ISSN 0022–9032

e-ISSN 1897–4279

October 2021, vol. 79, number 10

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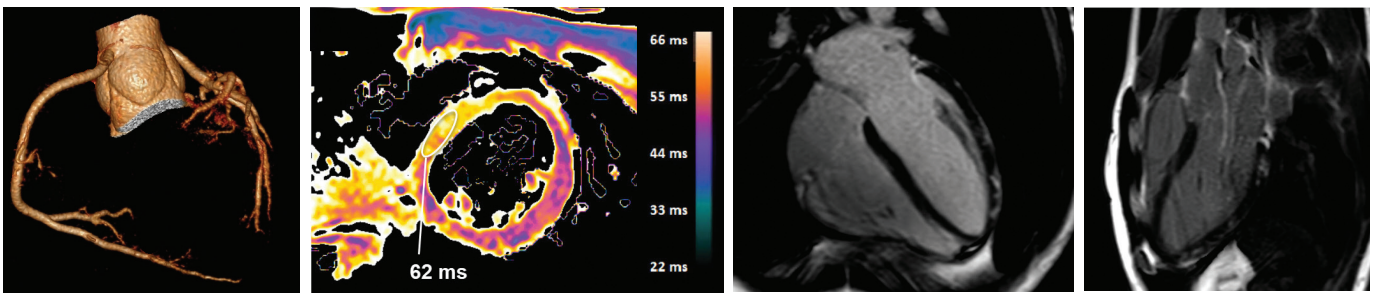


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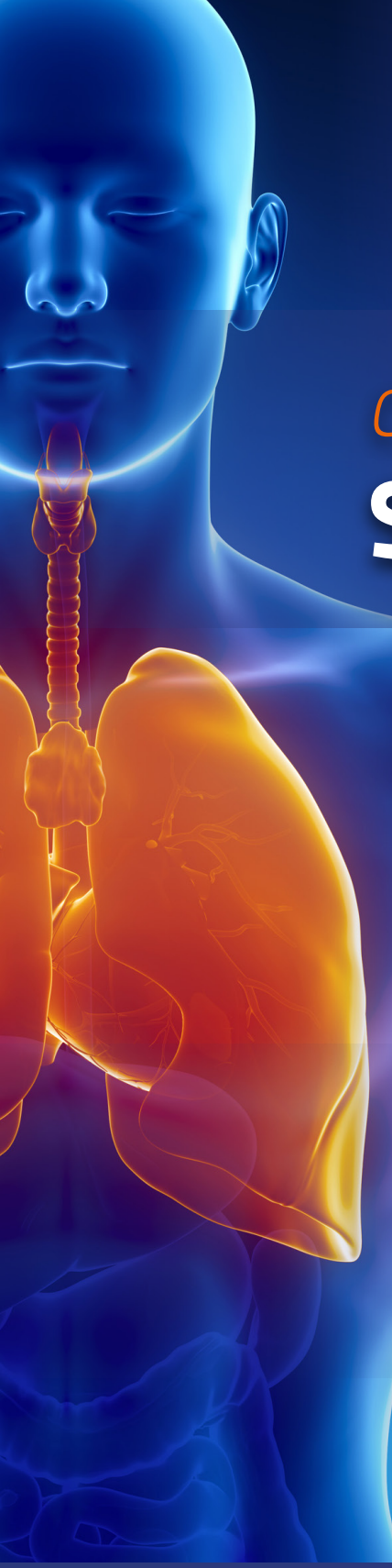

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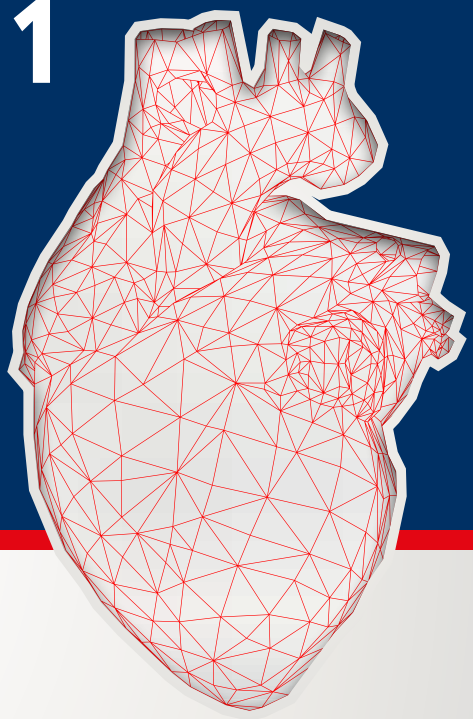

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# Gentamicin-collagen sponge and prevention of cardiac implantable electronic device infections: bargain basement or penthouse suite?

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Kardiol Pol. 2021; 79 (10): 1055–1057;
DOI: 10.33963/KP.a2021.0122

**Received:**
September 17, 2021

**Revision accepted:**
September 24, 2021

**Published online:**
October 5, 2021

Although cardiac implantable electronic device infections (CIEDI) remain a rare complication, its financial and human burdens are staggering [1, 2]. Thus, it is no wonder that CIEDI prevention has been the focus of multiple investigations and, currently, the only area in which clinical trial data are available regarding this syndrome. The search for cost-effective strategies to reduce the risk of CIEDI has led to the development of improved antibiotic prophylaxis (AP) protocols, drug-eluting envelopes, and novel device designs (i.e., leadless pacemakers) (Figure 1). For over two decades, meta-analysis [3] results have bolstered the notion that perioperative AP is beneficial in reducing the rate of CIEDI as a complication of surgical site infection. Since the bulk of these infections are due to staphylococcal species, one dose of pre-operative cefazolin has been advocated. A recent large, randomized, double-blind, placebo-controlled trial [4] demonstrated a five-fold lower incidence of CIEDI in the group who received pre-operative cefazolin vs. that of the placebo group (0.63% vs. 3.28%). As a result, the study was terminated early, and AP administration for the prevention of CIEDI was further solidified as a standard of care.

More recently, Krahn and colleagues [5] tested whether a single dose of pre-operative cefazolin was as efficacious as an "incremental" perioperative antibiotic regimen to reduce CIEDI in a cluster randomized crossover trial (PADIT Trial)

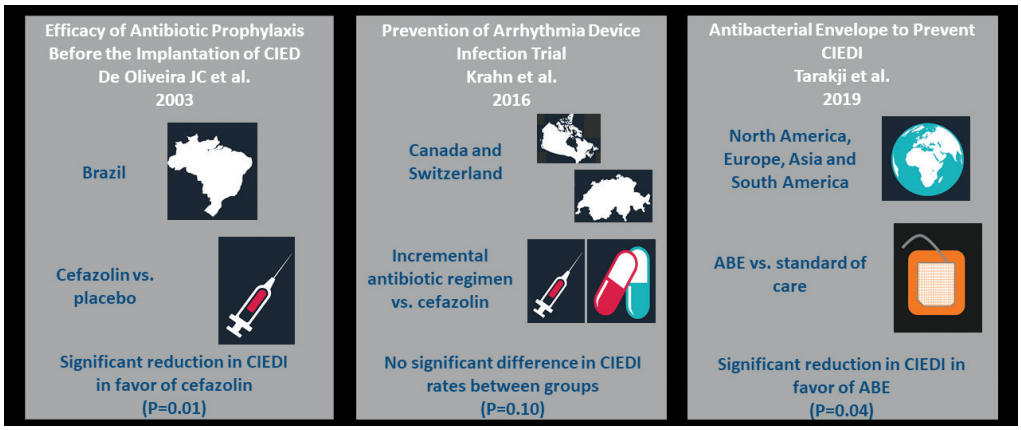


**Figure 1.** Summary of randomized clinical trials studying prevention of cardiovascular implantable electronic device infection

Abbreviations: ABE, antibacterial envelope; CIED, cardiovascular implantable electronic device; CIEDI, cardiovascular implantable electronic device infection

that included 28 institutions with over 19 000 patients. The incremental regimen consisted of pre-procedural cefazolin plus vancomycin, intraprocedural bacitracin pocket wash, and two-day post-procedural oral cephalexin. The reported CIEDI rates were lower (1.03% vs. 0.78%) than expected for both groups and were not statistically different.

Following the publication of multiple non-randomized trials of the efficacy of an absorbable "antibiotic envelope" impregnated with minocycline and rifampin in preventing CIEDI, a sentinel multinational, randomized controlled clinical trial was conducted with almost 7 000 patients enrolled in the WRAP-IT study [6]. Overall, the use of a "second generation" antibiotic envelope resulted in a 40% reduction in the major CIEDI rate (0.7% in the envelope group vs. 1.2% for the standard of care group) during a 12-month follow-up period. Moreover, there was a 60% reduction in CIEDI involving pocket sites, an infection presentation seen in 75% of randomized patients. Importantly, no increased risk of complications or allergic reactions among the envelope group was reported. However, the number needed to treat (NNT) to prevent one CIEDI was 200, raising concerns regarding the clinical impact and cost-effectiveness of this adjunct in the prevention of CIEDI.

The use of a gentamicin-collagen sponge (GCS) at the time of device placement to prevent surgical site infection has been investigated in other prosthetic device-related procedures [7] and showed promising results. The proposed mechanism of action involves the release of a high local concentration of gentamicin for several days, which prevents bacterial colonization of a prosthetic device. Furthermore, the collagen fibers promote blood coagulation and reduce the risk of hematoma formation, which is a well-recognized factor that predisposes to CIEDI. Its efficacy for CIEDI prevention, however, has not been widely studied.

In this issue of *Kardiologia Polska* (*Polish Heart Journal*), Kaczmarek et al. [8] present a single-center, retrospective study to evaluate the efficacy, safety, and cost-effectiveness of a gentamicin-collagen sponge (GCS) in preventing CIEDI in 312 patients with 6-month follow-up after device and sponge implantation.

Based on a comprehensive multi-component CIEDI risk score developed by the study group, patients considered to have a low risk of infection received ceftriaxone (or vancomycin if allergy reported) 60–120 minutes prior to the procedure. In contrast, high-risk patients received AP for 72 hours after CIED-GCS implantation. The authors report a single case of CIEDI (0.33%) and an NNT between 149 and 200, based on extrapolation from previously reported data [5]. No safety issues associated with the use of GCS were noted. The analysis of the cost associated with the management of CIEDI and that of GCSs to prevent one CIEDI concluded that the use of GCS may be a cost-effective intervention.

The authors acknowledge that relatively low rates of CIEDI observed in their study may not be solely attributed to the use of GCS. A predominant inclusion of patients at low risk of CIEDI, broad-spectrum AP (with longer duration in some cases [17%]), and the surgical technique employed (i.e., separate pocket closure with absorbable sutures) may have contributed to a low CIED rate.

In addition, the short follow-up (6 months) and exclusion of patients who did not survive the study period may have overestimated the effect of GCSs, as CIEDI can occur up to 12 months or longer following device placement [1, 9, 10]. Moreover, the lack of a control group prevented a comprehensive analysis of the cost-effectiveness of the proposed bundle strategies against standard of care.

The results of this study are encouraging; however, several questions remain. First, as suggested by this study, is it time to recommend GCSs for all patients undergoing CIED implantation?

The estimated cost of GCS can vary depending on the country, local geographic area, and, in some cases, type of healthcare system model and insurance coverage, if applicable. Kaczmarek and colleagues mentioned that the cost of one GCS at their institution was approximately 79 USD (we assume that this was an acquisition cost), which is considerably less than that of the currently available second-generation antibiotic envelope. Based on the reported low rates of CIEDI and high NNT, we believe that not all patients would benefit from GCSs. Whether this strategy would impact outcomes of patients at high risk of CIEDI is yet to be determined. However, it is important to highlight that although risk factors associated with CIEDI have been widely reported in the literature [1], at present, a risk score to define a population at high risk of CIEDI has not been validated, and a decision to use adjunctive local AP in a given patient is usually left at the discretion of the treating physician. Moreover, a comparison of the cost-effectiveness of this approach versus emerging technologies with a presumably lower risk of CIEDI, such as leadless pacemakers is lacking [11, 12]. Second, if a patient is deemed a candidate for a local antibiotic-delivered therapy at the time of CIED implantation, then should GCS or the minocycline and rifampin envelope be used?

To date, there are no clinical trial data that have examined outcomes in patients randomized to receive either of these two adjunctive therapies at the time of CIED implantation. In a comprehensive analysis of breakthrough CIEDI cases in the WRAP-IT study [13], a small but sizable proportion of cases were due to Gram-negative aerobic bacteria. The use of GCSs could, in theory, have better activity against this group of organisms compared to minocycline and rifampin. Although systemic absorption of locally delivered gentamicin is almost nil, it would also be important to examine if the broader-spectrum coverage of gentamicin could lead to breakthrough infections due to multidrug-resistant organisms or fungi. Lastly, the authors comment that the unit price of GCS is much lower than the minocycline and rifampin envelope. The cost may ultimately influence clinical decisions if similar efficacy and

adverse events related to the type of adjunct therapy are determined in future clinical trials.

Until randomized clinical trials compare the use of GCSs to the standard of care, other commercially available antibiotic envelopes [14], and newer device technologies become available, recommendations on the use of GCSs in patients undergoing CIED implantation will remain inconclusive.

## *Article information*

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**How to cite:** Baddour LM, Esquer Garrigos Z. Gentamicin-collagen sponge and prevention of cardiac implantable electronic device infections: Bargain basement or penthouse suite?. Kardiol Pol. 2021; 79(10): 1055–1957, doi: 10.33963/KP.a2021.0122.

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# Biomarkers for atrial fibrillation and chronic kidney disease: what is the evidence?

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Kardiol Pol. 2021; 79 (10): 1058–1059; DOI: 10.33963/KP.a2021.0124

**Received:**
September 30, 2021

**Revision accepted:**
September 30, 2021

**Published online:**
October 5, 2021

Atrial fibrillation (AF) and chronic kidney disease (CKD) are a bad combination which leads to an increased risk of ischemic stroke and major bleeding [1]. Although CKD and biomarkers were not components of the $CHA_2DS_2$-VASc score, many studies have shown that CKD and certain biomarkers are independent risk factors for clinical outcomes in patients with AF [2–4]. The ABC (Age, Biomarkers, Clinical history) risk score [4] and impaired renal function [3] have been proposed and validated to have an incremental prognostic value compared to the $CHA_2DS_2$-VASc score. In fact, CKD has been listed in the prediction model for ischemic stroke, major bleeding, and death in the GARFIELD study [5].

Based on our current knowledge, several bleeding risk scores have been studied in patients with AF, such as HAS-BLED, ORBIT bleeding score, or ABC-bleeding scores [4, 6]. In the ABC-risk score, growth differentiation factor-15 (GDF-15) (a marker of oxidative stress), high-sensitivity cardiac troponin (cTn-hs) (a marker of myocardial injury), and cystatin C (a marker of renal dysfunction) were predictors of major bleeding events. The ABC-bleeding score using alternative biomarkers (hematocrit, cTnI-hs, cystatin C, or creatinine clearance) outperformed both the HAS-BLED and the ORBIT scores [4]. However, it has not been proven if these biomarkers could predict bleeding events in severe CKD.

Matusik et al. reported prospective data in 182 patients with AF and CKD stage 4 looking at the predictive value of many biomarkers such as GDF-15, cystatin-C, and cTnT-hs, and prothrombotic state parameters, i.e., plasma fibrin clot permeability (Ks) for ischemic stroke, clinically relevant bleeding and death [7]. The median $CHA_2DS_2$-VASc score was 3.0. Half of the patients were prescribed vitamin-K antagonist (VKA) while non-VKA oral anticoagulant (NOAC) was used in the other half. The results demonstrated that age and decreased plasma fibrin clot permeability (Ks) are predictors for ischemic stroke events (4.7% per year); growth differentiation factor-15 (GDF-15), cystatin C, high-sensitivity troponin T, and a history of bleeding are predictors of bleeding (7.1% per year), and only cystatin C is a predictor for death (6.5% per year). In this study, none of the other clinical parameters could be used as a prognostic marker. This study had limitations such as the small sample size and a relatively short follow-up time. Therefore, other clinical parameters that have been shown to be important prognostic markers could not be demonstrated in this study. However, the results of this study imply that biomarkers may have a more prominent prognostic value compared to many clinical data in patients with AF and severe CKD.

To date, the mechanisms underlying the role of GDF-15 and cystatin C in a bleeding risk assessment remains unclear. A previous study showed that elevated GDF-15 was associated with reduced endothelium-dependent vasodilatation in resistance vessels, plaque burdens, reduced left ventricular ejection fraction, coronary artery disease, and heart failure, all of them [8] were risk factors for major bleeding [9]. Heart failure is associated with an increased GDF-15 level and may increase the risk of bleeding from hepatic congestion and impaired coagulopathy resulted from vitamin K antagonist (VKA) [8]. Cystatin C is a marker of renal function and is used to calculate eGFR.

A previous study showed that the estimated glomerular filtration rate (eGFR) equation, based on combined creatinine and cystatin C, was more accurate than creatinine or cystatin C alone for calculating eGFR [10]. Elevated cystatin C is a marker of accurate renal dysfunction that is related to an increased bleeding risk according to the HAS-BLED and the ORBIT bleeding scores [6].

Oral anticoagulant (OAC) is usually required in patients with AF and CKD to decrease the risk of ischemic stroke [11]. Guidelines recommended NOAC over VKA for AF patients at increased risk of stroke [2]. Data are limited in patients with CKD. Major clinical trials comparing NOAC with VKA usually excluded patients with an eGFR less than 30 ml/min/1.73 $m^2$ [12]. Based on the observational data, guidelines recommended that some NOACs at a reduced dose, such as apixaban and rivaroxaban, could be used in patients with advanced CKD including those who required dialysis [2, 13].

Asian population had an increased risk of major bleeding compared to non-Asian patients with AF [14]. A prospective cohort study of AF in Thailand showed that CKD accounts for approximately 60% of AF cases [11] and is a predictor for ischemic stroke and major bleeding. NOAC had a trend towards reducing ischemic stroke and major bleeding compared to warfarin [11]. Analysis of clinical outcomes for patients with AF and CKD who were on warfarin demonstrated that high_time in the therapeutic range (TTR) is essential for the good effectiveness of anticoagulation [15]. However, the average TTR in this population was 54%, and only approximately one-third had a good TTR control [15].

The study by Matusik et al. [7] explored many biomarkers in patients with AF and CKD stage 4. Several questions remain open. The elevation of biomarker levels may begin early in the course of disease before clinical abnormalities. As such, a biomarker-based bleeding risk score is a better predictor than the clinical risk score [1, 4]. More studies are needed to verify whether the bleeding risk score e.g., the HAS-BLED, ORBIT bleeding score, including biomarkers such as GDF-15, cTnT-hs, and cystatin C, will be better predictors of clinical outcomes in AF patients with oral anticoagulant therapy. Whether the results of this study can be applied in patients with AF without CKD or those who require dialysis is unknown. Also, whether the results can be applied in patients without OAC, with VKA, or with NOACs remains uncertain. Even in patients with CKD stage 4, it also remains to be confirmed in a larger sample size cohort. Most importantly, it remains to be proven whether the implementation of a biomarker-based prediction model for patients with AF is cost-effective.

## *Article information*

**Conflict of interest:** None declared.

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**How to cite:** Krittayaphong R, Methavigul K. Biomarkers for atrial fibrillation and chronic kidney disease: What is the evidence? Kardiol Pol. 2021; 79(10): 1058–1059, doi: 10.33963/KP.a2021.0124.

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REVIEW

# Diabetes mellitus as a risk factor for aortic stenosis: from new mechanisms to clinical implications

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Kardiol Pol. 2021; 79 (10): 1060–1067; DOI: 10.33963/KP.a2021.0137

**Received:** October 5, 2021

**Revision accepted:** October 11, 2021

**Published online:** October 12, 2021

## ABSTRACT

Aortic stenosis (AS) is a progressive disease, with no pharmacological treatment. The prevalence of diabetes mellitus (DM) among AS patients is higher than in the general population. DM significantly increases the risk of AS development and the rate of its progression from mild to severe. However, the mechanism of the interaction between AS and DM is not fully understood. Limited data regarding the influence of hyperglycemia on valvular calcification are available while understanding the cross-talk between them is pivotal in designing an effective therapeutic approach to prevent or at least retard AS development and/or progression in DM patients. Analysis of aortic stenotic valves revealed that increased accumulation of advanced glycoxidation end products (AGEs) was associated with enhanced valvular oxidative stress, inflammation, expression of coagulation factors and markers of calcification. Moreover, AGEs valvular expression correlated with AS severity. Interestingly, in diabetic AS patients, valvular inflammation correlated only with long-term glycemic control parameters, i.e. glycated hemoglobin and fructosamine but not with serum glucose levels. It has been demonstrated that transcatheter aortic valve replacement (TAVI) is beneficial for AS patients also with concomitant DM and safer as compared to surgical aortic valve replacement (SAVR). Moreover, new antidiabetic drugs, such as glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors, targeting inhibition of AGEs-mediated oxidative stress, have been proposed to reduce the risk of AS development in DM patients. This review aimed to comprehensively discuss the impact of DM on AS and its potential therapeutic implications.

**Key words:** aortic stenosis, diabetes, hyperglycemia, inflammation, risk factors

Kardiol Pol 2021; 79, 10: 1060–1067

## INTRODUCTION

Valvular heart diseases represent an important public health burden worldwide. With a decrease in the incidence of rheumatic disease, aortic valve stenosis (AS) has now become the most common valvular disease in Western countries. Its prevalence increases with age, affecting about 0.2% in 55- to 64-year-old individuals [1] and 2%–7% in subjects older than 65 years [2]. It is estimated that 4.5 million cases of AS will be present worldwide by the year 2030 [3]. In patients with the bicuspid aortic valve, which is the most common congenital heart disease occurring in 1%–2% of the population, AS development occurs statistically more frequently [2]. Growing evidence indicates that diabetes mellitus (DM) can increase the risk of AS development and the rate of AS progression [4–11]. The diagnosis of AS is based on echocardiographic assessment. The criteria for severe high-gradient AS include peak transvalvular velocity ≥4 m/s, the mean transvalvular pressure gradient ≥40 mm Hg, and aortic valve area <1 $cm^2$. In low-gradient or asymptomatic patients with AS when the valve morphology suggests AS, stress echocardiography is recommended [reviewed in 12].

The only definitive treatment for AS is surgical aortic valve replacement (SAVR) or transcatheter aortic valve replacement (TAVI). Both methods present great outcomes; however, surgical intervention remains the treatment of choice for the majority of AS patients [13]. Currently, there is a discussion whether TAVI is a better method of AS treatment than SAVR in patients with concomitant DM. The prevalence of DM is markedly higher among AS patients compared to the general population and was increasing during the last decade [14, 15].

AS is considered an atherosclerosis-like process. This concept is supported by a large number of studies showing

that the development of AS is associated with cardiovascular risk factors such as smoking, obesity, hypercholesterolemia, arterial hypertension, chronic kidney disease, DM, and metabolic syndrome [5, 14]. Patients with DM are at 2- to 4-fold higher cardiovascular risk as compared to non-diabetic individuals, and cardiovascular disease (CVD) remains the leading cause of mortality in patients with this condition [16, 17]. DM accompanied by inflammation is thought to be involved in the pathophysiological mechanism of atherosclerosis and is an important factor enhancing this disease [11]. Based on similarities between AS and atherosclerosis one might suspect the major importance of DM on AS progression; however, the mechanism underlying the cross-talk between DM and AS is not fully understood to date.

This review summarizes available data on the relationship between DM and AS, including the underlying mechanisms and clinical implications. Novel therapeutic approaches for AS patients with concomitant DM have also been discussed.

## PATHOMECHANISMS OF DEGENERATIVE AS

AS initiated as aortic valve sclerosis is characterized by valve endothelial damage caused by high shear stress [18] and subendothelial accumulation of lipids and lipoproteins together with enhanced oxidative stress [19]. These processes result in the activation of local inflammation and drive cell-dependent mechanisms that regulate calcium load on the valve leaflets, leading to its calcification [20]. Under these pathological conditions, valvular interstitial cells (VICs), a predominant cell population within aortic valves, which are responsible for differences in the pathobiology of AS and atherosclerosis, play a substantial role in valvular calcification [21]. VICs differentiate into osteoblast-like cells, at least partially through epigenetic modifications [22]. Valvular calcification has been defined as a consequence of tightly regulated processes that culminate in the creation of an organized extracellular matrix deposition of osteoblast-like cells [22]. These activated cells are responsive to typical osteogenic mediators, such as transforming growth factor-β superfamily members, and bone morphogenetic proteins (BMPs) [23, 24]. BMPs stimulate the valve calcification by activating Smad1/5/8 and Wnt/β-catenin signaling pathways, which leads to up-regulation of the master osteoblast transcription factor, Runx2/Cbfα1 (Runt-related transcription factor 2/core-binding factor α-1) [25]. Runx2/Cbfα1 increases the expression of proteins directly associated with calcification and osteoblast differentiation: osteopontin, bone sialoprotein, and osteocalcin [23–25]. Several studies confirmed the up-regulation of these calcification markers in AS, both on mRNA and protein levels [23]. The late propagation phase of AS is driven by pro-osteogenic and pro-calcific factors, resulting in a complex and well controlled self-perpetuating calcification process [24, 26]. Moreover, it has been demonstrated that the regulation of valvular ossification and calcification is controlled by the nuclear factor κB (NF-κB) [27], suggesting its important role in the pathophysiology of AS. NF-κB is a master regulator of inflammatory responses that plays an essential role in the evolution as well as the resolution phase of inflammation. Overactivation of NF-κB is associated with many inflammatory diseases, i.e. with atherosclerosis [27]. NF-κB is activated by the tumor necrosis factor α, secreted by monocytes/macrophages and causes an upstream of interleukin 6, which has been implicated in calcification of aortic valve leaflets in AS patients *via* BMP-2 stimulation [27]. Moreover, the p65/c-Rel heterodimer of NF-κB has been shown to critically regulate the expression of tissue factor (TF) [28]. Indeed, it has been shown that stenotic aortic valves exhibit a procoagulant state [29–32]. The immunohistochemistry studies of twenty-one stenotic aortic valves have revealed the presence of large amounts of fibrin, which is the final product of blood coagulation. Interestingly, fibrin has been observed both on the surface and within stenotic valves [30]. The fibrin positive valve areas correlated with TF positive areas, suggesting that the conversion of fibrinogen to fibrin occurs *in loco* within the aortic valve [30]. In addition, it has been shown that the expression of coagulation proteins is associated with inflammation as the regions positive for TF and fibrin co-localized with regions of valve infiltration by macrophages [31, 32]. The presence of both TF and fibrin and the number of macrophages correlated with the severity of AS (expressed as transvalvular maximum aortic gradient) and with the degree of valvular calcification [30]. These studies, as well as observations of other authors [32], suggest that coagulation might play a significant role in valvular fibrosis and calcification. Breyne et al. [32] have also shown that thrombin produced *in loco* leads to osteopontin activation and generation of the N-terminal domain with pro-inflammatory properties. Interestingly, both the quantity of fibrin and the degree of valve calcification correlated with factor (F)XIII expression derived mainly from the alternatively activated macrophages recruited to the valve leaflets [29]. Recently, it has been shown that VICs are also able to express prothrombin and active FX [11]. Moreover, growing evidence indicates that AS patients are characterized by impaired clot susceptibility to fibrinolysis [33, 34], the process closely regulated by specific inhibitors, such as plasminogen activator inhibitor type-1 and thrombin-activatable fibrinolysis inhibitor [35]. In severe AS patients, the amounts of valvular fibrin positively correlated with prolonged fibrinolysis [34]. Although the direct relationship between vascular calcification and blood coagulation is still open for investigation, it seems that coagulation and fibrinolysis may be of major importance in the development/progression of AS.

## INFLUENCE OF DM ON ATHEROSCLEROSIS

DM is a chronic disease characterized by hyperglycemia and frequently manifested by macrovascular myocardial infarction, stroke, peripheral arterial disease, and microvascular

(retinopathy, nephropathy, and neuropathy) complications [36]. A global age-standardized prevalence of DM in the general population is 9.0% (7.2–11.1) in men and 7.9% (6.4–9.7) in women [37]. However, DM incidence is still increasing worldwide, and it is estimated that by the year 2045, there will be 700 million diabetic patients [38]. Type 2 DM constitutes 90-95% of diabetes cases worldwide and about one-third of type 2 DM patients presents CVD, with the highest prevalence of coronary artery disease (21.2%) and much lower that of stroke (7.6%) [39]. CVD comprised about 50% (95% confidence interval [CI] 37%–64%) of all deaths in type 2 DM patients [39, 40]. Type 2 DM involves the combination of insulin resistance in peripheral tissues, due to obesity and genetic factors, with an inadequate pancreatic insulin response (or relative beta-cell failure). Hyperglycemia has multiple atherogenic effects that lead to the development of atherosclerosis in subjects with type 2 DM, based on longitudinal analysis [41]. Serum glycated albumin level and the ratio of glycated albumin to glycated hemoglobin ($HbA_{1c}$) were identified as potential surrogate parameters that are associated with or predict the progression of atherosclerosis in type 2 DM subjects [41, 42].

The pathophysiology of diabetic vascular disease is complex. An impact of DM on vascular complications is linked with hyperglycemia-induced leptin-to-adiponectin imbalance inflammation leading to local hypoxia, vascular dysfunction, and hemodynamic changes, favoring a prothrombotic state [43, 44]. The impact of high blood glucose levels on vasculature is mediated by the high sensitivity of endothelial cells to persistent hyperglycemia, which leads to reactive oxygen species overproduction [45]. Additionally, hyperglycemia promotes the upregulation of genes responsible for the production of pro-inflammatory cytokines and matrix metalloproteinases that render atheromatous plaques more unstable, with a greater propensity for rupture [46]. Finally, platelet dysfunction and increased production of pro-thrombotic proteins, like fibrinogen and thrombin, contribute to a prothrombotic milieu in patients with DM [46].

## A PREVALENCE OF DM IN AS

According to large clinical trials, the prevalence of DM was shown to be higher among AS patients than in the general population. In 2015 the CURRENT AS study comprising 3815 AS patients showed that 11.4% of individuals had concomitant DM [47]. Two years later, the PRIMID AS study revealed a 14.4% incidence of DM among AS patients [48]. Another study performed by Ljungberg et al. [15] showed in the Swedish population-based cohort study that the prevalence of DM was 15.8% ten years before aortic valve replacement due to AS. Notably, Culler et al. [14] showed that in the United States the prevalence of DM concomitant to AS increased from 19.7% to 31.6% between 2009 and 2015. Similar results have been reported in the Spanish population during a 15-year follow-up [49].

## CLINICAL TRIALS ON DM INFLUENCE ON AS DEVELOPMENT AND PROGRESSION

Clinical interactions between DM and AS progression have been investigated by several authors (Table 1). However, available data are inconsistent, probably due to different methodological approaches implemented by researchers and further studies are needed. Aronow et al. [4] reported in 2001 in a retrospective study performed on 180 AS patients, including 48 with concomitant DM, that diabetic patients had higher annual progression in a peak systolic gradient than individuals without DM. In 2006 Katz et al. [5] have extended the previous observation by showing that both DM and metabolic syndrome increased the risk of valvular calcification. Kamalesh et al. [6], in a retrospective study

**Table 1.** Trials on diabetes mellitus (DM) and/or metabolic syndrome influence on aortic stenosis (AS) progression

| Study type | No. of patients | Conclusion | Ref. No. |
|---|---|---|---|
| Retrospective | 180 mild AS patients, including 48 subjects with concomitant DM | 42.5% higher annual progression in peak systolic gradient in DM vs. non-DM patients | [4] |
| Prospective (the MESA cohort) | 6 780 participants, including 1 016 DM and/or metabolic syndrome subjects | Not only DM but also metabolic syndrome increases the risk of aortic valve calcification both in women ([RR] 1.45; 95% CI, 1.11–1.90 for metabolic syndrome and RR = 2.12; 95% CI, 1.54–2.92 for DM) and in men (RR = 1.7; 95% CI, 1.32–2.19 for metabolic syndrome and RR = 1.73; 95% CI, 1.33–2.25 for DM) | [5] |
| Retrospective | 166 AS patients, including 72 with DM | AS progression measured as AVA is faster in DM vs. non-DM patients (change during a median, 2.5 years follow-up was 0.26 $cm^2$/ /year in DM vs. 0.20 $cm^2$/year in non-DM patients; $P = 0.02$) | [6] |
| Prospective (CANHEART) | 1.12 mln individuals observed for a median of 13 years | 20 995 subjects developed severe AS and a prevalence of DM was 6% higher compared to individuals who did not develop AS | [50] |
| Observational | 71 483 participants, including 2 377 DM patients | Type 2 DM was associated with increased risk of AS (HR = 1.34; 95% CI, 1.05–1.71) | [8] |
| Prospective | 5 079 participants including 1 311 DM patients | 69 participants developed AS during a mean follow-up of 16.5 years and DM was an independent risk factor for AS development (HR = 3.18; 95% CI, 1.51–6.69) | [51] |
| Prospective | 203 AS patients, including 99 participants with metabolic syndrome and 50 with DM observed for a mean of 3.2 years | Metabolic syndrome and DM had no impact on AS progression | [9] |

Abbreviations: AS, aortic stenosis; AVA, aortic valve area; CI, confidential interval; DM, diabetes mellitus; HR, hazard ratio; RR, relative risk

**Table 2.** Advanced glycation end products (AGEs) influence on multiple biological processes.

| The type of response | Biological effects | Ref. No. |
|---|---|---|
| Oxidative stress<br>Reactive oxygen species production ↑<br>Superoxide dismutase function ↓<br>Nitric oxide ↓ | <br>Lipid peroxidation ↑<br>Endothelial dysfunction ↑<br>Vasoconstriction ↑ | [11, 54, 56, 59, 60] |
| Inflammation<br>VCAMs ↑<br>IL-1, TNF-β, IGF-1 ↑<br>Mononuclear cell chemotaxis ↑ | <br>Tissue remodeling and thickening of the basement membrane ↑ | [11, 53, 56, 58, 61–63] |
| Structural changes<br>Collagen changes leading to premature ageing<br>Irreversible cross-linking of structural fibers<br>Cell membrane and matrix changes ↑ | <br>Stimulation of pathological cellular activity ↑ | [51, 58, 64, 65] |
| Coagulation and fibrinolysis<br>Tissue factor ↑<br>Platelet aggregation and fibrin stabilization ↑<br>Sensitivity of fibrin to plasmin ↓ | <br>Thrombosis ↑<br>Fibrinolysis ↓ | [11, 56, 66, 67] |

Abbreviations: IGF-1, insulin-like growth factor 1; IL-1, interleukin-1; TNF-β, tumor necrosis factor β; VCAMs, vascular cell adhesion molecules

performed on 166 consecutive AS patients, have shown faster disease progression in diabetics than in non-diabetic individuals; however, only in those with moderate AS. In a large cohort study comprising 1.12 mln individuals followed for a median of 13 years, DM was associated with a 49% higher risk for AS development [50]. Similar results were obtained by Larsson et al. [8], who have shown that type 2 DM was associated with a 34% increased risk of AS and Martinsson et al. [51], who have reported DM as an independent risk factor for AS development. On the other hand, Testuz et al. [9] have failed, during a 3-year follow-up, to observe the association between AS progression and metabolic syndrome or diabetes; however, in this study only fasting glucose levels were analyzed while it has been shown that long-term glycemic control may be of key importance [10, 11].

## MOLECULAR LINKS BETWEEN AS AND DM

Despite the proven impact of DM on atherosclerosis and similarities between AS and atherosclerosis, limited data regarding the influence of hyperglycemia on valvular inflammation and calcification are available. However, hyperglycemia has been proposed among other metabolic factors to initiate or at least escalate valvular calcification through a complex mechanism involving vascular and inflammatory cell interactions [7, 52, 53]. Immunohistochemistry analysis of AS valves revealed that concomitant DM was associated with an increased percentage of C-reactive protein-positive areas and correlated with the percentage of TF-positive areas [7]. Moreover, increased valvular protein glycation due to an accumulation of advanced glycoxidation end products (AGEs) has been suggested as a contributor to faster AS progression [54–57]. AGEs are a heterogonous group of proteins or lipids irreversibly glycated by the attachment of reducing sugars onto the free amino groups. AGEs modify tissue structure and function through cross-linking of intra-/extracellular matrix proteins or binding to the cell surface receptor for AGEs (RAGE), which affects multiple cellular processes (Table 2) [11, 51, 53, 54, 56, 58–67]. Exposure to increased blood levels of glucose in DM rapidly accelerates AGEs formation [68]. The rabbit and mouse models of AS proved that AGEs accumulation within aortic valves resulted in osteoblastic differentiation of VICs [68, 69]. Moreover, increased concentrations of AGEs lead to enhanced oxidative stress and NF-κB overexpression in the rabbit model of AS [69]. Moreover, RAGE-mediated NFκB activation has been implicated in the synthesis of inflammatory cytokines and TF by monocytes/macrophages [70]. Recently, AGEs-associated influence on AS progression has been shown in AS patients with concomitant DM, in whom a 6.6- and 12-fold increase in valvular and plasma AGEs was associated with AS severity, measured by the reduced aortic valve area [56]. Similarly, diabetic AS patients had 1.3-fold higher RAGE in plasma and 1.8-fold higher RAGE expression within aortic stenotic valves compared to non-diabetics [56]. Notably, solely plasma RAGE levels correlated with AS severity, while in patients with well-controlled type 2 DM ($HbA_{1c}$ <7%), the influence of hyperglycemia on AS severity was negligible [56]. Diabetic AS patients compared to the non-diabetic ones had also enhanced NF-κB valvular expression in association with increased valvular expression of coagulation factors II and Xa and a marker of calcification, BMP-2 [11]. This observation has been confirmed by an in vitro study using VICs isolated from stenotic aortic valves, in which inhibition of either reactive oxygen species or NF-κB prevented calcification [11]. Interestingly, in diabetic AS patients valvular NF-κB expression correlated not only with long-term glycemic control parameters, namely $HbA_{1c}$ and fructosamine but also with AS severity. Moreover, AS patients with poorly controlled type 2 DM defined as $HbA_{1c}$ ≥6.5% were characterized by markedly higher plasma concentrations of TF and FVIIa-antithrombin complex [11].

Available data suggest that poorly controlled DM in AS patients is associated with enhanced valvular oxidative stress, inflammation, and coagulation activation, as well as systemic prothrombotic state, which all together can trigger faster AS progression (Figure 1).

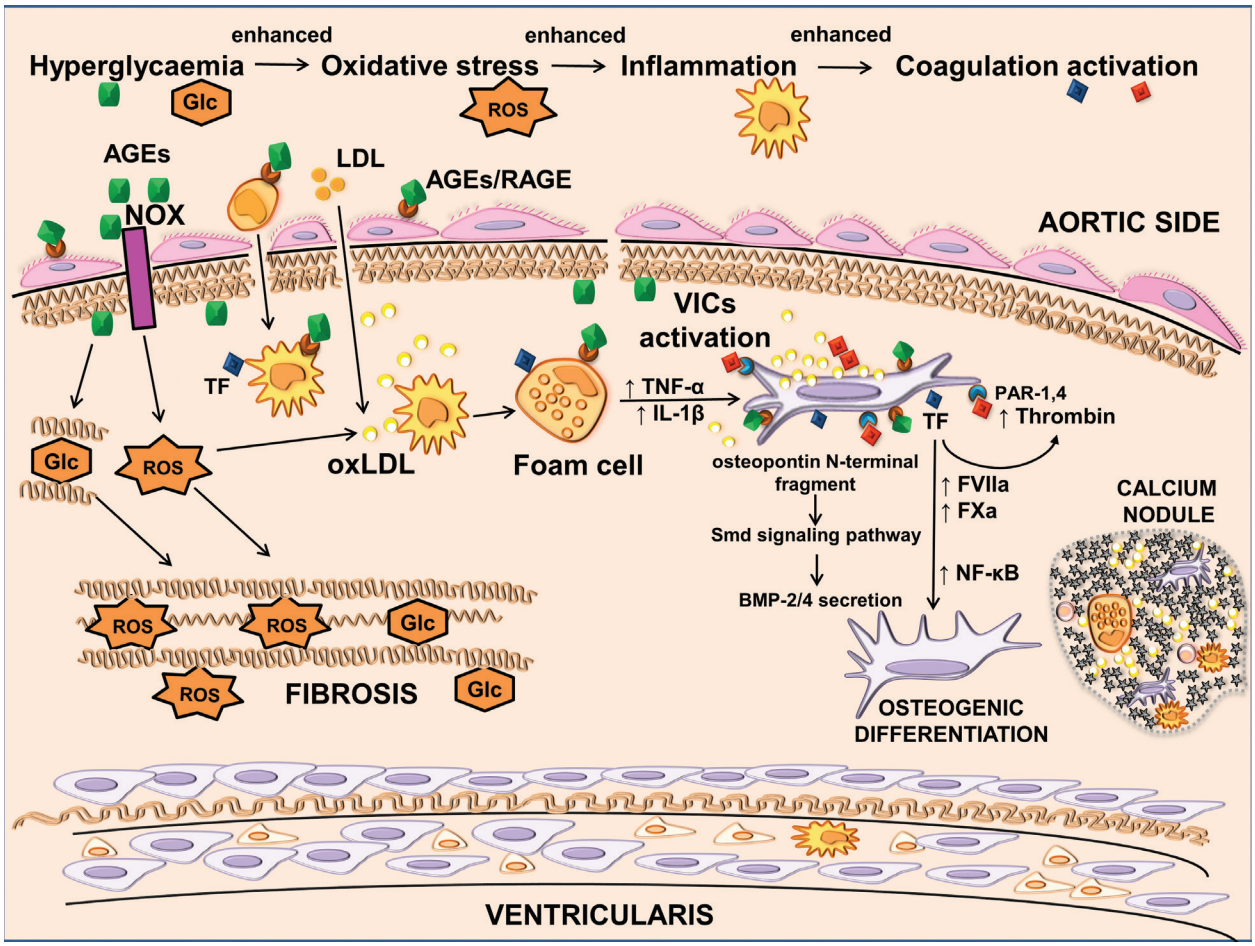


**Figure 1.** Links between diabetes and aortic stenosis progression. Hyperglycemia is associated with tissue accumulation of advanced glycation end products (AGEs), which are bound by a specific receptor (RAGE). AGEs accelerate aortic stenosis (AS) progression by several actions, including endothelial dysfunction and enhanced reactive oxygen species (ROS) generation *via* NADPH oxidase 2 (NOX2), the most important cellular producer of ROS. Amplified ROS generation leads to enhanced oxidation of low-density lipoproteins (LDL) and the formation of foam cells. AGEs/RAGE interaction enhances the synthesis of tumor necrosis factor α (TNF-α) and interleukin 1β (IL-1β) by foam cells, which induces inflammation and activation of valvular interstitial cells (VICs), the most abundant cell population within aortic valves. VICs activation is associated with a transformation into cells with osteogenic phenotype *via* Smd-signalling pathway and secretion of bone morphogenetic proteins (BMPs) as potent osteogenic factors. Activated VICs, like macrophages, express tissue factor (TF), which together with activated factor VII (FVIIa) initiates a coagulation cascade. AGEs enhance coagulation activation and, consequently, increased expression of FXa and prothrombin are observed within aortic stenotic valves obtained from diabetic patients. Activated VICs express also nuclear factor κB (NF-κB), and its valvular expression is enhanced in AS patients with concomitant type 2 diabetes. Activation of the protease-activated receptors (PAR-1, PAR-4) by thrombin additionally amplifies the inflammatory response of VICs. Accumulation of AGEs within aortic valves is also associated with glycation (Glc) of elastin and collagen fibers, scaffold fibers of aortic valves, with subsequent fibrosis of the valve leaflet

Thus, it can be assumed that maintaining long-term glycemic control parameters within normal values in AS patients with concomitant DM may slow the rate of AS progression.

## PRACTICAL IMPLICATIONS

Although current data suggest an impact of DM on AS progression, there is a lack of treatment strategies for diabetic patients with AS to either improve the survival of AS patients or slow down the rate of AS progression. It is tempting to suggest that in diabetic AS patients, besides good glycemia control, long-term glucose dynamic control by measuring $HbA_{1c}$ or fructosamine levels may be beneficial to prevent or at least slow down AS progression or its complications. However, large clinical trials are highly needed to verify whether maintaining $HbA_{1c}$ or fructosamine within the normal range can retard AS progression in patients with mild-to-moderate AS and concomitant DM.

Based on animal and human studies, some therapies have been proposed, which may help to reduce cardiovascular complications in diabetic patients including those with AS. They include agents targeting inhibition of the AGEs-RAGE axis or its interaction with oxidative stress using pioglitazone or alagebrium (ALT-711), as well as new antihyperglycemic agents, such as glucagon-like peptide-1 receptor (GLP-1) agonists (liraglutide, luraglutide, and semaglutide) and sodium-glucose cotransporter-2 (SGLT-2) inhibitors (empagliflozin, canagliflozin, dapagliflozin, and ertugliflozin) [71]. However, to date there is no convincing evidence on their cardioprotective effect beyond blood-glucose control in

diabetics. Another issue is that despite growing evidence that AGEs accumulation is associated with increased cardiovascular risk [71], their measurement has not been clinically validated.

Based on the COMPASS study, which was a multicenter, double-blind trial that included patients with a history of stable chronic atherosclerotic vascular disease, it has been shown that treatment with rivaroxaban 2.5 mg twice daily combined with aspirin 100 mg once daily was associated with a decreased risk of cardiovascular death, stroke, or myocardial infarction compared to patients treated with aspirin alone [72, 73]. Taking into consideration that in vitro study performed on VIC cultures showed a substantial influence of rivaroxaban on suppression of inflammation, coagulation activation, matrix metalloproteinases, and finally cellular calcification [74], it might be hypothesized that NOACs are able to retard AS progression, at least in AS patients who require anticoagulation.

SAVR or TAVI are current treatment options for severe AS. TAVI is beneficial for AS patients with concomitant DM, who are subjected to this procedure instead of SAVR. However, data on the impact of DM on the prognosis of patients with severe AS who undergo TAVI vs. SAVR are limited and inconsistent. On one hand, a single-center large retrospective study showed that DM patients compared to non-DM individuals did not differ in the short-term outcome with regard to TAVI or SAVR [75]. On the other hand, Lindman et al. [76] in a post-hoc analysis of the PARTNER cohort showed that all-cause one-year mortality was lower among DM patients after TAVI compared to those undergoing SAVR. A recent study performed on 254 DM patients compared to 548 non-DM individuals undergoing TAVI showed that this procedure is not associated with an increased risk of short-term complications or mortality [77]. Similarly, Ando et al. [78] in a large cohort study performed on 70 815 AS patients showed that all-cause mortality in diabetic patients treated with TAVI was 2.8% compared to 3.6% in the SAVR group. Notably, a randomized trial performed on 586 AS patients treated with TAVI showed no difference in 30-day mortality between DM and non-DM patients [79]. Sun et al. [80] reported in a meta-analysis of 13 253 AS patients that 1-year all-cause mortality after TAVI was similar in DM and non-DM individuals.

## CONCLUSIONS

Available data suggest that DM is associated with increased prevalence of AS, leading to faster AS progression. However, it is not fully understood how DM influences AS progression, especially at early stages. It was also shown that glycemic control is not sufficient to prevent DM complications due to accumulation of AGEs, which are more important mediators of advanced glycation than hyperglycemia, resulting in enhanced oxidative stress and inflammation. Moreover, AGEs levels are better predictors not only for DM progression but also vascular calcification than $HbA_{1c}$ [81]. In AS patients with concomitant type 2 DM valvular inflammation and calcification, markers were associated with $HbA_{1c}$ and fructosamine, underlying the need for strict long-term glycemic control. However, this observation should be confirmed in large prospective randomized trials.

## *Article information*

**Conflict of interest:** None declared.

**Acknowledgements:** This work was supported by the grant from the Polish National Science Centre (UMO- 2018/29/B/NZ5/02629 to JN).

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**How to cite:** Natorska J. Diabetes mellitus as a risk factor for aortic stenosis: from new mechanisms to clinical implications. Kardiol Pol. 2021; 79(10): 1060–1067, doi: 10.33963/KP.a2021.0137.

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REVIEW

# Syncope: new solutions for an old problem

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Kardiol Pol. 2021; 79 (10): 1068–1078; DOI: 10.33963/KP.a2021.0138

**Received:** October 10, 2021

**Revision accepted:** October 14, 2021

**Published online:** October 14, 2021

## ABSTRACT

Syncope is a frequent event in the general population. Approximately 1%–2% of all emergency department admissions are due to syncope and at least one-third of all people experience fainting in their life. Although consequences of cardiac syncope are generally feared, non-cardiac syncope is much more common and may be associated with severe injuries and quality-of-life impairment, particularly in older adults. Various diagnostic and therapeutic strategies have been created and implemented over decades, leading to significant improvements in diagnostic accuracy and treatment effectiveness. In recent years, diagnosis and treatment have further evolved according to an innovative approach focused on the hemodynamic mechanism underlying syncope, based upon the assumption that knowledge of the syncope mechanism is a prerequisite for effective syncope prevention and treatment. Therefore, a new classification of syncope has been proposed, which defines two main syncope phenotypes with different predominant mechanisms: the hypotensive phenotype, where hypotension or vasodepression prevails, and the bradycardic phenotype, where cardioinhibition prevails. Identification of syncope phenotype — bradycardic or hypotensive/vasodepressive — represents the first step towards personalized management of syncope, characterized by customized interventions for prevention. The present review aims to illustrate these new developments in the diagnosis and therapy of non-cardiac syncope within a mechanism-based perspective. Diagnosis and therapy of bradycardic and hypotensive phenotypes are discussed, with a focus on recent evidence.

**Key words:** reflex syncope, bradycardia, hypotension, cardioinhibition, vasodepression, low blood pressure

Kardiol Pol 2021; 79, 10: 1068–1078

*This article is dedicated to our late friend and great syncope expert, Dr. Artur Pietrucha (1964–2020)*

## INTRODUCTION

Syncope is a very common event, affecting more than one third of the general population over the course of life. Although etiology is often benign, syncope is estimated to be severe in approximately 14% of cases, carrying a high risk of severe injuries and/or substantial impairment of the quality of life [1]. Even in the case of rare episodes, syncope may be responsible for serious fall-related complications, such as fractures and intracranial hemorrhage [2]. Moreover, recurrent syncope may cause patients' anxiety and restriction in social and working activities, thus affecting psychosocial functioning as in chronic diseases [3, 4].

The negative impact of syncope on patients' prognosis and quality of life is dramatically enhanced in older adults. At an advanced age, fall-related injuries frequently result in hospitalization, reduced mobility, and deconditioning, which may, in turn, lead to a decline of autonomy in daily life activities and increased risk of nursing-home admission [5]. Moreover, older adults frequently develop a "post-fall syndrome" characterized by fear of falling, depression, and sedentary lifestyles to avoid falling, which may further contribute to the functional decline [6]. Indeed, data from community-dwelling older adults sustaining severe fall-related injuries indicate that nearly half of individuals with no or mild-to-moderate pre-fall disability do not return to the pre-fall level of autonomy [7]. Apart from direct consequences, unexplained and often poorly managed syncope is associated with an increased risk of

cardiovascular events and mortality [8]. Thus, accurate syncope diagnosis and effective prevention of recurrences represent an important healthcare challenge, particularly in older people.

Syncope is an old problem in medicine, discussed from the time of Hippocrates. However, in the 20th century, the first specific diagnostic tools were designed, taking inspiration from electrocardiogram (ECG) recording methodology, experimental data, and aerospace medicine [9]. Diagnostic testing for syncope has then evolved over decades and structured pathways have been created, leading to significant improvements in the diagnostic capacity and accuracy [10, 11]. In parallel, treatment strategies have been developed based on syncope etiology and clinical features [1]. Recently, some new concepts have been presented with particular reference to non-cardiac syncope.

In recent years, increasing attention has been focused on the hemodynamic mechanisms underlying syncope, and innovative diagnostic approaches have been proposed to achieve a mechanism-based diagnosis on the assumption that identification of the syncope mechanism is a necessary prerequisite for effective treatment. Concurrently, new treatment options have emerged, allowing for the implementation of mechanism-guided prevention of syncope recurrences.

The present review aims to illustrate new developments in the diagnosis and therapy of syncope, with special emphasis on non-cardiac syncope. Diagnosis and therapy of bradycardic and hypotensive phenotypes are discussed, with a focus on the most recent evidence.

## RECENT ADVANCES IN THE PATHOPHYSIOLOGY OF SYNCOPE

**WHAT'S NEW?**

Deeper insights into the cardiovascular physiology of reflex syncope, including hemodynamic profile predisposition to syncope and relative contributions of vasodepression and cardioinhibition

A comparison of 6 community-based cohort studies with a large dataset of reflex syncope patients (64 968 and 6 516 observations, respectively) has revealed that individuals with reflex syncope have a different hemodynamic profile compared with the general population, characterized by lower systolic blood pressure (BP), higher diastolic BP and heart rate (HR) [12].

These hemodynamic features suggest that reflex syncope patients have reduced venous return and a lower stroke volume, which induces compensatory increases in HR and vascular resistance. This hemodynamic framework draws fragile cardiovascular homeostasis, characterized by a latent predisposition to reflex syncope, which is counteracted by means of chronic activation of compensatory mechanisms to preserve organ perfusion. This implies that syncope may occur in the presence of triggering conditions, such as prolonged standing, that overcome the capacity of compensatory mechanisms, resulting in BP fall, cerebral hypoperfusion, and syncope. The reasons for these hemodynamic differences between syncope patients and the general population remain currently unknown, although assumptions have been made calling into question a lower circulating blood volume, a tendency to increased venous pooling [13], and abnormal neuroendocrine activation [14].

Recent research indicates that a neuroendocrine cascade is activated immediately before orthostatic syncope, characterized by epinephrine and vasopressin release [15–18]. Higher levels of epinephrine and vasopressin during Tilt Testing (TT) were found to be associated with a shorter time to syncope, suggesting an important contribution of the neuroendocrine system to individual syncope susceptibility [15, 16].

Individual hemodynamic features not only determine the predisposition to reflex syncope but also affect TT response. Another recent study has demonstrated that tilt-positive patients have lower systolic BP, diastolic BP, and HR compared with tilt-negative patients with similar presentations, independently of age and sex [19]. The above pathophysiological findings suggest the reduced capacity to compensate for lower systolic BP, expressed by lower diastolic BP and HR. Consistently, lower resting systolic BP (≤128 mm Hg) and absence of hypertension have been identified as independent predictors of TT positivity, confirming that reflex syncope susceptibility is strongly related to hemodynamic reserve, which is reduced in presence of lower BP [19]. Therefore, three different hemodynamic profiles can be outlined, including (1) individuals with stable cardiovascular homeostasis; (2) individuals with a predisposition to syncope and well-functioning compensatory mechanisms, allowing for increased tolerance to orthostatic stress and TT; (3) individuals with a more pronounced predisposition to syncope due to the suboptimal compensatory capacity, making them more prone to develop reflex syncope during TT.

In parallel with research investigating the hemodynamic profile determining predisposition to reflex syncope, some studies have allowed for a better understanding of hemodynamic changes occurring during TT-induced syncope. The BP fall occurring during reflex syncope is traditionally attributed to vasodepression, consisting of a reduction of sympathetic arteriolar tone and vascular peripheral resistance, and cardioinhibition, consisting of a vagal impact on sinus and atrioventricular nodes possibly leading to asystole [20]. A recent study by van Dijk et al. [21] suggests a different scenario, showing the reduced stroke volume as the first determinant of BP fall, with vascular resistance providing only a minor contribution. The reduced stroke volume is likely attributable to venous pooling, which is incompletely compensated by HR increase. Then, cardioinhibition follows starting as a weakening of initial compensatory HR increase, which adds to BP fall, thus

**Table 1.** Mechanism-based classification of non-cardiac syncope

| Non-cardiac syncope | |
|---|---|
| **Hypotensive phenotype** | **Bradycardic phenotype** |
| Vasodepressor or mixed reflex syncope during TT | Cardioinhibitory response to TT |
| Vasodepressor or mixed carotid sinus syndrome | Cardioinhibitory carotid sinus syndrome |
| Blood pressure falls detected on 24h-ambulatory blood pressure monitoring | Syncopal reflex asystole (>3 sec) or non-syncopal reflex asystole (>6 sec) detected by ILR |
| | Low adenosine syncope |

Abbreviations: ILR, implantable loop recorder; TT, Tilt Testing

acting as a turning point in the hemodynamic cascade of reflex syncope.

A detailed analysis of TT responses across age decades revealed that the relative contribution of cardioinhibition and vasodepression varies with age [22]. Prevalence of vasodepression progressively increases with advancing age while cardioinhibitory responses show an opposite trend, with a breakpoint around the age of 50, allowing the conclusion that the cardioinhibition component of reflex syncope declines with age. This gradient is likely to result from age-related changes in cardiovascular autonomic control, including decreased baroreceptor sensitivity, reduced cardiac responsiveness to beta-adrenergic stimulation, and a decline in vagal drive to the heart, which makes older adults more prone to develop vasodepressor reflex syncope [23, 24]. In addition, hypotensive medications and comorbidities may further contribute to vasodepression in older patients.

## CLASSIFYING NON-CARDIAC SYNCOPE

WHAT'S NEW?

An innovative mechanism-based classification of non-cardiac syncope to guide therapy

Non-cardiac syncope has traditionally been classified based on its etiology and clinical presentation, i.e. as reflex syncope or autonomic failure (orthostatic hypotension), which is different from primary cardiac syncope, typically presenting as brady- or tachyarrhythmia [1]. Yet, recent advances in the understanding of the pathophysiology of syncope have set the stage for a new classification, which can also be helpful in the identification of the most suitable strategies for recurrence prevention. Non-cardiac syncope can be classified into different phenotypes according to the predominant underlying hemodynamic mechanism, i.e., hypotension (vasodepression) or bradycardia, corresponding to hypotensive and bradycardic phenotypes (Table 1) [2].

Syncope with hypotensive phenotype manifests as hypotension and is the prevalent mechanism typically occurring in patients with a constitutional or acquired (i.e., drug- or disease-induced) predisposition to hypotension, which can be referred to as hypotensive susceptibility [25]. While hypotension is present in all patients during syncope, hypotensive susceptibility implies a tendency to predominant vasodepression, often associated with reduced cardiac filling, which can be detected using TT, carotid sinus massage (CSM), or 24 h-ambulatory blood pressure monitoring (ABPM) (Table 1). Patients with hypotensive susceptibility are most likely to benefit from treatment strategies that counteract hypotension.

In contrast, some patients show cardioinhibitory susceptibility, resulting in syncope with bradycardic phenotype, i.e., with a predominant cardioinhibitory mechanism. These patients are more likely to benefit from therapies that counteract bradycardia and asystole. Some degree of cardioinhibition is present in all patients during reflex syncope, but cardioinhibitory susceptibility is typical of those presenting with cardioinhibitory responses (including asystole) to TT and CSM with typical reflex features detected by long-term ECG monitoring [26]. Bradycardic phenotype also include syncope associated with idiopathic paroxysmal atrioventricular block and low plasma adenosine ("low adenosine syncope", see paragraph *Bradycardic phenotype*). Cardioinhibition is typically not present in patients with orthostatic hypotension, although neurogenic forms may be associated with cardiovascular autonomic dysfunction, chronotropic insufficiency, and reduced heart rate variability [27]. Further, the delayed form of orthostatic hypotension may lead to vasovagal reflex, which can be cardioinhibitory [28]. Hypotensive and bradycardic phenotypes may coexist in some patients, who require a comprehensive therapeutic approach to address both hypotensive and bradycardic susceptibility.

## MECHANISM-BASED APPROACH TO SYNCOPE DIAGNOSIS

WHAT'S NEW?

The pivotal role of the syncope phenotype in diagnosis implying the growing importance of ambulatory blood pressure and ECG monitoring, and low-adenosine syncope as an emerging clinical entity.

Identifying the syncope phenotype represents the first step towards effective syncope prevention. The syncope phenotype reveals which hemodynamic mechanism should be addressed by customized therapeutic interventions. Thus, a mechanism-based approach is required, aimed at doc-

umenting the correlation of syncope with hypotension and/or bradycardia.

### The hypotensive phenotype

Hypotensive susceptibility leading to hypotensive phenotype syncope typically presents in patients with persistent or episodic hypotension, including orthostatic and post-prandial hypotension [2].

Persistent hypotension may be constitutional or drug-related. Constitutional hypotension is a chronic condition characterized by inappropriately low BP in the absence of underlying diseases or specific causes. It is defined by World Health Organization as a systolic BP <100 mm Hg in women and <110 mm Hg in men [29] while some authors suggest considering the 5$^{th}$ percentile of ambulatory BP as the lower limit of normal [30]. In these patients, low BP itself qualifies as a disease, with recurrent symptoms impairing the quality of life [31, 32]. The prevalence reaches 4% in the general population, with higher rates in females [33].

Drug-related persistent hypotension is characterized by BP values persistently below the recommended target in patients receiving hypotensive medications [2]. It more frequently occurs in hypertensive patients, particularly in those receiving intensive antihypertensive treatment, which is more likely to result in hypotension-related complications [34, 35]. However, drug-related hypotension may also derive from non-cardiovascular medications with hypotensive effects [36].

Drug-related hypotension cannot be determined using a simple cut-off or definition. Drug-related hypotension occurs when unfavorable consequences of hypotension prevail over cardiovascular advantages of the BP reduction. Therefore, it can be stated that recommended BP targets correspond to the best balance of hypotensive and cardiovascular risk, i.e. BP values carrying the minimum cumulative risk of cardiovascular and hypotensive adverse events [37]. Such BP values are not uniform within the general population but rather vary greatly depending upon the age and frailty status. Indeed, old age and frailty are associated with an increased risk of hypotension, syncope, and falls, which severely impact functional autonomy and survival [38–40]. In parallel, the prognostic value of hypertension seems to reduce or even revert with age, thus increasing the risk/benefit ratio of BP reduction [41, 42]. Drug-related hypotension should thus be defined accordingly, using personalized cut-off values based on individual hypotensive and cardiovascular risks [37].

Diagnosis of persistent hypotension — be it constitutional or drug-related — may be achieved using repeated office BPs or ABPM (Figure 1) [33, 43]. The latter may be especially useful in patients presenting office BP within the normal range, such as white-coat-effect potentially hampering detection of low BP [43, 44]. Moreover, ABPM provides BP levels through 24 hours, permitting detection of episodic hypotension, profound BP drops in the context of normal mean BP.

ABPM is becoming recognized as a syncope diagnostic tool, with findings of both persistent and episodic hypotension (Table 2). ABPM may also reveal orthostatic, post-prandial, and post-exercise hypotension [1, 45–47], or hypotensive episodes following drug administration, as may be observed in Parkinsonian patients receiving dopaminergic drugs [46]. Moreover, ABPM may help to identify hypotensive susceptibility in reflex syncope. Recent data indicate that one or more episodes of daytime systolic BP <90 mm Hg on ABPM permit a diagnosis of hypotensive susceptibility in reflex syncope with 91% specificity and 32% sensitivity [48]. Therefore, ABPM has an important role in the diagnosis of syncope while being low cost and easy to perform. Taking into consideration its tolerability in older patients, even if cognitively impaired [49], ABPM is likely to increase in value in the diagnosis of syncope.

While diagnostic pathways of syncope expand with new resources, well-known instruments such as the active standing test and TT still maintain their clinical place [50]. The active standing test may identify episodic hypotension by showing orthostatic hypotension, which is extremely common in unexplained syncope [51]. Orthostatic hypotension may also be diagnosed during TT, which is particularly helpful for the identification of initial and delayed forms — the latter may herald classical orthostatic hypotension as a prodromal manifestation of autonomic dysfunction [51]. TT in reproducing syncope accurately documents underlying hemodynamics, which constitutes the treatment target. The diagnosis of the hypotensive phenotype is achieved during TT if syncope is reproduced with vasodepression or mixed responses, which suggest hypotension as the dominant syncope mechanism. TT has proven to have a high diagnostic yield of hypotensive phenotype while CSM may have a more limited role. In a study involving 3 293 patients aged >40 years undergoing autonomic evaluation for suspected reflex syncope, the prevalence of hypotensive phenotype during TT and CSM was 53% and 1%, respectively; 98% of patients with hypotensive phenotype were identified by TT, while 2% had both TT and positive CSM [52]. These data reaffirm the central role of TT in the mechanism-based diagnosis of non-cardiac syncope, particularly regarding the detection of hypotension susceptibility [25, 50]. The diagnostic value of TT becomes even more prominent at old age when syncope diagnosis is more challenging due to frequent atypical manifestations, such as retrograde amnesia and unexplained falls. Patients' referrals for TT tend to increase with advancing age [22], parallel to an increase in atypical presentations which make achieving a diagnosis from clinical history alone more difficult.

### The bradycardic phenotype

Non-cardiac syncope with bradycardic phenotype is diagnosed if asystole >3 seconds is documented during syncope, thus indicating cardioinhibitory reflex susceptibility [2]. Asystole is most commonly a sinus arrest or atrioventricular

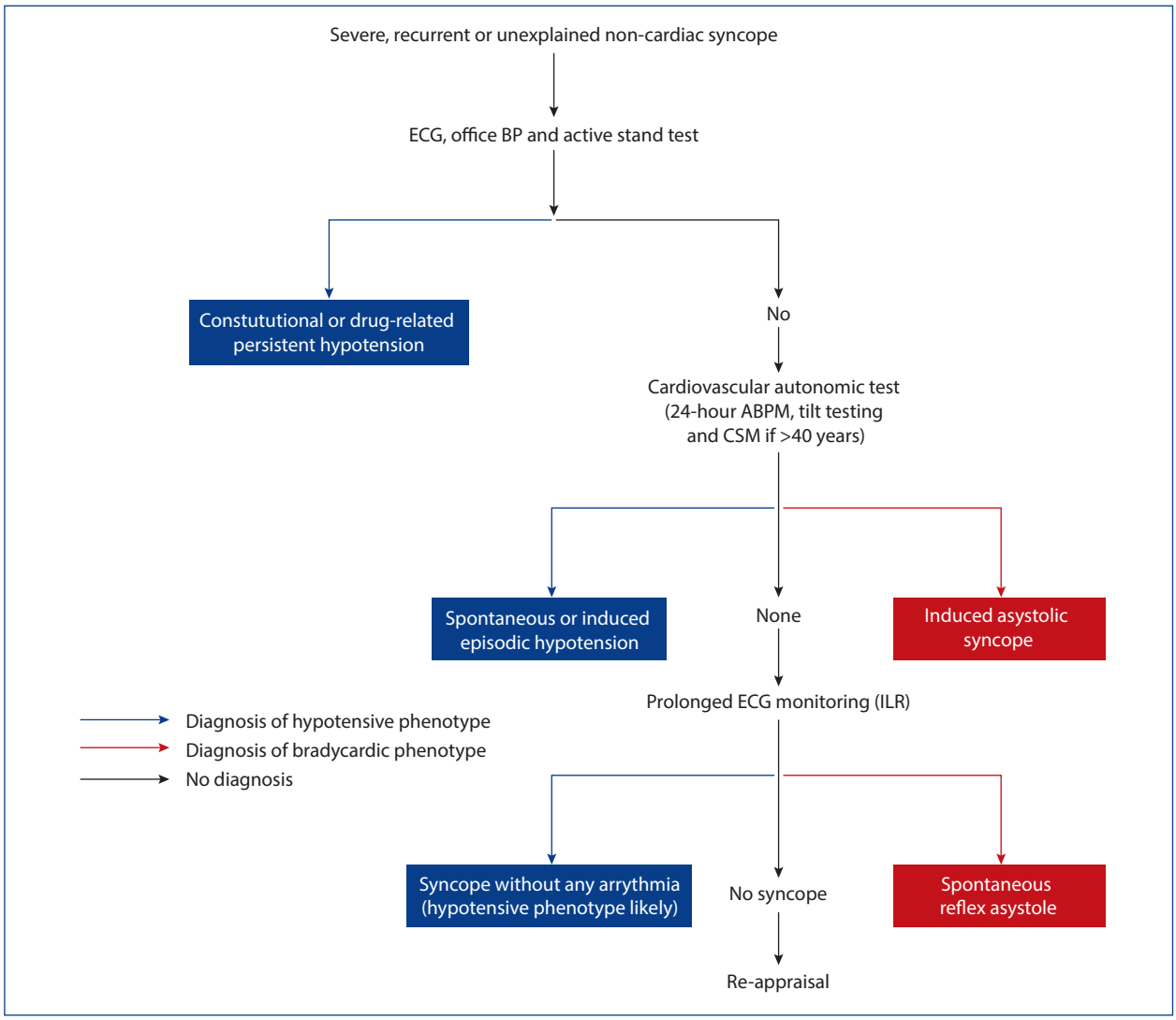


**Figure 1.** Diagnostic pathways for the hypotensive and bradycardic phenotype. Diagnosis of hypotensive phenotype may be achieved using office BPs, active stand test, 24-h ABPM or TT, showing constitutional/drug-related persistent or episodic hypotension (including orthostatic hypotension) (blue arrows). Diagnosis of bradycardic phenotype may be achieved using CSM, TT, or ILR, showing asystolic syncope (red arrows). A reappraisal should consider causes of loss of consciousness different from non-cardiac syncope, e.g, epilepsy, psychogenic pseudo-syncope, falls, etc.

Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CSM, carotid sinus massage; ILR, implantable loop recorder

**Table 2.** Diagnostic role of 24-hour ambulatory blood pressure monitoring in patients with syncope.

| Diagnosis | Definition | BP cut-offs | |
|---|---|---|---|
| Constitutional hypotension | Blood pressure values <5$^{th}$ percentile of blood pressure appropriate for sex and time of day [30, 93] | Male<br>24-hour SBP <105 mm Hg<br>Daytime SBP <115 mm Hg<br>Nighttime SBP <97 mm Hg | Female<br>24-hour SBP <98 mm Hg<br>Daytime SBP <105 mm Hg<br>Nighttime SBP <92 mm Hg |
| Drug-related persistent hypotension | Blood pressure values persistently below the recommended target [37] | Customized blood pressure cut-off based on hypotensive and cardiovascular risks [37] | |
| Hypotensive drops | Episodic hypotension | ≥1 episodes of daytime SBP <90 mm Hg [48] | |
| Orthostatic hypotension | Blood pressure drops during standing | Hypotensive episodes <90 mm Hg while standing (on patient's daily diary) may suggest OH<br>A reverse dipping profile frequently coexists in patients with autonomic failure [46] | |
| Post-prandial hypotension | Blood pressure falls during or immediately after meals | Drop in SBP of 20 mm Hg within 75 min of eating meals, compared to the mean of the last three blood pressure measurements before the meal [45, 47, 94] | |

Abbreviations: OH, orthostatic hypotension; SBP, systolic blood pressure

(AV) block which is not related to cardiac conduction disorders but is reflex [53, 54]. Diagnosis may be achieved using CSM, TT, and prolonged ECG monitoring [1].

A cardioinhibitory positive response indicating a bradycardic phenotype is present in 10% of patients undergoing TT with a prevalence decreasing with age from 18% in individuals younger than 50 to 3% in older patients above the age of 80 [22]. Among patients undergoing CSM, the prevalence of bradycardic phenotype (i.e., cardioinhibitory carotid sinus syndrome) reaches 8% [52]. When performed in the same patients, CSM identifies approximately 60% of patients with bradycardic phenotype while 37% can be identified using TT, and 3% show a positive cardioinhibitory response in both tests [52]. Given this minimal overlap between TT and CSM, it can be stated that both tests are relevant to the diagnosis of bradycardic phenotype. Therefore, TT and CSM are complementary in the diagnosis of syncope, as both are needed for a thorough investigation of syncope mechanisms to target treatment interventions.

If both TT and CSM are negative, prolonged ECG monitoring using implantable loop recorder (ILR) may contribute to the mechanism-based diagnosis and identifying the bradycardic phenotype showing asystole during spontaneous syncope [55].

In the last decade, a new clinical entity has been defined in the context of non-cardiac syncope with bradycardic phenotype from prolonged ECG monitoring. Syncope with absent or very short prodrome has been observed in patients without cardiac disease (i.e., normal ECG and echocardiogram) and was frequently associated with sudden onset idiopathic AV block or — less frequently — sinus arrest [56, 57]. Another common clinical feature is very low levels of plasma adenosine (≤0.36 mmol/l) [56, 57], a purine derivative with cardiovascular effects. High-affinity A1 adenosine-receptors are located in the AV node and lesser quantity in the sinus node, where they mediate bradycardia [58]. When plasma adenosine is low, a high number of high-affinity A1 receptors is available for binding due to upregulation, and a transient release of adenosine may be sufficient to block conduction in AV and sinus nodes, providing an explanation for a sudden AV block or sinus arrest. Thus, low plasma adenosine has been hypothesized to play a major role in the pathogenesis of syncope without prodromes with a normal heart and a normal electrocardiogram. Low adenosine syncope is considered an additional subtype of the bradycardic phenotype.

## EXISTING AND NEW STRATEGIES FOR SYNCOPE TREATMENT

WHAT'S NEW?

Promising pharmacological treatment options for hypotensive syncope and a more definite role for cardiac pacing as a therapy for bradycardic non-cardiac syncope

Treatment interventions for non-cardiac syncope should now have a mechanism-guided approach, starting from hemodynamic and rhythm phenomena observed during diagnosis.

### *Hypotensive phenotype*

#### Medication review and optimization

Alongside lifestyle measures aimed to counteract hypotensive susceptibility, a medication review and optimization should be carried out in all patients with syncope with the hypotensive phenotype (Figure 2) [1].

Medications with potential hypotensive effects should be revised and their indications reassessed to assess dose reduction or withdrawal. For antihypertensive medication careful assessment of BP control with deprescription if BP is below an individual-specific recommended target. Recent studies have provided data on the association between BP and hypotension-mediated adverse events, which may guide BP management in hypotensive susceptibility [34, 59, 60]. From this evidence, systolic BP targets of 130–140 mm Hg can be recommended in hypertensive patients with hypotensive susceptibility, as more intensive treatment is expected to substantially increase the hypotensive syncope risk [37]. Systolic BPs up to 160 mm Hg can be tolerated in older adults with severe frailty or disability – a vulnerable population in which fall risk is extremely high and the benefits of BP reduction remain doubtful [42]. In patients with excessive BP control, deprescribing should be carried out starting with drug classes of higher hypotension risk, such as α-blockers, nitrates, diuretics, and non-selective β-blockers while prescribing should rely more on ACE-inhibitors and angiotensin receptor antagonists (Figure 2) [36]. Deprescribing of antihypertensive medications does not seem to increase mortality and cardiovascular risks and can be safely performed if BP control is deemed too intensive [61].

In patients with constitutional hypotension or untreated normal BPs, attention should be paid to potentially hypotensive psychoactive drugs. These include medications with α-mediated vasodilating effects, such as antipsychotics, trazodone, tricyclic antidepressants, and benzodiazepines, which have been reported to impair orthostatic BP response in older and deconditioned subjects [36]. Medication optimization should be aimed at achieving the lowest effective dose, and the use of prolonged-release formulations or fractioned doses should be considered to minimize hypotensive effects [62]. In patients with prostatic hyperplasia, α-blockers should only be prescribed in the presence of symptoms suggesting bladder outflow obstruction, and uroselective molecules, such as silodosin, should preferably be used, given their low impact on BP [36].

#### Pharmacological therapies

Despite non-pharmacological treatments, some patients may still complain of severe, recurrent syncope, leading to

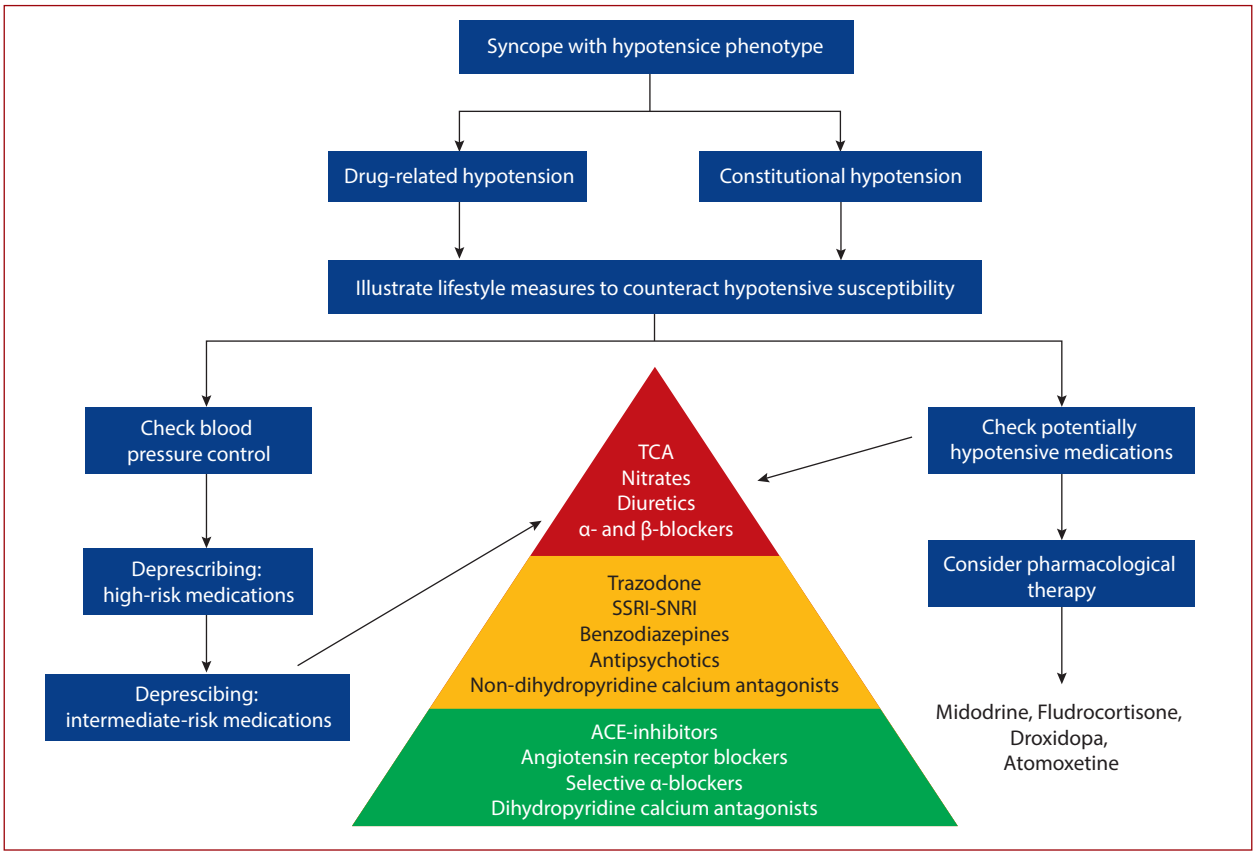


**Figure 2.** Therapeutic strategies for syncope with hypotensive phenotype. To guide deprescribing, the pyramid indicates the hypotensive risk associated with different drug classes: high risk (red), intermediate risk (yellow), low risk (green)

high injury risk and poor quality of life. They may benefit from pharmacological therapies to counterbalance hypotensive susceptibility.

The α1-agonist midodrine is one available option in patients with the hypotensive phenotype. Midodrine increases BP in patients with constitutional hypotension[63] and has demonstrated positive effects on symptoms due to neurogenic orthostatic hypotension and recurrent reflex syncope [36, 64, 65]. The recent Prevention of Syncope Trial (POST) 4 [66] re-emphasizes the value of midodrine in reflex syncope. The trial involved patients with severely symptomatic reflex syncope and showed a 40% relative risk reduction of recurrence using c.10 mg 3/day compared with placebo; adverse events were modest and balanced in the two study groups. Notably, midodrine appeared more effective with baseline systolic BPs >120 mm Hg. Midodrine is contraindicated in patients with hypertension, heart failure, urinary retention, and glaucoma.[36] Short half-life may limit long-term compliance.

As an alternative, the synthetic mineralocorticoid fludrocortisone may provide benefits in the hypotensive phenotype. In the POST 2 study [67], fludrocortisone (0.2 mg/day) was found to reduce syncope recurrences by 49% in young patients with vasovagal syncope, with significantly greater benefits with lower baseline systolic BP (<110 mm Hg) and higher syncope frequency (>8 episodes/year) [67]. Moreover, fludrocortisone might improve orthostatic BP in patients with neurogenic orthostatic hypotension, although evidence in this clinical context is weak [65, 68, 69]. Side effects include hypokalemia, supine hypertension, and volume overload, prompting caution in patients with heart failure and renal dysfunction [36].

The norepinephrine prodrug droxidopa was found to improve standing BP and orthostatic tolerance in patients with neurogenic orthostatic hypotension, reducing symptoms in daily life [70–72]. Yet, evidence supporting droxidopa is moderate and long-term efficacy remains unclear [72].

Recent research has provided promising data on atomoxetine, a selective norepinephrine transporter (NET) inhibitor. Atomoxetine potentiates adrenergic drive to the heart, which may help to increase the heart rate, maintain cardiac output and BP during orthostatic stress. Atomoxetine was shown to reduce the risk of TT-induced syncope by attenuating reflex bradycardia and preventing the progression of presyncope to syncope [73, 74]. Moreover, in a recent double-blind placebo-controlled trial, atomoxetine significantly reduced the risk of (pre)syncope and prolonged presyncope-free survival in vasovagal syncope with greater benefit in participants with systolic BP <110 mm Hg [75].

Pharmacological therapies are mainly targeted at patients who are not receiving hypotensive drugs if severe symptoms persist despite adherence to lifestyle measures. A pharmacological approach may be considered also in patients with drug-related hypotension in case hypoten-

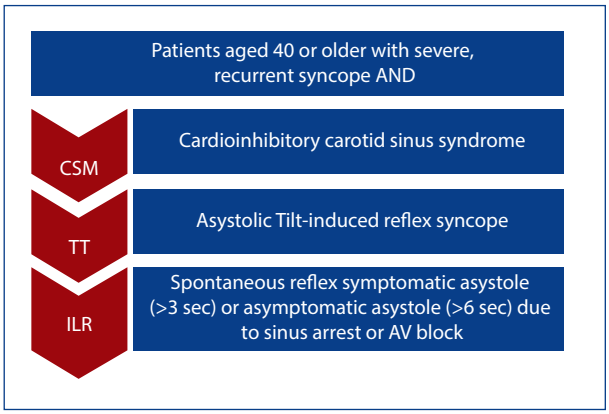


**Figure 3.** Indications for cardiac pacing in patients with bradycardic phenotype

Abbreviations: see Table 1 and Figure 1

sive medications are deemed necessary, e.g., in patients with Parkinson's disease receiving L-Dopa. In either case, pharmacological treatment should not aim at achieving pre-defined BP values, but rather improving symptoms and the quality of life. As available evidence on drug therapy is mainly in young adults [2], future studies should clarify the safety and effectiveness of pharmacological strategies in older patients.

## *The bradycardic phenotype*

### Cardiac pacing

Over the last decades, randomized controlled trials have provided evidence for the effectiveness of cardiac pacing in patients with predominant cardioinhibition documented by TT, CSM, or ILR, showing a significantly lower risk of syncope recurrence with pacing [2]. The SPAIN study [76] confirmed that pacing significantly reduces syncope events and time to the first recurrence in patients with cardioinhibitory TT-induced syncope (recurrence rate 9% and 46% in dual-chamber pacing with closed-loop stimulation vs. pacing-off, respectively). The results of the multicentre randomized placebo-controlled BIOSync trial have reinforced this conclusion, showing a significantly lower risk of (pre)syncope recurrence in patients with cardioinhibitory positive TT receiving dual-chamber pacing with closed-loop stimulation compared with pacing-off (a 77% and 46% relative and absolute risk reduction at 2 years, respectively) [77]. Based on this evidence, the guidelines of the European Society of Cardiology (ESC) have upgraded the indication for pacing in reflex syncope from IIb to I [78]. It must be understood that cardiac pacing is not always necessary but only indicated in patients aged >40-years affected by severe, recurrent, unpredictable syncope (i.e., often without prodrome) associated with a high risk of injuries [78]. At present, there is no evidence to support pacing in patients <40-years presenting even with severe symptoms [78]

Patients indicated for pacing can be identified by a multistep diagnostic pathway including CSM, TT, and ILR, as recommended by ESC guidelines [78]. Indications for cardiac pacing in syncope with the bradycardic phenotype are summarized in Figure 3.

Beneficial effects of pacing are related to the role of HR in the hemodynamic cascade of syncope. Pacing may prevent the reduction of HR at cardioinhibition onset if the sensor is ideal. An increase in HR will combat bradycardia and asystole and limit BP falls. Much depends on the fine-tuning of the sensor to individual needs. Patients with hypotensive susceptibility may be at risk of syncope recurrences after pacing, due to persistence of vasodepression. Syncope recurs after pacing in ~15%–20% of patients, due to the coexistence of bradycardic and hypotensive phenotypes [54, 77, 79, 80]. Specific treatment interventions against hypotensive susceptibility are necessary in addition to pacing to minimize recurrence risk.

TT has a pivotal role in patients' selection for cardiac pacing. Asystole on TT is highly specific for reflex syncope [81] and predictive of asystole in spontaneous syncope documented by ILR [82]. When TT-induced asystole occurs in a recurrently syncopal patient of >40-years, pacing is indicated. TT is also helpful to identify hypotensive susceptibility, which carries higher risks of syncope recurrences after pacing. In a meta-analysis involving 201 patients with asystolic syncope documented by ILR, benefits of cardiac pacing were greater in patients with negative TT (<6% recurrence risk within 3 years) while a positive TT independently predicted syncope recurrence after pacing (13%–53% recurrence risk; hazard ratio 4.3; 95% CI, 1.4–13) [54]. Similar results have been reported in cardioinhibitory carotid sinus syndrome [83]. Video recording during TT further clarified recurrences in patients with the bradycardic phenotype; Saal et al. [84] demonstrated that ~33% of patients with asystolic TT-induced syncope have late cardioinhibition, occurring <3 seconds before the loss of consciousness, which may limit or prevent pacemaker effectiveness against syncope recurrence.

### Theophylline

Recent studies advocate theophylline as a promising treatment in patients with low adenosine syncope, raising a potential alternative to cardiac pacing. Theophylline is a non-selective adenosine receptor antagonist, which competes with adenosine for receptor binding. In patients with low adenosine syncope, theophylline may prevent A1 receptor activation with subsequent bradycardia when plasma adenosine increases. Moreover, theophylline antagonizes adenosine A2 receptors mediating vasodilation, offering opposition to reflex vasodepression. Minor side effects including palpitations, headache, insomnia, and gastrointestinal complaints may limit tolerability.

Preliminary data from a small group of patients with low adenosine and asystolic syncope showed good responses to theophylline (400–600 mg twice daily) targeting a therapeutic plasma range of 12–18 μg/ml [57]. Furthermore, in a small study of low-adenosine syncope patients, a significant reduction of syncope and asystole burden during

theophylline therapy compared with no treatment was observed [85]. The therapeutic role of theophylline has yet to be defined.

### Cardioneuroablation

Cardioneuroablation (CNA) is an endocardial electrophysiological procedure to ablate epicardial postganglionic efferent parasympathetic fibers, which induces partial parasympathetic denervation of sinus and AV nodes [86–88]. CNA reduces vagal drive to the heart which mediates reflex cardioinhibition. It was introduced in 2005 by JC Pachon [88].

Preliminary data from case series and observational studies indicate successful vagal denervation and benefit on syncope burden [88–91]. However, available evidence on CNA is very limited and uncertainties persist on the methodology and long-term consequences of denervation [2, 92]. There are no randomized controlled trials. Therefore, the use of CNA currently is experimental and requires more evidence.

## CONCLUSIONS

Recently, diagnostic strategies and therapeutic options for non-cardiac syncope have evolved into a new approach, centered around an innovative, mechanism-based perspective. This new approach sets the basis for personalized management of syncope, characterized by customized interventions to prevent recurrences. Identification of syncope phenotype — bradycardic or hypotensive — represents the first step towards personalized syncope medicine. Future research should provide broader insights into customizing available treatment strategies.

### Article information

**Conflict of interest:** None declared.

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**How to cite:** Rivasi G, Ungar A, Moya A, et al. Syncope: new solutions for an old problem. Kardiol Pol. 2021; 79(10): 1068–1078, doi: 10.33963/KP.a2021.0138.

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# The safety, efficacy, and cost-effectiveness of gentamycin-collagen sponge in multicomponent prevention strategy of cardiac implantable electronic device infections — a single-center experience

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***Editorial***
by Baddour et al.
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Kardiol Pol. 2021; 79 (10): 1079–1085;
DOI: 10.33963/KP.a2021.0089

**Received:**
April 30, 2021

**Revision accepted:**
August 9, 2021

**Published online:**
August 9, 2021

## ABSTRACT

**Background:** Cardiac implantable electronic device (CIED) infections are associated with significant morbidity, mortality, and increased healthcare expenses. Apart from standard systemic antibiotic therapy, locally acting agents are under investigation as a potential approach for the prevention of this complication.

**Aims:** The study aimed to summarize our experience with a gentamycin-collagen sponge (GCS) in a multi-component prevention strategy of cardiac implantable electronic device infection.

**Methods:** We retrospectively analyzed medical records of 312 consecutive patients who underwent CIED-related surgery and had at least a 6-month follow-up. All the individuals had GCS applied during surgery. An incidence of CIEDs-related infection in our group was compared to the risk level calculated according to the commonly used scores. Analysis of cost-effectiveness was also performed.

**Results:** Incidence of CIED-related infection, defined as a primary endpoint, occurred relatively rarely (0.33%) as compared to the infection risk calculated according to commonly used scores Prevention of Arrhythmia Device Infection Trial (PADIT) — 0.83%; CIED-AI — 0.90% or Mittal score — 1.00%; $P < 0.001$ — for all). We did not record any complications related to GCS. We analyzed the cost-effectiveness of our GCS-based approach, which appeared to be financially beneficial (number needed to treat 149–200; difference of CIED infection treatment cost and GCSs price was 5093–26525 $).

**Conclusions:** We conclude that: (1) the use of GCS to reduce CIEDs infections is feasible and safe; (2) our multicomponent prevention strategy involving the GCS application seems to significantly reduce the rate of CIED infection, and it is cost-effective.

**Key words:** antibiotic prophylaxis, cardiac implantable electronic device, gentamycin-collagen sponge, infection

Kardiol Pol 2021; 79, 10: 1079–1085

## INTRODUCTION

Cardiac implantable electronic devices (CIED), excluding subcutaneous implantable cardioverter-defibrillator (ICD), have a direct connection with the bloodstream and the cardiovascular system. As a result, a CIED infection (CDI) frequently leads to a life-threatening severe systemic infection (sepsis or/and infective endocarditis). The CDI rate 6–12 months after implantation was reported as 2.3%–3.4% [1, 2] in retrospective studies, and 0.6–1.3% in prospective observational studies [3, 4], registries [5], the cross-over cluster Prevention of Arrhythmia Device Infection Trial (PADIT) [6], and randomized trials, World-wide Randomized Antibiotic Envelope Infection Prevention (WRAP-IT) [7]. CDIs are associated with a significant mor-

## WHAT'S NEW?

The use of gentamycin-collagen sponge (GCS) to reduce cardiac implantable electronic devices infections (CDI) is feasible and safe. Our multi-component prevention strategy involving the GCS application seems to significantly reduce the rate of CDI and it is cost-effective.

tality rate, morbidity, and a significant financial healthcare burden [8–10].

Adequate prevention procedures should be implemented to avoid these catastrophic consequences. According to the European Heart Rhythm Association (EHRA) international consensus document [8], preventive measures are recommended to modify or eliminate several factors associated with CDI, present in pre-, peri- and postoperative periods. It is well-known that bacterial colonization and bacterial biofilm, ubiquitous in nature, are the most important cause of device-associated infection. As systemic antibiotic therapy has a limited impact on biofilm formation, antimicrobial agents that act locally or even on the surface of implants are thought to be promising [11]. In our center, we have implemented a multi-component prevention strategy involving systemic antibiotics and the administration of a local gentamycin-collagen sponge (GCS; garamycin). Gentamicin sulfate inhibits the synthesis of bacterial proteins and has a broad spectrum of antibacterial efficacy. Naturally structured collagen fibers of GCS activate blood coagulation, which prevents hematoma formation and, therefore, reduces the risk of bacterial colonization. GCS is successfully used to prevent a local infection of high-risk patients and in procedures in orthopedics and traumatology [12], cardiac surgery [13–15], and proctology [16]. There is only one single report in the Congress proceedings related to the prevention of CDI [17]. To the best of our knowledge, we present the first complete study on the application of GCS in the prevention of CDI.

## METHODS

This retrospective observational study included all consecutive patients who underwent CIED implantation at the Electrocardiology Department of the Central University Hospital in Lodz in the third and fourth quarter of 2019. This analysis covered all classic devices implanted in the subclavicular region and connected to transvenous leads. Subcutaneous ICD, leadless pacemakers, and devices with epicardial leads were excluded. Data regarding demographics, laboratory tests, treatment, and clinical course including hospitalizations, procedural details, as well as out-patients clinic visits, were collected based on the hospital's electronic medical records. The follow-up was at least six months. In the case of missing follow-up records, we made phone calls to fill in this information. Special attention was paid to patient-related risk factors, including the history of device infection, chronic kidney disease, immunosuppression, chronic obstructive pulmonary disease (COPD), diabetes, chronic heart failure, New York Heart Association class, skin disorders, malignancy, and antithrombotic medications. Then procedure-related details were collected: the type of procedure (de novo implantation, device replacement, revision, or upgrade), procedure duration, hematoma, need for early reintervention, temporary pacing, and antibiotic prophylaxis. Additionally, device-related details, such as the type of generator pocket (i.e., subclavian, abdominal pocket), type of lead (endocardial and epicardial), and the number of leads implanted were recorded. CDI was considered as a primary endpoint of our study; however, any type of complication related to CIED was carefully analyzed.

Infective complications were defined following the EHRA international consensus [8] and included: superficial incisional infection and CDI with 2 variants: pocket infection and CIED systemic infection/infective endocarditis. For precise pocket hematoma classification, we used the hematoma grading based on the recently published classification [18].

We have performed CIED implantation according to a locally established standard regarding pre-, intra-, and postoperative periods. Our preoperative management included an appropriate selection of patients eligible for CIED implantation, identification of risk factors associated with CDI and, if possible, their elimination (e.g., avoiding central venous catheters, discontinuation of antithrombotic therapy). We excluded patients with any current infection. Moreover, we inspected oral cavities and performed sanitation when required. Electrocoagulation used as a supportive measure for surgical hemostasis was considered as the standard of care. GCS with a dimension of $10 \times 10 \times 0.5$ cm, containing the aminoglycoside antibiotic gentamicin sulfate (200 mg: 2 mg/cm$^2$) and purified bovine collagens (type I — 95% and type III — 5%), was routinely put into the generator pocket. GCS provides a high local concentration of gentamicin (reached after 1–2 hours and maintained at this level for several days) with corresponding low serum levels [19, 20]. Based on relevant papers published previously, as well as nearly 20 years of experience at our center, in 2018 we implemented our recommendation for antibiotics prophylaxis, which was approved by the hospital team for the control and prevention of infections. We created a multi-component risk score system of CIED infections that defined the score 3 points as high risk (Table 1) [21]. Accordingly, in low CDI-risk patients, we recommended an intravenous administration of ceftriaxone (2.0 g) within 60–120 minutes before the planned beginning of a procedure (vancomycin in case of allergy to cephalosporins or carriers of methicillin-resistant

**Table 1.** Multicomponent CDI risk score system

| Factor | Points |
|---|---|
| Early CIED-related surgical reintervention (within 90 days) | 3 |
| Pocket hematoma | 3 |
| Temporary endocardial pacing | 3 |
| History of CDI | 3 |
| Infection or fever within 48 hours before CIED-related procedure | 3 |
| Hemodialysis | 3 |
| Chronic skin disorder | 3 |
| Immunosuppressive therapy | 3 |
| History of more than 3 CIED-related procedures | 2 |
| Index procedure duration of more than 2 hours | 2 |
| Diabetes mellitus | 1 |
| Chronic obstructive pulmonary disease | 1 |
| Chronic kidney disease (eGFR <60 ml/min/1.73 m$^2$) | 1 |
| Many comorbidities defined as Charlson index of more than 3 | 1 |
| Congestive heart failure | 1 |
| Sum of the points | |

<3 — low-risk of CDI; 3 or more — high-risk of CDI
Abbreviations: CDI, cardiac device infection; CIED, cardiac implantable electronic device; eGFR, estimated glomerular filtration rate

staphylococcus aureus). In the case of high-risk patients, we recommend prolonging antibiotic prophylaxis treatment up to 72 hours after the procedure. As described above, a fragment of GCS was obligatorily inserted into each generator pocket, which was subsequently closed with absorbable sutures. Thereafter, the remaining portion of GCS (approximately 1/5) was placed below sutures on the subcutaneous tissue. A prolonged course of antibiotics was also indicated in the case of a pocket hematoma, fever, or symptoms of infection. If the patient's discharge was planned before the completion of antibiotic treatment, ambulatory oral therapy was prescribed (cefuroxime 0.5 g 2 times a day or in the case of allergy to cephalosporin clindamycin 0.6 g 3 times a day).

Cost-effectiveness estimations were performed with the use of our own data and information published in the United Kingdom. Costs of CDI-related hospitalizations, CIEDs extractions, and implantations of new CIEDs systems, if necessary, were summed up as an approximation of expenses connected to CDI. Additionally, data from the United Kingdom were also used for cost-effectiveness calculations to give a broader perspective. These costs were recalculated in United States dollars (USD). The price of one GCS in our institution was approximately 79 USD, and in the data published in the United Kingdom — £80 [22], whereas the costs related to one patient with CDI in Great Britain were estimated at £30 958 [3].

The study was performed in compliance with the Helsinki Declaration and with Good Clinical Practice standards and was approved by the local Bioethical Committee (No. RNN/175/20/KE). All the patients gave informed consent before the CIED-related procedure.

### *Statistical analysis*

Statistical analysis was done using Statistica software (ver. 13, StatSoft Inc., Tulsa, OK, USA). Continuous variables are shown as mean (standard deviation [SD]) if normally distributed or as median (interquartile range [IQR]) otherwise. Categorical data are shown as numbers and frequencies. For CDI rate frequency and 95% confidence intervals were calculated [6, 23, 24]. A comparison between the expected CDI risk and the CDI rate was done in our study with the non-parametric one-sample Wilcoxon signed-rank test. Values of $P<0.05$ were deemed statistically significant.

For the cost-effectiveness analysis, the absolute risk reduction (ARR) was calculated according to common principles, as a difference between the estimated event rate and the experimental event rate. The number needed to treat (NNT) was estimated according to the equation: NNT = 1/ARR [25]. The financial benefit of preventing one CDI was calculated as (NNT) × (GCS price) and was compared to CDI-related costs.

## RESULTS

We included 312 patients, who had undergone CIED implantations. We acquired all patients data mostly from the hospital or out-patient clinic data sets. In the case of 22 patients (7.1%), the information was completed via phone calls. The study population consisted mainly of males (193 patients; 61.9%). The mean age (SD) of our patients was 74.1 (10.8) years, and more than one-third (37.5%) were elderly (over 80 years old). The majority of patients (219; 70.2%) suffered from hypertension, almost half of the study population (151; 48.4%) had chronic kidney disease with eGFR lower than 60 ml/min, approximately one-third (34.9%) had diabetes, and one in ten (30; 9.6%) patient had COPD. Atrial arrhythmias were diagnosed in 141 patients (45.2%), and almost one-third (88; 28.2%) had heart failure with reduced ejection fraction. Immunosuppression, the history of CIED infection or hemodialysis were rare. Fever just before implantation (within 48 hours) was not recorded for any individual. A vast majority (249; 79.8%) of patients received antithrombotic therapy, most often antiplatelets (103; 33.0%) and direct oral anticoagulants (96; 30.8%). Detailed characteristics of the study population are shown in Table 2.

*De novo* implantations were performed in 219 (70.2%) individuals, 57 (18.3%) had device replacements, and 36 (11.5%) patients underwent CIEDs revision or upgrade, of which 18 (5.8%) had a transvenous lead extraction. A history of at least one surgery related to CIED, performed prior to the index procedure, was disclosed in 93 individuals (29.8%). The duration of surgery longer than 2 hours was recorded in 32 patients (10.3%). Procedural data are presented in detail in Table 3.

Periprocedural antibiotic therapy longer than recommended was applied in 53 (17.0%) patients, and 8 (2.6%)

**Table 2.** Demographic and clinical characteristics of the study population

| | |
|---|---|
| Total number of patients | 312 |
| Age, years | 74.1 (10.8) |
| Female/Male | 119 (38.1%)/193 (61.9%) |
| NYHA class | 2.0 (1.0–4.0) |
| Atrial fibrillation/Atrial flutter | 128 (41.0%)/13 (4.2%) |
| LVEF (%) | 53.0 (36.0–58.0) |
| HFrEF — LVEF <40% | 88 (28.2%) |
| Hypertension | 219 (70.2%) |
| eGFR, ml/min | 62.5 (46.9–78.1) |
| <30 ml/min | 25 (8.0%) |
| Hemodialysis | 4 (1.3%) |
| Prosthetic valve | 24 (7.7%) |
| Chronic obstructive pulmonary disease | 30 (9.6%) |
| Immunosuppressive drugs | 6 (1.9%) |
| Diabetes mellitus | 109 (34.9%) |
| History of previous CIED infection | 3 (1.0%) |
| Transvenous temporary pacing | 24 (7.7%) |
| Antithrombotic treatment | 249 (79.8%) |
| SAPT | 70 (22.4%) |
| DAPT | 33 (10.6%) |
| DOAC | 96 (30.8%) |
| VKA | 29 (9.3%) |
| Others | 31 (9.9%) |
| Previous CIED-related procedure | 93 (29.8%) |
| 1 | 61 (19.6%) |
| 2 | 25 (8.0%) |
| ≥3 | 7 (2.2%) |

Abbreviations: CIED, cardiac implantable electronic device; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulants; eGFR, estimated glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SAPT, single antiplatelet therapy; VKA, vitamin K antagonists

**Table 3.** The details of CIED-related procedures

| | |
|---|---|
| No. of procedures | 312 |
| New pacemaker | 168 (53.8%) |
| New ICD | 34 (10.9%) |
| New CRT pacemaker/defibrillator | 17 (5.4%) |
| Pacemaker generator replacement | 31 (9.9%) |
| ICD generator replacement | 9 (2.9%) |
| CRT generator replacement | 17 (5.4%) |
| Revision/up-grade | 36 (11.5%) |
| Transvenous lead extraction | 18 (5.8%) |
| Early <3 months | 13 (4.2%) |
| Duration of procedure | |
| ≤2 hours | 280 (89.7%) |
| >2 hours | 32 (10.3%) |
| Left-sided CIED system implantation | 306 (98.1%) |
| Right-sided CIED system implantation | 6 (1.9%) |
| Subcutaneous pocket | 312 (100%) |
| Submuscular pocket | 0 (0.0%) |

Abbreviations: CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; other — see Table 2

had an atypical antibacterial regimen administered, which consisted of different than suggested antibiotics and dosage. Temporary intravenous pacing (16; 5.1%), respiratory or urinary tract infection (11; 3.5%), early surgical reintervention related to CIED (5; 1.6%), delay due to rescheduling of implantation (5; 1.6%), and concomitant Lyme disease (4; 1.3%) were the most frequently reported reasons for prolonged and atypical antibiotic therapy.

**Table 4.** Risk of cardiac device infection and study outcomes

| | |
|---|---|
| Mittal risk, % | 1.00 [1.00–3.40][a] |
| CIED-AI risk, % | 0.90 [0.00–0.90][a] |
| PADIT risk, % | 0.83 [0.46–1.06][a] |
| Cardiac device infection | 1 (0.33%)[a] |
| Superficial incisional infection | 3 (0.99%)[a] |
| Death (causes) | 20 (6.4%) |
| Stroke | 5 (1.6%) |
| Malignancy | 5 (1.6%) |
| Heart failure | 3 (1.0%) |
| Electric storm | 1 (0.3%) |
| Chronic kidney disease | 1 (0.3%) |
| Unknown | 5 (1.6%) |
| Lead dislocation | 8 (2.6%) |
| Pocket hematoma | 4 (1.3%) |

Data are shown as median [IQR] and number

[a]Calculated for patients who stayed alive for more than 6 months (n = 302)

During the in-hospital stay, we observed 4 cases of pocket hematomas (1.3%). There were 2 patients with first-grade pocket hematoma and 2 patients with third-grade pocket hematoma requiring discontinuation of antithrombotic therapy with prolongation of the antibiotic course and hospitalization. Hematomas were completely absorbed without any sequelae.

During the follow-up of at least 6 months (median [IQR]: 343 [266–420] days), 20 patients (6.4%) died; of these, 10 patients (3.2%) died within half a year from CIED-related surgery. None of the deaths was related to CDI or sepsis (Table 4). Eventually, the vast majority of patients (303; 97.1%) completed a 6-month follow-up alive; therefore, these individuals were taken for further analysis of infectious complications related to CIEDs surgery.

Cardiac electronic device infection was disclosed in only one case (0.33%; 95% CI, 0.01%–0.97%). It was an isolated pocket infection that was diagnosed 45 days after an upgrade from a dual-chamber ICD to a cardiac resynchronization therapy-defibrillator (CRT-D). The infection was diagnosed in a 68-year-old male with persistent left superior vena cava and a high risk of CDI, according to all analyzed scores (our score — 3 points; calculated CDI risk from CIED-AI score 2.50%, Mittal score — 3.40% and PADIT score — 3.45%) [6, 23, 24]. This patient underwent extraction of the whole CIED system, and following intravenous antibiotic therapy, had a new CRT-D system implanted at the right side of the thorax. Additionally, a superficial incisional infection was diagnosed in other 3 patients (0.99%; 95% CI, 0.0–2.1%). All of them made a full recovery with completely healed wounds as a result of ambulatory oral antibiotic therapy.

We assessed the risk of CDI in the patients who completed 6 months' follow-up using 3 popular score systems: CIED-AI score [23], PADIT score [6], and Mittal score [24]. The study population's CDI mean risk was approximately 1% if estimated with PADIT score (median [IQR]: 0.83 [0.46–

–1.06]%), CIED-AI score (median [IQR]: 0.90 [0.0–0.90]%), and Mittal score (median [IQR]: 1.00 [1.00–3.40]%). The CDI rate in our study was significantly lower than the calculated risks ($P$ <0.001 – for any score compared to the study results).

The number needed to treat with our GCS-based strategy to prevent one CDI ranged from 149 to 200, depending on which risk estimation was taken for calculations (0.83%–1.00%). CDI-related costs in our region were analyzed in a group of 12 consecutive patients referred to our center due to infection caused by implanted devices. The expenses related to the treatment of these patients ranged from 7531 USD to 36928 USD (mean [SD]: 20893 [8961] USD). Furthermore, the costs that resulted from the application of GCS to avoid one CDI were estimated at 11791–15800 USD, if based on our local data, or £11940––16000 (16653–22315 USD) for the United Kingdom. Therefore, the difference between the costs related to CDI and the costs of avoiding this complication could be estimated between 5093–9102 USD and £14958–19018 respectively (20862–26525 USD), in favor of the GCS-based strategy.

## DISCUSSION

The main findings of our study were that: (1) gentamycin-collagen sponges can be safely used for CDI prevention, and such a strategy seems to be beneficial in terms of the low infection rate; (2) the use of gentamycin-collagen sponges seem to be cost-effective.

Although systemic antibiotic treatment is highly effective in the prevention of bacterial contamination (and CIEDs infection) [26, 27], it is inefficient in the elimination of bacterial biofilm, therefore, locally acting antibiotics were thought to be an interesting additive option. An antibacterial multifilament mesh envelope (TYRX™, Medtronic, Plymouth, MN, USA) eluting minocycline and rifampin reduced the incidence of CIED infection in the WRAP-IT trial (40% lower incidence of a major CIED infection than standard-of-care infection-prevention strategies alone) [7]. An experimental study, using an in-vitro biofilm system, demonstrated that the antibacterial envelope inhibited the ability of *Staphylococcus aureus* to form biofilms on mock CIEDs [28]. Like TYRX, GCS releases antibiotics locally, and its efficacy in the eradication of bacterial biofilm was proved in vitro (on hydroxyapatite surface) [19]. Therefore, a high local concentration of antibiotics (in the case of GCS — gentamicin) maintained for several days in the generator pocket may prolong the inhibition of bacterial colonization [20]. In our center, a few years ago the above-mentioned rationale led to multidisciplinary consultations, which resulted in the elaboration of a multi-component prevention strategy of CDI that included application GCS during each CIED implantation apart from standard systemic antibiotic prophylaxis. This approach was incorporated into the internal recommendations of our institution, which were approved by the hospital team for infection control and prevention.

In our retrospective study, we showed the safety and efficacy of our strategy that included GCS. No complication related to GCS was observed, and the low rate of CDI was recorded (only one case, 0.33%). It would have been expected approximately 3 patients with CDI (c.a. 1% in PADIT score, CIED-AI score and Mittal score). Additionally, the risk of CDI infection in retrospective studies is generally significantly higher than in prospective trials (2.3%–3.4%) [1, 2], which forecasts up to 10 CDI in our population. If such predictions are compared with our results, it seems that our strategy might have saved from 2 to 8 patients from CDI.

Nonetheless, it must be underlined that our approach was not only based on GCS but included more aggressive systemic antibiotic therapy (ceftriaxone *iv* at least twice — one dose before the procedure and one the day after) [8], and additionally, a specific surgical technique of separate pocket closure with absorbable sutures. A worldwide survey [29] showed that longer than recommended [8] periprocedural antibiotic therapy is commonly applied, which is mainly due to the threat of CDI, recognized as a devastating complication. The surgical technique that we use could potentially reduce the rate of pocket hematoma, whose occurrence is related to an even nine-fold increased risk of CDI [30]. The rate of hematoma in the study population was 1.3%, which was lower than rates generally reported in previously published studies (3.2%–9%) [31–33]. However, it should be noticed that GCS applied to the pocket might activate blood coagulation and prevent the hematoma [12, 16]. Therefore, it could be possible that the use of GCS and our specific surgical technique might be considered as efficient measures to reduce the rate of pocket hematoma. Another important factor influencing CDI is the need for early reintervention, as well as long complex TLE procedures, which are connected with the higher risk of hematoma and prolonged hospital stay [34]. In our group, 13 CIED surgeries were performed less than 3 months after the index procedure. The most frequent reasons were lead dislocation (2.5%) and "dry" perforations (0.95%), which were also reported elsewhere [31, 33, 35].

Our CDI-prevention strategy with the use of GCS seems to be cost-effective. Depending on which risk score is used, the number needed to treat for saving one patient with CDI was 149 to 200 for GCS, which was similar (40–166) to the TYRx antibacterial envelope [7, 36]. Moreover, the unit price of GCS is much lower than the competing envelope (79-110 USD vs. 895 USD) [22, 36]. Thus, the use of gentamycin sponges would remain still cost-effective even if only 0.3% of patients were spared from CDI. As CDI is connected with catastrophic consequences [37], the GCS-based CDI prevention strategy should be considered in patients with a high risk of infective complication. However, having in mind the relatively favorable cost-effectiveness of such an approach, using the GCS strategy might be useful in all patients undergoing CIEDs-related surgery.

The study had several limitations, among them the most important were a single-center location, retrospective

analysis, including a medium-size study population, and relatively short follow-up. On the other hand, this study reflected real-world management. The lack of personal contact with the patients, which was substituted with phone teleconsultations, could be a potential reason for the under-detection of CIED-related infections. However, due to the COVID-19 pandemic, this was the only possible option in some cases. Additionally, cost-effectiveness calculations have the potential of imprecision due to different equipment which is used for removal of CIEDs systems implanted 12 months or longer before the extraction than those inserted earlier.

Based on our results the following conclusions can be drawn. The use of gentamycin-collagen sponges to reduce cardiac electronic device-related infections is feasible and safe. Our multi-component prevention strategy involving the application of GCS seems to significantly reduce the rate of CIED infection and to be cost-effective. A further prospective and randomized multicenter study is needed to confirm our findings.

## *Article information*

**Conflict of interest:** None declared.

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**How to cite:** Kaczmarek K, Strzelecki A, Ptaszyński P, et al. The safety, efficacy, and cost-effectiveness of gentamycin-collagen sponge in multicomponent prevention strategy of cardiac implantable electronic device infections — a single-center experience. Kardiol Pol. 2021; 79(10): 1079–1085, doi: 10.33963/KP.a2021.0089.

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# Thromboembolism and bleeding in patients with atrial fibrillation and stage 4 chronic kidney disease: impact of biomarkers

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***Editorial***
by Krittayaphong
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Kardiol Pol. 2021; 79 (10): 1086–1092; DOI: 10.33963/KP.a2021.0088

**Received:** July 20, 2021
**Revision accepted:** August 9, 2021
**Published online:** August 9, 2021

## ABSTRACT

**Background:** Chronic kidney disease (CKD) is considered a risk factor for thromboembolic and bleeding events in patients with atrial fibrillation (AF).

**Aims:** We sought to assess predictors of clinical outcomes among AF patients with advanced CKD.

**Methods:** In a prospective cohort study, we enrolled 180 AF patients with stage 4 CKD, defined as estimated glomerular filtration rate of 15–29 ml/min/1.73 $m^2$, on vitamin K antagonists (n = 90), and non-vitamin K antagonists oral anticoagulants (n = 90). We assessed biomarkers, including growth differentiation factor-15, cystatin C, and high-sensitivity cardiac troponin T, and prothrombotic state parameters, including plasma fibrin clot permeability ($K_s$).

**Results:** The median age of the patients was 71.0 (64.0–75.0) years (men 65.0%). The median estimated glomerular filtration rate was 24.0 (21.0–25.0) ml/min/1.73 $m^2$ while the median $CHA_2DS_2$-VASc score was 3.0 (2.0–4.0). Age (hazard ratio [HR], 1.11; 95% confidence interval [CI], 1.02–1.20) and decreased $K_s$ (HR, 0.55; 95% CI, 0.34–0.90) were associated with thromboembolic events (n = 18; 4.7% per year). Previous bleeding (HR, 3.21; 95% CI, 1.22–8.45), growth differentiation factor-15 (HR, 1.48; 95% CI, 1.29–1.69), cystatin C (HR, 9.24; 95% CI, 2.15–39.67), and high-sensitivity cardiac troponin T (HR, 1.30; 95% CI, 1.14–1.48) were independent predictors of major or clinically relevant non-major bleeding (n = 27; 7.1% per year). After adjustment for age and comorbidities, only cystatin C (HR, 3.95; 95% CI, 1.08–14.37) predicted mortality (n = 25; 6.5% per year).

**Conclusions:** Novel biomarkers might be useful in risk stratification of thromboembolic and bleeding events in AF patients with stage 4 CKD receiving oral anticoagulants.

**Key words:** atrial fibrillation, biomarkers, bleeding, chronic kidney disease, stroke

Kardiol Pol 2021; 79, 10: 1086–1092

## INTRODUCTION

Atrial fibrillation (AF) constitutes the most prevalent type of sustained cardiac arrhythmia in adults and increases the risk of ischemic stroke, systemic thromboembolism, left ventricular dysfunction, heart failure, vascular dementia, and mortality [1, 2]. Chronic kidney disease (CKD) is associated with incident AF, which increases rates of stroke and death in patients with CKD [3]. Moreover, AF itself is associated with a higher risk of developing or progression of CKD [4]. Patients with concomitant stage 4 CKD, defined as estimated glomerular filtration rate (eGFR) of 15–29 ml/min/1.73 $m^2$, are at increased risk for thrombo-

## WHAT'S NEW?

The present cohort study identifies novel biomarkers which might predict clinical outcomes in anticoagulated patients with atrial fibrillation and stage 4 chronic kidney disease. Age and denser fibrin clots have been found to be associated with thromboembolic events. Previous bleeding, growth differentiation factor-15, cystatin C, and high-sensitivity cardiac troponin T can predict major or clinically relevant non-major bleedings. In these high-risk patients on oral anticoagulation, cystatin C is independently associated with mortality.

embolic events (TE) compared to those with better kidney function [5]. However, CKD has not been included in the CHADS-65 or $CHA_2DS_2$-VASc score [6].

Vitamin K antagonists (VKA) and non-VKA oral anticoagulants (NOACs) are effective in the prevention of cerebrovascular ischemic events in AF patients [7, 8]. The latter are currently the preferred therapeutic option also in patients with CKD, except for those with creatinine clearance below 15 ml/min [9]. In AF patients with creatinine clearance of 15–29 ml/min, the recommended daily doses are 15 mg daily for rivaroxaban and 2.5 mg twice a day for apixaban, but in the US, dabigatran 75 mg twice a day is another option [9, 10]. In this patient group, education is of key importance for anticoagulation safety [11].

N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin have been identified as independent predictors of TE in AF [12]. It has been shown that the combination of the two biomarkers with basic clinical data may improve stroke risk assessment in AF [13] while mortality in AF can be predicted by combining age and heart failure status with growth differentiation factor-15 (GDF-15), NT-proBNP, and high-sensitivity cardiac troponin T (cTnT-hs) [14]. Cystatin C, a glomerular filtration marker associated with cardiovascular diseases, has been recently demonstrated as a predictor of acute ischemic stroke [15]. Renal function may affect circulating levels of biomarkers [16]. Landmark AF trials, which assessed biomarkers, generally excluded subjects with creatinine clearance below 30 ml/min [9, 17]. Therefore, little is known about the prognostic value of biomarkers in this subset of AF patients with CKD. It has been suggested that increased density of fibrin networks and prolonged clot lysis can predict TE and major bleeding events in anticoagulated AF patients [18–20]. Although we have recently shown that stage 4 CKD in AF patients is associated with unfavorable fibrin clot phenotype [5], its predictive value in terms of clinical outcomes, in this subgroup of patients, has not been evaluated yet.

We tested the hypothesis that GDF-15, cTnT-hs, and cystatin C, along with prothrombotic variables can predict complications of AF in patients with stage 4 CKD during anticoagulant therapy.

## METHODS

We included 180 adults with a history of AF and stage 4 CKD, defined as 2 or more eGFR values in the range of 15–29 ml/min/1.73 $m^2$ assessed using the CKD Epidemiology Collaboration (CKD-EPI) formula [10], enrolled in Kraków, Poland, between January 2014 and October 2017, with complete clinical and laboratory data. The inclusion and exclusion criteria were presented previously [10]. Briefly, the exclusion criteria were acute infection, liver injury, acute coronary syndrome in the preceding 12 months, and known active malignancy. The study was approved by the Bioethical Committee of the Jagiellonian University. All patients provided written informed consent.

Using a standardized questionnaire, we collected data on demographics, cardiovascular risk factors, comorbidities, and medications used. Definitions of risk factors and comorbidities were described previously [10].

### Laboratory studies

Fasting venous blood samples were taken from the antecubital vein from the patients off anticoagulation. The patients on VKA were switched to a low-molecular-weight heparin, and blood samples were collected at least 12 hours after the last heparin injection. In the group of patients receiving rivaroxaban, or apixaban, blood samples were taken at least 24 h after the last dose. Routine laboratory tests were performed by standard laboratory techniques. The Clauss method was used to determine fibrinogen. Plasminogen activator inhibitor-1 (PAI-1) and thrombin-activatable fibrinolysis inhibitor were assessed by ELISAs (American Diagnostica, Stamford, CT, USA and Chromogenix, Lexington, MA, USA, respectively) [21]. Biomarkers such as GDF-15 and NT-proBNP were measured using electrochemiluminescence immunoassays (Roche Diagnostics, Mannheim, Germany) [21]. Endogenous thrombin potential (ETP) was quantified using calibrated automated thrombography, as previously described [21]. Fibrin clot permeability ($K_s$), reflecting the average size of fibrin clot network pores, was calculated using the following equation: $K_s = Q \times \eta \times L / t \times A \times \Delta p$, where Q indicates the flow rate in percolating time (t), $\eta$ reflects the viscosity of liquid in the poise, L is the length of a fibrin gel, $\Delta p$ is a differential pressure in dyne/$cm^2$, while A indicates the cross-sectional area in $cm^2$. Clot lysis time (CLT), indicating fibrin clot susceptibility to lysis was assessed as described [21]. CLT was measured from the midpoint of the clear-to-maximum-turbid transition to the midpoint of the maximum-turbid-to-clear transition.

### Follow-up

The participants were followed up via phone calls at least twice a year or through clinic visits till January 2019. The occurrence of stroke/transient ischemic attack was the primary study outcome that was diagnosed based on

**Table 1.** Baseline patient characteristics in relation to the presence or absence of thromboembolic or bleeding events in the follow-up

| Variable | Whole group (n = 180) | No TE (n = 162) | TE (n = 18) | *P*-value | No bleeding (n = 153) | Bleeding (n = 27) | *P*-value |
|---|---|---|---|---|---|---|---|
| Demographics | | | | | | | |
| Age, years | 71.0 (64.0–75.0) | 70.0 (64.0–75.0) | 73.0 (69.0–78.3) | 0.07 | 71.0 (64.0–75.0) | 71.0 (66.0–76.0) | 0.50 |
| Male sex, n (%) | 117 (65.0) | 106 (65.4) | 11 (61.1) | 0.72 | 102 (66.7) | 15 (55.6) | 0.26 |
| BMI, kg/m$^2$ | 27.8 (25.6–31.6) | 27.8 (25.6–31.5) | 27.0 (25.3–32.7) | 0.88 | 28.1 (25.6–32.2) | 26.6 (25.3–29.5) | 0.08 |
| Persistent AF, n (%) | 84 (46.7) | 76 (46.9) | 8 (44.4) | 0.84 | 73 (47.7) | 11 (40.7) | 0.50 |
| Permanent AF, n (%) | 96 (53.3) | 86 (53.1) | 10 (55.6) | | 80 (52.3) | 16 (59.3) | |
| $CHA_2DS_2$-VASc score | 3.0 (2.0–4.0) | 3.0 (2.0–4.0) | 3.0 (3.0–4.0) | 0.25 | 3.0 (2.0–4.0) | 3.0 (2.0–4.0) | 0.76 |
| Past bleeding, n (%) | 11 (6.1) | 11 (6.8) | 0 (0.0) | 0.61 | 5 (3.3) | 6 (22.2) | 0.002 |
| Comorbidities and CVD risk factors, n (%) | | | | | | | |
| Hypertension | 105 (58.3) | 96 (59.3) | 9 (50.0) | 0.45 | 89 (58.2) | 16 (59.3) | 0.92 |
| Diabetes mellitus | 64 (35.6) | 56 (34.6) | 8 (44.4) | 0.41 | 55 (35.9) | 9 (33.3) | 0.79 |
| Dyslipidemia | 134 (74.4) | 122 (75.3) | 12 (66.7) | 0.41 | 114 (74.5) | 20 (74.1) | 0.96 |
| Smoking history | 27 (15.0) | 24 (14.8) | 3 (16.7) | 0.74 | 22 (14.4) | 5 (18.5) | 0.56 |
| CAD | 83 (46.1) | 73 (45.1) | 10 (55.6) | 0.40 | 72 (47.1) | 11 (40.7) | 0.54 |
| Previous MI | 39 (21.7) | 37 (22.8) | 2 (11.1) | 0.37 | 32 (20.9) | 7 (25.9) | 0.56 |
| Heart failure | 44 (24.4) | 40 (24.7) | 4 (22.2) | 1.0 | 38 (24.8) | 6 (22.2) | 0.77 |
| COPD | 24 (13.3) | 21 (13.0) | 3 (16.7) | 0.71 | 22 (14.4) | 2 (7.4) | 0.54 |
| Medications, n (%) | | | | | | | |
| β-blocker | 152 (84.4) | 139 (85.8) | 13 (72.2) | 0.17 | 133 (86.9) | 19 (70.4) | 0.04 |
| ACE-I | 119 (66.1) | 106 (65.4) | 13 (72.2) | 0.56 | 103 (67.3) | 16 (59.3) | 0.42 |
| ARB | 22 (12.2) | 20 (12.3) | 2 (11.1) | 1.0 | 20 (13.1) | 2 (7.4) | 0.54 |
| CCB | 38 (21.1) | 32 (19.8) | 6 (33.3) | 0.22 | 32 (20.9) | 6 (22.2) | 0.88 |
| Aspirin | 73 (40.6) | 64 (39.5) | 9 (50.0) | 0.39 | 61 (39.9) | 12 (44.4) | 0.66 |
| Clopidogrel | 8 (4.4) | 7 (4.3) | 1 (5.6) | 0.58 | 6 (3.9) | 2 (7.4) | 0.34 |
| Statin | 125 (69.4) | 115 (71.0) | 10 (55.6) | 0.18 | 108 (70.6) | 17 (63.0) | 0.43 |
| Digoxin | 34 (18.9) | 32 (19.8) | 2 (11.1) | 0.53 | 29 (19.0) | 5 (18.5) | 0.96 |
| Amiodarone | 28 (15.6) | 25 (15.4) | 3 (16.7) | 1.0 | 22 (14.4) | 6 (22.2) | 0.39 |
| Anticoagulants used during follow-up, n (%) | | | | | | | |
| NOAC | 90 (50.0) | 79 (48.8) | 11 (61.1) | 0.32 | 76 (49.7) | 14 (51.9) | 0.84 |
| Vitamin K antagonist | 90 (50.0) | 83 (51.2) | 7 (38.9) | | 77 (50.3) | 13 (48.1) | |

Data are presented as median (IQR) or number (%)

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BMI, body mass index; CAD, coronary artery disease; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; MI, myocardial infarction; n, number; NOAC, non-vitamin K antagonist oral anticoagulant; TE, thromboembolism

the World Health Organization criteria. Major bleeding or clinically relevant non-major bleeding (CRNMB) were the secondary outcomes, which were defined as described previously [22, 23]. Deaths were also recorded.

### Statistical analysis

Continuous variables are shown as the means (standard deviations) or medians (interquartile ranges) and were compared using the Student's or Welch's t-test or Mann-Whitney U test, as appropriate. *P*-values <0.05 were considered statistically significant. Statistical analyses were performed with the use of IBM SPSS Statistics for Windows (version 26, IBM Corp., Armonk, NY, USA) or STATISTICA (version 13.3, TIBCO Software Inc., Palo Alto, CA, USA), for Youden indexes and areas under the curves (AUC) calculations. For details see supplemental material.

## RESULTS

### Patients

A total of 180 AF patients (men 65%, median age; 71.0 [64.0–75.0] years) with stage 4 CKD (median eGFR, 24.0; interquartile range 21.0–25.0 ml/min/1.73 m$^2$) and a median $CHA_2DS_2$-VASc score of 3.0 (2.0–4.0) were studied (Table 1). The majority of the patients had hypertension, while diabetes mellitus was diagnosed in 35.6% of them, which were the main causes of CKD in this cohort (Table 1). None of the patients had proteinuria above 1 g per day. No lupus nephritis cases were included. Half of the patients were treated with VKA, while the other half was on apixaban or rivaroxaban (Table 1). Among the patients on VKA, the mean time in the therapeutic range was 65.6 (16.5)% while the percentage of patients with time in the therapeutic range ≥70.0% was 42.2% (n = 38).

Age, sex, and body mass index (BMI) were not associated with NT-proBNP, GDF-15, or cTnT-hs. An inverse association was observed between BMI and cystatin C (R = –0.16; *P* = 0.04). The $CHA_2DS_2$-VASc score did not correlate with any of the four biomarkers. GDF-15 was positively associated with cTnT-hs (R = 0.35; *P* <0.0001) while other correlations between the major studied biomarkers were generally weaker or absent. Analysis of the four biomarkers in relation to the prothrombotic markers did not reveal potent associations among them (R between –0.23 to 0.23) in stage 4 CKD.

**Table 2.** Laboratory and hemostatic parameters in relation to the presence or absence of thromboembolic or bleeding events in the follow-up

| Variable | Whole group (n = 180) | No TE (n = 162) | TE (n = 18) | *P*-value | No bleeding (n = 153) | Bleeding (n = 27) | *P*-value |
|---|---|---|---|---|---|---|---|
| eGFR, ml/min/1.73 m$^2$ | 24.0 (21.0–25.0) | 24.0 (21.0–25.0) | 24.0 (21.0–26.0) | 0.54 | 24.0 (21.0–25.0) | 23.0 (22.0–26.0) | 0.60 |
| Hemoglobin, g/dl | 12.2 (1.3) | 12.2 (1.3) | 12.2 (1.7) | 0.99 | 12.2 (1.3) | 12.2 (1.3) | 0.84 |
| Platelets, ×1000/µl | 217.5 (189.0–288.0) | 217.5 (189.0–280.0) | 216.5 (184.8–328.0) | 0.72 | 221.0 (189.0–293.0) | 209.0 (184.0–254.0) | 0.18 |
| Cystatin C, mg/l | 1.2 (1.0–1.3) | 1.2 (1.0–1.3) | 1.2 (1.1–1.2) | 0.80 | 1.1 (1.0–1.2) | 1.2 (1.2–1.3) | <0.0001 |
| hs-CRP, mg/l | 2.8 (1.5–4.1) | 2.8 (1.5–4.0) | 2.9 (1.8–5.7) | 0.30 | 3.0 (1.5–4.1) | 2.6 (1.3–4.0) | 0.46 |
| GDF-15, pg/ml | 1729.0 (1564.5–2051.8) | 1734.0 (1568.0–2085.0) | 1630.0 (1472.0–1887.5) | 0.18 | 1675.0 (1543.0–1862.0) | 2319.0 (2165.0–2498.0) | <0.0001 |
| NT-proBNP, pg/ml | 684.0 (399.0–1092.5) | 674.5 (399.0–1073.5) | 850.5 (127.0–1149.5) | 0.74 | 665.0 (408.5–1054.5) | 836.0 (265.0–1166.0) | 0.59 |
| cTnT-hs, ng/l | 7.8 (6.1–9.7) | 7.9 (6.1–9.9) | 6.5 (5.6–8.2) | 0.07 | 7.2 (6.0–9.0) | 10.6 (9.6–11.9) | <0.0001 |
| Hemostatic parameters | | | | | | | |
| Fibrinogen, g/l | 3.2 (2.4–3.9) | 3.2 (2.4–3.9) | 3.3 (2.5–4.5) | 0.45 | 3.2 (2.5–3.9) | 3.0 (2.4–4.1) | 0.37 |
| D-dimer, ng/ml | 369.5 (240.8–515.3) | 361.0 (240.0–512.3) | 386.0 (246.5–734.5) | 0.50 | 374.0 (244.5–514.5) | 337.0 (237.0–550.0) | 0.94 |
| TAFI: Ag (%) | 102.0 (93.0–113.8) | 102.0 (93.0–113.0) | 99.5 (91.0–116.0) | 0.76 | 102.0 (93.0–114.0) | 100.0 (94.0–112.0) | 0.64 |
| PAI-1: Ag, ng/ml | 27.4 (8.4) | 27.5 (8.5) | 26.6 (7.5) | 0.66 | 27.2 (8.4) | 29.0 (8.3) | 0.29 |
| ETP, nM × min | 1672.2 (1510.9–1889.8) | 1672.2 (1512.3–1878.3) | 1670.1 (1495.3–2047.6) | 0.76 | 1670.0 (1510.1–1873.0) | 1691.0 (1543.5–2096.0) | 0.36 |
| $K_s$, × 10$^{-9}$ cm$^2$ | 6.4 (1.0) | 6.4 (0.9) | 6.0 (0.9) | 0.08 | 6.4 (1.0) | 6.4 (0.7) | 0.84 |
| CLT, min | 105.0 (21.4) | 104.8 (21.5) | 107.5 (20.4) | 0.61 | 102.9 (20.5) | 117.0 (22.7) | 0.001 |

Data are presented as mean (SD) or median (IQR)

Abbreviations: Ag, antigen; CLT, clot lysis time; cTnT-hs, high-sensitivity cardiac troponin T; eGFR, estimated glomerular filtration rate; ETP, endogenous thrombin potential; GDF-15, growth differentiation factor-15; hs-CRP, high-sensitivity C-reactive protein; $K_s$, clot permeability; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PAI-1, plasminogen activator inhibitor-1; TAFI, thrombin-activatable fibrinolysis inhibitor; other — see Table 1

**Table 3.** Cox regression analysis for clinical outcomes in patients with atrial fibrillation and stage 4 chronic kidney disease

| | Univariable analysis | | Multivariable analysis | |
|---|---|---|---|---|
| **Predictors of stroke, TIA, or systemic embolism** | **HR (95% CI)** | ***P*-value** | **HR (95% CI)** | ***P*-value** |
| Age, years | 1.10 (1.01–1.19) | 0.02 | 1.11 (1.02–1.20) | 0.01 |
| $K_s$, × 10$^{-9}$ cm$^2$ | 0.61 (0.39–0.96) | 0.03 | 0.55 (0.34–0.90) | 0.02 |
| **Predictors of major bleeding or CRNMB** | **HR (95% CI)** | ***P*-value** | **HR (95% CI)** | ***P*-value** |
| Cystatin C, mg/l | 2.70 (0.92–7.90) | 0.07 | 9.24 (2.15–39.67) | 0.003 |
| cTnT-hs, ng/l | 1.24 (1.13–1.36) | <0.0001 | 1.30 (1.14–1.48) | 0.0001 |
| GDF-15, per 100 pg/ml | 1.37 (1.25–1.51) | <0.0001 | 1.48 (1.29–1.69) | <0.0001 |
| CLT, min | 1.03 (1.01–1.05) | 0.001 | — | — |
| Past bleeding | 5.76 (2.32–14.33) | 0.0002 | 3.21 (1.22–8.45) | 0.02 |

Abbreviations: CRNMB, clinically relevant non-major bleeding; TIA, transient ischemic attack; other see Figure 1, Table 1, and Table 2

## Thromboembolism

During the median follow-up at 25.5 (23.0–29.0) months, thromboembolic events occurred in 18 (10%) patients (4.7% per year). There were 16 (8.9%) ischemic cerebrovascular events and 2 (1.1%) systemic thromboembolic episodes. There were no differences in the variables studied in relation to these events (Table 1 and Table 2). However, in univariable and multivariable analyses, increased age and decreased $K_s$ were associated with thromboembolism (Table 3).

## Bleeding

Twenty-seven (15%) patients experienced bleeding (13 major and 14 clinically relevant non-major bleedings) while on anticoagulation (7.1% per year). No differences in the variables studied were observed between the 27 subjects and the remaining participants except for the increased prevalence of prior major bleeding and less frequent beta-blocker use (Table 1). The patients with a history of major bleeding were over 8-fold more likely to develop gastrointestinal (n = 12, 3.2% per year) bleeding (HR, 8.29; 95% CI, 2.49–27.62; *P* = 0.001) as compared to the others. Past bleeding, use of beta-blockers, increased GDF-15, cystatin C, and cTnT-hs were associated with major bleeds and CRNMB, along with prolonged CLT (Table 1 and Table 2), which, however, did not independently predict bleeding in contrast to previous bleeding and the three biomarkers (Table 3). The optimal cut-off points for the occurrence of bleeding estimated for, GDF-15, cTnT-hs and cystatin C were 1930.0 pg/ml (Youden index = 0.74; AUC, 0.885; 95% CI, 0.828–0.942; *P* <0.0001), 9.3 ng/l (Youden index = 0.62; AUC, 0.823; 95% CI, 0.747–0.899; *P* <0.0001) and 1.16 mg/l (Youden index = 0.48; AUC, 0.740; 95% CI, 0.657–0.823; *P* <0.0001), respectively (Supplementary material, *Figure S1*).

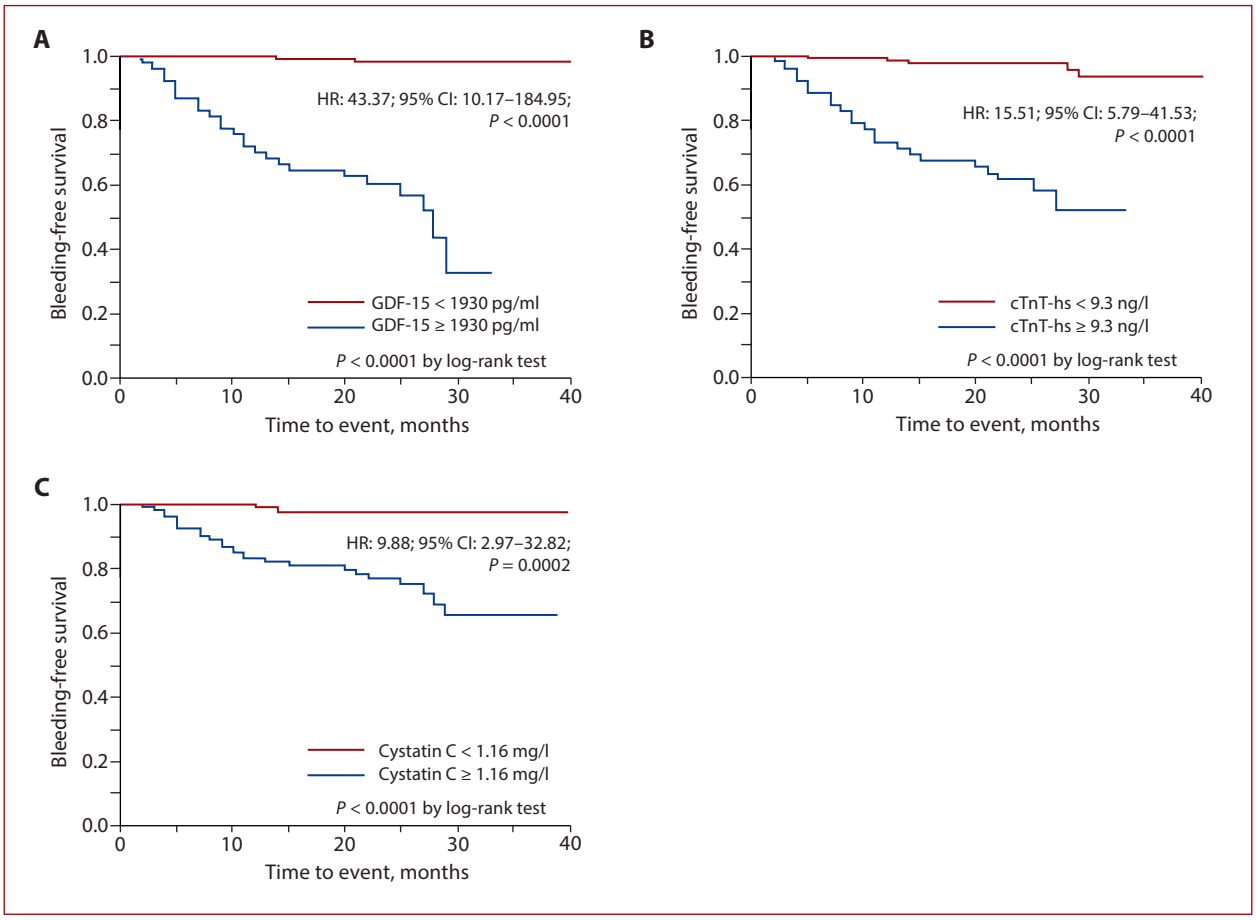


**Figure 1.** Association of growth differentiation factor-15 (**A**), high-sensitivity cardiac troponin T (**B**) and cystatin C (**C**) optimal cut-off points and the occurrence of clinically significant bleedings among patients with stage 4 chronic kidney disease and atrial fibrillation

Abbreviations: CI, confidence interval; cTnT-hs, high-sensitivity cardiac troponin T; GDF-15, growth differentiation factor-15; HR, hazard ratio

The Kaplan-Meier survival analysis showed that GDF-15, cTnT-hs, and cystatin C discriminated AF patients with stage 4 CKD at high risk of bleeding on anticoagulation, with the highest value observed for GDF-15 ≥1930 pg/ml (Figure 1).

### *Mortality*

Twenty-five (13.9%) patients died during the follow-up (6.5% per year), including 9 (5.0%) cardiovascular deaths. None of the four biomarkers and hemostatic parameters differed between non-survivors and survivors except for the fibrinogen concentration, which was slightly higher in the latter group. Mortality analysis is presented in Supplementary material, *Table S1–S3*. Regression analysis adjusted for age and comorbidities showed that solely cystatin C was independently associated with poor survival (HR, 3.95; 95% CI, 1.08–14.37; $P = 0.04$; Supplementary material, *Table S3*, Panel B).

## DISCUSSION

In this cohort study, we have shown for the first time that in AF patients with stage 4 CKD, decreased fibrin clot permeability, indicating the formation of more compact fibrin networks, along with increased age, independently predict thromboembolic events that occur despite oral anticoagulation, while cystatin C, cTnT-hs, and GDF-15, together with past bleeding can independently predict clinically significant bleeding. Cystatin C was identified as the only independent predictor of all-cause death. The current findings expand our knowledge on the prediction of adverse events by suggesting that in AF patients with stage 4 CKD, emerging biomarkers might help identify the patients, who require closer ambulatory surveillance and education, as well as those who might particularly benefit in terms of anticoagulation safety from the measurement of biomarkers, especially GDF-15.

### *Biomarkers and prothrombotic state*

We provided evidence that concentrations of GDF-15 in these high-risk AF patients are positively associated with a key marker of thrombin generation measured in plasma, i.e. ETP, and a marker of impaired fibrinolysis, i.e. CLT, which extends previous findings [5]. Similar observations were made in AF patients with a median eGFR of 73.0 ml/min/1.73 $m^2$ [21]. There was no association between ETP and cardiac troponin I in patients with a median eGFR of 70.0 ml/min/1.73$m^2$ [24]. The 3 biomarkers, which could be useful in risk stratification

in AF patients and also acute pulmonary embolism [25], reflect, to some extent, the prothrombotic state typical of this arrhythmia, but their associations with other markers and prothrombotic state parameters at least in part seem to be diminished in severe CKD [5, 21, 24, 26].

### Prediction of TE

Of importance, we found that low fibrin clot permeability, a key measure of fibrin clot density [18, 19], can predict TE outcomes in AF patients with stage 4 CKD, which extends our previous findings [18, 19] and highlights the role of fibrin properties in the pathophysiology of thromboembolism in AF. In contrast to $K_s$, we failed to observe a similar impact of hypolysability on this outcome, which suggests that changes in fibrin networks are more sensitive to most likely posttranslational modifications in severe CKD and in this subgroup have a stronger effect on the TE risk [20]. It might be speculated that therapies aimed at 'normalizing' fibrin clot structure might be useful in TE prevention [27].

### Prediction of bleeding

We demonstrated that apart from prior major bleeding, cystatin C, GDF-15, and cTnT-hs can predict clinically relevant bleeding (not only major bleeds) also in AF patients with severe CKD, which supports previous observations on bleeding risk stratification [14, 28–30]. The 2020 European Society of Cardiology guidelines on the management of AF stated that biomarkers-based bleeding risk scores outperform clinical scores, for example, HAS-BLED, but there is insufficient evidence to implement them in practice [2]. Our study might suggest that in patients with low eGFR the predictive value of the novel biomarkers (but not eGFR assessed using the CKD-EPI formula) might be higher as compared to patients with better renal function, which warrants further studies.

### Prediction of death

Our findings on a predictive role of cystatin C (but not eGFR assessed using the CKD-EPI formula) in terms of mortality in patients with AF and stage 4 CKD are novel. In line with our results, cystatin C was shown — when included in eGFR calculation – to yield the highest C index in terms of cardiovascular death prediction [31]. These data might be related to the fact that cystatin C is a better marker of renal function than creatinine because it is constantly produced, freely filtrated, and less influenced by age and sex [31]. Moreover, cystatin C has been suggested to be more strongly associated with adverse clinical outcomes or states as compared to creatinine, beyond solely reflecting renal function [32]. Mechanisms underlying our observation linking cystatin C with mortality in stage 4 CKD remain to be elucidated.

### Limitations of the study

The current cohort was relatively small. We measured biomarkers and hemostatic parameters only once. The assessment of proteinuria in the current study was based on the records from nephrologists. It is unclear whether mild proteinuria can impact the hemostatic variables assessed in this study. Our results might not be extrapolated to patients on dialysis.

## CONCLUSIONS

In AF patients with stage 4 CKD while on anticoagulation, circulating biomarkers, apart from a history of major bleeding, have the highest clinical usefulness in the prediction of future bleeding events while low fibrin clot permeability, along with advanced age, may predict thromboembolic outcomes. The present study provides additional evidence that the current approach to risk stratification in AF patients with stage 4 CKD on oral anticoagulation may be suboptimal.

### Supplementary material

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

### Article information

**Acknowledgments:** This work was supported by a grant from Jagiellonian University Medical College (K/ZDS/007717, to A.U). P.T.M. was supported by the Ministry of Science and Higher Education stipend for outstanding young scientists.

**Conflict of interest:** AU received lecture honoraria from Bayer, Boehringer Ingelheim, and Pfizer, PTM received speech honorarium from Boehringer Ingelheim, while the rest of the authors declared no conflict of interest.

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**How to cite:** Matusik PT, Leśniak WJ, Heleniak Z, et al. Thromboembolism and bleeding in patients with atrial fibrillation and stage 4 chronic kidney disease: Impact of biomarkers. Kardiol Pol. 2021; 79(10): 1086–1092, doi: 10.33963/KP.a2021.0088.

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# Acute myocardial infarction in young patients

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Kardiol Pol. 2021; 79 (10): 1093–1098; DOI: 10.33963/KP.a2021.0099

Received: March 24, 2021

Revision accepted: August 31, 2021

Published online: August 31, 2021

## ABSTRACT

**Background:** Acute myocardial infarction (AMI) is an incredibly destructive disease when it occurs in a young patient. Thus, the investigation of the disease presentation and treatment options seem to be particularly important in young patients with AMI.

**Aims:** The study objective was to investigate the differences between young and older patients diagnosed with AMI in terms of clinical characteristics and treatment strategies.

**Methods:** The patient data comes from the National Registry of Procedures of Invasive Cardiology (ORPKI). Between 2014 and 2017, data of more than 230 000 patients with a diagnosis of AMI were collected in that registry. Young patients were defined as under 40 years old.

**Results:** Young patients with AMI (n = 3208, 1.3%) compared with older patients with AMI were more often men (86.3% vs. 65.8%; *P* <0.001) with higher body weight (mean 85.9 vs. 79.7 kg; *P* <0.001). Typical risk factors of coronary heart disease were less frequent in younger patients than in older patients. However, in the under-40 group, there was a significantly higher number of current smokers (37.5% vs. 23.0%; P<0.001). Young patients with AMI were more often diagnosed with ST-segment elevation myocardial infarction (STEMI; 62.0% vs. 50.0%; *P* <0.001). Moreover, they had more frequently non-significant stenosis in coronary arteries diagnosed (14.4% vs. 6.8%; *P* <0.001). The left anterior descending artery was more frequently an infarct-related artery in young patients (51.3% vs. 36.3%; *P* <0.001). Bioresorbable vascular scaffolds were more commonly implanted in young patients with AMI than in the older ones (5.6% vs. 0.9%; *P* <0.001). The relative number of AMI in the young patients increased from 1.20% in 2014 to 1.43% in 2017.

**Conclusions:** Smoking is the most common risk factor in young adults. The relative number of AMI in young patients is growing.

**Key words:** acute myocardial infarction, angiography, coronary artery disease, percutaneous coronary intervention

Kardiol Pol 2021; 79, 10: 1093–1098

## INTRODUCTION

Acute myocardial infarction (AMI) is one of the leading causes of mortality in the Polish population. Thus, many efforts are directed towards the primary prevention of coronary artery disease, and fast diagnostic methods are used. A network of invasive cardiology centers is developed to provide the optimal diagnostic and treatment options for the whole population.

In recent years, the relative incidence of ST-segment elevation myocardial infarction (STEMI) has been decreasing while the relative incidence of non-ST-segment elevation myocardial infarction (NSTEMI) has been expanding [1]. AMI is an incredibly destructive disease, especially when it occurs in a young patient. It is associated with significant morbidity, psychological consequences, and financial restraints for the patient and the family. Thus, the investigation of the AMI causes, presentation, and management options seems to be particularly important in young patients.

## METHODS

The data analyzed in this publication come from the National Registry of Procedures of Invasive Cardiology (ORPKI). ORPKI is a Polish national registry that collects data on percutaneous procedures in invasive cardiology

## WHAT'S NEW?

Acute myocardial infarction (AMI) in young patients is often a slightly different disease than in older patients. The prevention of acute myocardial infarction in a young patient should primarily focus on smoking cessation. The left anterior descending artery is the most common infarct-related artery in young patients. The additional diagnostic tools should be considered during angiography to diagnose the reasons for AMI other than atherosclerosis. The relative number of AMI in young patients is growing.

performed in 163 cardiac catheterization laboratories and invasive cardiology departments. From January 1, 2014, the Jagiellonian University Collegium Medicum in Kraków is the entity responsible for maintaining the database. The design and details of the ORPKI registry have been previously described [2, 3]. Because of the data nature (registry of procedures), the ethics committee approval or patients' written informed consent was not required.

The study investigated differences in patient characteristics and the disease presentation and treatment between young and older patients. The young patients were defined as under 40 years old.

### *Statistical analysis*

Categorical variables were presented as numbers and percentages. Continuous variables were expressed as mean, standard deviation (SD), median, and interquartile range (IQR). The Mann-Whitney U test was used to compare differences between groups, although the age and weight of subjects were compared using h's t-test. The normality was assessed by the Kolmogorov-Smirnov-Lilliefors test (or by the Shapiro-Wilk test for less than 2000 observations). Ordinal variables were compared by Cochran-Armitage test for trend or Mann-Whitney U test. Categorical variables were compared by Pearson's chi-squared test or Fisher's exact test if 20% of cells had an expected count of less than 5.

The linear regression model was created to investigate a trend in quarter data of the percentage of young patients' procedures. The Shapiro-Wilk test checked the normality of model residuals. To check heteroscedasticity, the Brown-Forsythe test was used to examine whether the upper half's residuals had different variability than those in the lower half (median split). The Durbin-Watson test checked the autocorrelation of residuals.

Two-sided *P*-values <0.05 were considered statistically significant. All calculations were performed with JMP®, Version 14.2.0 (SAS Institute Inc., Cary, NC, USA).

## RESULTS

The data of 237 747 patients with a diagnosis of myocardial infarction were collected in the ORPKI Registry between 2014 and 2017. In that group, 3 208 (1.3%) patients were under 40 years old (mean [SD] age, 34.5 [4.6] vs. 67.3 [11.3] years).

Young patients with myocardial infarction were more frequently men with significantly higher body weight than their older counterparts (Table 1). Typical risk factors of coronary heart disease in young patients were slightly different from those in the older population, namely diabetes mellitus, arterial hypertension, and chronic kidney disease were less frequent in younger patients than in older patients. However, in the under-40 group, there was a significantly higher number of current smokers. Detailed data regarding the medical history of both groups of patients are presented in Table 2.

Based on patient characteristics on admission to the hospital (Table 3), young patients with AMI had significantly more often diagnosed STEMI with cardiac arrest during the index hospitalization. Even though the rate of direct transport to the primary Percutaneous Coronary Interventions (PCI) center was similar in both groups, time delays from the onset of symptoms to the treatment were lower in the younger group (Table 4).

Radial access was used more frequently in the group of young patients. Still, additional diagnostic devices including intravascular ultrasound (IVUS), optical coherence tomography (OCT), or fractional flow reserve (FFR) were used with similar frequency in both study groups.

**Table 1.** Demographic data — summary

| Variable | Measure/level | Age <40 | Age ≥40 | Total | Test | *P*-value |
|---|---|---|---|---|---|---|
| Year | N | 3208 | 234539 | 237747 | CA | <0.001 |
| | 2014 | 882 (27.49%) | 72612 (30.96%) | 73494 (30.91%) | | |
| | 2015 | 827 (25.78%) | 61347 (26.16%) | 62174 (26.15%) | | |
| | 2016 | 782 (24.38%) | 51185 (21.82%) | 51967 (21.86%) | | |
| | 2017 | 717 (22.35%) | 49395 (21.06%) | 50112 (21.08%) | | |
| Age, years | N | 3208 | 234539 | 237747 | W | <0.001 |
| | Mean (SD) | 34.53 (4.57) | 67.25 (11.29) | 66.81 (11.85) | | |
| Gender | N | 3166 | 232788 | 235954 | P | <0.001 |
| | Female | 435 (13.74%) | 79699 (34.24%) | 80134 (33.96%) | | |
| | Male | 2731 (86.26%) | 153089 (65.76%) | 155820 (66.04%) | | |
| Weight, kg | N | 3208 | 234539 | 237747 | W | <0.001 |
| | Mean (SD) | 85.94 (18.89) | 79.73 (17.37) | 79.81 (17.40) | | |

Abbreviations: CA, Cochran–Armitage test; P, Pearson's chi-squared test; W, Welch's t-test

**Table 2.** Myocardial infarction (MI) risk factors

| Variable | Measure/level | Age <40 | Age ≥40 | Total | Test | *P*-value |
|---|---|---|---|---|---|---|
| Diabetes | N | 3208 | 234539 | 237747 | P | <0.001 |
| | Yes | 171 (5.33%) | 53106 (22.64%) | 53277 (22.41%) | | |
| | No | 3037 (94.67%) | 181433 (77.36%) | 184470 (77.59%) | | |
| Previous stroke | N | 3208 | 234539 | 237747 | P | <0.001 |
| | Yes | 19 (0.59%) | 8845 (3.77%) | 8864 (3.73%) | | |
| | No | 3189 (99.41%) | 225694 (96.23%) | 228883 (96.27%) | | |
| Previous MI | N | 3208 | 234539 | 237747 | P | <0.001 |
| | Yes | 230 (7.17%) | 53269 (22.71%) | 53499 (22.50%) | | |
| | No | 2978 (92.83%) | 181270 (77.29%) | 184248 (77.50%) | | |
| Previous PCI | N | 3208 | 234539 | 237747 | P | <0.001 |
| | Yes | 225 (7.01%) | 52974 (22.59%) | 53199 (22.38%) | | |
| | No | 2983 (92.99%) | 181565 (77.41%) | 184548 (77.62%) | | |
| Previous CABG | N | 3208 | 234539 | 237747 | P | <0.001 |
| | Yes | 15 (0.47%) | 10418 (4.44%) | 10433 (4.39%) | | |
| | No | 3193 (99.53%) | 224121 (95.56%) | 227314 (95.61%) | | |
| Smoking status | N | 3208 | 234539 | 237747 | P | <0.001 |
| | Yes | 1203 (37.50%) | 53878 (22.97%) | 55081 (23.17%) | | |
| | No | 2005 (62.50%) | 180661 (77.03%) | 182666 (76.83%) | | |
| Psoriasis | N | 3208 | 234539 | 237747 | P | 0.39 |
| | Yes | 17 (0.53%) | 1009 (0.43%) | 1026 (0.43%) | | |
| | No | 3191 (99.47%) | 233530 (99.57%) | 236721 (99.57%) | | |
| Hypertension | N | 3208 | 234539 | 237747 | P | <0.001 |
| | Yes | 961 (29.96%) | 156084 (66.55%) | 157045 (66.06%) | | |
| | No | 2247 (70.04%) | 78455 (33.45%) | 80702 (33.94%) | | |
| Kidney disease | N | 3208 | 234539 | 237747 | P | <0.001 |
| | Yes | 48 (1.50%) | 13894 (5.92%) | 13942 (5.86%) | | |
| | No | 3160 (98.50%) | 220645 (94.08%) | 223805 (94.14%) | | |
| COPD | N | 2374 | 166443 | 168817 | P | <0.001 |
| | Yes | 2 (0.08%) | 4654 (2.80%) | 4656 (2.76%) | | |
| | No | 2372 (99.92%) | 161789 (97.20%) | 164161 (97.24%) | | |

Abbreviations: CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention; other — see Table 1

**Table 3.** Patient status on admission

| Variable | Measure/level | Age <40 | Age ≥40 | Total | Test | *P*-value |
|---|---|---|---|---|---|---|
| Killip class IV on admission | N | 2468 | 164245 | 166713 | P | <0.001 |
| | Yes | 43 (1.74%) | 4800 (2.92%) | 4843 (2.90%) | | |
| | No | 2425 (98.26%) | 159445 (97.08%) | 161870 (97.10%) | | |
| Indication | N | 3208 | 234539 | 237747 | P | <0.001 |
| | Stemi | 1988 (61.97%) | 117264 (50.00%) | 119252 (50.16%) | | |
| | Nstemi | 1220 (38.03%) | 117275 (50.00%) | 118495 (49.84%) | | |
| Cardiac arrest at baseline | N | 3035 | 196878 | 199913 | P | 0.03 |
| | Yes | 138 (4.55%) | 7420 (3.77%) | 7558 (3.78%) | | |
| | No | 2897 (95.45%) | 189458 (96.23%) | 192355 (96.22%) | | |
| Hypothermia at baseline | N | 3035 | 196878 | 199913 | F | 0.15 |
| | Yes | 8 (0.26%) | 298 (0.15%) | 306 (0.15%) | | |
| | No | 3027 (99.74%) | 196580 (99.85%) | 199607 (99.85%) | | |
| Direct transport | N | 3035 | 196878 | 199913 | P | 0.39 |
| | Yes | 452 (14.89%) | 28230 (14.34%) | 28682 (14.35%) | | |
| | No | 2583 (85.11%) | 168648 (85.66%) | 171231 (85.65%) | | |

Abbreviations: F, Fisher's exact test; NSTEMI, non-ST segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; other — see Table 1

Moreover, the young patients had more frequently non-significant stenosis in coronary arteries and a single-vessel disease when significant lesions were diagnosed (Table 5).

During the PCI procedure, aspiration thrombectomy was used in the young patients twice as often as in their older counterparts (Table 6). Moreover, the young patients received thrombolytic therapy more often, and new antiplatelet agents were used more frequently than in the older group. In more than half of the young patients, an infarct-related artery was the left anterior descending artery (LAD, Table 7). Drug-eluting stents (DES) were used with similar frequency in both study groups, but bare-metal stents (BMS) were implanted more often in the older patients. On the contrary, bioresorbable vascular scaffolds

**Table 4.** Reported time delays in patients transport

| Variable | Measure/level | Age <40 | Age ≥40 | Total | Test | *P*-value |
|---|---|---|---|---|---|---|
| Time from pain to first contact, min | N | 2641 | 170995 | 173636 | U | <0.001 |
| | Median (IQR) | 170.00 (60.00–420.00) | 180.00 (69.00–480.00) | 180.00 (68.00–480.00) | | |
| Time from pain to inflation or angiogram, min | N | 2538 | 173132 | 175670 | U | <0.001 |
| | Median (IQR) | 375.00 (180.00–910.75) | 480.00 (210.00–1294.75) | 480.00 (209.00–1290.00) | | |
| Time from the first contact to inflation or angiogram, min | N | 2552 | 173325 | 175877 | U | <0.001 |
| | Median (IQR) | 120.00 (63.00–330.75) | 150.00 (73.00–461.00) | 150.00 (73.00–460.00) | | |

Abbreviations: IQR, interquartile range; Me, median; U, Mann–Whitney U test; other — see Table 1

**Table 5.** Coronary angiography — procedure details

| Variable | Measure/level | Age <40 | Age ≥40 | Total | Test | *P*-value |
|---|---|---|---|---|---|---|
| Access site during an angiogram | N | 3035 | 196705 | 199740 | P | <0.001 |
| | Femoral | 666 (21.94%) | 52123 (26.50%) | 52789 (26.43%) | | |
| | Radial right | 1905 (62.77%) | 112938 (57.41%) | 114843 (57.50%) | | |
| | Radial left | 456 (15.02%) | 30200 (15.35%) | 30656 (15.35%) | | |
| | Other | 8 (0.26%) | 1444 (0.73%) | 1452 (0.73%) | | |
| FFR during angiogram | N | 3035 | 196878 | 199913 | P | 0.01 |
| | Yes | 0 (0.00%) | 397 (0.20%) | 397 (0.20%) | | |
| | No | 3035 (100.00%) | 196481 (99.80%) | 199516 (99.80%) | | |
| IVUS during angiogram | N | 3035 | 196878 | 199913 | F | 0.46 |
| | Yes | 6 (0.20%) | 287 (0.15%) | 293 (0.15%) | | |
| | No | 3029 (99.80%) | 196591 (99.85%) | 199620 (99.85%) | | |
| OCT during angiogram | N | 3035 | 196878 | 199913 | F | 0.30 |
| | Yes | 2 (0.07%) | 70 (0.04%) | 72 (0.04%) | | |
| | No | 3033 (99.93%) | 196808 (99.96%) | 199841 (99.96%) | | |
| Results of angiography | N | 3034 | 196518 | 199552 | P | <0.001 |
| | No evidence of atherosclerosis | 606 (19.97%) | 3640 (1.85%) | 4246 (2.13%) | | |
| | Without significant stenosis | 438 (14.44%) | 13268 (6.75%) | 13706 (6.87%) | | |
| | 1-vessel disease | 1456 (47.99%) | 69590 (35.41%) | 71046 (35.60%) | | |
| | LMCA disease | 12 (0.40%) | 590 (0.30%) | 602 (0.30%) | | |
| | Multivessel disease | 480 (15.82%) | 90428 (46.02%) | 90908 (45.56%) | | |
| | Multivessel and LMCA disease | 42 (1.38%) | 19002 (9.67%) | 19044 (9.54%) | | |

Abbreviations: FFR, fractional flow reserve; IVUS, intravascular ultrasonography; LMCA, left main coronary artery; OCT, optical coherence tomography; other — see Table 1 and 3

**Table 6.** Percutaneous coronary intervention (PCI) — procedure details

| Variable | Measure/level | Age <40 | Age ≥40 | Total | Test | *P*-value |
|---|---|---|---|---|---|---|
| FFR during PCI | N | 2060 | 198088 | 200148 | P | 0.34 |
| | Yes | 5 (0.24%) | 732 (0.37%) | 737 (0.37%) | | |
| | No | 2055 (99.76%) | 197356 (99.63%) | 199411 (99.63%) | | |
| IVUS during PCI | N | 2060 | 198088 | 200148 | P | 0.05 |
| | Yes | 18 (0.87%) | 1099 (0.55%) | 1117 (0.56%) | | |
| | No | 2042 (99.13%) | 196989 (99.45%) | 199031 (99.44%) | | |
| OCT during PCI | N | 2060 | 198088 | 200148 | F | 0.008 |
| | Yes | 7 (0.34%) | 211 (0.11%) | 218 (0.11%) | | |
| | No | 2053 (99.66%) | 197877 (99.89%) | 199930 (99.89%) | | |
| Aspiration thrombectomy during PCI | N | 2060 | 198088 | 200148 | P | <0.001 |
| | Yes | 319 (15.49%) | 14447 (7.29%) | 14766 (7.38%) | | |
| | No | 1741 (84.51%) | 183641 (92.71%) | 185382 (92.62%) | | |
| Rotablation during PCI | N | 2060 | 198088 | 200148 | P | 0.03 |
| | Yes | 1 (0.05%) | 624 (0.32%) | 625 (0.31%) | | |
| | No | 2059 (99.95%) | 197464 (99.68%) | 199523 (99.69%) | | |
| P2Y12 during PCI | N | 2060 | 198088 | 200148 | P | <0.001 |
| | Clopidogrel | 651 (31.60%) | 73792 (37.25%) | 74443 (37.19%) | | |
| | Prasugrel | 42 (2.04%) | 1190 (0.60%) | 1232 (0.62%) | | |
| | Ticagrelor | 244 (11.84%) | 10981 (5.54%) | 11225 (5.61%) | | |
| | No | 1123 (54.51%) | 112125 (56.60%) | 113248 (56.58%) | | |
| Thrombolysis during PCI | N | 2060 | 198088 | 200148 | P | <0.001 |
| | Yes | 17 (0.83%) | 533 (0.27%) | 550 (0.27%) | | |
| | No | 2043 (99.17%) | 197555 (99.73%) | 199598 (99.73%) | | |

Abbreviations: see Table 1–3 and 5

**Table 7.** Percutaneous coronary intervention (PCI) procedure — lesion localization

| Variable | Measure/level | Age <40 | Age ≥40 | Total | Test | *P*-value |
|---|---|---|---|---|---|---|
| LMCA | N | 2060 | 198088 | 200148 | P | <0.001 |
| | Yes | 38 (1.84%) | 6396 (3.23%) | 6434 (3.21%) | | |
| | No | 2022 (98.16%) | 191692 (96.77%) | 193714 (96.79%) | | |
| RCA | N | 2060 | 198088 | 200148 | P | <0.001 |
| | Yes | 516 (25.05%) | 63947 (32.28%) | 64463 (32.21%) | | |
| | No | 1544 (74.95%) | 134141 (67.72%) | 135685 (67.79%) | | |
| LAD | N | 2060 | 198088 | 200148 | P | <0.001 |
| | Yes | 1056 (51.26%) | 71949 (36.32%) | 73005 (36.48%) | | |
| | No | 1004 (48.74%) | 126139 (63.68%) | 127143 (63.52%) | | |
| Circumflex | N | 2060 | 198088 | 200148 | P | <0.001 |
| | Yes | 290 (14.08%) | 38253 (19.31%) | 38543 (19.26%) | | |
| | No | 1770 (85.92%) | 159835 (80.69%) | 161605 (80.74%) | | |
| SvG | N | 2060 | 198088 | 200148 | P | <0.001 |
| | Yes | 1 (0.05%) | 2234 (1.13%) | 2235 (1.12%) | | |
| | No | 2059 (99.95%) | 195854 (98.87%) | 197913 (98.88%) | | |
| LIMA/RIMA | N | 2060 | 198088 | 200148 | F | 0.06 |
| | Yes | 0 (0.00%) | 348 (0.18%) | 348 (0.17%) | | |
| | No | 2060 (100.00%) | 197740 (99.82%) | 199800 (99.83%) | | |

Abbreviations: LAD, left anterior descending artery; LIMA, left internal mammary artery; LMCA, left main coronary artery; RCA, right coronary artery; RIMA, right internal mammary artery; SvG, saphenous vein graft; other — see Table 1–3

**Table 8.** Percutaneous coronary intervention (PCI) procedure — final summary

| Variable | Measure/level | Age <40 | Age ≥40 | Total | Test | *P*-value |
|---|---|---|---|---|---|---|
| TIMI 3 flow after PCI | N | 1982 | 190419 | 192401 | P | 0.008 |
| | Yes | 1863 (94.00%) | 175955 (92.40%) | 177818 (92.42%) | | |
| | No | 119 (6.00%) | 14464 (7.60%) | 14583 (7.58%) | | |
| The total amount of contrast used during the procedure, ccm | N | 3080 | 223456 | 226536 | U | <0.001 |
| | Median (IQR) | 130 (80–190) | 150 (100–200) | 150 (100–200) | | |
| Total radiation dose during the procedure, mGy | N | 3054 | 222467 | 225521 | U | <0.001 |
| | Median (IQR) | 543.50 (267.75–1126.50) | 737.00 (391.00–1316.00) | 734.00 (389.00–1313.00) | | |

Abbreviations: ccm, cubic centimeter; mGy, miliGrey; TIMI, thrombolysis in myocardial infarction; other — see Table 1 and 2

(BVS) were more commonly chosen for the young patients (Supplementary material, *Table S1*). The percentage of patients with the final complete flow (TIMI grade 3 flow) in the infarct-related artery was similar in both groups. Even though the younger patients have higher body weight than the older ones, the total amount of contrast and total radiation dose during the procedures were lower in the under-40 group (Table 8). The frequency of periprocedural complications during coronary angiographies and PCI procedures was relatively small and similar in both study groups (Supplementary material, *Table S2*).

The absolute number of AMI decreased from year to year, but the relative number of AMI in the young patients increased from 1.20% in 2014 to 1.43% in 2017. This surge is statistically significant when calculated quarterly ($\beta = 0.0240$; 95% CI, 0.0051–0.0429; $R^2 = 34.66\%$; $P = 0.02$).

## DISCUSSION

According to our study, AMI in young patients seems to be a slightly different medical problem than in older patients. These differences could be observed in several distinct areas. When it comes to demographic data, a typical young patient with AMI is a smoking man. A similar observation was found in other studies [4–6]. Other specific AMI risk factors — like arterial hypertension, diabetes mellitus, or chronic kidney disease — are more often observed in older patients with AMI. Our results are concordant with the results of the study by Chhabra et al. [7]. As we know from previously published studies, the correlation of even one risk factor with the patient's age may significantly affect his prognosis [12]. Apart from the abovementioned, a significant risk factor of AMI, especially in young patients, is familial hypercholesterolemia. Due to the nature of the data, it was not possible to assess this risk factor's occurrence in our study population. Clinically, in young patients with AMI, STEMI is more prevalent [1]. It was also described that in young patients with AMI, significant coronary artery stenosis is observed more frequently in the LAD than in other arteries [8], which is concordant with our findings.

Unfortunately, because of the data characteristics (registry), it is impossible to distinguish between true atherosclerotic lesions and spontaneous coronary artery dissection (SCAD), which might be an underlying cause of AMI, especially in young women. Similarly, the domination of non-significant lesions and one-vessel disease in young patients was described previously in the Russian

population [9]. Patients with non-significant lesions on coronary angiography, as well as with no evidence of atherosclerosis, but with the diagnosis of myocardial infarction (MINOCA, almost 35% of young patients in contrary to the older ones — 9%), are eventual candidates for extended diagnostic workup of coronary arteries, like IVUS or OCT. Unfortunately, this management was rarely reported in our registry (approx. 0.3%). Even though our patients' groups had similar rates of periprocedural complications, the extended follow-up results may differ. As it was published previously, early coronary artery disease is strongly associated with AMI and death within 30 days of presentation in patients hospitalized for chest pain [10].

In comparison to older patients with AMI, in patients under 40 with this medical condition, the reason for their troponin elevation is more often not so obvious. Accurate differential diagnosis may require in this case the use of more sophisticated diagnostic tools. During long-term follow-up in young patients with AMI, the risk of myocardial ischemia recurrence may be higher when the underlying cause of ischemia is not thoroughly diagnosed. Close follow-up and post-hospital cardiac control, whose positive effects have been studied and described [13], seem to be particularly justified in the group of young patients with AMI.

## CONCLUSION

AMI in young patients (defined as under 40 years old) is a different disease than in their older counterparts. Younger patients with AMI have distinct risk factors profiles and angiographic findings in coronary arteries. The primary prevention of AMI in young patients should mainly focus on smoking cessation. During coronary angiography, additional diagnostic tools, such as IVUS, OCT, or microvascular examination should be considered, as reasons other than atherosclerosis are particularly frequent in this group of patients.

### *Limitations*

Despite a relatively large group of patients, the data acquisition methodology (the ORPKI registry) does not allow the collection of data regarding familial hypercholesterolemia or hyperuricemia, which may play a role in the development of coronary artery disease [11]. We could not perform a standardized analysis of patient angiography, so it was not possible to assess the role of muscle bridge in LAD stenosis and SCAD.

### *Supplementary material*

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

### *Article information*

**Conflict of interest:** None declared.

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**How to cite:** Zasada W, Bobrowska B, Plens K, et al. Acute myocardial infarction in young patients. Kardiol Pol. 2021; 79(10): 1093–1098, doi: 10.33963/KP.a2021.0099.

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ORIGINAL ARTICLE

# Frequency and predictors of diagnostic coronary angiography and percutaneous coronary intervention related to stroke

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Kardiol Pol. 2021; 79 (10): 1099–1106; DOI: 10.33963/KP.a2021.0100

**Received:** June 6, 2021

**Revision accepted:** August 31, 2021

**Published online:** August 31, 2021

## ABSTRACT

**Background:** Stroke related to percutaneous coronary interventions (PCIs) is an infrequent complication, which can be potentially life-threatening and can lead to serious disability.

**Aims:** This study aimed to assess the relationship between the type of coronary procedure and incidence of stroke, as well as its predictors.

**Methods:** This retrospective analysis was performed on prospectively collected data gathered in the Polish National Registry of Percutaneous Coronary Interventions (ORPKI) between January 2014 and December 2019 and included 1 177 161 coronary procedures. Among them, 650 674 patients underwent isolated diagnostic coronary angiography (DCA), and 526 487 PCI. Stroke was diagnosed in 157 patients (0.013%), of which 100 (0.015%) happened during DCA and 57 (0.011%) during PCI. Multivariable logistic regression analysis was performed to separate predictors of stroke in patients undergoing coronary angiography and PCI.

**Results:** The percentage of patients with periprocedural stroke was higher in the group treated with isolated DCA during the analyzed time. Among predictors of stroke in patients undergoing DCA, we confirmed prior stroke ($P$ <0.001), contrast amount ($P$ = 0.007), femoral access ($P$ = 0.002), unfractionated heparin use ($P$ = 0.01), direct transport to the catheterization laboratory ($P$ = 0.04), older age ($P$ <0.001) and multi-vessel disease ($P$ <0.001). While for PCI ± DCA, these were prior stroke ($P$ <0.001), thrombolysis ($P$ = 0.003), treatment with bivalirudin ($P$ <0.001), and acetylsalicylic acid loading during PCI ($P$ = 0.003).

**Conclusions:** Based on the large national registry, PCI ± DCA is associated with fewer risk factors and a lower rate of periprocedural strokes than isolated DCA.

**Key words:** coronary angiography, percutaneous coronary intervention, periprocedural complication, stroke

Kardiol Pol 2021; 79, 10: 1099–1106

## INTRODUCTION

Both diagnostic coronary angiography (DCA) and percutaneous coronary interventions (PCIs) are the gold standard and daily performed procedures in modern cardiology for the diagnosis and treatment of coronary artery disease. Clinical and epidemiological data have shown that one of the most severe and life-threatening complications related to high mortality is periprocedural stroke; however, modern diagnostic and therapeutic strategies make it possible to significantly reduce the adverse effects of cardiac catheterization related cerebrovascular events [1–3]. Stroke is considered the second leading cardiovascular cause of death worldwide and is a major cause of disability, as ischemic heart disease is known to be the most common.

## WHAT'S NEW?

Both diagnostic coronary angiography (DCA) and percutaneous coronary interventions (PCIs) are the gold standard for the diagnosis and treatment of coronary artery disease. This study aimed to assess the relationship between the type of coronary procedure and incidence of stroke, as well as its predictors. This analysis included 1 177 161 coronary procedures. We found that the incidence of periprocedural stroke did not change in patients undergoing DCA while it decreased in patients treated with PCI ± DCA. Among the non-modifiable predictors of stroke in patients undergoing DCA (prior stroke, age, more advanced and disseminated coronary atherosclerosis, femoral access and contrast amount), we also distinguished intravascular ultrasound, optical coherence tomography, unfractionated heparin use during DC, and direct transport to the catheterization laboratory. The predictors of periprocedural stroke in patients treated with PCI ± DCA included, among others, those well-recognized ones, such as thrombolysis and prior stroke, treatment with bivalirudin, and acetyl-salicylic acid loading during PCI.

It affects patients undergoing isolated DCA as well as PCI. The previously available registries indicate that periprocedural stroke occurs in 0.05%–0.1% of DCA and 0.18%–0.44% of PCIs [4]. However, formerly provided data may be limited [5]. The last years have shown a significant upward trend in the number of elder patients with a higher number of risk factors treated with cardiovascular procedures [6]. Other worth-mentioning factors that may have an impact on the frequency of periprocedural stroke are vascular access, clinical presentation, type of catheter, the progress of atherosclerosis, and type of procedure (thrombectomy, rotational atherectomy, etc.) [7–9]. Despite all the improvements in reperfusion strategies, such as using radial access, smaller catheters, and pharmacotherapy, achieved in the last few years, the incidence of periprocedural stroke remains the same or has even slightly increased [10].

In the present study, we aimed to assess the frequency of periprocedural stroke in patients undergoing DCA and PCI ± DCA to determine their predictors in comparison with other available registries.

## METHODS

### Study design and patient population

This retrospective analysis was performed on prospectively collected data. Data for conducting the current study were obtained from the Polish National Registry of Percutaneous Coronary Interventions (ORPKI, *Ogólnopolski Rejestr Procedur Kardiologii Inwazyjnej*) [11]. Data were collected between January 2014 and December 2019. We selected 1 177 161 patients qualified for diagnostic coronary angiography (DCA) alone or followed by PCI during the analyzed period. Among them, 650 674 patients underwent DCA alone, and 526 487 DCA underwent DCA and PCI, or PCI alone. There were 100 periprocedural strokes in the DCA group (0.015%) and 57 periprocedural strokes in the DCA ± PCI group (0.011%) (Figure 1). Technical aspects of the procedure, such as the choice of access site (femoral or radial sheath), catheter size, as well as guidewires, type of thrombectomies, and other devices, were at the operator's discretion. Patients were qualified for percutaneous revascularization and treated according to the current European Guidelines [12]. Antiplatelet therapy was implemented according to the current European Guidelines [13]. Periprocedural stroke was diagnosed according to the current recommendations [14]. The protocol complied with the 1964 Declaration of Helsinki, and all participants provided their written informed consent for the percutaneous intervention. Due to the retrospective nature as well as anonymization of the collected data and registry, obtaining the consent of the Bioethics Committee was not required.

### Endpoints

The primary endpoint of the current study was to assess the frequency of periprocedural strokes in patients undergoing percutaneous coronary diagnostics and/or intervention and its possible fluctuation through the 6-year-long period. The secondary endpoint was to assess the predictors of periprocedural stroke in the group of patients undergoing DCA and PCI ± DCA.

### Statistical analysis

Categorical variables are presented as numbers and percentages. Continuous variables are expressed as mean (standard deviation). Normality was assessed via the Shapiro-Wilk test. Equality of variance was evaluated using Levene's test. Differences between the 2 groups were compared using the Student's or Welch's t-test, depending on the equality of variances for normally distributed variables. The Mann-Whitney U test was applied for non-normally distributed continuous variables. Categorical variables were compared with Pearson's chi-squared or Fisher's exact test if 20% of the cells had an expected count of less than 5 (Monte Carlo simulation for Fisher's test using tables of higher dimensions than 2 × 2). All baseline/demographic characteristics were used as potential predictors of stroke in univariable logistic regression models. Then variables with *P*-value <0.2 or variables of clinical importance were included in the multivariable model. Final multivariable logistic regression models were constructed using minimization of Akaike Information Criterion to find predictors of stroke in the DCA and PCI ± DCA group. Statistical analysis was performed using the R, version 3.5.3 (R Foundation for Statistical Computing 2019, Vienna, Austria) with the 'lme4', version 1.1–21 package.

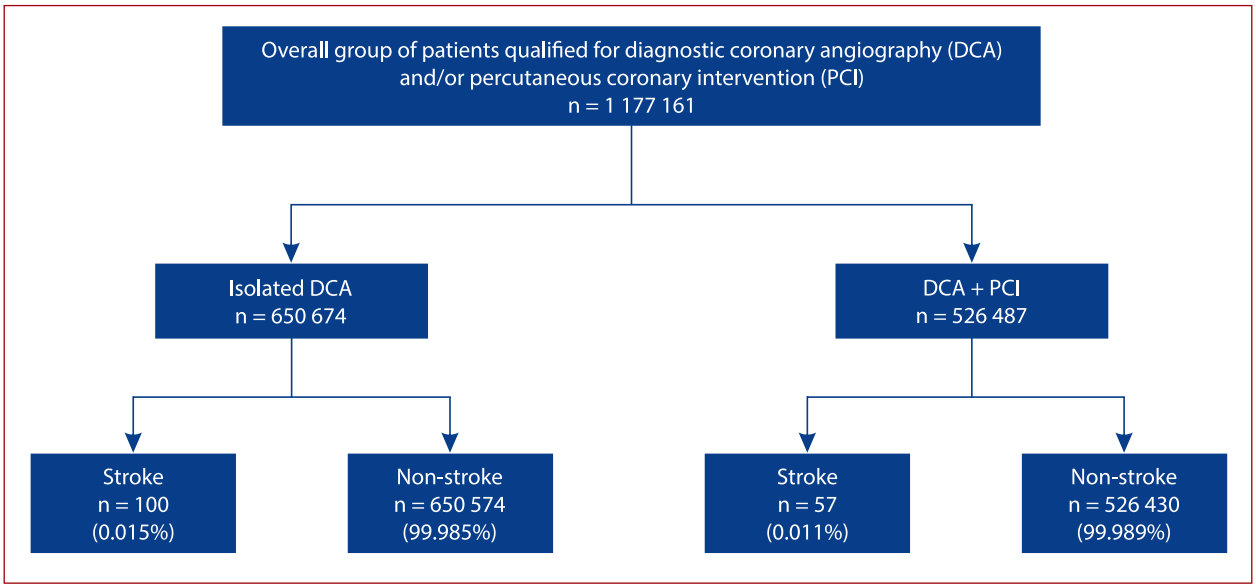


**Figure 1.** Patient flow chart

**Table 1.** Baseline patient characteristics and` clinical presentation according to type of performed coronary procedure

| Years | Isolated diagnostic coronary angiography | | | PCI ± coronary angiography | | |
|---|---|---|---|---|---|---|
| | Stroke n = 100 | Non-stroke n = 650 574 | Total n = 650 674 | Stroke n = 57 | Non-stroke n = 526 430 | Total n = 526 487 |
| 2014 | 20 (0.017) | 114 129 (99.983) | 114 149 (100) | 18 (0.019) | 92 597 (99.981) | 92 615 (100) |
| 2015 | 16 (0.014) | 110 771 (99.986) | 110 787 (100) | 13 (0.014) | 92 774 (99.987) | 92 787 (100) |
| 2016 | 12 (0.01) | 113 055 (99.99) | 113 067 (100) | 9 (0.009) | 94 425 (99.991) | 94 434 (100) |
| 2017 | 17 (0.015) | 110 908 (99.985) | 110 925 (100) | 6 (0.007) | 89 624 (99.993) | 89 630 (100) |
| 2018 | 18 (0.017) | 104 553 (99.983) | 104 571 (100) | 7 (0.009) | 81 131 (99.991) | 81 138 (100) |
| 2019 | 17 (0.017) | 97 158 (99.983) | 97 175 (100) | 4 (0.005) | 75 879 (99.995) | 75 883 (100) |
| *P*-value | 0.35 | — | — | 0.001 | — | — |

Abbreviations: PCI, percutaneous coronary intervention

## RESULTS

### Frequency and trends of periprocedural stroke

The frequency of periprocedural stroke assessed in the groups of patients is presented in Figure 1. While trends in the frequency of periprocedural stroke did not change significantly in the group undergoing DCA alone ($P = 0.35$), it decreased significantly in the PCI ± DCA group ($P = 0.001$) (Table 1).

### General characteristics

Patients from the DCA group and with periprocedural stroke were significantly older when compared to the non-stroke sub-group (72.6 [8.7] vs. 66.3 [10.7] years; $P < 0.001$). There were no significant differences in age between stroke and non-stroke patients from the DCA and PCI ± DCA groups (69.5 [13.1] vs. 67.1 [10.9] years; $P = 0.1$). Considering sex differences, there were significantly more females in the stroke sub-group compared to non-stroke patients from the DCA and PCI groups (67.5% vs. 52%; P = 0.02). This and other indices are presented in the Supplementary material, *Table S1*.

### Clinical presentation

There were no significant differences in the clinical state before percutaneous intervention between the sub-group of stroke and non-stroke patients in the isolated DCA and PCI ± DCA groups of patients, as assessed by Killip-Kimball class grade (Supplementary material, *Table S1*). When considering the clinical presentation of coronary artery disease in the DCA group, significantly more patients in the stroke subgroup presented with acute myocardial infarction (AMI) at baseline (non-ST segment elevation myocardial infarction [NSTEMI] and ST-segment elevation myocardial infarction [STEMI]), while fewer patients presented with chronic coronary syndrome when compared to the non-stroke subgroup (Supplementary material, *Table S1*).

### Procedural indices

Statistically, significantly more patients with periprocedural stroke were treated from femoral access when compared to radial (left and right radial) in the DCA alone and PCI ± DCA group (Supplementary material, *Table S2*). The patients from the DCA-alone group and with a periprocedural stroke presented significantly more with significant coro-

nary atherosclerosis compared to the non-stroke patients (Supplementary material, *Table S2*). There were no such significant differences in the group of patients undergoing PCI ± DCA (Supplementary material, *Table S2*).

### *Periprocedural pharmacotherapy*

Acetyl-salicylic acid (ASA), unfractionated heparin, and $P2Y_{12}$ inhibitors were significantly more frequently used in the patients with periprocedural stroke when compared to the patients without stroke in the DCA-alone group, while this significance was maintained only for ASA in the PCI ± DCA group (Supplementary material, *Table S1*). This and other pharmacotherapy treatments are presented in the Supplementary material, *Table S1*.

### *Periprocedural complications and others*

Considering the periprocedural occurrence of cardiac arrests, there were no significant differences between the patients with or without periprocedural stroke in the DCA alone and PCI ± DCA groups (Supplementary material, *Table S1*). However, direct transport took place significantly more often in the case of patients with periprocedural stroke when compared to the non-stroke group in the DCA alone and PCI ± DCA groups (Supplementary material, *Table S1*).

### *Predictors of stroke in patients undergoing DCA alone assessed by multivariable logistic regression analysis*

Among the independent predictors of periprocedural stroke occurrence in patients undergoing DCA, we confirmed, via multivariable logistic regression analysis, prior stroke ($P$ <0.001), intravascular ultrasound during angiography ($P$ = 0.03), optical coherence tomography performed during angiography ($P$ = 0.03), greater contrast dose used during angiography ($P$ = 0.007), femoral compared to radial access ($P$ = 0.002), unfractionated heparin used during angiography ($P$ = 0.01), direct transport to the catheterization laboratory (P = 0.04), older age ($P$ <0.001), left main coronary artery disease when compared to single-vessel disease ($P$ <0.001), and presence of multi-vessel disease in coronary angiography when compared to single-vessel disease ($P$ <0.001) (Figure 2).

### Predictors of stroke in patients undergoing PCI ± DCA assessed by multivariable logistic regression analysis

When considering PCI ± DCA among the predictors of periprocedural stroke, we confirmed, by multivariable logistic regression analysis, prior stroke ($P$ <0.001), thrombolysis ($P$ = 0.003), treatment with bivalirudin ($P$ <0.001), and ASA loading during PCI ($P$ = 0.003) (Figure 3).

## DISCUSSION

In summary, first of all, we confirmed that in the analyzed registry between the years 2014 and 2019, the incidence of periprocedural stroke did not change in the patients undergoing DCA, while it decreased significantly in the patients treated with PCI ± DCA. Secondly, among the non-modifiable and confirmed predictors of periprocedural stroke (prior stroke, age, more advanced and disseminat-

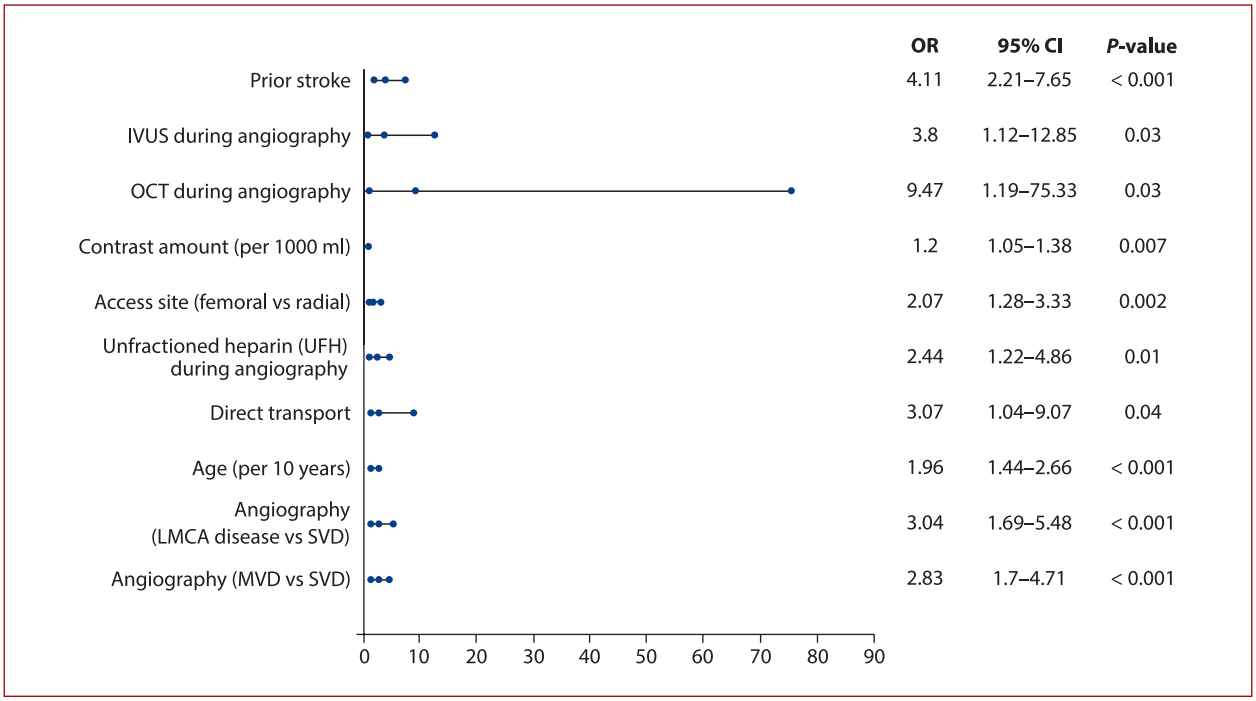


**Figure 2.** Predictors of periprocedural stroke in patients undergoing diagnostic coronary angiography assessed by multivariable logistic regression analysis

Abbreviations: CVD, cardiovascular disease; IVUS, intravascular ultrasound; LMCA, left main coronary artery atresia; MVD, multivessel coronary disease; OCT, optical coherence tomography; SVD, single vessel disease

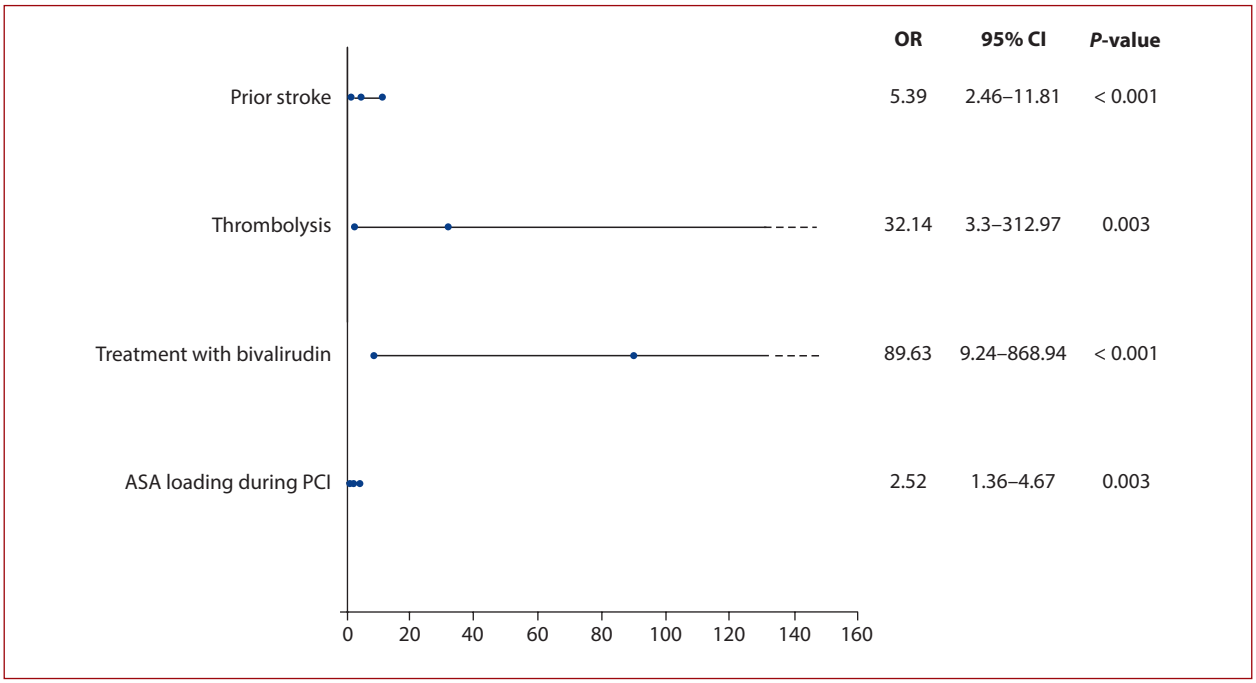


**Figure 3.** Predictors of periprocedural stroke in patients undergoing percutaneous coronary intervention ± coronary angiography assessed by multivariable logistic regression analysis

Abbreviations: ASA, acetyl-salicylic acid; other — see Table 1

ed coronary atherosclerosis with the left main coronary artery atresia (LMCA) involvement, femoral access, and contrast amount) in the patients undergoing DCA, we also distinguished intravascular ultrasound (IVUS) and optical coherence tomography (OCT) use during DCA, as well unfractionated heparin use during DCA, and direct transport to the catheterization laboratory. Thirdly, we also identified predictors of periprocedural stroke in the patients treated with PCI ± DCA, which included, among others, such well-recognized predictors as thrombolysis and prior stroke, treatment with bivalirudin, and ASA loading during PCI.

The frequency of reported periprocedural stroke in patients undergoing DCA and PCI depends on several factors, which include, inter alia, the type of study (registry or prospective clinical trial), the duration of observed periprocedural period (periprocedural, in-hospital, or even post-discharge period), and the manner of stroke confirmation (computed tomography, cardiac magnetic resonance [CMR], or clinical symptoms). It may be concluded that in some circumstances, the incidence of periprocedural stroke is lower because the patients were observed only for a short-term period in the catheterization laboratory or when there was no diagnosis in the direction of the silent stroke (CMR). Therefore, in previously published studies, the rate of cerebrovascular disease complications after DCA and PCI was reported to be 0.1%–1% for DCA and 0.1%–0.6% for PCI, which remains in line with our results [15]. The frequency of strokes related to DCA and PCI was usually lower in papers based on registries [16]. Nonetheless, the frequency of asymptomatic procedure-related strokes could be even higher than 10% [17]. In the majority of recently published studies, a stable frequency of periprocedural strokes related to DCA and PCI has been reported; however, in some studies, it was noted that there is an increasing trend in the overall group of patients treated with PCI [5]. The authors concluded that this is owing to the increasing complexity of PCI over time (radial access, chronic total occlusions, use of mechanical circulatory support devices, or multivessel disease with higher atherosclerotic plaque burden) [5].

Identifying predictors of stroke related to DCA and PCI could help to develop effective prevention strategies, especially against modifiable predictors. Older age, female sex, vascular disease, renal failure, prior stroke, or transient ischemic attack, heart failure, use of mechanical circulatory devices, or vein graft interventions were reported among predictors of stroke [16]. In the current study, we divided predictors of stroke into two groups: those related to DCA and those related to PCI ± DCA.

### *Predictors of stroke related to DCA*

Prior stroke is a common, usually strong, and sanctioned finding as a predictor of stroke related to DCA and PCI ± DCA [15]. Intravascular ultrasound is often used in patients treated due to advanced atherosclerosis that is frequently located in the aorto-ostial area, which could, in some cases, predispose to embolization by small debris released during PCI. Additionally, IVUS is recommended for the assessment of possible embolic etiology of AMI in patients with non-obstructive coronary arteries. These maneuvers with the IVUS probe could, in some circum-

stances, be related to thrombus dislodgement and further cerebrovascular embolization [18]. In recently published studies, it has been reported that the currently used non-occlusive technique of optical coherence tomography improves its feasibility and reduces the complication risk [19]. The complication risk based on smaller studies varies between 0%–2%, but on a large-scale registry by van der Sijde et al. [19], it was demonstrated that complications occur there rarely (<0.2%). However, major complications during OCT occur, including coronary spasm, vessel dissection, thrombus, and ventricular fibrillation, and some of them may lead to cerebrovascular adverse events [20]. Greater contrast amount used during DCA and PCI ± DCA is usually related to more complicated procedures, more advanced and disseminated atherosclerosis, more severe state, lower left ventricular ejection fraction, or use of left ventricular support mechanical devices, which are strictly related to the increased probability of thrombus formation and the risk of procedure-related stroke [7].

Shoji et al. [21] demonstrated that consecutive patients undergoing PCI from transradial access were at a reduced risk of periprocedural stroke compared to transfemoral intervention. Jurga et al. [22] revealed that radial access used for DCA generates more particulate cerebral microemboli than femoral access and thus, it may influence the occurrence of silent cerebral injury. They also suggested that manipulation in the subclavian artery may cause silent cerebral microemboli; otherwise, clinically relevant cerebral infarction may originate from large plaques, mainly located in the aortic arch [22]. Khatibzadeh et al. [23] demonstrated that localization of atherosclerotic plaques prone to dislodgement in the thoracic aorta (descending and arch) predispose to ischemic stroke in patients treated from femoral access.

Using heparin during angiography may lead to heparin-induced thrombocytopenia syndrome (HITS) in a short period, especially among patients in a serious condition with a prevalence of additional risk factors. HITS is an uncommon immune disorder mediated by antibodies to the heparin-platelet factor 4 complex [24]. It can cause new or worsening of previously present blood clots, which can even result in a periprocedural stroke. The occurrence of immune thrombocytopenia may be treated as an independent risk factor of ischemic stroke [25]. In the case of direct transport, patients treated in an emergency mode are associated with a greater rate of periprocedural strokes. It has been reported that periprocedural stroke occurs more often in patients treated with PCI due to AMI (0.8%–1.4%) than those treated for unstable angina (0.4%–10.8%) [9, 26]. This was also confirmed in the study published by Budaj et. al. [27], in which the frequency of stroke was 1.3% in STEMI, 0.9% in NSTEMI, and 0.5% in unstable angina patients. In another study published by Werner et al. [15], it was confirmed that hemodynamic instability, which is strictly related to direct transport, was among predictors of stroke related to PCI.

It has been found that not only older age, type of plaque, and its location in the aorta (ascending, descending, and arch) are related to a greater amount of debris that can be scraped from the artery wall, but it has also been confirmed that the catheter type plays an important role. Among those more prone to scrape debris from the internal wall of the aorta, Keeley et al. [28] found Judkins left, multipurpose, and voda left. Tokushige et al. [8] demonstrated that asymptomatic strokes detected by CMR within 48 hours after DCA could even reach up to 20% in older patients, following coronary artery by-pass grafting (CABG). In most publications, older age was present among the predictors of PCI-related stroke; however, in our study, this was confirmed only for isolated DCA [15]. In several previously published studies, a relationship between PCI in patients with triple vessel disease and procedure-related stroke has been verified [4].

### *Predictors of stroke related to PCI ± DCA*

In various publications, prior stroke (as well as female sex, atrial fibrillation, heart failure, diabetes mellitus, chronic renal failure atherosclerotic cardiovascular disease, left ventricular thrombus, hypercoagulable state, and CABG during admission) was confirmed as a predictor of periprocedural stroke in patients treated with PCI due to AMI [10].

Most of the strokes related to DCA and PCI are supposed to be of embolic etiology, from either dislodgement of a clot or atheromatous debris from the aortic arch or thrombus formation on the guide catheter [29]. However, in the case of thrombolysis, it seems that the root cause is partial fragmentation of coronary artery thrombus and its dislodgement to the aorta during any manipulation in the ostium of the target coronary artery.

The use of eptifibatide and bivalirudin was found to be non-protective in patients undergoing cardiac catheterization in terms of the frequency of periprocedural stroke [4]. The authors explained these results by the dominance of the non-thrombotic mechanism of embolus etiology [4]. Our analysis even allowed us to demonstrate that bivalirudin was significantly correlated with the greater rate of intraprocedural strokes. Nowadays, bivalirudin is used in patients with AMI, and this could be the key factor that determines this relationship.

Acute antiplatelet (ASA and $P2Y_{12}$ receptor inhibitors) therapy was found to be an independent predictor of ischemic stroke related to PCI due to AMI, which was also confirmed in our analysis [30]. Hachet et al. demonstrated that relationship for patients with AMI treated via PCI, whereas a relationship that was found in our patients undergoing CLA, included also patients with non-obstructive AMI. It could be also hypothesized that preprocedural treatment with ASA could decrease a potential risk of procedure-related stroke in patients undergoing percutaneous coronary catheterization.

In previously published studies, it has been reported that prior CABG was found to be independently related to

periprocedural stroke in patients undergoing DCA. However, in our study, this factor was not confirmed by multivariable logistic regression analysis [8]. In another study published by Kawamura et al. [31], it was demonstrated by multivariable logistic regression analysis that left ventricular ejection fraction was the only independent predictor for stroke in patients treated with PCI due to acute myocardial infarction. We were not able to assess this relationship because our dataset did not include this parameter.

### Limitations

Periprocedural complications, including stroke, depend on self-initiated reporting by the operator, under-reporting cannot be excluded. The diagnosis of stroke was predominantly based on clinical symptoms, made by the treating interventional cardiologist. We did not have information on the type of catheters and their diameter. Furthermore, the data on left ventricular ejection fraction, the frequency of atrial fibrillation, or details on potential complications were unavailable. The ORPKI registry does not allow to count all procedure-related strokes which occur during hospitalization after leaving the catheterization laboratory, nor were the outcomes of patients beyond hospital discharge available. All the data gathered in the ORPKI registry referred to the stay in the catheterization laboratory. A typical feature of a large national registry is dataset completeness, which undoubtedly, could cause certain bias in the statistical calculation, apart from a wide range of statistical possibilities to decrease this influence.

## CONCLUSIONS

Based on the large national registry, the incidence of periprocedural stroke did not change in the patients undergoing DCA, while it decreased significantly in the patients treated with DCA and/or PCI. Among the non-modifiable and confirmed predictors of periprocedural stroke in patients undergoing DCA (prior stroke, age, more advanced and disseminated coronary atherosclerosis with the LMCA involvement femoral access, and contrast amount), we also distinguished IVUS and OCT use during DCA, as well unfractionated heparin use during DCA, and direct transport to the catheterization laboratory. There were fewer predictors of periprocedural stroke in patients treated with DCA and/or PCI, which included, among others, such well-recognized predictors as thrombolysis and prior stroke, treatment with bivalirudin, and ASA loading during PCI.

### Supplementary material

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

### Article information

**Conflict of interest:** None declared.

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**How to cite:** Staszczak B, Malinowski KP, Wańha W, et al. Frequency and predictors of diagnostic coronary angiography and percutaneous coronary intervention related to stroke. Kardiol Pol. 2021; 79(10): 1099–1106, doi: 10.33963/KP.a2021.0100.

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ORIGINAL ARTICLE

# The effect of exercise training and physiotherapy on diastolic function, exercise capacity and quality of life in patients with heart failure with preserved ejection fraction: a systematic review and meta-analysis

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Kardiol Pol. 2021; 79 (10): 1107–1115; DOI: 10.33963/KP.a2021.0101

**Received:** June 18, 2021

**Revision accepted:** September 1, 2021

**Published online:** September 1, 2021

## ABSTRACT

**Background:** Exercise and physiotherapy are accepted as an important contribution to the rehabilitation of patients with heart failure with preserved ejection fraction (HFpEF). But the previous results are unclear partly because of their limited power and small sample sizes.

**Aims:** We aimed to understand better the effects of two exercise training interventions and two modalities of physiotherapies on exercise capacity, quality of life (QoL), and diastolic dysfunction in HFpEF patients.

**Methods:** The Cochrane Library, EMBASE, and MEDLINE via PubMed were searched for randomized controlled trials from their inception to May 2021. The effect size was estimated as mean differences (MD) with 95% confidence intervals (CI).

**Results:** A total of 14 articles on 13 trials were included in this meta-analysis with 673 HFpEF patients. The pooling revealed that peak oxygen uptake was improved by endurance training, functional electrical stimulation (FES), and inspiratory muscle training (IMT). Similar results were observed for a 6-minute walk test and QoL. A combination of endurance and resistance training (combined exercise) was beneficial to the ratio of peak early to late diastolic mitral inflow velocities (MD [95% CI]: –2.90 [–4.97, –0.83]; $P = 0.006$) and the early diastolic mitral annual velocity (MD [95% CI]: 1.40 [0.68, 2.12]; $P = 0.006$]. IMT improved the ventilation/carbon dioxide ratio slope (MD [95% CI]: –3.36 ml/kg/min [–6.17, –0.54]; $P = 0.019$].

**Conclusions:** FES and IMT improve functional capacity and QoL without a change in diastolic function in HFpEF patients, and the outcomes are similar to endurance training. Notably, combined exercise may improve diastolic function.

**Key words:** diastolic function, exercise training, functional electrical stimulation, heart failure with preserved ejection fraction, inspiratory muscle training

Kardiol Pol 2021; 79, 10: 1107–1115

## INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) accounts for nearly half of heart failure (HF) patients in the community, and the mortality and morbidity are high [1]. However, the established neurohormonal-based therapies, used for treating heart failure with reduced ejection fraction (HFrEF), have failed to improve exercise intolerance and provide favorable clinical outcomes for HFpEF [2]. The study of Lelonek [1] reported that although angiotensin receptor neprilysin inhibitors (ARNIs) may benefit from treatment with HFpEF, the relevance of ARNI in HFpEF still has not been clarified.

Cardiac dysfunction appears in diastolic dysfunction in echocardiography, exercise intolerance may be objectively measured by peak oxygen uptake (peak $VO_2$), and poor quality of life (QoL) completes the typical clinical image of HFpEF [3]. Exercise training appears to be a promising strategy to improve peak $VO_2$ and QoL in HFpEF patients [4, 5]. However, previous meta-analyses hold inconsistent opinions on diastolic function

## WHAT'S NEW?

Exercise and physiotherapy are accepted as an important contribution to the rehabilitation of patients with heart failure with preserved ejection fraction (HFpEF). This study aimed to evaluate the effect of endurance training and a combination of endurance and resistance training (combined exercise), functional electrical stimulation (FES), and inspiratory muscle training (IMT) on HFpEF patients, measured by diastolic function, exercise capacity, and quality of life. This is the first study to evaluate different modalities of physical therapy on HFpEF patients. Our results showed that FES and IMT, as well as endurance training, improved functional capacity and quality of life (QoL). Moreover, combined exercise was beneficial to the ratio of peak early to late diastolic mitral inflow velocities and the early diastolic mitral annual velocity. These findings suggest that FES and IMT improve functional capacity and QoL in HFpEF patients, and the outcomes are similar to endurance training. Additionally, combined exercise may improve diastolic function.

in HFpEF patients experiencing exercise training [6–8] partly due to their failure to assess different modalities of exercise training.

HFpEF is more common in elderly patients, and these patients have poor adherence to exercise training [9]. It is time to carry out physiotherapy to relieve the symptoms of HFpEF. At present, physiotherapy mainly includes inspiratory muscle training (IMT) and functional electrical stimulation (FES), which are effective interventions to improve exercise intolerance in HFrEF [10, 11]. HF has been commonly associated with inspiratory muscle weakness [12]. IMT, a training stimulus directly to the inspiratory muscles, improves inspiratory muscle weakness, cardiorespiratory fitness, and QoL, like exercise training, leading a better adaptation to posterior exercise training [13]. The other physiotherapy involves a neuromuscular stimulation FES, which delivers a specific recruitment pattern for performing a muscular movement necessary for exercise [14]. FES has shown potential beneficial effects in HF patients, including increased muscle mass and improved QoL [15, 16]. IMT and FES may serve HF patients excluded from exercise training and constitute interesting treatment options for clinicians. Accordingly, both IMT and FES may have potential benefits to HFpEF patients, which may not only be limited in HFpEF patients unable to undergo exercise training but also may be extended to the general HFpEF population. However, so far there have been no published meta-analyses to evaluate the impact of IMT and FES on exercise tolerance in HFpEF patients. In this meta-analysis, we aimed to evaluate the effects of different modalities of exercise training (endurance, and a combination of endurance and resistance training, combined exercise), and physiotherapies (FES and IMT) on exercise capacity, QoL, and diastolic function in HFpEF patients.

## METHODS

The present study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [17]. The protocol was prospectively registered with Open Science Framework (*https://osf.io/sufc8*).

### *Search strategy*

The studies on the effect of physical therapy in HFpEF patients published before May 20, 2021 were searched in the Cochrane Library, EMBASE, and MEDLINE via PubMed. We used a mix of medical subject headings (MeSH) and keywords including exercise training, aerobic exercise, endurance training, inspiratory muscle training, functional electrical stimulation, and heart failure with preserved ejection fraction.

### *Study selection*

Studies were considered eligible if they (1) were published as randomized controlled trials (RCTs); (2) included patients (aged ≥18 years) with HFpEF; (3) included patients undergoing physical therapy; (4) included a comparison of physical therapy with standard medical care or placebo control group. Articles that failed to meet the inclusion criteria were removed, including reviews, animal studies, non-RCTs, non-English language, and intervention duration of fewer than 4 weeks.

### *Main outcomes*

The primary outcomes of this study were exercise capacity measured by peak $VO_2$ and a 6-minute walk test (6MWT), QoL measured by the Minnesota Living with Heart Failure Questionnaire (MLHFQ) total score. Secondary outcomes were evaluated by the ventilation/carbon dioxide ratio slope ($VE/VCO_2$) and diastolic function, measured by peak early to late diastolic mitral inflow velocities (E/A), the ratio of early diastolic mitral inflow to annular velocities (E/e'), and the early diastolic mitral annular velocity (e').

### *Data extraction*

Two reviewers (CCZ and XFL) extracted the following data independently: study characteristics (authors, year of publication, and country), participant characteristics (age and sample size of different groups), study methods/design, and the period of exercise intervention.

### *Risk of Bias*

We evaluated the risk of bias for inclusion in this meta-analysis by the Physiotherapy Evidence Database (PEDro)

scale [18]. When a disagreement occurred, a third reviewer was consulted.

### Statistical analysis

For each outcome, the effect size in our study was assessed by change from the baseline to follow-up. We used weighted mean difference (MD) and 95% confidence intervals (CI) for the same scale of the outcomes. When the $I^2$ statistic was lower than 30% and $P$ <0.10, a fixed-effect model was used; otherwise, a random-effect model was used. All analyses were used by STATA version 14.0 (StataCorp, College Station, TX, USA). Furthermore, meta-regression analyses were also performed with STATA software using the restricted maximum likelihood method. Two dependent variables (peak $VO_2$ and QoL) were tested against several independent variables including age, sex, and an exercise period. A value of $P$ <0.01 was considered significant.

## RESULTS

### Included studies

The flow chart is shown in Figure 1, screening identified 129 potential reports. After the removal of duplicates, 152 records remained. 117 studies were excluded after scanning titles and abstracts. Then 21 were excluded because they did not report HFpEF. Ultimately, 11 RCTs on exercise training [5, 19–28] and 3 RCTs on physiotherapies were included in this meta-analysis [14, 29, 30].

### Characteristics of studies

The basic characteristics of each study were summarized in *Table S1*. The present meta-analysis included 673 HF-pEF patients. The mean age of participants ranged from 60.5 to 75 years, and the proportion of men ranged from 0% to 64%.

### Quality assessment

The quality of included RCTs is presented in Supplementary material, *Table S2*. In none of the studies was there objective evidence of imbalance in the baseline characteristics between the intervention and control groups. The moderate risk of bias was due to inadequate blinding of participants and therapists, allocation concealment, and intention-to-treat methodologies.

### Functional capacity indicator

Our meta-analysis could be performed for two functional capacity indicators: a 6MWT and peak $VO_2$. Eight trials with 411 patients reported on 6MWT (Figure 2A). The heterogeneity was small ($I^2$ = 0.0%; $P$ = 0.560, fixed-effect). The 6MWT was increased by endurance training (MD [95% CI]: 38.79 m [19.97, 57.61]; $P$ <0.001) and FES (MD [95% CI]: 52.77 m [30.61, 74.93]; $P$ <0.001). However, there was no change after IMT (MD [95% CI]: 84.00 m [–31.73, 199.73]; $P$ = 0.155) and combined exercise (MD [95% CI]: 7.00 m [–37.61, 51.61]; $P$ = 0.758).

Thirteen trials with 411 patients reported on peak $VO_2$ (Figure 2B). The heterogeneity was small ($I^2$ = 0.0%; $P$ = 0.739, fixed-effect). Peak $VO_2$ was improved by endurance training (MD [95% CI]: 1.89 ml/kg/min [1.32, 2.46], $P$ <0.001), FES (MD [95% CI]: 2.28 ml/kg/min [0.92, 3.65]; $P$ = 0.001), IMT (MD [95% CI]: 2.72 ml/kg/min [1.44, 3.99]; $P$ <0.001) and combined exercise (MD [95% CI]: 3.30 ml/kg/min [0.44, 6.16]; $P$ = 0.024). Meta-regression

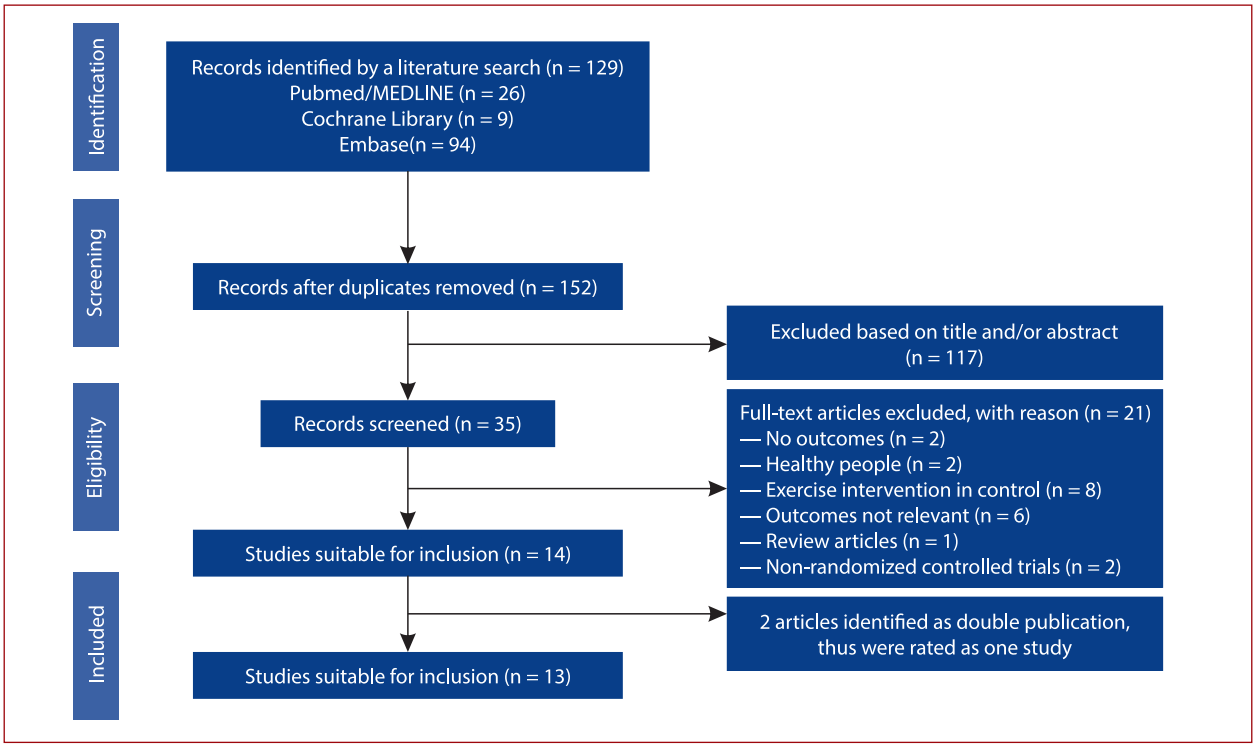


**Figure 1.** Flow chart of the study selection procedure

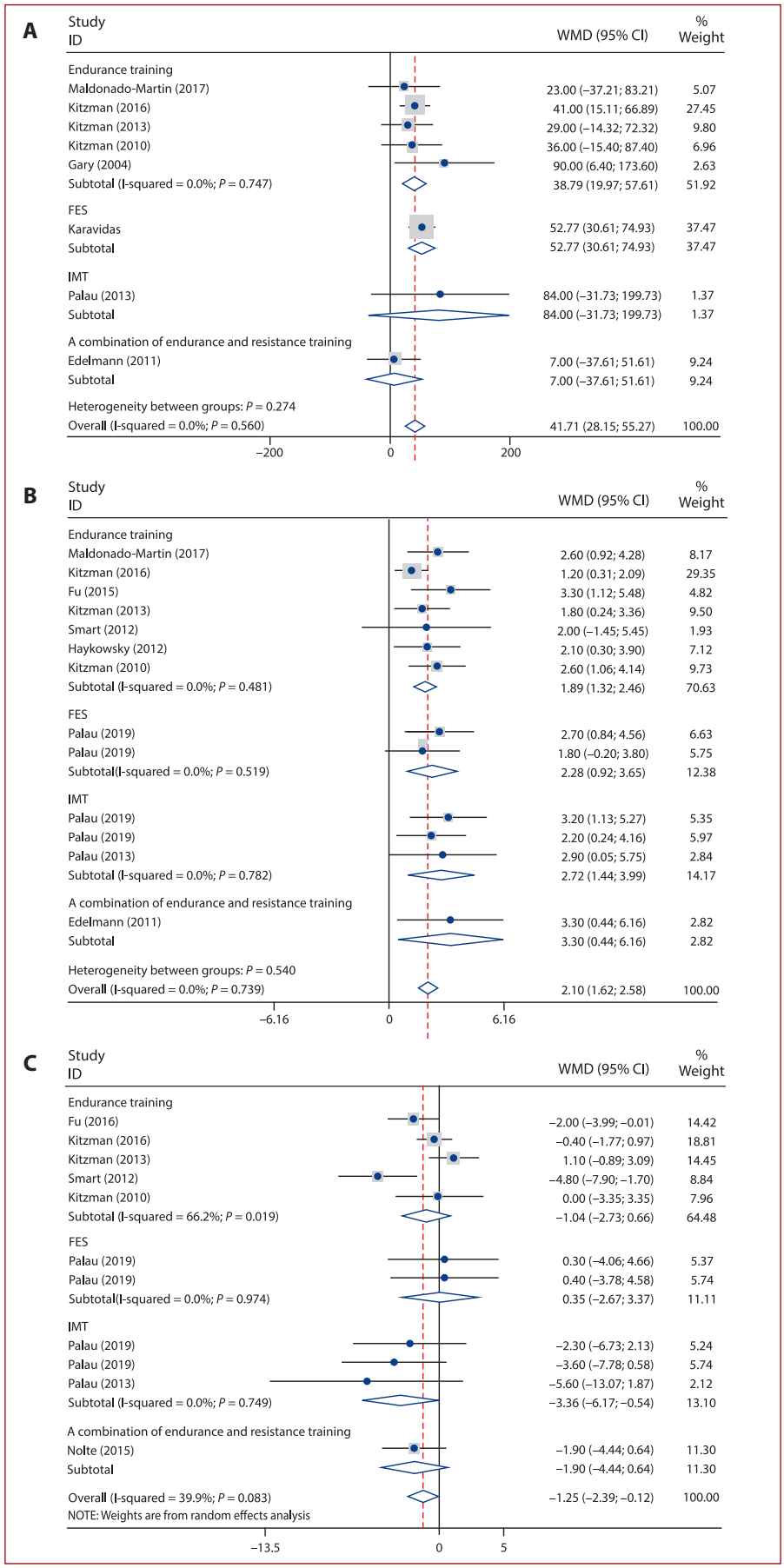


**Figure 2. A.** Effects of exercise on exercise performance: 6-minute walk test (6MWT). **B.** Change in peak oxygen consumption (peak $VO_2$), ventilation/carbon dioxide ratio slope ($VE/VCO_2$ slope)

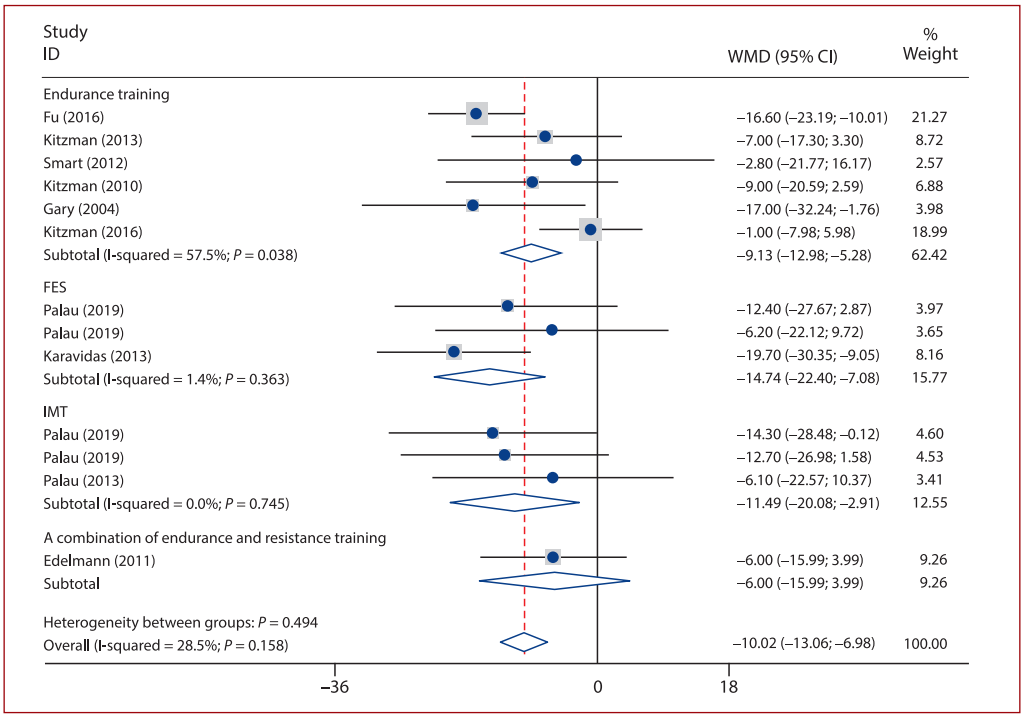


**Figure 3.** Effects of exercise on Minnesota Living With Heart Failure Questionnaire (MLHFQ) total score

analysis showed no significant effect of age (coefficient, 0.007; $P = 0.989$), sex (coefficient, 0.010; $P = 0.826$), or exercise period (coefficient, –0.736; $P = 0.036$).

### Quality of life

Thirteen trials with 560 patients reported on the MLHFQ total score (Figure 3). The heterogeneity was small ($I^2 = 28.5\%$; $P = 0.158$, fixed-effect). The MLHFQ total score was improved by endurance training (MD [95% CI]: –9.13 [–12.98, –5.28]; $P < 0.001$], FES (MD [95% CI]: –14.74 [–22.44, –7.08]; $P < 0.001$) and IMT (MD [95% CI]: –11.49 [–20.08, –2.91]; $P = 0.009$). However, no difference was found in the case of combined exercise (MD [95% CI]: –6.00 [–15.99, 3.99]; $P = 0.239$). Meta-regression analysis showed no significant effect of exercise period (coefficient, 1.116; $P = 0.574$), age (coefficient, –0.689; $P = 0.800$), or sex (coefficient, –0.523; $P = 0.852$).

### Diastolic function

Eight trials with 416 patients reported on E/A (Figure 4A). The heterogeneity was small ($I^2 = 0\%$; $P = 0.606$, fixed-effect). E/A was no change by endurance training (MD [95% CI]: 0.03 [–0.03, 0.09]; $P = 0.307$), combined exercise (MD [95% CI]: –0.03 [–0.17, 0.11]; $P = 0.678$), and FES (MD [95% CI]: –0.12 [–0.29, 0.05]; $P = 0.162$).

Ten trials with 416 patients reported on E/e' (Figure 4B). There was a statistical heterogeneity ($I^2 = 43.1\%$; $P = 0.071$, random-effect). E/e' was improved by combined exercise with one included study (MD [95% CI]: –2.90 [–4.97, –0.83]; $P = 0.006$). There was no change in E/e' by endurance training (MD [95% CI]: –0.03 [–2.83, 2.78]; $P = 0.983$), FES (MD [95% CI]: –2.16 [–4.41, 0.09]; $P = 0.060$) and IMT (MD [95% CI]: –1.10 [–4.56, 2.36]; $P = 0.533$).

Four trials with 215 patients reported on e' (Figure 4C). There was a statistical heterogeneity ($I^2 = 81.3\%$; $P = 0.001$, random-effect). e' was improved by combined exercise in one included study (MD [95% CI]: 1.40 [0.68, 2.12]; $P < 0.001$). There was no change in e' by endurance training (MD [95% CI]: –2.90 [–4.97, –0.83]; $P = 0.140$) and IMT (MD [95% CI]: 0.30 [–1.28, 1.88]; $P = 0.709$).

### Exercise physiology parameter

Eleven trials with 502 patients reported on the $VE/VCO_2$ slope (Figure 2C). There was a statistical heterogeneity ($I^2 = 39.9\%$; $P = 0.083$, random-effect). The $VE/VCO_2$ slope was improved by IMT (MD [95% CI]: –3.36 [–6.17, –0.54]; $P = 0.019$). No significant difference was found after endurance training (MD [95% CI]: –1.04 [–2.73, 0.64]; $P = 0.226$), FES (MD [95% CI]: 0.35 [–2.67, 3.37]; $P = 0.819$) or combined exercise (MD [95% CI]: –1.90 [–4.44, 0.64]; $P = 0.142$). Smart et al. [22] may be the source of heterogeneity due to the small sample.

## DISCUSSION

The present meta-analysis summarized data that evaluated the effects of two exercise interventions and two physiotherapy modalities in HFpEF patients. FES and IMT improved exercise performance and QoL, and the outcomes were similar to endurance training. Notably, combined exercise has the potential to improve diastolic function in HFpEF patients.

The previous studies have focused on overall exercise training rather than the different types of exercise training.

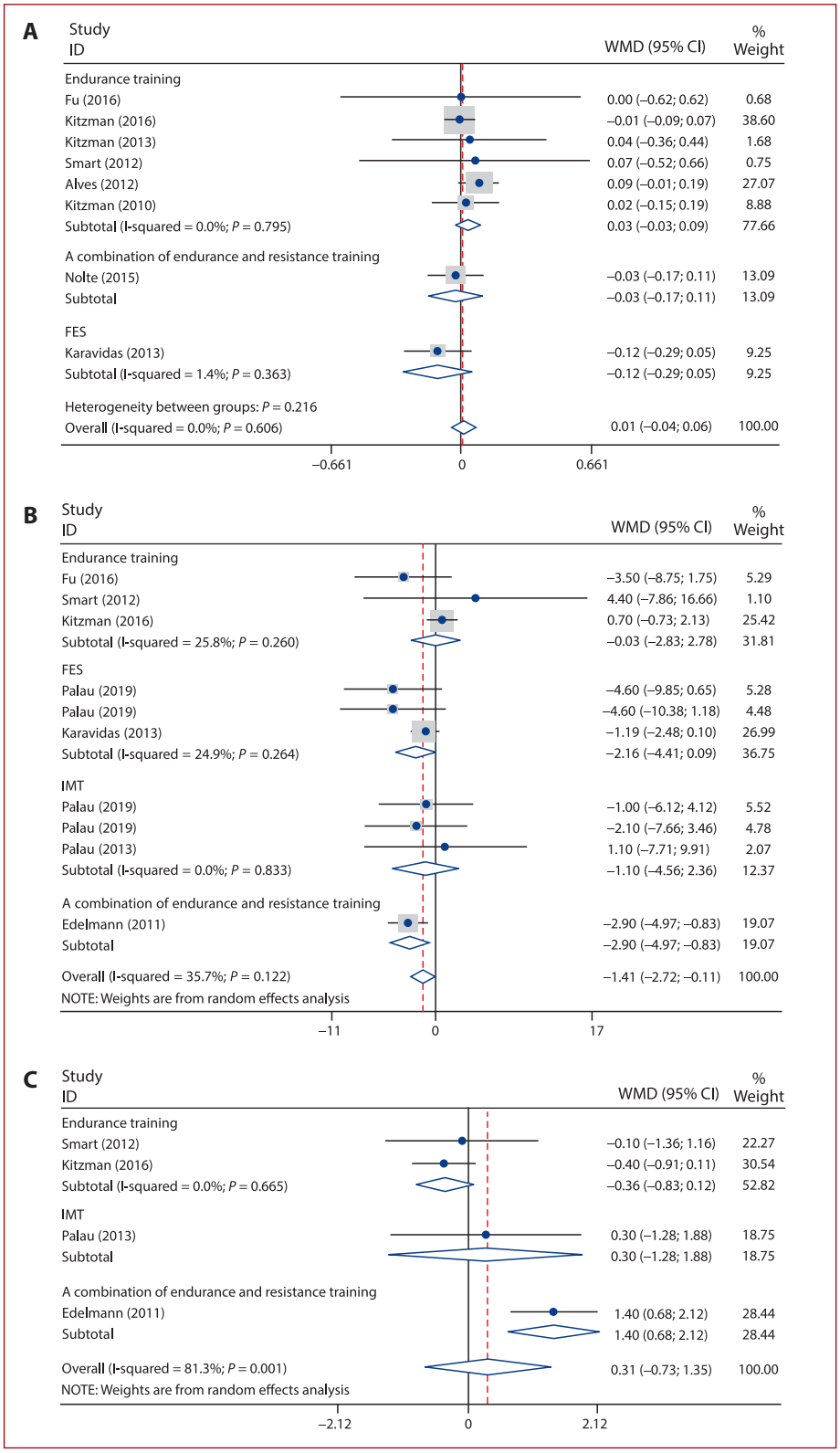


**Figure 4.** Effects of exercise on diastolic function: **A.** the ratio of peak early to late diastolic mitral inflow velocities (E/A). **B.** Change in the ratio of early diastolic mitral inflow to annular velocities (E/E'). **C.** The early diastolic mitral annular velocity (e')

The meta-analysis of Gomes-Neto et al. [31] only conducted endurance training and failed to represent other exercise modalities. Some meta-analyses [8, 32] showed that exercise training improved exercise capacity and QoL in HFpEF patients, but a methodological limitation was the combination of endurance training and combined exercise. The previous meta-analyses held inconsistent opinions on diastolic function in HFpEF patients during exercise training [6–8, 32]. Thus, the present meta-analysis compensated for the weakness of the previous studies.

The present meta-analysis observed that peak $VO_2$, 6MWT, and QoL were improved by exercise training, as well as FES and IMT. The peak $VO_2$ may affect oxygen delivery and/or utilization via cardiac, vascular, and skeletal muscle function [33]. Therefore, active skeletal muscle is the major reason to induce the augment of peak $VO_2$ in HFpEF patients, including oxidative enzyme activity and capillary density [25].

Left ventricular (LV) diastolic dysfunction plays a pivotal role in the pathophysiological hallmark of HFpEF [34]. In assessing patients for diastolic dysfunction and possible HFpEF, the use of the 2009 consensus guideline on diastolic function yielded a sensitivity of 47% to rule out HFpEF, whereas other proposed classification schemes actually had higher sensitivities between 72% and 77% to rule out HFpEF [35, 36]. Notably, echocardiography for impaired diastolic dysfunction has been the sine qua non of diagnosis in HFpEF [37]. Earlier occurring LV diastolic pressure relates best with E/A, E/e', and e' [38]. With respect to the estimation of LV filling pressures, early work suggested that E/e' could be used to estimate reliably the LV filling pressure in HFpEF and even in atrial fibrillation. The E-wave is smaller, leading to the diastolic dysfunction filling pattern, where E/A <1, occurring with hypertension, hypertrophic cardiomyopathy, ischemia, and myocardial infarction. Reduced e' velocity results from a variety of comorbidities related to impaired myocardial relaxation and restoration forces. Edelmann et al. [19] reported that combined exercise improved diastolic function. Our findings showed that combined exercise improved E/e' and e', suggesting an improvement in left ventricular filling pressures. However, endurance training failed to improve diastolic function. Smart et al. [22] suggested that 16-week endurance training may not be sufficient to elicit alteration in myocardial properties. Fujimoto et al. [39] reported that 1-year endurance training had little effect on left ventricular compliance in HFpEF patients. In response to exercise training, cardiac relaxation may be compounded by abnormalities in skeletal muscle oxygen use, which augments cardiac output and flow into a small, stiff, and slowly relaxing heart [40].

The hemodynamic changes that occur during exercise constitute the primary stimulus for diastolic function [41]. Endurance training sustained elevations in cardiac output with reduced peripheral vascular resistance by an increased mitochondrial biogenesis and capillary density, aiding in the transport and use of oxygen to generate energy [42]. Resistance intense bouts of increased peripheral vascular resistance and only slightly evaluated cardiac output by training add muscle bulk to peripheral muscles and increase bone mass, leading in turn to an increase in muscle strength and power [43]. Thus, the difference in diastolic function may be induced by resistance training.

FES and IMT had no substantial changes in the E/e', E/A, and e', despite the improvement in exercise capacity and QoL [14, 30]. Extra-cardiac effects not related directly to an improvement in cardiac function may play a critical role in the beneficial effect of physiotherapy. Our result showed that IMT significantly improved the $VE/VCO_2$ slope alone. Various studies of HF patients have shown that selective respiratory muscle training improved submaximal and maximal exercise capacity during daily living activities [13]. The development of diaphragmatic fatigue is delayed, leading to a reduction in the recruitment of accessory respiratory muscles, and an improved ventilatory efficiency [44]. Although FES fails to improve the $VE/VCO_2$ slope, the beneficial effects of FES on functional capacity and QoL is similar to those of IMT. FES and IMT interventions improve the recruitment of accessory respiratory muscles and ventilatory efficiency by delaying diaphragmatic fatigue, which increases muscle strength, muscle mass, and aerobic-oxidative capacity [10, 29]. Both IMT and FES interventions are simple, low-cost, and harmless for patients with HFpEF, and may serve as "bridge therapies" to exercise training.

Physical therapy may be a safe approach for the treatment of HFpEF. However, a demanding challenge for exercise training will be translating these programs to HFpEF patients with relevant comorbidity (i.e. frailty) after cardiac surgery or due to advanced age. Notably, FES and IMT seem to be alternative treatments for patients who are unable to perform exercise training. In fact, many patients with HFpEF, unable to exercise, pay more attention to medication treatments. Thus, the greatest challenge is to implement the existing knowledge about training benefits in HFpEF as a standard in clinical practice and to increase participation rates of patients with a clear indication for physiotherapy-based cardiac rehabilitation in existing programs.

### *Strengths and limitations*

This study is the first to evaluate different modalities of exercise training and physiotherapy on exercise capacity, QoL, and diastolic function in HFpEF patients. However, several limitations should be addressed. Firstly, the major limitation of this analysis is the small sample size in most of the RCTs. There were only two studies that reported combined exercise, and they shared one set of data using different results [19, 20]. New large-scale RCTs are needed to confirm the findings of this meta-analysis. Secondly, few studies compared exercise training and physiotherapy to exercise capacity, QoL, and diastolic function. Accordingly, it is not possible to asess which intervention modality would be most beneficial for HFpEF patients. Thirdly, heterogeneity scores suggested the majority of analyses were justified, but this of e' may display heterogeneity at levels too high to justify this analysis. Finally, more standardized, high-quality? qualitative, larger-scale, and longer intervention trials are needed in order to estimate the most effective training modality.

## CONCLUSIONS

Our meta-analysis suggests that FES and IMT, as well as endurance training, have a positive effect on functional

capacity and QoL without causing a significant change in diastolic function. Notably, combined exercise may improve diastolic function and peak $VO_2$. Further trials are required to determine which training modalities are effective forms of training to improve aerobic capacity in HFpEF patients.

## Article information

**Funding:** This study was supported by the National Natural Science Foundation of China (NSFC 81960086), and the Cuiying Scientific and Technological Innovation Program of Lanzhou University Second Hospital (CY2017-BJ02).

**Conflict of interest:** None declared.

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**How to cite:** Zhang C, Luo X, Wang Q, et al. The effect of exercise training and physiotherapy on diastolic function, exercise capacity, and quality of life in patients with heart failure with preserved ejection fraction: a systematic review and meta-analysis. Kardiol Pol. 2021; 79(10): 1107–1115, doi: 10.33963/KP.a2021.0101.

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# Prognostic value of the triglyceride-glucose index among non-diabetic patients with acute myocardial infarction at one-year follow-up

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Kardiol Pol. 2021; 79 (10): 1116–1123; DOI: 10.33963/KP.a2021.0104

**Received:** August 5, 2021

**Revision accepted:** September 3, 2021

**Published online:** September 6, 2021

## ABSTRACT

**Background:** The triglyceride-glucose index (TyG index) is a novel metabolic marker initially used as an indicator of insulin resistance. Recently, its use as a cardiovascular risk factor has been taken into consideration; however, there is a shortage of evidence for its clinical importance.

**Aims:** The study aimed to assess the relationship between the TyG index = ln (fasting triglyceride [mg/dl] × fasting glucose [mg/dl]/2) and the incidence of major adverse cardiovascular events (MACE) at a 1-year follow-up among non-diabetic patients with acute myocardial infarction (MI). In addition, the predictive value of the TyG index concerning all-cause mortality in the study group was evaluated.

**Methods:** For the study, 1340 non-diabetic patients with acute MI (median age, 67 years, 70.4% male) were consecutively enrolled between 2013 and 2019. The fasting lipid profile and the fasting glucose level were assessed within 24 hours of admission.

**Results:** MACE occurred in 8.13 % (n = 109) of the study group, whereas 1-year mortality rate was 14.5% (n = 195). There was no difference in the median TyG index value among patients with and without incidence of MACE at a 1-year follow-up (8.73 [8.36–9.08] vs. 8.81 [8.5–9.17]; $P = 0.09$). Moreover, the TyG index was not a predictor of these events ($P = 0.06$). In multivariable regression analysis, only previously diagnosed coronary artery disease (CAD) was an independent predictor of MACE (odds ratio [OR], 1.54; 95% CI, 1.02–2.32; $P = 0.03$). Finally, the TyG index was not an indicator of all-cause mortality ($P = 0.25$).

**Conclusions:** The TyG index should not be used as a predictor of MACE and all-cause mortality among non-diabetic patients with MI at a 1-year follow-up.

**Key words:** all-cause mortality, MACE, myocardial infarction, triglyceride-glucose index

Kardiol Pol 2021; 79, 10: 1116–1123

## INTRODUCTION

In modern non-invasive cardiology, great emphasis is placed on the prevention of coronary artery disease (CAD) which can manifest as acute or chronic coronary syndromes and/or heart failure. There are several unmodifiable and modifiable cardiovascular risk factors, but considerable research concerning new factors has been conducted worldwide, and numerous previous studies reveal that insulin resistance (IR) is significantly related to the occurrence of CAD among diabetic and non-diabetic patients [1, 2]. A practical indicator to measure IR is the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) test; however, its usefulness is limited due to the necessity of measuring the level of insulin, which is not always possible in the circumstances that prevail. Recently, the triglyceride-glucose index (TyG index) has been suggested as a new tool to measure IR [3].

The primary aim of the study was to examine the association between TyG index value and the occurrence of major adverse cardiovascular events (MACE) at a 1-year follow-up among non-diabetic patients with acute myocardial infarction (MI). The secondary aim was the evaluation of its predictive value concerning 1-year mortality in the study group.

## METHODS

This was a cohort study based on data collected from the medical records of 2300 patients with acute MI admitted to

WHAT'S NEW?

The triglyceride-glucose index (TyG index) is a metabolic marker recently considered as a novel cardiovascular risk factor. In our study, we assessed a potential relationship between the TyG index and the incidence of major adverse cardiovascular events (MACE) and all-cause mortality at a 1-year follow-up among non-diabetic patients with acute myocardial infarction (MI). We demonstrated no clinical evidence for the importance of this marker. The TyG index value does not appear to predict the incidence of MACE and all-cause mortality among non-diabetic patients with MI at a 1-year follow-up.

our hospital between 2013 and 2019. Patients who met inclusion criteria were consecutively recruited for the study.

Inclusion criteria were diagnosis of STEMI (ST-segment elevation myocardial infarction) or NSTEMI (non-ST-segment elevation myocardial infarction), coronary angiography undergone on admission with the presence of hemodynamically relevant atherosclerosis, and full medical documentation. Exclusion criteria were diabetes or prediabetes diagnosed prior to admission, use of glucose-lowering drugs or insulin, MI with non-obstructive CAD (MINOCA), acute heart failure on admission, and incomplete medical records.

All the patients had undergone emergency coronary angiography followed by percutaneous angioplasty with stent implantation or coronary artery bypass grafting if indicated. CAD severity was assessed with the Gensini score system [4] and performed by 2 experienced invasive cardiologists. Additionally, basic blood tests and echocardiography were performed. Data concerning MACE and 1-year mortality were obtained via telephone consultations scheduled with the patients or their families 1 year after MI.

### Laboratory tests

Lipid profile and blood fasting glucose level (FGL) were evaluated from fasting blood samples collected within 24-hours of admission. Lipid profile was measured by the direct enzymatic colorimetric method, using commercial in vitro diagnostic devices (Cobas C, Roche, Basel, Switzerland), whereas FGL was measured by the enzymatic hexokinase technique, using in vitro equipment (Cobas C, Roche, Basel, Switzerland). The TyG index was calculated manually using the following formula: TyG index = ln (fasting triglyceride [mg/dl] × fasting glucose [mg/dl]/2) [5].

### Definitions

Acute MI was defined according to the European Society of Cardiology guidelines, the Third (2012) or Fourth (2018) Universal Definition of Myocardial Infarction [6, 7]. MACE was a composite of myocardial infarction, in-stent restenosis, unstable angina, stroke or transient ischemic attack, and hospitalization due to heart failure. Being overweight was defined as a body mass index (BMI) ranging from 25 to 29.9 kg/m$^2$, whereas obesity was determined as a BMI of 30 kg/m$^2$ or higher. Diabetes was defined according to guidelines valid on the day of hospital admission [8]. Furthermore, in the current report, impaired glucose tolerance or impaired fasting glucose before hospital admission were reported as prediabetes. Acute heart failure was diagnosed in the patients admitted with signs and symptoms of heart failure due to decompensation of pre-existing cardiomyopathy or a new-onset heart failure caused by MI. A blood pressure of 140/90 mm Hg or higher, on at least 2 separate measurements, or the use of antihypertensive drugs were defined as hypertension.

### Ethics

The study protocol was approved by the local Ethics Committee (Jagiellonian University Medical College — KBET: 1072.6120.189.2020 to EK). Each study participant provided written informed consent before enrolment.

### Statistical analysis

All calculations were made using the STATISTICA 13.3 software package (TIBCO Software Inc., Palo Alto, CA, USA). A 2-sided *P*-value <0.05 was considered to be statistically significant. Continuous variables were expressed as medians, using the first and third quartiles, while categorical variables were shown as numbers and percentages. The normality of variables was assessed with the Shapiro-Wilk test. The Mann-Whitney and Kruskal-Wallis tests were used for non-normally distributed continuous variables, and categorical variables were compared using the Chi-square test. Stepwise logistic regression analysis was performed for determining the independent predictors of MACE and all-cause mortality. The final multivariable model included variables that were significant univariate predictors.

## RESULTS

### Patients

For our initial analysis, we enrolled 2300 patients admitted to our department. A total of 807 patients were excluded due to diabetes or prediabetes diagnosed prior to admission; 153 patients were excluded because of incomplete medical records. In addition, among those excluded, there were 18 cases of acute heart failure on admission. Finally, we analyzed data collected from 1340 patients at a median age of 67 years, among whom 70.4% were male. Most of the patients were overweight, with a median BMI of 26 kg/m$^2$. For 66% of them, MI was the first manifestation of CAD. Baseline characteristics of the study population are shown in Table 1.

**Table 1.** General characteristic of the study group

| Variables | All study patients n = 1340 | Men n = 944 | Women n = 396 | *P*-value |
|---|---|---|---|---|
| Age, years[a] | 67 (59–76) | 64 (58–74) | 72 (64–80) | <0.01 |
| BMI, kg/m$^2$[a] | 26 (24–29) | 26 (24–29) | 26 (23–29) | 0.06 |
| First episode of MI, n (%) | 887 (66.2) | 614 (65) | 273 (69) | 0.16 |
| STEMI, n (%) | 587 (43.8) | 425 (45) | 162 (40.9) | 0.16 |
| NSTEMI, n (%) | 752 (56.2) | 519 (55) | 234 (59.1) | |
| Gensini score | 50 (28–86.5) | 56 (32–88) | 40 (24–81) | 0.08 |
| Hypertension, n (%) | 1073 (80) | 748 (79) | 325 (82) | 0.2 |
| eGFR, ml/min/1.73 m$^2$[a] | 59 (48–69.5) | 56 (47–65) | 65.5 (55–79.5) | <0.01 |
| FGL, mmol/l[a] | 6.6 (5.7–7.9) | 6.6 (5.7–7.8) | 6.8 (5.8–8) | 0.08 |
| Lipid profile | | | | |
| LDL-C, mmol/l[a] | 2.8 (2.1–3.6) | 2.7 (2.1–3.6) | 2.9 (2.2–3.6) | 0.09 |
| HDL–C, mmol/l[a] | 1.2 (0.98–1.4) | 1.1 (0.95–1.4) | 1.2 (1–1.5) | <0.01 |
| Non-HDL-C, mmol/l[a] | 3.1 (2.5–4) | 3.1 (2.4–4) | 3.2 (2.6–4) | 0.08 |
| TC, mmol/l[a] | 4.4 (3.7–5.2) | 4.3 (3.6–5.2) | 4.6 (3.8–5.3) | <0.01 |
| TG, mmol/l[a] | 1.2 (0.95–1.6) | 1.2 (0.93–1.6) | 1.3 (0.98–1.6) | 0.55 |
| TyG index value[a] | 8.8 (8.5–9.1) | 8.8 (8.5–9.1) | 8.8 (8.5–9.2) | 0.2 |
| Medical therapy prior to admission | | | | |
| Statins, n (%) | 1103 (82) | 765 (81) | 338 (85) | 0.14 |
| Fibrates, n (%) | 36 (2.7) | 26 (2.8) | 10 (2.5) | 0.2 |
| ACEI/ARB, n (%) | 1099 (82) | 782 (83) | 317 (80) | 0.1 |
| B-adrenolitics, n (%) | 576 (43) | 415 (44) | 161 (41) | 0.12 |
| Calcium blockers, n (%) | 1072 (80) | 764 (81) | 308 (78) | 0.14 |
| ASA, n (%) | 498 (37) | 363 (38) | 135 (34) | 0.09 |
| Clopidogrel, n (%) | 25 (1.9) | 17 (1.8) | 8 (2) | 0.4 |
| Occurrence of MACE at 1-year follow-up, n (%) | 109 (8.13) | 78 (8.2) | 31 (7.8) | 0.79 |
| In-hospital mortality, n (%) | 22 (1.6) | 14 (1.5) | 8 (2) | 0.48 |
| One year mortality, n (%) | 195 (14.5) | 130 (13.8) | 65 (16.4) | 0.21 |

[a]Data are shown as median (interquartile range) unless otherwise indicated. P <0.05 was considered significant

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASA, aspirin; BMI, body mass index; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; FGL, fasting glucose level; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MACE, Major Adverse Cardiovascular Events; MI, myocardial infarction; non-HDL-c, non-high-density lipoprotein cholesterol; NSTEMI; non-ST segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; TC, total cholesterol; TG, triglyceride; TyG index, triglyceride-glucose index

### *Analysis of MACE*

MACE occurred in 8.13 % (n = 109) of the study group. There were 35 cases of MI, 19 cases of in-stent restenosis, 49 cases of unstable angina, 4 cases of stroke or transient ischemic attack, and 13 hospitalizations due to heart failure. Furthermore, among these cases, there were 12 patients who developed 2 incidents of MACE at a 1-year follow-up, and there were 5 cases of unstable angina and in-stent restenosis, 5 cases of MI, and in-stent restenosis, and 2 of myocardial infarction and hospitalization due to heart failure.

Analysis of the groups of patients, with and without incidence of MACE at a 1-year follow-up, revealed that there were no statistically significant differences in median age, ejection fraction, BMI, Gensini score, glucose, high-density lipoprotein cholesterol (HDL-C), the TyG index value, the occurrence of hypertension, or sex, and lipid-lowering therapy prior to admission. The patients with incidence of MACE had lower low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC), triglycerides (TG), and estimated glomerular filtration rate (eGFR). Moreover, 46.8% of them had been diagnosed with CAD prior to admission, whereas in the second group this was only 32.6%. Detailed demographic and clinical characteristics of those groups are presented in Table 2.

### *Univariate and multivariable regression analysis of MACE*

Univariate regression analysis showed that previously diagnosed CAD, eGFR, LDL-C, and TC were significant predictors of MACE. However, in the multivariable model, only previously diagnosed CAD proved to be an independent predictor (odds ratio [OR], 1.54; 95% CI, 1.02–2.32; $P = 0.03$). The TyG index was not an indicator of MACE in the study group ($P = 0.06$). The significant predictors of MACE are presented in Table 3.

### *Patients with potential glucose metabolism disorders*

To deepen our analysis, we divided the patients according to their glycemic control status into 2 groups: one with a lower fasting glucose level (FGL <7.8 mmol/l) and the other with potential, previously undiagnosed, glucose metabolic disorder or stress hyperglycemia caused by MI (FGL ≥7.8 mmol/l). Hyperglycemia occurred in 25.2% of the patients (n = 338). There was a difference in medians

**Table 2.** Demographic and clinical characteristics of patients with and without incidence of MACE in one year follow-up

| Variables | Patients with incidence of MACE at 1-year follow-up n = 109 | Patients with no incidence of MACE at 1-year follow-up n=1231 | *P*-value |
|---|---|---|---|
| Male sex, n (%) | 78 (71.5) | 866 (70.3) | 0.8 |
| Age, years[a] | 67 (62–79) | 67 (59–76) | 0.15 |
| BMI, kg/m$^2$[a] | 25.8 (23.2–29.4) | 26.3 (23.8–29) | 0.6 |
| CAD diagnosed prior to admission, n (%) | 51 (46.8) | 402 (32.6) | <0.01 |
| Ejection fraction, %[a] | 50 (35–55) | 50 (35–60) | 0.7 |
| Hypertension, n (%) | 86 (78.9) | 987 (80.2) | 0.74 |
| Gensini score | 58 (24–96) | 48 (28–96) | 0.85 |
| eGFR, ml/min/1.73 m$^2$[a] | 54.9 (47.3–64.8) | 59.2 (48.4–70) | 0.04 |
| FGL, mmol/l[a] | 6.9 (5.9–8) | 6.6 (5.7–7.8) | 0.18 |
| FGL ≥7.8 mmol/l, n (%) | 32 (29.3) | 306 (24.8) | 0.29 |
| LDL-C, mmol/l[a] | 2.45 (1.96–3.44) | 2.8 (2.15–3.6) | <0.01 |
| HDL-C, mmol/l[a] | 1.18 (0.99–1.48) | 1.17 (0.98–1.41) | 0.56 |
| Non-HDL-C, mmol/l[a] | 2.92 (2.26–3.69) | 3.18 (2.53–4.08) | <0.01 |
| TC, mmol/l[a] | 4.06 (3.41–4.9) | 4.4 (3.76–5.26) | <0.01 |
| TG, mmol/l[a] | 1.13 (0.9–1.44) | 1.26 (0.96–1.68) | <0.01 |
| TyG index[a] | 8.73 (8.36–9.08) | 8.81 (8.5–9.17) | 0.09 |
| Statins therapy prior to admission, n (%) | 88 (80.7) | 1015 (82.4) | 0.9 |
| Fibrates therapy prior to admission, n (%) | 3 (2.7) | 33 (2.7) | 0.7 |
| All-cause mortality, n (%) | 15 (13.7) | 180 (14.6) | 0.8 |

[a]Data are shown as median (interquartile range, IQR) unless otherwise indicated. *P* <0.05 was considered significant

Abbreviations: see Table 1

**Table 3.** Predictors of MACE in one year follow-up (univariate regression analysis)

| Predictors of MACE in 1-year follow-up | OR | 95% CI | *P*-value |
|---|---|---|---|
| CAD diagnosed prior to admission | 1.81 | 1.22–2.69 | <0.01 |
| eGFR, ml/min/1.73 m$^2$ | 0.98 | 0.97–0.99 | 0.03 |
| LDL-C, mmol/l | 0.73 | 0.59–0.89 | <0.01 |
| TC, mmol/l | 0.77 | 0.64–0.92 | <0.01 |

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

**Table 4.** Predictors of MACE in one year follow-up after exclusion of patients with higher FGL (univariate regression analysis)

| Predictors of MACE in 1-year follow-up | OR | 95% CI | *P*-value |
|---|---|---|---|
| CAD diagnosed prior to admission | 1.69 | 1.06–2.69 | <0.01 |
| eGFR, ml/min/1.73 m$^2$ | 0.98 | 0.96–0.99 | <0.01 |
| LDL-C, mmol/l | 0.6 | 0.46–0.78 | <0.01 |
| TC, mmol/l | 0.62 | 0.51–0.82 | <0.01 |

Abbreviations: see Table 1 and Table 3

of the TyG index between those 2 groups: 8.7 (8.4–9) in the lower FGL group, versus 9.17 (8.86–9.5) in the higher one (*P* <0.01). There was, however, no significant difference between glycemic control status during hospitalization and incidence of MACE at a 1-year follow-up. MACE occurred in 7.68% (n = 77) of patients with lower FGL and in 9.47% (n = 32) of those with potential glucose metabolic disorder (*P* = 0.29). Additionally, after excluding from the analysis the patients with higher FGL, only CAD diagnosed prior to admission, eGFR, LDL-C and TC were statistically significant predictors of MACE in univariate regression analysis (Table 4). The TyG index value was insignificant (*P* = 0.12).

### *Univariate and multivariable regression analysis of one-year mortality*

The all-cause mortality rate at a 1-year follow-up was 14.5% (n = 195) for the whole study group, whereas in-hospital mortality was 1.6% (n = 22). In univariate regression analysis, the TyG index value appeared to be an irrelevant indicator of all-cause mortality (*P* = 0.25), whereas age, BMI, Gensini score, eGFR, LDL-C, and TC were statistically significant. Finally, multivariable regression analysis showed that only age was an independent predictor of all-cause mortality at a 1-year follow-up (OR, 1.1; 95% CI, 1.06–1.13; *P* <0.01). Predictors of all-cause mortality are shown in Table 5.

## DISCUSSION

To the best of our knowledge, this study is the first that assesses the TyG index, measured during acute MI among non-diabetic patients, as a potential predictor of MACE and all-cause mortality at a 1-year follow-up. Previously, this metabolic marker was used as an easily accessible indicator of insulin resistance [9], a predictor of diabetes [10], and

**Table 5.** Predictors of all-cause mortality in one year follow-up (univariate regression analysis)

| Predictors of all-cause mortality at 1-year follow-up | OR | 95% CI | *P*-value |
|---|---|---|---|
| Age | 1.08 | 1.07–1.1 | <0.01 |
| BMI | 0.91 | 0.87–0.94 | <0.01 |
| Gensini score | 1.01 | 1–1.1 | <0.01 |
| eGFR, ml/min/1.73 $m^2$ | 0.97 | 0.96–0.98 | <0.01 |
| LDL-C, mmol/l | 0.7 | 0.59–0.81 | <0.01 |
| TC, mmol/l | 0.76 | 0.65–0.87 | <0.01 |

Abbreviations: see Table 1 and Table 3

**Table 6.** Medical treatment at discharge

| Medical treatment at discharge | Number of patients (%) |
|---|---|
| Statins, n (%) | 1332 (99.4) |
| Ezetimibe, n (%) | 166 (12.4) |
| Fibrates, n (%) | 3 (0.2) |
| ACEI, n (%) | 575 (42.9) |
| ARB, n (%) | 324 (24.2) |
| β-adrenolytics, n (%) | 1139 (85) |
| Calcium blockers, n (%) | 753 (56.2) |
| Diuretics, n (%) | 624 (46.6) |
| ASA, n (%) | 1338 (99.8) |
| Clopidogrel, n (%) | 1170 (87.3) |
| Prasugrel/ticagrelor, n (%) | 168 (12.7) |

Abbreviations: see Table 1

a biomarker of glycemic control in type 2 diabetes mellitus [11]. Since the TyG index is a quite novel IR marker, there is no internationally recognized cut-off value. Unger et al. [12] suggested that this value for metabolic syndrome in the general population was 8.8 in men and 8.7 in women, and in the study by Lee et al. [13], where the cut-off value for the TyG index was set at 8.8, this marker was a statistically significant predictor for incidental diabetes in 4-year follow-up. For the current study, the population's median TyG index value was 8.8, which may suggest a high incidence of IR among patients with MI.

In many patients with MI, the level of fasting glucose is elevated and called "stress hyperglycemia". This condition usually occurs in critically ill patients without diabetes mellitus diagnosed prior to admission [14, 15]. It appears to be connected with a stress mechanism, which is associated with steroid hormones, temporary IR, and a high level of free fatty acids [16]. According to the American Diabetes Association, stress hyperglycemia in hospitalized patients is related to a random glucose level greater than 7.8 mmol/l at any time [17]. In our research, this condition occurred in 25.2% of patients. There was no correlation between higher glucose level and incidence of MACE at 1-year follow-up. Furthermore, even after excluding from the analysis the patients with higher FGL, the TyG index, which is directly related to levels of TG and glucose, was not a predictor of MACE.

The usefulness of the TyG index as a predictor of cardiovascular events has previously been investigated in several studies, mostly among healthy individuals or patients with stable CAD.

A recent Chinese retrospective study [18] among 6076 healthy individuals aged over 60 years showed in a 6-year follow-up that a higher risk of CAD events was associated with an increasing value of the TyG index. Another study on that subject, conducted by Park et al. [19] and performed among healthy individuals with no traditional cardiovascular risk factors, showed that a TyG index value over 8.48 was a predictor of CAD. Finally, in an Iranian study [20], the risk of developing CAD increased with increasing quintiles of the TyG index in a long-term follow-up period (16 years).

To the best of our knowledge, little is known about the predictive value of the TyG index in patients with MI. Luo et al. [21] conducted a study on patients with STEMI, undergoing percutaneous coronary intervention, to assess the clinical outcomes of that marker during a follow-up period of 1 year. Those clinical outcomes were defined as major adverse cardiac and cerebrovascular events (MACCE) and included all-cause death, target vessel revascularization, MI, unstable angina pectoris, heart failure, stroke, and transient cerebral ischemia. In that study, patients were divided into 4 groups according to TyG-index quartiles. The incidence of MACCE and all-cause mortality was higher among patients with TyG index values in the highest quartile. Analysis of the predictors of MACCE showed statistical significance for a TyG index value ≥9.098, age, hypertension, diabetes, eGFR, number of implanted stents, and multivessel CAD in univariate analysis. In multivariable analysis, however, only a TyG index value ≥9.608 and the number of implanted stents were significant.

In our analysis, on the other hand, the TyG index value was not significant in univariate regression analysis ($P = 0.06$). In addition, in the multivariable model, only CAD diagnosed prior to admission was relevant (OR, 1.54; 95% CI, 1.02–2.32; $P = 0.03$).

In the study by Luo et al. [21], the percentage of patients with incidence of MACCE was higher than in our study — 34.3% vs. 8.13%. Moreover, patients in the MACCE group had higher mean values of FGL (9, standard deviation [SD] = 4.2 mmol/l vs. median value of 6.9 [5.9–8] mmol/l in our study), and 31.2% of them had diabetes. Furthermore, those patients had higher values of LDL-C, TC, and TG (mean value –1.9 [SD = 1.6] mmol/l vs. median value of 1.13 [0.9–1.44] mmol/l). Consequently, their TyG index value was higher, with a mean value of 10.076 (SD = 0.483)

in the highest quartile group. Additionally, in that research, only 2.4% of patients with incidence of MACE had been diagnosed with CAD prior to admission, whereas in our study, this was 46.8%. Both study populations were similar concerning age, BMI, and the proportion of males. Finally, no correlation between 1-year mortality and the TyG index was found in our report, whereas in the study by Luo et al. [21] that correlation was statistically significant.

In another Chinese study presented by Mao et al. [22], patients with NSTEMI were initially divided into 2 groups according to their TyG index value, these being low (<8.8) and high (>8.8) scores. In that study, more than half of the patients had diabetes or glucose metabolism disorder. Additionally, the incidence of MACE. including cardiac death, nonfatal myocardial infarction, target vessel revascularization, congestive heart failure, and nonfatal stroke, was higher in the high TyG index group at a 1-year follow-up (12.8% vs. 22.8%; $P$ <0.01).

To deepen the analysis, Mao [22] divided patients into 4 groups, depending on the TyG index value and the occurrence of glucose metabolism disorder. There was a statistically significant difference between the incidence of MACE among the patients without glucose metabolism disorder with low (10.7%) and high (33.8%) TyG index values. Finally, in univariate analysis, the TyG index was significantly associated with MACE (hazard ratio [HR], 1.951; 95% CI, 1.416–2.688; $P$ <0.01). Furthermore, in the multivariable model, the TyG index also remained an independent predictor of MACE. In the Mao [22] research, the study group was not divided according to the incidence of MACE, so a simple comparison with our study is difficult to perform. In a relatively small population of 438 patients, the incidence of MACE was 17.8%, whereas in our population of 1340 patients, MACE occurred only in 8.13%.

On the other hand, a simple correlation of the value of the TyG Index with the incidence of atherosclerosis, its severity, and incidence of MACE, is questionable. Alizargar et al. [23], in their article assessing the practical value of the TyG index, emphasize that using this marker can be easily biased by hyperlipidemia, diabetes, or other glucose metabolic disorders, as the TyG index has a direct relationship with levels of TG and glucose (based on the TyG index formula). In conclusion, these factors should be carefully considered to justify the use of the TyG index as a biomarker. In the Polish population, we can still observe insufficient adherence to guidelines concerning the proper level of glucose, lipid profile, blood pressure, BMI, physical activity, and smoking [24]; therefore, the potential use of the TyG index might be limited.

Dziedzic et al. [25] in their study concerning educational programs among Polish elderly patients showed that several training meetings performed to change lifestyle in that group had an impact on the lipid profile of the participants, particularly concerning the level of TG ($P$ = 0.02). Finally, Wybraniec et al. [26] revealed that patients enrolled on a similar program (Managed Care After Acute Myocardial Infarction Program) had a lower rate of MACE at a 1-year follow-up (11.3% vs. 19.1%; $P$ = 0.0006). We believe that similar programs should be implemented in order to properly manage basic cardiological risk factors, reduce the rate of MACE, and improve patient survival.

Vega et al. [27] also presented concerns concerning the predictive value of the TyG index. In that study, this index was a positive predictor of coronary heart disease, cardiovascular disease, and all-cause mortality, but only unadjusted and, after adjustment, for age, smoking, BMI, and systolic blood pressure. After an additional adjustment for non-HDL-C level, the HR was lower — 0.83 for coronary heart disease, 0.89 for cardiovascular disease, and 0.89 for all-cause mortality. Our findings correspond with Vega's conclusions that the TyG index does not predict all-cause mortality.

In our opinion, this metabolic biomarker should not be used as a predictor of clinical outcomes among non-diabetic patients with MI for several reasons. Firstly, the TyG index has a direct relationship with glycemia which can be labile in acute conditions such as MI. Secondly, in our study, the TyG index was not a predictor of MACE even after we excluded from the study the group of patients with FGL ≥7.8 mmol/l. Finally, there was no association between the TyG index value and all-cause mortality.

We should also briefly discuss other predictors that were statistically significant in our study. Surprisingly, LDL-C and TC were negative predictors of MACE and all-cause mortality. We believe that this was caused by the fact that the patients with incidence of MACE had lower values of those parameters as compared with those without it. Moreover, the patients with MACE had lower concentrations of non-HDL-C and TG. Even though there was no difference between the use of statins and fibrates prior to admission among the patients with and without the incidence of MACE at 1-year follow- up, we can assume that the lipid-lowering therapy of those patients with the incidence of MACE was more intensive, and their compliance with prescribed therapy was better because 46.8% of them were previously diagnosed with CAD. Unfortunately, we are unable to verify those assumptions. Moreover, data concerning lipid-lowering therapy was obtained from anamnesis and the patients' compliance with prescribed treatment remains unknown.

### Study limitations

This study has several limitations. Firstly, a relatively short follow-up period. Secondly, insufficient information concerning the patients' compliance with prescribed therapy and data regarding changes in lipid-lowering therapy, which might have improved cardiovascular outcomes of the patients [28] and affected our study. Thirdly, we had no information concerning the date of MACE. Finally, short follow-up and unknown causes of death in patients without 1-year survival represented other study limitations.

## CONCLUSIONS

The TyG index does not appear to be a predictor of MACE among non-diabetic patients with MI. We believe that its potential use in acute conditions is limited by acute metabolic changes accompanying MI, and it does not help to identify non-diabetic individuals at a greater risk of poor clinical outcomes. Furthermore, no association between the TyG index value and all-cause mortality at a 1-year follow-up also reflects the questionable clinical value of that parameter. Moreover, comprehensive evaluation of cardiovascular risk factors should focus primarily on basic risk factors. Additional markers may be useful but after the effective management of these risk factors.

### *Article information*

**Acknowledgments:** The study was supported by a grant from Jagiellonian University Medical College N41/DBS/000098; to EK).

**Conflict of interest:** None declared.

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**How to cite:** Drwiła D, Rostoff P, Gajos G, et al. Prognostic value of the triglyceride-glucose index among non-diabetic patients with acute myocardial infarction at one-year follow-up. Kardiol Pol. 2021; 79(10): 1116–1123, doi: 10.33963/KP.a2021.0104.

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# Recognition of emerging cardiac diagnoses by echocardiography in 5th-year medical students — the role of focused e-learning

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Kardiol Pol. 2021; 79 (10): 1124–1126; DOI: 10.33963/KP.a2021.0090

**Received:** July 18, 2021

**Revision accepted:** August 15, 2021

**Published online:** August 15, 2021

## INTRODUCTION

Echocardiography has become one of the most widely used diagnostic tests in modern medicine. With the increasing availability of echocardiographic equipment and the advent of miniaturized, portable cardiac-echo technology, the inclusion of echocardiography-derived data in routine physical examinations may soon become common for cardiologists and non-cardiologists [1]. The role of echocardiography in emergency departments has been recently acknowledged [2, 3]. Therefore, providing future physicians with skills on how to acquire and interpret cardiac-echo data is becoming highly expected in medical curricula [4–6]. To meet these expectations the Board of the Faculty of Medicine of the Jagiellonian University Medical College (JUMC), supported by recent literature on online teaching [7–9] and by the experience of successful implementation of ECG e-learning [10, 11], introduced in 2020/2021 academic year a subject entirely dedicated to this field. The subject has been included in the program of the 5th year of the 6-year JUMC Faculty of Medicine curriculum. The 10-hour course, with a synchronous online seminar design, is aimed at improving the students' knowledge of the application of basic echocardiographic projections, their ability to evaluate the morphology and function of heart structures and chambers, and their ability to interpret results in relation to clinical contexts. The online mode of the course was chosen to ensure, equally to all students, synchronous presentation and discussion of essential elements of the echocardiographic examination. In this study, we aimed to evaluate the didactic effectiveness of such an approach.

## METHODS

All 5th-year students of the 2020/2021 academic year at the JUMC Faculty of Medicine were eligible to participate in the study. Participation was voluntary. All students were informed about the topic and the purpose of the study. An invitation along with a link to an online questionnaire was disseminated using a university mailbox, discussion groups, and social media on February 26, 2021, with a completion deadline of April 6, 2021.

The specifically designed questionnaire for this study was composed of 2 sections (Supplementary material). The first contained 8 echocardiographic recordings of different cardiovascular pathologies (one major diagnosis per recording), and the second presented 8 real-life descriptions of echocardiographic findings, which included data on the morphology and function of different cardiac elements. The students were asked to answer 16 multiple-choice questions with five distractors (Supplementary material) including one "I don't know" option. There was no time limit for the completion of the questionnaire, but only one attempt was available. Correct answers were published after finishing the survey. The maximum score was 16 points, with 8 points for image recordings (image score) and 8 points for echocardiographic descriptions (description score).

The threshold for a positive result was defined at ≥9 points (>56%) in accordance with the guidance of the Polish Medical Final Examination (LEK). Both the recordings and the descriptions were provided by trained cardiologists and were assessed before the start of the study by two other independent cardiologists.

### Statistical analysis

The students, who gave consent to take part in the study and completed the online questionnaire, were divided into 2 groups. The first was comprised of those who had already completed their echocardiography course before the study start (the post-course group), and the second was those who had not (control group). The minimal size of the sample was calculated based on available literature (Supplementary material).

The study groups were compared in terms of the total score (max. 16 points), images score (max. 8 points), descriptions score (max. 8 points), and the number of correct answers to each question. Data were expressed as median and interquartile range or as numbers and percentages. The Mann-Whitney U test was used to compare continuous variables, and the Chi-square test to compare the categorical variables. The significance level was set at $P < 0.05$. Statistical analysis was performed using jamovi 1.2.27 software.

## RESULTS AND DISCUSSION

A group of 63 students completed the questionnaires. Twenty-five students were assigned to the post-course group and 25 to the control group. The students who were participating in the course when completing the questionnaire (n = 2) and those who chose only "I don't know" answers to all the questions (n = 11) were excluded from the analysis (7 students from the post-course group and 4 students from the control group). As presented in the supplementary material, the response rate was 25% in both groups.

Students from the post-course group achieved a higher total score (10 [6–12] vs. 5 [3–8]; $P = 0.001$) respectively, image score (5 [4–6] vs. 2 [1–4]; $P = 0.001$) and description score (5 [2–6] vs. 2 [2–4]; $P = 0.01$) than the control group. As few as 5 (20%) students from the control group reached >56% of points (9 or more points) of correct answers, whereas in the experimental group it was 14 (56%) students ($P = 0.008$).

Students of the post-course group, as compared to the control group, more often made a correct diagnosis of images presenting acute aortic dissection (56% vs. 28%; $P = 0.045$, respectively), acute pulmonary embolism (52% vs. 24%; $P = 0.41$, respectively), acute myocardial infarction (68% vs. 12%; $P = 0.001$, respectively) and severe systolic dysfunction of the left ventricle (72% vs. 28%; $P = 0.002$, respectively).

Moreover, the post-course students correctly interpreted the descriptions of high risk of pulmonary hypertension (64% vs. 36%; $P = 0.048$), acute pulmonary embolism (48% vs. 16%; $P = 0.015$), severe systolic dysfunction of the left ventricle (76% vs. 36%; $P = 0.004$), and severe aortic stenosis (56% vs. 12%; $P = 0.001$); they did it more frequently than the students from the control group.

The distribution of correct answers for each question is shown in Figure 1.

The results of this study show that 5$^{th}$-year medical students have insufficient competencies to interpret cardiac echo data, as the threshold for a positive result was achieved by only 20% of students who had not completed the online echocardiography course. However, this score can be significantly improved with the use of an internet-based course specifically focused on echocardiography (56% of students achieved positive results).

An important strength of our study is its novelty. Although echocardiographic e-learning has been previously assessed as a method of education in several studies (Supplementary material, Discussion and Supplementary references [1]), thus far the scientific question: "Does an online course of transthoracic echocardiography improve recognition of emergency cardiac conditions and understanding of echocardiographic results in medical students?" has not been answered.

This study has some limitations. First, the sample size seems low, although it was predefined based on previous studies. Second, our study has a case-control design, which is prone to a certain bias inherent in such studies [12].

In summary, a routine 10-hour online echocardiographic course allowed the 5$^{th}$-year medical students to improve their competencies in recognition of acute or severe cardiac diseases with the use of cardiac echo examination.

### Supplementary material

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

### Article information

**Conflict of interest:** None declared.

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**How to cite:** Gallina T, Żuławińska B, Stępniewski J, et al. Recognition of emerging cardiac diagnoses by echocardiography in 5th-year medical students — the role of focused e-learning. Kardiol Pol. 2021; 79(10): 1124–1126, doi: 10.33963/KP.a2021.0090.

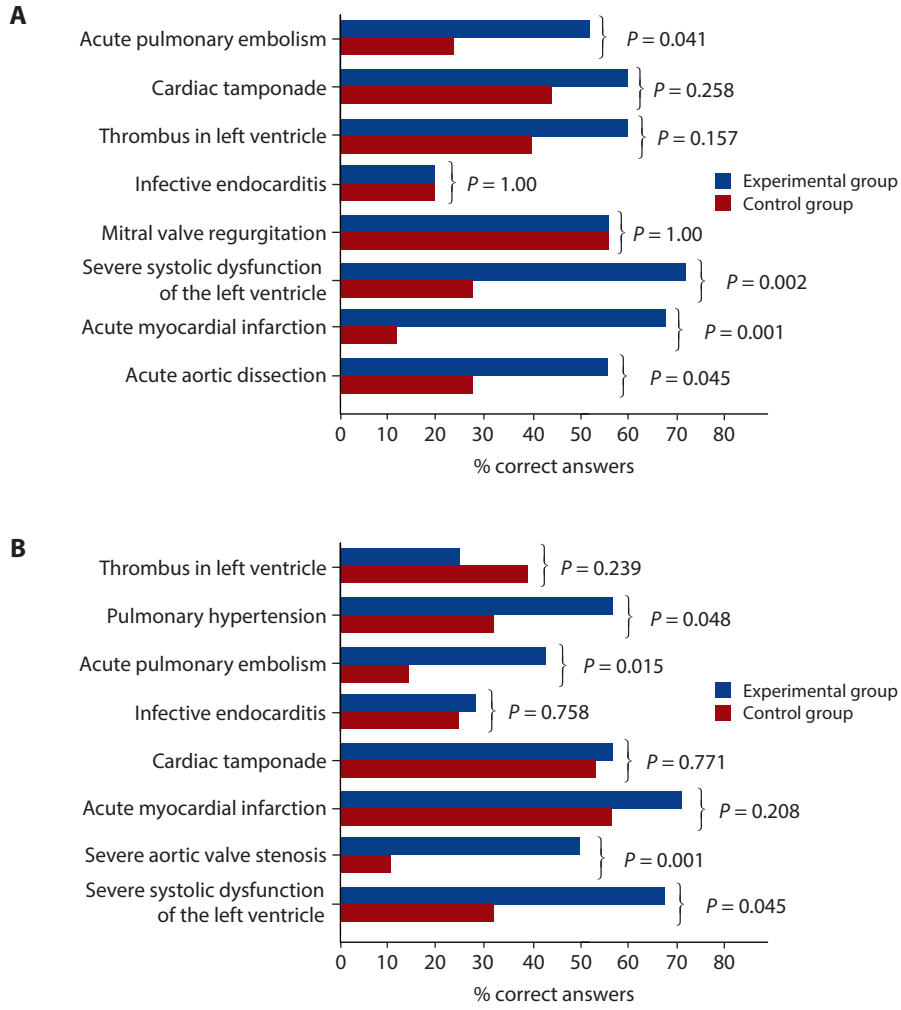


**Figure 1.** Percentage of correct answers for each question in the control and the experimental groups. **A.** Recognition of echocardiographic images. **B.** Interpretation of echocardiographic description

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# Left bundle branch pacing in patients with right bundle branch block

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Kardiol Pol. 2021;
79 (10): 1127–1129;
DOI: 10.33963/KP.a2021.0091

**Received:**
May 26, 2021

**Revision accepted:**
August 15, 2021

**Published online:**
August 15, 2021

## INTRODUCTION

The paced morphology similar to right bundle branch block (RBBB) in lead V1, which usually featured Qr, qR, rSR′, or QS patterns, is one of the expected parameters during left bundle branch pacing (LBBP) implantation [1–3]. It is due to the early activation of the left ventricle (LV) and delayed activation of the right ventricle (RV) (Figure 1A). A possible explanation for this phenomenon is that since LV excitation precedes RV excitation precedes RV excitation, then the paced QRS morphology of patients with RBBB produced by LBBP can be significantly different from the intrinsic one, especially that the paced QRS duration has been always narrower than the intrinsic duration. (Supplementary material, *Figure S1A–S1D*). We herein discuss several possible mechanisms to explain this shortening.

## METHODS

This single-center prospective self-control study enrolled 32 patients who underwent LBBP, with complete right bundle branch block (cRBBB) but not incomplete or intermittent RBBB, and without other conduction disturbance (left posterior fascicular block, left anterior fascicular block, or septal fascicular block). The surface electrocardiograms (ECGs) with the preoperative diagnosis of cRBBB were carefully identified according to the criteria that included the QRS duration >0.12 sec, a rSR′ or RR′ pattern in leads V1 and/or V2 and a wide and slurred S wave in leads V6 and I (S >R duration or S wave duration ≥0.06 sec). The process of LBBP has been previously described [1, 2]. Both selective LBBP (SLBBP) and non-selective LBBP (NSLBBP) were acceptable. The definition of LBB capture was the constant Stim-LVAT (measured from the onset of the stimulus artifact to peak R-wave in lead V6), regardless of different outputs. We used the criteria proposed by Jastrzębski M et al. [4] to differentiate between LBBP and left ventricular septal pacing in patients with cRBBB. On each pair of ECGs, we measured both intrinsic QRS duration (iQRSd), from the onset to the end of the QRS, and paced QRS duration (pQRSd), following closely the pacing spike from the first deviation from baseline to the end of QRS. The local Ethics Committee approved the study protocol, and all of the patients provided their informed, voluntary, and written consent for participation.

### *Statistical analysis*

The continuous variables were expressed as the means (SD), and the categorical variables were expressed as percentages. QRS duration before and after LBBP in each pair of subjects was compared by using paired-samples t-tests. Statistical analyses were performed with SPSS 22.0 (SPSS Inc, Armonk, NY, USA). *P*-values of less than 0.05 were considered to be statistically significant.

## RESULTS AND DISCUSSION

The mean age of the participants was 72.76 (8.71) years, and there were 25 males in total (73.53%). Three patients had sick sinus syndrome (SSS) whereas the rest of the participants had high-grade atrioventricular conduction blocks (AVBs). Postoperative ECGs were recorded under unipolar pacing configuration in 15 patients and under bipolar pacing configuration in the remaining patients. There was a significant decrease (compared to the iQRSd) with the pQRSd (144.31 [4.83] ms vs. 115.58 [5.80] ms, respectively; $P$ <0.001), and the pQRSd

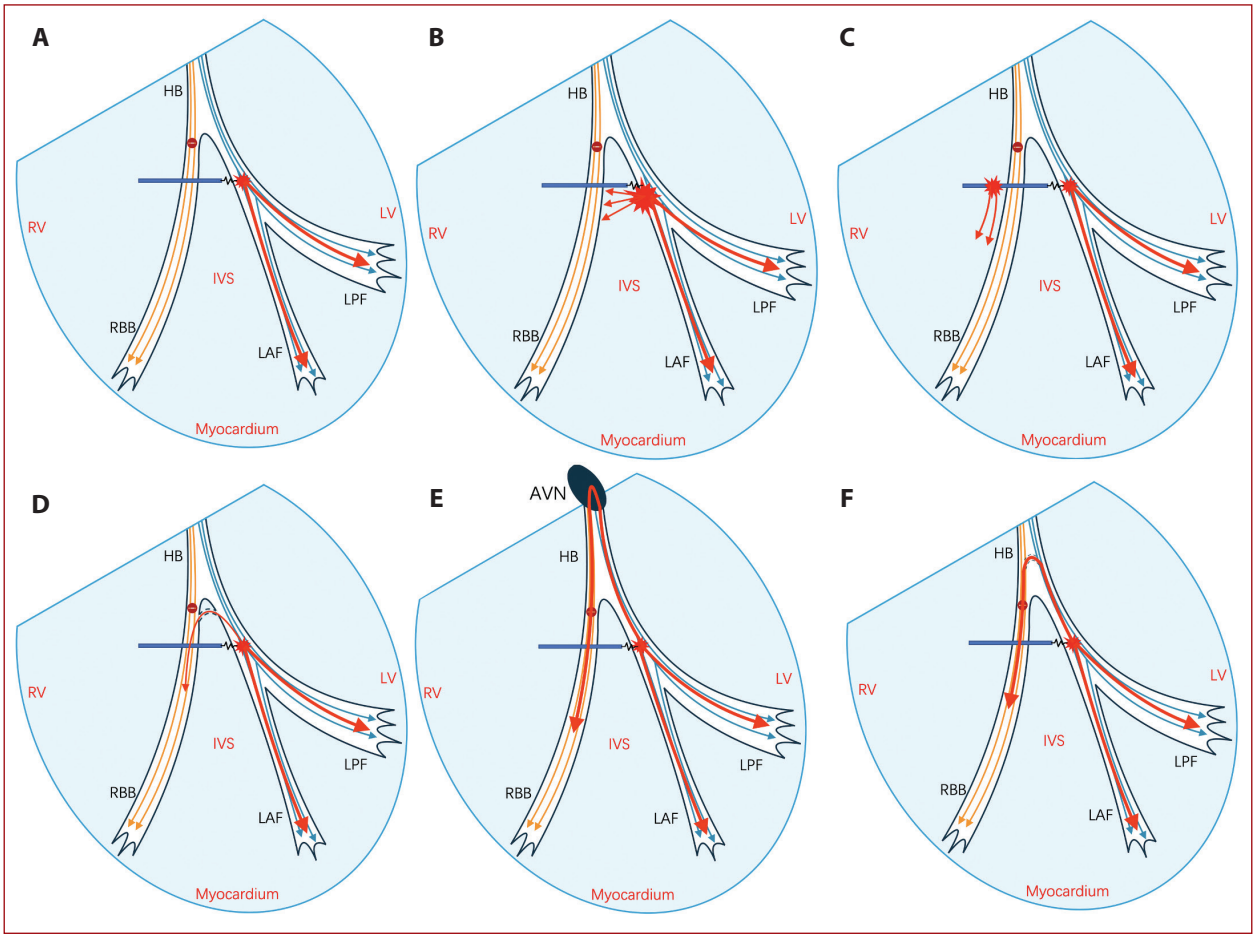


**Figure 1.** Schematic diagram of excitation conduction of left bundle branch pacing. **A.** Selective left bundle branch pacing (SLBBP) captures only the left bundle branch (LBB) to excite the left ventricle (LV) and then excites the right ventricle (RV) via the intercalated discs of the myocardium. **B.** Non-selective left bundle branch pacing (NSLBBP) causes fusion of excitation of the LV, the LBB area, and the local RV septum. **C.** Anodal capture occurred in the bipolar pacing configuration, wherein a portion of the RV septum was pre-excited by the anodal right ventricular ring. **D.** LBBP may bypass the right bundle branch (RBB) block through transverse interconnection fibers (TF)/functional transverse interconnection (FTI) (dashed line) and eventually activate RBB. **E.** The impulse is anterogradely conducted through the LBB to activate the LV, after which it is retrogradely conducted to the atrioventricular node and then recruits the RBB. **F.** TF/FTI (dashed line) may also exist within His bundle (HB), wherein it laterally connects to LBB and RBB, which can transmit the retrograde impulse from LBB to RBB and then capture RBB. See the text for details

Abbreviations: LPF, left posterior fascicular; LAF, left anterior fascicular; IVS, intraventricular septum

was 28.74 (3.30) ms shorter than the iQRSd. A similar shortening was observed in both unipolar (Figure 1B) and bipolar (Figure 1C) pacing configurations, as shown in Supplementary materials, *Table S1*.

The 3 possible mechanisms for these results are as follows.

### *An excited fusion of the LV and local RV septum*

NSLBBP and anodal capture induce excited fusion of the LV and local septum. Some studies have described LBBP in a patient with RBBB, where the R' wave peak time (measured from the onset of the stimulus artifact to peak R'-wave in lead V1) and R' wave duration in the end of QRS complex were shorter in NSLBBP than in SLBBP [5, 6]. With the increase in pacing output, SLBBP is converted into NSLBBP with no isoelectric interval (Figure 1B), thus indicating that both LBB and local adjacent septal myocardium are captured.

The cathode tip of lead was placed in the LBB area (trunk or left anterior and posterior fascicle of the LBB), and the anode ring was located in the right ventricular septum. During a bipolar pacing configuration at high output, the anodal right ventricular ring can pre-excite a portion of the right septum to compensate for the RV delay (Figure 1C). This minimizes QRS duration because at least 2 depolarization wavefronts activate the ventricles, thus shortening the conduction time from the LV to the RV. The QRS morphology generated by anodal capture is the general shortened QS pattern without R wave on lead V1, which is significantly different from the Qr pattern generated by NSLBBP in the presence of short Stim-LVAT.

### *Transverse interconnection between the LBB and the RBB*

The His-Purkinje system is complex, variable, and interconnected. In the 1970s, Lazzara et al. suggested that

a functional transverse interconnection (FTI) exists in the His bundle (HB) and in the bundle branches (Figure 1F), which transmit impulses across the fibers [7]. Chu et al. [8] described LBBP as a possible treatment for correcting the RBBB through transverse interconnection fibers (TFs) that connect the LBB and RBB (Figure 1D). However, based on the properties of anisotropic conduction of longitudinal dissociation [7], it is suspected that the combination of the rapid longitudinal conduction of the impulse to the LV and the slow lateral conduction to the RV would result in a shortened pQRSd. If transverse interconnection coexists with longitudinal dissociation, then the impulse generated by LBBP circumnavigates the structure block to excite the RV without a paced morphology of the RBBB. In addition, the anatomical structure of these fibers has not been previously reported.

### *Retrograde conduction from LBB to RBB*

It is clear that impulses can be bidirectionally transmitted in the His–Purkinje system. During LBBP, the impulse anterogradely captured the LBB to excite the LV and retrogradely captured the RBB to excite the RV [9]. In these circumstances, the pulse will retrogradely propagate in the LBB fibers to a turnaround point on its way up and create a deviation from the LBB to the RBB. Of course, the location of the turnaround point is important, wherein it is possibly located in the LBB and RBB (Figure 1D), in the proximity of HB (Figure 1F), and in the atrioventricular node (Figure 1E). However, even if the impulse can deflect from the LBB to the RBB, it is not clear whether it can recruit the distal RBBB.

In summary, excited fusion is most likely to shorten QRS duration after LBBP in patients with RBBB, and the specific mechanisms may be multifactorial, which requires more precise mapping and further anatomical study of the conduction system of the heart.

### *Supplementary material*

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

### *Article information*

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**How to cite:** Zhu K, Sun Y, Cai B, et al. Left bundle branch pacing in patients with right bundle branch block. Kardiol Pol. 2021; 79(10): 1127–1129, doi: 10.33963/KP.a2021.0091.

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# The use of Amplatzer devices in the percutaneous treatment of congenital heart defects in children and adults based on own experience

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Kardiol Pol. 2021;
79 (10): 1130–1132;
DOI: 10.33963/KP.a2021.0092

**Received:** June 28, 2021

**Revision accepted:** August 15, 2021

**Published online:** August 17, 2021

## INTRODUCTION

Amplatzer devices (AD) introduced to the clinical practice in the world in 1997 (first presentation) were a major breakthrough in congenital heart defects transcatheter treatment (TT). In 2021 our Department is celebrating the 24th anniversary of implementing/using this method. The first author (JB) managed the Clinic from 1998 till now, and prof. M Szkutnik was the head of our catheterization laboratory until 2017 (now it is led by Dr R. Fiszer, MD, PhD).

## METHODS

We presented here our 15 most important scientific papers on AD application in the percutaneous closure of: (1) atrial septal defect (ASD); (2) patent ductus arteriosus (PDA); (3) postinfarction ventricular septal defect (PIVSD); and (4) vascular malformation. The total number of citations of this articles according to Web of Science was 317.

## RESULTS AND DISCUSSION

### *Atrial septal defect*

We performed 1847 procedures of ASD transcatheter closure at our Institute in the years 1997–2021 according to the guidance of the Association of Cardiovascular Interventions and the Grown-Up Congenital Heart Disease Section of the Polish Cardiac Society [1] (Figure 1). We published our preliminary data on the efficacy of TT of ASD in 2004 [2]. The article was recognized by the Spanish Society of Cardiology as the best publication of the year on pediatric cardiology. We demonstrated that ASD closure with Amplatzer atrial septal occluders (ASO) is safer than surgical treatment and leads to fewer complications [3]. Also, data on the better outcomes of transcatheter vs surgical ASD closure in regard to heart rate variability (HRV) parameters were documented. The experience in the closure of double ASDs with a single ASO was also presented [4]. We have concluded that double ASDs, which are very close to each other, can be occluded with one device. If the distance between both defects exceeds 7 mm (the difference in radius of the device and its waist is 7 mm), the device should be slightly oversized. A small residual shunt is observed in those patients after the procedure, however, it usually disappears for up to a year. This phenomenon is the result of a slow and constant expansion of the device to its primary shape or the endothelialization (which takes approximately 6 months), or both.

The article related to adult patients underlined very good results of ASD closure also among 150 patients >60 years old and was most frequently cited [5]. Small children are another interesting group of patients. According to many textbooks, ASD should be closed at the age of 5–6 years. In 2018, we presented our experiences of successful ASD closure in 156 children aged <3 years old [6].

The issue of occurrence of arrhythmias and conduction abnormalities after ASD closure was discussed in the article published in 2008 [7]. Tachyarrhythmia was observed in 1.3% of patients up to 3 months after ASD closure (n = 9/738): 8 patients had atrial fibrillation and 1 supraventricular tachycardia. All were successfully treated with antiarrhythmic drugs or cardioversion. The endothelialization process was suspected to be the major reason of tachyarrhythmias. Moreover, a complete

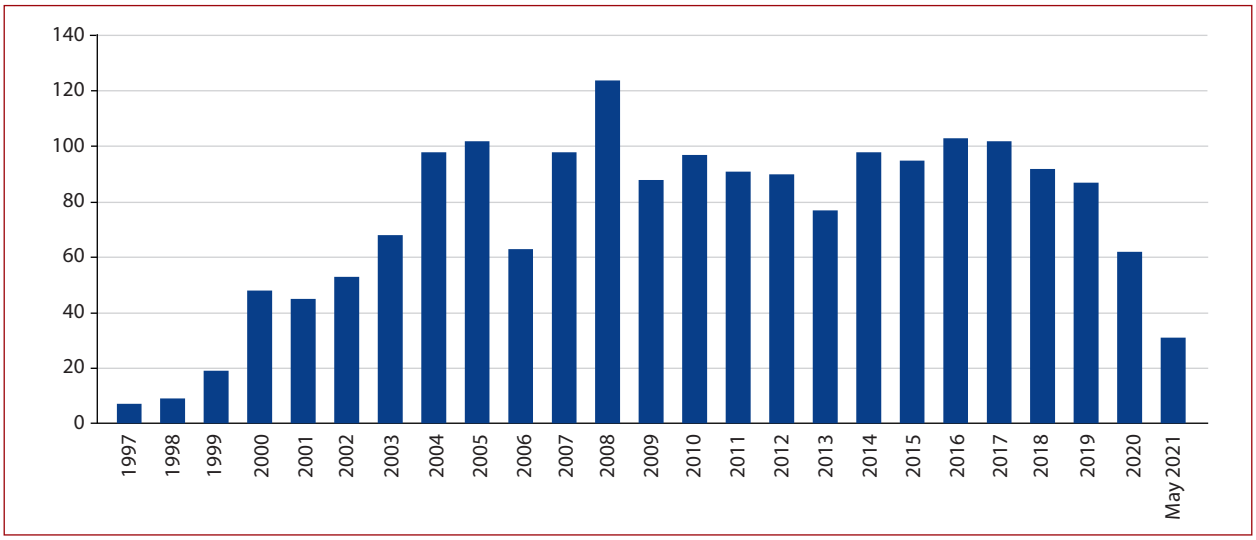


**Figure 1.** The number of procedures of transcatheter closure of atrial septal defect per year in Silesian Center for Heart Diseases in Zabrze (Poland) in the years 1997–2021

atrioventricular block occurred after 4.3 and 1.5 years, in two children with relatively small defects (at the age of 15 and 16, respectively), and both needed pacemaker implantation. This strongly underlines the necessity of constant follow-up of those patients. The delayed/incomplete process of endothelialization (or even absence of endothelialisation) is a rare finding after ASD closure with ASO, which was documented in our 20 years old patient with meningitis and infective endocarditis, which occurred two years after ASD closure [8].

### *Patent ductus arteriosus*

We have performed over 1000 procedures of PDA transcatheter closure from 1993 to 2021, with different devices — 558 with nitinol wire occluders [9]. Amplatzer Duct Occluder (ADO) type II Additional Sizes (ADOIIAS) originally was designed for small children. It should be highlited that it introduced in our team by Professor M. Szkutnik also in adult patients. ADOIIAS replaced coils to close small to medium PDAs in daily practice in our Clinic because of its high effectiveness and lack of complications [10]. Our three training trips to La Paz in Bolivia, which is situated at the level of 3600 meters above sea level, resulted in an interesting finding that PDAs at such high altitudes are considerably larger and that the ADOI is especially useful in those patients. The next step was to compare PDAs' characteristics between inhabitants of high-altitude cities (Mexico City, Guatemala City, La Paz, Bolivia) and low-altitude cities (Madrid, Spain; Zabrze, Poland). Patients from the last two cities had lower pulmonary artery pressures and smaller PDAs diameter vs. high-altitude inhabitants, which may have resulted from the higher partial pressure of oxygen [11]. This work was completed under the patronage of the Latin Pediatric Cardiology Society and carried out with this Society by the Interventional Cardiology Working Group (of which JB was the chairman in the years 2008–2012).

### *Postinfarction ventricular septal defect*

PIVSD closure is a challenging problem in both the percutaneous and surgical approach. In the publication from 2003, we highlighted the low success rate of transcatheter PVSD closure in the acute phase after infarct (up to 3 weeks) due to friability of necrotic tissues [12]. Moreover, we found the ASO especially useful in such defects as its short waist suits well in thin scar tissue. We are currently collecting the long-term follow-ups on 23 patient survivors of this intervention. The general recommendation is to close the PIVSD in the acute phase with a surgical approach (patients in the worst clinical condition), and with TT in both subacute and chronic phases. Likewise, PIVSDs after surgery and with recanalization (not so rare) are also suitable for device closure.

### *Vascular malformations*

In cooperation with colleagues from the National Institute of Cardiology in Mexico City, we described 5 patients with severe cyanosis, in whom we closed large pulmonary arteriovenous fistulas with the use of ADOI and with very good results [13].

In a 5-years-old child after Kawashima surgery (modified Fontan palliation) and with severe desaturation, we used the ASO to close a major intrahepatic venovenous malformation shunting to the atrium (over 2 cm in diameter). Both discs of the ASO device 'stented' the fistula and closed it completely [14]. Our experiences in percutaneous closure of ruptured sinuses of Valsalva aneurysm (RSVA) with various devices like ADOI and ASO were described in several papers reflecting various stages of our growing experience and longer patient observation. The last paper (published together with colleagues from the Amosov Institute in Kyiv, Ukraine) summarized results of RSVA closure in 23 patients, which is one of the largest reported cohorts [15]. We concluded that percutaneous closure of RSVA is (1) safe and effective, however, recanalizations are possible

(in a different location); (2) it is also suitable for a second percutaneous attempt.

## *Article information*

**Conflict of interest:** None declared.

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**How to cite:** Białkowski J, Szkutnik M. The use of Amplatzer devices in the percutaneous treatment of congenital heart defects in children and adults based on own experience. Kardiol Pol. 2021; 79(10): 1130–1132, doi: 10.33963/KP.a2021.0092.

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# Feasibility of the intravascular lithotripsy in coronary artery disease. Short-term outcomes of the Lower-Silesia Shockwave Registry

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Kardiol Pol. 2021; 79 (10): 1133–1135; DOI: 10.33963/KP.a2021.0093

**Received:** May 23, 2021

**Revision accepted:** August 20, 2021

**Published online:** August 20, 2021

## INTRODUCTION

The presence of calcified lesions has a substantial impact on percutaneous coronary intervention (PCI) outcomes. The severity of calcifications impairs stent crossing and correlates with a higher rate of periprocedural complications including vessel dissection or perforation, acute or chronic in-stent thrombosis as well as in-stent restenosis. A response to these unfavorable clinical events is aggressive plaque modification prior to coronary stent implantation.

Numerous strategies aiming at the appropriate preparation of calcified plaques have been implemented [1]. The two main techniques include the balloon-depended and the atherectomy devices. Even though they remain an essential part of contemporary practice, all of them have some limitations [2]. To overcome them, a new balloon-based coronary system for IVL — Shockwave C2 Intravascular Lithotripsy (S-IVL) (Shockwave Medical Inc, Santa Clara, CA, USA) has been introduced. It is a novel method of calcified plaque modification, which transforms electrical energy into mechanical one, leading to calcium nodules defragmentation. In this brief report, we present the short-term outcomes of the S-IVL registry — the Lower-Silesia Shockwave Registry (LSSR).

## METHODS

We retrospectively enrolled patients from the two cooperating Cardiac Departments in the Lower Silesia Region with a clinical indication for PCI, where due to a presence of "undilatable" lesion, advanced plaque modification methods were needed. Undilatable lesion was defined as a lesion after unsuccessful high-pressure inflation (20% diameter at least 18 atm) of a non-compliant (NC) balloon catheter (sized 1:1 to the reference vessel diameter balloon), with or without prior plaque preparation with smaller NC balloon or rotational atherectomy (RA).

There were no angiographic exclusion criteria regarding lesion anatomy, such as the length, tortuosity, severity, or prior stent placement. Angiography was used to determine the appropriate number of pulses and the size of the S-IVL catheter for optimal vessel preparation. Subsequent stent implantation and percutaneous coronary intervention optimization (including the use of intravascular imaging) were performed at the discretion of the operator.

The study had two primary endpoints: clinical success and safety outcomes. Clinical success was defined as an effective stent deployment or optimization of the previously implanted not fully expanded stent (with less than <20% in-stent residual stenosis) and the presence of Thrombolysis in Myocardial Infarction (TIMI) 3 flow at the end of the procedure.

Safety outcomes were defined as the absence of procedural complications (coronary perforation, slow- or no-reflow, new coronary thrombus, ventricular arrhythmias, vessel closure), and device failure (inability to cross the lesion, malfunction, or rapture). Also, major adverse cardiac and cerebrovascular events (MACCE) were recorded. MACCE was defined as acute coronary syndrome, cerebrovascular events, major bleeding, need for repeated re-

vascularization, or death. Clinical follow-up was obtained by telephone 30-day after the index procedure (additional 6- and 12-month follow-up is ongoing and will be reported when completed).

The study was based on retrospective registry data. No ethics committee approval nor patient consent was required.

### *Statistical analysis*

The data is presented as the mean with the standard deviation (SD) or the median with the interquartile range (IQR), dependent on the normality of distribution, assessed previously using the Shapiro-Wilk test, as appropriate. All calculations were made with the R language.

## RESULTS AND DISCUSSION

From May 2019 to January 2021, we enrolled 52 patients (54 treated lesions) — 35 males and 17 females with an average age of 71.2 (7.3) years with a high prevalence of cardiovascular risk factors and comorbidities (hypertension 90.3%, hypercholesterolemia 96.1%, diabetes mellitus 57.7%). Most S-IVL procedures were performed in acute coronary syndrome (ACS) settings (82.7%) — mainly at the time of the index PCI. Forty-one procedures were related to lesions that had not undergone prior coronary angioplasty, the remaining 13 concerned in-stent restenosis due to significant stent under-expansion. The majority (69.2%) of these cases were treated with additional prolonged inflation of the drug-eluting balloon (DEB) — the rest (4 out of 13 — 30.8%) required additional DES implantation due to the operator's decision. Table 1 provides the details on the clinical, procedural, and postprocedural characteristics.

The median SYNTAX score was 11 (7–24) points. In six cases, before S-IVL, a rotational atherectomy was performed as a part of lesion preparation. The average S-IVL balloon catheter size was 3.3 (0.4) and a median of 40 (30–80) sonic pulses was delivered. Hospital observation revealed three procedure-related complications. In the first case, the patient developed a ventricular arrhythmia during the procedure, which was interrupted by ALS and electrical defibrillation. The second case was related to the rupture of the S-IVL balloon after 30 pulses. In the third case, we observed failure of S-IVL therapy — residual stenosis of more than 50% — after 100 sonic pulses. This patient was qualified for coronary artery bypass grafting. One stroke was recognized during the index hospitalization. Two major bleedings in the postprocedural period were recorded. The first patient required transfusion of 6 units of packed red blood cells for gastrointestinal bleeding. The second patient required transfusion of 2 units of packed red blood cells due to vascular access complications. No other MACCE were recorded for 30 days after hospital discharge.

Artery calcification remains one of the greatest challenges in the management of coronary artery disease. Armamentarium for optimal lesion preparation includes the pre-dilation with NC or ultrahigh-pressure balloons, utilization of scoring or cutting balloons, and RA devices. Success rates using these strategies are high and reach over 90.0% [3, 4]. Nevertheless, some limitations are still observed. In the presence of eccentric calcium, the dilation force of the balloon is limited and may be redirected to less resistant, noncalcified parts of the vessel. Rotational devices perform atheroablation by sanding/abrasion, resulting in pulverization of the superficial plaque. However, the deep calcifications may remain untouched [5]. S-IVL could respond to the aforementioned superficial mech-

**Table 1.** Clinical, procedural, and postprocedural characteristics of the study population

| | Overall (n = 52) |
|---|---|
| Age, mean (SD) | 71.2 (7.3) |
| Male, n (%) | 35 (67.3) |
| Diagnosis | |
| Stable angina, n (%) | 9 (17.3) |
| Unstable angina, n (%) | 2 (3.8) |
| NSTEMI, n (%) | 38 (73.0) |
| STEMI, n (%) | 3 (5.9) |
| Hypercholesterolemia, n (%) | 50 (96.1) |
| Diabetes, n (%) | 29 (55.7) |
| Hypertension, n (%) | 47 (90.3) |
| Kidney failure, n (%) | 10 (19.2) |
| Post PCI status, n (%) | 35 (67.3) |
| Primary diagnosis MI, n (%) | 28 (53.8) |
| Syntax score, median (IQR) | 11 (7–24) |
| LVEF, %, mean (SD) | 52.3 (13.8) |
| Treated vessel | 10 (19.2) |
| LM, n (%) | 18 (34.6) |
| LAD, n (%) | 6 (11.6) |
| Cx, n (%) RCA, n (%) | 18 (34.6) |
| Primary lesion, n (%) | 41 (78.8) |
| Stent underexpansion, n (%) | 13 (25) |
| CTO lesions, n (%) | 5 (9.6) |
| Primary rotablation, n (%) | 6 (11.5) |
| Previously predilatation, n (%) | 43 (82.6) |
| Predilatation pressure, atm, mean (SD) | 19.8 (4.2) |
| Initial diameter stenosis, %, mean (SD) | 83.3 (9.7) |
| Final diameter stenosis, %, median (IQR) | 5 (0–14) |
| IVL diameter, mm, mean (SD) | 3.3 (0.4) |
| Number of pulses, median (IQR) | 40 (30–80) |
| Postdilatation, n (%) | 49 (94.2) |
| Postdilatation pressure, atm, mean (SD) | 18.5 (5.0) |
| Number of DES per procedure, mean (SD) | 1.4 (0.3) |
| Total DES length per procedure, median (IQR) | 38 (26–71) |
| Number of DEB inflation, n (%) | 9 (17.3) |
| OCT/IVUS guided PCI, n (%) | 11 (21.2) |
| Clinical success, n (%) | 51 (98.1) |
| Radial access, n (%) | 48 (88.8) |
| Femoral access, n (%) | 6 (12.2) |
| 6F guide catheter, n (%) | 32 (59.2) |
| 7F guide catheter, n (%) | 22 (40.8) |
| Radiation doses, mGy, median (IQR) | 1334 (699–2105) |
| Contrast amount, ml, median (IQR) | 180 (135–230) |
| In-hospital MACCE, n (%) | 3 (5.7) |
| 30-days after procedure MACCE, n (%) | 3 (5.7) |

Abbreviations: CTO, chronic total occlusion; Cx, circumflex artery; DEB, drug eluting balloon; DES, drug eluting stent; IVL, intravascular lithotripsy; IVUS, intravascular ultrasound; MACCE, major adverse cardiac and cerebrovascular events; LAD, left anterior descending; LM, left main; LVEF, left ventricular ejection fraction; NSTEMI, no ST-elevation myocardial infraction; OCT, optical coherence tomography; RCA, right coronary artery; STEMI, ST-elevation myocardial infraction

anisms of plaque modification. It generates sonic pulses that propagate through the lesion and selectively interact even with profound calcified plaques. The efficiency and safety of S-IVL were initially confirmed in a Disrupt II study [6]. Although preliminary data are encouraging [7, 8], convincing clinical evidence from randomized trials is missing.

We obtained a higher clinical success rate, in comparison to the previously described (98.1% vs. 84.6%–95.0%) [7, 8]. This finding might be related to the simultaneous use of RA and S-IVL (6 cases) in the most challenging lesions. Rota-lithotripsy is a novel bail-out strategy used for resistant lesions. Only a few case reports [9–11] regarding this method are available. A high rate of clinical success was maintained despite the relatively high prevalence of patients with under-expansion of previously implanted stents in our registry (25.0% vs. 21.7%) [7]. A clinical success rate in these non-option patients is overall lower (64.7% vs. 87.1%) [7, 8, 12]. The severity of coronary artery disease (median of SYNTAX score, 11) with coexisting complexity of PCI procedures (5 CTO, 6 Rota-lithotripsies) included in the LSSR led to the relatively high average use of contrast volume (median of 180 ml) and radiation dose (median of 1334 mGy**)**. These findings are partially consistent with previously reported data [7, 8, 12]

Preliminary safety outcomes are also encouraging. We observed one balloon ruptured during treatment without any sequelae, as well as one episode of ventricular arrhythmias probably connected to ongoing ischemia induced by ACS (high-risk patient with NSTEMI and multivessel disease-accumulated SYNTAX score, 33.5). However, in view of the reports suggesting that S-IVL can induce ventricular arrhythmias [13], future studies are necessary. Probably due to the high prevalence of trans-radial access (88.8%) with accompanying predominance of 6F guiding catheter (59.2%), we observed only one access-related bleeding in this high-risk group. These data might suggest that wider use of S-IVL may reduce the number of complex PCI performed with femoral access and decrease the rate of access points complications [14].

Retrospectively the data collected from the LSSR suggest intravascular lithotripsy is relatively safe and effective as a method of modifying calcified plaque in short-term observation, especially when performed via radial access. Moreover, subsequent studies are needed to evaluate the long-term results.

## *Article information*

**Conflict of interest:** None declared.

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**How to cite:** Rola P, Włodarczak A, Kulczycki JJ, et al. Feasibility of the intravascular lithotripsy in coronary artery disease. Short-term outcomes of the Lower-Silesia Shockwave Registry. Kardiol Pol. 2021; 79(10): 1133–1135, doi: 10.33963/KP.a2021.0093.

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# The impact of the COVID-19 pandemic on the echocardiographic services and training in Poland

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Kardiol Pol. 2021; 79 (10): 1136–1139; DOI: 10.33963/KP.a2021.0102

**Received:** August 4, 2021

**Revision accepted:** September 1, 2021

**Published online:** September 1, 2021

## INTRODUCTION

COVID-19 pandemic has dramatically influenced the healthcare systems around the world, including cardiology services. When infections rates were peaking, a significant part of available resources was repurposed towards fighting the pandemic. Moreover, in 2020 cardiology practitioners were advised by numerous guidelines and official recommendations to defer scheduled elective procedures, especially those associated with an increased risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission, such as transesophageal echocardiography (TEE) [1]. On top of that, patients' fear of infection and the desire not to overburden the healthcare systems kept them from seeking medical care in case of symptoms unrelated to COVID [1].

Therefore, it comes as no surprise, that data published so far indicates a significant and abrupt reduction in cardiac care services in numerous countries and regions. It has been reported that the cumulative number of hospitalizations for acute and chronic cardiovascular conditions, as well as the number of outpatient cardiovascular visits, had substantially de-

creased [1, 2]. The latter was only partly compensated using telemedicine. There has also been a significant drop in the number of various inpatient and outpatient cardiac procedures and examinations, including echocardiography [1, 2].

Importantly, the COVID-19 pandemic has affected medical education, not only for undergraduates but also for residents and post-graduate trainees [1]. The reduction in the number of cases and supervised procedures, as well as canceled educational activities, a shift of educational curricula towards online didactics, postponed examinations and altered rotations have already been documented in some specializations [2, 3].

However, details of the pandemic's impact on echocardiographic laboratories are still unclear. Furthermore, there is no data on the current state of post-graduate hands-on training in echocardiography. In order to shed more light on this issue and to identify the most important implications and possible obstacles for restoring the pre-pandemic activity of echocardiographic services and training, the Working Group on Echocardiography of the Polish Cardiac Society performed a national survey to evaluate echocardiographic practices and postgraduate training in echocardiography in Poland during the pandemic.

## METHODS

This retrospective survey was based on questionnaires filled out by 23 participating Polish echocardiographic centers. We attempted to include a large number of laboratories to cover all regions of the country in order to account for practice variations related to differences in infection rates and local regulations regarding healthcare. To encourage participation, we reached out via e-mails and phone calls to experts working in echocardiographic laboratories with active post-graduate education programs identified in the database of the Working Group on Echocardiography of the Polish Cardiac Society. Each center was asked to fill out a questionnaire regarding their practices in the 9-month period representative of the pre-pandemic activity (April–December 2019) and in the 9-month pandemic period (April–December 2020). Importantly, because during the pandemic there were phases with various infection rates and different degrees of the potential impact on the echocardiographic practices, we concentrated not only on the average monthly test volume but also on the minimal monthly test volume in the analyzed periods.

### Statistical analysis

Continuous variables were initially tested for normality of data distribution by the Kolmogorov-Smirnow test. Normally distributed variables are expressed as mean (standard deviation [SD]). Non-normally distributed variables are presented as median (interquartile range [IQR]). Categorical variables are presented as percentages (%). Paired samples t-test was used to compare the examination of volume between the pre-pandemic and the pandemic periods for data with normal distribution whereas, for non-normally distributed data, the Wilcoxon test was used (MedCalc Software, Frank Schoonjans, Belgium). The differences in the examination volume were considered statistically significant at $P < 0.05$.

## RESULTS AND DISCUSSION

The mean and minimal monthly test volumes in the participating centers in the pre-pandemic and pandemic period are presented in Table 1. During the pandemic, 9 centers (39.1%) were partially transformed into COVID-19 facilities, whereas 3 others (13.0%) were transformed into centers only for COVID-19 patients. Transthoracic echocardiography (TTE) and TEE were performed in patients with COVID-19 in 18 (78.2%) and 9 (39.1%) centers, respectively (the median/mean of cumulative numbers of tests were 21 (20–100) and 5 (6), respectively). Stress echocardiography was not performed in patients with COVID-19.

Three labs (13.0%) underwent temporary suspension of all their activities due to either quarantine or diagnosis of COVID-19 in all staff members. Three sites (13.0%) suspended temporarily only their out-patients services due to local regulations. In 21 (91.3%) centers at least one staff member (on average 3 [2]) was quarantined, whereas in 18 (78.2%) labs there were confirmed cases of COVID-19 among the personnel (on average 2 [1]). Seven (30.4%) sites reported temporary shortages of personal protective equipment, which on average lasted 70 (83) days.

A negative COVID-19 test was required before TTE, TEE, and stress echocardiography in 9 (39.1%), 17 (73.9%), and 10 (43.5%) centers, respectively. Body temperature check was performed before TTE, TEE, and stress echocardiography in 18 (78.3%), 17 (73.9%), and 14 (60.9%) labs, respectively.

The indications for TTE, TEE, and stress echocardiography were limited in 6 (26.1%), 12 (52.1%), and 10 (43.5%) sites, respectively. Additional disinfection procedures visibly reduced temporal availability of resources in 12 (52.2%) labs by 21 (11)% on average. The examination protocols for TTE, TEE, and stress echocardiography were shortened in 5 (21.7%), 5 (21.7%), and 1 (4.3%) centers, respectively.

The scheduled examinations were delayed or canceled in 12 (52.2%) and 6 (26.1%) labs, respectively. Similarly, waiting times for elective procedures following echocardiography — cardiac surgery, percutaneous coronary intervention, structural transcatheter procedure, and electrotherapy — were prolonged in 15 (65.2%), 12 (52.2%), 13 (56.5%), and 12 (52.2%) centers, respectively. Furthermore, there was no possibility of scheduling elective cardiac surgeries, percutaneous coronary interventions, structural transcatheter procedures, or electrotherapy after echocardiographic examination in 3 (13.0%), 1 (4.3%), 2 (8.7%), and 1 (4.3%) sites, respectively.

Importantly, the pandemic significantly affected post-graduate hands-on training in echocardiography. The overwhelming majority (90.9%) of centers, which had been actively teaching before the pandemic, reported that

**Table 1.** Monthly examination volume in the pre-pandemic period (April–December 2019) and during the COVID-19 pandemic (April–December 2020) in the Polish echocardiographic laboratories

| | Pre-pandemic period, mean (SD) or median (IQR) | Pandemic period, mean (SD) or median (IQR) | Mean relative change in test volume (%) | *P*-value |
|---|---|---|---|---|
| **In-patient services** | | | | |
| Mean monthly test volume | | | | |
| TTE | 389 (261) | 273 (226) | –29.9 | <0.001 |
| TEE | 37 (30) | 21 (18) | –45.9 | 0.004 |
| TPM | 8 (6) | 5 (5) | –37.5 | 0.0497 |
| Stress tests | 8 (7) | 3 (4) | –62.5 | <0.001 |
| Minimal monthly test volume | | | | |
| TTE | 298 (202) | 159 (147) | –46.4 | <0.001 |
| TEE | 27 (23) | 9 (12) | –64.3 | <0.001 |
| TPM | 1 (0–5) | 0 (0–1) | | 0.008 |
| Stress tests | 4 (6) | 1 (1) | –75.0 | 0.02 |
| **Out-patient services** | | | | |
| Mean monthly test volume | | | | |
| TTE | 147 (127) | 100 (91) | –32.0 | 0.009 |
| TEE | 12 (12) | 4 (5) | –66.7 | 0.012 |
| Stress tests | 7 (5) | 3 (3) | –57.1 | 0.04 |
| Minimal monthly test volume | | | | |
| TTE | 61 (27–200) | 2 (0–15) | | <0.001 |
| TEE | 3 (2–8) | 0 (0–0)[a] | | 0.004 |
| Stress tests | 1 (0–5) | 0 (0–0)[a] | | 0.03 |

[a]Only 2 centers maintained minimal monthly test volume higher than 0 throughout the pandemic period

Abbreviations: IQR, interquartile range; SD, standard deviation; TEE, transesophageal echocardiography; TPM, transcatheter procedure monitoring; TTE, transthoracic echocardiography

they had either no or fewer trainees involved in activities (13 [59.1%] and 7 [31.8%] sites, respectively). At the same time, practical workshops, which had been regularly organized or accredited by the Working Group on Echocardiography of the Polish Cardiac Society before the pandemic, were either canceled or reformatted into online webinars and lecture-based courses.

To summarize, this survey documents a dramatic reduction of echocardiographic services, especially TEE and stress echocardiography, and confirms the need to urgently restore the full capacity of echocardiographic laboratories, as recommended in our recent Expert Opinion [2]. Furthermore, our data demonstrate a long pause in hands-on post-graduate training in echocardiography, which may adversely influence the quality of cardiology services for many years to come. To avoid such detrimental effects, we recommend a prompt reactivation of full-scale post-graduate hands-on training programs in the teaching centers, as soon as pandemic-related restrictions allow. Obviously, the level of personal protection of all trainees should be identical to the protection provided for the staff members (see the aforementioned recent Expert Opinion for details). Moreover, echo laboratories and other medical services should be prepared to maintain their activities despite the possible future pandemic waves.

## *Article information*

**Conflict of interest:** None declared.

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**How to cite:** Lipiec P, Gackowski A, Kasprzak JD, et al. The impact of the COVID-19 pandemic on the echocardiographic services and training in Poland. Kardiol Pol. 2021; 79(10): 1136–1139, doi: 10.33963/KP.a2021.0102.

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# The effect of 1-year mean step count on the change in the atherosclerotic cardiovascular disease risk calculation in patients with high cardiovascular risk: a sub-study of the LIGHT randomized clinical trial

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Kardiol Pol. 2021;
79 (10): 1140–1142;
DOI: 10.33963/KP.a2021.0108

**Received:**
August 5, 2021

**Revision accepted:**
September 5, 2021

**Published online:**
September 6, 2021

## INTRODUCTION

Increased physical activity has been one of the main recommendations for both the primary and secondary prevention of cardiovascular diseases [1]. Consistent physical activity has already proven its protective and therapeutic value in numerous conditions, such as metabolic syndrome and cardiovascular diseases [2, 3]. Despite the well-defined beneficial effects, physical activity is still not performed at the desired level, especially for the primary prevention of the disease in patients with multiple cardiovascular risk factors. Smartphone applications offer an up-and-coming infrastructure to potentiate suggestions regarding physical activity, especially about a daily step count [4].

The atherosclerotic cardiovascular disease (ASCVD) risk score has been widely approved for patient follow-up and to guide primary prevention strategies [1]. It is invaluable in decreasing or maintaining a steady state in these risk estimator scores. However, there are no daily-step-count recommendations particularly in patients at high cardiovascular risk. Thus, we aim to assess the effect of the 1-year mean step count (MSC) on the 1-year change in ASCVD risk scores in patients at high risk of cardiovascular disease.

## METHODS

Our study was a sub-study of the lifestyle intervention using mobile technology in patients with high cardiovascular risk: a pragmatic randomized clinical (LIGHT) trial conducted in a tertiary hospital between February 2018 and March 2020 [5] (NCT03397849). All patients were randomized into usual care or usual care plus the lifestyle intervention using mobile technology. The randomization and patient enrolment were described previously [6]. The study population comprised 242 patients allocated into usual care plus intervention in the LIGHT trial. All patients were given information about a mobile application specially designed for that study, which included sections for step counts, weight, blood pressure, and diet. Wristbands (Xiaomi Mi Band 2; Beijing Xiaomi Technology Co., Beijing, China) were used to record the patients' daily step counts. The daily data were monitored from the main study server and defined automatic messages were delivered according to the study design [6]. Patients were followed up for 12 months after randomization. Demographic characteristics associated with clinical data and ASCVD risk scores were recorded prospectively at baseline and the 1-year follow-up. A change in ASCVD risk score (ΔASCVD) between randomization

and the final stage was also determined. The study population was divided into two groups according to their ΔASCVD risk scores as follows: Group 1, the patients with a decrease in the ASCVD risk score at 1-year; Group 2, the patients with an increase in the ASCVD risk score at 1-year (Supplementary material, *Table S1*). The relationship between the mean daily step count at 1-year and the ASCVD risk score was comprehensively analyzed. The 1-year mean daily step count was calculated by dividing the total number of steps recorded by the number of data entry days. The investigation was approved by the local ethics committee.

### *Statistical analysis*

Data were presented as mean (standard deviation [SD]) for normally distributed data and as median (interquartile range [IQR]) for continuous variables that were not normally distributed. Categorical data were presented as number (%). The Mann-Whitney U test was applied for comparisons of the data that were not normally distributed. Categorical data were analyzed with Pearson's chi-square test. Univariable and multivariable logistic regression analyses were performed to determine independent predictors of a decrease in the ASCVD risk score. Variables that could be predictors of a decrease in the ASCVD risk score were entered into the univariable analysis. Variables with a *P*-value <0.1 in univariable regression were incorporated into the multiple logistic regression analysis. The results of the regression analysis were shown as odds ratios with 95% confidence intervals. Cut-off values of the MSC at 1 year to predict a decrease in ASCVD risk scores with the highest sensitivity and specificity were calculated by nonparametric receiver operating characteristics (ROC) curve analysis. To introduce the association between MSC at 1-year and ΔASCVD, a correlation analysis was performed using the Spearman test. P values of <0.05 were considered significant. Data were analyzed with the Statistical Package for Social Sciences software, version 22.0 (SPSS; IBM, Armonk, NY, USA).

## RESULTS AND DISCUSSION

A total of 242 patients were enrolled (mean age 58.3 [7.1] years; 51.2% male) in the study population and evaluated according to the changes in their ASCVD risk scores for 1 year after enrolment. Data input frequency was 75% for the least compliant patient, and data entry compliance was similar between the patients with and without a decrease in ASCVD risk scores at 1 year ($P = 0.595$).

The univariable analysis revealed age, systolic and diastolic blood pressure, hypertension, diabetes mellitus, left atrial volume index, HDL-cholesterol, HbA1c, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), and MSC over 1 year as predictors of a decrease in the ASCVD risk score at 1 year. In the multivariable analysis, age (odds ratio [OR], 0.908; CI, 0.849–0.971; $P = 0.005$), diabetes mellitus (OR, 0.200; CI, 0.076–0.527; $P = 0.001$), use of ACE inhibitors or ARBs (OR, 3.422; CI, 1.320–8.870; $P = 0.011$), and MSC over 1 year (OR, 1.103; CI, 1.071–1.136; $P < 0.001$) were determined to be independent factors that predict a decrease in the ASCVD risk score.

The Spearman rank correlation proved that 1-year MSC is correlated with the ΔASCVD risk score. (Rho: –0.523; $P < 0.001$) (Figure 1A). ROC analysis showed that the best cut-off value of the 1-year MSC to predict a decrease in ΔASCVD was 7250 with 81% sensitivity and 82% specificity (area under the curve: 0.88; 95% CI, 0.84–0.93; $P < 0.001$) (Figure 1B).

Our investigation demonstrated that daily step count may play an important role in the management of a cardiovascular disease. In addition, age, diabetes mellitus, and the use of ACE inhibitors or ARBs as baseline medications were determined to be independent predictors of a decrease in the ASCVD risk score at the 1-year follow-up. The correlation between 1-year MSC and the ΔASCVD risk score also emphasized the significance of daily step count in the primary prevention strategies for patients at high cardiovascular risk.

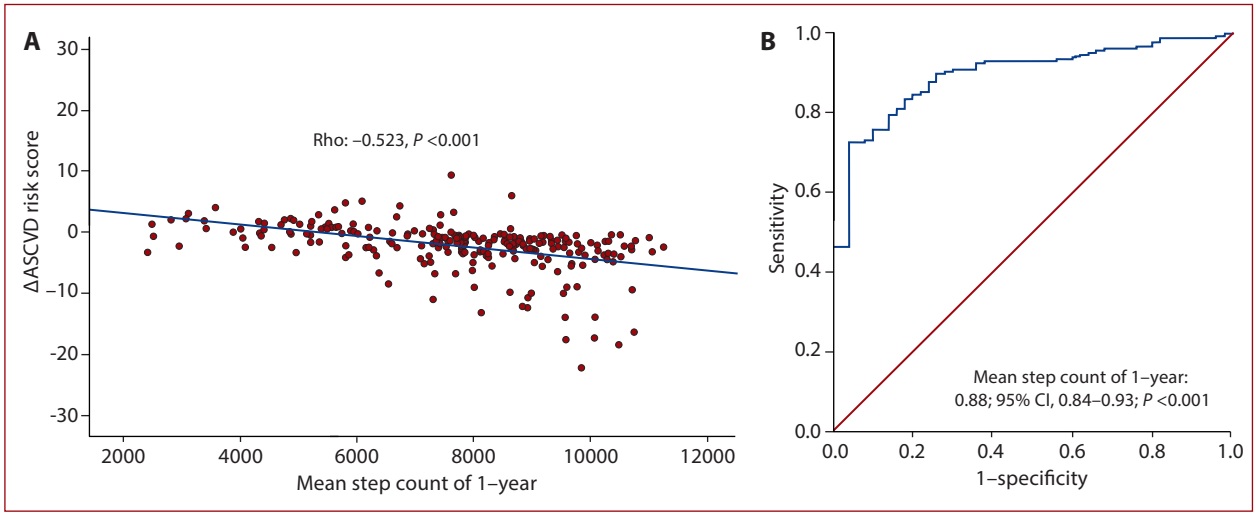


**Figure 1. A.** The correlation between 1-year mean daily step count and ΔASCVD and ΔSCORE risk calculations is presented with a scatter-dot analyses. **B.** ROC analysis showing the best cut-off value of the 1-year mean step count to predict a decrease in ΔASCVD and ΔSCORE

Mobile health applications have already demonstrated their instrumentality and practicality in the screening of atrial fibrillation and hypertension [7, 8]. Our results may have an indispensable value for setting targets for patients considering daily step counts to decrease their long-term cardiovascular risk. Several daily step count targets have been recommended for promoting healthy lifestyles in patients without cardiovascular diseases [9], and completing 10 000 steps per day has been shown to be a rational objective for healthy people [10]. However, there is a lack of evidence for determining a cut-off value for decreasing well-accepted risk scores such as ASCVD. This should be emphasized as one of the most important strengths of our investigation. However, the quality and target of the therapy in patients with hypertension and diabetes may have an important role in risk reduction for patients with high cardiovascular risk similar to our study population [11]. Thus, a novel strategy based on the COMPASS trial could be used to properly evaluate both the effect of the medications and MSC on the change in the cardiovascular risk [12].

Our investigation has several limitations secondary to the study design and implementation OF WHAT AUTHORS UNCLEAR. First, the patients were recruited and followed up in a single center. Second, the data entry was not 100%, but the compliance was provided with the aid of automatic messages and individualized phone calls inviting the patients for an outpatient visit. 83% data input frequency was accomplished using the methods in the study design; however, it may not represent correctly the 1-year follow-up due to missing data. Third, the study was implemented with individually provided data; however, if the data had not been compatible, they were verified through invitations to outpatient visits. Fourth, the association between MSC and the change in the 1-year ASCVD risk score does not prove causality.

## *Supplementary material*

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

## *Article information*

**Conflict of interest:** None declared.

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**How to cite:** Hayıroğlu MI, Çınar T, Çinier G, et al. The effect of 1-year mean step count on the change in the ASCVD risk calculation in patients with high cardiovascular risk: a sub-study of the LIGHT randomized clinical trial. Kardiol Pol. 2021; 79(10): 1140–1142, doi: 10.33963/KP.a2021.0108.

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# Young women with acute myocardial infarction. Where to look for the causes?

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Kardiol Pol. 2021; 79 (10): 1143–1144; DOI: 10.33963/KP.a2021.0061

**Received:** June 22, 2021

**Revision accepted:** July 13, 2021

**Published online:** July 14, 2021

In recent decades, the incidence of myocardial infarction (MI) has significantly declined in the general population [1]. However, MI rates in young people, especially women, have not decreased as much as among older adults. On the contrary, based on some studies, the incidence of MI in young people has increased over the past few years [2]. The underlying reason is probably an underestimation of cardiovascular risk and the resulting lack of treatment for young people [3]. Nevertheless, as the current case shows, an acute MI can also occur in young people without typical cardiovascular risk factors. Moreover, in the current pandemic, a COVID-19 infection should be additionally considered as a possible risk factor for an acute MI.

A 27-year-old woman with neither cardiovascular risk factors nor a history of coronary artery disease (CAD) was admitted to the local hospital with an ST-segment elevation myocardial infarction (STEMI) of an anterior wall. Importantly, RT-PCR (real-time polymerase chain reaction) tests for COVID-19 were negative, and she did not present any symptoms of SARS-CoV-2 infection earlier. Coronary angiography revealed a total occlusion of the left descending artery (LAD) in the middle segment (Figure 1A), requiring in an immediate primary percutaneous coronary intervention. Despite numerous attempts, it was not feasible to pass the guidewire distally through the lesion and restore the arterial flow. The patient was treated with heparin and a glycoprotein (GP) IIb/IIIa inhibitor in a bolus, followed by an intravenous infusion, and was transferred to the intensive cardiology care unit. A control coronary angiography performed two days later showed persistent LAD occlusion (Figure 1B). The second percutaneous coronary intervention attempt was also unsuccessful.

Within a few months, the patient was admitted to our hospital for another attempt of the LAD recanalization. On admission, she presented the Canadian Cardiovascular Society class III symptoms. Cardiac magnetic resonance confirmed post-infarction transmural scar of the interventricular septum and apex area with segmental impairments in contractility and preserved global ejection fraction

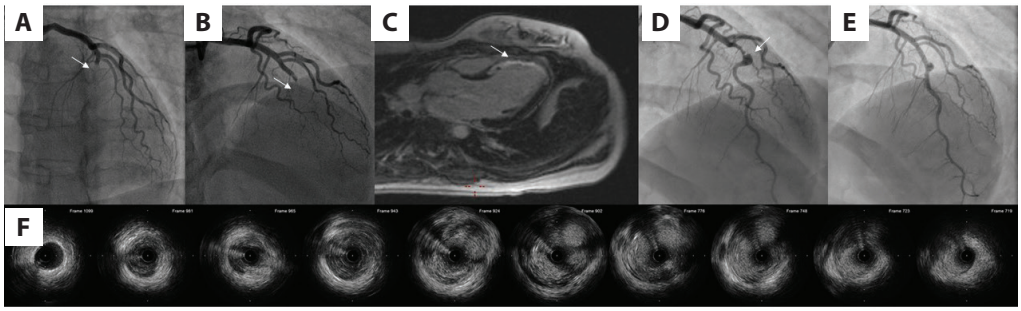


**Figure 1. A.** Anteroposterior cranial view of LCA. Acute occlusion of LAD artery (arrow). **B.** RAO view of LAD after 2 days with persistent LAD occlusion (arrow). **C.** Cardiovascular magnetic resonance, 4-chamber view. Late gadolinium enhancement of the interventricular septum and apex area (arrow). **D.** RAO view of LAD after 4 months with patent severe stenosed LAD and aneurysm in the middle segment (arrow). **E.** IVUS imaging of middle segment of LAD. **F.** RAO view of LAD after percutaneous coronary intervention with stent implantation in the middle segment

Abbreviations: IVUS, intravascular ultrasound; LAD, left anterior descending; LCA, left coronary artery; RAO, right anterior oblique

(59%) (Figure 1C). Coronary angiography demonstrated recanalized LAD with severe stenosis and a saccular aneurysm distal to the target lesion (Figure 1D). The size of the aneurysm was evaluated as 7.8 mm × 8.7 mm on quantitative coronary angiography. In the arterial segments, both proximally and distally to the lesion, intravascular ultrasound (IVUS)showed a normal vessel wall free of atherosclerotic lesions (Figure 1E). Furthermore, an intima dissection was confirmed, significantly narrowing the vessel lumen. Only after pre-dilatation of the lesion with a noncompliant (NC) balloon, was the drug-eluting stent (XIENCE PRO 2.5 × 23 mm, Abbott Vascular, Chicago, IL, US) successfully implanted across the diagonal branch. The procedure was finalized with Proximal Optimalisation Technique using a 3.0 mm NC balloon (Figure 1F). IVUS confirmed optimal stent apposition as well as residual flow in the saccular aneurysm.

In conclusion, the most probable cause of our patient's condition is a coronary aneurysm, as it poses a risk of MI, arrhythmias, or even sudden cardiac death. The causative factors behind coronary aneurysms include atherosclerosis, inflammatory diseases, congenital or iatrogenic arteries defects, connective tissue disorders, or drug-induced side effects [4].

## *Article information*

**Conflict of interest:** None declared.

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**How to cite:** Iwańczyk S, Klotzka A, Woźniak P, et al. Young women with acute myocardial infarction. Where to look for the causes? Kardiol Pol. 2021; 79(10): 1143–1144, doi: 10.33963/KP.a2021.0061.

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# Impella protected percutaneous coronary intervention on the last remaining highly calcified coronary artery facilitated by shockwave intravascular lithotripsy and levosimendan infusion

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Kardiol Pol. 2021; 79 (10): 1145–1146; DOI: 10.33963/KP.a2021.0062

**Received:** June 14, 2021

**Revision accepted:** July 13, 2021

**Published online:** July 14, 2021

A 67-year-old male, with hyperlipidemia, hypertension, type 2 diabetes mellitus, and persistent atrial fibrillation was admitted to the Department of Cardiology with a non-ST segment elevation myocardial infarction. Physical examination revealed tachycardia, dyspnea with rales and crackles on auscultation (Killip-Kimball II). Transthoracic echocardiography showed the enlarged hypokinetic left ventricular with coexisting akinesia of the inferior wall (left ventricular end-diastolic/left ventricular end-systolic diameters of 59 mm/53 mm), reduced left ventricular ejection fraction (25%), severe functional mitral regurgitation, and a moderate amount of fluid in both pleural cavities.

After initial pharmacological stabilization, coronary angiogram was performed and revealed a chronic total occlusion of the right coronary artery (Figure 1A) and circumflex, with coexisting significant highly calcified stenosis of the left main artery (LM) and multilevel high-grade stenosis of the left anterior descending artery (LAD) (Figure 1B). The patient was referred to the local Heart Team and due to high risk (SYNTAX Score = 49.5 points; EuroSCORE II = 9%) and subtotal occlusion of the distal part of the LAD, he was unsuitable for surgery and a rescue percutaneous coronary intervention (PCI) was proposed.

In order to optimize the treatment of heart failure before PCI, we performed a puncture of both pleural cavities and beyond standard pharmacotherapy (beta-blocker, intravenous loop diuretic, angiotensin-converting-enzyme inhibitors, mineralocorticoid receptor antagonist) we administrated 24-hour intravenous infusion of levosimendan (0.1 μg/kg/min — cumulative dose 12.5 mg). Two days later, we performed PCI by the right radial approach using the EBU 3.5 Guide Catheter (7F) (Medtronic Ireland, Galway, Ireland) with additional Impella CP (Abiomed, Denver, CO, USA) support (flow 3.3 l/min), implemented by the right femoral access. After wiring the LAD with Fielder XT (Asahi-INTECC Co., Aichi, Japan) enhanced by Caravel microcatheter (Asahi-INTECC) and subsequent exchange of a guidewire on Sion blue ES (Asahi-INTECC), we performed multiple high pressure (up to 22 atm) inflation of the semi-compliant 1.5 × 20 mm and non-compliant (NC) 2.5 × 20 mm and 3.0 × 20 mm balloon catheter. Three overlapping drug-eluting stents (DES) Resolute Onyx (Medtronic) were implanted from the middle to distal the part of the LAD — 2.5 × 30 mm (18 atm); 2.25 × 38 mm (16 atm); 2.0 × 26 mm (14 atm). In the next step, we performed pre-dilation of the LM and proximal part of the LAD. However, despite using high-pressure inflation (24 atm), we observed a significant "dogbone effect" on the 3.0 mm NC-catheter (Figure 1C).

Hence, we performed the shockwave intravascular lithotripsy (S-IVL) using a 3.0 × 12 mm catheter (Shockwave Medical Inc, Santa Clara, CA, USA), and after 80 ultrasonic pulses, we achieved full expansion (Figure 1D). From the proximal part of the LM, we implanted two additional overlapping DES (3.5 × 18 mm and

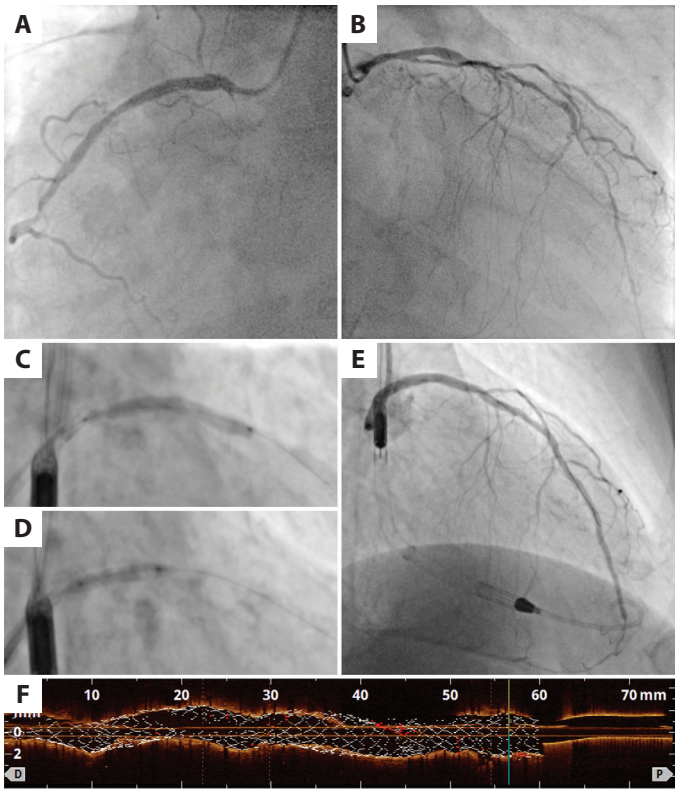


**Figure 1. A.** Coronary angiography of the right coronary artery. **B.** Coronary angiography of the left main and the left anterior descending. **C.** Significant under-expansion on the 3.0 mm non-complaint balloon catheter. **D.** Full expansion of Shockwave Intravascular Lithotripsy 3.0 × 12 mm balloon catheter. **E.** Final angiographic result of the procedure. **F.** Final result confirmed in optical coherence tomography.

3.0 × 38 mm). Finally, a proximal optimization technique was performed with NC 4.0 × 15 mm (20 atm). The reasonable angiographic result (Figure 1E) was confirmed by the optical coherence tomography imaging (Figure 1F). The support pump was removed immediately after the procedure-vascular access point was closed with 2 co-acting AngioSeal 8F (Terumo Corporation, Tokyo, Japan) vascular closure devices. The patient was discharged after 13 days of hospitalization with a mild improvement of the LV function (ejection fraction of 35%) and with reduced (moderate) mitral regurgitation.

PCI to the last remaining patent vessel is a high-risk procedure, as evidenced by the fact that about a quarter of patients die at 1-year follow-up [1]. In the therapy of a patient with such a poor clinical prognosis, any available armamentarium that may improve the prognosis should be involved in the therapeutic process. In this challenging case, we used a wide range of factors potentially affecting the outcome — an intravenous infusion of levosimendan [2], mechanical circulatory support with Impella [3], and plaque modification with S-IVL [4, 5] in order to obtain a favorable clinical outcome. Initial intensive heart-failure pharmacotherapy allowed to restrict hemodynamic support to the periprocedural period. If adequate optimization could not be achieved earlier, maintaining Impella CP assistance might be a valuable support to conventional HF therapy; yet bleeding or access-related complications may affect potential benefits.

## *Article information*

**Conflict of interest:** None declared.

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**How to cite:** Rola P, Włodarczak A, Jastrzębski A, et al. Impella protected percutaneous coronary intervention of last remain highly calcified coronary artery facilitated by Shockwave Intravascular Lithotripsy and levosimendan infusion. Kardiol Pol. 2021; 79(10): 1145–1146, doi: 10.33963/KP.a2021.0062.

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# Isolated papillary muscle hypertrophy in a professional soccer player: the end of an athlete's career?

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Kardiol Pol. 2021; 79 (10): 1147–1148; DOI: 10.33963/KP.a2021.0063

**Received:** May 25, 2021

**Revision accepted:** July 13, 2021

**Published online:** July 14, 2021

A 21-year-old male, a totally asymptomatic professional football player, was referred for a routine cardiovascular check-up. He had no relevant medical history and a positive family history of cardiac, renal, neurologic, or genetic diseases. Physical examination was unremarkable.

His electrocardiogram showed left ventricular hypertrophy, non-pathological Q waves, and asymmetric inverted T-waves in the inferior and lateral leads. Transthoracic echocardiography (TTE) showed concentric hypertrophy, left ventricular ejection fraction of 56%, and global longitudinal strain of –17%. Remarkably, the papillary muscles were hypertrophied (Figure 1, Supplementary material, *Video S1–S3*). No intraventricular gradient was provoked with Valsalva maneuver. Diastolic function was normal.

On cardiopulmonary stress testing, he achieved 15 metabolic equivalents of task and maximal oxygen consumption of 52.6 ml/kg/min. Blood pressure response to exercise was normal. No ST-segment deviation nor arrhythmias were induced by the exercise.

No rhythm disturbances were found during 48-hour Holter monitoring that included a training session.

A genetic analysis including the following genes was performed: *ACTC1*, *GLA*, *MYH7*, *PLN*, *TNNC1*, *TMP1*, *DES*, *LAMP2*, *MYL2*, *PRKAG2*, *TNNI3*, *TTR*, *FLNC*, *MYBPC3*, *MYL3*, *PTPN11*, and *TNNT2*. No variants with clinical significance were found in the analyzed genes. However, it should be noted that genetic testing is not recommended for risk stratification by recent guidelines [1].

A cardiac magnetic resonance was attempted for tissue characterization and myocardial fibrosis assessment. Unfortunately, it could not be accomplished because the patient became claustrophobic and refused to receive sedation. We recognize this as a limitation; however, this patient had an excellent acoustic window for TTE, and there were no segments with increased wall thickness which could have been of diagnostic value when hypertrophic cardiomyopathy (HCM) is suspected [2].

Deconditioning was recommended, and after 3 months, papillary muscle hypertrophy was not changed on TTE. The patient has remained competitive and asymptomatic for 18 months since his diagnosis and no increase in left ventricular mass nor an increase in papillary muscle hypertrophy have been found on his follow-up TTE.

Papillary muscle hypertrophy (PMH) has been defined as a ≥1.1 cm diameter of at least one papillary muscle in the horizontal or vertical direction in the parasternal short-axis view [3]. PMH and accessory papillary muscles have been associated with sudden cardiac arrest of unknown cause [4]. Moreover, football is a specific sport that may pose a higher risk for sudden cardiac death because of its highly dynamic and start-stop exercise [1].

A few reports have suggested that isolated PMH could be an initial form of HCM [3, 5]. Conversely, recent guidelines do not consider isolated PMH diagnostic of HCM [2]. Until now, no clear recommendations exist regarding sport participation in high-endurance athletes with isolated PMH. In our case, it was decided to allow the patient to to continue competitive sports participation with close monitoring due to (1) the favorable cardiopulmonary stress test

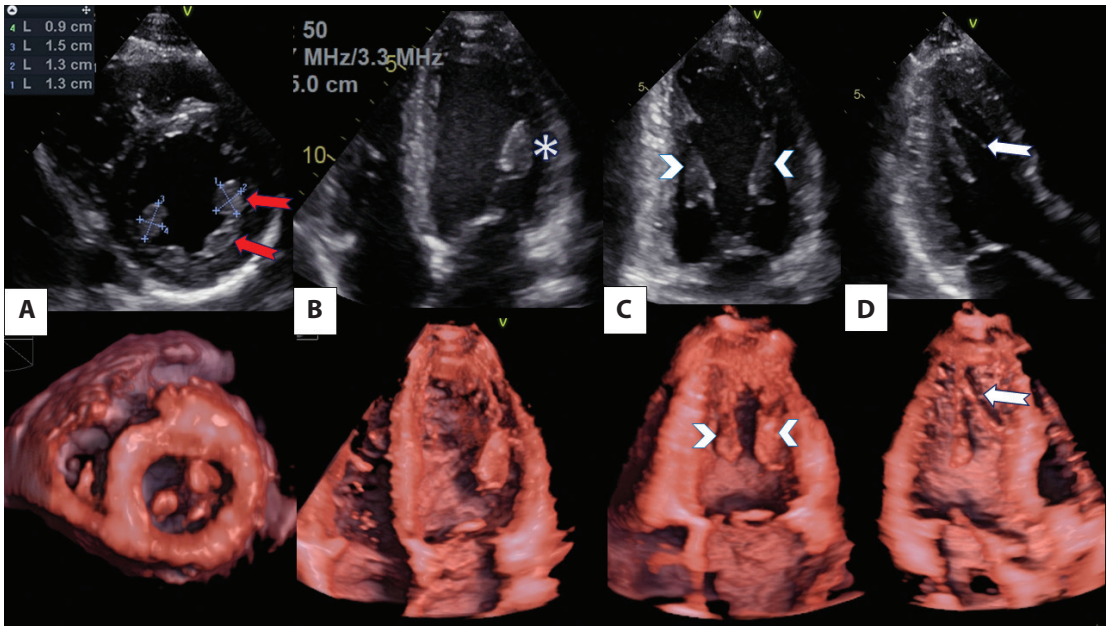


**Figure 1.** Comparative 2D and 3D transthoracic echocardiogram images (top and bottom panels respectively). **A.** Parasternal short- axis view demonstrating the measurement of papillary muscles and a double headed anterolateral papillary muscle (red arrows). **B.** Apical 4-chamber view showing the prominent anterolateral papillary muscle (asterisk). **C.** Apical 2-chamber view showing the hypertrophied papillary muscles (arrowheads). **D.** Apical 3-chamber view demonstrating a false chordae tendineae (white arrow)

result; (2) the absence of intraventricular gradient; (3) the absence of arrhythmias on 48 h Holter monitoring, (4) the absence of both syncope and exercise-induced ventricular tachycardia; (5) the exclusion of Fabry disease and the most common sarcomeric mutations. Further studies are needed to better understand the clinical relevance of this morphological abnormality.

## *Supplementary material*

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

## *Article information*

**Conflict of interest:** None declared.

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**How to cite:** Zulema C, Leyva M, Arroyo-Rodruguez C, et al. Isolated papillary muscle hypertrophy in a professional soccer player: the end of an athlete's career? Kardiol Pol. 2021; 79(10): 1147–1148, doi: 10.33963/KP.a2021.0063.

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# Bioprosthetic Aortic Scallop Intentional Laceration to prevent Iatrogenic Coronary Artery obstruction (BASILICA): the first experience in Poland

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Kardiol Pol. 2021; 79 (10): 1149–1150; DOI: 10.33963/KP.a2021.0069

**Received:** March 22, 2021

**Revision accepted:** July 19, 2021

**Published online:** July 20, 2021

Transcatheter aortic valve implantation (TAVI) is a recognized treatment method for severe aortic stenosis as an alternative to surgical aortic valve replacement in high-risk patients [1]. However, despite being less invasive, TAVI may require specific considerations. Low coronary take-off, a small sinus of Valsalva diameter, and elongated aortic leaflets are associated with the risk of iatrogenic coronary obstruction during transcatheter heart valve (THV) deployment, whereby up to 50% of cases of such obstruction are fatal [2]. In these patients, the recently developed Bioprosthetic Aortic Scallop Intentional Laceration to prevent Iatrogenic Coronary Artery obstruction (BASILICA) technique may be considered.

The method involves bioprosthetic or native transcatheter leaflet laceration to prevent coronary obstruction during valve deployment. The lacerated leaflet creates a triangular space in front of the coronary ostium, which allows the coronary flow to be maintained after THV implantation. The procedure was reported to have a success rate of 95%, with no cases of coronary obstruction [3].

We present a case of a 75-year-old woman with symptomatic severe aortic stenosis (aortic valve area, 0.7 $cm^2$; average gradient, 63 mm Hg), concomitant coronary artery disease (percutaneous coronary intervention of the left main artery in 2018), and low Euroscore II (1.47%), in whom the Heart Team recommended TAVI due to frailty and advanced osteoarthritis.

Preoperative computed tomography revealed a low take-off of the left main artery (8.2 mm), left aortic leaflet (10.8 mm), the annulus diameter of 22.9 mm, the sinus of Valsalva width of 26.2 mm, and the virtual THV to coronary distance of 1.65 mm. Considering a high risk of left main obstruction with a native leaflet, a decision to perform BASILICA was made.

TAVI was conducted under conscious sedation. The right ventricular pacing lead was placed through the right internal jugular vein. Judkins left (JL) 4.0 6F guide catheter was introduced through the right radial artery, and the left anterior descending artery was wired in case of emergency. Extra back-up (EBU) 3.5 6F and IM 5F (mother-in-child) catheters were placed through the right common femoral artery. A multipurpose (MP) catheter introduced from the left common femoral artery was used to deliver a 20-mm vascular snare, which was placed in the left ventricular outflow tract. A Piggyback® (Teleflex, Wayne, PA, USA) wire converter catheter with 300-cm Astato® (ASAHI, Irvine, SA, USA) wire inside, connected to an electrosurgical pencil, was placed via the IM catheter. The left coronary leaflet was punctured using 50-W energy, and the wire was snared and externalized contralaterally. Next, the wire was V-shaped and introduced until the V-bend reached the exact position of the leaflet puncture. The V-shaped wire was used to lacerate the leaflet using 70-W energy, with simultaneous pulling of the MP and EBU/IM catheters. After laceration, the Astato® wire, Piggyback® converter, MP and EBU/IM catheters were removed. The Medtronic Evolut Pro® (Medtronic, Fridley, MN, USA) 26 valve was implanted via the left common femoral artery. Angiography with a repositioned JL catheter showed preserved blood flow to the left main artery.

The patient made an uneventful postoperative recovery and was discharged home after 7 days. She received single antiplatelet therapy

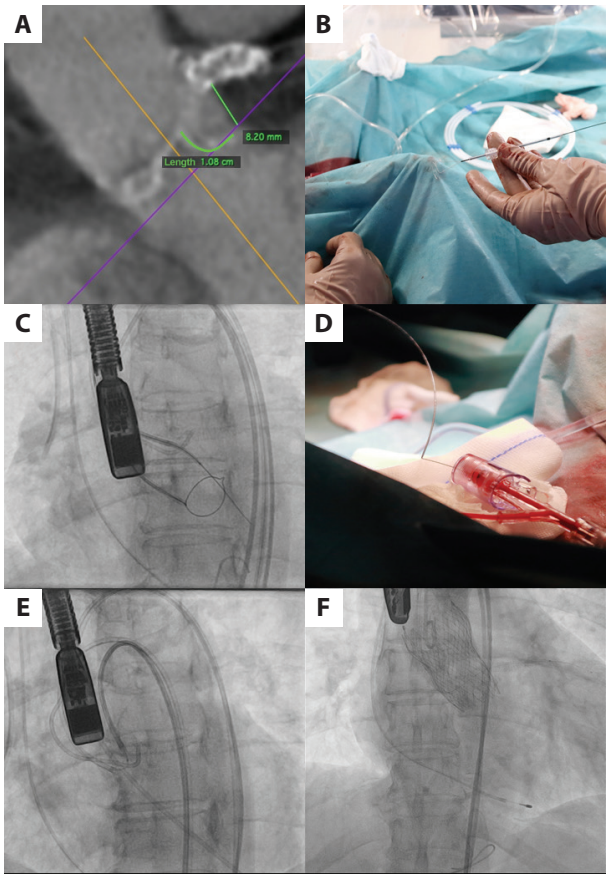


**Figure 1. A.** Computed tomography scan showing the left main artery take-off height of and leaflet length. **B.** A snare loop in left ventricular outflow trackt. **C.** Wire retrieval. **D.** V-shaped wire. **E.** Snapshot of leaflet laceration sequence. **F.** Final outcome with a deployed valve and preserved coronary flow

according to the local protocol [4]. After 3 months, she was in New York Heart Association functional class I, and transthoracic echocardiogram showed good prosthetic valve function with mild aortic regurgitation.

We would like to underline that when performing BASILICA procedure one should be aware of possible complications, such as hemodynamic instability from leaflet laceration, nontarget Astato® wire traversal (most commonly left atrial entry), and embolic debris release [5].

## *Article information*

**Conflict of interest:** None declared.

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**How to cite:** Protasiewicz M, Kosowski M, Onisk G, et al. Bioprosthetic aortic scallop intentional laceration to prevent iatrogenic coronary artery obstruction (BASILICA): the first experience in Poland. Kardiol Pol. 2021; 79(10): 1149–1150, doi: 10.33963/KP.a2021.0069.

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# Cardioneuroablation for the treatment of vagally mediated atrial fibrillation and vasovagal syncope

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Kardiol Pol. 2021; 79 (10): 1151–1152; DOI: 10.33963/KP.a2021.0073

**Received:** May 18, 2021

**Revision accepted:** July 22, 2021

**Published online:** July 22, 2021

Autonomic nervous system activation can induce multifarious changes in atrial electrophysiology and provoke atrial tachyarrhythmias, such as atrial tachycardia and vagally mediated atrial fibrillation (VM-AF) [1, 2]. This type of atrial fibrillation (AF) was defined as paroxysmal AF that occurs following vagal activation in such situations as after a big meal, during sleep, or in response to other recognized vagal triggers. Episodes of AF may be induced by neurally mediated reflex syncope (NMRS). Cardioneuroablation (CNA), a relatively novel technique based on percutaneous radiofrequency ablation of the vagal ganglia, can be used in patients with NMRS and VM-AF [3, 4].

A 33-year-old man was admitted to the hospital for AF ablation and CNA. He reported repeated episodes of syncope and palpitation since the age of 15. Syncope was preceded by prodromal symptoms, such as weakness, dizziness, and palpitation. Several 24-hour Holter monitoring tests revealed sinus bradycardia (mean heart rate, 40–44 beats per minute [bpm]; minimum heart rate, 28–30 bpm; the longest RR interval, 2.8 s [sinus arrest]). A 12-lead electrocardiogram (ECG) showed sinus bradycardia and inverted T waves in leads $V_3$–$V_5$. Echocardiography revealed no abnormalities. A positive tilt test response was classified as type 2B (cardioinhibition with asystole) according to the modified Classification by the Vasovagal Syncope International Study (Figure 1A, B; Supplementary material, *Figure 1S*). Based on the current guidelines and tilt test results, VM-AF, NMRS, and bradycardia-tachycardia syndrome were diagnosed. The patient was referred for pulmonary vein isolation as well as modified anatomically-guided binodal and biatrial CNA with bilateral extracardiac vagal nerve stimulation (ECANS) according to Pachon et al. [3]. Prior to CNA and pulmonary vein isolation (PVI), detailed electrophysiology study (EPS) excluded atrioventricular nodal reciprocating tachycardia and atrioventricular reentry tachycardia. Additionally, ultrasound-guided ECANS was performed from the nonsubcranial region of the internal jugular vein, which showed repetitive sinus asystole and complete atrioventricular block for 8 seconds during AF. Proximal coronary sinus stimulation caused recurrent AF. Sinus rhythm was restored with electrical cardioversion. Pulmonary vein isolation was followed by endocardial ablation at 5 anatomic sites of the ganglionated plexi in the left and right atria, mapped according to the modified Pachon's method (Figure 1C, D). Left and right ECANS postprocedure did not elicit cardioinhibition or arrhythmia (AF or ventricular tachycardia). Sinus rhythm increased from 55–60 bpm to 85–90 bpm. Following atropine administration, resting sinus rhythm increased from 87 to 92 bpm at 10 minutes (≤6%). On the control tilt test at 1 month, nitroglycerine administration resulted in presyncope with nausea (Supplementary material, *Figure 2S*). Heart rhythm and blood pressure decreased. Syncope was not observed. Intravenous atropine administration (1.5 mg) led to an increase in resting sinus rhythm from 61 to 82 bpm at 10 minutes (34%). Holter ECG monitoring at 6 weeks revealed sinus rhythm with a mean heart rate of 68 bpm (53–90 bpm) without arrhythmia.

There is growing evidence that AF can be triggered by vagal hyperactivity [3, 4]. Cardioneuroablation is an effective and safe treatment for vasovagal syncope and can be used during AF ablation. There are some limitations

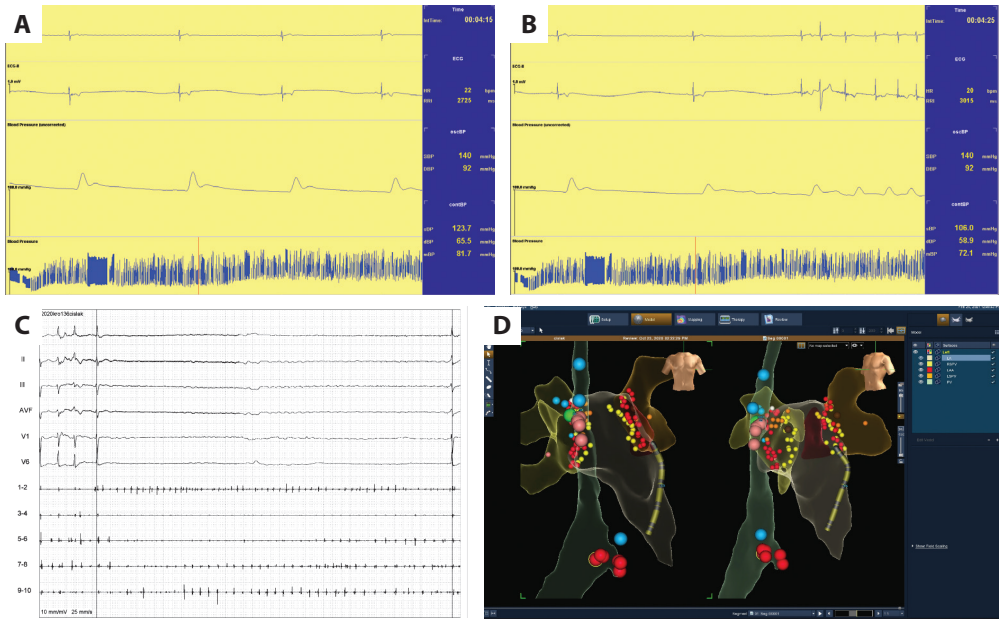


**Figure 1. A–D.** Noninvasive continuous beat-to-beat blood pressure monitoring during head-up tilt test in a patient with syncope. Nitroglycerin administration (0.4 mg sublingually), loss of consciousness and syncope; a decrease in sinus rhythm to 20 bpm, followed by 4 seconds of sinus asystole was documented. **A**. A decrease in sinus rhythm induced atrial fibrillation. **B**. Vagally mediated atrial fibrillation occurred after table lowering; then, within 3 minutes, AF resolved with symptomatic sinus arrest lasting 2 seconds. **C**. Surface ECG and diagnostic bipolar potentials recorded with a diagnostic decapolar catheter located in the CS 9–10 being in the proximal CS. Extracardiac vagal nerve stimulation generated an artifact on surface ECG (bold line) and ventricular asystole lasting 8 seconds, with no effect on atrial rhythm. **D.** Left-hand side, anteroposterior view; right-hand side, left anterior oblique projection. Large blue dots in the upper part represent right phrenic nerve stimulation sites in the SVC. A single blue dot in the lower part represents His-Bundle pacing. Small red and yellow dots represent ablation sites during pulmonary vein isolation and GP ablation on the anterior and posterior left atrial wall, respectively. Large pink dots represent GP ablation sites in the SVC. A yellow decapolar catheter is placed in the coronary sinus

Abbreviations: CS, coronary sinus; ECG, electrocardiogram; GP, ganglionated plexi; SVC, superior vena cava

to our management due to the lack of preprocedural atropine test. However, non-invasive tests prior to inducibility of AF excluded neuropathy. Previously described atropine test (post-CNA) showed a significant increase in heart rhytm. The long-term clinical utility of partial innervation vs. complete denervation, as shown by atropine test, as well as tilt test, was not fully validated, especially during follow-up. Although clinical follow-up is excellent and baseline mean heart rhythm remains higher, simultaneous performance of PVI and CNA cannot confirm the superiority of one of these techniques for AF. Moreover, the current standards for AF prevention require PVI, therefore both techniques were simultaneously applied [3, 5].

## *Supplementary material*

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

## *Article information*

**Conflict of interest:** SS is author of several patents and share holder of Medicine S.A. No products were used in this case.

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**How to cite:** Wróblewska A, Wileczek A, Reichert A, et al. Cardioneuroablation for the treatment of vagally mediated atrial fibrillation and vasovagal syncope. Kardiol Pol. 2021; 79(10): 1151–1152, doi: 10.33963/KP.a2021.0073.

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# Every rose has its thorns — acute myocarditis following COVID-19 vaccination

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Kardiol Pol. 2021; 79 (10): 1153–1154;
DOI: 10.33963/KP.a2021.0075

Received:
July 14, 2021

Revision accepted:
July 23, 2021

Published online:
July 27, 2021

A 21-year-old man was admitted to the hospital with severe chest pain. Apart from atopic asthma in childhood, pollen and pet allergy, and appendectomy a few years ago, his past medical history was unremarkable, and he did not have a symptomatic COVID-19 infection in the past. He worked physically as a warehouse worker and trained regularly Brazilian Jiu-Jitsu without any health problems. The family history was negative for cardiovascular disease.

Three days before hospitalization, the patient received the first dose of mRNA COVID-19 vaccination (Comirnaty, Pfizer). Apart from mild muscle pain at the site of vaccine administration, he did not experience any other symptoms during the first two days. On admission day, he woke up at night due to a tight and squeezing sensation in his chest, which he rated as 8 points in the 0–10 Numeric Rating Scale used to estimate the intensity of pain. The chest discomfort lasted about 3 hours despite taking a painkiller; it resolved spontaneously and did not return later.

On admission to the hospital, the patient was hemodynamically stable. Electrocardiography showed sinus rhythm at a heart rate of 50 beats per minute, an incomplete right bundle branch block, Q wave and ST-segment elevation less than 1 mm in leads II, III and aVF, negative T-wave in lead V1 and patterns of precordial early repolarization (Figure 1A). Blood tests demonstrated elevated levels of high-sensitive cardiac troponin I (6490–6559 pg/ml; reference range <34 pg/ml), N-terminal fragment of the prohormone brain natriuretic peptide (337 pg/ml; reference range <125 pg/ml), and C-reactive protein (82 mg/l; reference range <5 mg/l).

Echocardiography demonstrated a normal-sized, non-hypertrophic left ventricle with normal ejection fraction (biplane, 58%) and borderline global longitudinal deformation (–16.3%) with a regional heterogeneity (Figure 1B). Coronary computed tomography angiography demonstrated normal coronary arteries (Figure 1C). Cardiac magnetic resonance revealed imaging findings typical of active myocarditis [1], including increased signal intensity on T2-weighted images, increased values on both T1 and T2 mapping (Figure 1D), and the presence of diffuse subepicardial late gadolinium enhancement (Figure 1E–F). During further laboratory workup, viral causes of myocarditis were excluded, i.e. COVID-19, influenza type A and B, hepatitis type B and C, Epstein–Barr-, human immunodeficiency- and cytomegalovirus infections. The vaccine-associated acute myocarditis was diagnosed.

Acute myocarditis following vaccination is a rare but serious complication, which has until now been recognized as associated almost exclusively with smallpox and influenza immunization [2]. Myocarditis in the course of COVID-19 infection was previously described [3, 4]; however, only recently have the first cases of acute myocarditis following administration of the mRNA-based anti-COVID-19 vaccines (Pfizer-BioNTech and Moderna) been reported [2, 5]. This complication typically occurs in young adult males within 4 days after administration of the second dose of the COVID-19 vaccine [2, 5]. Acute myocarditis diagnosed shortly after the first dose of mRNA vaccine, as in our case, is unusual and appears mainly in COVID-19 convalescents [5]. Longer follow-up is needed to assess the further course of the disease. Comprehensive imaging is helpful in establishing the diagnosis of myocarditis and should be included in the diagnostic workup in patients suspected of having myocardial complications of COVID-19 infection or COVID-19 vaccination.

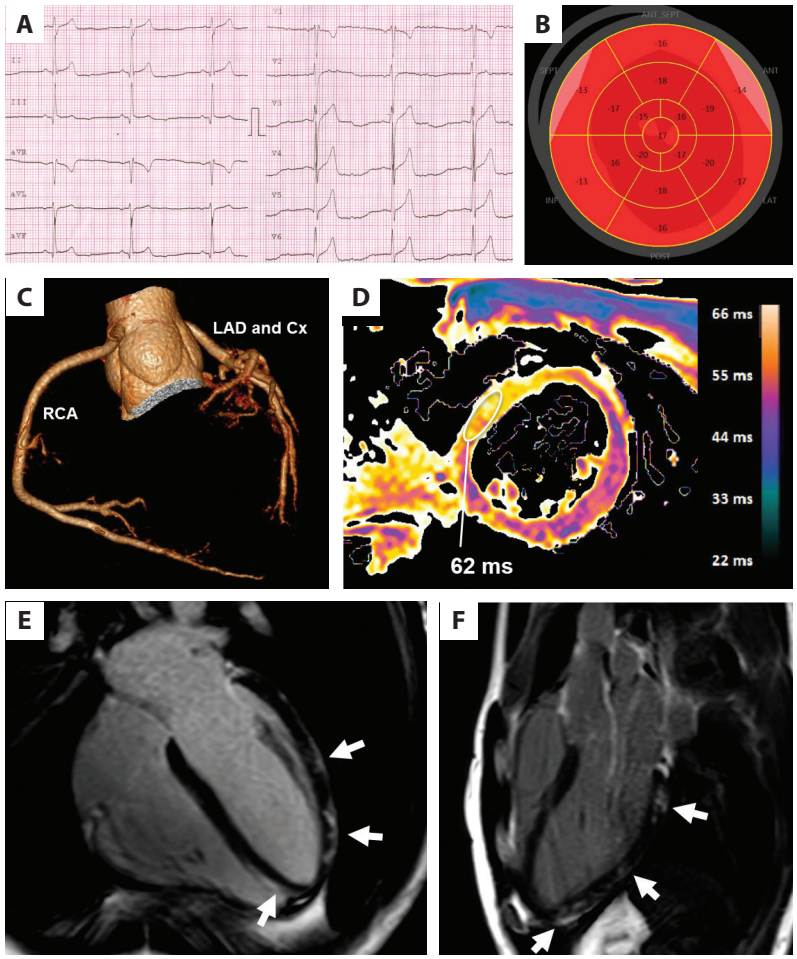


**Figure 1. A**. 12-lead electrocardiogram on admission showing sinus rhythm, normal axis, an incomplete right bundle branch block, Q wave and ST-segment elevation less than 1 mm in leads II, III and aVF, negative T-wave in lead V1 and patterns of precordial early repolarization. **B**. Speckle tracking echocardiography demonstrated a borderline global longitudinal strain (-16.3 %) with a regional heterogeneity (abnormal values in the basal inferior, anterior and septal segments). **C**. Coronary computed tomography angiography visualized normal coronary arteries with the strongly dominant right coronary artery. **D–F**. Cardiac magnetic resonance imaging demonstrating typical findings of active myocarditis. **D**. T2 mapping confirming global myocardial edema, short-axis view. **E–F**. Diffuse subepicardial late gadolinium enhancement (arrows), 4- and 3-chamber view

Abbreviations: Cx, circumflex artery; LAD, left anterior descending artery; RCA, right coronary artery

## *Article information*

**Conflict of interest:** None declared.

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**How to cite:** Sokolska JM, Kurcz J, Kosmala W, et al. Every rose has its thorns — acute myocarditis following COVID-19 vaccination. Kardiol Pol. 2021; 79(10): 1153–1154, doi: 10.33963/KP.a2021.0075.

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# Impact of photoplethysmography on therapeutic decisions in atrial fibrillation

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Kardiol Pol. 2021; 79 (10): 1155–1156;
DOI: 10.33963/KP.a2021.0076

**Received:**
May 20, 2021

**Revision accepted:**
July 23, 2021

**Published online:**
July 27, 2021

In the era of the SARS-CoV-2 pandemic, the global health crisis required limiting face-to-face patient consultations. This situation demanded rapid identification and implementation of remote healthcare delivery methods.

A 42-year-old man with a 4-year history of paroxysmal palpitations (European Heart Rhythm Association IIb) and a documented first episode of atrial fibrillation (AF) a year before was admitted to the department for catheter ablation. He had a history of stable ischemic heart disease, hypertension, and hyperlipidemia. The pulmonary vein isolation procedure was performed with a CARTO 3D mapping system and NaviStar Smart SF catheter (Biosense Webster, Irvine, CA, USA). The left atrium and pulmonary veins were mapped with PentaRay multielectrode catheter (Biosense Webster) and merged with 3D reconstruction from rotational angiography. At the end of the procedure, sinus rhythm was documented, and the patient was discharged from the hospital in good condition without any periprocedural complications. Three months after the discharge, and therefore after the blanking period, the patient was included in a novel pan-European project TeleCheck-AF, designed to facilitate remote management of patients with AF [1, 2]. Participation consisted of measuring heart rate, rhythm, and symptoms using the FibriCheck mobile app on-demand at scheduled time points after AF ablation procedures. The FibriCheck app uses a photoplethysmography (PPG) technique through the camera built into a smartphone. Measurements are made by placing a finger over the camera for 1 minute.

Our patient was instructed to perform rate and rhythm measurements 3 times a day and in case of symptoms for one week. The PPG recordings were instantly transferred to a secured cloud, which was then evaluated by an attending physician and further discussed with the patient during a teleconsultation [3]. The PPG recordings indicated a recurrence of AF, and nearly half of the measurements were accompanied by palpitations (Figure 1), which was confirmed during a physical examination. Due to these measurements, the patient was scheduled for another re-do catheter ablation procedure qualification. The patient had standard electrocardiogram, ECHO, and Holter electrocardiogram before making a decision. The re-do procedure included the left atrial roof and cavotricuspid isthmus ablation. There were no periprocedural complications.

Many mobile apps and wearable devices used to control cardiac arrhythmias are currently available. Many studies have shown high sensitivity and specificity of PPG-based apps ranging between 91.5%–98.5% and 91.4%–100% compared to an electrocardiogram. Despite these optimistic values, they should be treated with caution because of the small populations studied and a possible bias due to signal selection [4]. The Fibricheck was established to have a sensitivity of 95.6% and a specificity of 96.6% in a diagnostic accuracy study [5]. Regular monitoring of heart rhythm increases the chances of detecting a recurrence of AF after an AF ablation procedure; it supports an informed treatment decision and ultimately reduces symptoms in our patients.

This case highlights the feasibility of PPG applications in monitoring patients after ablation and shows how the results can be used to guide further therapeutic decisions. Further

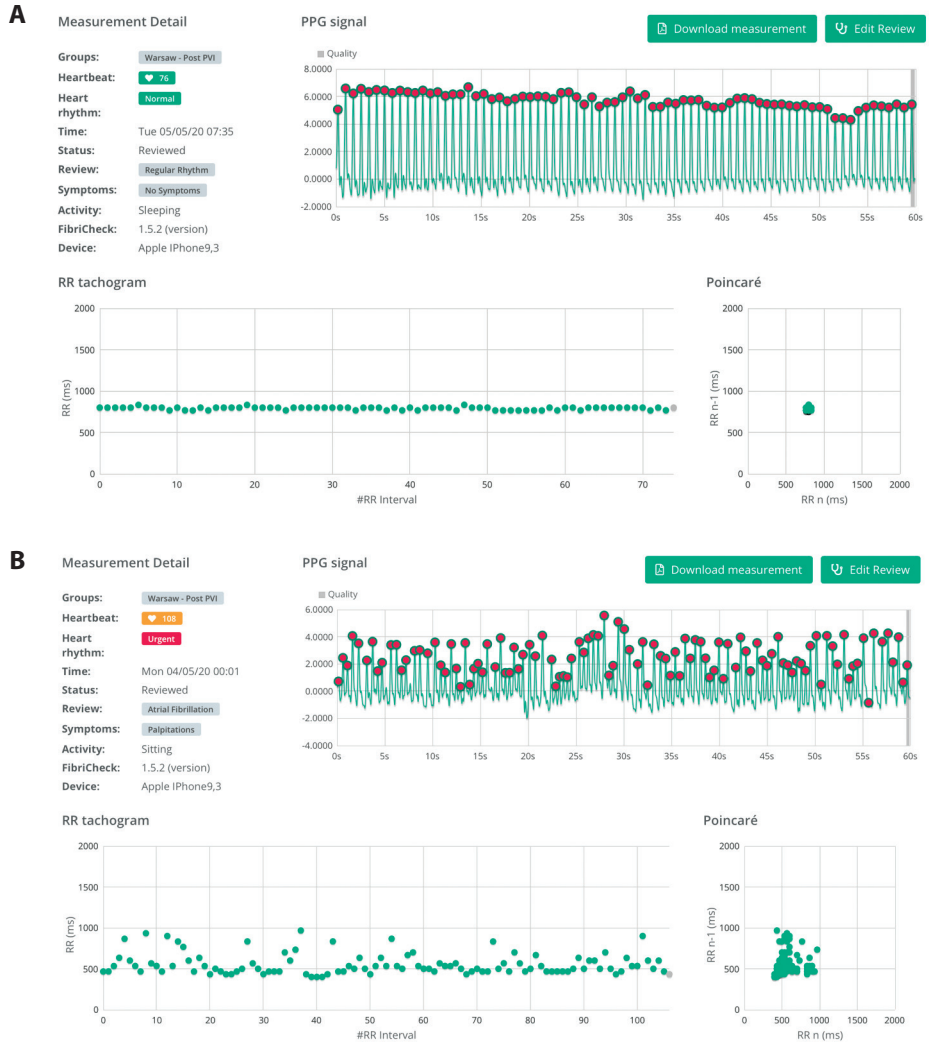


**Figure 1.** Photoplethysmography signal during **A.** normal sinus rhythm and **B.** during atrial fibrillation with concomitant palpitations

study is warranted to investigate if the PPG technology can be used as routine rhythm monitoring for the follow-up after AF ablation.

## *Article information*

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**How to cite:** Starczyński M, Krzowski B, Gawałko M, et al. Impact of photoplethysmography on therapeutic decisions in atrial fibrillation. Kardiol Pol. 2021; 79(10): 1155–1156, doi: 10.33963/KP.a2021.0076.

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# Hybrid percutaneous atrial septal defect closure with surgical occluder fixation

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Kardiol Pol. 2021; 79 (10): 1157–1158; DOI: 10.33963/KP.a2021.0078

**Received:** April 28, 2021

**Revision accepted:** July 26, 2021

**Published online:** July 28, 2021

A 62-year-old woman with a history of dyspnea in ordinary activities was admitted for an atrial septal defect (ASD) type 2 treatment. Transthoracic echocardiography revealed diastolic dysfunction of the left ventricle, right heart enlargement, atrial septal aneurysm, and an atrial septal defect with a left-to-right shunt. The Qp:Qs was 1.7. The probability of pulmonary hypertension was moderate. The transesophageal echocardiogram showed a 17 × 10 mm ostium secundum ASD with a left-to-right shunt, an atrial septal aneurysm protruding into the right atrium, a deficiency of the superior vena cava rim and the short aortic rim (Supplementary material, *Video S1* — ASD). The inferior vena cava (IVC) rim was limp. Following the European Society of Cardiology recommendations, this morphology is an indication to surgical repair; however, due to the patient's moderate frailty, the Heart Team chose device closure instead, as it seemed technically suitable [1, 2].

The pressures in the right heart were assessed: right ventricle — 27/4 mean 7 mm Hg, pulmonary artery — 18/8 mean 13 mm Hg, mean wedge pressure 8 mm Hg, transpulmonary gradient 5 mm Hg, cardiac output 5.5 l/min, pulmonary vascular resistance 0.9 Wood units. After the "stop-flow" technique balloon sizing, the 20-mm "Cera" occluder was successfully placed. Despite the rim deficiency, the device was stable during the tug test. However, due to the atrial septum aneurysm, the IVC rim was loose, providing poor support for the device with a risk of detachment. The device was removed, and the concept of hybrid intervention came up.

Under general anesthesia, a lateral thoracotomy and an opening of the pericardial sac were performed. The Lifetech Cera 20-mm occluder was delivered through the right femoral vein. Both discs were expanded at optimal positions. Compression of the right atrium wall by forceps localized in transesophageal echocardiography pointed where the suture should be placed. Simultaneously, the cardiologist pulled the device to an optimized position for suturing. The right atrial disc was fixated to the limp IVC rim by a single suture placed by the surgeon through the right atrium wall (Supplementary material, *Video S2* — device suturing). A standard tug test was performed (Supplementary material, *Video S3* — tug test). The device had efficient support from the inferior-posterior side. The occluder was then released (Supplementary material, *Video S4* — device detachment from delivery cable). The pericardial sac and the thoracic wall were closed. The patient was extubated the same day. Transthoracic echocardiography performed the next day showed an insignificantly small residual shunt (Supplementary material, *Video S5* — final result). The patient was discharged after 8 days.

To the best of our knowledge, it was the first case of a hybrid percutaneous ASD closure. This unique approach allowed us to perform device closure in a patient that, due to frailty, could have had an uncertain clinical course if operated classically. This type of hybrid procedure may prove helpful in future interventions.

## Supplementary material

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

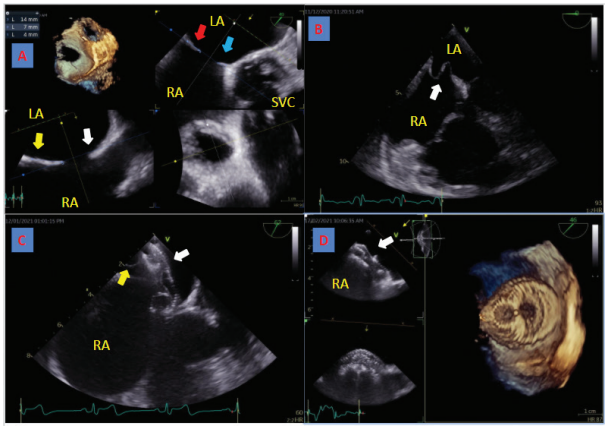


**Figure 1. A.** 3D reconstruction of interatrial septum with an atrial septal defect type II localized in the superior and anterior aspect of the septum. The postero-superior rim (superior vena cava rim) is absent (white arrow), the postero-inferior rim is 14 mm (yellow arrow), the posterior rim is 7 mm (red arrow), the antero-superior rim (aortic rim) is minimal (blue arrow — 4 mm). The shape of the ASD is elliptical with diameters of 10 and 17 mm, respectively. **B.** Transesophageal echocardiography, midesophageal 4-chamber view. The white arrow points to the interatrial septal aneurysm. **C.** The first attempt for ASD closure. Transesophageal echocardiography: a modified mid-esophageal aortic valve view during the push test. The white arrow points to the implanted occluder device, the yellow arrow points to the interatrial septal aneurysm giving poor support to the implanted device. **D.** The hybrid approach. The 3D reconstruction of the implanted Lifetech Cera 20-mm occluder after it was successfully secured by a single surgical suture

Abbreviations: ASD, atrial septal defect

## *Article information*

**Acknowledgments:** We thank Mr Przemysław Węglarz for the support given during planning of the procedure.

**Conflict of interest:** None declared.

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**How to cite:** Przybylski R, Reczuch J, Bochenek M, et al. Hybrid percutaneous atrial septal defect closure with surgical occluder fixation. Kardiol Pol. 2021; 79(10): 1157–1158, doi: 10.33963/KP.a2021.0078.

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# Intravascular lithotripsy for the treatment of a heavily calcified recurrent in-stent restenosis in a patient with chronic coronary syndrome

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Kardiol Pol. 2021; 79 (10): 1159–1160; DOI: 10.33963/KP.a2021.0079

**Received:** March 15, 2021

**Revision accepted:** July 29, 2021

**Published online:** August 2, 2021

We present a case of a 67-year-old male patient admitted to our Department due to recurrence of angina class II according to the Canadian Cardiovascular Society scale. The past medical history included primary percutaneous coronary intervention (PCI) of the left anterior descending artery (LAD) with a bare-metal stent in 2005 and repeated PCI of the LAD with a sirolimus-eluting stent for in-stent restenosis (ISR) in 2007. Coronary angiography, fluoroscopic digital stent enhancement (DSE), and intravascular ultrasound revealed recurrence of ISR in the proximal segment of the LAD caused by stent under-expansion and heavily calcified neoatherosclerosis (Figure 1A, 1C). Physiology lesion assessment confirmed ischemia (resting full-cycle ratio 0.69 and fractional flow reserve 0.70) (Figure 1B). The patient refused minimally invasive direct coronary artery bypass grafting but agreed to high-risk repeated PCI. A transradial approach with a 6 F extra-back-up guiding catheter was chosen. Several attempts of lesion predilatation with a non-compliant balloon (NCB) and cutting balloon were ineffective. A very-high-pressure non-compliant balloon deployed at 48 atmospheres did not fully open (Figure 1D). Finally, we performed successful intravascular lithotripsy (IVL) using 3.0 × 12 mm IVL balloon catheter (Shockwave Medical, Fremont, CA, USA), which fully expanded at 4 atmospheres. After application of 80 pulses of ultrasound energy, full balloon expansion was achieved (Figure 1E).

New-generation sirolimus-eluting stent was implanted (3.5 × 48 mm) at 18 atm with subsequent NCB optimization. Control angiography showed optimal PCI result with <10% residual diameter stenosis and excellent stent expansion confirmed by DSE (Figure 1F). No complications occurred during the hospital stay, and the patient was discharged home 2 days after PCI with no symptoms of angina.

Adequate preparation of diffuse, heavily calcified in-stent neoatherosclerosis for stent implantation remains a challenge. In our case several attempts of lesion predilatation with NCB and cutting balloon, or even super-high-pressure NCB, were unsuccessful — no balloon fully expanded. Rotational atherectomy is another option, however, it usually requires the use of a large-size burr (≥2.0 mm), which significantly increases procedural risk [1]. Coronary laser atherectomy could be an option; yet, it is not widely available. Therefore, we decided to use a novel method of calcified lesion preparation for stent implantation — IVL [2]. The effectiveness of IVL has been already described in the primary treatment of severely calcified native coronary lesions [2, 3]. There is a single published case report describing off-label IVL application to treat calcified in-stent neoatherosclerosis as an adjunct to rotational atherectomy [4]. Salazar et al. reported successful IVL application as treatment of recurrent, calcified in-stent atherosclerosis in a diagonal branch [5]. We report for the first time a direct application of IVL to treat ISR caused by 13-year-old neoatherosclerosis in the previously double stented lesion in the proximal LAD. This represents a new, extremely promising, and easy-to-use treatment strategy (without a learning curve) for this high-risk lesion subset. However, its short-time safety and long-time effectiveness need to be proven in large-scale clinical trials.

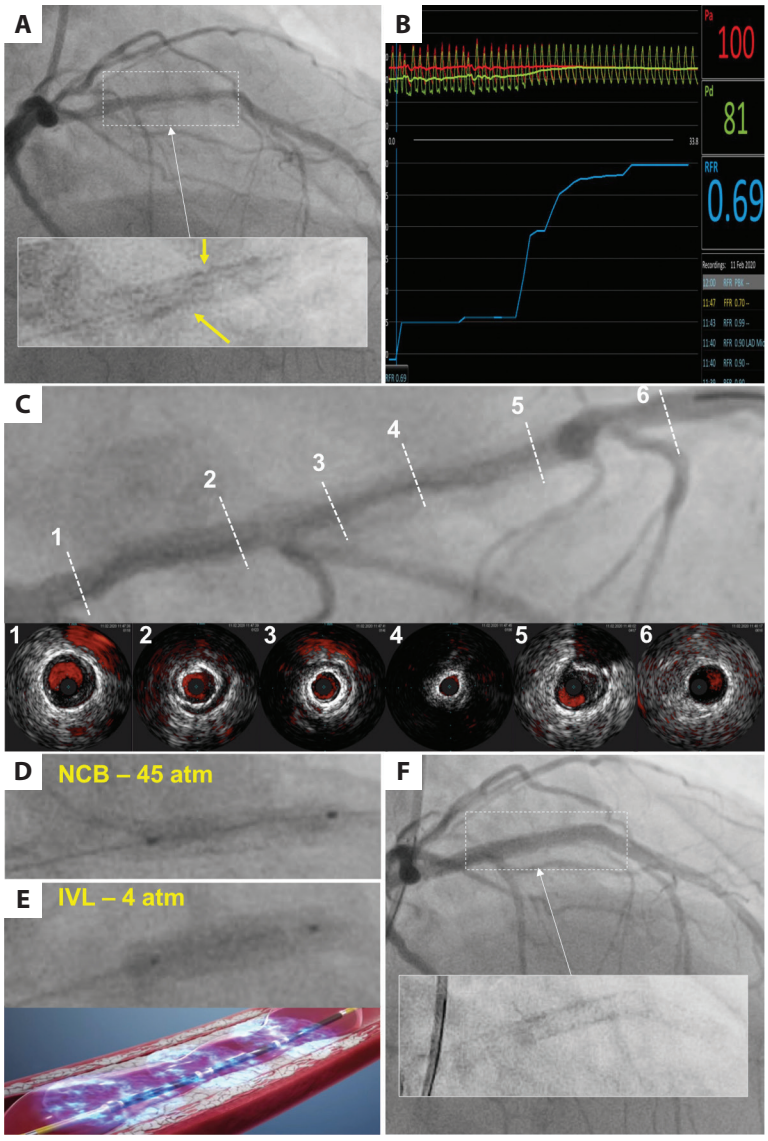


**Figure 1. A.** Coronary angiography revealed diffuse in-stent restenosis in the proximal segment of the LAD. Severe calcifications within stented segment of LAD and stent underexpansion (arrows) visible on fluoroscopic DSE. **B.** Physiology lesion assessment confirmed ischemia in LAD. **C.** IVUS revealed heavily calcified neoatherosclerosis as a cause of ISR (diffuse, multi-layered neointima with severe calcifications [up to 360° of superficial calcium arc at the site of maximum lumen narrowing]) within double stent strut layer. **D.** Very-high-pressure non-compliant balloon deployed at 48 atmospheres not fully opened in fluoroscopy. **E.** Intravascular lithotripsy balloon fully expanded at 4 atmospheres (upper picture). Schematic illustration of intravascular lithotripsy balloon catheter (lower picture). **F.** Final angiographic result with <10% diameter stenosis and optimal stent expansion confirmed by DSE

Abbreviations: DSE, digital stent enhancement; ISR, in-stent restenosis; IVUS, intravascular ultrasound; LAD, left anterior descending artery

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**How to cite:** Szolc P, Guzik B, Wiewiórka Ł, et al. Intravascular lithotripsy for the treatment of a heavily calcified recurrent in-stent restenosis in patient with chronic coronary syndrome. Kardiol Pol. 2021; 79(10): 1159–1160, doi: 10.33963/KP.a2021.0079.

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# Transcatheter mitral valve replacement with Tendyne™ Device: overview of three-dimensional echocardiography monitoring

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Kardiol Pol. 2021; 79 (10): 1161–1162; DOI: 10.33963/KP.a2021.0080

**Received:**
June 16, 2021

**Revision accepted:**
August 4, 2021

**Published online:**
August 4, 2021

A 77-year-old Caucasian male with post-ischemic dilated cardiomyopathy was referred to our Emergency Department with recurrent acute pulmonary edema. He reported multiple previous hospitalizations for heart failure despite maximal tolerated medical therapy.

Echocardiography showed a dilated left ventricle with systolic dysfunction and severe secondary mitral regurgitation (left ventricular end diastolic volume of 135 ml/m$^2$; ejection fraction of 25%; effective regurgitant orifice area of 0.42 cm$^2$; regurgitant fraction of 53%). These features, together with the above-mentioned clinical history, posed a very high surgical risk to the patient in the absence of feasibility criteria for a percutaneous edge-to-edge mitral valve repair ("proportionate" mitral valve regurgitation with inadequate coaptation length, borderline valve area). Therefore, our local Heart Team suggested the procedure of a transcatheter mitral valve replacement as an alternative therapeutic option [1].

The Tendyne Mitral Valve System (Tendyne Holdings, LLC, a subsidiary of Abbott Vascular, Roseville, MN, USA) consists of a delivery system, an 18 G needle; a 36 French sheath and a D- shaped tri-leaflet porcine pericardial valve, supported by a synthetic circular inner frame. The replacement procedure is performed by a trans-apical approach. An alternative hybrid technique for transcatheter mitral valve replacement has been previously adopted with success in a different high-risk setting, such as infective endocarditis in pediatric patients [2].

In this surgical setting, echocardiography plays a paramount role both in procedure planning and intra-operative monitoring. Initially, after having identified the thoracic access, the sheath is inserted rigorously orthogonally to the mitral annulus plane (Figure 1A). Subsequently, the sheath is advanced and stopped 1 cm above the mitral annulus (Figure 1B), and the valve is finally deployed (Figure 1C–D).

Postprocedural transesophageal echocardiography showed correct valve seating with no residual motion of the prosthesis and no left ventricular outflow tract obstruction (Figure 1E–F).

This case underscores the paramount relevance of 3D echocardiographic monitoring in interventional cardiology in order to achieve the most favorable procedural outcomes.

## Article information

**Acknowledgments:** IRB approval, consent statement and clinical trial registration are not applicable for this study.

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

**Conflict of interest:** None declared.

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**How to cite:** Polizzi V, Pergolini A, Zampi G, et al. Transcatheter mitral valve replacement with Tendyne™Device: overview of three-dimensional echocardiography monitoring. Kardiol Pol. 2021; 79(10): 1161–1162, doi: 10.33963/KP.a2021.0080.

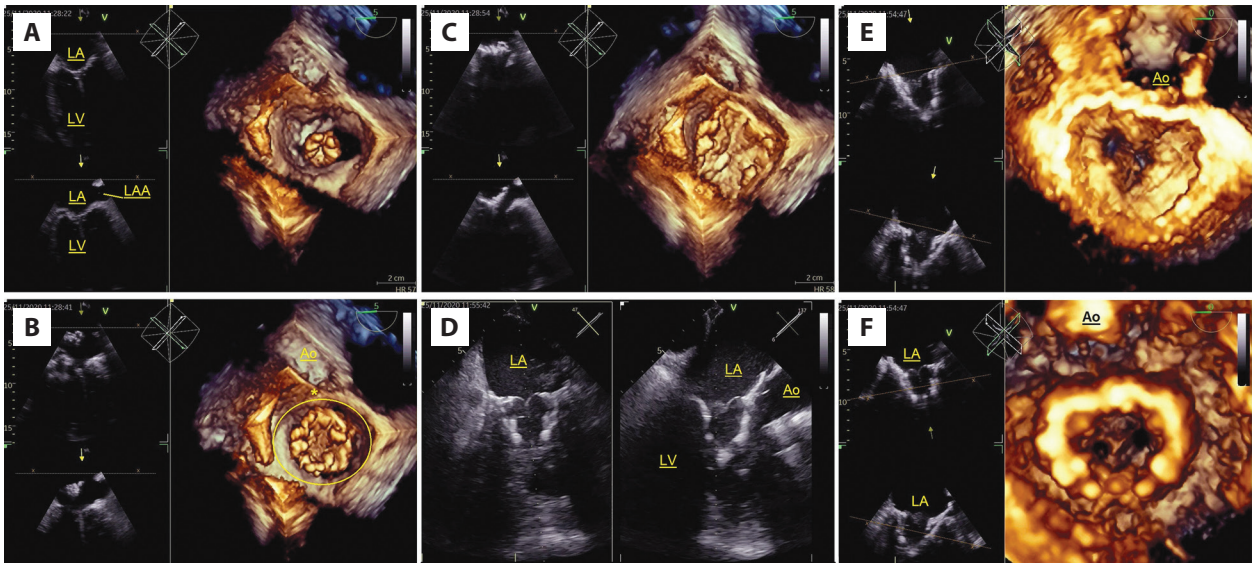


**Figure 1. A.** Transesophageal echocardiography, biplanar imaging, obtained from inter commissural view showing the Tendyne valve partially deployed within the mitral annulus. **B.** 3D transesophageal echocardiography surgeon's view, showing sheath positioning (asterisk showing the part facing LVOT; circle showing the D-shape of the valve). **C.** 3D transesophageal echocardiography en face (surgeon's view). Valve clocking (determining the radial orientation of the valve) should be performed to align the anterior cuff of Tendyne with A2 scallop, along the anterior atrial wall and behind the aortic valve. **D.** Transesophageal echocardiography, orthogonal biplanar imaging obtained from inter commissural view (left panel) showing the correct valve seating with no residual motion of the prosthesis and no LVOT obstruction (right panel: long axis view). **E.** 3D transesophageal echocardiography en face (surgeon's view) — the final result. **F.** 3D transesophageal echocardiography ventricular view showing the final result

Abbreviations: Ao, aorta; LA, left atrium; LAA, left atrial appendage; LV, left ventricle

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# Heart Failure Heart Team — time to act… now

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Kardiol Pol. 2021;
79 (10): 1163–1164;
DOI: 10.33963/KP.a2021.0123

**Received:**
September 22, 2021

**Revision accepted:**
September 23, 2021

**Published online:**
October 6, 2021

## TO THE EDITOR

The world has changed. Not only due to the COVID-19 pandemic and enormous challenges it brought along but also due to clear evidence that postponement means… failure. Heart failure.

This year, the European Society of Cardiology (ESC) in cooperation with the Heart Failure Association (HFA) of the ESC released updated guidelines for the diagnosis and treatment of acute and chronic heart failure. While previously published documents deepened our knowledge in modern pharmacology, the 2021 update focuses more on timely action. Experts move away from lengthy and (over-) complicated algorithms and point our attention and therapeutic decisions towards a more simplified, patient-focused approach. The goal is simple: to diagnose and treat myocardial dysfunction as soon as possible to prevent patients from developing end-stage heart failure, which remains not only difficult to target therapeutically but also has an enormous impact on healthcare, so severely struck by the ongoing pandemic.

Heart failure affects nowadays almost 65 million people worldwide and this number is expected to increase with sustained poor prognosis of advanced heart failure despite continuous advances in medical management [1]. Heart transplantation (HTx) holds its strong position as the cornerstone of advanced therapy for heart failure. It is the ultimate replacement of the failing organ, offering one-year survival of 90% and median survival of 12.5 years with an exceptionally good quality of life. Yet, long organ waiting time, extremely distressing for individuals placed on the elective list, has dreadful effects as a substantial percentage of them expire while waiting. Poland is fortunate in this regard, as the number of heart transplantations has visibly increased over the past 4 years from an average of 90–80 to 140–150 cases per annum. Much more is to be improved in terms of early morbidity and mortality, which is undoubtedly related to the preoperative state of the recipient — often referred to HTx late, in poor clinical condition. The same principles apply to mechanical circulatory support (MCS). Recently published outcomes of large-volume, multicenter clinical trials revealed a phenomenal safety profile in contemporary, long-term left ventricular assist devices (LVADs), which are now recommended for the broader patient population at early stages of the disease. Technological breakthroughs will continue, with wireless charging and connectivity not far on the horizon. Yet… the perception of the unattainability of these therapeutic solutions so often dominates our talks and discussions. Assist devices are on-the-shelf or in storage, ready-to-use products frequently covered with dust. The devices are mobilized when a barely alive patient is finally rushed to the Transplant Center after weeks of ineffective peripheral mechanical support and maximally up-titrated vasoactive and inotropic medications. The ESC screams out loud in just-published guidelines — Do not wait! Time is of the essence! Team up with centers of excellence, create, run and maintain heart failure meetings where true experts in heart failure review and decide on how to proceed with a patient diagnosed with heart failure. It is now up to the heart team's decision when and how to treat mitral insufficiency (clip vs. surgery), revascularize the myocardium (percutaneous coronary intervention vs. coronary artery bypass grafting), implant intravascular or subcutaneous implantable cardioverter defibrillator (ICD), propose durable or temporary mechanical circulatory support or enlist the patient for heart transplantation. Countless patients frequently fly back to cardiology de-

partments due to exacerbation of cardiac disease and are not offered treatment that is within reach. Or the opposite — are offered half-way solutions which are thrown away as the heart is excised during transplantation a couple of weeks later. We need to come together as one true heart team involving surgeons, cardiologists, anesthesiologists, and intensivists supported by social workers, nurses, and physiotherapists as the disease is extremely complex and requires a collaborative and convergent approach.

Novel guidelines provide a patient-centered approach with a simplified triage algorithm, in which patients suffering from HF are directed to centers of excellence in advanced heart failure (AHFC), managed in local cardiology service with a clinical re-evaluation every 3–6 months, or offered a palliative care option. The end-stage heart failure management model seen before often revealed a delayed referral where multiorgan failure has already been or finished developing. Again, our national efforts to create a network of primary and specialized ambulatory care and out-patient clinics collaborating with centers of excellence seem to precede the ESC guidelines. The concept of "Krajowa Sieć Kardiologiczna" (or the National Cardiology and Cardiac Surgery Network) reflects what European Experts advocate for — a broad-range, an accessible network of centers focused on the in-depth diagnosis and treatment of the disease at its early and advanced stages. Yet, the concentration of expertise and experience justifies higher spending only if outcomes and quality are routinely measured and evaluated (structure, process, and outcomes measure) by independent agencies or committees.

This year's ESC/EACTS heart failure and valvular disease guidelines are one of the best published documents of this type. Not because they collect the most valuable and accurate clinical and experimental data, review and assess the quality of registries and randomized trials, emphasize the concept of a true heart team, but because they concentrate on the patient.

## *Article information*

**Conflict of interest:** Michał Zembala received consultant fees from Abbott Inc. and Boston Scientific. Other authors declare no conflict of interest.

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**How to cite:** Zembala M, Hryniewiecki T, Wita K, et al. Heart Failure Heart Team — time to act… now. Kardiol Pol. 2021; 79(10): 1163–1164, doi: 10.33963/KP.a2021.0123.

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# Transcatheter mitral valve repair and replacement. Expert consensus statement of the Polish Cardiac Society and the Polish Society of Cardiothoracic Surgeons

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Kardiol Pol. 2021; 79 (10): 1165–1177; DOI: 10.33963/KP.a2021.0116

**Received:**
September 13, 2021

**Revision accepted:**
September 17, 2021

**Published online:**
September 21, 2021

## INTRODUCTION

The need for an expert consensus statement of the Polish Cardiac Society and the Polish Society of Cardiothoracic Surgeons on transcatheter mitral valve repair and replacement in patients with significant mitral valve regurgitation (MR) has been triggered by dynamic progress in the development of new technologies, publication of data from randomized clinical trials and registries, increasing availability of these techniques, and growing experience of Polish operators. While in the case of patients with primary MR and acceptable operative risk, cardiac surgery is the treatment of choice (the primary surgical repair is associated with a better prognosis than valve replacement), the indications and long-term results of surgical treatment in patients with secondary (functional) MR related to left ventricular dysfunction are less documented, except for patients undergoing simultaneous revascularization or replacement of the aortic valve [1]. Patients with heart failure (HF) and secondary MR have an increased risk of mortality, a higher rate of hospitalizations for decompensated HF, and deterioration in the quality of life. The necessity to develop alternative treatment options for patients with increased or prohibitive surgical risks with both primary and secondary MR led to rapid advances in transcatheter mitral valve repair (TMVR). The current document primarily

discusses edge-to-edge TMVR techniques, which have been validated in randomized clinical trials and large registries in populations of patients with chronic primary and secondary MR. Other techniques of TMVR and transcatheter mitral valve implantation (TMVI) are at the early stages of clinical testing and are currently not available in Poland, except for ongoing clinical trials.

## TRANSCATHETER METHODS OF MITRAL VALVE REPAIR

Transcatheter mitral valve interventions can be divided into:

1. Repair methods using CE-marked devices
   a) Percutaneous repair by edge-to-edge approximation of anterior and posterior mitral valve leaflets (MitraClip and PASCAL devices), which mimics the surgical method developed by Alfieri;
   b) Percutaneous reduction of mitral annulus dilatation (annuloplasty):
      - Indirect (the device is implanted in the coronary sinus [Carillon]);
      - Direct annuloplasty (Cardioband device);
   c) Transapical implantation of artificial tendinous chords (Neochord, Harpoon);
   d) Combination of the techniques listed in subparagraphs a–b.
2. Techniques of transcatheter mitral valve implantation (TMVI)
   a) Implantation of balloon-expandable transcatheter aortic valve implantation (TAVI) bioprosthesis into a malfunctioning surgically implanted biological prosthesis (valve-in-valve) (CE mark for Sapien valve), surgically implanted mitral ring (valve-in-ring), or mitral annular calcification (valve-in-MAC);
   b) Implantation of dedicated TMVI device either *via* transseptal (still under clinical investigation) or transapical access (currently one bioprosthesis with CE mark).

Two TMVR (percutaneous edge-to-edge repair) systems are available in Poland: MitraClip (Abbott Vascular, Santa Clara, CA, USA) and recently introduced Pascal (Edwards Lifesciences, Irvine, CA, USA). It should be emphasized that most of the data from randomized clinical trials, providing results based on the evidence-based medicine methodology and clinical experience (over 150 000 patients), relate primarily to the MitraClip edge-to-edge repair system.

## THE EDGE-TO-EDGE REPAIR: MITRA CLIP SYSTEM

### *Clinical trial results*

#### Primary (degenerative) mitral regurgitation

Most of the currently available recommendations of scientific societies are based on the EVEREST study (Endovascular Valve Edge-to-Edge REpair STudy) and EVEREST II utilizing the MitraClip system. In the EVEREST study, in patients disqualified from conventional surgery, the use of this system was safe and technically feasible. MR grade reduction was less effective than surgical repair/replacement due to the higher prevalence of residual MR. Nevertheless, it reduced the severity of MR (to ≤2 + in approximately 75% of patients), clinical symptoms, and left ventricular remodeling [2]. The EVEREST II study involving 279 patients was the only randomized trial comparing the transcatheter approach to conventional surgery in patients with mostly primary MR. In the intention-to-treat analysis, the transcatheter procedure was less effective in MR reduction and in terms of the composite endpoint (death, surgery for mitral valve dysfunction, and grade 3+/4+ MR at 2 years). This was mainly because 20% of the patients treated with MitraClip required reintervention within one year of the procedure. However, there were no differences in the mortality rates. Percutaneous treatment emerged as superior in terms of safety at 30 days, which was driven by a decreased transfusions rate. At the same time, 37 patients (20%) in the percutaneous-repair group subsequently required mitral-valve surgery in the early postoperative period [3, 4]. It is important to remember that in EVEREST II, 73% of patients had primary MR and a relatively low operational risk. At the same time, modern European registries include patients with secondary MR and high or prohibitive operative risk. There is currently an ongoing randomized controlled trial to compare the clinical outcomes of the MitraClip system versus surgical repair in patients with primary mitral insufficiency who are at moderate surgical risk (REPAIR MR, NCT04198870).

#### Secondary (functional) mitral regurgitation

##### *Randomized trials*

The data concerning procedural success rate and effectiveness of MitraClip comes from two randomized clinical trials: MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) and COAPT (Cardiovascular Outcomes Assessment of the Mitra-Clip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation), published in 2018. The MITRA-FR study enrolled 304 patients with HF, severe secondary MR, and impaired left ventricular ejection fraction (LVEF) (15%–40%) despite guideline-recommended optimal medical therapy and cardiac resynchronization therapy (CRT). Patients were randomized (1:1) to receive either TMVR or conservative treatment. The number of periprocedural complications was low. At discharge, 91.9% of patients had a reduction in MR to ≤2+. Regardless, there were no significant differences in the primary endpoint rate (death or unplanned hospitalization for HF) at 12 months (54.6% vs. 51.3%). The mortality rate (24.3% vs. 22.4%) or unscheduled hospitalization rate (48.7% vs. 47.4%) did not differ significantly between the groups. Both groups achieved comparable symptomatic improvement (NYHA

[New York Heart Association] class reduction at one year). Complete clinical data was provided on as many as 99% of patients. The limitation of the study was an incomplete echocardiographic follow-up [5].

The COAPT study enrolled 614 patients with moderate to severe secondary MR and HF (NYHA II–IV) despite the use of maximal doses of guideline-recommended medical therapy and implantation of CRT (36.5%). The cause of cardiomyopathy was ischemic in 60.7% of the patients and nonischemic in 39.3%. Patients were randomly assigned to the MitraClip-device group (n = 302) or medical therapy alone — the control group (n = 312). The study revealed a significantly lower rate of hospitalization for heart failure (35.8% vs. 67.9%; HR 0.53; 95% CI, 0.40–0.70; *P* <0.001; NNT= 3.1) and lower all-cause mortality (29.1% vs. 46.1%; HR 0.62; 95% CI, 0.46–0.82; *P* <0.001) within 24 months of follow-up in the patients with device-based treatment compared with medical therapy alone. Moreover, their quality of life was significantly better, functional capacity was more preserved, and mitral regurgitation and left ventricular end-diastolic volume were reduced (secondary endpoints) [6].

The discrepancies between the results of both above-mentioned trials may be due to heterogeneous inclusion criteria and direct effects of the procedure (Table 1), which requires a comment. The studied groups differed in sample size (304 vs. 614 patients) and the duration of clinical follow-up for the primary endpoint (12 vs. 24 months).

In COAPT, the primary endpoint was hospitalization for HF, while in MITRA-FR, it was a composite endpoint (all-cause mortality and unscheduled hospitalization for HF). Inclusion criteria and MR definition were also different (MITRA-FR: effective regurgitant orifice area [EROA] ≥20 mm$^2$ and/or regurgitant volume >30 ml; COAPT: EROA ≥30 mm$^2$ and regurgitant volume >45 ml), as well as left ventricular ejection fraction (LVEF) (MITRA-FR: 15%–40%; COAPT: 20%–50%), and end-systolic left ventricle diameter (COAPT: <70 mm, lack of this criterion in MITRA-FR). As a result, in the MITRA-FR study, the mean left ventricular volume was higher (135 ml/m$^2$ vs. 101 ml/m$^2$), and the mitral regurgitation was less severe (EROA 31 ± 10 vs. 41 ± 15 mm$^2$), with comparable LVEF values (33 ± 7 vs. 31 ± 7%). Therefore, in the COAPT trial, the percentage of patients with severe MR (EROA ≥40 mm$^3$) was significantly higher (41 vs. 16%). Although the percentage of successful procedures in the MITRA-FR study was high, it was significantly higher in the COAPT study. Inclusion in the COAPT study required optimization of pharmacological therapy, confirmed by an independent team of experts prior to enrolment. MITRA-FR imposed less strict inclusion criteria, which is more similar to "real-world" practice [7]. Detailed post-hoc analyzes indicated that the inclusion and exclusion criteria for both trials led to the COAPT study enrolling patients with clinically predominant MR as the major mechanism of heart failure. In contrast, the MITRA-FR study included more patients with severe left ventricular dysfunction and a relatively less severe MR as a major cause of HF. Results of the extended 3-year follow-up of patients in the COAPT study confirmed the effectiveness of TMVR with the MitraClip system in reducing mortality and rehospitalization rates and improving the quality of life [8].

From a practical point of view, patients enrolled by the multidisciplinary Heart Team for MitraClip TMVR should meet the criteria of the high probability of a favorable response to this type of treatment.

The ongoing Reshape-HF2 trial (A Clinical Evaluation of the Safety and Effectiveness of the MitraClip System in the Treatment of Clinically Significant Functional Mitral Regurgitation [Reshape-HF2], *https://clinicaltrials.gov/ct2/show/NCT02444338*) has similar eligibility criteria in terms of MR as the COAPT study and intermediate criteria between COAPT and MITRA-FR for the assessment of left ventricular dysfunction.

To date, we have not obtained any results of randomized clinical trials comparing the effectiveness of transcatheter and surgical repair of mitral valve insufficiency in patients with secondary (functional) MR. The evaluation of these two strategies is the subject of an ongoing MATTERHORN study (Multicenter, Randomized, Controlled Study to Assess Mitral vAlve reconsTrucTion for advancEd Insufficiency of Functional or iscHemic ORigiN).

**Table 1.** Similarities and differences between MITRA-FR and COAPT studies with respect to echocardiographic characteristics and procedural outcomes immediately and at one year post-procedure

| | Mitra FR (n = 304) | COAPT (n = 614) |
|---|---|---|
| Severe MR criteria | EROA >20 mm$^2$<br>RV >30 ml | EROA >30 mm$^2$<br>RV >45 ml |
| Mean EROA | 31 ± 10 mm$^2$ | 41 ± 15 mm$^2$ |
| LVEDV/m$^2$ | 135 ± 35 ml/m$^2$ | 101 ± 34 ml/m$^2$ |
| LVEF | 15%–40% | 20%–50% |
| Medical therapy at baseline and during follow-up | Multiple adjustments in medical treatment were allowed | Medical treatment was optimized prior to randomization, only minor adjustments in treatment occurred during follow-up |
| Post-procedural MR ≥moderate-to-severe (3+) | 9% | 5% |
| Procedural complications | 14.6% | 8.5% |
| MR ≥3+ at 12 months | 17% | 5% |

Abbreviations: COAPT, Cardiovascular Outcomes Assessment of the Mitra-Clip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation; EROA, effective regurgitant orifice area; LVEDV, ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; MITRA-FR, Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation; MR, mitral valve regurgitation; RV, regurgitant volume

### *Registries*

Important data on edge-to-edge TMVR comes from registers — pan-European ACCESS-EU and German TRAMI. In the ACCESS-EU registry, approximately 70% of patients had secondary MR. MitraClip procedures were highly effective (99.6%) and safe (30-day mortality 3.4%). Additionally, after 6 months, 80% of patients achieved MR reduction to ≤2+ and symptomatic improvement to NYHA class I/II. The 6-month mortality rate was 11.2%. Data from the TRAMI registry of 486 patients indicate low (2.5%) in-hospital mortality and 12.5% mortality after three months [9, 10]. Expanding the anatomical indications for the procedure beyond those applicable in the EVEREST trial does not reduce the effectiveness of this method.

The Getting Reduction of Mitral Insufficiency by Percutaneous Clip Implantation (GRASP) registry compared patients who met the EVEREST criteria with those whose mitral valve anatomy was less favorable. It has been demonstrated that in both groups, incidence rates of the composite endpoint were similar, which indicates that it is justified to extend the inclusion criteria to inoperable/high-risk patients for whom the procedure is technically feasible. Similarly, the MitraSwiss, TRAMI, and Taramasso et al. registries covering patients with primary and secondary MR showed that the long-term prognosis in the groups that did not strictly meet EVEREST criteria was not inferior to the patients who did [10–12].

Increasing experience with the MitraClip system, especially in centers with a trained team and sufficient experience (≥50 procedures), shows that edge-to-edge repair may be a safe alternative to surgery in selected cases. However, the MR recurrence rate is significantly higher than in the case of surgical treatment.

A meta-analysis that included 1015 patients from 7 studies comparing both techniques has shown comparable 30-day and 6-month mortality rates despite higher EuroSCORE in the transcatheter group. Nevertheless, the severe MR recurrence rate was almost five times higher in the TMVR group [13]. It should be emphasized that recurrent MR, as well as residual regurgitant jet size, are strong predictors of long-term mortality in patients after mitral valve repair procedures in both primary and secondary mitral regurgitation [1].

Clinical experience with the PASCAL system (another edge-to-edge TMVR system) includes registry studies from European heart valve centers. They indicate the effectiveness of this system in reducing MR and functional improvement of HF, mainly in patients with secondary MR [14]. The PASCAL system has recently been registered in Poland.

## *Recommendations of scientific societies*

Newest ESC/EACTS Guidelines on the management of valvular heart disease had been published in 2021, so they reflect the progress of knowledge on transcatheter TMVR in patients with secondary MR. 2017 valvular heart disease guidelines included only the EVEREST and EVEREST II findings, which served as the basis for the approval of the MitraClip system in the US in patients with primary MR. 2021 Guidelines expand the indication to patients with heart failure and secondary MR in accordance with the results of the randomized COAPT and MITRA.Fr studies. The guidelines reinforce the heart team-based approach to patients' selection and qualification for edge-to-edge repair. Preferably the patients should fulfill the clinical and anatomic criteria compatible with the COAPT (high likelihood of improvement). The class of indications is IIa with level of evidence (LOE) B for patients not eligible for surgery and with high likelihood of improvement and IIb LOE C in selected high-risk symptomatic patients not eligible for surgery and not meeting the criteria of increased chance of response to edge-to-edge repair [15]. In general the guidelines pave the way to more widespread use of the edge-to-edge treatment in symptomatic HF patients with the aim to reduce the symptoms burden and heart failure rehospitalizations.

The American College of Cardiology/American Heart Association's guidelines for the management of patients with valvular heart disease published in 2021 include new, less restrictive recommendations for edge-to-edge TMVR, which extend the pre-existing indications, in the case of 1) severe primary MR in symptomatic patients (NYHA class III-IV) with high or prohibitive surgical risk, favorable valve anatomy and estimated survival time over one year (class of recommendation IIa); 2) severe secondary MR associated with left ventricular dysfunction (LVEF <50%), symptoms in functional classification II-IV despite optimal pharmacotherapy of HF, favorable valve anatomy on echocardiography, LVEF 20%–50%, left ventricular end systolic diameter ≤70 mm and pulmonary artery systolic pressure ≤70 mm Hg (class of recommendation IIa) [16]. If coronary revascularization is not necessary, the recommendations for surgical treatment in this particular group of patients are class IIb. The classification algorithm for transcatheter mitral valve procedures based on the American Heart Association/American College of Cardiology's guidelines is presented in Figure 1.

## *Determining patients' eligibility for TMVR*

### The role of the multidisciplinary Heart Team in determining proper treatment strategies

Decision-making for intervention should be made by a "Heart Team" with particular expertise in valvular heart disease, comprising cardiologists, cardiac surgeons, interventional cardiologists, anesthetists, and imaging specialists, experienced in mitral valve anatomy assessment and interventional imaging in structural heart disease. In some cases, the professional opinion of a radiologist performing multislice computed tomography of the heart is necessary.

Due to the high risk associated with comorbidities, patients should be treated in centers with highly specialized multidisciplinary teams, trained in both surgical and tran-

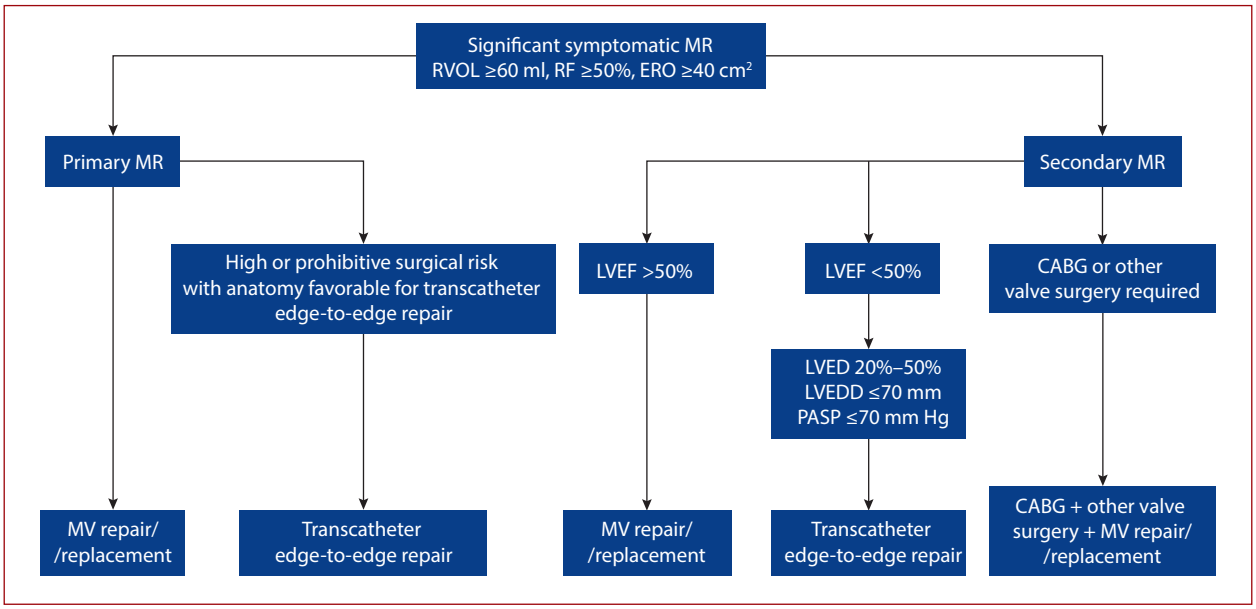


**Figure 1.** Algorithm for management of patients with significant symptomatic MR. Based on: [15] and [16].
Abbreviations: CABG, coronary artery bypass grafting; other — see Table 1

scatheter procedures to deliver high-quality care ("heart valve centers"). In addition to an interventional cardiologist or a cardiac surgeon experienced in a given interventional technique, a cardiologist experienced in procedural transesophageal echocardiographic imaging plays an important role in a minimally invasive valve repair or implantation procedure because, unlike other transcatheter procedures (e.g., TAVI), the use of fluoroscopy is of less importance and proper planning of the procedure and surgical navigation are possible only based on a transesophageal examination, optimally with three-dimensional imaging. Patients treated with TMVR should undergo a periodic clinical and echocardiographic evaluation to exclude late complications and determine long-term efficacy. The Heart Team's opinion is of particular importance in patients with primary MR, in whom conventional surgical treatment is the procedure of choice, and the referral for transcatheter treatment applies to the surgically ineligible patients. In the group of patients with secondary MR, it is crucial to provide optimal pharmacological therapy in accordance with the guidelines and, if applicable, implantation of CRT. Patients eligible for the transcatheter procedure are those with symptomatic HF despite pharmacotherapy optimization. Cooperation with HF specialists may be helpful to facilitate patient management and to decide on heart transplant or left ventricular assist devices (LVAD) implantation in uncertain cases.

## Clinical evaluation

1. Symptomatic HF (NYHA II–IV) despite optimal medical pharmacotherapy in maximum tolerated doses, in line with the guidelines for the management of heart failure, including CRT implantation if indicated, as well as complete revascularization;
2. Shared decision of the multidisciplinary heart team on TMVR. In patients with primary MR, edge-to-edge TMVR can be considered for inoperable or high-risk surgical patients. However, in the case of secondary MR, the edge-to-edge repair is the treatment of choice in patients meeting clinical and anatomical criteria who are not candidates for surgical revascularization. Transcatheter edge-to-edge repair may also be beneficial in patients waiting for a heart transplant or LVAD implantation;
3. Estimated life expectancy should be at least 12 months in patients with primary MR. In patients with secondary MR, the futility of interventions in patients unlikely to benefit from the treatment must be taken into account;
4. It is recommended to avoid surgery in patients with a low chance of improved expected quality of life due to their general condition (emaciation, advanced frailty syndrome), and comorbidities. Important determinants include the presence of severe pulmonary hypertension, severe right ventricular dysfunction with significant tricuspid regurgitation, extremely high NT-proBNP levels (>5000 pg/ml), and LVEF <20%. The coexistence of pulmonary hypertension, right ventricular dysfunction, and LVEF <20% drastically worsens the prognosis;
5. Optimal pharmacotherapy.

Since the COAPT study confirmed the benefit of edge-to-edge repair treatment in patients for whom optimization of pharmacotherapy was an essential element of referral for the procedure, it is recommended that all implanting centers should assess the pharmacotherapy in the screening protocol following ESC recommendations.

It is recommended to consider the following drug groups: (1) angiotensin-converting-enzyme inhibitors/an-

giotensin II receptor antagonist or sacubitril/valsartan; (2) a beta-blocker in an optimal dose – with dose adjustments based on the patient's heart rate and blood pressure; (3) mineralocorticoid receptor antagonists; (4) loop diuretic; (5) ivabradine. The abovementioned pharmacotherapy should be continued for a minimum of 3 months in an outpatient clinic before deciding on the referral. The ineffectiveness of the therapy or lack of the possibility of its further optimization should be documented.

## Echocardiographic criteria

Patients' referrals for procedures performed without extracorporeal circulation are based on the information obtained by three-dimensional (3D) transthoracic and transesophageal echocardiography. Echocardiographic evaluation should provide information on 1) the severity and mechanism of MR; 2) the validity of the procedure based on the MR assessment in relation to the volume of the left ventricle, by dividing patients into groups with "proportionate" and "disproportionate" MR in patients with secondary regurgitation; 3) anatomical assessment of the mitral valve and subvalvular apparatus in terms of feasibility of the procedure; 4) evaluation of other parameters influencing the long-term outcomes of the procedure (left and right ventricular function, presence of other valvular diseases, including tricuspid valve regurgitation, presence of pulmonary hypertension); 5) contraindications.

1. Primary MR
   a) Presence of severe MR based on qualitative, semi-quantitative, and quantitative assessments
   b) No anatomical contraindications
2. Secondary MR
   a) Presence of severe MR based on qualitative, semi-quantitative, and quantitative parameters assessment — at least moderate to severe MR as assessed with qualitative parameters (EROA ≥0.3 $cm^2$, EF ≥40%). Due to the asymmetric nature of the regurgitant orifice, quantitative assessment should be based, if possible, on a 3D reconstruction, and where 3D techniques are not available, an integrated approach is strongly recommended instead of referring to single measurements. Imaging should take into account vena contracta measured in two perpendicular planes, including along the coaptation line.
   b) Disproportionate MR should be evaluated as EROA to the left ventricular end-diastolic volume (LVEDV) ratio (the higher the EROA/LVEDV [$mm^2/ml \times 100$] ratio, the greater the profitability of the procedure compared to pharmacotherapy) or regurgitant volume to EDV ratio (RV/LVEDV). The left ventricular volume alone and LVEF (especially <20%) are also important prognostic factors for the lack of clinical improvement. Additionally, the presence of global vs. regional wall motion abnormalities, presence of symmetrical vs. asymmetrical regurgitant jet is assessed. This concept facilitates the decision-making process, but it is not the only parameter that should be taken into consideration. Simply put — it is reasonable to consider patients as eligible for the procedure, with LVEF ≥20% and left ventricular end systolic diameter ≤70 mm; however, these parameters, especially regarding the end-diastolic dimension of the left ventricle, should be treated as indicative only and should be interpreted depending on the clinical condition, the severity of regurgitation, nature of left ventricular remodeling and the morphology of the valve itself.
   c) Shared echocardiographic criteria for primary and secondary MR
      - Primary morphological criteria for patient eligibility were based on a pre-specified EVEREST study protocol. Key inclusion criteria included a regurgitant jet origin associated with the abnormal coaptation of A2 to P2 segments, and the mitral valve area was equal to or greater than 4.0 $cm^2$. Currently, it is more common to use the criteria which determine the feasibility of the intervention based on extensive experience and new surgical techniques, mainly from German and American centers. The evolution of the MitraClip system is also significant (introducing two lengths and widths of the clip arms and the possibility of independently gripping the leaflets in the G4 system). Nevertheless, mitral stenosis following Mitra-Clip insertion remains the primary concern, particularly in patients who require more than one clip due to broad regurgitant jet. Published in 2013, an expert opinion of the international group of experienced operators and echocardiography specialists divide patients into three groups in terms of mitral valve (MV) morphology:
        – Ideal valve morphology for a MitraClip procedure: MR originating from the mid-portion of the valve (A2P2), no evidence of calcification in the grasping area of the A2 and/or P2 scallops, mitral valve area >4.0 $cm^2$ (3D-echo planimetry measurements are the first-choice method), posterior leaflet mobile length ≥10 mm, coaptation depth <11 mm, a width of the flail segment ≥15 mm, or flail gap ≥10 mm.
        – Unsuitable valve morphology for a Mitra-Clip procedure: Severe calcification in the grasping area, perforated mitral leaflets or clefts, increased risk of postoperative mitral stenosis (mitral valve area <3.5–4.0 $cm^2$ — EVEREST exclusion criterion, which is not currently a key decision parameter), length of posterior leaflet <7 mm, Barlow's disease with multiple mitral regurgitation jets, pres-

ence of a broad jet especially in patients with intermediate mitral valve area at baseline, which may indicate the need for multiple clips in order to successfully approximate leaflets and increase coaptation, rheumatic valve disease — with restriction in systole and diastole or endocarditic valve disease. The use of longer clips and the ability to independently grasp the leaflets make the limitations resulting from a large coaptation gap less significant.

- Complex: intermediate morphology between a and b. The feasibility of the procedure depends on the experience of the center and the operators.

- The exclusion criteria for the MitraClip therapy are the evidence of intracardiac, inferior vena cava or femoral venous thrombus, cardiac tumor, or active endocarditis. Understanding the interatrial septum anatomy is of great importance. The presence of interatrial masses, such as an aneurysm, lipomatous hypertrophy of the interatrial septum, and patent foramen ovale, makes the procedure more challenging.

The feasibility of the procedure in other cases depends mainly on the experience of the operators and the quality of periprocedural imaging [17]. The procedure can be performed safely in patients who previously underwent transcatheter left atrial appendage occlusion.

### *Recommendations*

Determining patients' eligibility for edge-to-edge TMVR should be in alignment with the consensus recommendations developed in centers with expertise in both surgical and percutaneous treatment of mitral valve disease by an experienced multidisciplinary team. It is the first-choice treatment in patients with severe degenerative MR and groups with high or prohibitive surgical risk. In patients with secondary MR and HF, TMVR may be considered as long as a medical therapy has already been dose-optimized and CRT-D has been implanted, if indicated.

As the COAPT clinical trial consistently demonstrated the benefits of MitraClip in patients with secondary MR, it is advisable to select patients whose clinical and anatomical characteristics are similar to the COAPT eligibility criteria, and the likelihood of symptomatic improvement is high.

## Planning the procedure and post-operative care

### *Procedural aspects*

The procedure is performed under fluoroscopy and with continuous transesophageal echocardiography (TEE) guidance with 3D imaging. It is imperative to establish means of communication about the anatomy of the heart that is understood by the entire team (nomenclature of mitral valve [MV] segments, directions of movement [medial-lateral, anterior-posterior]).

TEE is crucial, from selecting the transeptal puncture site (fossa ovalis, approximately 4 cm above the mitral annulus and at a safe distance from the aorta and free atrial wall) to releasing the last clip. The site of transseptal puncture depends on the origin of mitral regurgitation jet (for medially directed jet, it is more beneficial to puncture the septum lower, in the bicaval projection, than for jet directed laterally). After a septal puncture, it is necessary to confirm the safe location of the guidewire in one of the pulmonary veins and during the navigation of the MitraClip device to confirm that it does not touch the atrium walls. If it is not feasible to insert a guidewire into the pulmonary vein (e.g., a significantly enlarged atrium), a pre-shaped stiff guidewire (e.g., Safari or similar) may be used and left behind in the atrium cavity until the guiding catheter is inserted. Optimal 2D imaging is usually feasible by tilting the TEE probe backward and placing it in the axis of the mitral valve and the left ventricle. The same axis should also be the trajectory of the clip insertion into the left ventricle, which is achieved by the proper introduction of the delivery system into the septum, its rotation, and setting the catheter deflection control knobs. Deviations from these rules usually cause difficulties in imaging the clip, skewed trajectory when passing the valve (diving), and subsequently uneven grasp of the leaflets, leading to an increased risk of valve deformation after the release of the device. The technique which facilitates and shortens this stage of the procedure is the intraoperative real-time 3D TEE imaging (RTTEE3D). The surgical view of the MV in RTTEE3D allows the maneuvers to position the clip arms perpendicularly to the line of coaptation at the intended implantation site. The crossing of the valve is usually done under the guidance of 2D TEE, preferably in 2 perpendicular planes (X-plane). After entering the ventricle, the position of the clip is once more assessed with RTTEE3D. The evaluation allows determining as well if the clip orientation is perpendicular to the line of MV coaptation.

The introduction of a new generation of MitraClip devices, including wider clips, allows obtaining a reduction of MR after a single clip application in a significant percentage of cases. However, in the presence of a broad jet, which requires multiple clips, it is reasonable to use the first one medially and the next ones laterally, which allows avoiding subsequent implantation in close proximity to the commissure.

To grasp the leaflets of the mitral valve, a 3-chamber mid-oesophageal view is sufficient, in which a cross-section through the arms of the device is visible simultaneously with the anterior and posterior leaflet (left ventricular outflow tract [LVOT] view). However, it is optimal to use two perpendicular views (three-chamber and two-chamber mid-oesophageal view — LVOT and intercommissural view), which allows for proper navigation, as well as determining when the clip is adequately positioned and whether arm orientation is perpendicular to the line of MV coaptation.

The decision to release the clip is made on the basis of:

1. Improved mitral valve coaptation/ reduced size of mitral regurgitation jet;
2. The stability of the device judged by the length of the leaflets grasped by its closed arms and compared with their pre-treatment length;
3. Mean MV pressure gradient <5 mm Hg.

Echocardiographic 3D-guided planimetry of the resulting double valve orifices is also helpful in the decision-making process.

During the procedure, significant manipulations should be avoided to minimize chordal and subchondral entanglement, which may damage the mitral subvalvular apparatus. The decision on multiple clip implantation depends on the MR reduction grade after the first MitraClip device deployment, the width of the baseline coaptation defect, the transvalvular gradient, and the presence of the clefts. Recently available clips with wider grasping areas allow reducing the number of clips required. Until the clip is released from the delivery system, it can be repositioned as needed. After the MitraClip system has been deployed and released, residual regurgitation and stenosis are assessed (with a mean gradient ≤5 mm Hg and heart rate ≤80 beats/min) as well as clip stability and presence of excessive pericardial fluid. 3D planimetry is also a useful tool in assessing the residual mitral valve area. The entire procedure should be preceded with a detailed analysis of each stage and in an agreement between the operator and interventional imaging cardiologist. It is of utmost importance to obtain an optimal MR reduction to provide better outcomes.

### *Type of anesthesia*

MitraClip implantation procedures are performed under general anesthesia. It enables a short-term respiratory arrest and facilitates positioning of the system and grasping the leaflets of the valve in certain cases of high respiratory mobility. Recently published data suggest the safety of MitraClip procedures under deep analgosedation instead of general anesthesia, but this is not yet the recommended standard of practice [18]. Furthermore, general anesthesia improves patients' tolerance to the TEE probe placement in the supine position and ensures complete immobilization, which is crucial for the precision of the procedure.

### *Hemostasis*

Due to the large-caliber delivery system (24F diameter; 8.1 mm), appropriate hemostasis management is required. The following techniques are available: (1) prolonged manual compression; (2) "8" or "Z" suture, as well as; (3) off-label use of the pre-closure technique (1–2 Proglide sutures); (4) combining techniques 1–3.

No prospective studies are aiming to compare the efficacy of these different methods [19].

### *Anticoagulant and antiplatelet therapy*

Activated Clotting Time (ACT) should be monitored regularly during the procedure. Target, therapeutic ACT level above 250–300 seconds should be maintained. The timing of heparin administration varies. Most operators administer the full dose prior to transseptal puncture (TSP), others wait until puncture has occurred or administer half of the dose prior to puncture and the other half after TSP. The optimal time to initiate anticoagulation has not been studied so far. There is no reliable scientific evidence that would enable the formulation of clear recommendations regarding anticoagulant and antiplatelet treatment after the procedure. In patients without indications for anticoagulation, dual antiplatelet therapy with acetylsalicylic acid for 6 months is used, together with clopidogrel for the first month. Oral anticoagulation (vitamin K antagonist or non-vitamin K antagonists oral anticoagulant) is required in patients with atrial fibrillation. An individual bleeding risk assessment is required. Each center should develop an antiplatelet treatment protocol and include the recommendations on the patient's hospital discharge form.

### *Hemodynamic assessment*

Along with echocardiographic assessment, additional information is provided by monitoring mean left atrial pressure (mLAP). No decrease or increase in mLAP after surgery is associated with a higher risk of readmission in a long-term follow-up for HF, regardless of residual MR on TEE [20]. It is reasonable to measure mLAP during edge-to-edge repair procedures to evaluate the effectiveness of the intervention and assess the prognosis. A postoperative evaluation of pulmonary venous flow reversal as an indirect parameter of the effectiveness of the procedure is also important.

### *Iatrogenic atrial septal defect after transcatheter mitral valve repair*

MitraClip placement requires interatrial transseptal puncture (IAS), which, due to the relatively large delivery system and guiding catheter (≥22 F), creates an atrial septal defect (ASD). It may close spontaneously or remain patent after the procedure (incidence 50%–85% after 30 days and <30% after 12 months, defects <7–8 mm are more likely to close spontaneously). Factors favoring the formation of iatrogenic ASD (iASD) include the diameter of the delivery system, long surgery duration, multiple manipulations with the delivery system, left ventricular hypertrophy, delivery system maneuvers, and an increased postoperative left atrial pressure.

In terms of hemodynamic consequences, postoperative ASD may cause:

1. Acute complications immediately after the procedure: a severe left-to-right shunt with hypoxemia and acute heart failure (approximately 1.5% of patients);
2. Chronic complications associated with a left-to-right or bi-directional shunt (right ventricular overload, pulmonary hypertension);
3. Pressure relief of the left atrium with no negative impact;
4. No hemodynamically significant consequences.

The right-to-left shunt is associated with a subsequent worse 12-month prognosis than the left-to-right shunt.

In case of acute respiratory failure, it is recommended to close the iASD immediately after the TMVR procedure with a dedicated occluder, using TEE guidance to assess the size of iASD. The long-term approach to postprocedural ASD with a persistent hemodynamic effect (L–R shunt) is controversial. The data from the registries are contradictory and show both the beneficial effect of left atrial decompression on HF symptoms, as well as the progression of HF and worsening of prognosis [21]. The randomized MITHRAS trial, in which the primary endpoint was changed in the 6-minute walk test distance, did not show transcatheter iASD closure superiority over conservative therapy in terms of functional outcomes [22].

#### *Summary*

Routine closure of the iASD is not recommended in patients after edge-to-edge repair procedures unless there is hemodynamic instability and periprocedural hypoxemia.

The decision to close the defect in an elective procedure depends on the hemodynamic significance of the shunt (right ventricular overload, pulmonary hypertension) and the risk of paradoxical embolism (venous thromboembolism, a history of pulmonary embolism). Operators should be acquainted with the ASD closure procedure; different sizes of ASD occluders ought to be available in the laboratory.

#### *Procedural Complications and Complication Management*

Periprocedural complications include:

- perioperative death (<2%);
- bleeding at the access site of various severity, including major bleeding requiring transfusion (to 17.2%) [23];
- early partial leaflet detachment (1%–4.8%);
- clip embolization (<0.05%);
- leaflet perforation, mitral chordae rupture (0.8%);
- cardiac perforation and pericardial tamponade (0.7%);
- thrombus formation within the left atrium (approx. 9%);
- stroke and transient ischemic attack (0.9%–1.3%);
- renal failure (4.2%);
- oesophageal damage (0.6%–2.8%);
- gas embolism.

The formation of an atrial thrombus and/or on the device is an indication for prolonged heparin therapy in therapeutic doses and echocardiographic control prior to hospital discharge. Once the thrombus resolves, the use of an oral anticoagulant and regular echocardiographic monitoring should be considered.

In a small percentage of cases, patients with transcatheter treatment failure require urgent cardiac surgery. The incidence is rare (<0.5%), and the number of cases decreases with the increasing experience of operators and centers [24]. In case of unsatisfactory MR reduction, dislocation of the clip, or relevant postprocedural mitral stenosis, surgical treatment should be considered. Complete clip detachment or clip embolization usually requires conventional surgery. Partial leaflet detachment of the clip may occur in the periprocedural period or after the procedure. Half of the patients with late MitraClip single leaflet detachment are treated conservatively. In case of unsuccessful initial repair and development of severe recurrent MR, a repeated MitraClip procedure is a feasible treatment option for high/prohibitive risk patients. In some patients, it is necessary to consider surgical treatment if the placement of the clip causes ischemia.

#### *Postprocedural clinical assessment*

Transthoracic echocardiography evaluation prior to hospital discharge is recommended. Echocardiographic reassessment after approximately 30 days, 6 months, and 1 year is justified.

It is useful to evaluate the volume of the left ventricle, the size of the left atrium, and the pulmonary venous flow (indirect parameters indicative of a permanent reduction of the regurgitant jet), as well as the size of the iASD, right ventricular function, and pulmonary hypertension. During the postoperative evaluation, it is also necessary to perform routine laboratory tests, optimize pharmacotherapy, and evaluate the compliance with guideline-recommended anticoagulant and/or antiplatelet therapy.

### *Alternative uses of MitraClip system (early stages of clinical testing)*

Limited data from the registers suggest safety and efficacy of MitraClip procedures in MR correction in selected patients from the following groups: patients considered for orthotopic heart transplantation (OHT) or implantation of a left ventricular assist device (LVAD) as a bridge procedure providing hemodynamic support; in patients with residual regurgitation jet after the surgical mitral valve repair; in patients with severe symptomatic MR related to obstructive hypertrophic cardiomyopathy to eliminate systolic anterior motion of the mitral valve; in therapy-resistant cardiogenic shock related to decompensated HF and concomitant severe chronic MR, and in patients with acute MR. There is no clinical data to support the long-term effectiveness of this approach. Decisions in such cases should be made by a multidisciplinary team [25]. Edge-to-edge procedures are increasingly performed in patients with concomitant or isolated tricuspid regurgitation in order to reduce the tricuspid regurgitant jet velocity [2, 3].

### *Institutional and operator requirements*

Operator: It is recommended that the learning curve of operators and echocardiographers include the first 50 patients with optimal MV morphology, and then patients in the conditionally acceptable MV anatomy group may be treated.

Pursuant to the regulation of the Ministry of Health of November 12, 2015, specifying the conditions for highly specialized services, transcatheter non-surgical repair of the mitral valve in high-risk patients may be performed

in centers that meet, among other things, the following requirements: (1) hybrid cardiac catheterization laboratory; (2) interventional radiology or catheterization laboratory; (3) intensive postoperative care in conditions equivalent to intensive care. The team performing the procedure should have extensive documented experience in mitral valve repair (cardiac surgeon) or transcatheter treatment of structural heart disease (cardiologist), as well as an available specialist in echocardiographic imaging, an anesthesiologist, surgical nurses, and a perfusionist. Supervision over the patient after the procedure is performed, apart from the intensive care or intensive cardiac care unit staff, also by a team consisting of a cardiac surgeon, a cardiologist, and a nurse specializing in the field of anesthetic and intensive care nursing.

In addition, the regulation specifies requirements for the team's experience (10 transcatheter non-surgical mitral valve repair/replacement procedures in high-risk patients performed) as well as the eligibility criteria:

a) Patients with severe symptomatic MR (EROA >0.3 for functional and >0.4 for primary MR);
b) Disqualified by a multidisciplinary team from classical (surgical) or minimally invasive surgical treatment due to a documented high cardiac surgery risk;
c) The patient selection process is performed by the heart team.

Procedures should be reported as a part of the National Registry of Cardiac Surgery Procedures — however, it seems advisable to create a dedicated register covering all transcatheter edge-to-edge procedures, enabling a reliable follow-up assessment of short and long-term results of the procedure.

### *Percutaneous mitral valve procedures during COVID-19 pandemic*

The recently published expert opinion of the Working Group on Valvular Heart Diseases, the Working Group on Cardiac Surgery, and the Association of Cardiovascular Interventions of the Polish Cardiac Society emphasizes the need to reduce the risk of patients and staff's infection with SARS-CoV-2 virus. Simultaneously, it is crucial that patients with symptomatic HF, despite guideline-directed medical therapy, can receive interventional treatment of the MR, which may favorably affect their quality of life and prognosis [26].

## DEVICES FOR PERCUTANEOUS CORRECTION OF MITRAL REGURGITATION, WITH THE "CE" MARK, THE USE OF WHICH HAS NOT BEEN INCLUDED IN THE CURRENT VHD GUIDELINES

**Carillon mitral contour system** (Cardiac Dimension Inc., Kirkland, WA, USA) is the only device for percutaneous indirect mitral valve annuloplasty which has obtained the "CE" mark. The device is intended for the treatment of patients with functional MR. The Carillon device incorporates two self-expanding anchors and a pre-shaped connecting bridge segment. The implantation procedure is performed using a venous approach under general anesthesia under the guidance of TEE. When delivered percutaneously to the coronary sinus, the Carillon device causes a decrease in the mitral annulus size and subsequently significantly reduces the mitral regurgitant volume. If the obtained effect is suboptimal or the compression of or the obstruction to the flow in the circumflex coronary artery or its branches is observed, the device can be folded and removed. AMADEUS (CARILLON Mitral Annuloplasty Device European Union Study), TITAN (Tighten the Annulus Now), and TITAN II studies have shown that mitral annuloplasty using the Carillon system significantly improves the quality of life by reducing MR, as well as physical performance assessed with the 6-minute walk test in patients with FMR [27]. In 2019, the results of a multicenter, blinded, randomized, sham-controlled REDUCE-FMR (Carillon Mitral Contour System for Reducing Functional Mitral Regurgitation) trial were published. One hundred twenty patients receiving optimal heart failure medical therapy were randomized to either the Carillon system implantation group for mitral annular reduction or the sham-controlled arm. At one year, a statistically significant reduction in mitral regurgitant volume in the treatment group compared to the control group (decrease of 7.1 ml/beat vs. an increase of 3.3 ml/beat, respectively; $P = 0.049$), left ventricular end-diastolic volume decrease (of 10.4 ml vs. an increase of 6.5 ml; $P = 0.03$), and left ventricular end-systolic volume decrease (of 6.2 ml vs. an increase of 6.1 ml; $P = 0.04$) were observed. When implanting the Carillon device, it should be remembered that perforation of the thin-walled coronary sinus is a possible procedural complication and that in some patients, the circumflex coronary artery may be compressed with subsequent flow obstruction. For the above reasons, 14% of patients were not implanted with Carillon in the REDUCE-FMR study [28]. Indirect mitral annuloplasty using Carillon is an effective treatment method that reduces MR and results in favorable left ventricular remodeling. However, the device is now used relatively infrequently in daily clinical practice.

**Cardioband mitral system** (Edwards Lifesciences, Irvine, CA, USA) is intended for percutaneous, direct mitral valve annuloplasty in patients with functional MR. The procedure is performed under general anesthesia guided by TEE. The device is delivered through a femoral venous puncture. The most crucial part of the Cardioband is a polyester-covered wire, which is successively attached to the back of the patient's native mitral ring with a number of anchors, and after the insertion, it resembles an incomplete surgical ring. The mitral annulus is then reduced in size using a unique regulating tool under the TEE guidance to minimize MR. In 2019, a multicenter study was published, which demonstrated the impact of Cardioband directly after implantation and at 12 months in 60 patients with

echocardiographically assessed moderate (27%) or severe (73%) secondary MR. Technical success was achieved in 97%, device success in 72%, and procedural success in 68% of patients. In addition, there was a significant reduction of the septolateral diameter (3.7 ± 0.4 vs. 2.6 ± 0.4 cm; $P < 0.01$). The mitral regurgitation grade (in alive patients free of reintervention) and at 12 months was mild in 69%, moderate in 26%, and severe in 5% of patients. Anchor disengagement was observed in 10 patients, resulting in device inefficacy in 5 patients. In none of these patients did the device migrate or detach from the mitral ring. In the follow-up, six patients required percutaneous MR correction. During Cardioband implantation, care should be taken not to injure a coronary artery with the anchor while securing the ring [29].

The Cardioband customized annular reduction procedure reduces MR; therefore, it can be assumed that role of Cardioband in the treatment of functional MR will significantly increase in the future.

## TRANSCATHETER CHORDAL REPAIR IN MR

**Neochord** DS 1000 (Neochord Inc., St. Louis Park, MN, USA) and **Harpoon** (MVRS, Edwards Lifesciences, Irvine, CA, USA) systems, which both received CE mark approval, allow transesophageal echocardiography-guided (2D and 3D) transapical, beating-heart MV repair with insertion of prosthetic chords. The Neochord system allows the implantation of artificial chords to the edges of MV leaflets by capturing the leaflets and their puncture with a needle. The Harpoon system obtains the leaflet capture via a double helix-shaped knot on the atrial aspect of the leaflet after its puncture by the integrated needle. In both systems, the length of the chords is adjusted under echocardiography guidance, and the apical end of the chords is secured on the external surface of the heart. In both methods, implantation of at least 3 chords is recommended. Neo-chord implantation is dedicated to patients fulfilling anatomical criteria, e.g. the sum of the leaflet lengths should be at least 20% larger than the anterior-posterior dimension of the mitral annulus to achieve the coaptation of 5 mm. In the Neochord group, the best results were obtained in patients with elongated or ruptured chordae tendineae to the P2 segment of the posterior leaflet [30]. So far the Harpoon system has been used only in patients with P2 pathology.

Numerous observational studies have demonstrated the safety and effectiveness of both methods; therefore, they are already widely used clinically [31, 32]. The Harpoon device is equipped with a hemostatic introducer that minimizes intraoperative bleeding. Due to the lack of a dedicated hemostatic sheath, it is recommended to use the Cell Saver system with the Neochord technique. The validity of these techniques has been documented extensively in a 5-year follow-up. Initial reports on large groups showed that 10%–35% of patients have greater than moderate MR postoperatively, which requires careful selection of patients [33].

## TRANSSEPTAL TRANSCATHETER IMPLANTATION OF DEDICATED MITRAL VALVE BIOPROSTHESIS (UNDER CLINICAL TRIALS)

Edge-to-edge MR correction procedures, although effective and safe in the majority of patients, are subject to numerous limitations. About 10% of patients have a significant residual in the postoperative evaluation. What is more, the use of the MitraClip/Pascal systems is technically not feasible in a number of candidates, and recurrent MR after the intervention remains a challenge. The learning curve for the MitraClip procedure flattens after 200 procedures. Therefore, it is justified to look for an alternative solution, such as percutaneous mitral valve implantation via the transseptal approach. Several systems are currently evaluated in preclinical and clinical trials. Use of some of the first-generation systems was discontinued, or the investigation has been temporarily suspended due to observed complications (e.g., valve thrombosis). TMVI is a far more complex procedure than TAVI due to the anatomy of the mitral valve, the risk of the obstruction of the LVOT, a larger size of the delivery systems, and sometimes difficulties in maneuvering the device in the left atrium. Furthermore, patients treated with TMVI often have multiple comorbidities, which result in a very high 30-day mortality ranging from 18% to up to 60% [4]. It should be noted that the papers published so far are based on a relatively small group of patients. At present, the prospect of routine trans-septal TMVI procedures is distant. The system described below was used in Poland in only a few eligible candidates.

**High Life Valve** (HighLife Medical Inc., Irvine, CA, USA) is a self-expanding bioprosthesis that consists of a nitinol alloy-based frame covered with a polyester graft and trileaflet bovine pericardium with an annular diameter of 28 mm.

The first stage of the procedure is placing a ring-shaped implant through the aortic valve around the subvalvular apparatus. The ring ensures proper fixation for the prosthesis. Subsequently, a self-expanding prosthesis is delivered transseptally and implanted into the ring. So far, five successful procedures have been performed in Poland with the use of High-Life bioprosthesis. In total, approximately 30 treatments have been performed using this valve in the world. In preparation for the procedure, computed tomography plays a key role, which allows assessing the risk of LVOT obstruction, one of the basic eligibility criteria.

## IMPLANTATION OF DEDICATED TRANSCATHETER MITRAL VALVE BIOPROSTHESIS VIA TRANSAPICAL ACCESS

Transapical TMVI has emerged to be a promising alternative to edge-to-edge repair. Transcatheter mitral valve replacement systems designed for transapical delivery, which are still evaluated in clinical trials but for which already quite extensive clinical experience is available, are Tendyne Bioprostehsis (Abbott Inc, USA), Intrepid Valve (Twelve Inc, Medtronic Inc., Fridley, MN, USA), CardiAQ (Edwards

Lifesciences, Irvine, CA, USA), Tiara (Neovasc, Richmond, Canada), and Gate Valve (Navigate Inc., James Bay, CA USA). Some of the abovementioned have already received the CE mark (Tendyne), and others are still in the clinical trial phase. In a simplified manner, the procedural technique consists of gaining access to the left ventricle through a large dedicated delivery sheath and precise off-pump implantation (during rapid ventricular pacing) of a mitral valve bioprosthesis into the native mitral annulus or the leaflets of the patient's calcified native valve. Procedural guidance is mainly performed under fluoroscopy and TEE assistance.

TENDYNE valve is currently the only CE-approved and commercially available transcatheter mitral valve implant. However, unlike the previous valves, it is implanted via a transapical approach. The valve consists of 2 nitinol self-expanding joined stents with three porcine pericardial leaflets sewn into the frame. The system is anchored with the use of a tether and epicardial pad to the apex of the heart. In a registry of 100 patients with severe heart failure and reduced left ventricular ejection fraction, the technical success of the procedure was 96%, the 30-day mortality was 6%, and the 1-year survival rate was 72.4%. Directly after the procedure, 98.9% of patients had none-trace mitral regurgitation, and 98.4% at one year [35].

## CONCLUSIONS

In patients with severe symptomatic primary MR, valve surgery is the treatment of choice. In patients at high or prohibitive surgical risk, a catheter-based percutaneous edge-to-edge repair technique to correct mitral regurgitation has emerged as a feasible alternative therapeutic option. Patients with secondary MR and HF, despite optimal pharmacological therapy and CRT, benefit from edge-to-edge procedures when the dominant mechanism of HF is mitral regurgitation rather than end-stage left ventricular dysfunction.

In both types of MR, referral for transcatheter treatment is a consensus of a multidisciplinary team consisting of a cardiac surgeon, an interventional cardiologist, a noninvasive cardiologist, an interventional imaging specialist, and an anesthesiologist. It is crucial to assess the predicted survival time and the probability of achieving an effective reduction of the regurgitation jet. It should be emphasized that LVAD implantation or OHT are highly effective treatment options for patients whose dominant symptom mechanism is heart failure and left ventricular damage. The results of the transcatheter treatment of MR should be quality controlled, preferably through a national registry. The population of patients requiring the minimally invasive transcatheter treatment because of the comorbidities and surgical risks is substantial. Access to such technologies in Poland is scarce and should be facilitated. The number of procedures is too low (<190 procedures in 2020) to meet the clinical needs. The Valve-for-Life initiative of the European Association of Percutaneous Cardiovascular Interventions supports the evidence-based implementation of transcatheter valve technologies in Poland (*www.aisn.pl*).

## *Article information*

**Conflict of interest:** WW received lecture fees and grants from Abbott. AG received consultant fees and proctoring fees from Edwards Lifesciences and proctorig fees from Abbott. KB received consultant and proctoring fees from Edwards Lifesciences. PS received proctoring fees from Abbott. ZK received proctoring fees (LAAC) from Abbott. JT received proctoring fees from Abbott. PŚ received speaker's and proctor's fees Abbott. KW received proctoring fees from Neochord. GS received proctoring fees from Abbott. SB received leture fees from Abbott. AW received lecture fees from Abbott and Edwards Lifesciences. Other authors declared no conflicts.

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**How to cite:** Wojakowski W, Chmielak Z, Widenka K, et al., Transcatheter mitral valve repair and replacement. Expert consensus statement of the Polish Cardiac Society and the Polish Society of Cardiothoracic Surgeons. Kardiol Pol. 2021; 79(10): 1165–1177, doi: 10.33963/KP.a2021.0116.

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# Percutaneous tricuspid edge-to-edge repair — patient selection, imaging considerations, and the procedural technique. Expert opinion of the Working Group on Echocardiography and Association of Cardiovascular Interventions of the Polish Cardiac Society

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Kardiol Pol. 2021; 79 (10): 1178–1191; DOI: 10.33963/KP.a2021.0125

**Received:** September 18, 2021

**Revision accepted:** October 4, 2021

**Published online:** October 5, 2021

## ABSTRACT

Tricuspid regurgitation (TR) is a common acquired valvular heart disease (VHD). TR has a progressive character and is associated with impaired long-term survival in both symptomatic and asymptomatic subjects. Despite this knowledge, the overall number of tricuspid valve surgeries is very low worldwide, and many patients with clear indications for intervention are left untreated. The development of less invasive transcatheter techniques may offer new treatment options in this growing population of patients. Out of various percutaneous methods proposed, tricuspid edge-to-edge repair has recently gained considerable attention. This article summarizes available data regarding this new treatment method.

Kardiol Pol 2021; 79, 10: 1178–1191

## INTRODUCTION

Tricuspid regurgitation (TR) is a common acquired valvular heart disease (VHD). Its prevalence is rapidly growing with the aging population, as a recent population study indicates its prevalence nearly equals that of severe aortic stenosis [1]. In most cases, TR has a functional character frequently secondary to left-sided congestive heart failure or VHD and a subsequent right ventricular enlargement. In a growing number of patients with preserved right ventricular function, an alternative mechanism of TR due to tricuspid annulus dilatation in the setting of longstanding atrial fibrillation has been reported [2]. Finally, secondary functional TR develops in a large portion of patients previously operated on for mitral or aortic valve disease, causing the recurrence of heart failure symptoms [3].

Tricuspid regurgitation is a progressive disease that is associated with impaired long-term survival in both symptomatic and asymptomatic subjects [4, 5]. The presence of severe TR is associated with a nearly 2-fold increase in the mortality rate of heart-failure patients. The reported overall 10-year survival rate is lower than 40% [6]. Moreover, a linear correlation between regurgitation severity, defined as effective regurgitant orifice area, and mortality has recently been reported [7].

The presence of a moderate or worse TR is a well-established risk factor and affects the long-term survival in patients undergoing both surgical and percutaneous procedures for left-sided VHD [8]. TR is not only a marker of disease severity but also a potential target for therapeutic intervention and thus current guidelines advocate using a liberal approach for a concomitant tricuspid valve (TV) repair in patients undergoing surgical treatment of left-sided VHD.

Despite this knowledge, the overall number of tricuspid valve surgeries is very low worldwide, and many patients with clear indications for intervention are left untreated. The development of less invasive transcatheter techniques may offer new treatment options in this growing population of patients. Out of various percutaneous methods proposed, tricuspid edge-to-edge repair has recently gained considerable attention.

## EDGE-TO-EDGE REPAIR FOR TRICUSPID REGURGITATION

During the last decade, percutaneous edge-to-edge repair has become a well-established treatment method in patients with mitral valve insufficiency. In approximately 25%–30% of patients referred for this therapy, concomitant severe TR is also documented. The treatment of mitral regurgitation alone led to a reduction of TR grade in only 30%–40% of cases [9], therefore the development of edge-to-edge tricuspid repair was a natural next step in the therapy of patients with concomitant mitral and tricuspid disease.

The first percutaneous tricuspid edge-to-edge repair was performed under the off-label use of the MitraClip system (Abbott Vascular, Santa Clara, CA, USA) via the jugular vein in 2015, followed shortly by successful transfemoral procedures [10]. An early feasibility study that was conducted in 64 patients with both isolated TR or concomitant mitral and tricuspid insufficiency and deemed unsuitable for surgery, showed high periprocedural success with 97% tricuspid clip implantation rate and 91% patients having at least one grade reduction in TR severity. The therapy proved to be safe with no periprocedural complications and effective in terms of the New York Heart Association (NYHA) class and exercise tolerance improvements [11].

Further studies have indicated a durable reduction to a moderate or less TR at 12-month follow-up. This was observed in 72% of patients and accompanied by a 22% reduction in heart failure hospitalizations and an improvement of a 1-year survival from 60% to 79% when compared to patients who failed a TR repair attempt [12]. Furthermore, in the absence of randomized data, a recent retrospective cohort study showed that the tricuspid edge-to-edge repair with the MitraClip NT system combined with the optimal medical therapy in patients with severe TR significantly reduced mortality (24.9% vs. 53.1%; median 14-month follow-up) when compared to the medical therapy only [13].

## POSSIBLE CLINICAL INDICATIONS FOR PERCUTANEOUS EDGE-TO-EDGE THERAPY FOR TRICUSPID REGURGITATION

The recently published guidelines of the European Society of Cardiology concerning the management of valvular heart disease introduced for the first time the possibility of percutaneous intervention in patients with TR. According to the document, the intervention may be considered by the local Heart Team at experienced centers in symptomatic, inoperable, and anatomically eligible patients. However, because of the data paucity, no specific recommendations regarding different clinical situations are given [14].

In patients with TR, we usually deal with two clinical scenarios: coexistence of tricuspid and mitral regurgitation in a patient scheduled for edge-to-edge mitral valve repair or a patient with isolated TR. Due to the lack of exact indications concerning percutaneous treatment, guidelines on surgical treatment might prove to be helpful in everyday clinical decision-making.

In the first scenario, according to the current guidelines, patients scheduled for left-sided valve surgery should undergo concurrent tricuspid repair if a severe TR is present.

This strategy should also be considered in subjects without significant TR but with a dilated tricuspid annulus (i.e., ≥40 mm or >21 mm/m$^2$ by 2D echocardiography), or with current or previous symptoms and signs of right-sided heart failure, as in such cases, the probability of TR progression during follow-up is substantial. This approach does not add risk to the index surgical intervention while reducing the need for higher risk re-intervention [15]. As previously said, up to 30% of patients treated with MitraClip for mitral

regurgitation (MR) have significant TR. The presence of TR independently worsens prognosis after isolated mitral edge-to-edge repair. There is only a moderate probability that successful MR repair will improve TR. However, it is possible to correct TR simultaneously by the off-label use of the same MitraClip device provided that the tricuspid valve anatomy is suitable, and echo visualization is of good quality. The results of several registries suggest that this strategy reduces heart failure symptoms and the total dose of diuretics. Recently the pooled data of patients with significant MR and TR from TRAMI and TriValve registries were retrospectively analyzed. Subjects enrolled in TriValve underwent concurrent mitral and tricuspid treatment while patients observed in the TRAMI registry only had an isolated mitral intervention performed. At one-year follow-up, concurrent TR treatment was independently associated with lower mortality (16.4% vs. 34%; $P = 0.035$) [16, 17]. Nevertheless, further controlled randomized studies are needed to confirm these promising observations.

According to available data, in our opinion, concurrent edge-to-edge correction of TR in patients scheduled for MR treatment may be considered in patients with good echocardiographic visualization of the tricuspid valve, favorable valve anatomy, and:

- moderate, if at least two of the specific criteria of severe TR are met (or borderline values are observed) and valve is significantly remodelled ("moderate-to-severe" TR), severe or greater TR regardless of symptoms of right-sided heart failure;
- moderate TR in patients with current or previous symptoms or signs of right-sided heart failure.

Currently, we do not recommend edge-to-edge tricuspid repair in patients with less than moderate TR and annular dilatation. These patients should be closely observed and if the TR progresses possibly scheduled for a staged isolated TR correction with a dedicated device.

In the case of patients with isolated TR, open-heart surgery is associated with a high periprocedural mortality risk that reaches 10%–25% in severely symptomatic patients [18]. This may be the result of unfavorable baseline clinical characteristics of the patients, who often suffer from secondary liver and/or renal failure. According to the current guidelines, surgery should be considered in patients with isolated significant TR with signs and symptoms of right-sided heart failure. The procedure should be optimally performed before the onset of right ventricular dysfunction or end-organ failure. The surgery might also be considered in patients with prior left-sided valve surgery and isolated TR but without right ventricular dysfunction or severe pulmonary hypertension. However, given the high surgical risk, many symptomatic patients with severe TR are denied surgery. Percutaneous TR treatment with an edge-to-edge technique may be a valid option for this population.

In our opinion, in the case of isolated TR, percutaneous edge-to-edge repair might be considered by the Heart Team in symptomatic, high surgical risk patients with moderate to severe TR, favorable valve anatomy, good echocardiographic valve visualization, and without significant pulmonary hypertension. The expected life expectancy should exceed 12 months to avoid futility.

## ECHOCARDIOGRAPHIC ASSESSMENT OF THE TRICUSPID VALVE IN THE CONTEXT OF INTERVENTION

When compared to other valves, the tricuspid valve has complex and variable anatomy. It is usually composed of three separate leaflets: an anterior and septal leaflet in addition to a smaller posterior leaflet; however, accessory leaflets can be also present. Only the septal portion of the annulus is relatively solid, while the remaining part is prone to dilatation, which is a typical reason for functional TR. The regurgitant orifice can be central, but in most cases, it has a complex shape due to pericommissural leakage. Primary and secondary chords connected to small and variable papillary muscles or directly to the myocardium can cause leaflet restriction — another mechanism of TR.

Both the thin leaflets and the subvalvular apparatus are poorly echogenic. The valve is located off axis from the esophagus (Figure 1). That is why, when compared to the mitral, the tricuspid valve is a much more demanding imaging target. Although multiple transthoracic (TTE) and transesophageal (TEE) 2D views, accompanied by biplane and 3D imaging, can overcome this problem, obtaining sufficient imaging quality for approx. 20% of patients may not be possible. Even for experienced echocardiographers, specific training is needed to distinguish the three leaflets and assess the valve's repairability. It is even more demanding to select the implantation target, provide navigation images, and check the coaxiality/perpendicularity of the clip prior to implantation. Ventricular pacing leads are frequently present in TR patients and require special attention due to their influence on the mobility of the leaflets. The presence of the pacemaker leads, especially when colliding with the valve leaflets, decreases the chances of a successful procedure. Commissural rather than central position can be accepted in patients referred for edge-to-edge repair.

A detailed TTE evaluation requires TV parasternal long- and short-axis views, an apical 4-chamber view with anterior and posterior modifications, and substernal views to distinguish the TV leaflets (Figure 2). The mechanism and localization of the main TR orifice, as well as TR severity, should be assessed (Table 1). In candidates for edge-to-edge intervention, TEE is needed to make sure the valve is sufficiently visible (when the patient is positioned on their back) and to pre-plan the valve clipping prior to the qualification for the procedure.

Understanding the orientation of the specific views and meaning of the anatomical landmarks are helpful both in TTE and TEE in distinguishing the leaflets and to localize the commissures (Figure 2). It can be practiced using a simulator — the most important images are explained in Figures 3–6. The antero-septal commissure is located close to the

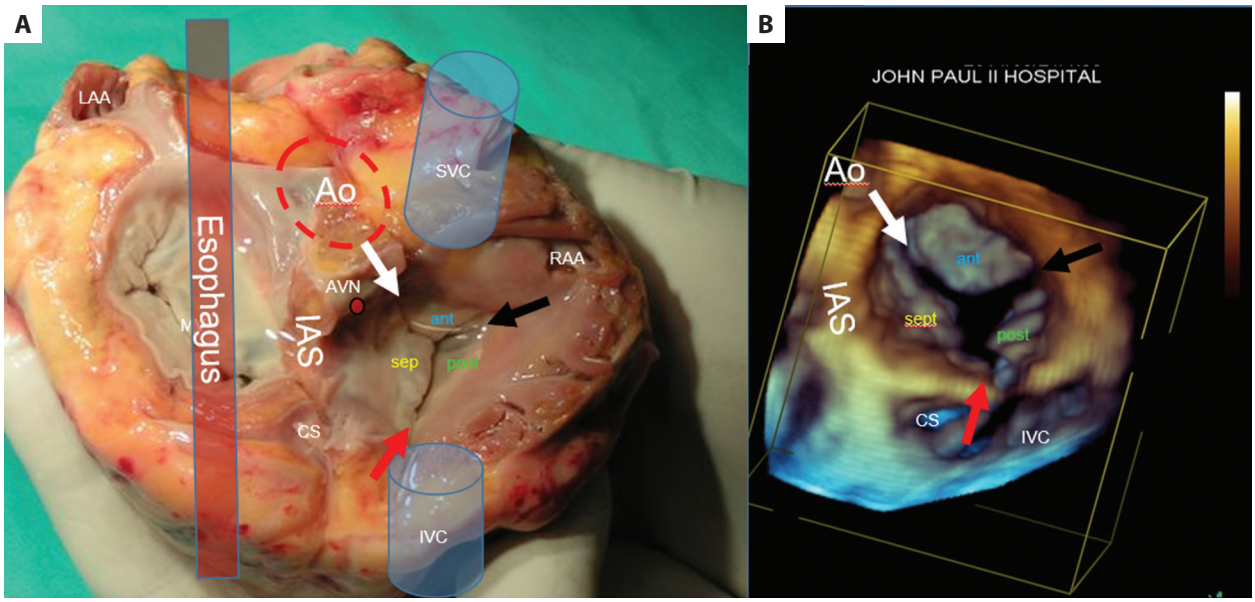


**Figure 1.** Anatomical specimen of the heart without atrial walls (**A**). Esophagus is located above the mitral valve, and the TV has to be imaged in an oblique way. Corresponding 3D view of the TV. The commissures are marked with arrows. Note anatomical landmarks: Ao, IAS, CS, IVC. Position of the AVN is also shown (**B**)

Abbreviations: ant, anterior; Ao, aorta; AVN, atrioventricular node; CS, coronary sinus; IAS, interatrial septum; IVC, inferior vena cava; LAA, left atrial appendage; post, posterior; RAA, right atrial appendage; TV, tricuspid valve; sept, septal; SVC, superior vena cava

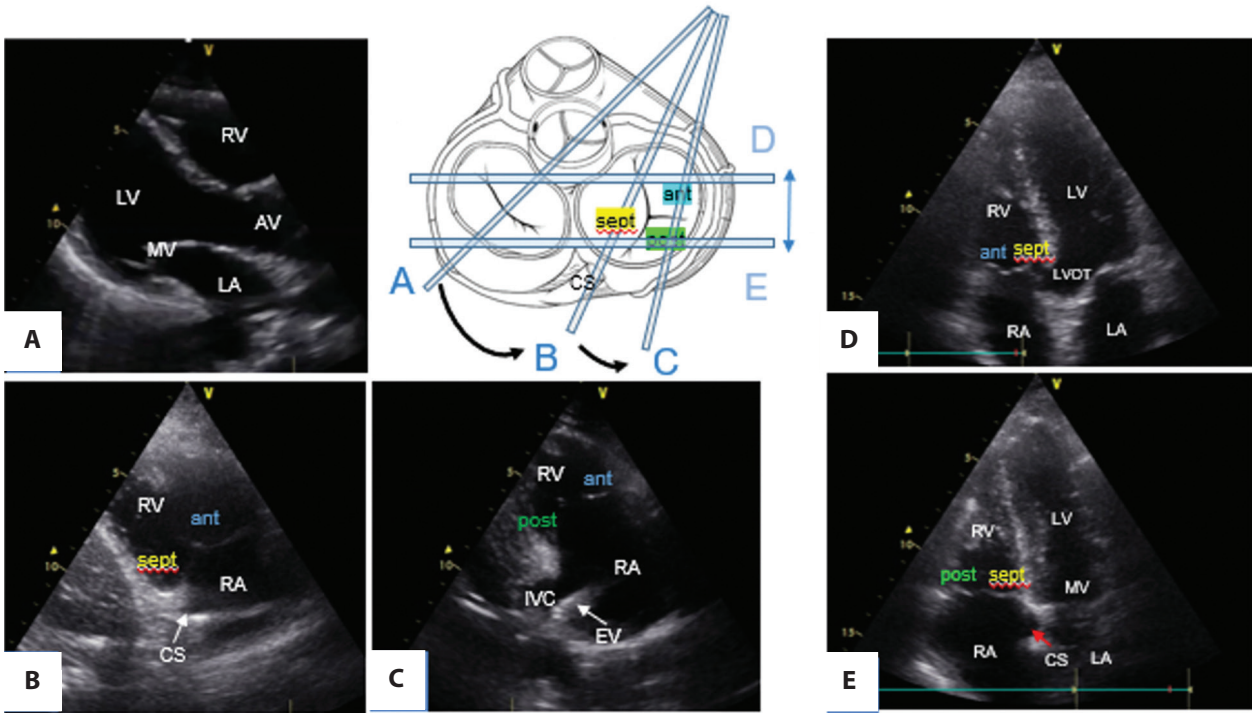


**Figure 2.** Main TTE views modified to differentiate the tricuspid valve leaflets. Left panel: Parasternal long axis view (**A**) modified to visualize the anterior and septal (**B**) or anterior and posterior leaflets (**C**). Right panel: 4-chamber view tilted anteriorly (**D**) and posteriorly (**E**). Note the landmarks — CS, IVC with EV and LVOT

Abbreviations: EV, Eustachian valve; LVOT, left ventricle outflow tract; TTE, transthoracic echocardiography; other — see Figure 1

aortic valve (next to the N-R commissure), and the postero-septal commissure lies between the coronary sinus and inferior vena cava (Figure 1). Due to anatomical limitations, 2D images cannot be fully coaxial with the trajectory of the device. If the imaging quality is sufficient, it can be solved by multiplanar live 3D imaging.

## ECHOCARDIOGRAPHIC CRITERIA OF PATIENT SELECTION

Two systems are currently approved (CE mark) for edge-to-edge tricuspid valve repair in Europe — TriClip and Pascal. According to the Instructions for Use, the TriClip

**Table 1.** Echocardiographic criteria of TR severity table modified, based on [19–21]. The most important parameters are marked in bold

| Parameter | Mild | Moderate | Severe | Massive | Torrential |
|---|---|---|---|---|---|
| Quantitative | | | | | |
| TV morphology abnormalities | None or mild | Moderate | | Severe lesions | |
| Interventricular septal motion | Normal | Usually normal | | Paradoxical/volume overload pattern | |
| TR jet | Small, not holosystolic | Moderate RA penetration or large telesystolic | | Deep holosystolic RA penetration | |
| Flow convergence zone | Not visible, transient or small | Intermediate size | | Large, holosystolic | |
| CW signal of TR jet | Faint/parabolic or partial contour | Dense, variable contour | | Dense, triangular, early peaking (peak <2 ms in very severe TR) | |
| IVC diameter | Normal | 21–25 mm | | >25 mm | |
| Semi-quantitative | | | | | |
| Color flow jet area (central jet) | <5 $cm^2$ | 5–10 $cm^2$ | | >10 $cm^2$ | |
| Color jet area/RA area | 10%–20% | 10%–33% | | >33% | |
| Vena contracta (Nyquist limit 50–60 cm/s) | <3 mm | <6 mm | 7–13 mm | 14–20 mm | ≥21 mm |
| PISA (Nyquist limit 28 cm/s) | ≤5 mm | 6–9 mm | | >9 mm | |
| Hepatic vein flow | Systolic dominance | Systolic blunting | | Systolic flow reversal | |
| Tricuspid inflow | E <1 m/s or A wave dominant | Variable | | E wave >1m/s | |
| Quantitative | | | | | |
| EROA (by PISA) | <20 $mm^2$ | 20–39 $mm^2$ | 40–59 $mm^2$ | 60–79 $mm^2$ | ≥80 $mm^2$ |
| EROA (by 3D vena contracta) | NA | NA | 75–94 $mm^2$ | 95–114 $mm^2$ | ≥115 $mm^2$ |
| Regurgitant volume | <30 ml | 30–45 ml | | ≥45 ml | |
| RV and RA size | Usually normal | Usually normal or mild dilation | | Usually dilated | |

Abbreviations: CW, continuous wave; EROA, effective regurgitant orifice area; IVC, inferior vena cava; NA, not applicable; PISA, proximal isovelocity surface area; RA, right atrium; RV, right ventricular; TR, tricuspid regurgitation; TV, tricuspid valve

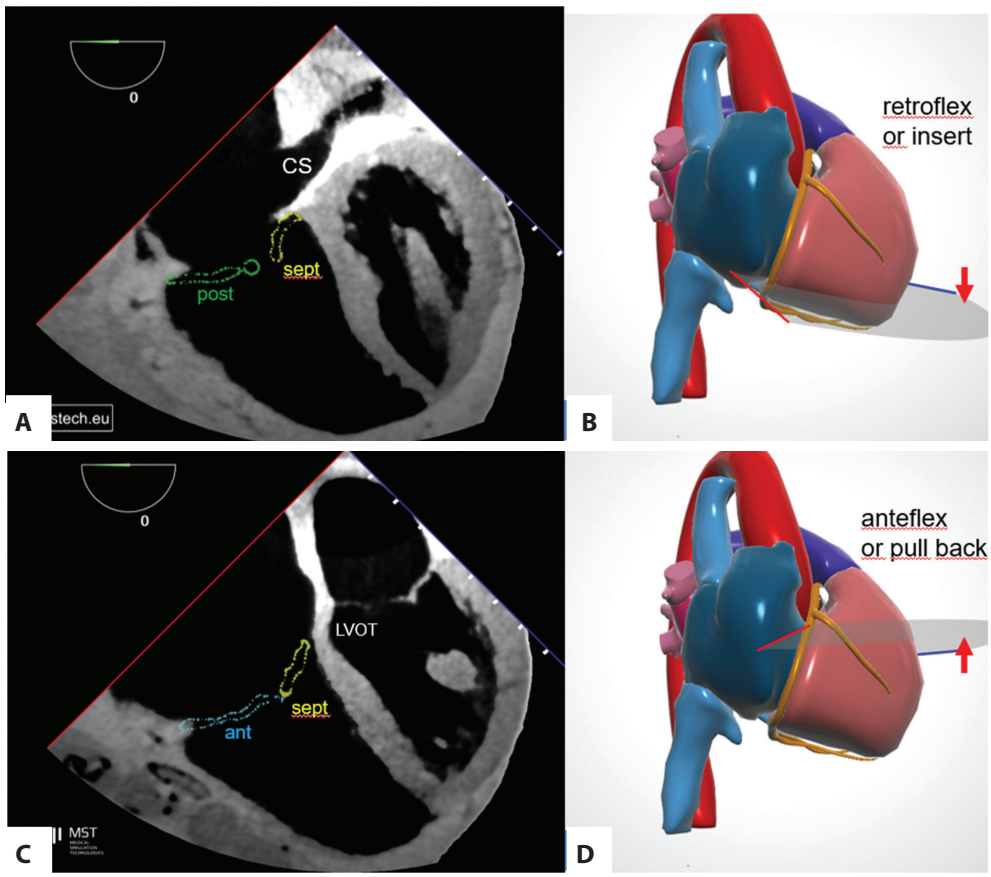


**Figure 3.** Simulation of the mid-esophageal 0° 4-chamber modified by retroflexing (**A**) or anteflexing the probe (**B**) to differentiate the posterior from the anterior leaflet, both coapting with the septal leaflet. Similar views can be obtained by inserting or pulling back the probe or by tilting the TTE 4-chamber plane (Figure 2D and 2E) . MrTEEmothy Simulator was used (Medical Simulation Technologies)

Abbreviations: see Figures 1 and 2

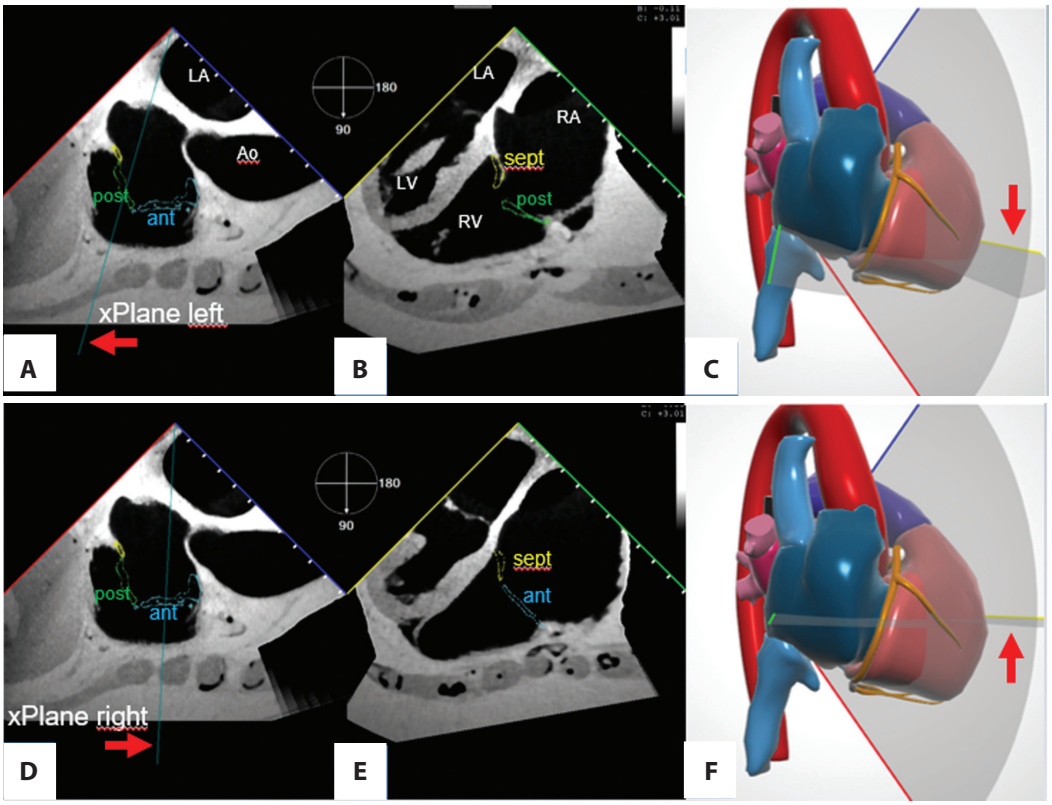


**Figure 4.** Simulation of the mid-esophageal xPlane study. Upper images show 90° view with xPlane cursor positioned on the posterior leaflet (**A**), the orthogonal plane shows septal and posterior leaflets (**B**). The model (**C**) explains orientation of the imaging planes marked with red-blue and yellow-green edges. Lower images explain the effect of moving the xPlane cursor to the right towards the anterior leaflet (**D–F**)

Abbreviations: LA, left atrial; LV, left ventricular; RA, right atrial; RV, right ventricular; other see Figure 1

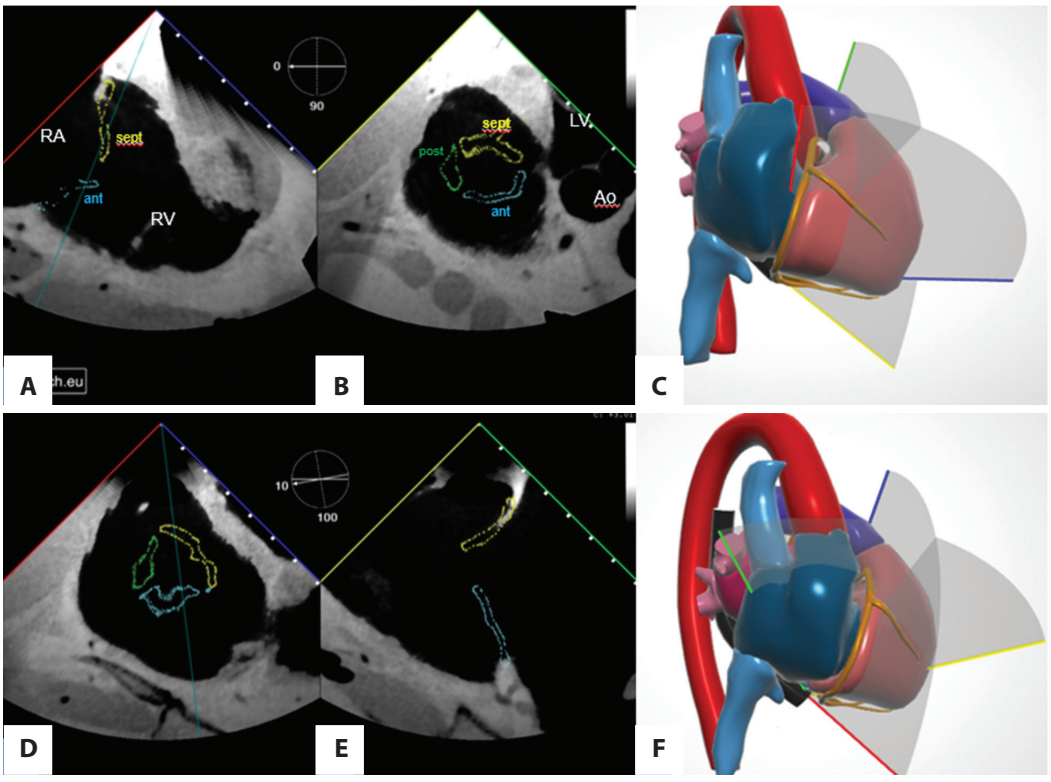


**Figure 5.** Simulation of the shallow-transgastric xPlane study. The probe is flexed anteriorly and towards the right. Left panel shows the 0° view with xPlane cursor positioned on the septal and anterior leaflets (**A**), while the orthogonal plane shows short axis of the valve with all three leaflets (**B**). The model (**C**) explains orientation of the imaging planes marked with red-blue and yellow-green edges. The lower panel (**D–F**) shows the opposite way to obtain similar views. Steering the xPlane cursor on the short image of the valve (**D**) can orient the long axis plane (**E**) on the desired leaflets

Abbreviations: see Figures 1 and 4

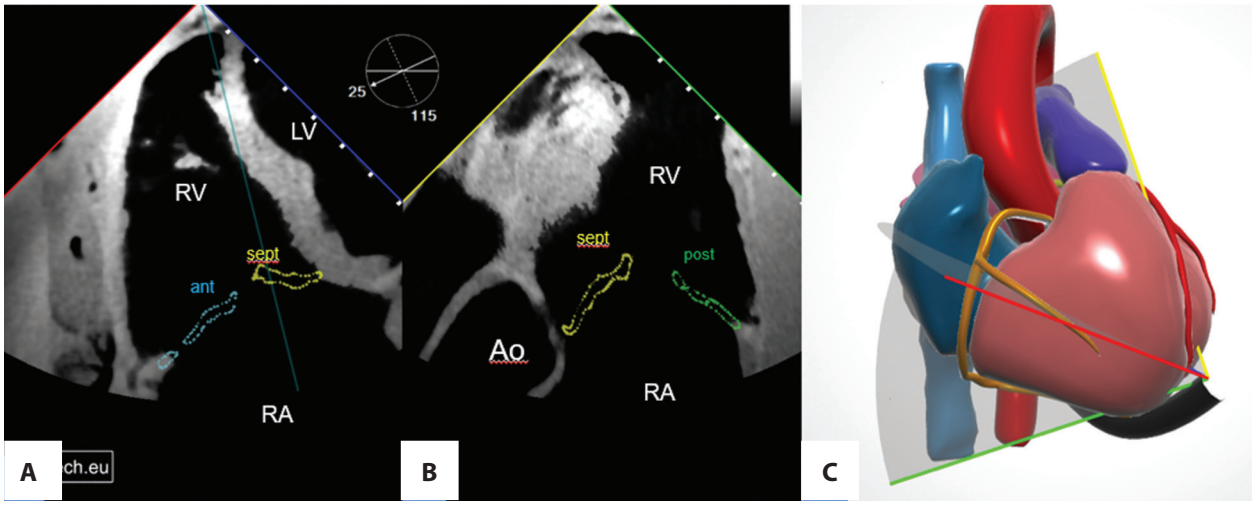


**Figure 6.** Simulation of the deep-transgastric xPlane study. The probe is maximally anteflexed, showing the long axis of the right ventricle and tricuspid valve (**A–B**). The model explains orientation of the imaging planes (**C**)

Abbreviations: see Figures 1 and 4

device is indicated for patients who have severe TR with valve anatomic coaptation gaps of ≤1.0 cm, are at high risk for tricuspid valve surgery, do not have severe mitral regurgitation or pulmonary hypertension (systolic pulmonary artery pressure >60 mm Hg), and are symptomatic despite medical therapy [22]. Contraindications include rheumatic tricuspid valve disease, active endocarditis, and thrombi both intracardiac and located in vena cava or femoral veins. The device is not approved for TR associated with congenital tricuspid valve lesions. The required minimum leaflet insertion (6 mm for smaller and 9 mm for larger devices) defines the minimum mobile leaflet length as 9 mm and 12 mm for NT and XT clips, respectively. As leaflet grasping may potentially cause valvular stenosis, a pre-implant mean pressure gradient ≤3 mm Hg is recommended (mean pressure gradient of ≥5 mm Hg should be considered a significant risk factor for creating tricuspid valve stenosis).

According to the manufacturer's instructions, the Edwards PASCAL transcatheter valve repair system is indicated for the percutaneous reconstruction of an insufficient or tricuspid valve through tissue approximation [23]. Echocardiographic contraindications include the inability to complete the screening with TEE and the presence of an intracardiac mass, thrombus, or vegetation. The operator should also consider the following anatomic patient characteristics: non-degenerative tricuspid valve disease, evidence of moderate to severe calcification in the grasping area, severe calcification in the annulus or subvalvular apparatus, presence of significant cleft or perforation in the grasping area, as well as leaflet mobility length <8 mm.

The optimal clinical echocardiographic criteria for percutaneous tricuspid edge-to-edge valve repair are still evolving. Clinical practice guidelines on the management of valvular heart disease provide no formal indications in the selection of patients for percutaneous edge-to-edge tricuspid valve repair.

Baseline right ventricular (RV) size and function, as well as estimates of systolic pulmonary artery pressure, did not predict clinical outcomes after transcatheter tricuspid valve repair in a substudy of the TriValve Registry [24]. Nevertheless, coaptation gap (≤7 mm), central or anteroseptal jet location, and tethering height (≤1 cm) determined procedural success, which was associated with improved survival [25]. Percutaneous tricuspid edge-to-edge valve repair is performed mainly in patients with torrential, massive, or severe TR. Patients with moderate-to-severe TR, may also sometimes be considered [26].

In summary: echocardiographic criteria predictive of procedural success include:

- ≤7 (10) mm coaptation gap;
- ≥7 (8) mm leaflet length;
- ≤10 mm tethering height;
- ≤3 (5) mm Hg mean tricuspid pressure gradient.

Echocardiographic exclusion criteria include:

- Technically inadequate examinations;
- Rheumatic/congenital etiology;
- Active endocarditis;
- Intracardiac thrombi;
- Significant leaflet and annular calcifications.

## ECHOCARDIOGRAPHIC INTRAOPERATIVE GUIDANCE DURING THE TRICUSPID TRANSCATHETER EDGE-TO-EDGE REPAIR

### *Phase 1. Navigating to the Tricuspid Valve*

During the tricuspid transcatheter edge-to-edge repair, the steerable guide catheter (SGC) is introduced into the inferior vena cava to the right atrium (RA) using a modified bi-caval view (90°–110°). After losing contact with the in-

teratrial septum, in the middle of the right atrium, the clip delivery system (CDS) should be gradually pushed out from the SGC. The next step is to flex the CDS by moving the tip of the system proximally to the tricuspid valve annulus. This step of the procedure is guided in multi-plane 2D-TEE or real-time 3D echocardiography (RT3DTEE, zoom acquired from 90°–110°). These views allow one to follow the tip of the system in the right atrium.

### *Phase 2. Navigating to the Implantation Zone*

Navigation to the area of implantation depends on the coaptation line which is the target of the procedure: antero-septal and/or postero-septal. The following steps are used for setting the device over the chosen area: the basal view used for the navigation to the coaptation line antero-septal/postero-septal is the Right Ventricle Outflow Tract (RVOT) View (60°–100°) obtained from the high/mid esophagus with the device placed medially, close to the aortic valve (AV). In the same reference plane, if the coaptation line postero-septal is chosen as the implantation target, the device should be moved laterally to the wall of the RA/RV. The use of bi-plane TEE helps with positional assessment in the medio-lateral axis. The position of the device is easy to assess when RT3DTEE is used. The RT3DTEE Zoom volume dataset is acquired from a mid-esophageal 4 chamber view (0°–20° or 160°–180°). The volume should include anatomical landmarks: aortic valve (non-coronary sinus), intra-atrial septum, right atrial appendage, and superior vena cava.

### *Phase 3. Implantation*

After confirmation of the device position over the desired implantation area, the perpendicularity of the clip to the coaptation line should be assessed. When the device is close to the leaflets, the arms of the clip and coaptation line can be seen using the trans-gastric short-axis view (20°–50°). In the in the latter view, the parallax artifact can interfere with the proper perpendicularity adjustment. When perpendicularity is confirmed, the clip should be closed again. In the majority of cases, a similar view can be acquired from RT3DTEE zoom as described above.

Under constant monitoring in several views, the device should be placed in the right ventricle just below the tricuspid leaflets to avoid entrapment in the subvalvular apparatus. This part of the procedure can be monitored using the trans-gastric long-axis view. However, the mid-esophageal 4 chamber view (0°–20° or 160°–180°) or bi-plane echocardiography based on the RVOT view (reference plane 60°–100°) can be also used. The latter is very helpful in cases with difficult anatomy or planned postero-septal implantation.

The perpendicularity to the coaptation line should be confirmed when the device is under the leaflets. This can be assessed using the trans-gastric short-axis view or mid-esophageal RT3DTEE zoom. Implantation in the antero-septal position can be monitored from the mid-esophageal 4 chamber view (0°–20° or alternate 160°–180°). During PS position implantation, monitoring from the deep-esophageal 4 chamber view (with coronary sinus in sight, 0°–20° or alternate 160°–180°) might be used. However, in cases of unfavorable anatomy, the RVOT bi-plane view (as the reference plane) may be helpful to monitor the grasping of the leaflets and the closing of the device.

### *Phase 4. Confirmation of proper implantation.*

Post implantation evaluation includes a leaflet insertion assessment. The remaining part of a leaflet (distance between the device and annulus) should be measured using the echocardiographic view used for implantation monitoring. Following the proper implantation, using the transgastric short-axis view, the valve should become double-orifice if one clip was implanted, or tri-orifice if 2 clips were used. The reduction in TR is checked by color Doppler in the high/mid esophageal 2D RVOT view, bi-plane view, or using RT3D-TEE. The trans-gastric long axis view can also be useful in measuring TR reduction. Finally, using a continuous wave Doppler, a measurement of the mean gradient through the tricuspid valve should be obtained, which should not exceed 5 mm Hg. In some cases, additional measurement during the transthoracic examination might be helpful to rule out the possibility of tricuspid stenosis.

## TRICUSPID REPAIR WITH THE MITRACLIP SYSTEM

Most of the percutaneous tricuspid repair procedures reported to date have been performed with the MitraClip system. This device has not been approved for the treatment of TR, and therefore, its use is considered off-label and should be limited to investigational purposes or compassionate procedures. Since the system was developed for the treatment of mitral valve dysfunction, its use in the right atrium causes it to lose much of its steerability and requires different handling. There are several techniques described, the following, most often used in our practice is one of the possible options.

Proper TEE imaging with clear visualization of the right atrium, tricuspid valve, and its leaflets, especially at the site of planned clip implantation is the most important element of the procedure. Fluoroscopic guidance requiring an RAO 30° view played an additional role in most cases. Because of the reimbursement restrictions, all the TR repairs in our practice were combined mitral tricuspid interventions. In this setting, the tricuspid repair starts after the successful completion of the mitral procedure, if the TEE shows a persistent TR jet. The procedural steps are descripted on Figure 7.

The main regurgitation jet should be identified using the short axis trans-gastric (TG-SAX) and 3D view. The tip of the clip should be pointed at the desired position using the basic SGC maneuvers presented in Figure 8. In the majority of cases, the clip is placed between the septal and anterior leaflets or, less frequently, between the

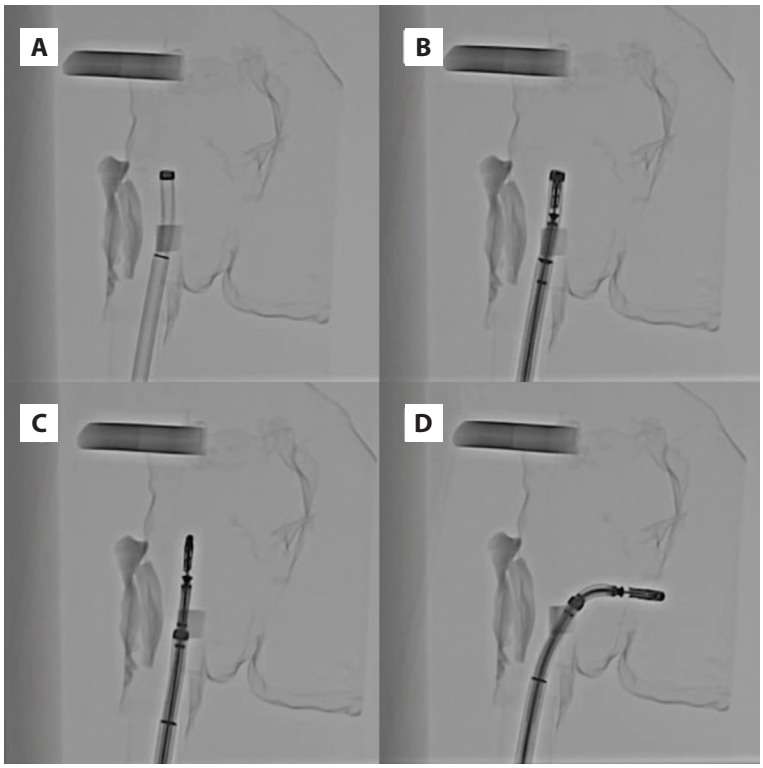


**Figure 7.** The procedural steps of the MitraClip insertion for tricuspid regurgitation repair (see also Figure 8). After the addition of "minus" on an SGC +/– knob, the straightened system is slowly removed from the intra-atrial septum (bicaval view or right atrium 3D view) (**A**). CDS is inserted into the SGC in a "mis-key" manner by turning the CDS 90° counterclockwise from the "bluetoblue" position. CDS is then advanced to the end of the SGC under fluoroscopic guidance (bicaval view or right atrium 3D view) (**B**). While the end of the clip is kept in the same position, the SGC is withdrawn to obtain straddling (bicaval view or right atrium 3D view) (**C**). SGC is rotated counterclockwise to point the clip at the TV. On CDS A/P knob "P" is added to steer down the tip of the clip to the TV (right atrium 3D view) (**D**)

Abbreviations: CDS, clip delivery system; SGC, steerable guide catheter

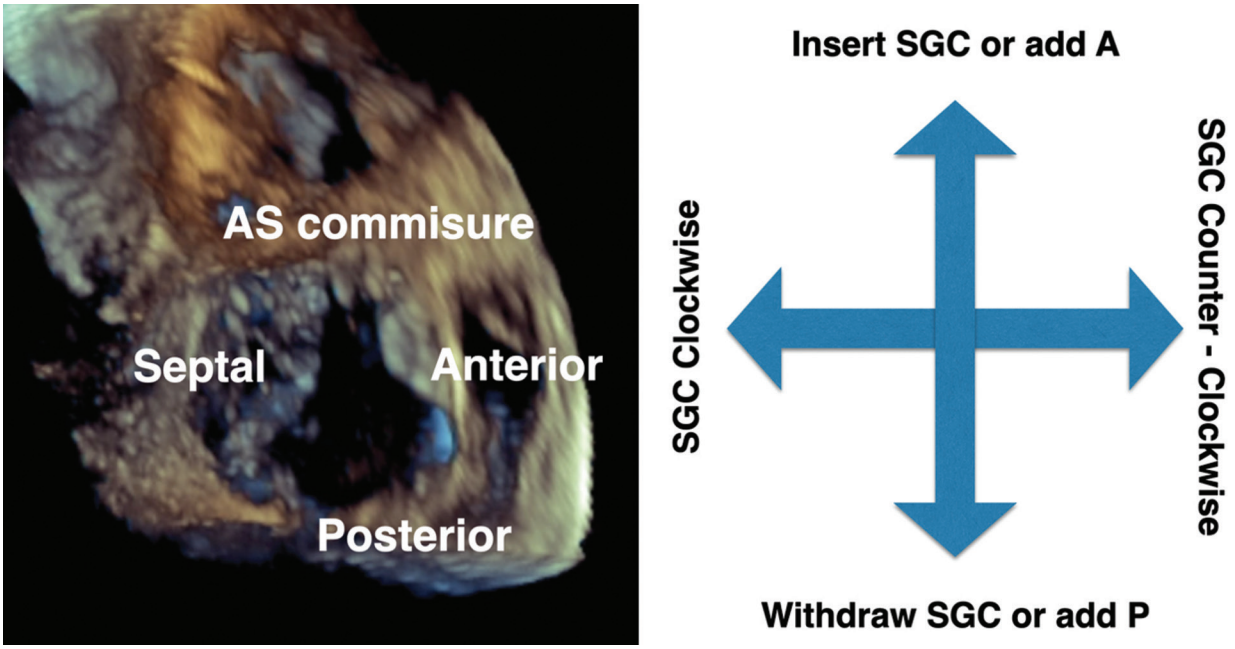


**Figure 8.** Basic maneuvers for the steerable guide catheter (SGC) orientation in the tricuspid valve

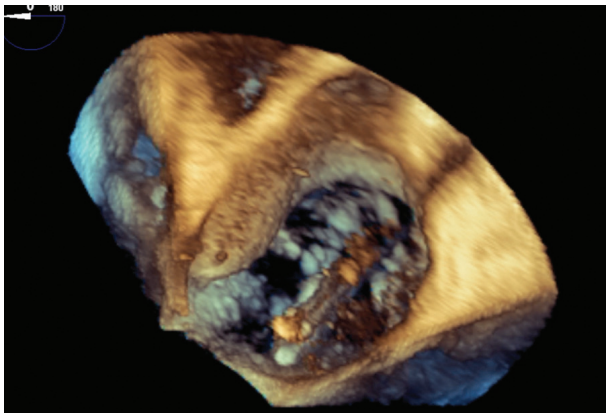

**Figure 9.** Perpendicularity adjustment in the 3D view

septal and posterior leaflets. Once in position, the clip is opened and the perpendicularity of the arms to the coaptation line is adjusted (TG-SAX, 3D) (Figure 9). After insertion of the system into the right ventricle, grasping of a leaflet can be attempted using the mid-esophageal views (Figure 10). The grasping can be confirmed by direct visualization of the leaflet insertion in the mid-esophageal views, by the reduction of regurgitation jet, and by leaflet immobilization visible in the TG-SAX view (Figure 11). Procedural success is defined as at least one grade reduction in TR severity and lack of a TV mean gradient of more than 3 mm Hg.

The MitraClip system's off-label use for this indication has several technical limitations which might hamper effective TV repair. In some patients, insufficient space between the inferior *vena cava* and the TV might result in low positioning of the device with the clip below the TV plane despite full CDS handle retraction. This might prevent successful grasping and result in clip entrapment in the right ventricle with an inability to move it into the right atrium. What is more, the unfavorable orientation of the inferior *vena cava* and the plane of the valve might cause a phenomenon known as "septal hugging" in which the path of the device is not perpendicular to the TV plane (Figure 12). These issues have mostly been resolved by the redesigned shape and additional steering options of the TriClip, a percutaneous system developed for the treatment of TR.

## THE TRICLIP SYSTEM

The TriClip device is a first-in-class transcatheter edge-to-edge repair system dedicated to a minimally invasive, percutaneous treatment of TR. The TriClip system evolved from the MitraClip NTR platform, which is commonly and successfully used not only for mitral valve repair but also for TR treatment [27]. Both MitraClip and TriClip systems consist of an SGC and a CDS with attached cobalt-chromium clips available in two sizes NT and XT (implant arm length 9 and 12 mm, respectively). When compared to the MitraClip, the SGC of the TriClip has two knobs (S/L and ±) and CDS one knob (F/E) for the multi-directional steering maneuvers and deflection of the system. Modification of the MitraClip system was crucial in overcoming the so-called septal huger phenomenon, defined as the tendency to self-position the delivery catheter towards the septal leaflet but also for precise control of perpendicularity and height adjustments.

The efficacy and safety of the TriClip system were established in the TRILUMINATE trial, which was a prospective, single-arm, feasibility study conducted at 21 sites in Europe and the USA. A total of 85 symptomatic patients with moderate or greater TR underwent a successful procedure (100% implant success rate) [28]. On average 2.2 TriClips were implanted, with a mean procedure time of 153 minutes. In the majority of cases (77%), the clips were located in the antero-septal commissure. The primary efficacy endpoint, defined as a reduction of TR

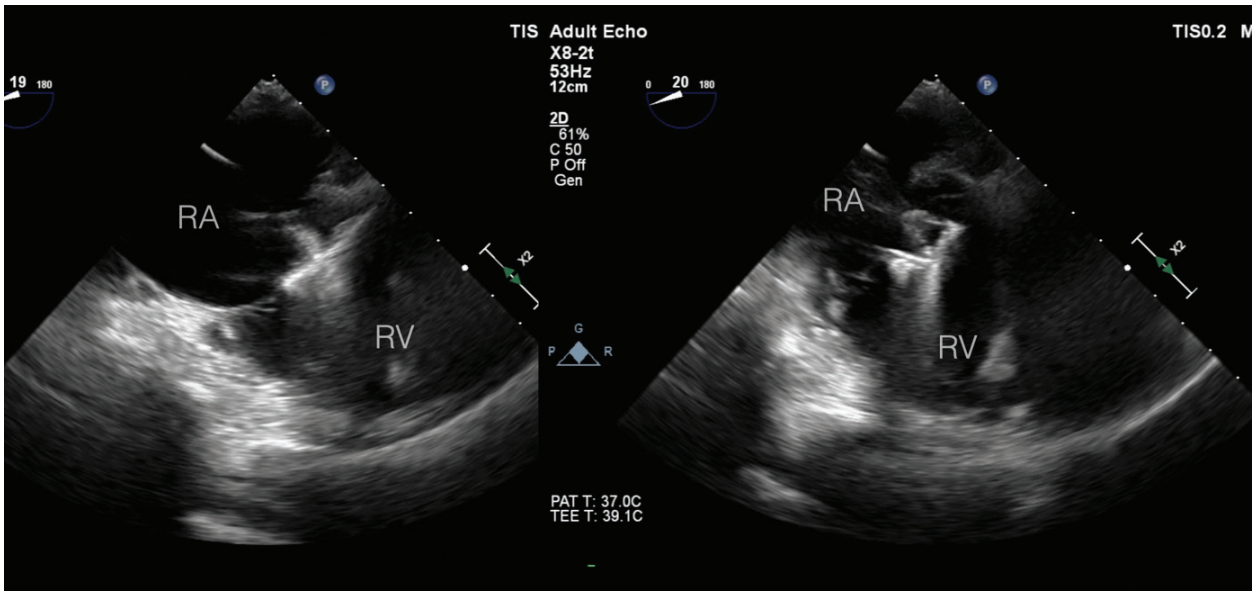


**Figure 10.** Grasping attempt in the mid esophageal view

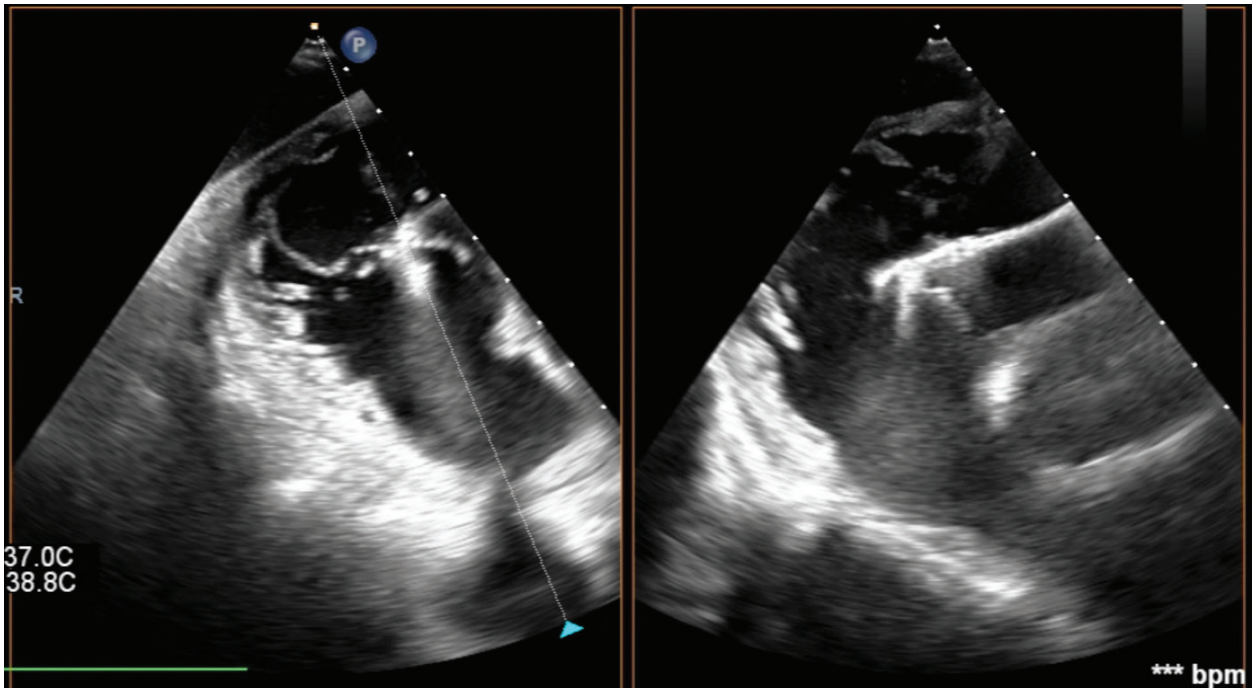


**Figure 11.** Grasping confirmation in the trans-gastric view

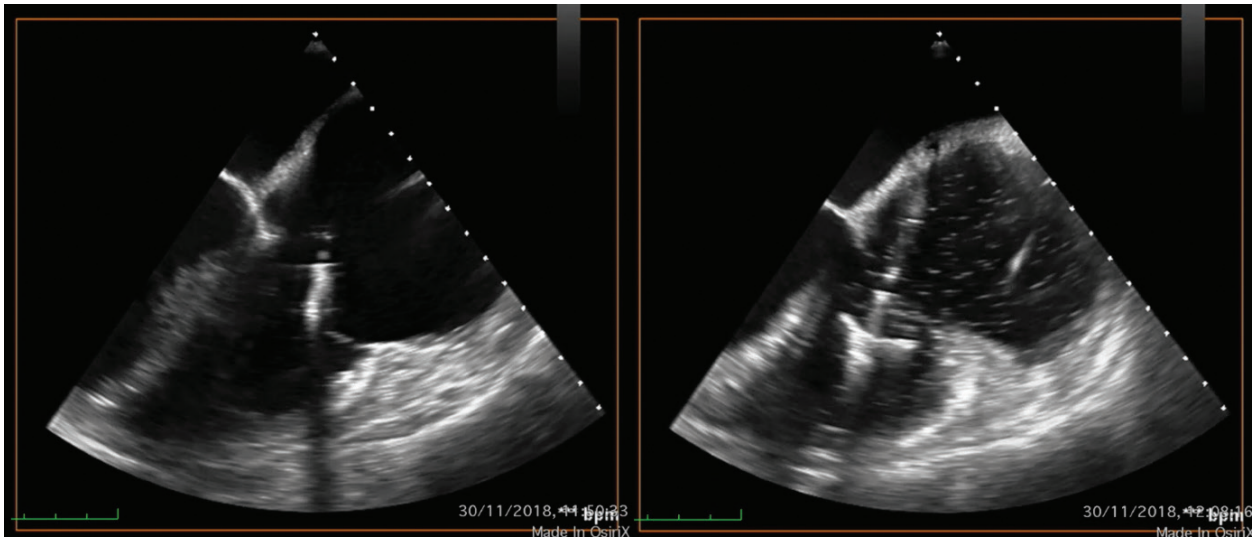


**Figure 12.** "Septal hugging" — clip path not perpendicular to the plain of the valve

severity by at least one grade at 30 days, was met in 86% of patients. At 1 year, a reduction in TR was sustained with 71% of the cases being classified as moderate or less TR, especially when compared with 8% at baseline ($P$ <0.0001). Echocardiographic assessment performed by the core lab revealed significant positive right heart remodeling in terms of a reduction of the right ventricular end-diastolic diameter (5.3 vs. 4.8 cm; $P$ <0.0001), a decrease in the right atrial volume (129 vs. 116 ml; $P$ = 0.0166), and a TAPSE improvement (1.44 vs. 1.59 cm; $P$ = 0.0002). Patients treated with the TriClip device experienced a significant clinical improvement in NYHA functional class (percentage of patients with NYHA class I/II 31% vs. 83%; $P$ < 0.0001) and exercise capacity (6-minute walk test increased from 272.3 to 303.2 meters; $P$ = 0.0023). The edge-to-edge therapy was also associated with substantial quality-of-life improvements and reduction in hospitalizations. The annual hospitalization rate decreased by 40% when compared to one year before the procedure ($P$ = 0.003).

These results were achieved with few safety concerns such as major bleeding observed in 10 patients, 5 cases of single leaflet device attachment, and 4 cases with tricuspid valve mean gradient equal or greater than 5 mm Hg. The occurrence of major adverse events through 1 year was also low with a total number of 6 events, including 4 cases of cardiovascular death. Safety and effectiveness of the TriClip procedure are currently under investigation in the pivotal

trial TRILUMINATE (Clinical TRIal to EvaLUate Cardiovascular OutcoMes IN Patients TreATEd with the Tricuspid Valve Repair System), which is a prospective, randomized study comparing the tricuspid valve edge-to-edge repair system (on top of medical therapy) to pharmacotherapy only in patients with severe, symptomatic TR [29].

## TRICUSPID REPAIR WITH THE PASCAL SYSTEM

The PASCAL transcatheter valve repair system (Edwards Lifesciences, Irvine, CA, USA) is a leaflet repair therapy initially designed for the treatment of MR, which shares the concept of edge-to-edge coaptation enhancement [30, 31]. Technical characteristics of both delivery systems and clipping devices appear to make the PASCAL transcatheter valve repair system a useful tool in the treatment of TR. It uses a pair of clasps and paddles designed to plicate valve leaflets and facilitate coaptation. The broad contoured paddles are designed to maximize leaflet coaptation and minimize stress concentration on the native leaflets. An anatomic spacer is used to fill the regurgitant orifice between the native valve leaflets to prevent backflow, further reducing regurgitant flow. The clasps are adjustable, which aids in the successful positioning of the leaflets. The clasps can be operated either simultaneously or independently to facilitate optimized leaflet capture in cases with complex anatomy. The delivery system consists of a 22-F guide sheath, with 3 independent catheters that facilitate maneuvering in 3 different planes and stabilizers that lock catheter handles in place. The PASCAL repair system implant can be elongated within the subvalvular anatomy to substantially decrease the implant profile for an atraumatic repositioning if deemed necessary.

The CLASP study (Edwards PASCAL Transcatheter Mitral Valve Repair System Study) was designed to assess the clinical benefit of PASCAL edge-to-edge mitral intervention. Results at 1-year follow-up in functional mitral regurgitation and degenerative mitral regurgitation were recently published [32]. Based on the convincingly positive results of this study, it was concluded that the PASCAL transcatheter valve repair system demonstrated a low complication rate, high survival rate, and a sustained MR reduction resulting in significant improvements in functional status and quality of life at 1 year.

The results of an observational first-in-human assessment of feasibility and safety of the PASCAL transcatheter valve repair system and its impact on short-term clinical outcomes in patients with severe TR were encouraging [33]. Twenty-eight patients with severe TR were treated with the PASCAL system in a compassionate use intervention at 6 sites. All patients had heart failure due to severe TR and were deemed to be a high surgical risk by local heart teams. The primary outcome was a procedural success, defined as the implantation of at least 1 device with post-procedural TR grade ≤2+, without mortality or conversion to surgery. TR etiology was functional in 92% of patients, with a mean tricuspid annular diameter of 49.5 ± 6 mm and a mean coaptation gap of 6.9 ± 3 mm. The procedural success was 86%, with 1.4 ± 0.6 devices implanted per patient. There were no intraprocedural complications. At 30-day follow-up, mortality was 7.1%, 88% of patients were in NYHA functional class I or II, and 85% had a TR grade of ≤2+. There were 2 single-leaflet device attachments, which were managed conservatively. The six-minute walk distance improved from 240 m (interquartile range: 172 to 337 m) to 335 m (interquartile range: 251 to 385 m) ($P$ <0.001). This first-in-human experience evaluating transcatheter tricuspid repair with the PASCAL system demonstrated a high procedural success, acceptable safety, and significant clinical improvement.

Efficacy and safety of PASCAL therapy in TR patients is further studied in an ongoing CLASP TR Early Feasibility Study. Of the 34 patients enrolled in this study, the mean age was 76 years, 53% were women, the mean Society of Thoracic Surgeons score was 7.3%, 88% had atrial fibrillation/flutter, 97% had severe or greater TR, and 79% had NYHA functional class III/IV symptoms. Twenty-nine patients (85%) received implants. Tricuspid regurgitation severity reduction of at least 1 grade at 30 days was achieved in 85% of them, with 52% with moderate or less TR ($P$ <0.001). The MAE rate was 5.9% and none of the patients experienced cardiovascular mortality, stroke, myocardial infarction, renal complication, or reintervention. Eighty-nine percent of patients improved to NYHA functional class I/II ($P$ <0.001), improved their mean 6-min walk distance by 71 m ($P$ <0.001), and improved the mean Kansas City Cardiomyopathy Questionnaire score by 15 points ($P$ <0.001). Investigators concluded that in this early experience, the repair system performed as intended, with substantial TR reduction, a low adverse events rate, no mortality or reintervention, and significant improvements in functional status, exercise capacity, and quality of life [34].

## SUMMARY

The approach to the management of valvular heart diseases was completely transformed by the advent of transcatheter valvular interventions. The use of transcatheter valve therapies allowed an expansion of indications to patients previously deemed inoperable. The TR was undertreated for a long time, despite its adverse impact on clinical outcomes, including mortality and heart failure, as well as associated poor quality of life. The contemporary TR treatment was redefined by several important discoveries. Since the first procedure of TR edge-to-edge-repair by Nickenig and colleagues, there has been growing evidence from registries (TriValve and others) and more recently from prospective clinical trials (Triluminate) that edge-to-edge repair using the MitraClip or more recently the TriClip provides a safe and effective treatment, with over 80% of patients having a significant reduction of TR to moderate or less postoperatively, which is sustained above 70% at one year. It also leads to a reduction of rehospitalizations and improvement

in symptoms [26]. Importantly, several prognostic factors related to the anatomy of the TV, clinical status (frailty, short life expectancy, severe RV failure, irreversible pulmonary hypertension) were identified. There is also a trend towards improved survival in patients undergoing transcatheter tricuspid repair in comparison with those treated conservatively. These studies have helped identify the patients in whom the therapy is unlikely to produce durable improvements and who should not be treated with a transcatheter repair. The technical feasibility of the procedure will surely evolve as operators gain clinical experience. This will lead to a higher rate of acceptance for the procedure as well as a higher rate of technical success. In addition, multiple new technologies based on transcatheter annuloplasty, implantation of valves in caval veins, as well as dedicated tricuspid bioprosthetic valves mounted on self-expandable stents were designed and are currently undergoing clinical evaluation.

From the Polish perspective, it is important to share our initial experience with heart valve centers experienced with mitral and tricuspid procedures, train operators and echocardiographers to build up the referral network, and follow-up patients within the registry. It seems that at least three groups of patients are likely to be discussed by Heart Teams: secondary TR coexisting with significant MR planned for one step mitral and tricuspid clipping, patients after left-sided valve surgery and significant TR, and patients with isolated TR. Last, but not least, it is important to secure the funding for these procedures which are currently not reimbursed. The current edition of the Valve-for-Life Initiative by the EAPCI and the European Society of Cardiology in Poland should be especially focused on these unmet clinical needs.

In summary, the transcatheter tricuspid edge-to-edge repair seems to be a safe and possibly effective treatment for patients with heart failure and significant TR, leading to the reduction of its severity and clinical improvement in a significant number of patients. This field is rapidly expanding, and Poland joined the group of countries which can offer carefully selected patients access to this innovative and effective therapy.

## *Article information*

**Conflict of interest:** AR received proctoring fees and speakers' honoraria from Abbott. PS received proctoring fees from Abbott. AG received proctoring fees and speakers' honoraria from Abbott and Edwards; Co-founder of Medical Simulation Technologies. PŚ received proctoring fees and speakers' honoraria from Abbott. PG received proctoring fees and speakers' honoraria from Abbott and Boston Scientific. AP received proctoring fees and speakers' honoraria from Abbott. JT received proctoring fees from Abbott. JK received proctoring fees and speakers' honoraria from Abbott. AW received speaker's fees from Abbott. WW received speakers' honoraria from Abbott and Edwards Lifesciences. MG received speakers' honoraria Abbott. KZ declares no conflict of interest.

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**How to cite:** Rdzanek A, Szymański P, Gackowski A, et al. Percutaneous tricuspid edge-to-edge repair — patient selection, imaging considerations, and the procedural technique. Expert opinion of the Working Group on Echocardiography and Association of Cardiovascular Interventions of the Polish Cardiac Society. Kardiol Pol. 2021; 79(10): 1178–1191, doi: 10.33963/KP.a2021.0125.

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HFrEF – niewydolność serca z obniżoną frakcją wyrzutową.
* Dorośli pacjenci z przewlekłą niewydolnością serca (klasy II, III lub IV wg NYHA) i zredukowaną frakcją wyrzutową (LVEF ≤ 40%)[2].
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# Skrócona informacja o leku JARDIANCE®

**Nazwa produktu leczniczego, dawka i postać farmaceutyczna:** Jardiance® 10 mg, 25 mg tabletki powlekane. Każda tabletka zawiera 10 mg empagliflozyny lub 25 mg empagliflozyny. Jardiance® 10 mg okrągła tabletka powlekana barwy bladożółtej, obustronnie wypukła, o średnicy 9,1 mm ze ściętą ostro krawędzią, z wytłoczonym symbolem „S10" na jednej stronie oraz logo Boehringer Ingelheim na drugiej. Każda tabletka zawiera ilość laktozy jednowodnej odpowiadającą 154,3 mg laktozy bezwodnej. Każda tabletka zawiera mniej niż 1 mmol (23 mg) sodu, to znaczy lek uznaje się za „wolny od sodu". Jardiance® 25 mg owalna, bladożółta, obustronnie wypukła tabletka powlekana z wytłoczonym symbolem „S25" na jednej stronie oraz logo Boehringer Ingelheim na drugiej (długość tabletki: 11,1 mm, szerokość: 5,6 mm). Każda tabletka zawiera ilość laktozy jednowodnej odpowiadającą 107,4 mg laktozy bezwodnej. Każda tabletka zawiera mniej niż 1 mmol (23 mg) sodu, to znaczy lek uznaje się za „wolny od sodu". **Wskazania do stosowania:** Cukrzyca typu 2 Produkt leczniczy Jardiance® jest wskazany do stosowania w leczeniu dorosłych z niewystarczająco kontrolowaną cukrzycą typu 2 łącznie z dietą i aktywnością fizyczną: w monoterapii, kiedy nie można stosować metforminy z powodu jej nietolerancji, w skojarzeniu z innymi produktami leczniczymi stosowanymi w leczeniu cukrzycy. Wyniki badań dotyczące różnych skojarzeń, wpływu na kontrolę glikemii i zdarzenia sercowo-naczyniowe oraz badane populacje, patrz punkt Specjalne ostrzeżenia i środki ostrożności dotyczące stosowania. Niewydolność serca Produkt leczniczy Jardiance® jest wskazany do stosowania u dorosłych w leczeniu objawowej przewlekłej niewydolności serca ze zredukowaną frakcją wyrzutową. **Dawkowanie i sposób podawania:** Dawkowanie Cukrzyca typu 2 Zalecana dawka początkowa wynosi 10 mg empagliflozyny raz na dobę w monoterapii oraz w terapii skojarzonej z innymi produktami leczniczymi stosowanymi w leczeniu cukrzycy. U pacjentów tolerujących dawkę 10 mg empagliflozyny raz na dobę z wartością eGFR ≥ 60 ml/min/1,73 m² i w wymagających ściślejszej kontroli glikemii, dawkę można zwiększyć do 25 mg raz na dobę. Maksymalna dawka dobowa wynosi 25 mg (patrz poniżej i punkt Specjalne ostrzeżenia i środki ostrożności dotyczące stosowania). 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 (patrz punkt Działania niepożądane). 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. 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 m²] lub CrCL [ml/min] | Całkowita dawka dobowa |
|---|---|---|
| Cukrzyca typu 2 | ≥60 | Rozpocząć od dawki 10 mg empagliflozyny.<br>U pacjentów tolerujących dawkę 10 mg empagliflozyny i wymagających dodatkowej kontroli glikemii dawkę można zwiększyć do 25 mg empagliflozyny. |
| | 45 do <60 | Nie rozpoczynać stosowania empagliflozyny.<br>Kontynuować stosowanie dawki 10 mg empagliflozyny u pacjentów, którzy już przyjmują produkt leczniczy Jardiance®. |
| | <45 | 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 Z uwagi na mechanizm działania empagliflozyny, jej skuteczność w odniesieniu do kontroli glikemii zależy od czynności nerek. Nie ma konieczności dostosowania dawki u pacjentów z wartością eGFR ≥ 60 ml/min/1,73 m² lub CrCl ≥ 60 ml/min. W przypadku leczenia cukrzycy typu 2 nie należy rozpoczynać leczenia empagliflozyną u pacjentów z wartością eGFR < 60 ml/min/1,73 m² lub z CrCl < 60 ml/min. U pacjentów tolerujących empagliflozynę, u których wartość eGFR obniżyła się i utrzymuje się poniżej 60 ml/min/1,73 m² lub z CrCl poniżej 60 ml/min, dawkę empagliflozyny należy dostosować lub utrzymywać na poziomie 10 mg raz na dobę. Należy przerwać leczenie empagliflozyną u pacjentów, których wartość eGFR utrzymuje się poniżej 45 ml/min/1,73 m² lub CrCl utrzymuje się poniżej 45 ml/min (patrz punkty Specjalne ostrzeżenia i środki ostrożności dotyczące stosowania, Działania niepożądane). 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 m² 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 (patrz punkt Specjalne ostrzeżenia i środki ostrożności dotyczące stosowania). *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 (patrz punkty Specjalne ostrzeżenia i środki ostrożności dotyczące stosowania i Działania niepożądane). Z uwagi na ograniczone doświadczenie w leczeniu pacjentów w wieku 85 lat i starszych, nie zaleca się rozpoczynania leczenia empagliflozyną w tej grupie wiekowej (patrz punkt Specjalne ostrzeżenia i środki ostrożności dotyczące stosowania). *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 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 (patrz punkt Dawkowanie i sposób podawania). *Cukrzyca typu 2* Ponieważ kontrola glikemii zależy od czynności nerek, nie należy rozpoczynać leczenia produktem Jardiance® u pacjentów z wartością eGFR poniżej < 60 ml/min/1,73 m² lub z CrCl < 60 ml/min. U pacjentów tolerujących empagliflozynę, których wartość eGFR utrzymuje się poniżej 60 ml/min/1,73 m² lub CrCl < 60 ml/min, dawkę empagliflozyny należy dostosować lub utrzymywać na poziomie 10 mg raz na dobę. Nie zaleca się stosowania empagliflozyny u pacjentów, których wartość eGFR utrzymuje się poniżej 45 ml/min/1,73 m² lub CrCl utrzymuje się poniżej 45 ml/min (patrz punkty Dawkowanie i sposób podawania, Działania niepożądane). *Niewydolność serca* Nie zaleca się stosowania produktu leczniczego Jardiance® u pacjentów z wartością eGFR <20 ml/min/1,73 m². 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 (patrz punkty Dawkowanie i sposób podawania, Działania niepożądane); przed rozpoczęciem leczenia jakimkolwiek innym jednoczesnie stosowanym produktem leczniczym, który może mieć niekorzystny wpływ na czynność nerek. Ryzyko zmniejszenia objętości płynów Z uwagi na mechanizm działania inhibitorów SGLT-2, diureza osmotyczna 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 (patrz punkt Działania niepożądane). W związku z tym należy zwracać szczególną uwagę na przyjmowaną objętość płynów w razie jednoczesnego podawania z produktami leczniczymi mogącymi prowadzić do zmniejszenia objętości płynów (np. leki moczopędne, inhibitory ACE). Doświadczenie dotyczące leczenia pacjentów w wieku 85 i więcej lat jest ograniczone. Nie zaleca się rozpoczynania leczenia empagliflozyną w tej grupie wiekowej (patrz punkt Dawkowanie i sposób podawania). Powikłane zakażenia dróg moczowych U pacjentów otrzymujących empagliflozynę zgłaszano przypadki powikłanych zakażeń dróg moczowych, w tym odmiedniczkowe zapalenie nerek i posocznicę moczopochodną (patrz punkt Działania niepożądane). 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 (patrz punkt Działania niepożądane). Laboratoryjna analiza moczu Z uwagi na mechanizm działania produktu Jardiance®, pacjenci przyjmujący go będą mieć dodatni wynik testu na zawartość glukozy w moczu. Wpływ na badanie stężenia 1,5-anhydroglucitolu (1,5-AG) Nie zaleca się monitorowania kontroli glikemii za pośrednictwem badania stężenia 1,5-AG, ponieważ oznaczanie stężenia 1,5-AG nie jest miarodajne w ocenie kontroli glikemii u pacjentów przyjmujących inhibitory SGLT2. Zaleca się stosowanie innych metod monitorowania kontroli glikemii. Laktoza Tabletki produktu leczniczego zawierają laktozę. Produkt leczniczy nie powinien być stosowany u pacjentów z rzadko występującą dziedziczną nietolerancją galaktozy, brakiem laktazy lub zespołem złego wchłaniania glukozy-galaktozy. **Działania niepożądane:** Podsumowanie profilu bezpieczeństwa *Cukrzyca typu 2* Łącznie 15 582 pacjentów z cukrzycą typu 2 wzięło udział w badaniach klinicznych oceniających bezpieczeństwo stosowania empagliflozyny, z czego 10 004 pacjentów otrzymywało empagliflozynę w monoterapii lub w skojarzeniu z metforminą, pochodną sulfonylomocznika, pioglitazonem, inhibitorami DPP-4 lub insuliną. W 6 badaniach przeprowadzonych z kontrolą placebo trwających od 18 do 24 tygodni wzięło udział 3534 pacjentów, z których 1183 otrzymywało placebo, a 2351 – empagliflozynę. Ogólna częstość występowania zdarzeń niepożądanych u pacjentów leczonych empagliflozyną była podobna do częstości w grupie otrzymującej placebo. Najczęściej obserwowanym działaniem niepożądanym była hipoglikemia przy stosowaniu w skojarzeniu z pochodną sulfonylomocznika lub insuliną (patrz opis wybranych działań niepożądanych). *Niewydolność serca* Do badania EMPEROR-Reduced włączono 3 730 pacjentów z niewydolnością serca i zmniejszoną frakcją wyrzutową, którzy otrzymywali leczenie 10 mg empagliflozyny lub placebo. U około połowy pacjentów występowała cukrzyca typu 2. Najczęściej zgłaszanym działaniem niepożądanym było zmniejszenie objętości płynów (10 mg empagliflozyny: 10,6%; placebo: 9,9%). Ciężką hipoglikemię (zdarzenia wymagające interwencji) obserwowano wyłącznie u pacjentów z cukrzycą. Ogólny profil bezpieczeństwa stosowania empagliflozyny był zasadniczo spójny w badanych wskazaniach. W badaniu niewydolności serca EMPEROR-Reduced nie zidentyfikowano żadnych nowych działań niepożądanych. Wykaz działań niepożądanych w postaci tabeli W poniższej tabeli przedstawiono działania niepożądane – sklasyfikowane według grup układowo-narządowych oraz według preferowanych terminów MedDRA – zgłaszane u pacjentów, którzy otrzymali empagliflozynę w badaniach prowadzonych z kontrolą placebo (Tabela 2). Działania niepożądane są wymienione według bezwzględnej częstości występowania. Częstość występowania zdefiniowana jest następująco: bardzo często (≥ 1/10); często (≥ 1/100 do < 1/10); niezbyt często (≥ 1/1000 do < 1/100); rzadko (≥ 1/10 000 do < 1/1000), bardzo rzadko (< 1/10 000), nieznana (częstość nie może być określona na podstawie dostępnych danych).

Tabela 2: Wykaz działań niepożądanych (MedDRA) obserwowanych w badaniach prowadzonych z kontrolą placebo i zgłoszonych po wprowadzeniu produktu do obrotu, w postaci tabeli

| Klasyfikacja układów i narządów | Bardzo często | Często | Niezbyt często | Rzadko |
|---|---|---|---|---|
| *Zakażenia i zarażenia pasożytnicze* | | kandydoza pochwy, zapalenie pochwy i sromu, zapalenie żołędzi i inne zakażenia narządów płciowych[a]<br>zakażenie dróg moczowych (w tym odmiedniczkowe zapalenie nerek i posocznica moczopochodna)[a] | | martwicze zapalenie powięzi krocza (zgorzel Fourniera)[b,*] |
| *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)<br>wysypka | pokrzywka<br>obrzęk naczynioruchowy | |
| *Zaburzenia naczyniowe* | zmniejszenie objętości płynów[a] | | | |
| *Zaburzenia nerek i dróg moczowych* | | zwiększone oddawanie moczu[a] | dyzuria | |
| *Badania diagnostyczne* | | zwiększenie stężenia lipidów w surowicy[a] | zwiększenie stężenia kreatyniny we krwi i (lub) zmniejszenie współczynnika filtracji kłębuszkowej[a]<br>zwiększenie hematokrytu[a] | |

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

Opis wybranych działań niepożądanych *Hipoglikemia* Częstość występowania hipoglikemii zależała od leczenia podstawowego stosowanego w poszczególnych badaniach i była podobna jak po zastosowaniu placebo u pacjentów stosujących empagliflozynę w monoterapii, jako leczenie skojarzone z metforminą, jako leczenie skojarzone z pioglitazonem w skojarzeniu z metforminą lub bez niej, jako leczenie skojarzone z linagliptyną i metforminą, jako leczenie dodane do terapii standardowej oraz w razie stosowania skojarzenia empagliflozyny z metforminą u nieleczonych uprzednio pacjentów w porównaniu z pacjentami leczonymi osobnymi lekami empagliflozyną i metforminą. Zwiększoną częstość zaobserwowano w przypadku stosowania jako leczenie skojarzone z metforminą i pochodnymi sulfonylomocznika (10 mg empagliflozyny: 16,1%; 25 mg empagliflozyny: 11,5%; placebo: 8,4%), jako leczenie skojarzone z insuliną podstawową w skojarzeniu z metforminą lub bez niej oraz w skojarzeniu z pochodną sulfonylomocznika lub bez niego (10 mg empagliflozyny: 19,5%; 25 mg empagliflozyny: 28,4%; placebo: 20,6% w ciągu pierwszych 18 tygodni leczenia, gdy nie można było dostosowywać dawki insuliny; 10 mg i 25 mg empagliflozyny: 36,1%; placebo: 35,3% w ciągu 78 tygodni badania) i jako leczenie skojarzone z insuliną MDI w skojarzeniu z metforminą lub bez niej (empagliflozyna 10 mg: 39,8%, empagliflozyna 25 mg: 41,3%, placebo: 37,2% podczas pierwszych 18 tygodni leczenia, gdy nie można było dostosować dawki insuliny; empagliflozyna 10 mg: 51,1%, empagliflozyna 25 mg: 57,7%, placebo: 58% w ciągu 52 tygodni badania). W badaniu niewydolności serca EMPEROR-Reduced obserwowano podobną częstość występowania hipoglikemii podczas stosowania w skojarzeniu z sulfonylomocznikiem lub insuliną (10 mg empagliflozyny: 4,2%; placebo: 4,6%). *Ciężka hipoglikemia (zdarzenia wymagające interwencji)* Nie zaobserwowano zwiększenia częstości występowania ciężkiej hipoglikemii przy stosowaniu empagliflozyny w porównaniu do placebo, w monoterapii, w leczeniu skojarzonym z metforminą, w leczeniu skojarzonym z metforminą i pochodną sulfonylomocznika, w leczeniu skojarzonym z pioglitazonem w skojarzeniu z metforminą lub bez niej, w leczeniu skojarzonym z linagliptyną i metforminą, jako leczenie dodane do terapii standardowej oraz w razie stosowania skojarzenia empagliflozyny z metforminą u nieleczonych uprzednio pacjentów w porównaniu z pacjentami leczonymi osobnymi lekami empagliflozyną i metforminą. Zwiększoną częstość zaobserwowano w przypadku stosowania jako leczenie skojarzone z insuliną podstawową w skojarzeniu z metforminą lub bez niej oraz w skojarzeniu z pochodną sulfonylomocznika lub bez niego (10 mg empagliflozyny: 0%; 25 mg empagliflozyny: 1,3%; placebo: 0% w ciągu pierwszych 18 tygodni leczenia, gdy nie można było dostosowywać dawki insuliny; 10 mg empagliflozyny: 0%; 25 mg empagliflozyny: 1,3%; placebo: 0% w ciągu 78 tygodni badania) i jako leczenie skojarzone z insuliną MDI w skojarzeniu z metforminą lub bez niej (empagliflozyna 10 mg: 0,5%, empagliflozyna 25 mg: 0,5%, placebo: 0,5% podczas pierwszych 18 tygodni leczenia, gdy nie można było dostosować dawki insuliny; empagliflozyna 10 mg: 1,6%, empagliflozyna 25 mg: 0,5%, placebo: 1,6% w ciągu 52 tygodni badania). W badaniu dotyczącym niewydolności serca EMPEROR-Reduced ciężką hipoglikemię obserwowano tylko u jednego pacjenta z cukrzycą podczas stosowania w skojarzeniu z sulfonylomocznikiem lub insuliną (10 mg empagliflozyny: 1,2%, placebo: 1,5%). *Kandydoza pochwy, zapalenie pochwy i sromu, zapalenie żołędzi i inne zakażenia narządów płciowych* Kandydoza pochwy, zapalenie pochwy i sromu, zapalenie żołędzi i inne zakażenia narządów płciowych były obserwowane częściej u pacjentów leczonych empagliflozyną (10 mg empagliflozyny: 4,0%; 25 mg empagliflozyny: 3,9%) w porównaniu z pacjentami otrzymującymi placebo (1,0%). Zakażenia takie obserwowano częściej u kobiet leczonych empagliflozyną w porównaniu z placebo. Różnica ta była mniej wyraźna w przypadku mężczyzn. Zakażenia narządów płciowych miały nasilenie łagodne lub umiarkowane. W badaniu dotyczącym niewydolności serca EMPEROR-Reduced częstość występowania tego typu zakażeń była większa u pacjentów z cukrzycą (10 mg empagliflozyny: 1,9%; placebo: 0,4%) niż u pacjentów bez cukrzycy (10 mg empagliflozyny: 1,4%; placebo: 0,9%) w trakcie leczenia empagliflozyną w porównaniu z placebo. *Zwiększone oddawanie moczu* Zwiększone oddawanie moczu (obejmujące określone wcześniej takie terminy jak częstomocz, wielomocz i oddawanie moczu w nocy) były obserwowane częściej u pacjentów leczonych empagliflozyną (10 mg empagliflozyny: 3,5%; 25 mg empagliflozyny: 3,3%) w porównaniu z pacjentami otrzymującymi placebo (1,4%). Zwiększone oddawanie moczu miało przeważnie nasilenie łagodne lub umiarkowane. Obserwowana częstość oddawania moczu w nocy była podobna dla empagliflozyny i dla placebo (< 1%). W badaniu niewydolności serca EMPEROR-Reduced zwiększone oddawanie moczu obserwowano z podobną częstością występowania u pacjentów leczonych empagliflozyną i placebo (10 mg empagliflozyny: 0,7%, placebo 0,4%). *Zakażenie dróg moczowych* Ogólna częstość występowania zakażeń dróg moczowych zgłaszanych jako zdarzenie niepożądane była podobna u pacjentów otrzymujących 25 mg empagliflozyny i placebo (7,0% i 7,2%), i wyższa u pacjentów otrzymujących 10 mg empagliflozyny (8,8%). Podobnie jak w przypadku placebo, zakażenia dróg moczowych były zgłaszane częściej u pacjentów leczonych empagliflozyną z przewlekłymi lub nawracającymi zakażeniami dróg moczowych w wywiadzie. Nasilenie (łagodne, umiarkowane, ciężkie) zakażenia dróg moczowych było podobne u pacjentów otrzymujących empagliflozynę i placebo. Zakażenia dróg moczowych były zgłaszane częściej u kobiet leczonych empagliflozyną w porównaniu z placebo; nie było takiej różnicy w przypadku mężczyzn. *Zmniejszenie objętości płynów* Ogólna częstość występowania zmniejszenia objętości płynów (obejmującego określone wcześniej takie terminy jak spadek ciśnienia krwi (określony ambulatoryjnie), spadek skurczowego ciśnienia krwi, odwodnienie, niedociśnienie, hipowolemia, hipotonia ortostatyczna oraz omdlenie) była podobna u pacjentów otrzymujących empagliflozynę (10 mg empagliflozyny: 0,6%; 25 mg empagliflozyny: 0,4%) i placebo (0,3%). Częstość występowania zmniejszenia objętości płynów była zwiększona u pacjentów w wieku 75 lat i starszych leczonych empagliflozyną (10 mg empagliflozyny: 2,3%; 25 mg empagliflozyny: 4,3%) w porównaniu z pacjentami otrzymującymi placebo (2,1%). *Zwiększenie stężenia kreatyniny we krwi i (lub) obniżenie współczynnika filtracji kłębuszkowej* Ogólna częstość występowania przypadków zwiększenia stężenia kreatyniny we krwi i obniżenie współczynnika filtracji kłębuszkowej była podobna u pacjentów otrzymujących empagliflozynę lub placebo (zwiększenie stężenia kreatyniny: empagliflozyna 10 mg 0,6%, empagliflozyna 25 mg 0,1%, placebo 0,5%; zmniejszenie szybkości filtracji kłębuszkowej: empagliflozyna 10 mg 0,1%, empagliflozyna 25 mg 0%, placebo 0,3%). Występujące początkowo zwiększenie stężenia kreatyniny we krwi i (lub) obniżenie współczynnika filtracji kłębuszkowej u pacjentów leczonych empagliflozyną jako terapią uzupełniającą leczenie metforminą zwykle ustępowało w trakcie ciągłego leczenia lub było odwracalne po zakończeniu leczenia tym lekiem. Konsekwentnie w badaniu EMPA-REG OUTCOME u pacjentów leczonych empagliflozyną obserwowano występujący początkowo spadek eGFR (średnia: 3 ml/min/1,73 m²). 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 triglyceryd ów 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:** 17.06.2021. **Kategoria dostępności:** Produkt leczniczy wydawany na receptę – Rp. **Cena urzędowa detaliczna:** Jardiance® 10 mg x 28 tabl. – 170,38 zł. Wysokość dopłaty pacjenta: 54,00 zł we wskazaniu: Cukrzyca typu 2, u pacjentów przed włączeniem insuliny, leczonych co najmniej dwoma doustnymi lekami hipoglikemizującymi od co najmniej 6 miesięcy, z HbA1c ≥ 8 % oraz bardzo wysokim ryzykiem sercowo-naczyniowym rozumianym jako: 1) otwierdzona choroba sercowo-naczyniowa, lub 2) uszkodzenie innych narządów objawiające się poprzez: białkomocz lub przerost lewej komory lub retinopatię, lub 3) obecność 3 lub więcej głównych czynników ryzyka spośród wymienionych poniżej: -wiek ≥ 55 lat dla mężczyzn, ≥ 60 lat dla kobiet, -dyslipidemia, -nadciśnienie tętnicze, -palenie tytoniu, -otyłość – na podstawie obwieszczenia Ministra Zdrowia z dnia 21 czerwca 2021 r. w sprawie wykazu refundowanych leków, środków spożywczych specjalnego przeznaczenia żywieniowego oraz wyrobów medycznych na 1 lipca 2021 r. (DZ. URZ. Min. Zdr. 2021.44).

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# XIII Konferencja hybrydowa

# Choroby Serca i Naczyń

## Gdańsk, 2–4 grudnia 2021 roku

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**Przewodniczący Komitetu Naukowego:**
prof. dr hab. n. med. Krzysztof Narkiewicz

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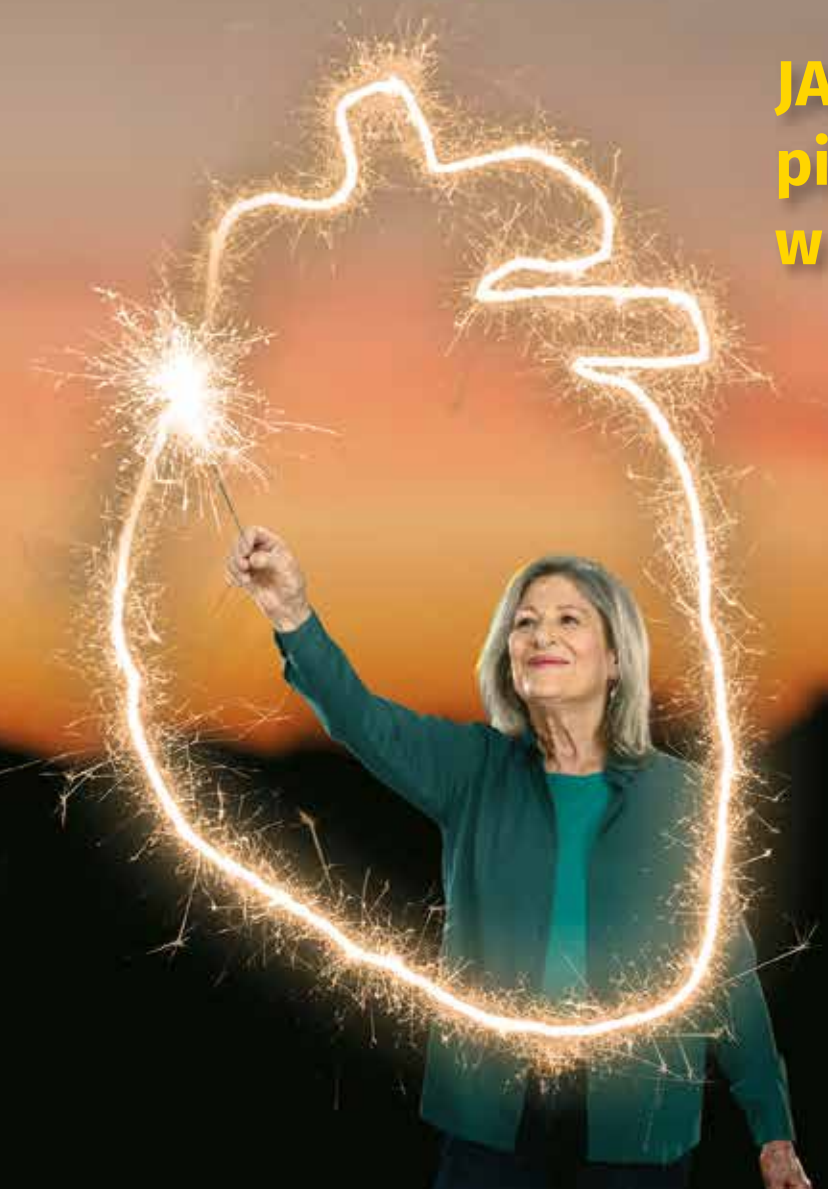

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