybrid operating room. Venous access was gained by puncture of the left subclavian vein. Fenestration in the Fontan baffle was cannulated with the Medtronic Attain Command™ delivery system (Medtronic, Minneapolis, MN, US), and the leads were advanced into the atrium [1]. A coronary sinus lead Biotronik Sentus OTW BP was positioned in a posterior cardiac vein using a sub-selection catheter Medtronic Attain Select™ II. Finally, the lumenless Medtronic SelectSecure™ 3830 lead was placed in the right atrium via Medtronic C315HIS Delivery Catheter.

The procedure and postoperative period were uneventful. The chest radiograph showed the correct position of both leads (Figure 1C). Pacing parameters were excellent, and appropriate pacemaker function was confirmed on ECG monitoring (Figure 1D). Echocardiography showed no intracardiac thrombi or pericardial effusion. Warfarin was commenced for thromboprophylaxis [2]. This case shows that transvenous pacemaker implantation can successfully and safely accomplish restoring atrioventricular synchrony and chronotropic competence.

Supplementary material

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

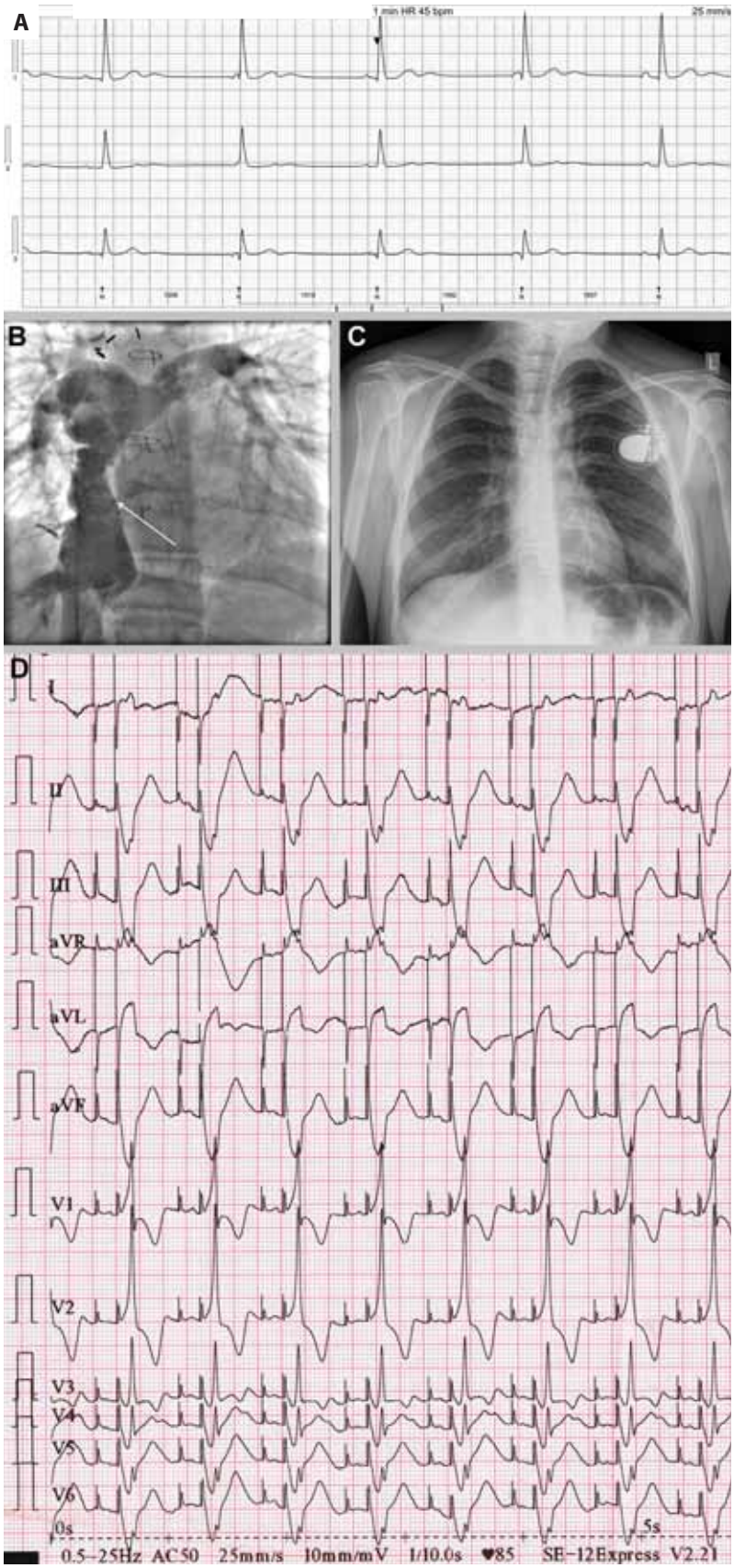

Figure 1. A. Electrocardiographic (ECG) monitoring with episodes of sino-atrial dissociation and chronotropic incompetence. **B.** Fluoroscopy of a heart catheterization with detailed hemodynamic and angiographic evaluation of the Fontan circulation. The arrow indicates fenestration between the Fontan circulation and the atrium. **C.** The chest radiograph after the procedure, showing the correct position of both pacing leads. **D.** ECG registration showing dual-chamber pacing

Article information

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Chronic thromboembolic pulmonary hypertension complicated by left main compression syndrome

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A 55-year-old-female was admitted with exertional dyspnea (World Health Organization functional class [WHO-FC] III/IV). Clinical evaluation revealed increased N-terminal-pro-brain-type natriuretic peptide (NT-proBNP, 3994 pg/ml) and reduced the six-minute walk test (6MWT, 330 meters). Echocardiography showed enlargement of the right atrium (area, 26.4 cm^2) and right ventricle (RV, 54 mm) with high-velocity tricuspid regurgitation (4.7 m/s), pulmonary artery (PA) dilatation (80 mm), elevated estimated RV systolic pressure (96 mm Hg) and mean pulmonary arterial pressure (mPAP, 56 mm Hg). Electrocardiogram indicated RV hypertrophy and overload (Supplementary material, *Figure S1*). Magnetic resonance imaging ruled out congenital heart defects. The right heart catheterization (the thermodilution method) indicated: mPAP of 58 mm Hg, PA wedge pressure of 12 mm Hg, pulmonary vascular resistance (PVR) of 10.8 Wood units (Wu), and cardiac index of 2.6 l/min × m^2. The patient's pulmonary angiography (Axiom Artis Zee, Siemens, Germany) and computed tomography scan (LightSpeed VCT 64 scanner GE, Chicago, IL, US) revealed a large main PA aneurysm (PAA, 86 mm), along with right and left PAAs (69 mm), and multiple organized thromboembolic lesions in lobar and segmental arteries, which allowed the diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH) (Figure 1A–D). Coronary angiography demonstrated severe left main coronary artery (LMCA) stenosis due to compression by PAA, confirmed by intravascular ultrasound (IVUS, Eagle Eye Platinum, Philips, Netherlands) (Figure 1E, Supplementary material, *Video S1*).

The case was carefully analyzed by the multidisciplinary CTEPH team, and the patient was not qualified for endarterectomy with PA reconstruction due to high risk. The combined pulmonary vasodilators, along with LMCA percutaneous intervention (PCI), were offered for the patient as bridging therapy before lung transplantation (LTx). PCI was performed and the LMCA ostium was expanded with a 4.0 mm × 28 mm drug-eluting stent (Synergy Megatron™, Boston Scientific, Marlborough, MA, US) and post-dilated with a 5.0 mm × 15 mm balloon (Pantera Pro, Biotronik, Berlin, Germany). The final angiogram and IVUS showed good stent expansion with relief of LMCA extrinsic compression (Figure 1F, Supplementary material, *Video S2*). The combined specific treatment was also subsequently introduced. The patient was started on oral riociguat titrated from 3 mg to 7.5 mg daily, along with a continuous subcutaneous infusion of treprostinil titrated to the maximum tolerated dosage (30 ng/kg/min).

A six-month follow-up examination demonstrated a significant reduction of mPAP (47 mm Hg) and PVR (6.25 Wu) without PAA diameter progression. The patient improved to II/III WHO-FC with a 390 m distance at 6MWT and NT-proBNP of 1007 pg/ml.

We describe a rare case of CTEPH-related PAA causing LMCA compression. In CTEPH, PAA seems to be associated with mural thickening, webs, or intramural calcified thrombi [1]. PAA may lead to life-threatening complications, including PAA dissection or acute coronary syndrome [2, 3]. To date, the optimal treatment of PAA has not been established. There are no criteria indicating urgent recon-

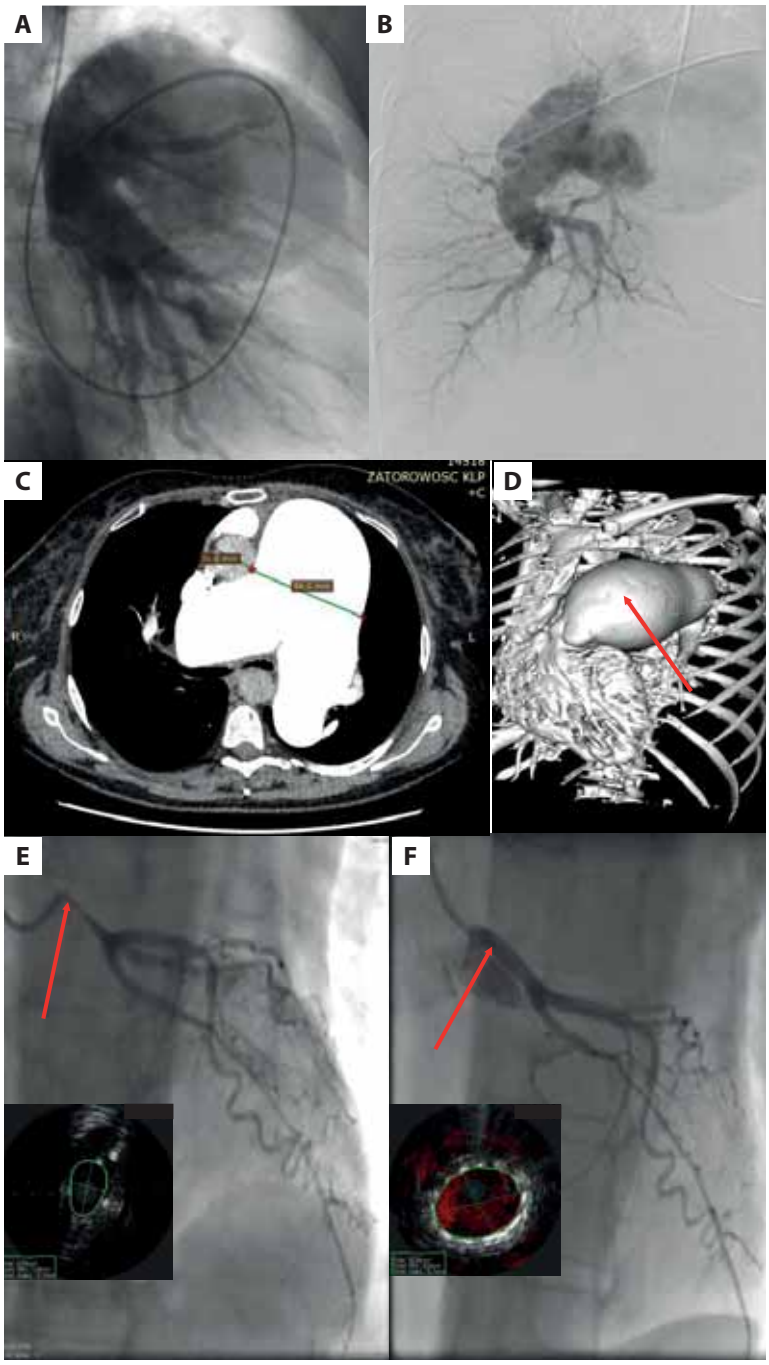

Figure 1. A, B. Angiography of the left (**A**) and right (**B**) pulmonary artery (PA) showing dilatation and calcified thromboembolic lesions. **C, D.** Computed tomography scan (**C**) with volume rendering reconstruction (**D**) showing a pulmonary artery aneurysm (PAA) (the arrow). **E.** Coronary angiography (CA) with an intravascular ultrasound (IVUS) showing critical stenosis of the left main coronary artery (LMCA) attributed to the PAA compression (the arrow). LMCA minimal lumen area (MLA) was 4.9 mm^2. **F.** CA with IVUS after LMCA stenting, with normal LMCA shape and size (the arrow). LMCA MLA after stenting was 15.9 mm^2

structive surgery or waiting for LTx, especially in asymptomatic patients [1, 3]. In the case of LMCA, the accumulated experience suggests stenting might be a first-choice strategy [3, 4]. Recently, treprostinil was proven to increase the exercise capacity in CTEPH [5]. In the presented case, LMCA stenting and pulmonary vasodilators led to the improvement of the patient's hemodynamic status.

Supplementary material

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

Article information

Conflict of interest: None declared.

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Giant left ventricular aneurysm following arterial switch operation

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Arterial switch operation (ASO) with coronary artery translocation and the Lecompte maneuver (positioning of the pulmonary artery anteriorly to the aorta) are the treatment of choice in newborns with d-transposition of the great arteries (d-TGA). The aorta and pulmonary trunk are transected and transferred with coronary arteries to the opposite semilunar valves. Early postoperative complications include excessive pericardial and pleural drainage, heart failure, cardiac arrhythmias, distortion of pulmonary arteries, infections, endocarditis, and coronary artery occlusion causing ischemia with contractility impairment, cardiac aneurysm formation, which necessitate surgical treatment [1–4].

We demonstrate an unusual presentation of a life-threatening left ventricular aneurysm which was successfully operated on with a noncellular xenogeneic extracellular matrix patch without sequelae.

A 2-week-old female infant was diagnosed with a congenital heart defect: d-TGA with large ventricular septal defect (VSD). The child underwent, at the age of 9 days, arterial switch operation, VSD closure, and simultaneous coronary artery translocation during cross-clamp. Epicardial intraoperative echocardiography showed mild distortion of pulmonary arteries, wide coronary arteries with sufficient flow, and normal myocardial contractility. Pericardial drainage was provided routinely. The general condition of the patient was poor with symptoms of cardiac compromise requiring vasopressors (dopamine, adrenaline) and inotrope (milrinone) infusions. On the first postoperative day, chest revision was necessary. The heart stimulation was established via temporary epicardial electrodes due to complete atrioventricular block (CAVB). The patient also required peritoneal dialysis with a Tenckhoff catheter. On the fifth postoperative day, CAVB converted into sinus rhythm. The electrocardiogram (ECG) revealed normal sinus rhythm, right axis deviation, right ventricular hypertrophy (positive T wave in lead V1) without signs of ischemia. Recurrent tachyarrhythmias with wide QRS complexes were treated effectively with amiodarone infusion.

Postoperative transthoracic echocardiography (TTE) revealed right diaphragm dysfunction, small residual VSD with L-R shunting, mild pulmonary artery stenosis, mild pulmonary and aortic regurgitation, and hyperechoic 5-mm cistern above the lateral wall of the left ventricle (LV) (Figure 1A–C). The contractility of the myocardium was slightly decreased (LV ejection fraction 50% using Simpson formula with the normal range of 55%–65%).

TTE suggested the diagnosis of localized pericardial effusion. However, the hyperechoic cistern communicated with the LV via two fistulae (Supplementary material, *Videos S1–S3*). The gradual distention of the aneurysm up to 12 mm provided a high risk of rupture with cardiac tamponade which prompted the reoperation on the 12th postoperative day. A noncellular xenogeneic extracellular matrix patch was used for fistulae and aneurysm closure and strengthening of the lateral wall. The postoperative course was uneventful.

The most probable causes of the aneurysm formation were technical difficulties during coronary arteries mobilization and

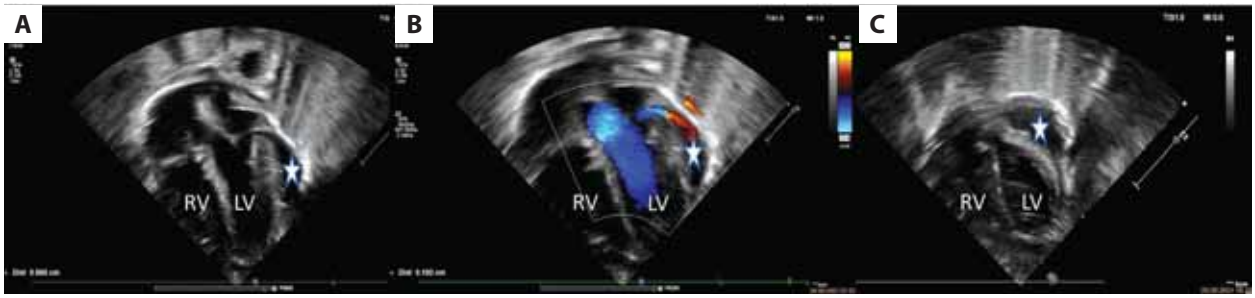

Figure 1. Transthoracic echocardiography. **A.** Five chamber view. Two-dimensional echocardiography. Large lateral ventricular wall aneurysm (white star) with a left ventricular fistula below the mitral annulus. **B.** Five chamber view with color Doppler flow through the fistula communicating the left ventricle with the aneurysm. **C.** Five chamber view. Left ventricular lateral wall view with the giant aneurysm distended up to 12 mm

Abbreviations: RV, right ventricle; LV, left ventricle

translocation, although the leading mechanism of aneurysm development is myocardial ischemia, which requires interventional or surgical procedures [5].

This is the first case in the literature on cardiac aneurysm with ventricular fistulae following arterial switch operation with successful surgical embolization.

In a 6-month follow-up, the condition of the patient was good. TTE revealed an occluded aneurysm without a residual shunt, normal contractility of the myocardium, and right diaphragm (Supplementary material, *Video S4*).

Supplementary material

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

Article information

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The extracorporeal membrane oxygenation as a bridge to delayed minimally invasive surgical treatment of a postinfarction papillary muscle rupture

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There is an ongoing discussion in the literature on the role of temporary mechanical circulatory support in the treatment of mechanical complications of myocardial infarction (MI) [1]. We present the use of venoarterial extracorporeal membrane oxygenation (V-A ECMO) as a bridge to surgery for patients with papillary muscle rupture to obtain hemodynamic and metabolic stabilization, unload the left ventricle for muscle regeneration, and reduce antiplatelet therapy effect to minimize perioperative bleeding. The 47-year-old patient was admitted to the cardiac surgery department with a cardiogenic shock and pulmonary edema due to acute mitral regurgitation following a postinfarction rupture of the posteromedial papillary muscle. Coronary angiography performed 7 days earlier (on the third day after acute cardiac pain onset) revealed total right coronary artery occlusion in the second segment (Figure 1A). There were no significant lesions in the remaining coronary vessels. After an unsuccessful attempt at revascularization, the patient was discharged home in good condition and re-admitted two days later due to pulmonary edema requiring mechanical ventilation. Transthoracic echocardiography unveiled severe mitral regurgitation due to rupture of the head of the posteromedial papillary muscle (Figure 1B) and deep anterior leaflet prolapse (Figure 1C), as well as extensive akinesis of the inferior wall and posterior part of the interventricular septum. The left ventricle ejection fraction was 40%. The patient was qualified for peripheral V-A ECMO as a bridge to delayed surgical treatment because of severe cardiogenic shock, antiplatelet therapy (ASA, prasugrel), and a recent MI. The risk of postoperative mortality, according to EuroSCORE II and STS scores, was 14.03% and 21.13%, respectively. ECMO was instituted under transesophageal echocardiography and ultrasound guidance through femoral vessels. In addition, a control chest X-ray was performed, which confirmed the correct position of the venous cannula (Figure 1D). The hemodynamical and metabolic status of the patient improved, and after 3 days of mechanical circulatory support, a mechanical mitral valve prosthesis was implanted through right-sided minithoracotomy without removal of the subvalvular apparatus (Figure 1E, F). The choice of the type of intervention and the prosthesis was motivated by the patient's age and the uncertain results of native valve repair shortly after MI. Importantly, the latest data indicate unfavorable results of the edge-to-edge transcatheter mitral valve repair in patients with cardiogenic shock demanding mechanical circulatory support [2]. V-A ECMO was weaned. The patient required inotropic support in a perioperative period. A gradual improvement in the general condition was observed. On day 10 after the operation, the patient was discharged home in a good overall condition.

Papillary muscle rupture is a rare and serious mechanical complication typically of transmural inferior MI [3]. Acute surgical intervention remains the treatment of choice,

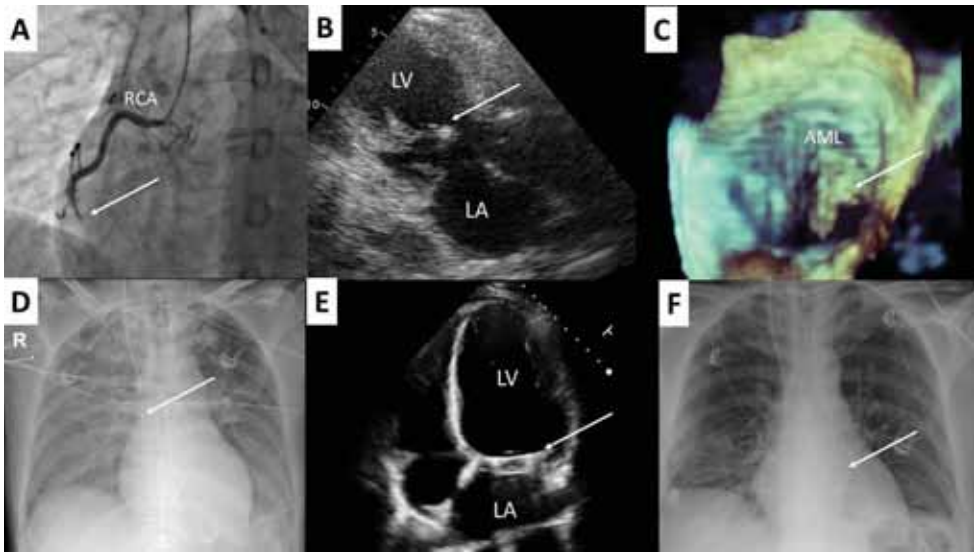

Figure 1A. Total occlusion of the right coronary artery in the second segment (the arrow); coronary angiography. **B.** Ruptured head of the posteromedial papillary muscle (the arrow); 2D TTE, long-axis view. **C.** Anterior mitral leaflet prolapse (the arrow); 3D TEE. **D.** Venous cannula of venoarterial extracorporeal membrane oxygenation placed thorough femoral vein, reaching the superior vena cava (the arrow); chest radiograph. **E.** Echo of implanted mechanical mitral valve prosthesis (the arrow); 2D TTE, four-chamber view. **F.** Mechanical mitral valve prosthesis (the arrow) implanted through right-sided mini-thoracotomy (lack of sternal wires); chest radiograph

Abbreviations: AML, anterior mitral leaflet; LA, left atrium; LV, left ventricle; RCA, right coronary artery; 2D TTE, two-dimensional transthoracic echocardiography; 3D TEE, three-dimensional transesophageal echocardiography

reducing the mortality rate in the course of this disease from approximately 80% to 39% in a large, experienced center series [5] with a high risk of other complications, often due to the patient's hemodynamic instability and increased risk of bleeding [3–5]. Preoperative V-A ECMO may increase the survival rate by improving the patient's hemodynamical status, protecting against tissue ischemia, reducing the antiplatelet effect, and getting time to enable postinfarction myocardial recovery.

Article information

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Unusual cardiac magnetic resonance findings in a young patient, years after the diagnosis of hypertrophic cardiomyopathy

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A twenty-four-year-old man who had been diagnosed with hypertrophic cardiomyopathy (HCM) at the age of 12, based on echocardiography findings of massive hypertrophy of the septum, anterior and inferior wall (maximum wall thickness of 31 mm) with typical electrocardiographic (ECG) features (Supplementary material, *Figure S1*), was intermittently followed up for over 12 years before cardiac magnetic resonance was performed. The family history was negative, the patient was asymptomatic, and at the age of 18, the 5-year sudden cardiac death risk score assessed by the online tool recommended by 2014 European Society of Cardiology (ESC) guidelines on HCM [1] was calculated at 2.6%. Hence, implantable cardioverter-defibrillator (ICD) placement was not indicated. Subsequently, the patient had been lost to follow-up for several years. At the age of 24, he contacted his cardiologist again and a cardiac magnetic resonance exam was scheduled for risk assessment. The study showed good biventricular function with normal chamber size. However, the images presented in Figure 1 and Supplementary material, *Videos S1–S3*, unexpectedly changed the long-established diagnosis of HCM. These findings were consistent with primary cardiac tumors — fibromas.

Primary cardiac tumors are rare (0.0017%––0.019% in the autopsy series), and fibromas constituted only 3.2 % of a large pathology study of 533 cardiac tumors [2]. They present as solitary tumors in most cases, and the initial

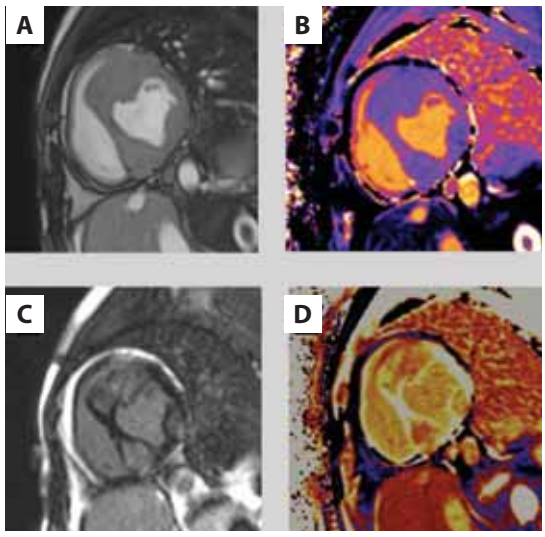

Figure 1. A. Mid-ventricular SAX bSSFP cine still-frame showing marked hypertrophy of the anterior, septal, inferior, and inferolateral segments. **B.** Native myocardial T1 mapping (MOLLI sequence) at the same slice location; no regional variation was visually apparent and the mean T1 time was 998 ms (the institutional reference range: 951-1035 ms). **C.** LGE image acquired at the same slice location at 10 min post-contrast administration (gadobutrol 0,1 mmol/kg), showing multiple highly enhanced lump tumors in the anterior, septal, inferior, and inferolateral segments. **D.** Post-contrast T1 mapping (MOLLI sequence) at the same slice location, showing marked homogenous shortening of post-contrast T1 within the tumors (Siemens Aera 1.5 T, Erlangen, Germany)

Abbreviations: bSSFP, balanced steady-state free precession; LGE, late gadolinium enhancement; MOLLI, modified Look-Locker inversion recovery; SAX, short axis

diagnosis of HCM is not uncommon based on asymmetric hypertrophy in echocardiography [3]. Conversely, multiple fibromas are an extremely rare finding. A single case of multiple fibromas in the left ventricle was found in a series of 18 symptomatic fibroma patients referred for surgical excision [4]. According to a large literature review, multiple fibromas can be found in one out of ten fibroma cases [5]. Cardiac fibromas are thought to be generally benign tumors with the greatest prevalence in the left ventricle followed by the right ventricle or the septum, and extremely rare in the atrial walls. However, younger age at diagnosis and larger relative tumor size have been linked to poor prognosis [5]. Moreover, tumors that involve the septum are more likely to cause arrhythmia and sudden cardiac death [5].

The management tends to be limited to watchful waiting in asymptomatic cases, and the pace of growth is generally very low after the age of 20 [5]. Conversely, surgical excision is the treatment of choice when either ventricular or valvular function is impaired or if significant arrhythmia occurs, with excellent early and late results in most cases [4]. Sudden death was reported to occur in a proportion of previously asymptomatic patients, and, therefore, the optimal management in these patients is still a matter of debate. Considering multiple tumor locations with massive septal involvement in this case, management options, including surgery, were discussed despite the asymptomatic course, good exercise tolerance, and uneventful 24-hour ECG monitoring. As the patient refused to consider an ICD as a treatment option, watchful waiting was finally recommended.

Supplementary material

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

Article information

Conflict of interest: KG is currently employed by Siemens Healthineers. The remaining authors declare no conflict of interest concerning this publication

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Massive atrial thrombus in sinus rhythm cardiac amyloidosis is not a wild goose chase?

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The recent diagnostic guidelines and therapeutic recommendations [1] in patients with cardiac amyloidosis (CA) have changed the approach to modern cardiological diagnosis of the causes of myocardial hypertrophy while facilitating hematological evaluation [2].

We present probably the first case in the Polish population of a massive thrombus of the left atrium appendage in a patient with IgG lambda multiple myeloma with concomitant CA in the presence of sinus rhythm.

In a 54-year-old woman, a significant deterioration in exercise tolerance (New York Heart Association [NYHA] class III), hypotension, and weight loss were observed for about a year. Echocardiography revealed concentric myocardial hypertrophy, good left ventricular systolic function, and impaired grade-II diastolic function. After five months, due to the persistence of symptoms, coronary angiography was performed, which showed no narrowing of the coronary arteries. Due to the lack of clinical improvement, the patient was referred to the cardiac magnetic resonance unit. T1 time mapping during stress perfusion was carried out before and after a gadobutrol injection. Cine images showed a decreased ejection fraction (41%) and concentric hypertrophy of the myocardium. Native T1 sequences and extracellular volume (ECV) maps showed diffused fibrosis with high native T1 values (mean, 1095 ms; normal values, 953–981 ms) and extended ECV (mean 51%) (Figure 1A, B). The late gadolinium enhancement images revealed subendocardial and transmural fibrosis.

The diagnostics were extended to a histopathological examination of the adipose tissue, in which amyloid deposits were found, and the bone marrow examination, which showed 15% infiltration of clonal plasma cells. Specific tests showed: protein M 1.17 g/dl, free light chain (FLC) λ 330 mg/l, FLC ratio κ/λ 0.03, monoclonal protein IgG λ and trace λ band in serum immunofixation, troponin T 31.78 pg/ml, N-terminal pro-brain natriuretic peptide (NT-proBNP) 2544 pg/ml, IgG 19.1 g/l, and urine protein 16.9 mg/dl. The treatment included four cycles of cyclophosphamide, bortezomib, and dexamethasone (CyBorD). Hematological response at the PR level was achieved, with a reduction in the NT-proBNP level from 2653 to 2037 pg/ml in the cardiac response.

The resting electrocardiography showed a sinus rhythm and a low voltage of the QRS complexes. The observation showed no atrial fibrillation. Echocardiography revealed a granular structure of the myocardium, left and right ventricular hypertrophy, a thickened interatrial septum, pericardial fluid, an apical sparing in global longitudinal strain (Figure 1C), and impaired diastolic function of the LV. The peak longitudinal left atrial strain was reduced (Figure 1D). Moreover, an additional echo in the left atrial appendage (LAA) was observed.

For this reason, 3D transesophageal echocardiography was performed, revealing a massive thrombus modeling the entire LAA (Figure 1E, F). Apixaban treatment was initiated and autologous hematopoietic stem

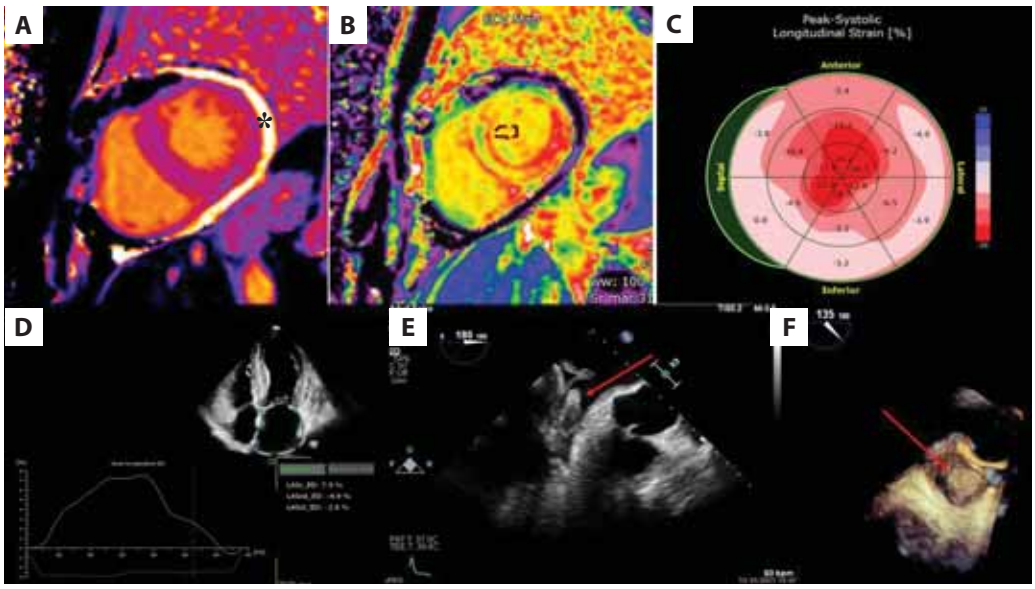

Figure 1. A. Diffusely increased T1 values on CMR native T1 map (1095 ms), *pericardial effusion, short axis view. **B.** Increased ECV values (51%) in extracellular volume map, short axis view. **C.** TTE global longitudinal strain — "apical sparing". **D.** TTE reduced longitudinal left atrial strain. **E.** TEE — an additional echo in the LAA (the red arrow). **F.** 3D TEE — a massive thrombus (the red arrow) modeling the LAA

Abbreviations: CMR, cardiac magnetic resonance; ECV, extracellular volume; LAA, left atrial appendage; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography

cell transplantation (aHSCT) was temporarily postponed. On control transesophageal echocardiography at 8 weeks, only self-contrast in the blood was observed in the LAA. Nowadays the patient is undergoing aHSCT with melphalan 200 mg/m^2 conditioning and low molecular weight heparin prophylaxis.

The most common form of amyloidosis is light chain amyloidosis, which accounts for about 70%–80% of all forms of the disease [3]. In untreated light-chain cardiac amyloidosis, survival is estimated to be less than six months from diagnosis. The prognosis may also be influenced by the presence of a thrombus in the LAA despite the presence of a sinus rhythm [4, 5]. Therefore, detailed and modern cardiac imaging should become the standard approach.

Article information

Conflict of interest: None declared.

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Clinical use of intracoronary imaging modalities in Poland. Expert opinion of the Association of Cardiovascular Interventions of the Polish Cardiac Society

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ABSTRACT

The article presents the most common, current indications for the use of intravascular invasive imaging diagnostic techniques, i.e. intravascular ultrasound and optical coherence tomography in Polish invasive cardiology centers. The application of the above-mentioned techniques in the diagnosis of stenosis of the left main coronary artery, optimization of stent implantation procedures, treatment of calcified lesions, and other clinically important issues are discussed.

Key words: intravascular ultrasound, optical coherence tomography, stent implantation, left main coronary artery

INTRODUCTION

This expert opinion presents the current views and indications for the clinical use of intravascular invasive diagnostic imaging techniques, i.e. intravascular ultrasound (IVUS) and optical coherence tomography (OCT). The document was developed by experts appointed by the Board of the Association of Cardiovascular Interventions of the Polish Cardiac Society.

According to the published registry of Polish authors [1], IVUS/OCT techniques are rarely used, as an experienced operator uses them every 5 weeks, while the results of the registry conducted by the European Association of Percutaneous Cardiovascular Interventions (EAPCI) [2] indicate that half of the operators use these techniques only in over 15% of patients. The main indications for the use of IVUS/OCT were optimization of stent implantation and angioplasty procedures in the area of the left coronary artery. The authors of the listed registries indicate that the main factors limiting the use of IVUS/OCT in clinical practice are costs and the duration of the procedure.

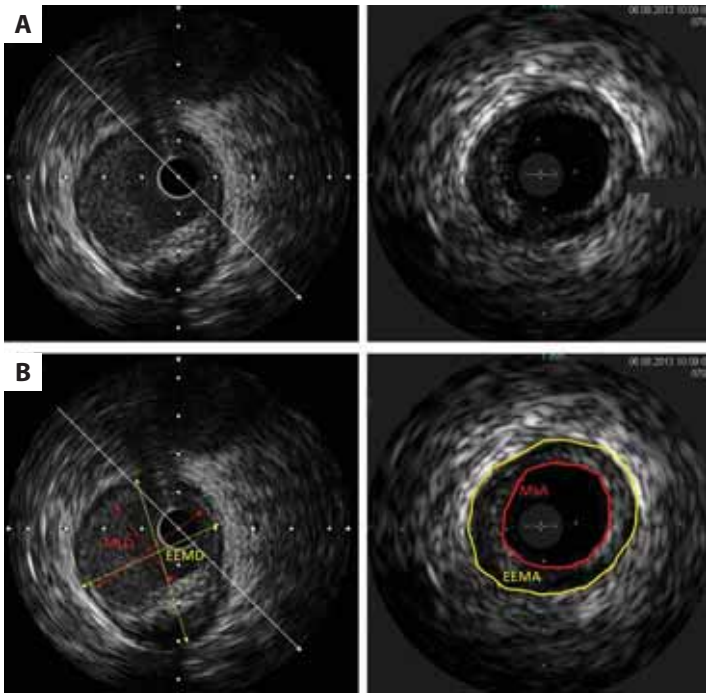


Figure 1. A. Ultrasound images obtained with a 40 MHz mechanical probe (Boston Scientific) (left panel) and a 20 MHz electronic probe (Philips IGT Co, Volcano Co) (right panel). In the first case, a single crystal emitting an ultrasound wave is mounted on a rotating shaft, which scans the vessel's circumference at an appropriate speed — the reflected echo is processed in the IVUS machine. In the second case (on the right), the probe is made of 64 piezoelectric crystals, which are electrically activated and send successively ultrasound waves, which are then processed in the IVUS machine. **B.** Examples of IVUS cross-sectional measurements — on the left side, there are examples of vessel diameter measurements — vessel diameter (external elastic membrane diameter, EEMD) and minimal lumen diameter (MLD). At least two measurements are made in perpendicular lines, determining the maximum and minimum dimensions — their quotient is the vessel/lumen symmetry index. On the right, measurements of the vessel area (external elastic membrane area, EEMA) and measurements of the vessel lumen area (minimal lumen area, MLA)

Abbreviations: IVUS, intravascular ultrasound

Table 1. A comparison of intravascular imaging modalities (IVUS vs. OCT)

Intravascular ultrasound			Optical coherence tomography
Greyscale	**High definition**		
Ultrasound (20–45 MHz)	Ultrasound (60 MHz)	Image source	Near-infrared light
100–200 µm/200–300 µm	40–60 µm/90–150 µm	**Resolution (axial/lateral)**	15–20 µm/20–40 µm
10 mm	4–8 mm	Tissue penetration	1–2.5 mm
+ + +	+ + +	Stent expansion	+ + +
+ +	+ +	Malapposition	+ + +
+	++	Thrombus	+ + +
+	++	Lipids	+ +
+ +	+ +	Calcifications	+ + +
+ +	+ ++	Edge dissection	+ + +

INTRAVASCULAR ULTRASOUND AND OPTICAL COHERENCE TOMOGRAPHY

Intravascular ultrasound is based on coronary tissue-mediated sound wave reflection and image acquisition [3]. A miniaturized ultrasound transducer generates ultrasound waves that reflect from structures in a coronary artery, return to the transducer, and are converted into an image (a two-dimensional and grayscale cross-section, Figure 1A and B). Detailed information on analyzing IVUS images can be found in expert documents describing this methodology [4]. In recent years, high-definition intravascular ultrasound modalities have been widely introduced into clinical practice [5].

OCT is a technique utilizing a near-infrared light source with a wavelength range of 1250–1350 nm. The use of a light beam allows for the acquisition of images with ten times higher resolution than IVUS (from 10 to 20 µm) and enables an OCT probe to move quickly inside a vessel at a speed of 40 mm per second, depending on the OCT system used [6]. A comparison of IVUS and OCT systems is presented in Table 1.

Examples of various types of atherosclerotic plaques on IVUS and OCT imaging are presented in Figure 2.

ASSESSMENT OF INTERMEDIATE LEFT MAIN LESIONS

Intermediate lesions of the left main coronary artery can be assessed using both invasive functional and imaging methods. However, the latter provides additional data for patients who have unstable plaques resulting in acute coronary syndrome or who are suspected of having spasm within the left main coronary artery. Moreover, they enable the visualization of the advancement of atherosclerosis both in the left coronary artery stem and its branches [7], which is essential when planning percutaneous revascularization.

Jasti et al. [8] showed that the minimum lumen area in the left main coronary artery, which correlates with the

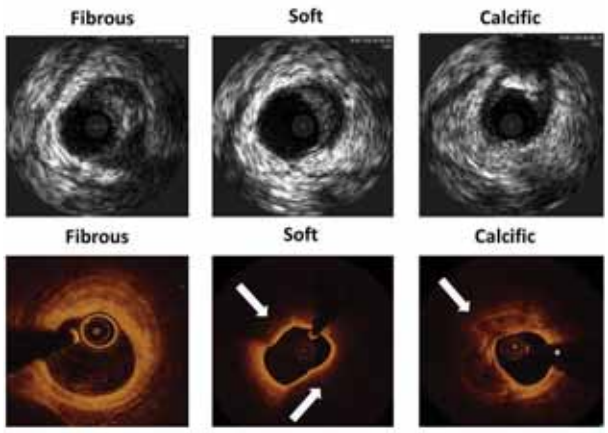


Figure 2. Examples of atherosclerotic plaques in intravascular ultrasound (top line) and optical coherence tomography (bottom line) imaging

fractional flow reserve (FFR) value <0.75, is 5.9 mm^2 with high sensitivity and specificity of the results. Based on these observations, Hernandez et al. [9] proved in the LITRO study that postponing the revascularization procedure based on the IVUS result (>6.0 mm^2) is safe within a 2-year follow-up period. Data from the publications of Polish authors indicate that the minimum left main coronary artery lumen area correlating with a negative FFR result (>0.75) is 8.9 mm^2 [10].

On the other hand, Kang et al. [11] showed in a population of 55 patients that the cut-off value for FFR <0.80 is the left main lumen area of 4.8 mm^2, while for FFR <0.75 it should be 4.1 mm^2 for the Asian population assessed in this study. It has been calculated that in patients with BMI <24 kg/m^2 or left ventricular mass <156 g, the surface area of the vessel lumen corresponding to FFR <0.80 should be at least 4.1 mm^2 [12]. This observation is consistent with the general opinion of experts who point out that the results obtained by the Korean authors are related to the demographic characteristics of Asian populations (body weight, height, overweight), which translates into smaller dimensions of the left main and coronary vessels in general. Recently, it has also been found that ethnic differences can influence the size of coronary arteries independently of parameters that determine body size, such as body weight, height, or body surface area (BSA) [13]. For this reason, the authors of the European position paper on intracoronary imaging recommend treating the interval 4.5–6.0 mm^2 as a gray zone and, in each case, consider the functional assessment of stenosis in the left main coronary artery [14] (Figure 3).

The use of OCT to assess the significance of intermediate left main stenosis cannot currently be recommended in everyday clinical practice. Data in this regard are limited to one study — Dato et al. [15]. Based on the criteria from their center, the authors assumed that the patient requires revascularization in the case of large plaque volume or the presence of ulceration in the left main or significant lesions in the left anterior descending (LAD) and/or circumflex (Cx) artery ostium [15].

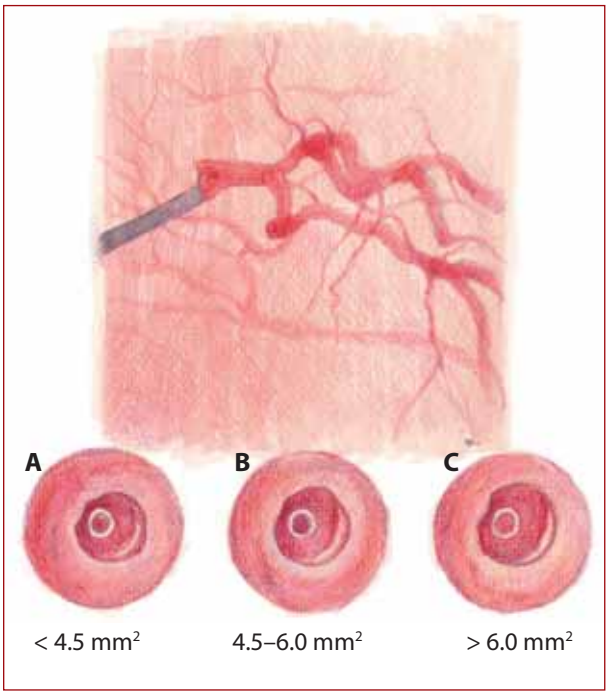


Figure 3. Schematic representation of borderline left main minimal lumen area seen on an intravascular ultrasound. According to [14], a lumen area less than 4.5 mm^2 (**A**) requires revascularization, but the lumen presented in subpanel **C** could be deferred from treatment. Values in between should be diagnosed with additional techniques (**B**, i.e. fractional flow reserve)

ASSESSMENT OF INTERMEDIATE NON LEFT MAIN LESIONS

The use of intracoronary imaging methods to assess the significance of stenosis in non-left main lesions is not currently recommended in the European position paper [14] mainly due to large discrepancies in the results obtained by different authors. A functional evaluation should be the method of choice. In some cases (20%–25%), the results of the significance assessment based on imaging methods were false positive, which was confirmed by the FIRST study [16] and a meta-analysis of clinical trials with IVUS and FFR [17].

OPTIMIZATION OF CORONARY ANGIOPLASTY PROCEDURES

Non left main lesions

Published studies and meta-analyses of studies using IVUS clearly indicate its benefits during coronary angioplasty procedures with stent implantation [18–25], including a reduction in long-term mortality and the frequency of re-revascularization and restenosis [18–21]. It should be emphasized that this also applies to patients undergoing

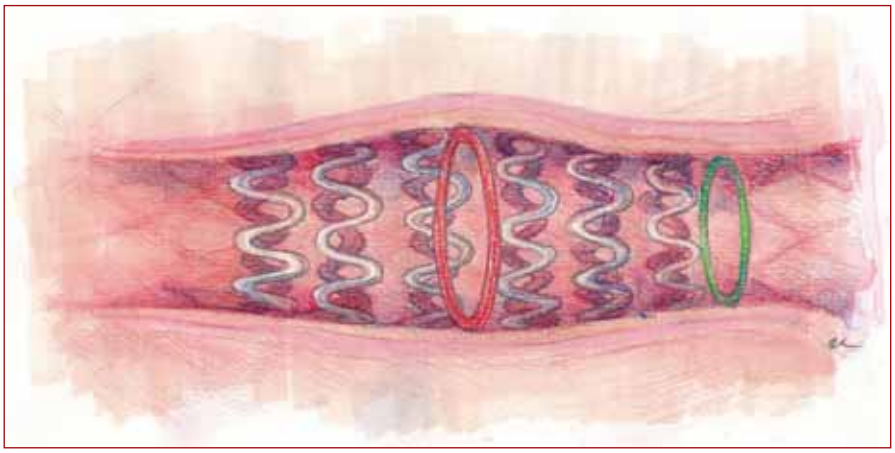


Figure 4. Optimization criteria after implantation of stents into non-LMS lesions. The minimal stent area (MSA) should be >5.5 mm^2 by intravascular ultrasound or >4.5 mm^2 by optical coherence tomography (red circle). Alternatively, MSA should be >80% of average reference lumen areas (i.e. distal reference — green circle). Additional criteria as follows: no significant dissection (<60 degrees, flap limited to the intima and <2 mm in length), no extensive protrusion, no significant strut malapossition (<1 mm in length, axial distance <0.4 mm), and finally plaque burden at stent edge <50 % without lipid pool) [26]

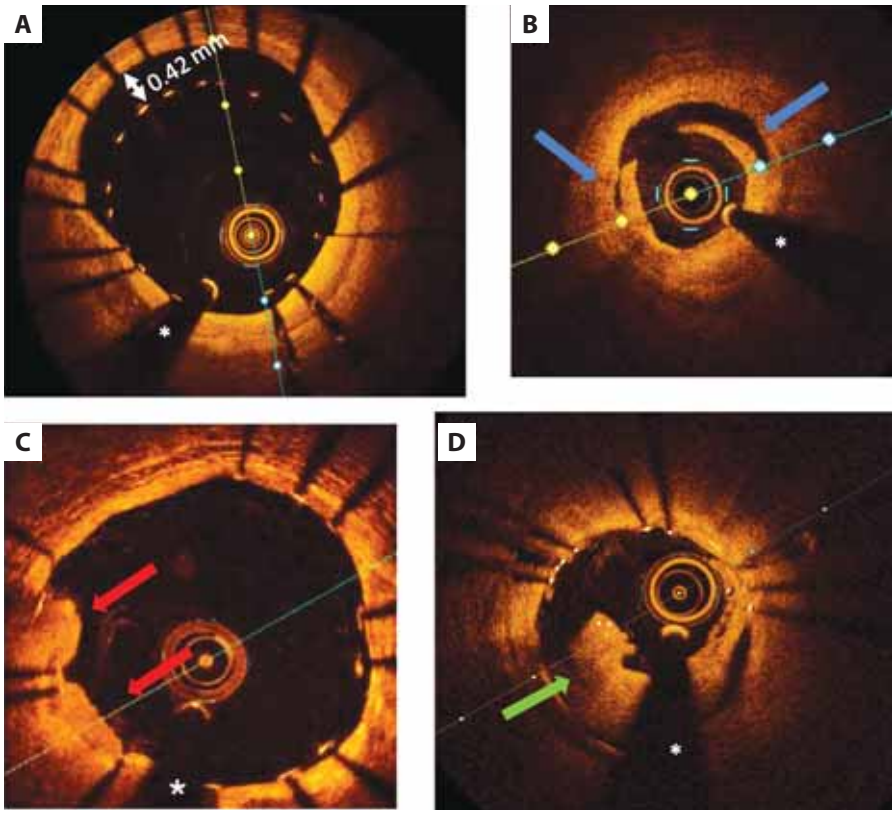


Figure 5. Intracoronary periprocedural imaging using optical coherence tomography and examples of post-percutaneous coronary intervention. **A**. Malapposition of stent struts (the malapposition distance was determined). **B.** Edge dissection (the blue arrows). **C.** Tissue protrusion (the red arrows). **D.** Thrombus (the green arrow)

*Wire shadow

comprehensive procedures (bifurcations, left main lesions, long lesions, etc.) [21]. Such clinical trial results and meta-analyzes are influenced by at least the following factors — a reduction of the frequency of underexpanded stenting and of the risk of wrong stent position ("geographic miss" [GM], the stent does not cover the entire atherosclerotic plaque), and the treatment of edge dissections [26]. Consequently, the risk of stent failure (STF) is reduced [27], as well as the incidence of periprocedural infarction, which ultimately improves the prognosis in long-term follow-up.

The benefits of optimizing PCI procedures with OCT have been confirmed in the articles by Prati et al. [28], the DOCTORS [29], and ILUMIEN III studies [30]. The meta-analysis by Buccheri et al. [23] confirmed that the risk of death and other cardiovascular events is lower with IVUS or OCT than with procedures performed under angiography guidance. Researchers note that the OCT resolution allows for the identification of abnormalities that require correction, such as malapposition >400 μm and length >1 mm, marginal dissection above 60 degrees of vessel circumference, length >2 mm, or disturbance in the structure of the medial/outer membrane of the vessel [26] (Figures 4 and 5).

In the opinion of the authors of the report, operators who decide to use intracoronary imaging should pay attention to several aspects, such as the reference size of the vessel and the composition of the atherosclerotic plaque (in terms of the occurrence of calcifications and the selection of the technique of lesion preparation). When choosing the method, i.e., IVUS or OCT, it should be remembered that in the OCT examination, the size of the vessel lumen is about

10% smaller than in IVUS [31]. Additionally, the reference segments (without changes observed on angiograms) usually have atherosclerotic plaque covering about 30%–50% of the vessel area [32]. The optimal site selected as the reference segment in the IVUS/OCT assessment should be the section of the vessel in which the plaque covers less than 50% of the vessel area. Both edges of the stent should be in such places. If this is not possible, the area with the smallest burden of the atherosclerotic plaque should be chosen. In the opinion of the authors of the report, it is additionally necessary to pay attention to the morphological features of the plaque — avoiding calcification, "soft" plaques (with a high lipid load), which could be responsible for a greater risk of dissection or flow disorders [26].

In the opinion of the authors, the selection of the stent diameter should be based on the criteria taken from the OPINION study [33]. The size (diameter) of the implanted stent should not exceed the obtained vessel diameter measurement (EEM diameter, the so-called media-to-media diameter measurement, dimension based on the outer membrane) increased by a maximum of 0.25 mm [33]. Dimensioning based on the averaged dimensions of two diameters (maximum and minimum) was also allowed – it is a good solution when the shape of the vessel is far from the circle [21].

Analyzing the results of clinical trials in terms of the minimum stent lumen area reducing the risk of adverse events during the observation period, it was found that it should be 5.5 mm^2 [34] in the case of IVUS studies and 4.5 mm^2 in the case of OCT [35], which also was confirmed by the European recommendations [14]. Alternatively, the second method of assessing the minimum stent area (MSA) is a reference vessel lumen area criterion (Figure 4) of at least 80% of the averaged proximal and distal lumen area of the vessel. It is also known that obtaining an MSA value larger than the lumen area in the distal reference segment allowed reducing the incidence of cardiac events by up to 1.5% per year [20].

At this point, it is necessary to mention the more and more widely used mnemonic principle of minimal lumen diameter (MLD) MAX, which helps in optimizing angioplasty procedures using OCT. More information can be found in the literature [36].

Another context, in which the authors of the opinion recommend the use of intracoronary imaging, especially OCT, is the failure of stent implantation (STF). It applies not only to in-stent restenosis, but primarily to stent thrombosis and the identification of pathologies such as stent underexpansion, edge dissection, GM, neoatherosclerosis, and stent struts fractures in OCT [37]. The use of IVUS/OCT imaging is, in the opinion of the authors, very useful in planning the re-treatment of revascularization and in identifying potential threats to these procedures (calcification, TCFA, etc.). Additionally, the resolution of OCT helps to identify the causes of acute coronary syndromes associated with neoatherosclerosis [38].

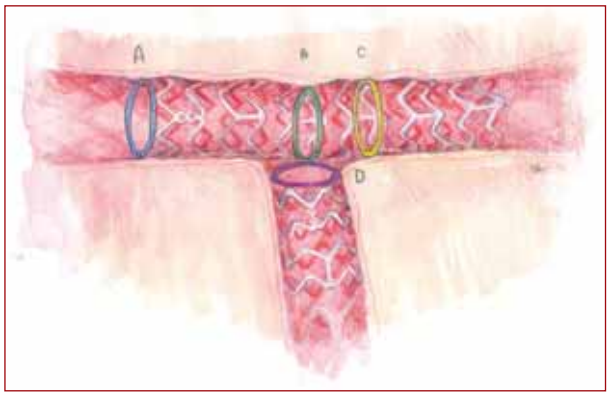


Figure 6. Schematic representation of optimal minimal lumen areas after left main stent implantation. The different values were shown in the Asian (Kang criteria) and in the European (EXCEL study) populations; **A** represents minimal stent area at the left main trunk (8.2 mm^2 for Kang and 9.3 mm^2); **B** indicates POC-transitional zone (polygon of confluence) and the 7.0 mm^2 for Kang criteria and no data for Excel study; **C** represents left anterior descending artery with 6.3 mm^2 of Kang criteria and 6.9 mm^2 for EXCEL trial; **D** indicates ostium of the circumflex artery and 5.0 mm^2 of Kang data and 5.3 mm^2 for EXCEL data

EXCEL data presented during Fellow Course 2021 (unpublished)

Left main lesions

The use of intra-coronary ultrasound during stent implantation in the left main coronary artery resulted in a significant reduction of the composite endpoint compared to angiography-guided procedures, including those performed in the distal segment of the left coronary artery [39, 40]. In other studies, the use of IVUS by operators reduced the incidence of stent thrombosis during the long-term follow-up [41, 42].

In a study assessing the mechanisms of in-stent restenosis, Kang et al. [43] showed that immediately after stent implantation in the two-stent technique in the left main coronary artery, the minimum lumen area should be 8.2 mm^2 in the left main coronary artery, 6.3 mm^2 at the ostium of the LAD and 5.0 mm^2 at the ostium of the Cx. The literature refers to it as the Kang criteria (Figure 6). They are now commonly used in the clinical practice of invasive cardiologists to evaluate the outcome of stent implantation in the left main coronary artery. However, they are obtained in populations of patients with lower body weight, and, due to ethnic differences, they may be of limited use in the Polish population. At this point, it should be noted that the reports from a conference based on European and American patients indicate higher values of the minimum stent surface areas after left main coronary artery angioplasty. In the work of the Spanish authors [44], using predefined optimization criteria for left main coronary artery angioplasty significantly reduced the frequency of

Table 2. A summary of the experts' opinion on the clinical use of intravascular imaging

Clinical scenario	Statement	Choice IVUS/OCT
Optimization of native coronary artery stenting	In the case of native coronary artery stenting, intracoronary imaging should be considered both before (for vessel sizing, assessment of calcifications, etc.) and after the procedure (assessment of stent expansion, edge dissections, geographic miss, etc.). It is recommended to achieve 5.5 mm^2 (MLA) (in IVUS) or 4.5 mm^2 (in OCT) and/or >80% of a vessel lumen area in its distal reference segment. An operator should be focused on correcting struts' malapposition and large edge dissections. In the case of long lesions and CTO recanalization procedures, it is recommended to use intracoronary imaging at every stage of the procedures	IVUS = OCT
Optimization of revascularization in patients with coronary calcifications	Intracoronary imaging is recommended to select an appropriate therapeutic technique, including ablation, in selected patients with moderate to severe coronary calcifications. Its use after stent implantation allows for optimizing prosthesis expansion	OCT >IVUS
Assessment of intermediate left main lesions	IVUS is recommended to assess an intermediate left main stenosis. The examination should evaluate the orifices of both main vessels, as well as morphology and extent (plaque continuity) of atherosclerosis. It is recommended to consider 6 mm^2 as the cut-off point for revascularization/deferral. In questionable cases, the examination may be supplemented with an FFR assessment	IVUS
Guidance of left main stenting	IVUS should be mandatory in every case of the left main stenting procedure, particularly for two-stent techniques. It is recommended to use IVUS both before (planning) and after stent implantation (verifying stent expansion, malapposition, etc.). OCT imaging for stenting is feasible but has some limitations due to the acquisition technique	IVUS >OCT
Intracoronary imaging in acute coronary syndromes	Intracoronary imaging is recommended in every case of suspected acute coronary syndrome with no obvious evidence of a culprit lesion. It should be performed to rule out abnormalities, such as plaque erosion or rupture, intravascular thrombus, or spontaneous dissection of a coronary artery. OCT is preferred for diagnosis and treatment of acute coronary syndrome related to stent failure caused by edge dissection, large malappositons, plaque prolapse, and neoatherosclerosis	OCT >IVUS
Imaging for spontaneous coronary artery dissection	Intravascular ultrasound is preferred due to no-contrast imaging that could expand intramural hematoma	IVUS >OCT
Stent failure	Intracoronary imaging is recommended to rule out mechanical causes of restenosis or stent thrombosis, such as stent underexpansion, edge dissection, acquired malapposition, and neoaterosclerosis. It can help choose an appropriate therapy	OCT >IVUS
Cardiac allograft vasculopathy	Intracoronary imaging (particularly IVUS) is recommended as a routine diagnostic tool for CAV after heart transplantation according to the recommendations of transplant societies	IVUS >OCT
Assessment of neoatherosclerosis	Intracoronary imaging is recommended in every patient with suspected transformation to neoatherosclerosis to diagnose the nature of the lesion and plan a revascularization strategy	OCT >IVUS
Other applications	CTO procedures (wire advancement, true/false lumen navigation) — studies on progression/regression of atherosclerosis	IVUS/OCT

Abbreviations: CAV, cardiac allograft vasculopathy; CTO, chronic total occlusion; FFR, fractional flow reserve; IVUS, intravascular ultrasound; OCT, optical coherence tomography

the composite endpoint compared to procedures guided only by angiography [44].

In the opinion of the authors of the statement, IVUS in conjunction with the above-mentioned optimization criteria should take place in each case of left main coronary angioplasty. Operators should also take into account ethnic differences and strive for maximum optimization of the stent dimensions in accordance with the principle "bigger is better". Indeed, this issue requires further research.

The work of Fujino et al. [45] showed that it is possible to perform OCT in the left main both before and after angioplasty. However, visualizing the entire left main segment is relatively tricky (ostial lesions), although detecting malapposition is significantly more frequent than in the case of intracoronary ultrasound. A recent report by Cortese et al. [46] revealed that the correction of underexpansion and malapposition of the stent struts might affect the angiographic outcome of the procedure in distal stenosis, although without a statistically significant change in the clinical prognosis.

It should be mentioned here that publications of the first clinical trials in which OCT was used to optimize left main stem (LMS) stent implantation procedures are already available in the literature. We talk about the LEMON [47] and ROCK II [48] studies.

Identification of culprit lesions in acute coronary syndrome

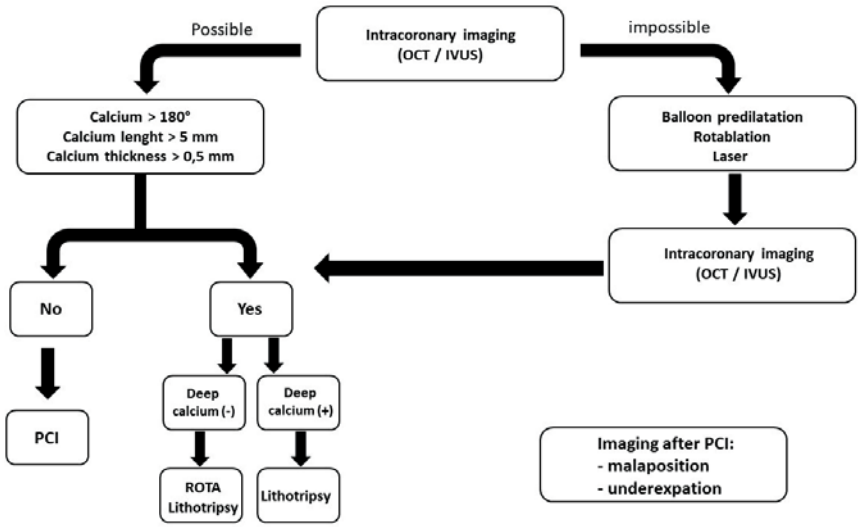
Invasive imaging should be recommended in patients with acute coronary syndrome who do not present typical coronary changes on angiography. It has been shown that the incidence of unstable lesions in patients with MINOCA reaches 25% despite angiographically normal coronary arteries or with a slight intensity of atherosclerotic lesions [49] in the vessel responsible for acute coronary syndrome (ACS). Unstable plaques are also found in patients with Tako-tsubo cardiomyopathy [50, 51], as described above.

In patients with acute coronary syndromes, it has been shown that changes that may be responsible for ACS affect many places in the coronary arteries [52], and the type of pathology associated with its occurrence may include atherosclerotic rupture or erosion, spontaneous coronary dissection, or coronary spasm [53]. Moreover, it should be emphasized that intracoronary imaging plays a significant role in the diagnosis of spontaneous dissection of the coronary artery [54].

The resolution of the OCT examination allows for the detection of a small thrombus, invisible in other imag-

Figure 7. An algorithm for the management of calcified lesions and technique preference

	IVUS	OCT
Mild/moderate calcifications	++	+++
Deep calcifications	+++	++
Superficial calcifications	+++	+++
Arc of calcium	+++	+++
Calcification thickness	0	+++



Abbreviations: PCI, percutaneous coronary intervention; other — see Table 2

ing tests, and therefore should be recommended as an additional diagnostic tool in the case of suspected acute coronary syndrome and no significant lesions on the coronary angiography.

The OCT resolution also allows direct measuring of the thickness of the fibrous cap of the plaque. Sawada et al. [55] showed in a population of 56 patients that neither VH-IVUS nor OCT used alone were sufficient for reliable identification of TCFA (thin cap fibrous atheroma). Moreover, the use of OCT enables the detection of intracoronary thrombus, ruptured plaque, and TCFA in vessels not responsible for ACS [55, 56]. This finding confirmed previous IVUS observations that plaque instability is a general coronary phenomenon [52].

THE ROLE OF INVASIVE IMAGING IN CALCIFIED LESIONS

Calcifications are a risk factor for abnormal stent deployment [57]. The work of Hoffmann et al. [58] and Fujino et al. [59] clearly showed that the presence of calcifications covering >180 degrees of the vessel circumference and the length of these calcifications >5 mm in the OCT assessment increase the risk of stent underexpansion. The recently published work by Wang et al. [60] shows that intracoronary ultrasound is more sensitive in detecting calcifications than optical coherence tomography and, of course, contrast angiography. On the other hand, the advantage of OCT is the possibility of measuring the thickness of the calcification [59], which is impossible in the case of IVUS due to the acoustic shadow. This makes it possible, together with the volumetric evaluation, to use OCT as a tool for the stent underexpansion prediction algorithm. The research of Yamamoto et al. [61] shows that high-speed rotablation and orbital atherectomy are effective in the case of superficial calcifications and vessels in which the lumen cross-section is smaller than the size of the devices as mentioned above (burr and orbital crown). At the same time, lithotripsy is effective in the case of lesions with calcifications of both superficial and deep localization [62], which may be necessary in the case of lesions within the left main coronary artery [63]. Figure 7 presents a diagram of the procedure depending on the anatomical conditions and the properties of both methods in detecting calcifications. Examples of other algorithms for dealing with calcified lesions are available in the literature [64].

OTHER APPLICATIONS — CARDIAC ALLOGRAFT VASCULOPATHY

Coronary vasculopathy (CAV) following cardiac transplantation [65] presents as progressive changes in epicardial arteries, often in the absence of lumen-narrowing lesions. For this reason, the use of intracoronary imaging is recommended, along with angiographic examination 4–6 weeks after heart transplantation to exclude coronary artery disease in the donor and its repeat after one year to assess disease progression. The use of OCT requires further research, but the results so far have been promising [66].

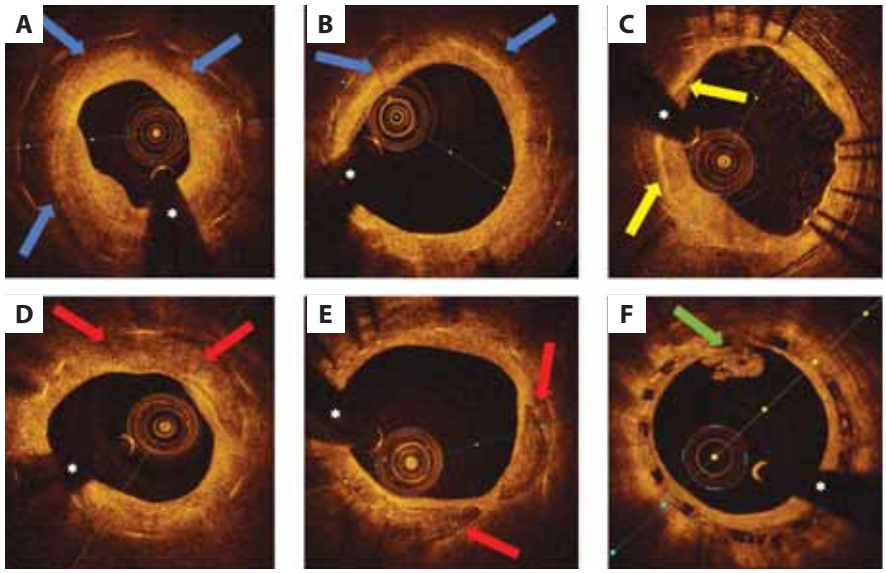


Figure 8. Long-term follow-up after percutaneous coronary angioplasty. **A–D.** Examples of neoatherosclerosis after bare-metal stent/drug-eluting stent implantation. The red arrows — calcifications; the blue arrows — lipid accumulation; the yellow arrows — macrophage accumulation, the green arrow — thrombus

*Wire shadow

Table 3. Reimbursement conditions in Poland

• Left main lesion severity assessment
• Proximal left anterior descendent artery lesion severity assessment
• Multivessel coronary artery lesion severity assessment
• Follow-up of left main stenting
• Assessment of mechanisms and treatment selection in case of stent failure (in-stent restenosis, stent thrombosis, suboptimal acute result suspicion)
• Diagnosis of myocardial infarction in case of ambiguous angiography result
• Diagnosis of cardiac allograft vasculopathy

OTHER APPLICATIONS — NEOATHEROSCLEROSIS

Long observation periods of patients with implanted coronary stents revealed a new phenomenon — neoatherosclerosis [67]. It often takes the form of in-stent restenosis when the degree of narrowing of the vessel exceeds 50% of the vessel lumen. However, only intravascular imaging allows for precise visualization of the vessel wall pathology (Figure 8), consisting of TCFA lesions, plaque ruptures, calcification, or stent thrombus [68]. For this reason, OCT is the technique of choice to visualize the changes mentioned above.

REFUND POLICY

The reimbursement of intravascular imaging in Poland is carried out based on Regulation No. 38/2017/DSOZ of the President of the National Health Fund of May 29, 2017. The reimbursement covers only intravascular ultrasound, both for chronic and acute coronary syndromes, and is assigned to the code: ICD-9 00.241. However, at the beginning of 2022, OCT was introduced by the Ministry of Health to the list of guaranteed benefits, which gives hope that it might be included in the reimbursement of the National Health Fund. Table 3 presents anatomical and clinical conditions of reimbursement in Poland.

CONCLUSIONS

Data from clinical trials and large registries demonstrate the benefits of intracoronary imaging. The long-term outcomes may be significantly improved with these modalities. In many cases, both these techniques complement each other in obtaining information on pathologies of a coronary artery wall. It should also be emphasized that cost-effectiveness analysis provided arguments in favor of using intracoronary imaging in everyday clinical practice [69], which should translate directly into financing of both intracoronary imaging methods. Nowadays, only intravascular ultrasound is reimbursed in Poland, but it should be highlighted that optical coherence tomography should also be reimbursed with a similar indication as IVUS.

Article information

Conflict of interest: TP reports speaking honoraria from Philips IGT and Abbott Vascular. JL reports speaking honoraria from Philips IGT and Abbott Vascular. JK reports Philips IGT and Abbott Vascular. JP reports speaking honoraria from Boston Scientific. WW reports speaking honoraria from Abbott Vascular and Boston Scientific. AW reports speaking honoraria from Abbott Vascular and Boston Scientific and proctoring fee from Boston Scientific. RG reports Philips IGT, Abbott Vascular, and proctoring fees from Philips IGT.

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Barbara Werner, MD, PhD (1924–2022) In memoriam

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Barbara Werner née Szurig was born on April 10, 1924 in Warsaw (Figure 1) [1, 2]. Before World War II, she graduated from the renowned Słowacki Secondary School for Girls. During the war, she continued her education at clandestine courses for physicians under the aegis of the Private Vocational School for Auxiliary Sanitary Personnel of Doctor Jan Zaorski (subordinated to the clandestine Council of the Faculty of Medicine) of the University of Warsaw.

After the war, she completed her medical studies at the Faculty of Medicine of the University of Warsaw, graduating from it in June 1947 and receiving her medical diploma in 1949.

After completing her internship at the surgical ward of the hospital in Płońsk, she took up a job as a volunteer and fellow at the surgical ward of the Institute of Tuberculosis in Warsaw led by prof. Leon Manteuffel-Szoege. During her 26 years of work at the Institute, she went through successive steps of her professional career, from the post of teaching assistant to the Head of the Department of Surgery.

Figure 1. Barbara Werner

In 1953, she completed first-degree, and in 1960 second-degree specialty training in surgical diseases, and in 1961 she completed specialty training in thoracic surgery. She was among the first female cardiac surgeons in Poland. She participated in many pioneering heart surgeries.

On October 7, 1966, she was awarded the title of Doctor of Medical Sciences on the basis of a dissertation entitled: "Surgical treatment of constrictive pericarditis (based on the experience with 100 pericardiectomies)".

In the years 1973–1980, she worked at the surgical ward of the Hospital at 17 Kasprzaka St. in Warsaw; from July 1975, she was its Deputy Head. From December 1980 until her retirement, she worked at the Institute of Cardiology in Warsaw as the Deputy Head of the 2nd Department of Cardiac Surgery headed by Professor Wacław Sitkowski.

She was an active member of the Warsaw Medical Society and the Polish Society of Cardiology. She was a co-author of scientific publications on the cardiosurgical treatment of constrictive pericarditis and mitral stenosis published in the *Kardiologia Polska* (*Polish Heart Journal*).

Barbara Werner had a beautiful war record [1–4]. She was a sanitary instructor of the Union of Polish Youth Future "Pet", then she served as a liaison officer in the Assault Groups of the Grey Regiments in the Warsaw District of the Home Army. From September 1943, she was a soldier of the "Zośka" battalion of the 2nd Rudy Company; her pseudonym was "Basia". She took part in the first assault of the battalion, codenamed "Wilanów", in the autumn of 1943, as a liaison officer of the

commander Władysław Cieplak, pseudonym "Giewont". During the assault, she was apprehended while carrying a gun by a German patrol. She saved herself by jumping into a moat in the courtyard of the Wilanów Palace [2, 3].

She participated in the Warsaw Uprising as a liaison officer of the legendary Andrzej Romocki "Morro" [1, 2, 4]. She took part in battles in Wola and the Old Town as a rifleman in the ranks of the "Broda 53" Regiment of the Home Army Grouping "Radoslaw". On 19 August 1944, she was seriously wounded. Treated at the hospital at Miodowa St., she miraculously survived bombardment of this insurgent hospital.

After the war, just like other soldiers of the "Zośka" battalion, she was victimized by the security services. She refused to collaborate despite the threat of being taken to the Vistula embankment "from which you could take a good jump into the river" [5].

She devoted herself to her work and family. She married Andrzej Werner, a maxillofacial surgeon and a Home Army soldier. They raised two sons, Stanisław and Jan.

Until the last moments of her life, she was interested in the achievements of modern medicine. She participated in the activities of medical societies, gave interviews, and took part in ceremonies commemorating the Warsaw uprising.

For her merits during World War II, she was honored with the Cross of Valour, the Cross of the Warsaw Uprising, and the Officer's Cross of the Order of Polonia Restituta. She also received the *Digno Laude* Medal: "To One Worthy of Glory", which is awarded by the Warsaw Medical Society and the Association of Warsaw Insurgents to recognize soldiers of the Insurgent Sanitary Service for their outstanding bravery and sacrifice [1, 2].

Barbara Werner died on March 23, 2022. She was buried at the Old Powązki Cemetery in Warsaw.

She will always remain in the memory of those who knew her as a righteous and modest person, a charismatic doctor dedicated to her patients, a beloved mother, grandmother, and great-grandmother.

For me, she was a model of patriotic attitudes and professional commitment, and also my best friend.

Article information

Conflict of interest: None declared.

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In the Review entitled "Mavacamten — a new disease-specific option for pharmacological treatment of symptomatic patients with hypertrophic cardiomyopathy" (Pysz P, Rajtar-Salwa R, Smolka G, et al. Kardiol Pol. 2021; 79 [9]: 949–954) an author's affiliation was missing. The correct affiliations for Prof. Paweł Petkow-Dimitrow are:

- Department of Cardiology and Cardiovascular Interventions, University Hospital, Kraków, Poland
- 2nd Department of Cardiology, Jagiellonian University Medical College, Kraków, Poland.

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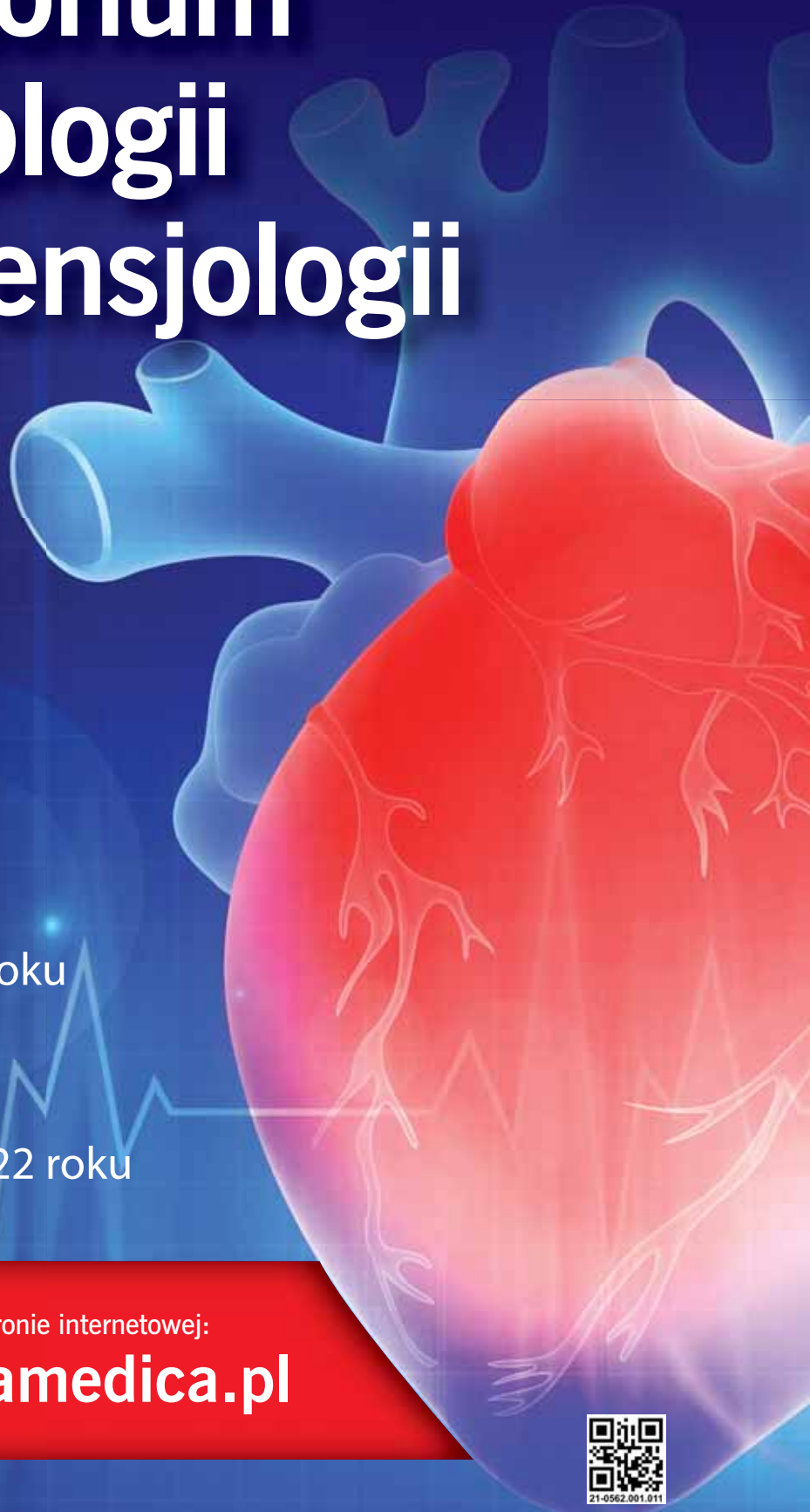

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Virtual Meeting jest skierowane tylko do osób uprawnionych do wystawiania recept lub osób prowadzących obrót produktami leczniczymi — podstawa prawna: Ustawa z dnia 6 września 2001 r. Prawo farmaceutyczne (Dz. U. z 2017 r. poz. 2211. z późn. zm.).

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. 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. **Wskazania do stosowania:** Cukrzyca typu 2 Produkt leczniczy Jardiance® jest wskazany do stosowania w leczeniu dorosłych z niewystarczającą 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. **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. *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 SGLT2, diureza osmotyczna towarzyszaca 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). Powikłane 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. Choroba naciekowa lub kardiomiopatia takotsubo Nie prowadzono specyficznych badań u pacjentów z chorobą naciekową lub kardiomiopatią takotsubo. Z tego powodu nie określono skuteczności u tych pacjentów. 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. Sód Każda tabletka zawiera mniej niż 1 mmol (23 mg) sodu, to znaczy lek uznaje się za „wolny od sodu". **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 3 534 pacjentów, z których 1 183 otrzymywało placebo, a 2 351 – 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 badań EMPEROR włączono pacjentów z niewydolnością serca i zredukowaną frakcją wyrzutową (N=3 726) lub zachowaną frakcją wyrzutową (N=5 985), którzy otrzymywali leczenie 10 mg empagliflozyny lub placebo. U około połowy pacjentów występowała cukrzyca typu 2. Najczęściej zgłaszanym działaniem niepożądanym łącznie w badaniach EMPEROR-Reduced i EMPEROR-Preserved było zmniejszenie objętości płynów (10 mg empagliflozyny: 11,4%; placebo: 9,7%). Ogólny profil bezpieczeństwa stosowania empagliflozyny był zasadniczo spójny w badanych wskazaniach. 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 (≥ 1/1 000 do < 1/100); rzadko (≥ 1/10 000 do < 1/1 000), 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	Bardzo 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 moczopochodną)[a]		martwicze zapalenie powięzi krocza (zgorzel Fourniera)*	
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		cewkowo--śródmiąższowe zapalenie nerek
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 * 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 badaniach niewydolności serca EMPEROR obserwowano podobną częstość występowania hipoglikemii podczas stosowania w skojarzeniu z sulfonylomocznikiem lub insuliną (10 mg empagliflozyny: 6,5%; placebo: 6,7%). *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 badaniach dotyczących niewydolności serca EMPEROR ciężką hipoglikemię obserwowano z podobną częstością występowania u pacjentów z cukrzycą podczas leczenia empagliflozyną i placebo w skojarzeniu z sulfonylomocznikiem lub insuliną (10 mg empagliflozyny: 2,2%, placebo: 1,9%). *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 badaniach dotyczących niewydolności serca EMPEROR częstość występowania tego typu zakażeń była większa u pacjentów z cukrzycą (10 mg empagliflozyny: 2,3%; placebo: 0,8%) niż u pacjentów bez cukrzycy (10 mg empagliflozyny: 1,7%; placebo: 0,7%) 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 badaniach niewydolności serca EMPEROR zwiększone oddawanie moczu obserwowano z podobną częstością występowania u pacjentów leczonych empagliflozyną i placebo (10 mg empagliflozyny: 0,9%, placebo 0,5%). *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:** 03 marca 2022 **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 wskazaniach: <1> 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) potwierdzona 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; <2> Przewlekła niewydolność serca u dorosłych pacjentów z obniżoną frakcją wyrzutową lewej komory serca (LVEF ≤40%) oraz utrzymującymi się objawami choroby w klasie II-IV NYHA pomimo zastosowania terapii opartej na ACEi (lub ARB/ARNi) i lekach z grupy betaadrenolityków oraz jeśli wskazane antagonistach receptora mineralokortykoidów – na podstawie obwieszczenia Ministra Zdrowia z dnia 20 kwietnia 2022 r. w sprawie wykazu refundowanych leków, środków spożywczych specjalnego przeznaczenia żywieniowego oraz wyrobów medycznych na 1 maja 2022 r. (DZ. URZ. Min. Zdr. 2022.41).

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GDYNIA,
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Przewodniczący Komitetu Naukowego:

prof. dr hab. n. med. Krzysztof J. Filipiak, FESC
dr hab. n. med. Iwona Gorczyca-Głowacka

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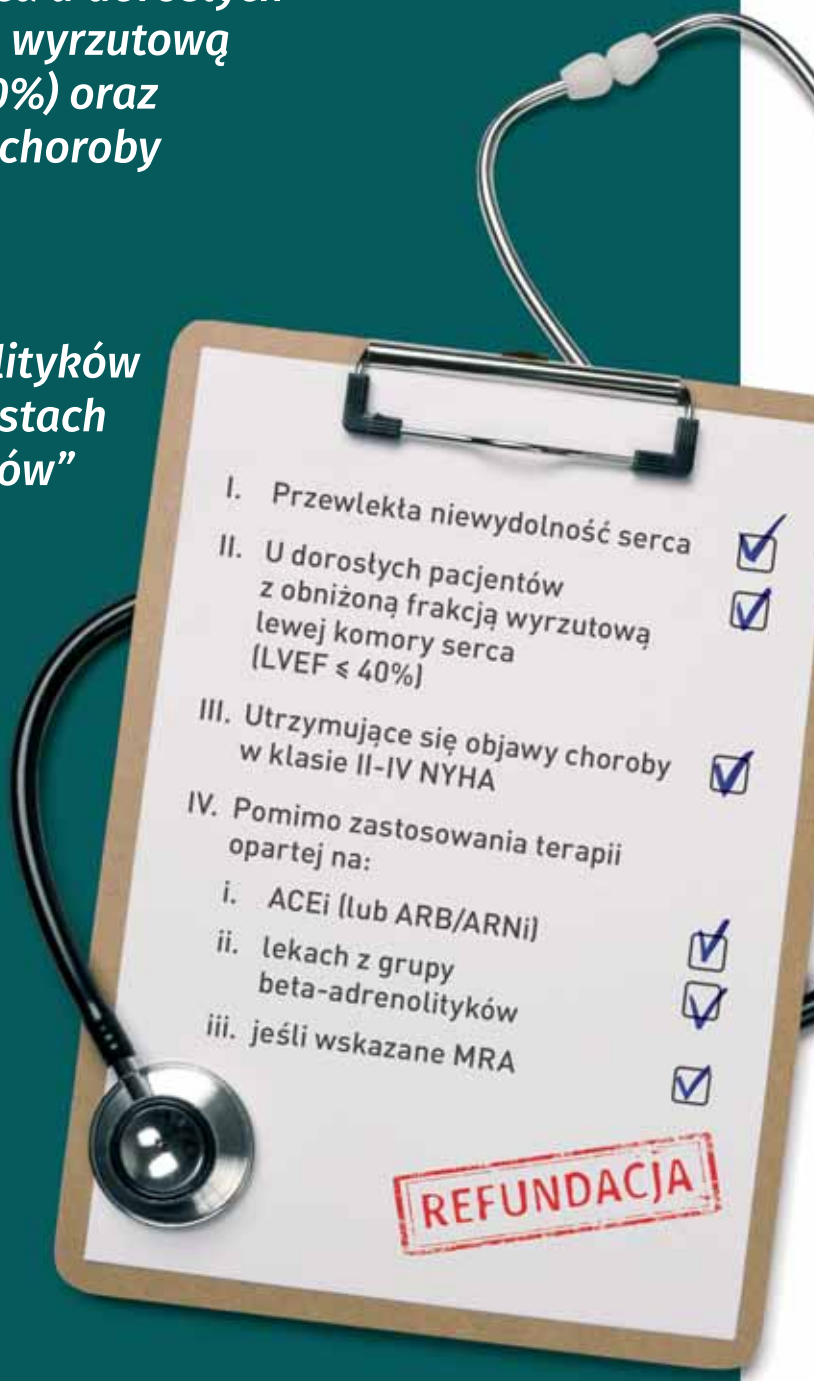
REFUNDACJA w HFrEF[1]

„Przewlekła niewydolność serca u dorosłych pacjentów z obniżoną frakcją wyrzutową lewej komory serca (LVEF ≤ 40%) oraz utrzymującymi się objawami choroby w klasie II-IV NYHA pomimo zastosowania terapii opartej na ACEi (lub ARB/ARNi) i lekach z grupy beta-adrenolityków oraz jeśli wskazane antagonistach receptora mineralokortykoidów”



Poziom odpłatności[1]:

30%

opakowanie 28 tabl.

Cena dla pacjenta[1]:

54,00 zł

HFrEF – niewydolność serca z obniżoną frakcją wyrzutową; LVEF – frakcja wyrzutowa lewej komory.

1. Obwieszczenie Ministra Zdrowia z dnia 20 kwietnia 2022 r. w sprawie wykazu refundowanych leków, środków spożywczych specjalnego przeznaczenia żywieniowego oraz wyrobów medycznych na 1 maja 2022 r. (DZ. URZ. Min. Zdr. 2022.41).

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