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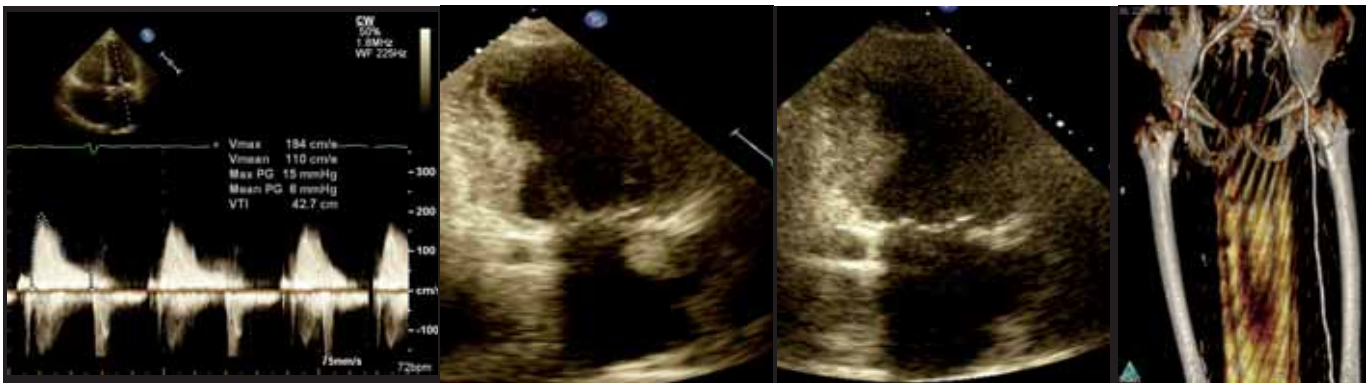

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CLINICAL VIGNETTE

LETTER TO THE EDITOR

T-wave inversions during conduction system pacing: A marker of more physiological ventricular activation

Karol Čurila[1], Pavel Jurak[2], Uyen Chau Nguyen[3]

Related article

by Geng et al.

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Permanent myocardial pacing can preserve adequate heart rates and improve symptoms and mortality in patients with bradycardia [1]. Conventional right ventricular (RV) pacing is far from the optimal treatment since up to 20% of patients experience a reduction in the left ventricular (LV) ejection fraction, which can lead to heart failure (HF) [2]. This was the main incentive for developing 'conduction system pacing (CSP)' techniques that target (directly or indirectly) the capture of conduction tissue, initiating more physiological ventricular activation. Although His bundle pacing (HBP) leads to the best ventricular synchrony [3], proper positioning is complicated, requires high pacing thresholds, and is associated with lower sensing values. For these reasons, left bundle branch area pacing (LBBAP), where the lead tip is deployed in the left subendocardial septal area, is currently preferred over HBP.

While ventricular activation is reasonably well understood [4, 5], little is known about the repolarization sequence during LBBAP. In a sizeable group of patients, Geng et al. [6] investigated the effect of LBBAP on occurrence and characteristics of T-wave inversions (TWIs). They showed that TWIs frequently (in 66% of cases) occurred one day after initiating LBBAP. TWIs appeared more frequently in patients with bundle branch blocks, and the main TWI predictor was QRS duration ≥120 ms. TWIs were unrelated to myocardial ischemia and, in most patients (88%), partially or entirely disappeared during a median follow-up of 10 days.

It is 40 years since Rosenbaum described the occurrence of transient TWIs in animal experiments [7]. He showed that temporary ventricular pacing could lead to changes in T-wave vectors and polarities that persisted after cessation of pacing and restoration of physiological ventricular activation. Interestingly, T-wave inversions were observed in the same leads in which the polarities of QRS complexes had been changed during pacing. Rosenbaum coined the term "cardiac memory" to note this phenomenon. This phenomenon has been observed in patients after cessation of RV pacing, successful ablation of accessory pathways associated with intermittent LBBB and ventricular tachyarrhythmias [8].

In a normal heart, the last activated regions of the ventricular wall generally have shorter action potential durations (APD) compared to the ones activated earlier. Myocytes that depolarize last will therefore repolarize first [9]. However, when the ventricular activation sequence suddenly changes, the distribution of APD does not immediately adapt to this change. Consequently, ventricular wall regions that were previously activated late (with shorter APD) may become activated sooner, creating a situation where myocytes that depolarize first also repolarize first. A similar situation was reported in patients with HF and wide QRS complexes [9].

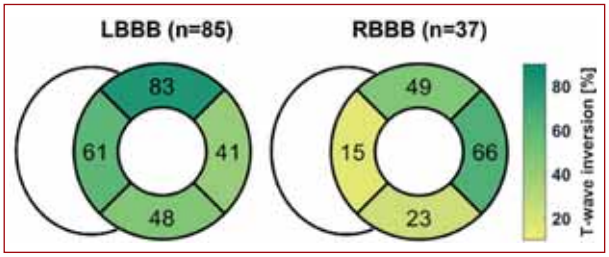

Figure 1. Visual representation of regional T-wave inversion distribution in LBBB (left) and RBBB (right) patients. data presented in Table 3 in the study by Geng et al. [6] was used as input. The regional TWI percentages were computed by averaging the percentages belonging to leads V1 and V2 (septum), V2 and V3 (anterior), V5, V6, I, and aVL (lateral), II, III, and aVF (inferior)

Abbreviations: LBBB, left bundle branch block; RBBB, right bundle branch block; TWI, T-wave inversion

This property appears to explain the observation by Geng et al. that TWI locations depend on the type of the bundle branch block; i.e., in LBBB patients, they occurred more frequently in leads V1–V4, II, III, and aVF, but in RBBB patients, leads I and aVL were affected more often. Figure 1 visualizes the incidence of TWIs per ECG-lead using data from Geng et al. (Table 3) [6] and assumes the following lead associations: leads V1 and 2 with the septum, V2 and V3 the anterior, V5, V6, I, and aV — the lateral wall, and II, III, and aVF — the inferior wall. In this representation (Figure 1), it becomes clear that TWIs in LBBB patients occurred most often in regions in which the sequence of ventricular activation and polarities of QRS complexes changed significantly during LBBAP. It would be interesting to determine if TWIs distribution in RBBB patients was associated with fascicular hemiblocks, which lead to less physiological LV activation. That was, however, not analyzed by the authors. Another reason may be including the patients with heart failure, which may lead to the inclusion of altered activation-repolarization relationships even in the absence of conduction disturbances [9]. Few studies have investigated repolarization changes following biventricular pacing in HF patients. Dispersion of repolarization appears to have a time-dependent character, with a high amount of dispersion observed within one month after implantation and decreasing over time [10].

Interestingly, computer simulations have demonstrated that acute biventricular pacing reduces LV repolarization dispersion on a regional level while increasing RV repolarization dispersion, leading to a higher degree of interventricular repolarization dispersion. During chronic biventricular pacing, however, an adaptation of APDs occurs, leading to a reduction in repolarization dispersion [10]. These processes are compatible with physiological adaptations to minimize dispersion of repolarization, so the disappearance of TWIs appears to be a physiological process.

Although inverted T-waves concern cardiologists, it is unclear to what extent TWIs related to cardiac memory are associated with an elevated risk for arrhythmias. Most clinical studies investigating the efficacy of conventional biventricular pacing did not find an association with ventricular tachyarrhythmias [11–13]. However, multiple individual cases describing the occurrence of electrical storm shortly after CRT implantation raised concerns about the pro-arrhythmic effect of LV epicardial pacing [14]. While Geng et al. [6] did not investigate T-wave changes during conventional biventricular pacing, Gupta et al. [15] recently demonstrated that CSP (both HBP and LBBAP) was associated with reduced repolarization heterogeneity (defined as Tpeak-Tend on a surface ECG) and greater cardiac memory resolution compared to conventional biventricular pacing. Additional studies comparing the temporal evolution of repolarization changes during biventricular vs. conduction system pacing are certainly warranted. More mechanistic insights can be obtained using invasive or non-invasive electro-anatomic mapping techniques.

Article information

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Atherosclerosis biomarkers and resting heart rate: Active players or simple bystanders?

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The resting heart rate (RHR), often referred to as cardiac frequency at rest, is perhaps one of the most accessible and clinically informative measures that can be taken. The normal reference range of this biological measure at rest is typically between 60 and 100 beats per minute (bpm) in healthy adult people, with values below or above such thresholds referred to as bradycardia and tachycardia, respectively [1]. Frequently, the RHR can decrease below 30 bpm in people with good physical condition, especially in physically active individuals and in the elderly [2], whilst it tends to be higher in women, in overweight subjects, and in the presence of a kaleidoscope of pathological conditions [3].

Convincing evidence has emerged that increased RHR may significantly predict the risk of death, especially in patients with cardiovascular disease (CVD) [4]. Thus, the RHR can be considered a "potentially modulable" risk factor since the cardiac frequency at rest can be straightforwardly lowered by enhancing the overall volume of aerobic exercise activities [5]. In a recent article published in this issue of the journal, Jiang and colleagues carried out a cross-sectional study in which plasma soluble low-density lipoprotein receptor-related protein-1 (sLRP1), soluble receptor for advanced glycation end products (sRAGE), and apolipoprotein E (*APOE*) gene polymorphisms were assayed in a cohort of nearly 1000 apparently healthy adults aged ≥40 years [6]. The most interesting finding was that both plasma biomarkers were significantly associated with the RHR after multiple adjustments for lifestyle, medical history, age, sex, and body weight, as well as for arterial blood pressure, glycemia, plasma lipids, and *APOE* genotype. This allowed the authors to conclude that the positive interplay between sLRP1 and sRAGE plasma concentrations and the RHR may represent a novel and intriguing mechanism influencing the development and/or progression of atherosclerotic disease.

The first important reflection that we could make on this finding is that it has been known for decades that an elevated RHR may be associated with CVD mortality, myocardial infarction, and stroke [7], as well as with numerous CVD risk factors, including hypertension, an atherogenic profile of plasma lipids, and hyperglycemia [8, 9]. It is hence predictable that an atherogenic plasma profile may significantly contribute to accelerating atherosclerosis, enhancing arterial impedance, and triggering other autonomic disturbances that may augment cardiac frequency at rest. To this end, it is also not surprising that increased values of both sLRP1 and sRAGE may be associated with an increased RHR. sLRP1 is an endocytic receptor, a member of the low-density lipoprotein (LDL) receptor family, which have important functions in lipoprotein metabolism and whose increased concentration is positively associated with the risk of ischemic syndromes due to its role in triggering inflammation, vascular remodeling, and even foam cell formation [10]. Similarly, impaired sRAGE clearance may cause their accumulation within the arterial wall, thus strongly fostering oxidative stress and LDL

accumulation, and ultimately leading to progression of atherosclerosis [11]. Therefore, the most important evidence that emerged from the study of Jiang and colleagues is that the concentration of both these atherosclerosis biomarkers may have an impact on the RHR independently from other well-known CVD risk factors, which would reflect an active role played by these two factors in influencing cardiac frequency and then promoting atherogenesis in apprently healthy subjects.

Nonetheless, the crucial questions that emerge here and now, irrespective of an active or passive role played by these two biomarkers in modulating atherogenesis, are (1) whether their assessment may be worth — more specifically cost-effective — in baseline estimation of the CVD risk and (2) whether specific therapeutic interventions shall be planned for targeting their eventually increased concentration in plasma. As concerns the former instance, the measurement of both sLRP1 and sRAGE appears challenging, expensive, low-throughput, and time-consuming in routine clinical laboratories (i.e., substantially based on enzyme-linked immunosorbent assay kits), where routine lipid testing (i.e., cholesterol, triglycerides, lipoprotein fractions) using fully-automated instrumentation would be easier, faster and cheaper, giving also a much greater yield in terms of CVD risk prediction [12]. Moreover, since sLRP1 and sRAGE may exert their final effect influencing the RHR, monitoring cardiac frequency using accurate portable devices appears simpler and perhaps even more clinically predictive [3].

Concerning possible therapeutic options for targeting sLRP1 and sRAGE, these most likely encompass drugs already used to lower CVD risk. For example, sLRP1 concentration could be consistently reduced by common hypocholesterolemic drugs like statins [13], while sRAGE treatment is still in embryo, with some promising results that emerged in patients taking statins and insulin-sensitizing medications [14]. Since most sLRP1and sRAGE-modulating agents are already part of standard care for patients at increased baseline risk of CVD, investing further efforts to identify additional medications tailored to specifically target these molecules seem unwarranted according to the current biological and clinical evidence. Even considering the intriguing association between these two biomarkers and increased RHR, which emerged from the study of Jiang et al. [6], directly targeting cardiac frequency with simple and safe interventions, such as enhancing the practice of physical exercise and dietary supplements (e.g., omega-3 fatty acids) [15], seems a more practical, safe and sustainable strategy.

In conclusion, although Jiang et al. have, indeed, provided an interesting contribution to unraveling additional aspects linking the puzzling and still partially unresolved relationship between HR, CVD, and mortality, further evidence would be needed before this intriguing link can have an effective translation into routine clinical practice.

Article information

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Summary of the European Society of Cardiology guidelines on dual antiplatelet therapy in patients after percutaneous coronary interventions

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ABSTRACT

This review is a summary of the European Society of Cardiology (ESC) guidelines focused on dual antiplatelet therapy in patients after percutaneous coronary interventions (PCI). Given a large number of recommendations concerning antiplatelet therapy published in various ESC guidelines, the main goal of this paper was to compile these separate recommendations into one document. In addition, we set out to present the current state of knowledge and create an algorithm that would be based on all of these guidelines in hope that it would allow quick navigation when selecting the type and duration of dual antiplatelet therapy (DAPT) depending on the clinical scenario with a special emphasis on evaluating both ischemic and bleeding risks.

The review is based on the ESC guidelines on the diagnosis and management of chronic coronary syndromes (2019), revascularization (2018), acute myocardial infarction in patients presenting with ST-segment elevation myocardial infarction (STEMI) (2017), DAPT (2017), and acute coronary syndromes in patients presenting without persistent ST-segment elevation (NSTE-ACS) (2020). The review also provides brief information on the most important studies and meta-analyses in this area, as well as practical pointers for management in the case of bleeding complications and before urgent surgery in patients on DAPT.

Key words: clopidogrel, dual antiplatelet therapy, percutaneous coronary intervention, prasugrel, ticagrelor

INTRODUCTION

Recently, a new generation of antiplatelet drugs has emerged that can be used in patients undergoing percutaneous coronary interventions (PCI). These more potent antiplatelet drugs have improved outcomes of both conservative and interventional treatments of patients with acute coronary syndrome (ACS). With technological progress and wide availability of secondand third-generation drug-eluting stents (DES) with improved design and drug delivery (biodegradable polymers, cobalt-chromium or platinum-chromium platforms, ultra-thin struts design), the recommended duration of dual antiplatelet therapy (DAPT) has also substantially evolved. Prolonged DAPT duration was associated with a reduced incidence of ischemic events but resulted in a significant increase in bleeding risk. Therefore, the debate on the optimization and individualization of antiplatelet therapy in patients after ACS and/or PCI remains open. Prevention of bleeding complications while maintaining effective protection against ischemic events is one of the main goals of medical treatment of patients after ACS and/or

PCI. The European Society of Cardiology (ESC) guidelines encourage clinicians to tailor DAPT duration and intensity according to the patients' individual bleeding and ischemic event risk.

In view of scientific and technological progress, expert recommendations regarding the DAPT strategy are constantly evolving. Our guide aims to compile these recommendations into one document so it would be readily available for quickly navigating the principles of selecting the type and duration of DAPT depending on the clinical scenario, including the bleeding and ischemic risk.

The need to make the correct decision regarding antiplatelet treatment may be challenging not only for cardiologists, but often for general practitioners, surgeons, or dentists alike [1]. Given the wide variety of recommendations concerning antiplatelet therapy algorithms, we set out to gather these recommendations in one document to facilitate an informed decision-making process in everyday clinical practice. It should be emphasized that this document presents only official recommendations without commenting on their content. Therefore, this review is based on the following ESC guidelines: the 2019 ESC guidelines on the diagnosis and management of chronic coronary syndromes (CCS), revascularization (2018), acute myocardial infarction in patients presenting with ST-segment elevation myocardial infarction (STEMI) (2017), dual antiplatelet therapy (2017), and acute coronary syndromes in patients presenting without persistent ST-segment elevation (NSTE-ACS) (2020).

CHOICE OF ANTIPLATELET THERAPY

A brief overview of antiplatelet drugs is included in the Supplementary material.

Acute coronary syndromes

The 2020 NSTE-ACS guidelines introduce significant changes to antiplatelet therapy, both in terms of the choice of $P2Y_{12}$ inhibitors, the time of initiation of therapy, and its duration. For the first time, there is a preference for prasugrel over ticagrelor in NSTE-ACS, making a significant difference in guiding antiplatelet management of STEMI and NSTE-ACS patients. Previous recommendations did not favor any of the more potent $P2Y_{12}$ inhibitors. The discrepancies in recommendations for prasugrel or ticagrelor use arise also from specific clinical scenarios and contraindications to their use. The 2017 STEMI guidelines allow the initiation of therapy with a potent $P2Y_{12}$ inhibitor at the time of diagnosis [2]. In turn, in the 2015 NSTE-ACS guidelines, initiation of treatment at diagnosis was possible only in the case of ticagrelor; the starting of prasugrel therapy had to be postponed until coronary angiography was performed and a decision on further invasive treatment was made. The recent 2020 NSTE-ACS guidelines recommend pretreatment only with acetylsalicylic acid (ASA). It is not recommended to apply routine pretreatment with a $P2Y_{12}$ inhibitor in patients in whom coronary anatomy is not known and early invasive management is planned (IIIA). Pretreatment with a $P2Y_{12}$ inhibitor may be considered in patients with NSTE-ACS who are not planned to undergo an early invasive strategy and do not have a high bleeding risk (HBR) (IIbC). These recommendations were based primarily on the results of the ACCOAST trial, which showed no reduction in ischemic events after pretreatment with $P2Y_{12}$ inhibitor, with a significant increase in bleeding complications with prasugrel [3]. Similar observations for all $P2Y_{12}$ inhibitors were made based on the analysis of the Swedish SCAAR registry [4]. In turn, the ISAR-REACT 5 trial did not demonstrate a benefit of pretreatment with ticagrelor [5]. A meta-analysis of 60 907 patients who underwent PCI has shown that the timing of ticagrelor or prasugrel loading dose had no effects on ischemic events in the acute setting; however, pretreatment with prasugrel in NSTE-ACS was associated with an increased risk of major bleeding events [6]. Postponing the addition of a $P2Y_{12}$ inhibitor to the therapy until coronary angiography is performed may result in multiple benefits, in particular reducing the risk of bleeding and avoiding unnecessary delay of coronary artery bypass surgery. Notably, a routine pretreatment strategy may be deleterious for a relevant proportion of patients with diagnoses other than NSTE-ACS (e.g. aortic dissection or bleeding complications including intracranial bleeding).

Another change concerns the position of prasugrel. Although both prasugrel and ticagrelor have retained their position (IB) as drugs that should be used with ASA for 12 months after PCI in patients with acute coronary syndrome if there are no contraindications to dual antiplatelet therapy, the 2020 NSTE-ACS guidelines recommend that prasugrel should be considered in preference to ticagrelor for NSTE-ACS patients who proceed to PCI [IIaB]. These recommendations are based on the results of the ISAR-REACT 5 trial [5], the first multicenter randomized trial comparing head-to-head prasugrel with ticagrelor in patients with acute coronary syndrome. This study generated a lot of controversies, mainly related to the study methodology. The obtained results, contrary to the hypothesis of the study, support the use of prasugrel (greater reduction in the composite endpoint at 12 months with no statistically significant difference in the incidence of bleeding complications). The primary endpoint event (death, myocardial infarction, or stroke at 1 year) occurred in 9.3% of patients in the ticagrelor group and 6.9% of patients in the prasugrel group (hazard ratio [HR], 1.36; 95% confidence interval [CI], 1.09–1.70; $P = 0.006$). The incidence rates of the individual components of the primary endpoint in the ticagrelor group and the prasugrel group were as follows: death 4.5% and 3.7% (HR, 1.23; 95% CI, 0.91–1.68); myocardial infarction 4.8% and 3.0% (HR, 1.63; 95% CI, 1.18–2.25); and stroke 1.1% and 1.0% (HR, 1.17; 95% CI, 0.63–2.15) [5]. Thus, the advantage of prasugrel over ticagrelor was driven exclusively by the excess of myocardial infarctions in the ticagrelor group.

Nevertheless, these data should be interpreted in light of their limitations, including (1) an open study plan; (2) a high percentage of patients who discontinued the assigned medication; (3) 83% of patient follow-up was done by telephone as opposed to face-to-face contact; (4) a lack of information on long-term bleeding complications (11.6% in the prasugrel arm vs. 1.1% in the ticagrelor arm), and (5) difficulties in interpreting the results in patients with different clinical settings (STEMI/non-ST-segment elevation myocardial infarction [NSTEMI]/unstable angina [UA]) with different timing strategies for $P2Y_{12}$ initiation.

Recently, Navarese et al. [7] published a network meta-analysis of twelve randomized controlled trials of 52 816 ACS patients. Compared to clopidogrel, ticagrelor significantly reduced cardiovascular mortality (HR, 0.82; 95% CI, 0.72–0.92) and all-cause mortality (HR, 0.83; 95% CI, 0.75–0.92), whereas there was no statistically significant mortality reduction with prasugrel (HR, 0.90; 95% CI, 0.80–1.01 and HR, 0.92; 95% CI, 0.84–1.02, respectively). When comparing ticagrelor and prasugrel to each other, there were no significant differences in mortality (HR prasugrel vs. ticagrelor 1.10 [95% CI, 0.94–1.29] and 1.12 [95% CI, 0.98–1.28]). In comparison with clopidogrel, prasugrel reduced myocardial infarction (HR, 0.81; 95% CI, 0.67–0.98), whereas ticagrelor showed no risk reduction (HR, 0.97; 95% CI, 0.78–1.22). Differences between prasugrel and ticagrelor with respect to myocardial infarction were not statistically significant. Compared with clopidogrel, both prasugrel (HR, 0.50; 95% CI, 0.38–0.64) and ticagrelor (HR, 0.72; 95% CI, 0.58–0.90) were associated with a significant reduction in definite or probable stent thrombosis. When compared to each other, prasugrel was linked to a significantly greater risk reduction of stent thrombosis than was ticagrelor (HR, 0.68; 95% CI, 0.50–0.90). In comparison with clopidogrel, both prasugrel (HR, 1.26 [95% CI, 1.01–1.56]) and ticagrelor (HR, 1.27 [95% CI, 1.04–1.55]) significantly increased major bleeding. However, the risk of major bleeding was similar when comparing ticagrelor to prasugrel (HR, 0.99; 95% CI 0.79–1.24) [7].

Recently, an expert opinion of the Association of Cardiovascular Interventions and the Working Group on Cardiovascular Pharmacotherapy of the Polish Cardiac Society on the place of prasugrel in the prevention of cardiovascular events in patients with acute coronary syndromes has been published. The document provides detailed characteristics of patients who can get the most benefit from prasugrel therapy. The experts concluded that prasugrel should be used in patients with ACS undergoing primary or delayed PCI. Compared to ticagrelor, prasugrel should be preferred in patients at increased risk of stent thrombosis. In patients with NSTEMI, the choice of a $P2Y_{12}$ inhibitor should be made after coronary angiography [8].

Chronic coronary syndromes

In patients with chronic coronary syndromes undergoing PCI, clopidogrel remains the preferred $P2Y_{12}$ inhibitor in addition to ASA. The recommendations for more potent $P2Y_{12}$ inhibitors are limited to patients at high risk of ischemic events — prasugrel or ticagrelor may be considered, at least as initial therapy, in specific high-risk situations of elective stenting (e.g. suboptimal stent deployment or other procedural characteristics associated with high risk of stent thrombosis, complex left main stem, or multivessel stenting) or if DAPT cannot be used because of ASA intolerance (IIbC) [9]. Similarly, if oral anticoagulation is needed (e.g., for stroke prevention in atrial fibrillation [AF]) in patients with chronic coronary syndrome, dual therapy with an oral anticoagulant (OAC) and either ticagrelor or prasugrel may be considered as an alternative to triple therapy with an OAC, ASA, and clopidogrel in patients with a moderate or high risk of stent thrombosis, irrespective of the type of stent used (IIbC) [9]. Notably, the use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with ASA and an OAC (IIIC) [9].

BLEEDING RISK ASSESSMENT TOOLS

The use of DAPT, especially with a potent $P2Y_{12}$ inhibitor, is associated with an increased risk of bleeding complications which increases with longer duration of DAPT [10]. In the TRITON-TIMI 38 trial, the use of prasugrel compared to clopidogrel was associated with more major bleeding (2.4% vs. 1.8%; $P = 0.03$) and life-threatening bleeding (1.4% vs. 0.9%; $P = 0.01$), including fatal bleeding (0.4% vs. 0.1%; $P = 0.002$) [11]. For ticagrelor, there was no statistically significant difference in the incidence of major bleeding (11.6% for ticagrelor, 11.2% for clopidogrel; $P = 0.43$), but the use of ticagrelor was associated with more major bleedings unrelated to coronary artery bypass surgery (4.5% vs. 3.8%; $P = 0.03$), including fatal intracranial hemorrhage (0.1% vs. 0.01%; $P = 0.02$) [12].

In patients at high risk of bleeding complications or significant anemia, special care should be taken in the selection of an antiplatelet regimen. Therefore, bleeding risk assessment is crucial in the management of these patients. The bleeding and ischemic risk assessments allow for individualization of antiplatelet therapy, but we need to keep in mind that most of them were designed to assess the in-hospital or the short-term risk. The risk of bleeding complications should be minimized by identifying risk factors and selecting the correct dose of an appropriate $P2Y_{12}$ inhibitor, as well as adding a proton pump inhibitor in selected patients.

One of the recommended tools for bleeding risk assessment is the PRECISE-DAPT score (Table 1), which allows evaluation of the outpatient bleeding risk after stent implantation and helps to modify DAPT duration. A score of ≥ 25 denotes a high bleeding risk and correlates with the clinical benefit of shortening DAPT duration (3–6 months).

The CRUSADE score (Supplementary material, *Table S1*) is recommended to assess the risk of bleeding complications after NSTE-ACS [13].

Table 1. PRECISE-DAPT score

	PRECISE-DAPT Score
Predictors	Hemoglobin, g/dl
	White blood cells count, $\times 10^3$ cells/μl
	Age, years
	Creatinine clearance, ml/min
	Prior bleeding
Score points from 0 to 100	
Score ≥25 → Short DAPT (increasing bleeding risk) Score <25 → Standard/long DAPT	
In the case of the PRECISE-DAPT score, it is necessary to use a scoring nomogram to determine the value for each of the five variables and to determine the number of points obtained for each clinical variable or to use a calculator: *www.precisedaptscore.com*.	

Abbreviation: DAPT, dual antiplatelet therapy

Table 2. List of clinical criteria to define patients at high bleeding risk according to the Academic Research Consortium for High Bleeding Risk (ARC-HBR)

High bleeding risk definition according to the ARC-HBR	
• Bleeding Academic Research Consortium (BARC) 3 or 5 bleeding ≥4% at 12 months after PCI • The risk of intracranial bleeding ≥1% at 12 months after PCI	
HBR = ≥1 major criteria or ≥2 minor criteria	
Minor criteria	• Age ≥75 years
	• Moderate CKD (eGFR, 30–59 ml/min/1.73 m^2)
	• Hemoglobin 11–12.9 g/dl for men or 11–11.9 g/dl for women
	• Spontaneous bleeding requiring hospitalization and/or transfusion within the past 12 months not meeting the major criterion
	• Any ischemic stroke at any time not meeting the major criterion
	• Chronic use of oral non-steroidal anti-inflammatory drugs or steroids
Major criteria	• Severe or end-stage CKD (eGFR <30 ml/min/1.73 m^2)
	• Liver cirrhosis with portal hypertension
	• Active malignancy (excluding non-melanoma skin cancer) within the past 12 months
	• Hemoglobin <11 g/dl
	• Moderate or severe baseline thrombocytopenia (platelet count $<100 \times 10^9$/l)
	• Previous spontaneous intracranial hemorrhage (at any time)
	• Previous traumatic intracranial hemorrhage within the past 12 months
	• Presence of a brain arteriovenous malformation
	• Moderate or severe ischemic stroke within the past 6 months
	• Chronic bleeding diathesis
	• Spontaneous bleeding requiring hospitalization and/or transfusion in the past 6 months or at any time, if recurrent
	• Anticipated use of long-term oral anticoagulant
	• Non-deferrable major surgery on DAPT
	• Recent major surgery or major trauma within 30 days before PCI

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtrated rate; HBR, high bleeding risk; PCI, percutaneous coronary intervention; other — see Table 1

Alternatively, the Academic Research Consortium High Bleeding Risk (ARC-HBR) [14] definition of high bleeding risk may be used (Table 2). The proposed ARC-HBR criteria are intended to standardize the previously used various high bleeding risk definitions for both clinical trials and everyday medical practice.

Table 3. Criteria for high bleeding risk according to the European Society of Cardiology guidelines on chronic coronary syndromes (2019)

Predictors of high bleeding risk
• Prior history of intracerebral hemorrhage or ischemic stroke • History of other intracranial pathology • Recent gastrointestinal bleeding or anemia due to possible gastrointestinal blood loss • Other gastrointestinal pathology associated with increased bleeding risk • Liver failure • Bleeding diathesis or coagulopathy • Extreme old age or frailty • Renal failure requiring dialysis or with eGFR <15 ml/min/1.73 m^2

Abbreviations: see Table 2

The ESC guidelines on CCS also list a set of criteria for high bleeding risk which are summarized in Table 3.

In the NSTE-ACS guidelines, DAPT duration and the selection of $P2Y_{12}$ inhibitor depend on the classification of the patient into one of three categories: low, high, and very high risk of bleeding using the above-mentioned risk scores (PRECISE-DAPT, ARC-HBR).

MANAGEMENT OF BLEEDING COMPLICATIONS

Bleeding complications are the major side effect of all antiplatelet drugs. In the case of overdose of antiplatelet agents, there is no specific antidote and, if necessary, transfusion of platelet concentrate (PC) may be considered. The use of PC for correction of platelet function in $P2Y_{12}$ inhibitors therapy is not as well documented as it is for the reversal of ASA. However, it seems that more units of PC need to be transfused to neutralize the effect of $P2Y_{12}$ inhibitors. When active metabolites in the blood are present or when reversible ticagrelor used, the transfused platelets will be blocked by the drug or active metabolite present in the patient's blood, thus reducing the effectiveness of the transfused PC. Following PC transfusion, in the case of clopidogrel a >40% rate of uninhibited platelet is considered a significant correction. In the case of prasugrel, the rate needs to be much higher (>60%), but achieving this level of correction only provides a partial reversal of the antiplatelet effect of prasugrel. If the time since the last dose of prasugrel and clopidogrel is less than 6 hours, PC transfusion may be ineffective. This period is significantly extended (up to 24 hours) when using ticagrelor due to the long half-life of the drug itself and its active metabolite. Even after the active drug is cleared from the circulation, large numbers of platelets may be needed within the first 48 hours to restore platelet function because transfused platelets do not correct the hemostatic defect in platelets inhibited by ticagrelor. The use of desmopressin may be considered in addition to PC transfusion; however, there is no clear evidence of the effectiveness of such an approach, which, given possible side effects, makes such a strategy questionable. If ticagrelor reversal is required, recombinant activated factor VII (rFVIIa) may decrease ticagrelor-induced

bleeding, but this approach is not supported by strong clinical evidence.

Given the potential rFVIIa-associated thrombosis risk, a careful assessment of the benefit-risk balance is warranted before using rFVIIa to reverse ticagrelor effects.

The treatment algorithm for bleeding patients receiving dual antiplatelet therapy is shown in Figure 1.

MANAGEMENT OF ANTIPLATELET THERAPY BEFORE URGENT SURGERY

Reversing the effects of antiplatelet therapy before urgent surgery remains an open topic. There is a possibility of continuing treatment with ASA or clopidogrel in monotherapy, which, however, may be associated with an increased risk of bleeding complications. An alternative may be the transfusion of PC 1–2 hours before surgery and then return to antiplatelet therapy 6–9 hours after the end of the surgical procedure in the case of ASA or 24–48 hours in the case of clopidogrel.

SHORTENING OF DUAL ANTIPLATELET THERAPY

Standard DAPT after PCI should be continued for 6 months in patients with CCS and for 12 months in patients with ACS. Depending on the ischemic-bleeding risk, as well as the presence of comorbid conditions, DAPT duration should be appropriately modified. Due to the risk of stent thrombosis, it can be shortened only in justified clinical scenarios. Most clinical trials are currently focused on evaluating the strategy of early withdrawal of ASA and continuation of treatment with a $P2Y_{12}$ inhibitor (GLOBAL LEADERS, STOP-DAPT-2, SMART-CHOICE, TWILIGHT — Table 4).

Ticagrelor in monotherapy is the most frequently considered regimen for modifying antiplatelet therapy. In the GLOBAL LEADERS trial among patients who underwent PCI with a biolimus-eluting stent, 1 month of DAPT followed by ticagrelor monotherapy for 23 months was noninferior, but not superior, to 12 months of DAPT followed by ASA monotherapy for 12 months. The composite outcome, components of the primary outcome, and major bleeding were similar between the treatment groups [15]. In turn, the TWILIGHT trial showed that short-duration DAPT (3 months) followed by ticagrelor monotherapy for 12 months resulted in less bleeding compared with longer-duration DAPT (additional 12 months) among patients undergoing PCI with DES and at high ischemic or bleeding risk; ischemic rates (risk of death, myocardial infarction, and stroke) met criteria for noninferiority [16]. There are also studies investigating the efficacy and safety of prasugrel in monotherapy (the ASET Pilot Study [17], Multivessel TALENT Study [18]).

Acute and chronic coronary syndromes

In patients with CCS, shortening DAPT duration to 3 months in the case of a higher risk of life-threatening bleeding should be considered (IIaA) [9]; however, in situations of a very high risk of life-threatening bleeding, shorter DAPT duration of 1 month may be considered (IIbC) [9].

In patients with ACS and stent implantation who are at high risk of bleeding (e.g. PRECISE-DAPT ≥25), discontinuation of $P2Y_{12}$ inhibitor therapy after 6 months should be considered (IIaB) [19].

The NSTE-ACS guidelines emphasize the need for a more personalized approach to choosing a DAPT strategy (duration and intensity). First and foremost, the patient should be appropriately classified into one of the three categories: low, high, or very high risk of bleeding. In patients with low bleeding risk, apart from standard DAPT for 12 months, in the presence of low ischemic risk, DAPT (ASA + ticagrelor) duration can be shortened to 3 months, followed by ticagrelor monotherapy. The guidelines do not precisely define the duration of ticagrelor monotherapy. In turn, in patients at high risk of bleeding (e.g. PRECISE-DAPT ≥25 or ARC-HBR criteria met), discontinuation of $P2Y_{12}$ inhibitor therapy after 3 months should be considered followed by long-term ASA monotherapy (IIaB) [20]. Finally, in patients deemed at very high bleeding risk, DAPT (ASA + clopidogrel) is indicated for only 1 month followed by clopidogrel monotherapy. A very high bleeding risk was defined as a bleeding event within the past month or scheduled surgery that is impossible to postpone in the near future. The above indications are presented in Figures 2 and 3.

The two recently published studies assessed the appropriate duration of DAPT in patients at high risk bleeding after PCI (MASTER DAPT [21] and TWILIGHT-HBR [22]) and confirmed the benefits of shortened DAPT duration. In the MASTER DAPT trial among patients with acute or chronic coronary artery disease who underwent PCI and were at increased bleeding risk, abbreviated DAPT was noninferior to standard DAPT regarding net adverse clinical events and major adverse cardiac or cerebral events. Abbreviated DAPT was superior to standard antiplatelet therapy regarding major or clinically relevant nonmajor bleeding [21]. These results are specific to patients who received biodegradable-polymer sirolimus-eluting stents. On the other hand, TWILIGHT-HBR showed that selected HBR patients who tolerated 3 months of DAPT with ticagrelor after PCI, withdrawing ASA, and continuing ticagrelor monotherapy for 1 year, had significantly decreased clinically relevant as well as major bleeding events without compromising their ischemic protection, as compared with ticagrelor plus ASA [22].

Indications for oral anticoagulation

In the case of uncomplicated PCI, early cessation (≤1 week) of ASA and continuation of dual therapy with an OAC and $P2Y_{12}$ inhibitor (preferably clopidogrel) for 6 months (CCS) or 12 months (ACS) is recommended if the risk of stent thrombosis is low or if concerns about bleeding risk prevail over concerns about the risk of stent thrombosis, irrespective of the type of stent used (class IIaB recommendation

Table 4. The most important clinical trials evaluating the strategy of early withdrawal of acetylsalicylic acid and continuation of treatment with $P2Y_{12}$ inhibitor[a]

	TWILIGHT [16]	STOPTDAPT-2 [50]	SMART-CHOICE [49]	GLOBAL LEADERS [15]
Study population	7119	3009	2993	15968
Follow-up duration, months	15	12	12	24
Short-term DAPT	ASA (81–100 mg) with ticagrelor 2 × 90mg for 3 months followed by ticagrelor alone	ASA (81–100 mg) with clopidogrel 1 × 75mg (or prasugrel 1× 3.75 mg — the study conducted in Japan) for 1 month followed by clopidogrel in monotherapy	ASA (81–100 mg) with $P2Y_{12}$ inhibitor (ticagrelor 2 × 90 mg, prasugrel 1 × 10 mg or clopidogrel 1 × 75 mg) for 3 months followed by ticagrelor, prasugrel or klopidogrel in monotherapy	ASA (81–100 mg) with ticagrelor 2 × 90 mg for 1 month followed by continuation of ticagrelor alone for 23 months
Standard DAPT	ASA + ticagrelor for 15 months	ASA + clopidogrel for 12 months	ASA + $P2Y_{12}$ inhibitor (ticagrelor, prasugrel or clopidogrel) for 12 months	ASA + clopidogrel or ASA + ticagrelor for 12 months
Acute coronary syndrome, %	63.9/65.7	37.7/38.6	58.2/58.2	47.0/46.8
STEMI, %	0/0	19.4/17.9	11.0/10.0	13.3/12.9
NSTEMI, %	28.8/30.8	5.4/6.6	16.0/15.4	21.1/21.1
UA, %	35.1/34.9	12.9/14.2	31.2/32.8	12.6/12.7
Chronic coronary syndrome, %	29.5/28.0	62.3/61.4	41.8/41.8	53.0/53.2
ASA, %	100/100	99.8/100	99.8/99.9	100/100
Clopidogrel, %	0/0	60.2/62.9	76.9/77.6	53.0/53.2
Prasugrel, %	0/0	39.6/37.0	4.1/4.5	0/0
Ticagrelor, %	100/100	0/0	19.0/17.9	47.0/46.8
MACCE (myocardial infarction, ischemic stroke, all-cause death)	HR, 0.99 (95% CI, 0.78–1.25)	NA	HR, 0.4 (95% CI, –∞ – 1.3)	HR, 0.83 (95% CI, 0.69–1.00)
All-cause death	HR, 0.75 (95% CI, 0.48–1.18)	HR, 1.18 (95% CI, 0.63–2.21)	HR, 1.18 (95% CI, 0.63–2.21)	HR, 0.82 (95% CI, 0.64–1.06)
Myocardial infarction	HR, 1.00 (95% CI, 0.75–1.33)	HR, 1.19 (95% CI, 0.54–2.67)	HR, 0.66 (95% CI, 0.31–1.40)	HR, 1.14 (95% CI, 0.92–1.41)
Stroke (ischemic or hemorrhagic)	HR, 2.00 (95% CI, 0.86–4.67)	HR, 0.50 (95% CI, 0.22–1.18)	HR, 2.23 (95% CI, 0.78–6.43)	HR, 1.07 (95% CI, 0.72–1.57)
Stent thrombosis (definite or probable)	HR, 0.74 (95% CI, 0.37–1.47)	HR, 4.03 (95% CI, 0.45–36.08)	HR, 1.51 (95% CI, 0.25–9.02)	HR, 1.30 (95% CI, 0.86–1.95)
Major bleeding (BARC, 3 or 5)	HR, 0.49 (95% CI, 0.33–0.74)	HR, 0.30 (95% CI, 0.13–0.65)	HR, 0.87 (95% CI, 0.40–1.88)	HR, 0.86 (95% CI, 0.67–1.11)

[a]The results presented in the table correspond to the published trial results [15, 16, 49, 50]

Abbreviations: ASA, acetylsalicylic acid; BARC, Bleeding Academic Research Consortium; CI, confidence interval; HR, hazard ratio; MACCE, major adverse cardiovascular and cerebrovascular events; NA, non-applicable; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina; other — see Table 1

in the 2019 CCS guidelines was upgraded to class IA in the 2020 AF guidelines) [9, 23]. This issue is discussed in more detail elsewhere [24–26]. However, triple therapy with ASA, clopidogrel, and an OAC for longer than 1 week should be considered when the risk of stent thrombosis outweighs the bleeding risk with the total duration (≤1 month) decided according to assessment of these risks, and the treatment plan should be clearly specified at hospital discharge (IIaC) [9, 23]. As shown in the AUGUSTUS study, ASA reduces the risk of ischemic events up to one month after PCI or an ACS event. Beyond this period, ASA further increases the bleeding rate without reducing the risk of ischemic events [27].

ISCHEMIC RISK ASSESSMENT

After PCI, especially with the use of secondor third-generation DES, it is important to assess the risk of thrombotic/ischemic events and select an appropriate antiplatelet strategy (Figures 2 and 3). Risk factors of ischemic events are listed in Tables 5 and 6. There have been few changes in the assessment of the ischemic risk in each of the following documents.

According to the ESC guidelines on DAPT, the use of risk scores designed to evaluate the benefits and risks of different DAPT durations may be considered (IIbA) [10]. Currently, only the DAPT and PRECISE-DAPT scores (for bleeding risk assessment) meet these requirements.

The DAPT score gives clinicians an opportunity to see how patients with particular characteristics fared when randomized to either 30 months or 12 months of dual antiplatelet therapy after receiving a stent (Supplementary material, *Table S2*). It includes 9 factors based on the results of the DAPT study [28]. Receiving ≥2 points indicates a high risk of ischemic events and may justify prolongation of DAPT duration. However, the DAPT score should be used to guide antiplatelet therapy duration in conjunction with clinical judgment and applied on an individualized basis. It is not a substitute for clinical judgment.

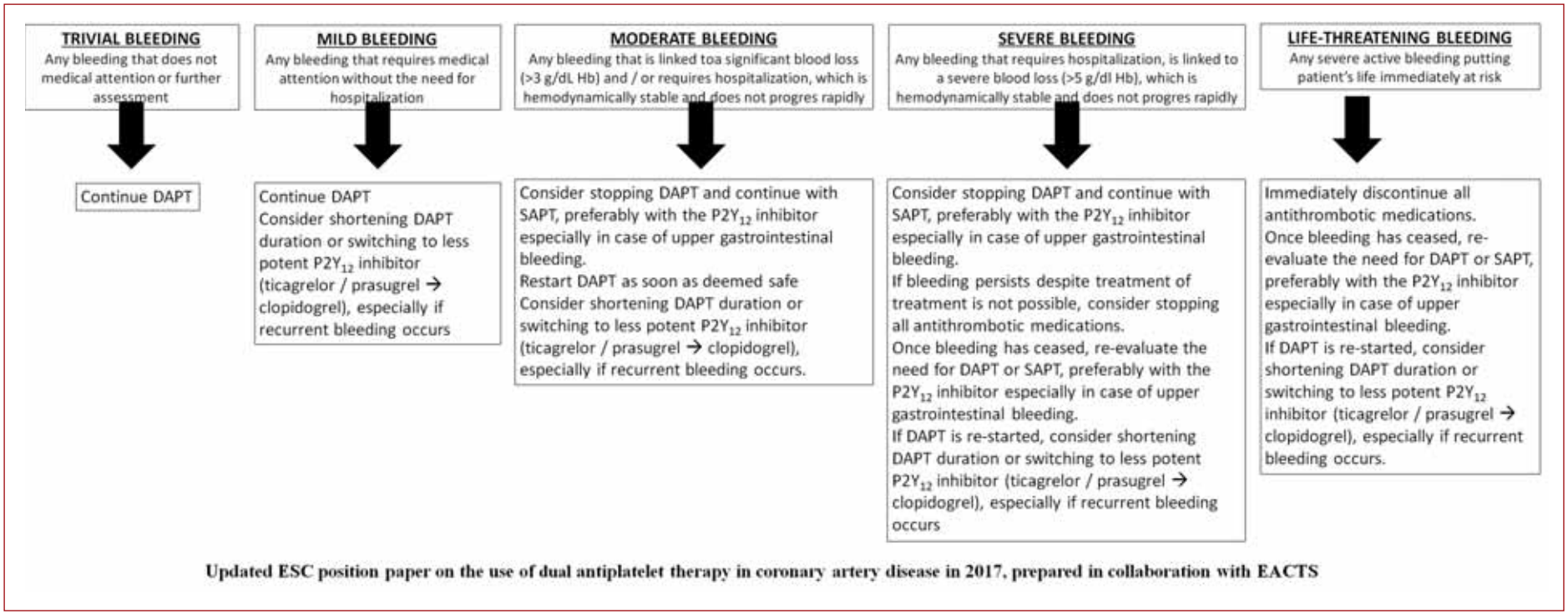


Figure 1. Algorithm for managing a bleeding patient on dual antiplatelet therapy (based on ESC-focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS [10])

Abbreviations: EACTS, European Association for Cardio-Thoracic Surgery; ESC, European Society of Cardiology; other — see Table 1

Table 5. Factors increasing the risk of recurrent ischemic events according to the ESC/EACTS guidelines on myocardial revascularization (2018)

High-risk features for ischemic events
• Prior stent thrombosis on adequate antiplatelet therapy
• Stenting of the last remaining patent coronary artery
• Diffuse multivessel disease, especially in diabetic patients
• Chronic kidney disease (i.e. creatinine clearance <60 ml/min/1.73 m^2)
• At least three stents implanted
• At least three lesions treated
• Bifurcation with two stents implanted
• Total stented length >60 mm
• Treatment of a chronic total occlusion
• History of STEMI

Abbreviations: see Figure 1 and Table 4

Table 6. Ischemic risk factors based on the ESC guidelines on chronic coronary syndromes (2019), modified in the ESC guidelines on NSTE-ACS (2020) **(bold)**

RISK STRATIFICATION OF STENT THROMBOSIS	
HIGH RISK: complex CAD[a] with at least one of the following:	
Clinical factors	• Diabetes mellitus requiring medication • History of recurrent MI • **Any multivessel CAD** • **Polyvascular disease (CAD + PAD)** • **Premature (<45 years old) or accelerated (new lesion within a 2-year time frame) CAD** • **Concomitant systematic inflammatory disease (e.g. HIV, systemic lupus erythematosus, chronic arthritis)** • CKD with eGFR 15–59 ml/min/1.73 m^2
Procedural factors	• At least three stents implanted • At least three lesions treated • Total stented length >60 mm • History of complex revascularization (i.e. stenting of the left main, proximal LAD, or last remaining patent artery; suboptimal stent deployment; bifurcation with at least two stents implanted; treatment of chronic total occlusion) • Previous stent thrombosis on adequate antiplatelet treatment
MODERATE RISK: non-complex CAD[a] and at least 1 criterion:	
Clinical factors	• Diabetes mellitus requiring medication • History of recurrent MI, • **Polyvascular disease (CAD + PAD)** • CKD with eGFR 15–59 ml/min/1.73 m^2

[a]Stratification of patients into complex vs. non-complex CAD is based on individual clinical judgment with knowledge of patients' cardiovascular history and/or coronary anatomy

Abbreviations: CAD, coronary artery disease; HIV, human immunodeficiency virus; MI, myocardial infarction; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; PAD, peripheral artery disease; other — see Table 2

Prolonging antithrombotic treatment duration

Adding a second antithrombotic agent ($P2Y_{12}$ inhibitor or low dose rivaroxaban) to ASA for extended long-term secondary prevention should be considered in patients with a high risk of ischemic events and without increased risk of major or life-threatening bleeding (IIaA) [9, 20]. In the case of a moderate risk of thrombotic events, such management may be considered (IIbA) [9, 20]. Treatment options for extended dual antithrombotic or antiplatelet therapies are summarized in Table 7.

The doses of antiplatelet agents remain the same as for standard therapy if treatment with clopidogrel or prasugrel is continued. These recommendations are based on the results of the DAPT study, in which continuation of DAPT beyond 12 months was associated with a reduced risk of stent thrombosis and major adverse cardiovascular and cerebrovascular events, with a simultaneous increase in bleeding complications and noncardiac mortality rate [23]. In turn, an increased risk of myocardial infarction and stent thrombosis was observed during the 3-month follow-up after discontinuation of thienopyridine therapy [28]. The positive effect of prolonging DAPT duration with a similar bleeding risk was more pronounced in the post-myocardial infarction (MI) group of patients [29]. However, in the case of ticagrelor, it is recommended to consider the continuation of treatment beyond one year at a reduced dose of 60 mg twice a day in patients after myocardial infarction who tolerated DAPT well for 12 months. In PEGASUS-TIMI 54, the use of both the standard dose (90 mg twice a day) and the reduced dose (60 mg twice a day) was associated with a reduction in thrombotic events and an increase in bleeding complications [30]; both doses showed a similar degree of platelet inhibition with a better safety profile of the reduced dose [30, 31]. A significant reduction in all-cause and cardiovascular mortality was achieved if the treatment with a lower dose of ticagrelor was initiated up to two years after the initial MI or within one year after stopping DAPT [32]. There is no evidence of significant benefits in prolonging DAPT in patients without a history of myocardial infarction [33]. In turn, based on the analysis of the RENAMI registry, the benefits of extending DAPT dura-

Table 7. Options for prolonged secondary antithrombotic regimens (including ASA, 75–100 mg/d)

Drug	Dose	Indication
Rivaroxaban (COMPASS trial)	2.5 mg BID	Patients with CAD or symptomatic PAD at high risk of ischemic events
Clopidogrel (DAPT trial)	75 mg/d	Post MI in patients who have tolerated DAPT for 1 year
Prasugrel (DAPT trial)	10 mg/d (5 mg/d if body weight <60 kg or age >75 years)	Post PCI for MI in patients who have tolerated DAPT for 1 year
Ticagrelor (PEGASUS-TIMI 54)	60 mg BID	Post MI in patients who have tolerated DAPT for 1 year

Abbreviations: BID, *bis in die* (twice a day); other — see Tables 1, 2 and 6

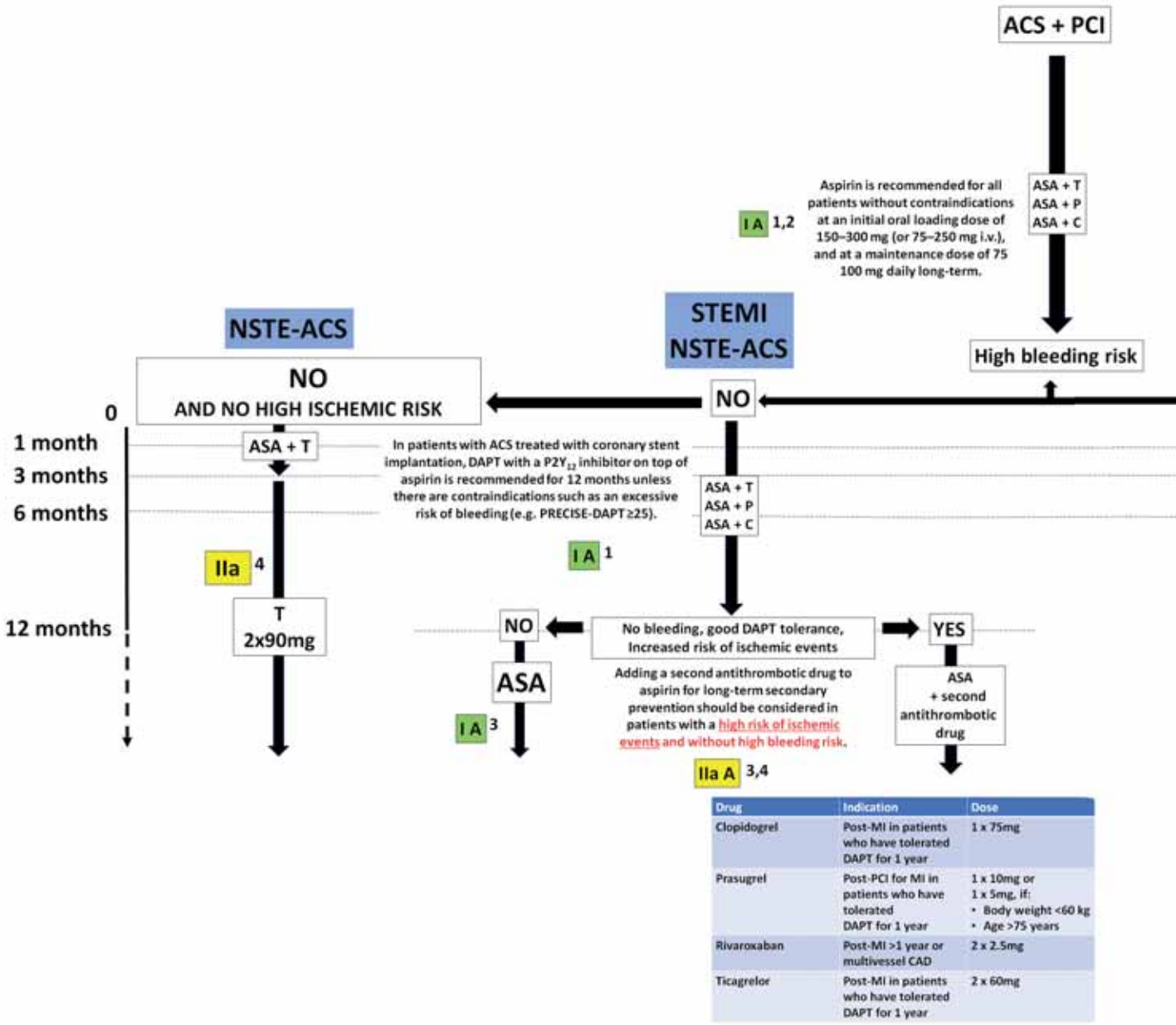
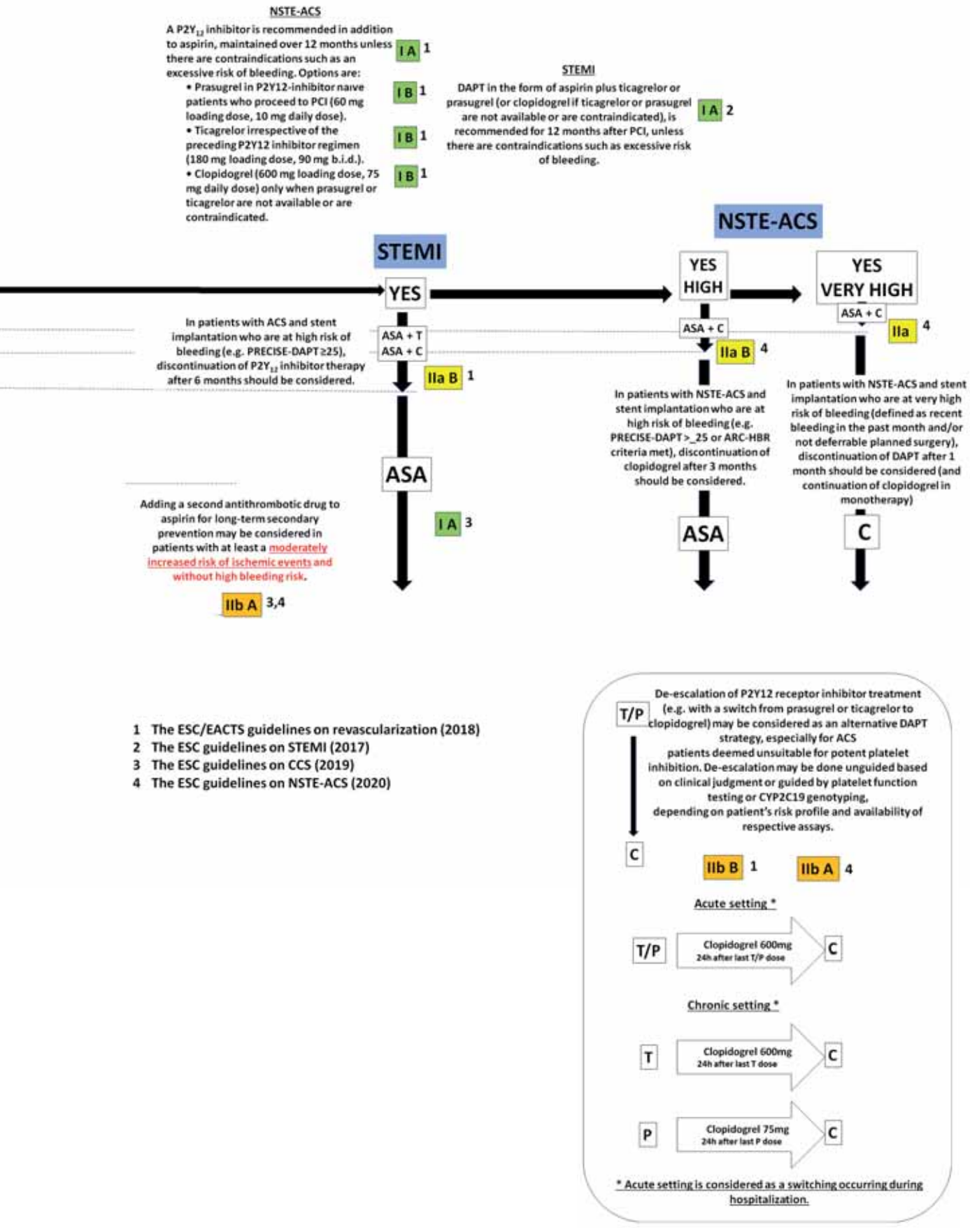


Figure 2. Algorithm for dual antiplatelet therapy after PCI in patients with ACS (ESC/EACTS Guidelines on myocardial revascularization [19]; ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation [2]; ESC Guidelines for the diagnosis and management of chronic coronary syndromes [9]; ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation [20])

Abbreviations: ACS, acute coronary syndrome; other — see Figure 1 and Table 2


NSTE-ACS
A P2Y12 inhibitor is recommended in addition to aspirin, maintained over 12 months unless there are contraindications such as an excessive risk of bleeding. Options are:
• Prasugrel in P2Y12-inhibitor naive patients who proceed to PCI (60 mg loading dose, 10 mg daily dose).
• Ticagrelor irrespective of the preceding P2Y12 inhibitor regimen (180 mg loading dose, 90 mg b.i.d.).
• Clopidogrel (600 mg loading dose, 75 mg daily dose) only when prasugrel or ticagrelor are not available or are contraindicated.
I A 1
I B 1
I B 1
I B 1
STEMI
DAPT in the form of aspirin plus ticagrelor or prasugrel (or clopidogrel if ticagrelor or prasugrel are not available or are contraindicated), is recommended for 12 months after PCI, unless there are contraindications such as excessive risk of bleeding.
I A 2
STEMI
YES
ASA + T
ASA + C
IIa B 1
In patients with ACS and stent implantation who are at high risk of bleeding (e.g. PRECISE-DAPT ≥25), discontinuation of P2Y12 inhibitor therapy after 6 months should be considered.
ASA
I A 3
Adding a second antithrombotic drug to aspirin for long-term secondary prevention may be considered in patients with at least a moderately increased risk of ischemic events and without high bleeding risk.
IIb A 3,4
NSTE-ACS
YES HIGH
ASA + C
IIa B 4
In patients with NSTE-ACS and stent implantation who are at high risk of bleeding (e.g. PRECISE-DAPT >_25 or ARC-HBR criteria met), discontinuation of clopidogrel after 3 months should be considered.
ASA
YES VERY HIGH
ASA + C
IIa 4
In patients with NSTE-ACS and stent implantation who are at very high risk of bleeding (defined as recent bleeding in the past month and/or not deferrable planned surgery), discontinuation of DAPT after 1 month should be considered (and continuation of clopidogrel in monotherapy)
C
1 The ESC/EACTS guidelines on revascularization (2018)
2 The ESC guidelines on STEMI (2017)
3 The ESC guidelines on CCS (2019)
4 The ESC guidelines on NSTE-ACS (2020)
T/P
De-escalation of P2Y12 receptor inhibitor treatment (e.g. with a switch from prasugrel or ticagrelor to clopidogrel) may be considered as an alternative DAPT strategy, especially for ACS patients deemed unsuitable for potent platelet inhibition. De-escalation may be done unguided based on clinical judgment or guided by platelet function testing or CYP2C19 genotyping, depending on patient's risk profile and availability of respective assays.
C
IIb B 1
IIb A 4
Acute setting *
T/P
Clopidogrel 600mg
24h after last T/P dose
C
Chronic setting *
T
Clopidogrel 600mg
24h after last T dose
C
P
Clopidogrel 75mg
24h after last P dose
C
* Acute setting is considered as a switching occurring during hospitalization.

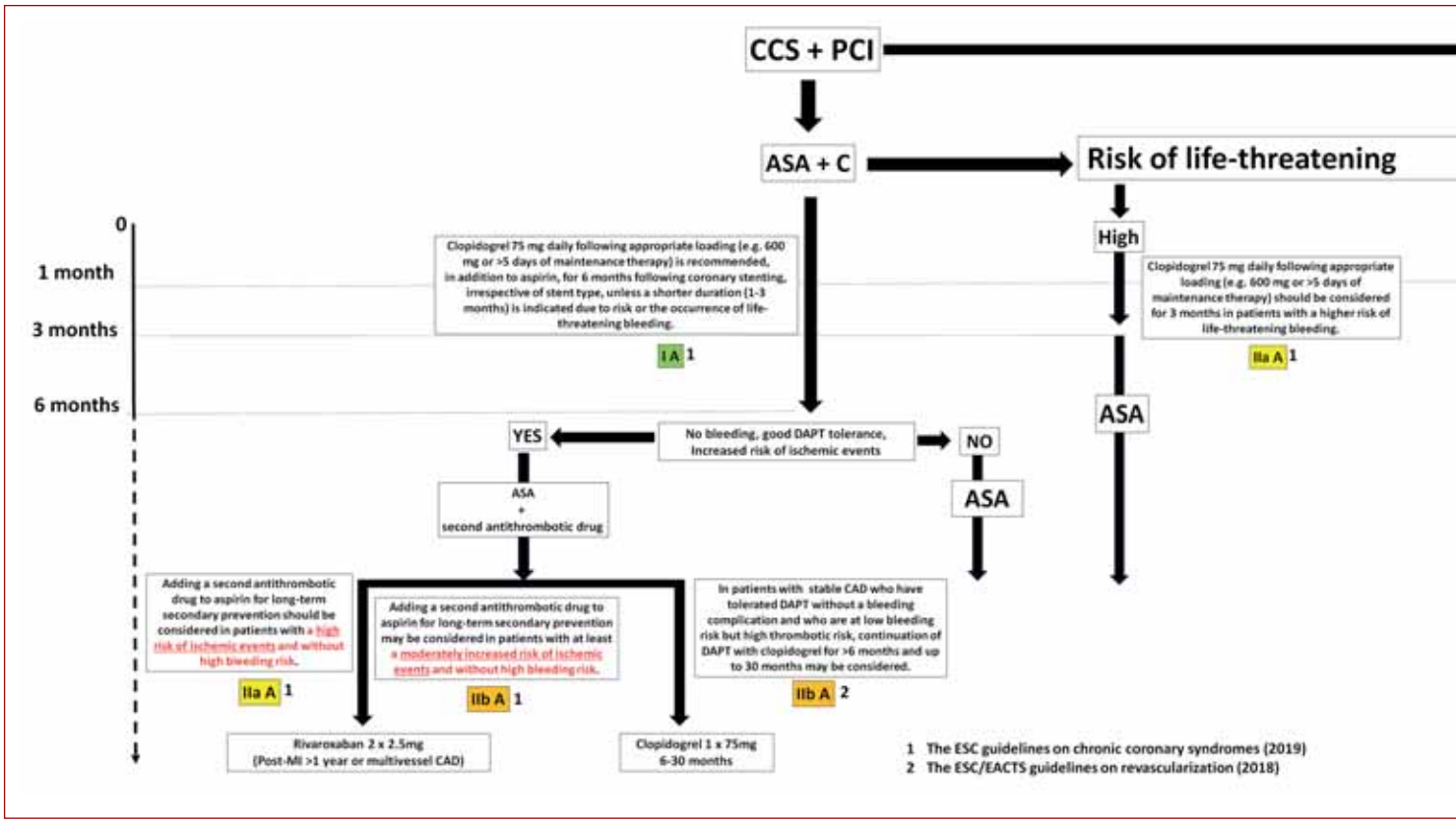
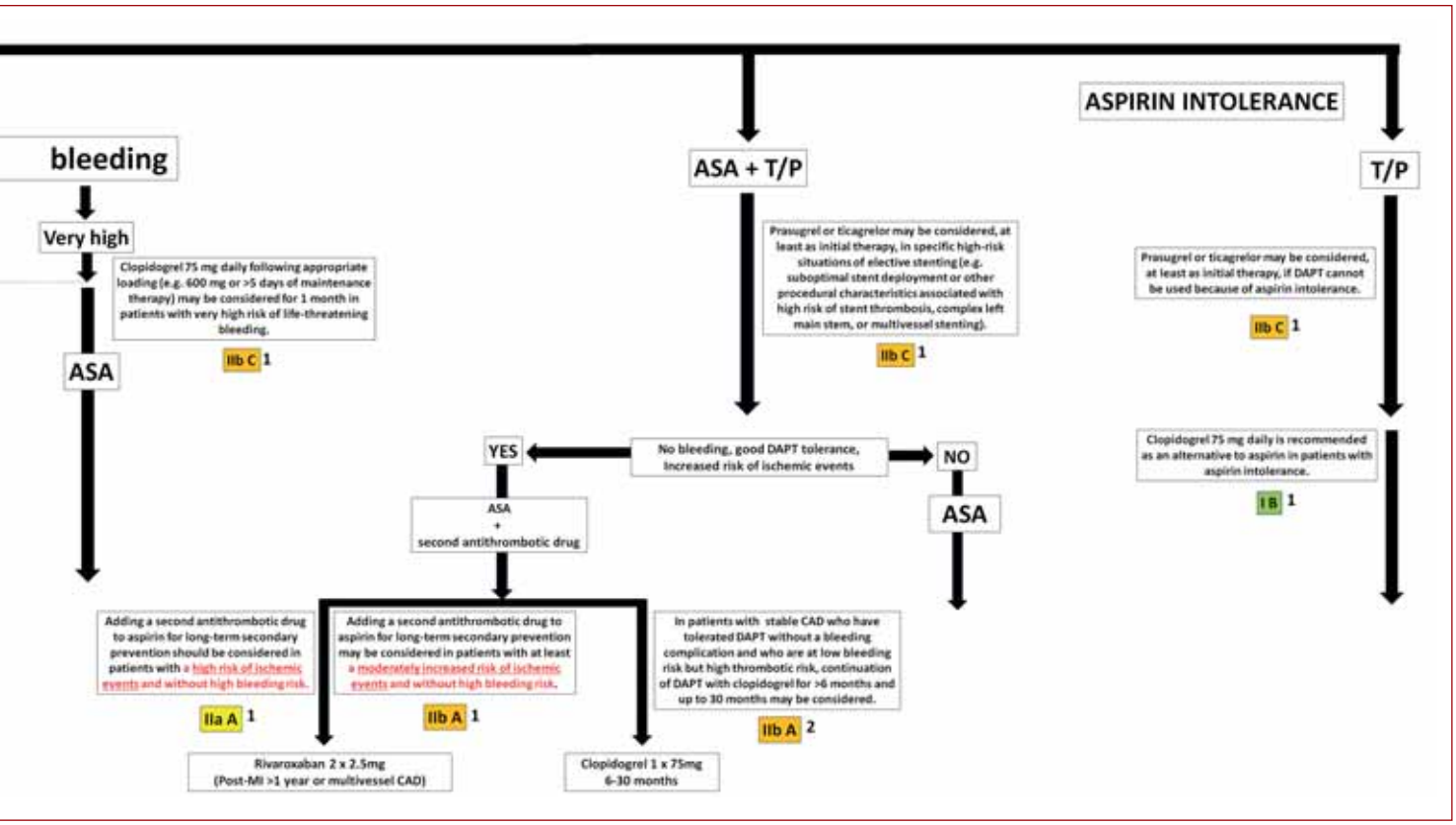


Figure 3. Algorithm for dual antiplatelet therapy after PCI in patients with CCS (ESC Guidelines for the diagnosis and management of chronic coronary syndromes [9]; ESC/EACTS Guidelines on myocardial revascularization [19])

Abbreviations: CCS, chronic coronary syndrome; other — see Figure 1 and Table 2


bleeding
Very high
Clopidogrel 75 mg daily following appropriate loading (e.g. 600 mg or >5 days of maintenance therapy) may be considered for 1 month in patients with very high risk of life-threatening bleeding.
IIb C 1
ASA
ASA + T/P
Prasugrel or ticagrelor may be considered, at least as initial therapy, in specific high-risk situations of elective stenting (e.g. suboptimal stent deployment or other procedural characteristics associated with high risk of stent thrombosis, complex left main stem, or multivessel stenting).
IIb C 1
ASPIRIN INTOLERANCE
T/P
Prasugrel or ticagrelor may be considered, at least as initial therapy, if DAPT cannot be used because of aspirin intolerance.
IIb C 1
No bleeding, good DAPT tolerance, increased risk of ischemic events
YES
NO
ASA
+
second antithrombotic drug
ASA
Clopidogrel 75 mg daily is recommended as an alternative to aspirin in patients with aspirin intolerance.
I B 1
Adding a second antithrombotic drug to aspirin for long-term secondary prevention should be considered in patients with a high risk of ischemic events and without high bleeding risk.
IIa A 1
Adding a second antithrombotic drug to aspirin for long-term secondary prevention may be considered in patients with at least a moderately increased risk of ischemic events and without high bleeding risk.
IIb A 1
In patients with stable CAD who have tolerated DAPT without a bleeding complication and who are at low bleeding risk but high thrombotic risk, continuation of DAPT with clopidogrel for >6 months and up to 30 months may be considered.
IIb A 2
Rivaroxaban 2 x 2.5mg
(Post-MI >1 year or multivessel CAD)
Clopidogrel 1 x 75mg
6-30 months

tion beyond 12 months after ACS with the use of prasugrel or ticagrelor were associated with a reduction of ischemic events with an increased risk of bleeding, but positive effects of extending DAPT duration were less pronounced in women and patients over 75 years due to the increased risk of bleeding complications [34].

Data on a novel strategy of dual antithrombotic therapy (DAT) consisting of factor-Xa inhibition with a very low dose of rivaroxaban (2.5 mg twice a day) plus ASA has emerged in secondary prevention in patients with CAD or symptomatic peripheral artery disease at high risk or moderate risk of ischemic events, based on data from the COMPASS trial [35]. On the other hand, the 2018 guidelines on myocardial revascularization state that in ACS patients with no prior stroke/transient ischemic attack who are at high ischemic risk and low bleeding risk and are receiving ASA and clopidogrel, low-dose rivaroxaban (2.5 mg twice a day for approximately 1 year) may be considered. This recommendation was upheld in the 2020 NSTE-ACS guidelines (IIbB) [19, 20]. This recommendation was made based on the results of the ATLAS-ACS-2-TIMI-51 study [36].

In the presence of indications for anticoagulant treatment, ASA 75–100 mg daily (or clopidogrel 75 mg daily) may be considered in addition to long-term OAC therapy in patients with AF, history of MI, and at high risk of recurrent ischemic events who do not have a high bleeding risk (IIbB) [9].

In patients treated with bioresorbable scaffolds (BRS), DAPT should be considered for at least ≥12 months and up to the presumed full absorption of the BRS, based on an individual assessment of bleeding and ischemic risk (IIaC) [10, 19].

ASSESSMENT OF PLATELET ACTIVITY DURING ANTIPLATELET TREATMENT

Currently, routine platelet reactivity testing is not recommended and should be limited to selected clinical situations such as occurrence of stent thrombosis despite using recommended antiplatelet therapy, suspicion of malabsorption of oral medications, or selected cases of increased risk of cardiovascular events where there is a reasonable suspicion of inadequate inhibition of platelet function.

Insufficient platelet inhibition mainly concerns clopidogrel. Substantial inter-individual variability has been demonstrated in the ability of clopidogrel to inhibit ADP-induced platelet aggregation [37]. Genetic polymorphism in *CYP2C19* (presence of the loss of function *CYP2C19*2* and *CYP2C19*3* alleles) is essential for metabolic activation of clopidogrel in the liver and the development of clopidogrel resistance. These alleles are relatively common and observed in about 30% of the European population [38]. However, two large meta-analyses show divergent data on adverse effects of *CYP2C19* gene variants on the occurrence of major adverse cardiovascular events (MACE). One of them showed that the presence of even a heterozygote within the *CYP2C19* gene is associated with a significant risk of adverse cardiovascular events, especially stent thrombosis [39], but further studies did not confirm these results [40]. A higher incidence of MACE in the presence of loss-of-function *CYP2C19* alleles in patients who received clopidogrel has also been shown in an observational study in patients with stable coronary artery disease or ASC undergoing PCI [41]. The studies available so far have not demonstrated the superiority of genetic testing for clopidogrel resistance in patients requiring the use of a $P2Y_{12}$ inhibitor compared to standard treatment [42]. In the POPular Genetics Study, the strategy of performing genetic testing and using clopidogrel instead of prasugrel or ticagrelor in the absence of the specific alleles was not less effective than the traditional approach; however, it was associated with fewer bleeding complications in a 12-month follow-up (9.8% vs. 1.5%; $P = 0.04$) [43]. Nonetheless, current guidelines, both European and American, do not recommend routine genetic testing before treatment with clopidogrel. There is also no proven benefit in increasing the daily dose of clopidogrel to 150 mg to overcome resistance [44, 45]. It seems that *CYP2C19* polymorphism does not appear to affect the activity of prasugrel [46] and ticagrelor [47].

Approximately 10% to 15% of ACS patients will undergo coronary artery bypass grafting (CABG) surgery for index event, and current guidelines recommend stopping clopidogrel at least 5 days before CABG. This waiting time may have clinical implications. Nakashima et al. reported that a strategy that is guided by platelet reactivity is noninferior to the standard of care in patients with ACS awaiting CABG regarding peri-operative bleeding: it significantly shortens the waiting time to CABG and decreases hospital expenses [48].

SWITCHING ANTIPLATELET REGIMENS

Switching between $P2Y_{12}$ inhibitors may be dictated by economic considerations or individual clinical circumstances such as ineffectiveness of the current antiplatelet therapy — confirmed by the platelet reactivity test, the presence of at least one *CYP2C19* loss-of-function mutant allele, or occurrence of thrombosis during treatment with a given drug. Modification of pharmacotherapy may also result from drug intolerance.

The recommendations for switching between $P2Y_{12}$ inhibitors vary depending on the patient's clinical timing. In the acute phase of ACS, a loading dose of the $P2Y_{12}$ inhibitor is always mandated. In patients with ACS who were previously exposed to clopidogrel, switching from clopidogrel to ticagrelor is recommended early after hospital admission at a loading dose of 180 mg irrespective of timing and loading dose of clopidogrel, unless contraindications to ticagrelor exist (IB) [10]. This switching strategy has the strongest class of recommendation and has been confirmed in clinical trials. Other $P2Y_{12}$ inhibitor switching algorithms have a weaker recommendation class — additional switching between oral $P2Y_{12}$ inhibitors

may be considered in cases of side effects/drug intolerance according to the proposed algorithms (IIbC) [10]. When de-escalating treatment and switching from prasugrel or ticagrelor to clopidogrel or switching between prasugrel and ticagrelor, the standard loading dose of the new drug should be administered 24 hours after the last dose of the discontinued drug. The adopted management algorithms are based on the ESC 2017 DAPT guidelines. The ESC 2020 NSTE-ACS guidelines duplicate the previously proposed strategies [10, 20]. In the chronic setting, defined as a switching occurring following hospital discharge in patients with ACS, administration of a loading dose of the introduced antiplatelet drug is not required when switching from clopidogrel to ticagrelor, clopidogrel to prasugrel, prasugrel to clopidogrel, or prasugrel to ticagrelor. The maintenance dose of a new $P2Y_{12}$ inhibitor should be given 24 hours after the last dose of the drug is withdrawn. In the case of switching ticagrelor to clopidogrel or ticagrelor to prasugrel, a loading dose (600 mg of clopidogrel or 60 mg of prasugrel, respectively) is required even in chronic settings. The loading dose should be given 24 hours after the last ticagrelor dose [10].

RECENT STUDIES AND FUTURE PERSPECTIVES

The optimal duration of DAPT after PCI to prevent thrombotic events while minimizing the risk of bleeding events remains a broadly debated issue. This topic is particularly relevant nowadays. We have an aging population and an increasing number of comorbidities (both of which substantially enhance bleeding risk). On the other hand, we have secondand third-generation DES with improved design and drug delivery (biodegradable polymers, cobalt-chromium or platinum-chromium platforms, ultra-thin struts design), which have recently led to a significant reduction in the risk of stent thrombosis (translating to a lower risk of ischemic events).

Various preclinical studies have demonstrated the key role of $P2Y_{12}$ inhibitors versus ASA in inhibiting platelet activation. These observations led to the hypothesis about the benefit of early ASA discontinuation after PCI for a better balance of bleeding and thromboembolism risks. More recently, new evidence from randomized trials, meta-analyses, and registries has emerged, which is not yet included in the guidelines. The subject of these analyzes is the early discontinuation of ASA after 1 month or 3 months of using DAPT, followed by monotherapy with a $P2Y_{12}$ inhibitor. The most significant recently published randomized trials, i.e. GLOBAL LEADERS [15], SMART-CHOICE [49], STOPDAPT-2 [50], and TWILIGHT [16], aimed to fill this gap in the scientific evidence (Table 4).

A meta-analysis [51] of these four studies showed that the rates of adverse cardiac and cerebrovascular events (defined as myocardial infarction, ischemic stroke, and allcause death) were similar comparing the efficacy of shortterm DAPT, followed by a $P2Y_{12}$ inhibitor in monotherapy, compared to 12-month standard DAPT. Interestingly, this effect was also observed for the individual components of the composite endpoint: myocardial infarction, ischemic stroke, and all-cause death. Most importantly, the frequency of definite or probable stent thrombosis was comparable in the short-term DAPT group followed by $P2Y_{12}$ inhibitor monotherapy versus 12-month DAPT. On the other hand, the rate of major bleeding (Bleeding Academic Research Consortium [BARC], 3 or 5) was significantly lower in the short-term DAPT group, followed by the use of $P2Y_{12}$ inhibitor alone, compared to the traditional duration of DAPT.

However, the main question that still needs to be answered is the choice of a $P2Y_{12}$ inhibitor (clopidogrel, ticagrelor, prasugrel) that would provide the most favorable efficacy (low ischemic risk) and safety (low bleeding risk) profile. Given the high interpatient variability in pharmacodynamic response — especially for clopidogrel — genotyping or testing of platelet activation may be an option before early ASA discontinuation and maintaining the $P2Y_{12}$ inhibitor (clopidogrel) in monotherapy.

The current evidence provided by four randomized trials, as well as a meta-analysis of these studies, does not indicate that early discontinuation of ASA followed by $P2Y_{12}$ inhibitor monotherapy lead to an increase in adverse cardiac and cerebrovascular events while maintaining a very good safety profile. However, the STOPDAPT-2 ACS trial showed that 1-month DAPT followed by clopidogrel monotherapy for 11 months did not meet the criteria for noninferiority compared with standard 12-month duration DAPT for the composite ischemic/bleeding endpoint among ACS patients undergoing PCI with a cobalt-chromium (CoCr) DES. The primary outcome, cardiovascular death, MI, stroke, stent thrombosis, Thrombolysis In Myocardial Infarction [TIMI] major or minor bleeding, for 1–2 months vs. 12 months of DAPT, was 3.2% vs. 2.8% (HR, 1.14; 95% CI 0.80–1.62; *P* for noninferiority = 0.06). In fact, the composite ischemic endpoint trended towards harm in the short-duration DAPT arm, with a significant nearly 2-fold increase in the risk of MI (1.6% vs. 0.9% [HR, 1.91; 95% CI, 1.06–3.44; *P* <0.05]). Both major and minor bleeding events were lower with short-term DAPT [52].

The TALOS-AMI trial showed that among patients undergoing PCI for AMI and who had completed 1 month of DAPT with ASA and ticagrelor uneventfully, switching to ASA plus clopidogrel for the next 11 months met the criteria for noninferiority and superiority compared with continuing with ASA plus ticagrelor. The primary endpoint of cardiovascular death, MI, stroke, BARC bleeding 2, 3, or 5, for de-escalation vs. active control between 1 and 12 months post-PCI, was: 4.6% vs. 8.2% (*P* for noninferiority <0.001; *P* for superiority <0.001). This was primarily driven by a reduction in major bleeding, but ischemic events were also numerically lower with a de-escalation strategy. De-escalation was performed without genotype testing or reload [53].

The HOST-EXAM trial showed that clopidogrel monotherapy is superior to ASA monotherapy as chronic maintenance therapy among patients who have successfully completed the required duration of DAPT regimen post-DES PCI. The primary endpoint of all-cause mortality, MI, stroke, readmission due to ACS, major bleeding, for clopidogrel vs. ASA, was 5.7% vs. 7.7% (HR, 0.73; 95% CI, 0.59–0.90; $P = 0.003$). Secondary endpoints: thrombotic composite outcome (cardiovascular death, MI, stroke, ACS readmission, stent thrombosis): 3.7% vs. 5.5% ($P = 0.003$) and any bleeding: 2.3% vs. 3.3% ($P = 0.003$) were also lower in the clopidogrel group [54].

One limitation of the STOPDAPT-2 ACS, TALOS-MI, and HOST EXAM trials is that they included exclusively East Asian patients.

Surely, all of these studies will likely have a significant impact on antiplatelet treatment strategies in patients after PCI in the upcoming new guidelines.

In conclusion, selected patients at high risk of thrombotic and/or bleeding events may benefit from personalized antiplatelet therapy based on an individual assessment of thrombosis and bleeding risks. It should be remembered that these risks (especially of bleeding) are dynamic and change over time, and therefore they should be reassessed periodically (e.g. at subsequent follow-up visits).

Article information

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What do we know about carcinoid heart disease in the present era?

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ABSTRACT

Carcinoid heart disease (CHD) is a severe complication of carcinoid syndrome (CS) found primarily in patients with small intestine neuroendocrine neoplasms (SI-NENs). Patients who develop CHD have significantly worse morbidity and mortality outcomes, highlighting the importance of clinical practice recommendations for CHD screening, diagnosis, and treatment that are both consistent and practical. CHD is characterized by white plaque-like deposits on the endocardial surface of heart structures, generally affecting the right heart valves, causing tricuspid and pulmonary regurgitation and, less commonly, valve stenosis. Cardiac imaging is essential for both the diagnosis and management of CHD. Previously, imaging for CHD was mostly achieved by echocardiography, but more recently, imaging has become multimodal. N-terminal pro-B-type natriuretic peptide (NT-proBNP) and 5-hydroxyindoleacetic acid in the urine (u5-HIAA) are currently the most effective markers used in screening CS patients and evaluating CHD severity. Managing patients with CHD is challenging since both systemic malignant disease and cardiac involvement must be treated concurrently. Early diagnosis and surgical intervention when required are critical to patient prognosis, especially in those without primary tumor resection. Valve replacement surgery is the most effective treatment for patients with advanced carcinoid heart disease for alleviating cardiac symptoms and contributing to survival outcomes. To deliver effective patient treatment, multidisciplinary team collaboration is needed. This review summarizes current research findings on CHD pathogenesis, clinical and epidemiological features, useful biomarkers and imaging modalities, and treatment strategies.

Key words: carcinoid heart disease, carcinoid syndrome, neuroendocrine neoplasms of the small intestine

INTRODUCTION

Neuroendocrine neoplasms (NENs) are a group of tumors that most commonly arise from the gastrointestinal tract and bronchopulmonary system. The incidence is estimated to be 6.9 cases per 100 000 people [1]. Gastro-entero-pancreatic neuroendocrine neoplasms/tumors (GEP NENs/NETs) derive from diffuse endocrine system (DES) cells located in the gastrointestinal tract and pancreas [2]. Neuroendocrine neoplasms of the small intestine (SI-NENs) originate in the midgut and are the third most common subtype of NENs in the gastroenteropancreatic system [3, 4]. GEP NETs are becoming more common across the world, particularly in North America, Asia, and Europe, with North America seeing the largest rise [5].

GEP NENs may be hormonally productive or not release enough hormones and/or biogenic amines. Non-functional neuroendocrine neoplasms are difficult to diagnose since they do not cause clinical symptoms of the disease.

Carcinoid syndrome (CS) is the most frequent paraneoplastic syndrome with a reported prevalence of approximately 19% in the NET patient population [1]. It is characterized by signs and symptoms linked to the hormonal activity of small intestine NENs. Increased synthesis and secretion to the systemic cir-

culation of 5-hydroxytryptamine (5-HT, serotonin) and/or other biologically active substances such as histamine, kallikrein, prostaglandins, and tachykinin lead to the development of the main clinical manifestations of carcinoid syndrome [4, 6]. Circulating hormones can be inactivated by the liver and lungs. However, in patients with liver metastases, production escapes the metabolism [7].

Carcinoid heart disease (CHD) is the most severe consequence of carcinoid syndrome, characterized by fibrotic valve degeneration, particularly in the right heart chambers. Isolated tricuspid valve regurgitation is found in up to 90% of patients; it causes progressive right heart failure and leads to a worsening of the patient's oncological prognosis [8–10]. CHD is observed in around 40% of patients with carcinoid syndrome [8].

The development of CHD is related to increased morbidity and mortality [11]. Patients with cardiac involvement have a markedly poorer long-term prognosis, with a 3-year survival rate of 31%, which is half that of patients who do not have cardiac involvement [9, 12–14]. Valvular carcinoid heart disease has a short life expectancy without treatment, with median overall survival (OS) of only 11 months in patients with advanced heart failure [15, 16].

All these facts indicate that, in the present era, focusing on accurate patient diagnosis, treatment, and management under the supervision of a multidisciplinary team, are essential to lengthen OS of patients with CHD. In this review article, we present a detailed description of the pathogenesis, clinical and epidemiological aspects, useful biomarkers and imaging modalities, as well as CHD management methods.

EPIDEMIOLOGY

CHD prevalence estimated in patients with carcinoid syndrome varies from 3% to 66% [8, 17–20], but in recent studies, has tended to be lower [17]. This might be due to an increase in somatostatin analogs usage and their impact on circulating serotonin levels, as well as improvements in diagnostic and surgical techniques [21–23].

Pellikka et al. [24] reported that the majority of CHD cases are associated with SI-NENs (72%), followed by lung, large bowel, pancreatic, and appendiceal neoplasms [24]. According to recent Mayo Clinic research, CHD is rare in individuals with bronchopulmonary NENs (1%) [25].

PATHOPHYSIOLOGY

CHD is characterized by formation of endocardial plaques on the surfaces of valve leaflets, chordae, papillary muscles, heart chambers, and in rare cases, the intima of the pulmonary arteries, and aorta [1, 26]. The plaque is formed as a result of dysregulated inflammatory and remodeling processes, which result in an inappropriate extracellular matrix formation, fibrosis, angiogenesis, and calcification, finally leading to structural valve deformation [1, 27].

The pathophysiology of fibrosis in NENs is still unknown, and few advances have been made in recent years toward a better understanding of the underlying processes of fibrogenesis. The effects of serotonin, growth factors, and other peptides released by neuroendocrine tumor cells are hypothesized to cause NEN-associated fibrosis although these substances do not act alone, and pathway crosstalk is critical in the pathophysiology of the fibrotic process [28]. Several growth factors, including transforming growth factor beta (TGF-β), platelet-derived growth factor (PDGF), basic fibroblast growth factor (FGF2), and connective tissue growth factor (CTGF or CCN2), stimulate fibroblasts both directly and indirectly [7].

Serotonin activity appears to be critical in the development of valvular carcinoid heart disease [15, 28]. Several animal studies have shown that 5-HT can promote cardiac fibrosis and valvulopathy, indicating that it may play an important role in the development of CHD [29–34]. In cardiac valve tissues, various subtypes of serotonergic 5-HT1 and 5-HT2 receptors are present, with subtype 5-HT2B receptors being the most common and playing a crucial role in valve pathology [35, 36]. Activation of the 5-HT2B receptor causes the release of inflammatory cytokines, increases the expression of TGF-β, and has mitogenic effects on fibroblasts and smooth muscle cells [1]. TGF is a serotonin downstream mediator and a big contributor to fibrosis [37].

There is also some evidence that serotoninergic pathways can cause oxidative stress, which can induce fibrosis in heart valves [38].

DIAGNOSIS

Clinical presentation

Cardiac symptoms are commonly subtle until CHD progresses [39]. This frequently leads to a delay in the diagnosis of CHD [11]. Early in the disease course, symptoms such as fatigue and exertional dyspnea may appear [40]. Valve disease does not always progress in a predictable manner, and valves can quickly deteriorate over several months [1]. According to a report by Bhattacharyya et al. [41], only around 57 percent of patients with moderate to severe tricuspid regurgitation will have no or mild symptoms [41].

Typical and common symptoms of right-sided heart failure, such as fatigue, peripheral edema, exertional dyspnea, and cardiac cachexia can occur as a result of progressive CHD. Left-sided cardiac failure occurs in approximately 10% of patients because vasoactive hormones are inactivated in the pulmonary vasculature and do not have a chance to reach the left-sided cardiac components [11, 24]. Patients with right-to-left shunts (patent foramen ovale and atrial septal defects), a poorly controlled disease with high levels of circulating hormones, or bronchopulmonary carcinoid disease are more likely to develop left-sided heart disease due to higher levels of vasoactive hormones reaching the left side of the heart [42].

A physical examination may reveal symptoms of right heart failure, such as increased jugular venous pressure,

a palpable right ventricular impulse, peripheral edema, hepatomegaly, and ascites. For cardiac auscultation, murmurs of tricuspid and pulmonary valve regurgitation are common although a systolic murmur of pulmonary stenosis or a diastolic murmur of tricuspid stenosis are seldom observed [23, 41].

CHD is also linked to coronary artery vasospasm, which is rare but may occur in patients with non-occlusive coronary artery disease [43, 44]. Serotonin can stimulate either vasodilatory or constrictive responses depending on endothelial conditions. 5-HT can promote vasoconstriction in dysfunctional endothelium, for example, in individuals with atherosclerotic disease, due to the superiority of vasoconstriction-inducing 5-hydroxytryptamine2 (5-HT2) receptors and lack of 5-HT1 receptors that mediate vasodilation [44–46]. Patients experiencing symptoms of acute coronary syndrome and with a history of carcinoid disease should be evaluated for possible coronary vasospasm [9].

Unfortunately, in CS patients, screening or routine assessment for CHD is commonly missed, resulting in late diagnosis when the disease is already advanced [47]. The proposed screening algorithm for carcinoid heart disease in all patients with NEN (especially SI-NEN) is presented in Figure 1.

Electrocardiogram

In 50% of patients, the electrocardiogram (ECG) is normal or may indicate nonspecific abnormalities including low-voltage QRS complexes and right bundle branch block [11]. Arrhythmias have been described occasionally in the setting of CHD [9]. In the literature, a single patient without ischemic heart disease, presented with carcinoid-induced ventricular tachycardia [48], which was controlled with the use of metoprolol, and two other identified cases were associated with CHD atrial arrhythmias [49, 50]. Serotonin has been linked to paroxysmal ventricular tachycardias and atrial arrhythmias in canine investigations [51]. The possible mechanism is assumed to be enhanced sympathetic activity caused by a vasoactive substance, resulting in cardiac excitation and tachyarrhythmias [48]. Serotonin-induced coronary vasospasm might result in ST-segment elevation [43].

Biomarkers

Many studies have investigated the usefulness of biochemical markers in monitoring cardiac function, CS activity, and oncologic disease state in CHD patients [17, 52–59].

Natriuretic peptides

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is currently the most effective marker used in echocardiographic screening of CS patients and evaluating CHD severity [8]. NT-proBNP is a neurohormone produced by cardiomyocytes in response to increased ventricular wall stress [54]. NT-proBNP at cutoff values of 235–260 pg/ml revealed sensitivity and specificity of 87%–92% and 80%–89%, respectively, for CHD detection. Levels of NT-proBNP are associated with the severity of CS symptoms, the New York Heart Association functional class, and overall mortality [55, 56].

Although plasma levels of atrial natriuretic peptide (ANP) are significantly elevated in individuals with CHD and indicative of cardiac dysfunction and heart failure, this biomarker is not employed in clinical practice [28, 57].

5-hydroxyindoleacetic acid in the urine

Platelet serotonin and, specifically, levels of the urinary catabolite 5-hydroxyindoleacetic acid (u5-HIAA) have been shown to have a high diagnostic and prognostic value in patients with CS. However, the clinical picture of CS may not correlate with u5-HIAA levels, possibly related to the tumor's inconsistent hormone release or the synthesis of other biologically active substances [60]. Studies demonstrate that the majority of patients with CHD have greater levels of u5-HIAA than those without [17, 57]. In individuals with worsening CS symptoms, defined as a >50% increase in the frequency of bowel movements or flushing, there was a positive correlation between higher u5-HIAA levels and echocardiographic findings of CHD advancement. In patients with CS, u5-HIAA levels of more than 300 mmol/24 hours indicate a 2- to 3-fold increase in the risk of developing or progressing carcinoid heart disease [52].

Chromogranin-A

Chromogranin A (CgA) is a glycoprotein that NET cells secrete [42]. CgA is a useful biomarker in the diagnosis of NEN since it is affordable and easy to measure using a blood sample for an immunological assay [61]. Modlin et al. [62] reported that CgA did not only reflect tumor burden but appears to be associated with tumor progression or response to treatment [62].

In a report by Tran et al. [63] increased CgA level before SI-NEN-related surgery was associated with lower overall survival (median 87.8 months vs. not reached; $P = 0.01$) [63]. These data suggest that sequential CgA concentration measurement is effective in both predicting and monitoring progression to CS, as well as progression from CS to CHD [61, 63].

Unfortunately, CgA has only 30% specificity for detecting severe carcinoid heart disease [42] and has therefore a limited value in CHD diagnosis and monitoring [53].

Activin A

Activin A is a TGF family member found to be an independent predictor of CHD although no statistically significant difference in activin A levels is found between patients with early and advanced disease. CHD was detected with 87% sensitivity and 57% specificity when activin A levels were less than 0.34 ng/ml [58].

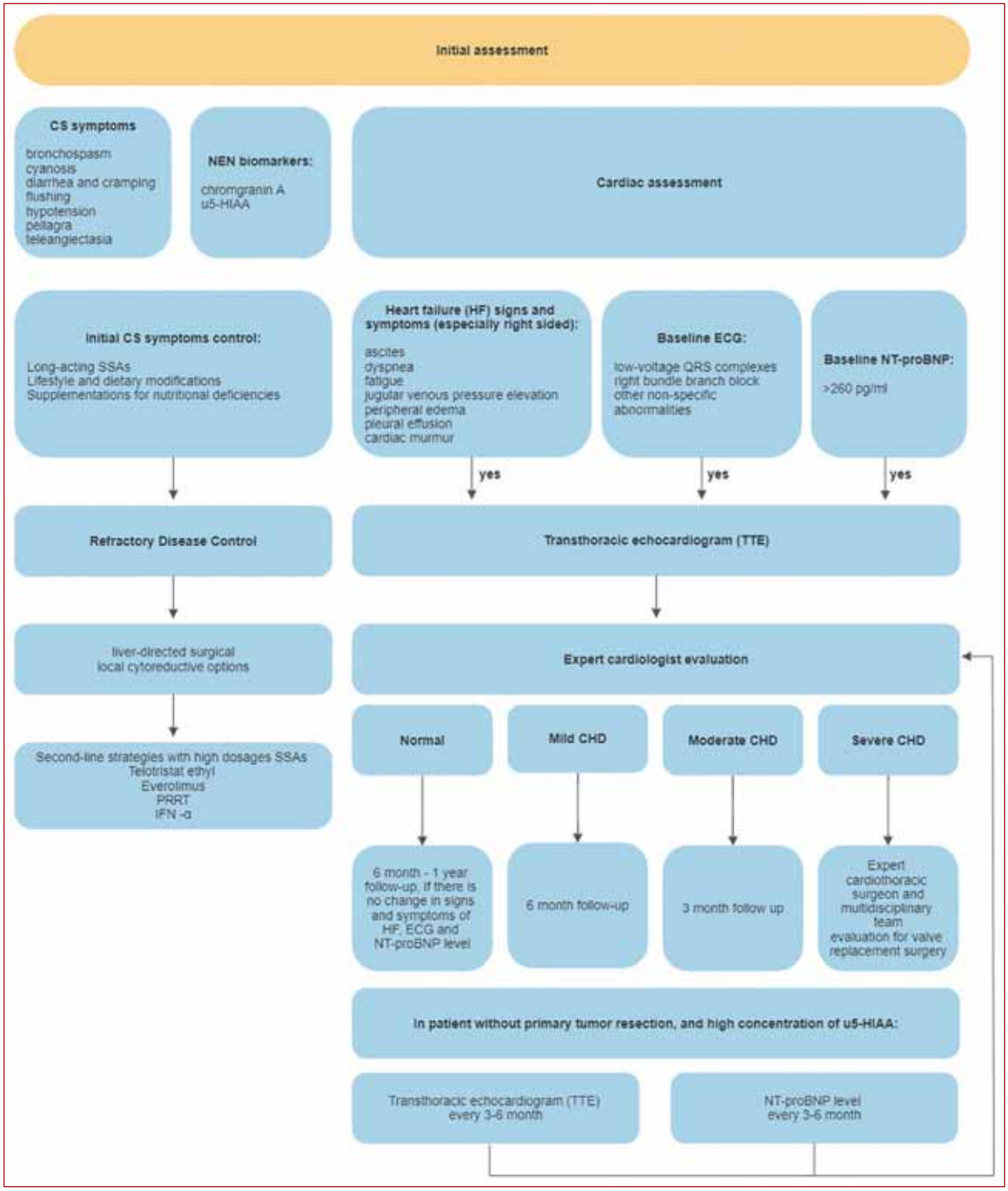

Figure 1. Proposed screening algorithm for carcinoid heart disease in all patients with NEN (especially SI-NEN) [1–3]

Abbreviations: CHD, carcinoid heart disease; CS, carcinoid syndrome; ECG, electrocardiogram; IFN-α, interferon-alpha; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PRRT, peptide receptor radionuclide therapy; SI-NEN, small intestine neuroendocrine neoplasms; u5-HIAA, 5-hydroxyindoleacetic acid in the urine

Chest radiography (X-ray)

Chest radiography is typically inefficient in CHD patients, as 50% of cases appear normal, and abnormalities are commonly non-specific [11]. However, the cardiothoracic ratio could be increased [64].

Transthoracic echocardiography

Echocardiography should be conducted in all patients with carcinoid syndrome and high suspicion of CHD, according to an expert statement released by the American College of Cardiology on the diagnosis and management of CHD.

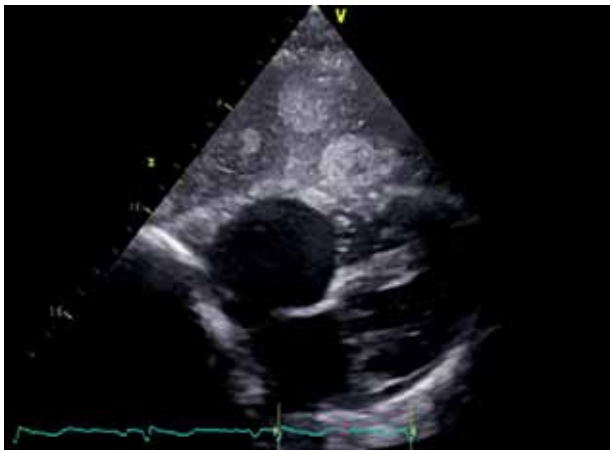

Figure 2. Transthoracic echocardiography (TTE): a 51-year-old patient with carcinoid heart disease and severe tricuspid regurgitation. Subcostal view: huge enlargement of the right atrium and liver metastases

Transthoracic echocardiography (TTE) should be performed in patients with known CHD every 3–6 months or if there is a change in clinical status [8]. In contrast, the European Neuroendocrine Tumor Society (ENETS) recommends TTE screening for patients with CS – once or twice a year for patients with or without cardiac involvement, respectively [9, 65]. Patients with CS should also be screened with TTE if their 5-hydroxyindoleacetic acid levels are markedly increased according to the ENETS recommendations. The severity of CHD can be determined by the constellation of abnormalities observed on TTE [66]. There have been several scoring systems based on echocardiographic findings, including the first (and possibly the most well-known) scoring system based on tricuspid valve morphology, tricuspid regurgitation severity, pulmonary stenosis severity, and pulmonary regurgitation severity [20].

Two-dimensional TTE is the most common imaging modality used in CHD evaluation because it can examine both, morphological and functional, components of the heart (Figure 2). Valvular involvement can range from mild thickening of a single valve leaflet with no major functional impairment to severe thickening, retraction, and immobility of several valves in advanced conditions. Tricuspid regurgitation is the most common right-sided valve abnormality, followed by pulmonary regurgitation and/or pulmonary stenosis. On 2D TTE, initial fibrous deposition of the tricuspid and/or pulmonary valve leaflets typically shows up as a thickening [67]. Fibrous deposition may also damage the chordae and papillae, causing further abnormal function of the valve. The leaflets become retracted and locked in a semi-open position as the condition progresses, resulting in stenosis and regurgitation [66]. When tricuspid regurgitation is present in CHD patients, the Doppler profile usually shows a typical "dagger-shaped" spectrum (early peak pressure rise with a subsequent rapid decline).

To determine the existence of a patent foramen ovale (PFO), a TTE with a "microbubble" contrast can be conducted [66].

CHD may have an impact on ventricular strain due to valvular anomalies. In one study, right ventricular (RV) strain was found to be lower in CHD patients than in controls (a mean of 20.6 versus 26.9). Patients with carcinoid syndrome showed identical RV strain regardless of whether they had evident valvular involvement, suggesting that abnormal RV strain might be a sensitive and early predictor of CHD before apparent valvular abnormalities occur. In addition to RV strain, patients with CHD have slightly decreased global left ventricular (LV) strain as compared to healthy individuals [68].

When compared to 2D TTE, three-dimensional TTE (3D TTE) has several notable advantages. In the case of the tricuspid and pulmonary valves, 3D TTE allows for simultaneous visualization of all valve leaflets. 3D TTE also provides a comprehensive image of subvalvular structures including chordae and papillary muscles, which might be affected by carcinoid "plaque". In advanced stages of CHD, 3D TTE can in addition detect abnormalities of neighboring structures, for example, poststenotic dilatation of the pulmonary artery. In comparison to 2D TTE, 3D TTE enables the detection of myocardial metastasis with a better ability to differentiate their borders from surrounding structures, allowing for a more precise estimation of the real dimensions and mass effects. 3D TTE may have value in operation planning in patients who are prepared for surgical valve repair [69].

Transesophageal echocardiography (TEE) offers better imaging of the pulmonary valve than TTE and may reveal minor tricuspid valve anomalies when TTE is ambiguous.

2D TTE is a useful tool for screening asymptomatic CS patients and monitoring established disease development with excellent sensitivity and specificity [70].

Cardiac magnetic resonance

Cardiac magnetic resonance (CMR) is becoming a useful technique for detecting CHD, particularly when echocardiographic findings are ambiguous [71], and is beneficial when echocardiography cannot offer good images of the pulmonary valve [69]. Late gadolinium enhancement of the tricuspid and/or pulmonary valves may show evidence of CHD when valvular anomalies are not visible on TEE. This is not specific and can occur in a variety of cardiovascular conditions [66]. When compared to echocardiography, CMR gives a better estimation of RV size and function with reduced interobserver variability [72].

CMR can be used for more accurate assessment of RV volumes, LV volumes, and cardiac index following a tricuspid valve replacement, in addition to predicting regurgitant volumes after surgical intervention [73]. CMR has various disadvantages, including a higher cost as compared to echocardiography, and the probable requirement for contrast [66].

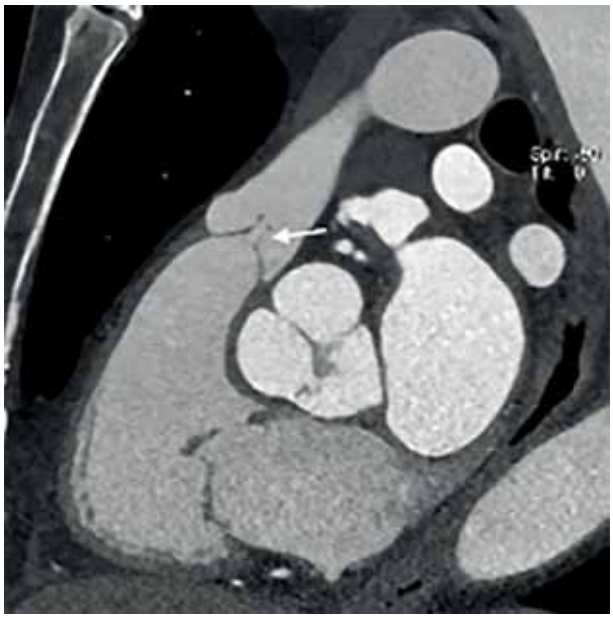

Figure 3. Cardiac computed tomography: multiplanar reconstructions at diastole, views centered on the pulmonary valve, severe thickening of the leaflets of the pulmonary valve with incomplete coaptation during diastole (the arrow)

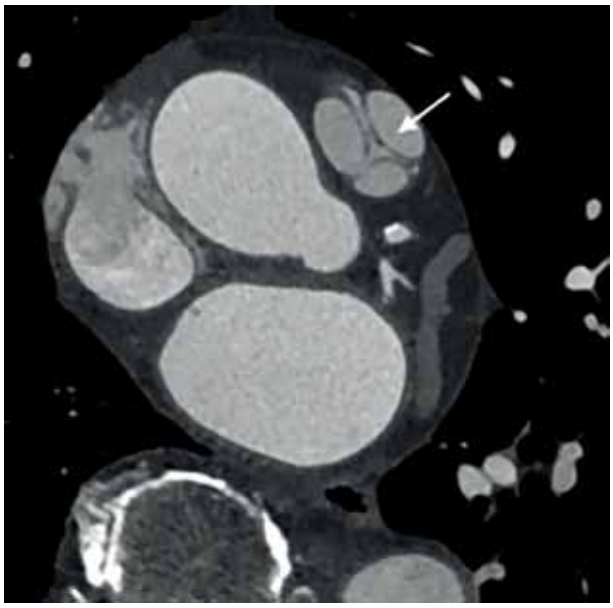

Figure 4. Cardiac computed tomography: multiplanar reconstruction, four-chamber view at diastole; enlargement of the right-sided chambers and thickening of the tricuspid valve and subvalvular apparatus (the arrow)

Cardiac computed tomography scanning

Cardiac computed tomography (CT) can also be used to assess the degree of valve damage, particularly in cases of severe calcification, as well as to quantify RV diameters, evaluate coronary arteries [66], and assess pulmonary post-surgical prosthetic valve thrombosis (Figures 3 and 4).

Positron emission tomography

Functional imaging with radiolabeled somatostatin analogs (typically Gallium-68-DOTATOC/DOTATATE positron emission tomography [PET]/CT) may help to detect carcinoid cardiac metastases (myocardial and/or pericardial) [66]. For the detection of metastatic neuroendocrine neoplasms, this approach has been shown to be >97% sensitive and 92% specific [74].

TREATMENT

The treatment of patients with CHD is multifaceted because of the need to treat both systemic cancer disease and cardiac pathology at the same time [75]. The aim of CHD management is symptom alleviation and increased survival rather than definitive treatment and cure, requiring a multidisciplinary approach involving both medical and surgical therapies for optimal care [76]. This multidisciplinary approach should be used to design a treatment strategy based on symptoms, histological grade, overall performance status, as well as nutritional status, NEN stage (stable disease, progressive, or metastatic disease), the function of major organs (mainly kidney and liver), and the impact of CHD on the proceedings of the underlying NEN [75, 76].

Pharmacotherapy for heart failure

To date, the standard of treatment for asymptomatic patients is to wait for symptoms to appear. On the contrary, loop or thiazide diuretics and aldosterone antagonists are recommended for treatment in individuals who develop signs of right-sided heart failure, particularly peripheral edema. However, because these drugs might cause intravascular volume depletion and decreased cardiac output, they should be used with caution. Other drugs, such as digoxin or angiotensin-converting enzyme inhibitors, have been used, but their benefit in CHD patients has yet to be established [77]. Improvement in heart failure symptoms with medication should not be seen as reassurance that management is adequate and sufficient, but rather as a window to optimize and assess the patient for consideration of valve surgery if required [39].

Cardiac surgery

In patients with well-controlled systemic disease, cardiac valve replacement remains the most effective treatment in severe stages of CHD [77]. Patients with symptomatic right heart failure or ventricular dysfunction, as well as at least 12 months of predicted survival due to their oncologic disease status, are usually candidates for a cardiac procedure [78]. Valve surgery has been shown to enhance long-term prognosis in CHD patients by reducing right heart failure, increasing functional capacity, allowing for more aggressive oncological treatment, and decreasing right heart failure. A multidisciplinary assessment of total operability in relation to oncological status and cardiac function should be used to decide whether to replace a valve [79]. Advances

in surgical techniques, better patient selection, anticancer and hormonal control treatments have resulted in tolerable early mortality rates and survival benefits [78].

The Mayo Clinic's 30-year study by Nguyen et al. [80] involving 240 CHD-operated patients, represents the largest study investigating the relationship between several clinical and echocardiographic factors and early mortality and late survival. Between 1985 and 1994, the early mortality rate was 29% but fell to 7% from 1995 to 2004, and 5% from 2005 onwards. Overall survival rates were 69%, 48%, and 34% after one, three, and five years, respectively [80]. According to the mortality rates reported, valve surgery for carcinoid heart disease is a high risk procedure, but may be beneficial to some patients due to symptomatic relief [81].

Preoperative preparation should mainly focus on optimizing patient status and symptoms with appropriate medical therapy. The severity of tricuspid valve disease, right ventricular dysfunction, right atrial dilatation, pulmonary hypertension, and high central venous pressures are significant risk factors [78]. Preoperative nutritional optimization and somatostatin analog treatment for carcinoid hormonal activity are critical parts of surgical planning [79]. Intravascular volume depletion and electrolyte disturbances are typical in CHD patients and must be treated. Patients with CS are at risk of developing a possibly life-threatening carcinoid crisis, which can be triggered by surgery or any invasive intervention, so therapies aimed at lowering high u5-HIAA levels, such as dose escalation with somatostatin analogs and add-on therapy with telotristat ethyl, should be used. Carcinoid crisis is characterized by hemodynamic instability, with predominant hypotension, tachycardia, arrhythmias, bronchoconstriction, and flushing caused by the release of biologically active substances. The administration of octreotide infusion at a dosage of 50 µg/h administered 12 hours before the procedure and continued throughout the operation and until the patient is hemodynamically stable and off inotropes is the primary preventative therapy aimed at reducing the occurrence of carcinoid crisis. The dosage can be increased to 100–200 µg/h if necessary [82]. Depending on the patient's recovery, the octreotide infusion should be progressively reduced postoperatively [78].

The type of valve selected for use (biological or mechanical valve prosthesis) is a complex matter that should be based on a particular patient's risk of bleeding, tumor-related life expectancy, and possible future therapeutic interventions [81, 83]. According to research by Albåge et al. [79], surgery of the left-sided valves is not linked to poorer outcomes and ought to be conducted concomitantly with right-sided valve surgery if needed [79].

Bioprosthetic valves are mostly favored when CHD patients have an enhanced bleeding risk due to significant liver disease and hepatic dysfunction, but still, thrombus formation on the tricuspid bioprosthesis is the most prevalent cause of valve dysfunction in right-sided valve replacements [98]. Postoperative right ventricular failure, an overall reduced flow condition on the right side of the heart, and a hypercoagulable state with high serotonin levels acting as a stimulus for platelet activation all seem to be risk factors for valve thrombosis [78]. Patients with bioprosthetic valves in sinus rhythm should begin and continue warfarin anticoagulation for 6 months, but patients with mechanical valve prosthesis or with atrial fibrillation and bioprosthetic valves should continue anticoagulation permanently [82].

TTE should be conducted as soon as possible after surgery [84]. In uncomplicated conditions during follow-up, TTE should be performed every 3 to 12 months, depending on comorbidities [8].

It should be highlighted that, despite medical and surgical developments, valve surgery in subjects with CHD is always challenging and associated with significant risk. In high-risk patients with severe CHD for whom open-heart surgery is hazardous, transcutaneous catheter-based interventions represent a minimally invasive option [84, 85].

In addition, the recent introduction of percutaneous valve-in-valve technology in subjects with a failing bioprosthetic valve has broadened treatment selections for less invasive procedures, and a transcatheter heart valve placed in the inferior vena cava may decrease carcinoid hormone levels and relieve symptoms in patients with severe carcinoid syndrome symptoms [86, 87].

Primary tumor resection

Primary tumor resection with metastatic disease (resectable and unresectable) has been shown to improve survival in all patients with SI-NENs (with and without CHD) [14]. This may relate to decreased synthesis of vasoactive substances [12], as well as a reduction in potentially fatal complications such as intestinal obstruction caused by tumor growth and blockage [14]. Uema et al. [88] found that removing the primary tumor reduced mortality in 139 patients with advanced disease, carcinoid symptoms, and/or elevated u5-HIAA [88].

Polcz et al. [89] recently published significant findings from a retrospective cohort analysis of 4076 patients with metastatic SI-NETs, with 2025 (61%) receiving primary tumor resection (PTR). Patients who were more likely to have PTR were younger, had been diagnosed sooner, and had lower-grade small intestine primary tumors. Patients who had PTR had longer median overall survival than those who did not (71 months vs. 29 months, $P = 0.001$). According to the findings of Polcz et al. [89], patients treated in an academic or research facility were, likewise, less likely to have PTR, and primary resection has become less common over time. One possible explanation is the increasing use of somatostatin analogs as first-line treatment for metastatic disease, which gives both excellent symptom alleviation and inhibition of tumor progression. Although these findings were also associated with improved survival, it should be noted that they apply to the entire group of SI-NET patients — both with and without CHD — and that, despite proven benefits in progression-free survival, no OS benefit with somatostatin analogs has been demonstrated

to date [89], which indicates that primary tumors should be removed when possible.

Management of carcinoid syndrome

Considering the significance of 5-HT in the sequence of events that leads to the development of CHD, controlling serotonin synthesis from the tumor is critical. This can be accomplished by either medical or surgical intervention methods. Long-acting somatostatin analogs, peptide receptor radionuclide therapy (PRRT), and the new drug telotristat ethyl are among the available medical treatments. Transcatheter arterial embolization (TAE) or chemoembolization (TACE), as well as surgical debulking of hepatic metastases, are interventional alternatives [8].

Long-acting somatostatin analogs

Long-acting somatostatin analogs (SSAs), synthetic octo-amino acid peptides, which primarily act on the somatostatin receptor subtype 2, are recommended for first-line antiproliferative therapy in advanced NETs due to their proven effectiveness in controlling symptoms of carcinoid syndrome [28, 75–77, 90]. The somatostatin analogs octreotide and lanreotide improved symptoms in 65%–72% of patients and had a biochemical response in 45%–46%. In 72%–84% of patients, increasing the dose or frequency or switching classes resulted in a decrease in flushes and/or diarrhea [90].

Long-acting somatostatin analogs extended time-to-tumor progression (TTP) in patients with metastatic well-differentiated, predominantly G1, midgut neuroendocrine tumors compared to placebo (NET; octreotide LAR: PROMID study) [91]. Progression-free survival (PFS) was as well enhanced in individuals with advanced, non-functioning enteropancreatic NETs of grade 1 or 2 with confirmed progression of the disease (lanreotide autogel: CLARINET study) [92].

Although the optimal levels of u5-HIAA used to reduce the development of CHD are yet to be determined, long-acting SSAs are unquestionably important in CHD patient management [78].

In CS patients, infusion of short-acting octreotides should begin in the perioperative setting to avoid the onset of carcinoid crisis. Furthermore, in patients with recurrent CS symptoms, short-acting octreotide (half-life 1.5 to 2 hours) may be administered as a rescue drug in addition to the long-acting formulations [78].

Telotristat ethyl

Telotristat, an oral inhibitor of peripheral 5-HT synthesis, was recently approved by the Food and Drug Administration for the treatment of symptomatic CS-related diarrhea that has not responded to SSAs therapy. Telotristat ethyl is converted to its active metabolite, telotristat, which inhibits tryptophan hydroxylase (TPH), the rate-limiting enzyme in serotonin production. Two double-blind, randomized phase 3 clinical trials (TELESTAR and TELECAST) found that telotristat ethyl reduced bowel movement in 40%–44% of patients treated, compared to 0–20% of patients who received a placebo [78, 93]. After three months, there was a substantial decrease in urinary 5-HIAA. The findings of this study supported the safety and effectiveness of telotristat when combined with somatostatin analog treatment in individuals with CS. The impact on the development of carcinoid heart disease and mesenteric fibrosis residues is unidentified because this endpoint has not been adequately powered in clinical studies [94].

Everolimus

Everolimus is a small molecule oral inhibitor of the serine/threonine protein kinase mammalian target of rapamycin (mTOR), which promotes cancer cell growth and survival in a variety of malignancies, including NETs [78]. Pavel et al. [95] reported that everolimus plus octreotide LAR increased progression-free survival in patients with advanced neuroendocrine tumors associated with carcinoid syndrome when compared to placebo plus octreotide LAR [95]. Due to everolimus-related adverse effects including infections, edema, and diarrhea, patients with CHD should be treated with caution [8, 78].

Interferon-alpha

For refractory CS and negative somatostatin receptor NETs, interferon-alpha (IFN-α) is a supplementary treatment to SSAs. However, usage of this drug is limited due to its adverse effects (e.g., flu-like symptoms, chronic fatigue, liver and bone marrow toxicity) [78]. The reported response rates of IFN monotherapy in CS patients ranged from 0% to 90% for clinical control and 50%–80% for biochemical control [90].

Peptide receptor radionuclide therapy

Peptide receptor radionuclide therapy (PRRT) is primarily used to inhibit growth in progressive NETs with high somatostatin receptor expression [96]. It has been shown to improve quality of life and symptoms such as diarrhea in patients with midgut NETs [97]. Due to the requirement for simultaneous amino acid and fluid infusions in patients with CHD and heart failure, caution is advised [8, 78].

Transcatheter arterial embolization, chemoembolization, selective internal radiotherapy, radiofrequency ablation

Transcatheter arterial embolization (TAE), local administration of high doses of chemotherapy (TACE), and selective internal radiotherapy (SIRT) employing Yttrium-90 microspheres are examples of vascularly accessed interventional methods that provide diverse treatment modalities [78].

TAE and TACE are implemented to minimize tumor burden and have been shown to be effective in the treatment of NET, particularly in individuals with liver involvement. Circulating hormone levels drop as tumor burden decreases, resulting in symptom control in 50%–100% of

patients with NET and liver metastasis [98]. Patients with severe CHD and/or a significant hepatic tumor burden may have serious treatment complications such as hemorrhage or even liver failure, and as such, loco-regional therapies must be used with extreme caution. TAE and TACE are relatively contraindicated in patients with total portal vein occlusion, poor performance status, or underlying hepatic impairment [77]. TAE, TACE, and SIRT radiological response rates were estimated to be 25%–92%, 22%–100%, and 22%–63%, respectively [78].

Radiofrequency ablation and microwave ablation, done either percutaneously or in association with surgical resection, have also been shown to improve symptom management [78].

Surgical debulking of hepatic metastases

Surgical debulking (cytoreductive surgery) of liver tumor burden has been shown to be a significant advancement in the management of NETs in recent years [77]. Bernheim et al. [99] reported that patients with CHD who undergo hepatic resection had delayed progression of the disease and a better prognosis [99]. This method may be risky in individuals with severe CHD since it is associated with significant morbidity and mortality. There is also a greater risk of preoperative hemorrhage due to elevated right atrial pressure and a pulsatile liver. In selected individuals, liver surgery may be an option following heart valve replacement and cardiac function restoration to lower circulating serotonin, relieve carcinoid symptoms, and avoid recurrence of CHD [8, 77].

Kinney et al. [100] presented peri-operative findings of 169 patients who had partial hepatic resection due to metastatic NETs at Mayo Clinic Rochester. The most prevalent adverse events were persistent tachycardia (8.9%), followed by hypotension (5.3%), flushing, cardiac conduction abnormalities, and acidosis with pH 7.2, with an occurrence of less than 1%. There were no incidents of carcinoid crises [100].

CONCLUSIONS

All patients with SI-NENs, particularly those without primary tumor resection and high concentration of u5-HIAA require a cyclic assessment of clinical status and TTE performance every 3-6 months to detect the onset of CHD. The therapeutic methods include pharmacotherapy for symptomatic management, as well as medications and interventional approaches, for successful control of serotonin excess, most notably somatostatin analogs.

Despite medical and surgical improvements, carcinoid heart disease remains a significant challenge. Valve surgery for carcinoid heart disease is a high-risk intervention, given the mortality rates, although it may be beneficial for patients with symptomatic severe right heart valve disease who have a 12-month survival prognosis owing to symptomatic improvement. It should be emphasized that early risk linked to valve surgery has decreased in the present era. A multidisciplinary team should be involved in patient selection for valve surgery, adequate preoperative planning, and perioperative treatment procedures.

Article information

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Reversible T-wave inversions during left bundle branch area pacing

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ABSTRACT

Background: Our clinical observation found that T-wave inversions (TWIs) appeared during left bundle branch area pacing (LBBAP); however, the incidence and influencing factors were unclear. The study aimed to investigate the effects of LBBAP on T-wave and explore possible factors associated with TWIs.

Methods: This was a retrospective cohort study. An electrocardiogram (ECG) was acquired at baseline and after LBBAP. Baseline characteristics, ECG parameters, LBBAP parameters, and troponin T (TnT) levels were compared between the non-TWIs and TWIs groups. Multivariable logistic analyses were performed to adjust for potential confounders to identify the predictive factors of TWIs during LBBAP.

Results: A total of 398 consecutive patients who underwent successful LBBAP were assessed for inclusion between May 2017 and Jan 2021, and 264 (66.3%) patients had TWIs. The mean (standard deviation [SD]) baseline QRS duration (QRSd) was longer in the TWIs group compared to the non-TWIs group (125.9 [34.5] ms vs. 98.2 [18.1] ms; P <0.001). Multivariable logistic regression analysis suggested that QRSd >120 ms was an independent predictor for TWIs. TWIs were partially or completely recovered in 151/172 (87.8%) patients during follow-up, the median (interquartile range [IQR]) follow-up duration was 10 days (7 days to 5.5 months). TWIs in patients with complete left bundle branch block (CLBBB) occurred more frequently in inferior wall leads (II, III, and aVF) and anterior wall leads (V1–V4) (P <0.05). Patients with complete right bundle branch block (CRBBB) were more prone to TWIs in high lateral wall leads (I and aVL) (P <0.05). There were no significant differences in TnT levels between the TWIs and non-TWIs groups.

Conclusions: TWIs during LBBAP were clinically frequent and recoverable. QRSd >120 ms was independently associated with TWIs.

Key words: cardiac memory, complete left bundle branch block, complete right bundle branch block, left bundle branch area pacing, T-wave inversions

INTRODUCTION

We first demonstrated the transient and recoverable T-wave inversions (TWIs) during left bundle branch area pacing (LBBAP) in a patient with prior temporary right ventricular (RV) pacing [1]. TWIs may be caused by cardiac memory (CM). LBBAP is an established treatment option for patients with symptomatic bradycardia [2], especially for patients with heart failure (HF) and a wide QRS complex [3]. Several studies reported the development of TWIs after resumption of normal cardiac conduction in patients undergoing RV pacing or cardiac resynchronization therapy (CRT) [4, 5]. TWIs were a common but infrequently recognized phenomenon, of which many

WHAT'S NEW?

To our knowledge, there are no cohort studies of left bundle branch area pacing (LBBAP) induced T-wave inversions (TWIs), and this is the first report o describe this phenomenon. The main findings are that: (1) TWIs during LBBAP were clinically frequent (66.3%) and recoverable (87.8%); (2) TWIs in patients with complete left bundle branch block (CLBBB) occurred more frequently in inferior and anterior leads; (3) Patients with complete right bundle branch block (CRBBB) were more prone to TWIs in high lateral wall leads; (4) Baseline QRS duration (QRSd) >120 ms predicts TWIs during LBBAP.

clinical practitioners are unaware, particularly in patients during LBBAP.

This study aimed to (1) investigate the epidemiology and characteristics of TWIs during LBBAP and (2) explore possible factors associated with TWIs.

METHODS

Study population

This was a retrospective cohort study conducted between May 2017 and Jan 2021 in the 1st Affiliated Hospital of Nanjing Medical University. Consecutive patients with a pacemaker indication according to the 2013 European Society of Cardiology guidelines [6] and those who also underwent attempts for LBBAP implantation were assessed. The study protocol was approved by the Institutional Review Board of the 1st Affiliated Hospital of Nanjing Medical University (2021-SR-211), and all patients gave written informed consent.

LBBAP procedure

The technical details of the LBBAP procedure had been described in previous reports [7, 8]. The pacing threshold, sensing and impedance of the 3830 lead (Medtronic, Minneapolis, MN, US) were recorded during operation. Successful LBBAP was defined as unipolar paced QRS with right bundle branch block (RBBB)-like morphology and QRSd ≤130 ms.

Data collection

All patients underwent a full clinical evaluation before the procedure, including their comorbidities (such as hypertension, coronary artery disease, diabetes mellitus, atrial fibrillation [AF], and stroke), indications for permanent pacemaker implantation, ECG parameters, and pacemaker history. Standard 12-lead ECGs were interpreted by two cardiologists. A standard 12-lead ECG was done before LBBAP. ECG data were collected and recorded including native QRS width, heart rate, paced V6 R-wave peak time, native QRS type (narrow, intraventricular conduction disturbance [IVCD], complete left bundle branch block (CLBBB) morphology [including CLBBB and CLBBB-like pattern during RV pacing] and complete right bundle branch block [CRBBB] morphology). All ECG parameters were rechecked and recorded immediately after LBBAP. ECG was performed at baseline and on the first day post-LBBAP.

During the follow-up period, ECG data of patients were collected and compared with the previous ECG. For each recording, T-wave direction of 12-leads was calculated. TWIs were defined as negative or isoelectric T-wave in leads I, II, III, aVL, aVF, V1–V6, or the presence of a positive or isoelectric T-wave in lead aVR. TWIs in two or more contiguous leads were considered significant. Accordingly, patients were divided into two groups: the non-TWIs group and the TWIs group.

Statistical analysis

Continuous variables were expressed as mean (standard deviation [SD]) for normally distributed variables, and categorical variables were expressed as frequencies and percentages. Non-normally distributed variables were expressed as the median with the interquartile range (IQR). Baseline characteristics were compared between patients with and without TWIs, using an independent-samples t-test, pairwise t-test, or Wilcoxon matched-pairs signed-ranks test for continuous data, and the χ^2 test for dichotomous data. Logistic regression analysis was performed to identify the predictive factors of TWIs. All the variables with a *P*-value <0.05 in the univariate analysis (Supplementary material, *Table S1*) were included in the multivariable logistic regression analyses. In the multivariable logistic regression analyses, QRSd <90 ms, 90 ms <QRSd ≤120 ms, 120 ms <QRSd ≤150 ms, and QRSd >150 ms were analyzed separately after adjustment for clinical variables (age, sex, and medical history), and TWIs were presented as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). The association between related factors two-sided *P*-value <0.05 was considered statistically significant. All statistical analyses were performed using the SPSS software (version 23.0).

RESULTS

Baseline characteristics

Overall, a total of 494 consecutive patients were assessed for inclusion between May 2017 and Jan 2021. Based on the definition of success provided above, successful LBBAP was achieved in 447 (90.5%) patients. Forty-nine cases without ECG on the day of operation were excluded (Supplementary material, *Figure S1*). Therefore, the study population consisted of 398 patients for further analysis. The baseline characteristics of study participants are

Table 1. Baseline characteristics of study participants according to TWIs during LBBAP

Patient characteristics	All patients (n = 398)	Non-TWIs group (n = 134)	TWIs group (n = 264)	*P*-value Non-TWIs vs. TWIs
Age, years, mean (SD)	69.8 (11.3)	67.3 (11.0)	71.1 (11.3)	<0.01
Male sex, n (%)	202 (50.8)	63 (47.0)	139 (52.7)	0.29
Medical history, n (%)				
Hypertension	252 (63.3)	78 (58.2)	174 (65.9)	0.13
Diabetes mellitus	78 (19.6)	19 (14.1)	59 (22.3)	0.052
Coronary heart disease	76 (19.1)	20 (14.9)	56 (21.2)	0.13
Atrial fibrillation	121 (30.4)	45 (32.4)	76 (28.8)	0.33
Stroke	63 (15.8)	19 (14.2)	44 (16.7)	0.52
Pacing indication, n (%)				<0.001
SSS	148 (37.2)	65 (48.5)	83 (31.4)	
AVB	200 (50.2)	66 (49.3)	134 (50.8)	
BBB	11 (2.8)	1 (0.7)	10 (3.8)	
Heart failure with CLBBB	39 (9.8)	2 (1.5)	37 (14.0)	
Native QRS type, n (%)				<0.001
Narrow	253 (63.5)	122 (91.0)	131 (49.6)	
IVCD	14 (3.5)	3 (2.2)	11 (4.2)	
CLBBB morphology	87 (21.9)	2 (1.5)	85 (32.2)	
CRBBB morphology	44 (11.1)	7 (5.2)	37 (14.0)	
ECG parameters, mean (SD)				
Intrinsic QRSd (ms)	116.6 (32.7)	98.2 (18.1)	125.9 (34.5)	<0.001
LBBAP QRSd (ms)	107.3 (11.7)	103.6 (11.5)	109.1 (11.4)	<0.001
Pacemaker history, n (%)				
Temporary pacemaker	26 (6.5)	4 (3.0)	22 (8.3)	0.04
DDD/VVI pacemaker	27 (6.8)	1 (0.7)	26 (9.8)	<0.01
CRT/CRTD/BIVP device	6 (1.5)	0	6 (2.3)	0.10

Abbreviations: AVB, atrioventricular block; BBB, bundle branch block; BIVP, bi-ventricular pacing; CLBBB, complete left bundle branch block; CRBBB, complete right bundle branch block; CRT, cardiac resynchronization therapy; CRTD, CRT with defibrillator; DDD, dual-chamber pacemaker; ECG, electrocardiogram; IVCD, intraventricular conduction disturbance; LBBAP, left bundle branch area pacing; QRSd, QRS duration; SD, standard deviation; SSS, sick sinus syndrome; TWIs, T-wave inversions; VVI, single-chamber pacemaker

summarized in Table 1. The mean (SD) age of these patients was 69.8 (11.3) years, and 202 (50.8%) were men. The patients had a high proportion of comorbidities, including hypertension (63.3%), diabetes mellitus (19.6%), coronary heart disease (19.1%), AF (30.4%), and stroke (15.8%). Two hundred and sixty-four of 398 (66.3%) patients had TWIs during LBBAP. The mean (SD) age of patients in the TWIs group was higher (71.1 [11.3] years vs. 67.3 [11.0]) years; *P* <0.01). The percentages of CLBBB (85/264 vs. 2/134; *P* <0.001) and CRBBB (37/264 vs. 7/134; *P* <0.01) were significantly higher in the TWIs group than that in the non-TWIs group. The mean (SD) of intrinsic QRSd (125.9 [34.5] ms vs. 98.2 [18.1] ms; *P* <0.001), and LBBAP QRSd (109.1 [11.4] ms vs. 103.6 [11.5] ms, *P* <0.001) were significantly longer in patients with TWIs than in patients without TWIs. As for the background pacemaker history, TWIs group patients received a higher proportion of temporary pacing (*P* = 0.04) and permanent pacemaker (*P* <0.01). There were no significant differences between the two groups in terms of sex or medical history.

LBBAP procedural and R-wave peak time in V6 characteristics

For 398 patients with successful LBBAP, the mean (SD) threshold was 0.6 (0.2) v, mean (SD) sensing was 12.5 (6.6) mv, and the mean (SD) impedance was 784.4 (269.0) Ω during implantation. There was no statistically significant difference in the parameters of LBBAP between the non-TWIs and TWIs groups. The mean (SD) paced V6 R-wave peak time (84.7 [13.5] ms vs. 78.2 [14.9] ms; *P* <0.001) was significantly longer in patients with TWIs than in patients without TWIs. The implantation procedure-related characteristics of the included patients are given in Table 2.

TWIs during LBBAP

Two hundred and sixty-four of 398 (66.3%) patients had T-wave changes after LBBAP. TWIs occurred immediately during LBBAP operation (Figures 1–3). Table 3 summarized TWIs on 12-lead ECG under treatment with LBBAP in patients with CLBBB or CRBBB. These patients were divided into two subgroups according to baseline QRS morphology (G1 — CLBBB morphology and G2 — CRBBB morphology). Compared with G2, TWIs occurred more frequently in leads: II (41/85 vs. 7/37; *P* <0.001), III (41/85 vs. 9/37; *P* <0.001), aVF (41/85 vs. 9/37; *P* <0.001),V1 (43/85 vs. 1/37; *P* <0.001),V2 (61/85 vs. 10/37; *P* <0.001), V3 (71/85 vs. 15/37; *P* <0.001), and V4 (70/85 vs. 21/37; *P* <0.001). TWIs occurred more commonly in leads I (16/85 vs. 22/37; *P* <0.001) and aVL (12/85 vs. 23/37; *P* <0.001) in patients with CRBBB than in patients with CLBBB.

Table 2. Parameters of left bundle branch area pacing and V6 R-wave peak time

	All patients (n = 398)	Non-TWIs group (n = 134)	TWIs group (n = 264)	*P*-value Non-TWIs vs. TWIs
Threshold, v, mean (SD)	0.6 (0.2)	0.6 (0.3)	0.6 (0.2)	0.97
Sensing, mv, mean (SD)	12.5 (6.6)	12.2 (6.7)	12.7 (6.5)	0.42
Impedance, Ω, mean (SD)	784.4 (269.0)	756.1 (164.4)	798.7 (308.1)	0.14
V6 RWPT, ms, mean (SD)	82.5 (15.1)	78.2 (14.9)	84.7 (13.5)	<0.001

Abbreviations: RWPT, R-wave peak time; other — see Table 1

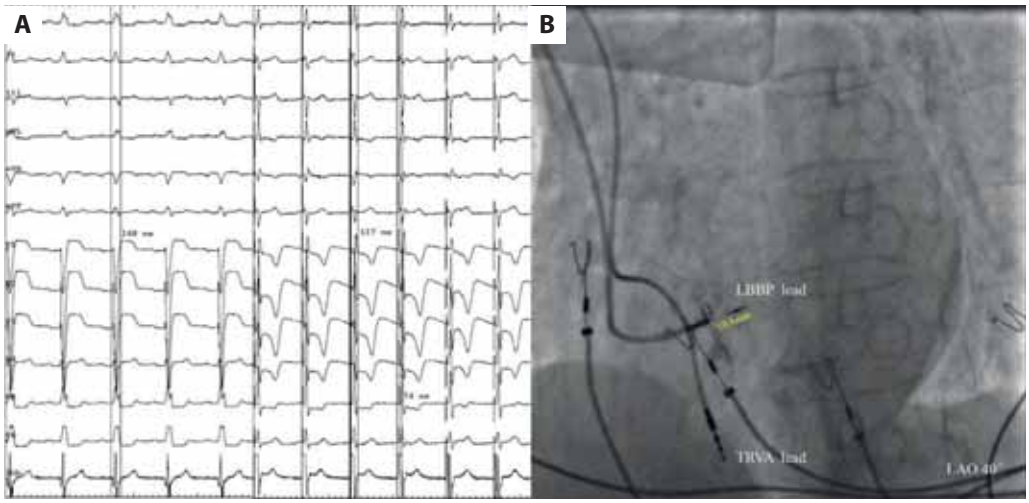

Figure 1. Immediate T-wave inversions on electrocardiogram (ECG) (V1–V5) during left bundle branch area pacing (LBBAP) in a patient with complete left bundle branch block (LBBP). We attempted to perform LBBAP on a patient (83 years/male) with heart failure and left bundle branch block (QRS duration [QRSd], 148 ms). Before the procedure, his computer tomography angiography work-up showed normal coronary arteries; the New York Heart Association (NYHA) class was III, and his left ventricular ejection fraction was 41.9%. During the procedure, when the tip reached the area of LBB, the unipolar pacing showed right bundle branch block liked morphology with QRSd 117 ms and Sti-LVAT 74 ms (**A**, continuous ECG and intracardiac electrogram record with speed 25 mm/sec). The implant depth of LBBAP lead was 10.8 mm (**B**, sheath angiography in the left anterior oblique [LAO] 40° view). After the procedure, his heart failure symptoms (NYHA I) significantly improved at follow-up of 3 months

Abbreviations: TRVA, temporary right ventricular apex

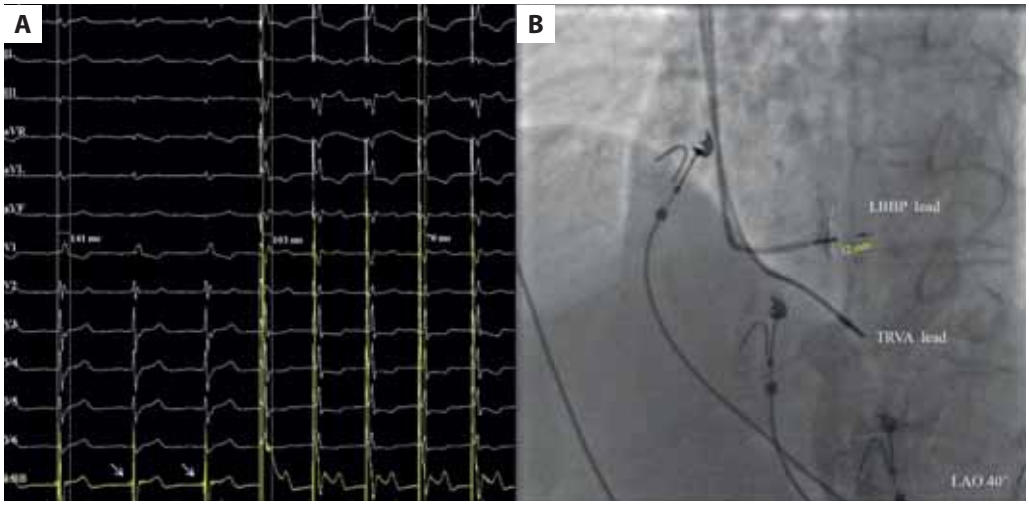

Figure 2. Immediate T-wave inversions on ECG (I, III, aVL, aVR, and V3–V6) during LBBAP in a patient with CRBBB. An 86-year-old man was admitted to our institution with recurrent syncope. Holter showed an intermittent AVB with a QRS complex morphology of CRBBB (QRSd, 141 ms). Given the documented symptomatic conduction trouble at the level of the AV node (HV interval 75 ms) and the existence of CRBBB, the patient was considered to be indicated for LBBAP. During the procedure, a sharp LBB potential pre-QRS was seen (the arrow) when conduction occurs *via* the left bundle, resulting in a narrow complex. When the tip reached the area of LBB, the unipolar pacing showed RBBB-like morphology with QRSd 103 ms and Sti-LVAT 70 ms (**A**, continuous ECG and intracardiac electrogram record with speed 50 mm/sec). Sheath angiography in the LAO 40° confirmed deep insertion (12 mm) of the LBBP lead into the septum (see **B**). No more syncope occurred during the follow-up

Abbreviations: CRBBB, complete right bundle branch block; other — see Figure 1

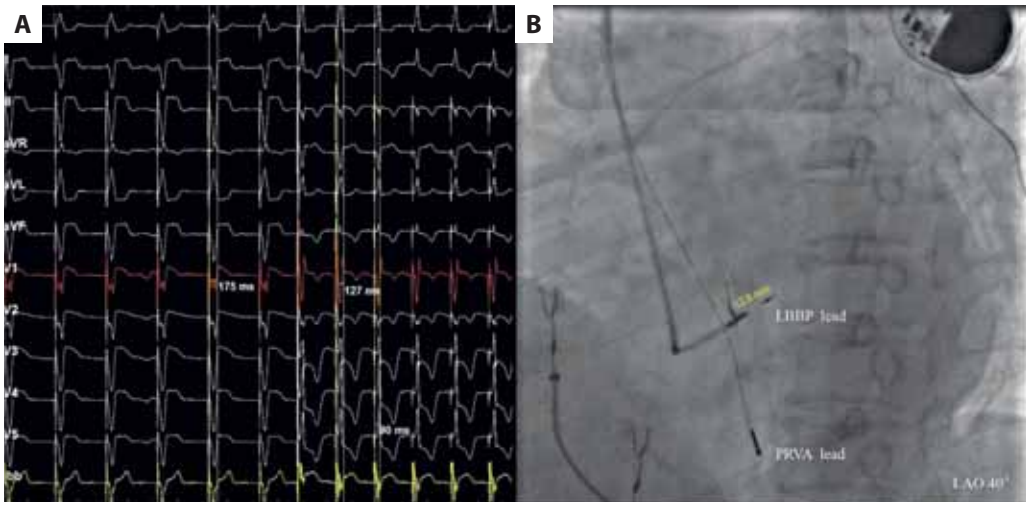

Figure 3. Immediate TWIs on ECG (II, III, aVL, aVR, aVF, and V1–V6) during LBBAP in a patient with RV pacing. A 60-year-old female with advanced AVB had undergone implantation of a single-chamber pacemaker about 9 years earlier. Holter indicated that the rate of RV pacing was 100 percent in external hospital. Given the important interventricular dyssynchrony due to RV pacing, as well as serious tricuspid valvular regurgitation, we upgraded RV pacing to LBBAP. **A.** Surface ECG and intracardiac electrograms from the LBBAP lead are shown at a sweep speed of 25 mm/sec. Intrinsic electrogram showed CLBBB-like morphology with QRS duration 175 ms; unipolar pacing electrogram of LBBAP showed RBBB-like morphology with QRS duration 127 ms and Sti-LVAT 90 ms. **B.** Sheath angiography in the LAO 40° view demonstrated the depth of the LBBP lead (12.8 mm) inside the septum (the dotted line)

Abbreviations: PRVA, permanent right ventricular apex; other — see Figure 1

Table 3. Incidence of T-wave inversions on 12-lead electrocardiogram

	CLBBB group (n = 85)	CRBBB group (n = 37)	*P*-value
Limb leads			
I	16 (18.8%)	22 (59.5%)	<0.001
II	41 (48.2%)	7 (18.9%)	<0.01
III	41 (48.2%)	9 (24.3%)	0.01
aVR	49 (57.6%)	24 (64.9%)	0.46
aVF	41 (48.2%)	9 (24.3%)	0.01
aVL	12 (14.1%)	23 (62.2%)	<0.001
Precordial leads			
V1	43 (50.6%)	1 (2.7%)	<0.001
V2	61 (71.8%)	10 (27.0%)	<0.001
V3	71 (83.5%)	15 (40.5%)	<0.001
V4	70 (82.4%)	21 (56.8%)	<0.01
V5	63 (74.1%)	28 (75.7%)	0.86
V6	49 (57.6%)	24 (64.9%)	0.46

Abbreviations: aVR, augmented vector right; aVF, augmented vector foot; aVL, augmented vector left; other — see Table 1

Predictors for TWIs

After multivariable adjustment for the confounding factors such as sex, age, and comorbidities (hypertension, diabetes mellitus, coronary heart disease, AF, and stroke), 120 ms <QRSd ≤150 ms (OR, 7.59; 95% CI, 2.88–19.96; *P* <0.001) and QRSd >150 ms (OR, 28.06; 95% CI, 8.40–93.71; *P* <0.001) independently predicted TWIs during LBBAP (Table 4).

Recovery of TWIs

One hundred and seventy-two of 264 patients had LBBAP-ECG at 3 days post LBBAP or during the follow-up. Figure 4 showed dynamic changes of T-wave on ECG after LBBAP in a patient with CLBBB. During the follow-up period, the median (IQR) follow-up duration was 10 days (7 days to 5.5 months). One hundred and fifty-one (87.8%) patients were found to have partial or complete recovery from TWIs, while 21 (12.2%) patients still had TWIs at follow-up (Supplementary material, *Figure S2*).

Effect of LBBAP on troponin T

Troponin T (TnT) was tested in 123 of 398 patients at baseline and 12 hours after operation, 83 of 123 had TWIs during LBBAP. Compared with those before implantation, the mean (SD) levels of TnT in all patients (11.9 [7.7–18.8] ng/l vs. 56.3 [37.7–120.1] ng/l; *P* <0.001), the non-TWIs group (9.6 [6.6–16.2] ng/l vs. 56.3 [35.0–124.7] ng/l; *P* <0.001), and the TWIs group (12.6 [8.5–20.6] ng/l vs. 53.8 [39.3–115.4]

Table 4. Multivariable logistic analysis for T-wave inversions

Intrinsic QRSd (ms)	Non-TWIs (n = 134)	TWIs (n = 264)	Multivariable analysis	
			OR (95% CI)	*P*-value
QRSd ≤90, n (%)	49 (36.5)	38 (14.4)	1.00	
90 <QRSd ≤120, n (%)	73 (54.5)	95 (36.0)	1.73 (0.88–3.38)	0.11
120 <QRSd ≤150, n (%)	8 (6.0)	54 (20.4)	7.59 (2.88–19.96)	<0.001
QRSd >150, n (%)	4 (3.0)	77 (29.2)	28.06 (8.40–93.71)	<0.001

The multivariable logistic regression analyses model adjusted for clinical variables (age, sex, and medical history)

Abbreviations: see Table 1

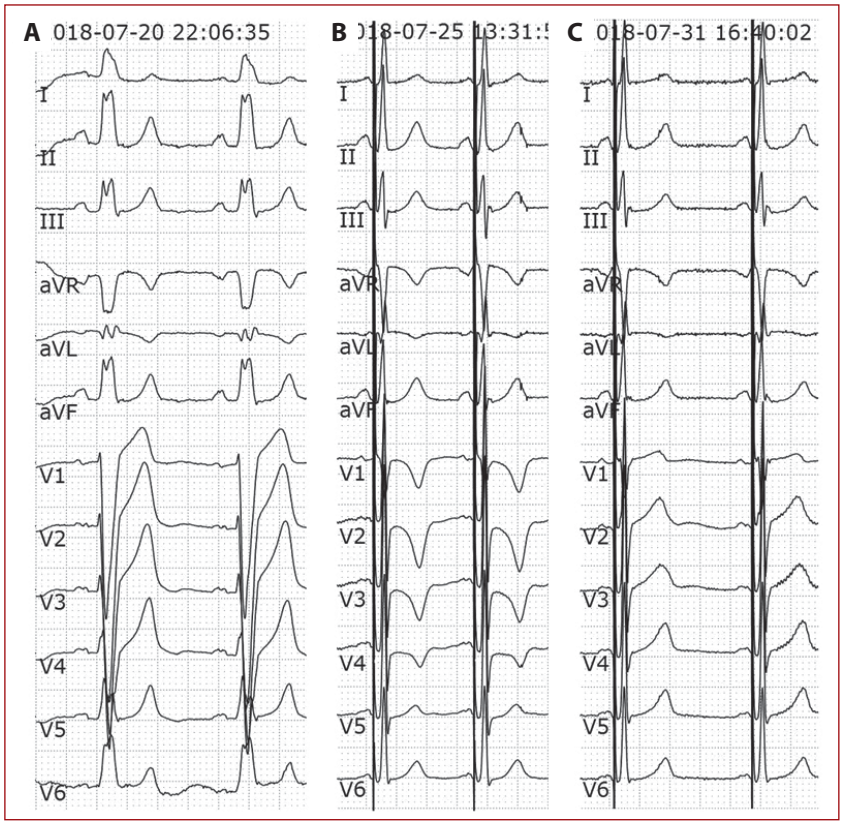

Figure 4. Dynamic changes of T-wave on ECG after LBBAP in a patient with CLBBB. **A.** Baseline ECG showed LBBB. **B.** ECG on first day post-LBBAP showed T-waves inverted in V1–V4; **C:** ECG 6 days post-procedure showed that T-waves returned to normal

Abbreviations: see Figure 1

ng/l; *P* <0.001) increased significantly after LBBAP. On the other hand, there was no statistical significance in TnT levels between the non-TWIs and TWIs groups.

DISCUSSION

To our knowledge, there are no cohort studies of LBBAP-induced TWIs, and this is the first report to demonstrate this phenomenon. The main findings are that: (1) 66.3% of patients have TWIs during LBBAP; (2) the prevalence of TWIs in inferior leads (II, III, and aVF) and anterior leads (V1–V4) is significantly higher than high side leads (I and aVL) in CLBBB patients, which is contrary to patients with CRBBB; (3) baseline QRSd >120 ms predicts TWIs during LBBAP; (4) TWIs are reversible in 87.8% patients; and (5) TWIs during LBBAP may be unrelated to acute myocardial ischemia.

TWIs and CM

Rosenbaum et al. [9] attributed TWIs to CM, as a change in myocardial repolarization manifested by a persistent change in the T-wave axis after restoration of normal cardiac excitation. They also described the property of accumulation in cardiac memory cells, where the magnitude of TWIs increased with repetitive activation by pacing or CLBBB and persisted for longer periods with increasing duration of the altered activation. TWIs due to CM is a frequently encountered electrical phenomenon that appears after the cessation of a period of abnormal ventricular depolarization. It occurs in response to several conditions including Wolff-Parkinson-White syndrome [10], ventricular arrhythmia [11], and ventricular pacing [12]. Previous studies showed that 59% of patients with Wolff-Parkinson-White syndrome had TWIs after undergoing successful catheter ablation [13] and TWIs after termination of idiopathic left ventricular tachycardia (ILVT) in 9/16 (56%) patients [14]. Grimm [12] has reported TWIs observed in one-third of patients following pacemaker implantation, with more than four-fifths of patients developing CM if the ventricular stimulation burden was 75% or greater. In the present

study, 264 of 398 (66.3%) patients had TWIs during LBBAP. This suggests that T-wave changes following LBBAP are not uncommon.

TWIs during LBBAP

LBBAP has recently emerged as a new promising pacing modality. During LBBAP, the His-Purkinje system was swiftly recruited by advanced activation of the area of the LBB trunk or proximal left anterior or posterior fascicle, which leads to good electrical synchrony and a short-paced QRS duration. Hou et al. [15] showed that cardiac electrical and LV mechanical synchrony of LBBAP were superior to that of right ventricular systolic pressure (RVSP) and similar to that of His bundle pacing. Previous studies also demonstrate that LBBP maintains ventricular synchrony at a level close to normal [16]. CM occurred after the ventricular activation altered or returned to normal because the changes in repolarization remained. Successful LBBAP can achieve narrow QRS complexes and maintain good LV electrical and mechanical synchrony, especially for patients with wide QRS complexes before operation, which can change ventricular activation sequence. This may be the reason for TWIs in patients during LBBAP.

CM had the property of accumulation, where the magnitude of the T-wave changes increased with repetitive activation by pacing or LBBB and persisted for longer periods with increasing duration of the altered activation [9]. During follow-up, we found that TWIs were partially or completely recovered in 151/172 (87.8%) patients. This was a retrospective study, and some patients only had a follow-up ECG 3 days to one week after LBBAP. This may be one reason why TWIs remained in 12.2% of patients. CM due to ventricular stimulation is benign and should not be confused with similar T-wave inversions due to acute coronary syndrome, ventricular hypertrophy, or myocarditis.

In our research, we found that TnT increased observably after LBBAP. The results are similar to our previous reports [17]. Meanwhile, we observed there were no significant differences in TnT levels and coronary heart disease prevalence between the TWIs and non-TWIs groups at baseline. These findings may indicate that TWIs may be unrelated to coronary heart disease.

TWIs in different leads

Another important result of the study is the observation of the QRS morphology before LBBAP, resulting in TWIs occurring in different ECG leads. Jeyaraj [18] found that there was mild action potential prolongation in the myocardial region that was close to the site of pacing (early activated), while significant action potential prolongation was noted in the myocardial region that was farthest from the site of pacing (late activated). The amplification of repolarization gradients between segments of the left ventricle is the electrophysiological basis for T-wave memory. The LV was activated only through transmyocardial conduction starting after the RV activation onset, and then the activation spread centrifugally over the anterior and inferior wall in patients with LBBB-like patterns [19]. The maximum repolarization gradients in patients with CLBBB are the anterior and inferior walls. Thus, TWIs in patients with CLBBB before LBBAP occurred more frequently in inferior leads (II, III, and aVF) and anterior leads (V1–V5). A previous study also found that patients with intermittent left bundle branch block frequently have TWIs in right and mid-precordial leads during normal conduction [20]. On the other hand, ventricular activation started in the inferior wall or lower septum of the LV and propagated toward the LV anterior or anterolateral walls in patients with RBBB [21]. Hence, patients with CRBBB were more prone to TWIs in high lateral wall leads (I and aVL).

Predictors of TWIs during LBBAP

Previous studies showed memory T-waves can be triggered by any conditions which produce wide QRSd transiently [5]. In this study, we also found that T-wave alterations occurred more frequently in patients with ventricular conduction abnormalities. One hundred and twenty-two of 264 (46.2%) patients had obvious conduction abnormalities (CLBBB morphology: 85 patients, CRBBB morphology: 37 patients), which is more frequent than that in the non-TWIs group (9/134, 6.7%). It was observed that the mean (SD) QRSd was longer (98.2 [18.1] ms vs. 125.9 [34.5] ms; P <0.001), and a higher percentage of CLBBB (2/134 vs. 85/264; P <0.001) was in the TWIs group. Multiple regression analysis showed that QRSd >120 ms was an independent predictor of TWIs during LBBAP. We also observed that the wider the baseline QRSd, the higher was the predictive value of TWIs. This may be because QRSd can reflect abnormal ventricular conduction. In the present study, dynamic T-wave changes during LBBAP also occurred in patients with a normal QRS complex before operation. The phenomenon cannot be explained by known mechanisms of CM.

Limitations

First, this was a retrospective study evaluating TWIs changes in patients with LBBAP. And the ECG analysis was qualitative and not quantitative. Second, coronary angiography was not performed during operation; it was difficult to exclude the damage to interventricular septum branches during the LBBAP procedure. According to the earlier studies, the prevalence of this complication was quite low, so it could not explain the high occurrence of TWIs during LBBAP. Additionally, the ECG leads related to TWIs were different from those caused by septum ischemia. Third, LBBP and left ventricular septal pacing (LVSP) were not further differentiated in the study. Through direct activation of the left bundle branch, LBBP was more physiological than LVSP. As a result, a higher prevalence of TWIs recovery could be expected after LBBP. Furthermore, the duration of follow-up varied, which may have influenced the recovery rate of TWIs. The results should be confirmed in future prospective cohort studies with a larger patient number.

CONCLUSION

This study demonstrated that nearly two-thirds of patients had TWIs during LBBAP. T-wave changes during LBBAP occurred more frequently in inferior leads (II, III, and aVF) and anterior leads (V1–V5) in patients with CLBBB. Patients with CRBBB were more prone to T-wave inversion in high side leads (I and aVL). QRSd >120 ms could predict TWIs during LBBAP. These findings could be used to avoid unnecessary testing for myocardial ischemia in patients with T-wave changes during LBBAP.

Supplementary material

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

Article information

Conflict of interest: None declared.

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Resting heart rate is associated with novel plasma atherosclerosis biomarkers

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ABSTRACT

Background: Resting heart rate (RHR) is a strong predictor of adverse cardiovascular outcomes. Both soluble low-density lipoprotein receptor-related protein-1 (sLRP1) and soluble receptor for advanced glycation end products (sRAGE) are novel plasma biomarkers for atherosclerosis. In this study, we examined the potential associations between RHR and plasma sLRP1 and sRAGE levels and whether any associations might be modified by apolipoprotein E (*APOE*) ε4 carrier status.

Methods: This cross-sectional study included 941 apparently healthy adults aged 40 years or older. Plasma sLRP1 and sRAGE levels were measured by a commercial enzyme-linked immunosorbent assay. *APOE* gene polymorphisms were analyzed by a polymerase chain reaction and Sanger sequencing.

Results: RHR was a significant determinant of log-transformed sLRP1 (β = 0.004; 95% confidence interval [CI], 0.002–0.007; $P = 0.001$) and log-transformed sRAGE (β = 0.005; 95% CI, 0.002–0.007; $P < 0.001$) independently of age, sex, body mass index, blood pressure, blood glucose, blood lipids, lifestyle, and medical history. Additionally, *APOE* ε4 carrier status was inversely associated with log-transformed plasma sLRP1 level (β = –0.072; 95% CI, –0.130 to –0.015; $P = 0.01$) and did not modify the relationship between RHR and plasma sLRP1 level.

Conclusions: An elevated RHR was associated with increased sLRP1 and sRAGE values, which was not modified by *APOE* genotype. The underlying mechanism of this effect may be relevant to the progression of atherosclerosis.

Key words: apolipoprotein E, atherosclerosis, coronary heart disease, heart rate

INTRODUCTION

Resting heart rate (RHR) is a routinely collected vital sign that is easily and noninvasively measured without requiring special training or equipment. A large body of evidence indicates that an elevated RHR can be considered an important determinant of atherosclerosis and a strong predictor of adverse cardiovascular outcomes [1]. However, the mechanisms underlying these correlations are not fully understood.

Low-density lipoprotein receptor-related protein-1 (LRP1) is a large multifunctional type 1 transmembrane receptor that participates in multiple physiological and pathological processes, including lipid and glucose metabolism, inflammation, atherosclerosis, acute myocardial infarction, myocardial ischemia-reperfusion injury, and adverse left ventricular remodeling [2, 3]. LRP1 β-chain proteolysis results in the release of soluble LRP1 (sLRP1), which can be detected in the plasma. Various *in vitro* models suggested that sLRP1 is a biologically active mediator of several cellular processes linked with atherosclerotic disease [4, 5]. More recently,

WHAT'S NEW?

Resting heart rate (RHR) was independently and positively associated with plasma soluble low-density lipoprotein receptor-related protein-1 (sLRP1) and plasma soluble receptor for advanced glycation end products (sRAGE) levels, and this association was not modified by *APOE* ε4 carrier status. These data suggest a relationship between RHR and atherosclerosis that may be both relevant to the pathology of coronary heart disease (CHD) and clinically useful for identifying patients who are at risk or in the early stages of CHD.

increasing evidence supports the hypothesis that sLRP1 is a novel biomarker for atherosclerosis and is associated with the development of coronary artery disease (CAD) [5, 6].

The receptor for advanced glycation end products (RAGE), which is found on the surface of numerous cells, is also involved in atherosclerosis development via activation of the inflammatory and oxidative stress pathways [7]. The soluble isoforms of RAGE (sRAGE), formed from the cleavage of the native membrane receptor and present in the circulation, can limit these signaling pathways by binding RAGE ligands as decoy receptors. In fact, sRAGE levels were reportedly higher in coronary disease or higher atherosclerotic burden cases than in control subjects in some studies [8], and elevated sRAGE levels are associated with an increased risk of cardiovascular disease [9]. Thus, both sLRP1 and sRAGE are associated with coronary atherosclerosis, but little is known about the association between RHR and plasma levels of sLRP1 and sRAGE.

The human apolipoprotein E (*APOE*) gene exists as three polymorphic alleles including ε2, ε3, and ε4; this polymorphism is among common genetic factors responsible for inter-individual differences in lipid and lipoprotein levels [10]. In several meta-analyses, the ε4 allele was associated with a moderately increased risk of ischemic heart disease, whereas the ε2 allele was associated with reduced risk [10, 11]. Some studies also suggested that *APOE* ε4 carriers are particularly prone to developing disseminated coronary lesions or are at an increased risk of coronary heart disease (CHD)-related mortality [12]. Moreover, synergistic effects were observed between the ε4 allele carrier state and some traditional risk factors, which largely increases an individual's risk of CAD [13].

The primary purpose of this analysis was to explore the relationship between RHR and plasma sLRP1 and sRAGE. We also examined whether any associations might be modified by *APOE* ε4 carrier status. We examined these questions using samples and data from a population-based cross-sectional study of middle-aged and elderly Chinese people.

METHODS

Participants

This study was conducted in the Qubao Village between October 2014 and March 2015 and described in detail elsewhere [14]. Briefly, the inclusion criteria were as follows: (1) age 40 years or older; (2) permanent resident living in Qubao Village for more than 3 years; and (3) consent to participate in the study. Individuals were excluded from the study if they had an acute or chronic infection, or severe cardiac, pulmonary, hematological, hepatic, renal disease, or tumors. Subjects who were taking antihypertensive, antidiabetic, antilipidemic, antithrombotic, nonsteroidal anti-inflammatory drugs, contraceptives, or vitamins were also excluded to avoid the confounding influence of these drugs on RHR and plasma atherosclerosis biomarkers. Subjects for whom at least one RHR, plasma sLRP1, or sRAGE concentration, *APOE* genotype, or covariable measurement was missing were also excluded, leaving an analytic sample of 941 subjects (Figure 1).

RHR measurements

RHR measurements were performed after each blood pressure reading in duplicate and then averaged. Before the measurement, the patients rested for at least 5 minutes and had avoided exercise, caffeine, alcohol, and tobacco use in the previous 12 hours. Blood pressure was measured using a manual mercury sphygmomanometer with a regular adult cuff on the right arm before breakfast in the morning (8:00–10:00 AM), and RHR was measured on the right radial artery for 1 minute by palpation.

Quantification of plasma atherosclerosis biomarkers

Overnight fasting venous blood samples were collected in ethylenediaminetetraacetic acid vacutainer tubes and centrifuged at 3000 × g for 10 minutes at 20°C immediately, and the plasma was separated and stored at –80°C until use. Plasma concentrations of sLRP1 and sRAGE were detected with commercially available quantitative enzyme-linked immunosorbent assay kits (Yuanye Co., Shanghai, China). Measurements were performed using an RT-6000 analyzer (Rayto Co., Shenzhen, China) at 450 nm while sample concentrations were calculated from the standard curve. Duplicate measurements were performed, and the average values were included in the analysis.

APOE genotype

Genomic deoxyribonucleic acid (DNA) was extracted from peripheral blood leukocytes using a TIANamp Genomic DNA Kit (Tiangen Co., Beijing, China). *APOE* gene polymorphisms, rs7412 and rs429358, which determine the *APOE* alleles ε2, ε3, and ε4, were analyzed by a polymerase chain reaction and Sanger sequencing (Sangon Co., Shanghai, China).

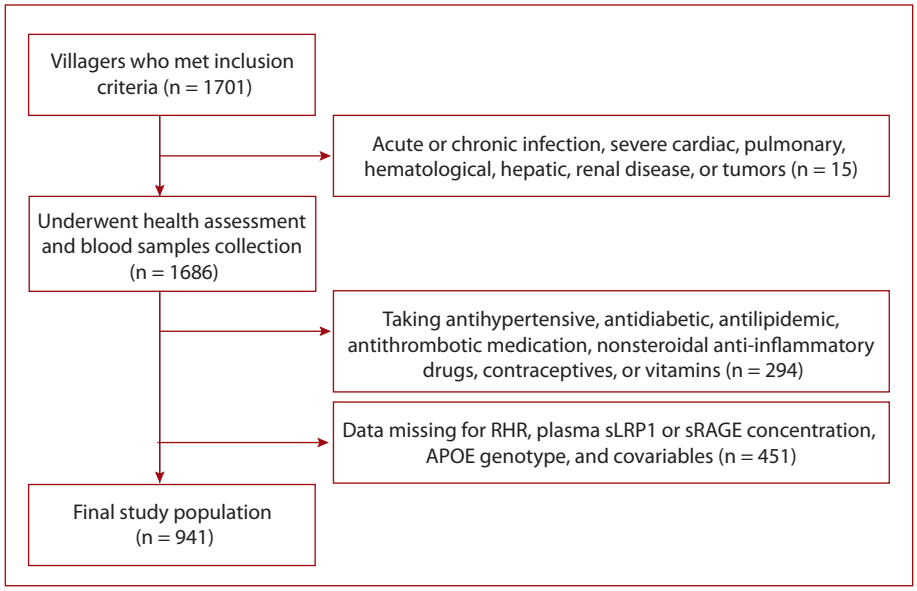

Figure 1. Flow chart showing the selection process for the present study

Abbreviations: RHR, resting heart rate; sLRP1, soluble low-density lipoprotein receptor-related protein-1; sRAGE, soluble receptor for advanced glycation end products

Demographic, clinical, and biological data collection

A standardized questionnaire was administered to collect the participants' demographic data (age, sex, and education years) and clinical data, including medical history (hypertension, diabetes mellitus, dyslipidemia, CHD, and transient ischemic attack [TIA], or stroke), medication use (antihypertensive, antidiabetic, antilipidemic, antithrombotic medication, nonsteroidal anti-inflammatory drugs, contraceptives, and vitamins), and lifestyle habits (smoking, drinking alcohol, and physical activity level). Body weight and height were measured, and body mass index (BMI) was calculated as weight/height squared (kg/m^2). Biochemical parameters such as fasting blood glucose, serum total low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, total cholesterol, and triglycerides were determined from non-fasting blood samples. A history of CHD was defined as any of the following: (1) a previous diagnosis of myocardial infarction; (2) known angina pectoris; (3) a history of hospitalization for unstable angina; or (4) previous coronary revascularization. The definitions of hypertension, diabetes, and hyperlipidemia were the same as in our previous study [14].

Statistical analysis

Continuous variables are presented as mean (standard deviation) or median (interquartile range), while categorical variables are presented as numbers (percentage). RHR values were grouped into thirds of their distribution. One-way analysis of variance (ANOVA) or the Kruskal-Wallis and χ^2 tests were used for the group comparisons. Next, a *post hoc* Bonferroni adjusted test was used to analyze differences in plasma sLRP1 and sRAGE levels in the lowest, medium, and highest tertiles. Differences between *APOE* ε4 non-carriers and *APOE* ε4 carriers were compared using an unpaired Student t-test, the Mann-Whitney U-test, or the χ^2 test as appropriate.

The binary logistic regression analysis was performed in the univariable and multivariable analyses to identify risk factors for CHD. In particular, three explanatory variables with a *P*-value of <0.1 were included in the multivariable logistic regression model. Because of their non-Gaussian distribution, plasma levels of triglycerides, fasting blood glucose, sLRP1, and sRAGE were log-transformed before the statistical analysis. Correlations between RHR and plasma biomarkers were examined using partial rank correlation coefficients, with adjustment for age and sex, and then additionally for BMI, systolic blood pressure, diastolic blood pressure, fasting blood glucose, triglyceride level, total cholesterol level, high-density lipoprotein cholesterol level, smoking, drinking, physical activity level, TIA or stroke, and CHD.

Multiple linear regression models were used to examine the associations between RHR and plasma levels of sLRP1 and sRAGE. Given that the *APOE* ε4 allele may exert differential influences on plasma atherosclerosis biomarkers, another linear regression model that included RHR and *APOE* ε4 carrier status was simultaneously applied. Furthermore, when RHR and *APOE* ε4 carrier status were associated with plasma atherosclerosis biomarkers, the interaction term (RHR × *APOE* ε4 carrier status) was included in the multivariable linear regression model to investigate the interaction effects after mean centering RHR and *APOE* ε4 carrier status.

All statistical analyses were performed using SPSS Statistics version 20.0 (IBM Corporation, Armonk, NY, US). Statistical significance was defined as a two-sided *P*-value of 0.05.

RESULTS

General characteristics of the study subjects

A total of 941 participants (59.7% women) aged 40–85 years (mean [standard deviation, SD] age, 54.7 [10.0] years) ultimately participated in our study. The patients were divided into three groups according to RHR tertile; the cut-offs were ≤71 beats per minute (bpm) for the first third, 72–77 bpm for the second, and ≥78 bpm for the third. Participants in the highest RHR tertile were more likely to have hypertension, CHD, and higher diastolic blood pressure than those in the lowest RHR tertile. In contrast, they were less likely to be male or to smoke. Participants in the lowest, medium, and highest RHR tertiles were similar in terms of *APOE* ε4 carrier status and other demographic, clinical, and biological data (Table 1).

Association between RHR and CHD

Considering that an increase in RHR may induce cardiovascular events, next we investigated the risk factors for CHD to clarify the effect of RHR on CHD. In the bivariable analysis, age, hypertension, a lack of physical activity, and the RHR category were identified (Table 2). However, a further analysis of three explanatory variables in the multiple logistic regression model showed that age, lack of physical activity, and the RHR category were significantly associated with CHD. Specifically, participants with the highest RHR had nearly four times higher odds of developing CHD than those with the lowest RHR (OR, 3.926; 95% CI, 1.303–11.832) (Table 3).

Association between RHR and plasma atherosclerosis biomarkers

In the present study, we found that there were significant differences in the plasma levels of sLRP1 and sRAGE among the three groups (Figure 2A–B). While the medium and highest RHR groups did not differ significantly from each other in plasma sLRP1 level (medium RHR vs. highest RHR, 315.29 [160.66–498.67] vs. 329.93 [168.33–462.47] ng/ml; $P = 1.00$), both groups showed a statistically significantly elevated mean sLRP1 concentration relative to the lowest RHR group (lowest RHR vs. medium RHR, 240.94 [135.35–416.72] vs. 315.29 [160.66–498.67] ng/ml; $P = 0.001$; lowest RHR vs. highest RHR, 240.94 [135.35–416.72] vs. 329.93 [168.33–462.47] ng/ml; $P = 0.001$, respectively). In addition, only the plasma concentration of sRAGE in the highest RHR group was significantly higher than in the lowest RHR group (lowest RHR vs. highest RHR, 1307.84 [759.03–2275.31] vs. 1724.45 [941.90–2766.62] pg/ml; $P = 0.001$). A similar trend, though not statistically significant, was observed in the medium RHR group (lowest RHR vs. medium RHR, 1307.84 [759.03–2275.31] vs. 1536.11 [821.06–2649.88] pg/ml; $P = 0.07$), whereas the medium and highest RHR groups did not differ significantly from each other (medium RHR vs. highest RHR,

Table 1. Characteristics of the total study population and that stratified by the resting heart rate category

Characteristics	Total (n = 941)	Lowest RHR tertile (n = 279)	Medium RHR tertile (n = 323)	Highest RHR tertile (n = 339)	*P*-value
Age, years	54.7 (10.0)	54.3 (9.6)	55.0 (10.0)	54.7 (10.4)	0.67
Male, n (%)	379 (40.3)	137 (49.1)	127 (39.3)	115 (33.9)	0.001
Education, years	7 (5–9)	8 (5–9)	7 (5–9)	7 (4–8)	0.42
Hypertension, n (%)	369 (39.2)	90 (32.3)	124 (38.4)	155 (45.7)	0.003
Diabetes mellitus, n (%)	58 (6.2)	11 (3.9)	21 (6.5)	26 (7.7)	0.15
Dyslipidemia, n (%)	461 (49.0)	129 (46.2)	155 (48.0)	177 (52.2)	0.30
CHD, n (%)	30 (3.2)	4 (1.4)	7 (2.2)	19 (5.6)	0.006
TIA or stroke, n (%)	42 (4.5)	12 (4.3)	14 (4.3)	16 (4.7)	0.96
Active smoking, n (%)	278 (29.5)	99 (35.5)	92 (28.5)	87 (25.7)	0.03
Alcohol drinking, n (%)	143 (15.2)	51 (18.3)	48 (14.9)	44 (13.0)	0.19
Lack of physical activity, n (%)	146 (15.5)	38 (13.6)	50 (15.5)	58 (17.1)	0.49
BMI, kg/m^2	24.9 (3.1)	24.7 (2.8)	24.9 (3.1)	25.1 (3.2)	0.15
RHR, bpm	75.2 (8.6)	66.4 (4.4)	74.5 (1.7)	83.2 (7.6)	<0.001
Systolic blood pressure, mm Hg	129.4 (17.2)	128.1 (16.2)	128.8 (16.9)	131.0 (18.1)	0.08
Diastolic blood pressure, mm Hg	80.6 (9.8)	79.8 (9.2)	80.0 (9.3)	82.0 (10.6)	0.007
Fasting blood glucose, mmol/l	5.35 (5.05–5.69)	5.29 (5.05–5.61)	5.37 (5.03–5.71)	5.41 (5.06–5.75)	0.09
Triglycerides, mmol/l	1.41 (1.01–1.96)	1.42 (1.00–1.94)	1.37 (1.01–1.93)	1.45 (1.05–2.09)	0.21
Total cholesterol, mmol/l	5.01 (0.97)	4.93 (0.93)	5.00 (0.93)	5.07 (1.03)	0.20
LDL-C, mmol/l	3.29 (0.91)	3.25 (1.00)	3.26 (0.79)	3.34 (0.92)	0.38
HDL-C, mmol/l	1.41 (0.31)	1.40 (0.29)	1.43 (0.32)	1.39 (0.32)	0.25
APOE ε4+ carrier status, n (%)	148 (15.7)	42 (15.1)	47 (14.6)	59 (17.4)	0.56

Data are shown as mean (standard deviation), median (interquartile range), or number (percentage)

Abbreviations: BMI, body mass index; CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TIA, transient ischemic attack; other — see Figure 1

Table 2. Univariable logistic regression analysis of coronary heart disease and other variables

Characteristic	CHD (n = 30)	No CHD (n = 911)	Univariate analysis		
			OR	95% CI	*P*-value
Age, years	62.2 (11.4)	54.4 (9.9)	1.070	1.035–1.107	<0.001
Sex					
Male, n (%)	12 (40.0)	367 (40.3)	0.988	0.470–2.076	0.98
Female, n (%)	18 (60.0)	544 (59.8)	1.000	reference	
Education, years	6 (3–8)	7 (5–9)	0.927	0.836–1.028	0.15
Hypertension					
Yes, n (%)	17 (56.7)	352 (38.6)	2.077	0.996–4.328	0.05
No, n (%)	13 (43.3)	559 (61.4)	1.000	reference	
Diabetes mellitus					
Yes, n (%)	3 (10.0)	55 (6.0)	1.729	0.509–5.878	0.38
No, n (%)	27 (90.0)	856 (94.0)	1.000	reference	
Dyslipidemia					
Yes, n (%)	13 (43.3)	448 (49.2)	0.790	0.379–1.646	0.53
No, n (%)	17 (56.7)	463 (50.8)	1.000	reference	
TIA or stroke					
Yes, n (%)	3 (10.0)	39 (4.3)	2.484	0.722–8.544	0.15
No, n (%)	27 (90.0)	872 (95.7)	1.000	reference	
Smoking					
Yes, n (%)	8 (26.7)	270 (29.6)	0.863	0.380–1.963	0.73
No, n (%)	22 (73.3)	641 (70.4)	1.000	reference	
Alcohol drinking					
Yes, n (%)	2 (6.7)	141 (15.5)	0.390	0.092–1.656	0.20
No, n (%)	28 (93.3)	770 (84.5)	1.000	reference	
Lack of physical activity					
Yes, n (%)	12 (40.0)	134 (14.7)	3.866	1.820–8.209	<0.001
No, n (%)	18 (60.0)	777 (85.3)	1.000	reference	
BMI, kg/m^2	24.7 (3.0)	24.9 (3.1)	0.974	0.863–1.099	0.67
RHR					
Lowest tertile, n (%)	4 (13.3)	275 (30.2)	1.000	reference	
Medium tertile, n (%)	7 (23.3)	316 (34.7)	1.523	0.441–5.258	0.51
Highest tertile, n (%)	19 (63.3)	320 (35.1)	4.082	1.372–12.143	0.01
APOE ε4+ carrier status					
Yes, n (%)	3 (10.0)	145 (15.9)	0.587	0.176–1.960	0.39
No, n (%)	27 (90.0)	766 (84.1)	1.000	reference	

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

Table 3. Multivariable logistic regression analysis of coronary heart disease and other variables

Characteristic	OR	95% CI	*P*-value
Age	1.060	1.024–1.097	0.001
Lack of physical activity	2.746	1.245–6.059	0.01
RHR			0.01
Lowest tertile	1.000	reference	
Medium tertile	1.451	0.415–5.066	0.56
Highest tertile	3.926	1.303–11.832	0.02

Abbreviations: see Figure 1 and Table 2

1536.11 [821.06–2649.88] vs. 1724.45 [941.90–2766.62] pg/ml, $P = 0.46$).

Partial rank correlation analyses and multiple linear regressions were performed to test these associations further when RHR was assessed as a continuous variable. After adjusting for age and sex, both plasma sLRP1 level and plasma sRAGE level were positively correlated with RHR ($r = 0.108$; $P = 0.001$; $r = 0.121$; $P < 0.001$, respectively) (Figure 3A–B), an additional adjustment in the multivariable analysis produced similar results (Figure 3C–D). As shown in Table 4, a multiple linear regression adjusted for age and sex revealed that RHR was positively associated with both log-transformed sLRP1 and log-transformed sRAGE (β = 0.004; 95% CI, 0.002–0.007; $P = 0.001$; β = 0.005; 95% CI, 0.002–0.007; $P < 0.001$, respectively). Furthermore, after adjusting for age, sex, BMI, blood pressure, fasting blood glucose, blood lipids, lifestyle, and medical history, RHR was still independently and positively associated with log-transformed sLRP1 and log-transformed sRAGE (β = 0.004; 95% CI, 0.002–0.006; $P = 0.002$; β = 0.005; 95% CI, 0.002–0.007; $P < 0.001$, respectively).

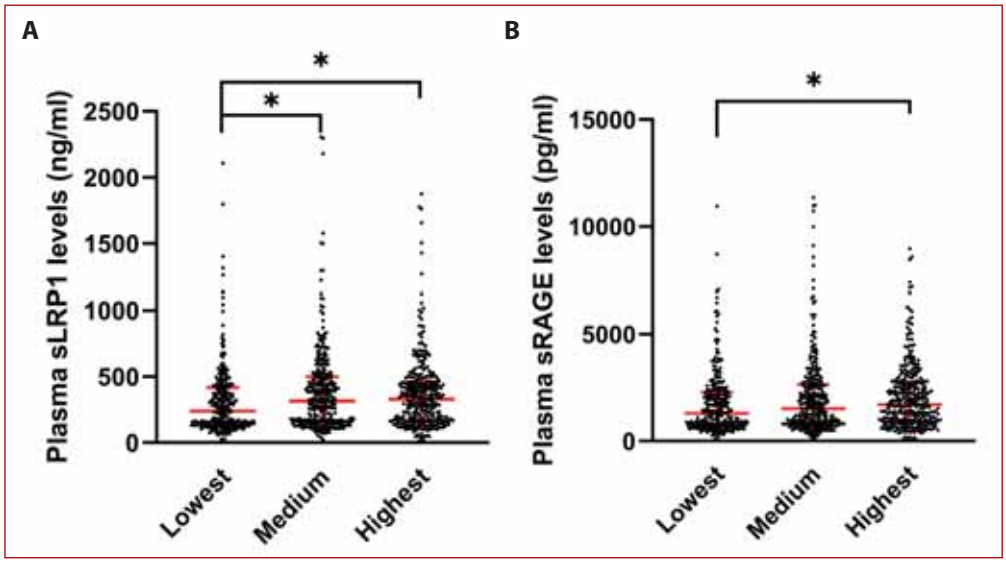

Figure 2. Comparison of plasma sLRP1 and sRAGE levels by RHR groups. Scatter plots for plasma sLRP1 levels (**A**) and sRAGE levels (**B**) in subjects with the lowest, medium, and highest RHR. The horizontal lines represent the median and interquartile range

Abbreviations: see Figure 1

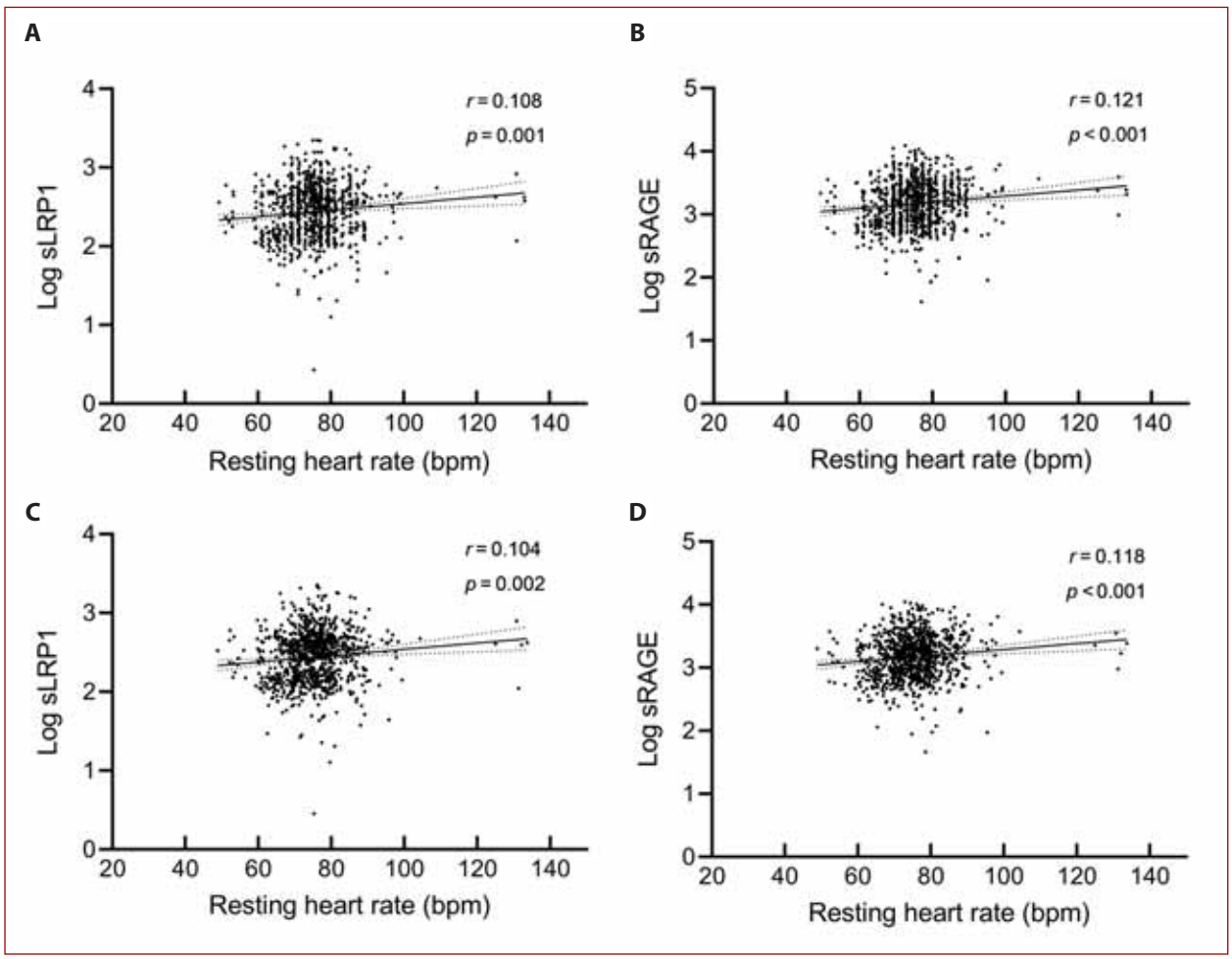

Figure 3. Partial correlations between plasma biomarkers and RHR. Partial correlations of RHR with plasma sLRP1 levels (**A, C**) and plasma sRAGE levels (**B, D**). Partial correlation coefficients and *p* values were obtained after the adjustment for age and sex (**A, B**), as well as for BMI, systolic blood pressure, diastolic blood pressure, log-transformed fasting blood glucose, log-transformed triglyceride level, total cholesterol level, HDL-C level, smoking, drinking, physical activity level, TIA or stroke, and CHD (**C, D**)

Abbreviations: see Figure 1 and Table 1

Table 4. Multiple linear regression models of RHR, *APOE* ε4 carrier status, log-transformed sLRP1, and log-transformed sRAGE in all 941 study participants

	Log sLRP1			Log sRAGE		
	β	95% CI	*P*-value	β	95% CI	*P*-value
Model 1						
RHR	0.004	0.002–0.007	0.001	0.005	0.002–0.007	<0.001
Model 1						
RHR	0.004	0.002–0.007	0.001	0.005	0.002–0.007	<0.001
APOE ε4 carrier status	–0.073	–0.130 to –0.016	0.01	–0.043	–0.103 to 0.016	0.15
Model 2						
RHR	0.004	0.002–0.006	0.002	0.005	0.002–0.007	<0.001
Model 2						
RHR	0.004	0.002–0.007	0.001	0.005	0.002–0.007	<0.001
APOE ε4 carrier status	–0.072	–0.130 to –0.015	0.01	–0.041	–0.102 to 0.019	0.18

β, unstandardized regression coefficient

Model 1: adjusted for age and sex

Model 2: adjusted for age, sex, BMI, systolic blood pressure, diastolic blood pressure, log-transformed fasting blood glucose, log-transformed triglyceride level, total cholesterol level, HDL-C level, smoking, drinking, physical activity level, TIA or stroke, and CHD

Abbreviations: see Figure 1, Table 1 and 2

Table 5. Comparison of demographic, clinical, and biological characteristics between *APOE* ε4 carriers and non-carriers

Characteristic	*APOE* ε4 non-carriers (n = 793)	*APOE* ε4 carriers (n = 148)	*P*-value
Age, years	54.7 (10.1)	54.7 (9.5)	0.98
Male, n (%)	328 (41.4)	51 (34.5)	0.12
Education, years	7 (4–9)	7 (5–8)	0.83
Hypertension, n (%)	311 (39.2)	58 (39.2)	1.00
Diabetes mellitus, n (%)	50 (6.3)	8 (5.4)	0.68
Dyslipidemia, n (%)	384 (48.4)	77 (52.0)	0.42
CHD, n (%)	27 (3.4)	3 (2.0)	0.61
TIA or stroke, n (%)	35 (4.4)	7 (4.7)	0.86
Active smoking, n (%)	243 (30.6)	35 (23.6)	0.09
Alcohol drinking, n (%)	123 (15.5)	20 (13.5)	0.53
Lack of physical activity, n (%)	126 (15.9)	20 (13.5)	0.46
BMI, kg/m^2	24.9 (3.1)	24.9 (3.0)	0.90
RHR, bpm	75.1 (8.3)	75.9 (9.7)	0.28
Systolic blood pressure, mm Hg	129.1 (16.9)	130.7 (18.8)	0.29
Diastolic blood pressure, mm Hg	80.6 (9.6)	80.9 (10.8)	0.68
Fasting blood glucose, mmol/l	5.35 (5.05–5.69)	5.35 (5.05–5.67)	0.75
Triglycerides, mmol/l	1.41 (1.01–1.97)	1.38 (1.06–1.89)	0.97
Total cholesterol, mmol/l	5.00 (0.96)	5.03 (0.99)	0.69
LDL-C, mmol/l	3.28 (0.91)	3.33 (0.87)	0.54
HDL-C, mmol/l	1.41 (0.31)	1.40 (0.31)	0.66
sLRP1, ng/ml	305.45 (158.16–465.50)	257.70 (131.96–425.99)	0.03
sRAGE, pg/mL	1605.71 (838.66–2607.51)	1351.97 (764.26–2435.87)	0.16

Data are shown as mean (standard deviation), median (interquartile range), or number (percentage)

Abbreviations: see Figure 1 and Table

Effect of APOE ε4 allele on RHR and plasma atherosclerosis biomarkers

The univariable analysis showed that plasma sLRP1 level (*APOE* ε4 non-carriers vs. *APOE* ε4 carriers, 305.45 [158.16–465.50] vs. 257.70 [131.96–425.99] ng/ml; $P = 0.03$) was significantly lower in *APOE* ε4 carriers than in non-carriers, but there were no significant intergroup differences in RHR (*APOE* ε4 non-carriers vs. *APOE* ε4 carriers, 75.1 [8.3] vs. 75.9 [9.7] bpm; $P = 0.28$) or plasma sRAGE level (*APOE* ε4 non-carriers vs. *APOE* ε4 carriers, 1605.71 [838.66–2607.51] vs. 1351.97 [764.26–2435.87] pg/ml; $P = 0.16$). The demographic, clinical, and other biological characteristics were similar between *APOE* ε4 carriers and non-carriers (Table 5).

Association between *APOE* ε4 allele and plasma atherosclerosis biomarkers

As shown in Table 4, when we included RHR and *APOE* ε4 carrier status simultaneously in every regression model, *APOE* ε4 carrier status was inversely associated with log-transformed plasma sLRP1 but not log-transformed plasma sRAGE. Meanwhile, the regression coefficients of

RHR were consistent with the previous results (Table 4). Furthermore, when the interaction term (RHR × *APOE* ε4 carrier status) was included in the multivariable linear regression models, it had a null effect in all models and the relationship between RHR, *APOE* ε4 carrier status, and log-transformed sLRP1 remained significant (data not shown).

DISCUSSION

This cross-sectional study demonstrated for the first time that RHR was positively associated with plasma sLRP1 and plasma sRAGE levels in rural Chinese adults aged 40 years and older. In addition, *APOE* ε4 carrier status was inversely associated with plasma sLRP1 level and did not modify the relationship between RHR and plasma sLRP1 level.

A large number of studies of healthy and asymptomatic subjects, as well as of patients with established CAD, demonstrated that RHR is a very important and major independent risk factor for cardiovascular morbidity and mortality [1]. Our results are in line with previous findings that demonstrated individuals with RHR of at least 78 bpm had nearly four times higher odds of developing CHD than those with the lowest RHR (≤71 bpm). Clinical observations and experimental evidence revealed that an elevated RHR enhances mechanical arterial wall stress and prolongs the exposure of the coronary endothelium to systolic low and oscillatory shear stress. Therefore, it can induce structural and functional changes in the endothelial cells that accumulate over time in atherosclerosis-prone regions, promoting atherosclerosis [15].

LRP1 is postulated to participate in numerous diverse physiological and pathological processes including vascular remodeling, foam cell biology, inflammation, and atherosclerosis [2]. Circulating sLRP1 levels indicate the presence of atherosclerosis-related conditions that lead to coronary events during follow-up [6]. De Gonzalo-Calvo et al. [5] found that patients with severe hypercholesterolemia had significantly higher sLRP1 concentrations than those with moderate hypercholesterolemia and normocholesterolemic controls, and sLRP1 levels were increased in the conditioned medium of coronary atherosclerotic plaque areas extracted from patients versus non-atherosclerotic areas of the same coronary arteries and patients. Furthermore, Chen et al. [16] demonstrated that sLRP1 was a novel biomarker for P_2Y_{12} receptor expression, which could aggravate atherosclerosis in atherosclerotic plaques. Thus, sLRP1 has been implicated as a novel biomarker for atherosclerosis [5]. The present study found that plasma concentrations of sLRP1 were significantly higher in the highest RHR group than in the medium and lowest RHR groups. Moreover, in partial rank correlation and multiple linear regression analyses, RHR was positively associated with log-transformed plasma sLRP1. All of these results strongly suggest that an elevated RHR was associated with increased plasma sLRP1 levels. Although the mechanism of how RHR affects plasma sLRP1 levels is unclear, many studies have shown that inflammation plays an important role in sLRP1 generation in plasma. In fact, sLRP1 is released when exposed to proinflammatory mediators and may promote inflammation by affecting macrophage physiology and activating microglia or other cells [4, 17]. Therefore, even though we did not measure inflammation biomarkers, it is possible to speculate that an elevated RHR stimulates plasma sLRP1 by increasing inflammation (Supplementary material, *Figure S1*). Moreover, an increased RHR reduces coronary perfusion and oxygen supply; this hypoxic condition upregulates LRP1 expression [18], thereby increasing plasma sLRP1 levels.

Mounting evidence strongly implicates the importance of RAGE in the initiation and progression of vascular atherosclerotic disease [7]. It is known that sRAGE acts as a decoy for RAGE ligands by sequestering RAGE ligands or competing with full RAGE for ligand binding and thus have cytoprotective effects against advanced glycation end products (AGEs)-RAGE interactions. Theoretically, low levels of sRAGE are markers of disease states. In a study of 2571 non-diabetic patients, Lindsey et al. [19] demonstrated using computed tomography that calcification in the coronary arteries is inversely related to plasma sRAGE levels, and similar results were obtained by Falcone et al. [20] in a study on 328 non-diabetic patients, in whom low sRAGE plasma levels were independently associated with the presence of CAD. However, several investigators reported contradictory findings that plasma levels of sRAGE were higher in patients with CAD and type 1 or type 2 diabetes [21, 22]. Moreover, sRAGE is directly positively associated with the extent of CAD, and elevated sRAGE is linked to a high risk of recurrent coronary events [8]. Circulating levels may be associated with both RAGE expression and proteolytic cleavage of RAGE mediated by matrix metalloproteinases (MMPs) and possibly other factors [23]. An elevated RHR could induce oxidative stress and thereby increase AGE production and accumulation [24]. Since AGEs upregulate both RAGE and MMP expression and production in various tissues [23], it is possible that elevated sRAGE levels in patients with a higher RHR may be due to a marked increase in serum AGE levels, which, in turn, would increase RAGE and MMPs. On the other hand, sRAGE levels might be elevated in higher RHR participants as a compensatory mechanism for increased AGE production. Moreover, the elevated RHR increases systemic inflammation [25], thereby stimulating MMP expression through AP-1 and nuclear factor-kappa beta activation [26], which would increase the cleavage of sRAGE from the cell surface. Conversely, it is also possible that the progression of atherosclerotic lesions in the coronary arteries may aggravate the release of atherosclerosis biomarkers [5], thereby increasing circulating sLRP1 and sRAGE concentrations (Supplementary material, *Figure S1*).

An interesting question arising from the present results is why *APOE* ε4 carrier status was associated with plasma sLRP1 levels rather than plasma sRAGE levels. The *APOE* ε4 allele impacts lipid and lipoprotein levels [10]. Studies of normolipidemic populations demonstrated an association

of *APOE* ε4 with increased total and low-density lipoprotein cholesterol levels, as well as increased apoB expression [10]. Although underlying mechanisms responsible for this phenomenon are less clear, LDL receptor family downregulation is perhaps the most commonly accepted explanation [27]. Such LDL receptor family downregulation in *APOE* ε4 carriers would thereby decrease their LRP1 levels and be associated with decreased sLRP1 level. In contrast, sRAGE changes in *APOE* ε4 carrier status are more complicated. Deo et al. [28] recently reported that sRAGE level was significantly (21%) higher in *APOE* ε4 carriers than in non-carriers while other researchers found a contrasting pattern for sRAGE, namely lower levels among *APOE* ε4 carriers than non-carriers [29]. Our study demonstrated no significant difference in plasma sRAGE levels between *APOE* ε4 carriers and non-carriers; this relationship remained nonsignificant after the adjustment for potential confounders. We speculate that this discrepancy might be due to the differences in characteristics of the study populations, which may have influenced the AGE-RAGE profile and the impact of *APOE* ε4.

Limitations

Our study has some limitations. First, only 30 patients with coronary heart disease met our inclusion and exclusion criteria; the small sample size would reduce the reliability of the conclusions. Second, many factors, such as congestive heart failure and hyperthyroidism, may affect RHR. Since we did not perform tests for brain natriuretic peptide (BNP), echocardiography, and thyroid function test, we cannot rule out that an elevated heart rate was a sign of mild heart failure or hyperthyroidism. Third, as heart rate is susceptible to different influencing factors [30], multiple recordings collected at shorter intervals could have shown a longitudinal course of RHR and may have increased its association with plasma atherosclerosis biomarkers. Fourth, although both sLRP1 and sRAGE participate in the pathogenesis of atherosclerosis, they do not fully reflect the extent of coronary atherosclerosis. Finally, although plasma atherosclerosis biomarkers were measured with RHR, they were measured only once, and pro-inflammatory mediators were not detected simultaneously. Therefore, our results need to be validated in additional longitudinal cohort studies.

CONCLUSIONS

In conclusion, we reported for the first time that RHR is positively associated with plasma levels of sLRP1 and sRAGE, which is not modified by *APOE* genotype. Since plasma sLRP1 and sRAGE levels are indicative of atherosclerosis, our findings suggest a potential link between RHR and the progression of coronary atherosclerosis, which may partially explain why the risk of CHD is associated with an increased RHR. Moreover, RHR monitoring may have clinical utility for identifying patients who are at risk of or in the early stages of CHD.

Article information

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Prognostic value of computed tomography derived measurements of pulmonary artery diameter for long-term outcomes after transcatheter aortic valve replacement

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ABSTRACT

Background: An increase in pulmonary artery diameter (PAD) on multi-detector computed tomography (MDCT) may indicate pulmonary hypertension. We assessed the prognostic value of MDCT-derived measurements of PAD on outcomes after successful transcatheter aortic valve replacement (TAVR).

Methods: Consecutive patients treated with TAVR from February 2013 to October 2017, with a 68.8% rate of new generation valves, underwent pre-interventional MDCT with measurements of PAD (in the widest short-axis within 3 cm of the bifurcation) and ascending aortic diameter (AoD; at the level of the PAD). The PAD/AoD ratio was calculated. Patients with high-density lipoprotein cholesterol levels ≤46 mg/dl and C-reactive protein levels ≥0.20 mg/dl at baseline were identified as the frail group. One-year mortality was established for all subjects.

Results: Among studied 266 patients (median age, 82.0 years; 63.5% women) those who died at 1 year (n = 34; 12.8%) had larger PAD and PAD/AoD (28.9 [5.0] vs. 26.5 [4.6] mm and 0.81 [0.13] vs. 0.76 [0.13] mm vs. the rest of the studied subjects; $P = 0.005$ and $P = 0.02$, respectively) but similar AoD. The cutoff value for the PAD to predict 1-year mortality was 29.3 mm (sensitivity, 50%; specificity, 77%; area under the curve, 0.65). Patients with PAD >29.3 mm (n = 72; 27%) had higher 1-year mortality (23.6% vs. 8.8%, log-rank $P = 0.001$). Baseline characteristics associated with PAD >29.3 mm were a bigger body mass index, more frequent diabetes mellitus, more prior stroke/transient ischemic attacks and atrial fibrillation, and lower baseline maximal aortic valve gradient with higher pulmonary artery systolic pressure (PASP). PAD >29.3 mm and frailty, but not baseline PASP, remained predictive of 1-year mortality in the multivariable model (hazard ratio [HR], 2.221; 95% CI, 1.038–4.753; $P = 0.04$ and HR, 2.801; 95% CI, 1.328–5.910; $P = 0.007$, respectively).

Conclusion: PAD >29.3 mm on baseline MDCT is associated with higher 1-year mortality after TAVR, independently of echocardiographic measures of PH and frailty.

Key words: TAVR, pulmonary hypertension, pulmonary artery diameter

WHAT'S NEW?

Pulmonary hypertension (PH) is common (75%) among patients undergoing transcatheter aortic valve replacement (TAVR) and is routinely diagnosed using echocardiography through pulmonary artery systolic pressure measurement (PASP). An increase in pulmonary artery diameter (PAD) on multi-detector computed tomography (MDCT) may indicate PH. We found that systolic PAD >29.3 mm measured at baseline angio-MDCT was associated with increased 1-year mortality after successful TAVR, whereas baseline PASP was not.

INTRODUCTION

In patients undergoing transcatheter aortic valve replacement (TAVR) for severe aortic stenosis (AS), pulmonary hypertension (PH) has a prevalence of up to 75% [1]. Transthoracic echocardiography (TTE) is recommended for measuring pulmonary artery systolic pressure (PASP) [2].

Multi-detector computed tomography (MDCT) provides very accurate structural images of the heart and enables repeatable measurements. Therefore, MDCT is the imaging method of choice used for planning TAVR procedures. An increase in pulmonary artery diameter (PAD) noticeable on MDCT is one of the characteristic features of PH [3]. However, the translation of MDCT data into clinical consequences through long-term prognosis after successful TAVR remains not entirely clear and documented, particularly whether this is an additive/independent prognostic marker to the measure of frailty and baseline aortic valve (AV) calcification [4, 5].

This study aimed to evaluate the value of PAD measurements obtained from MDCT in predicting outcomes after successful TAVR.

METHODS

From the hospital database at the National Institute of Cardiology in Warsaw, Poland, we identified 294 patients who underwent successful TAVR (according to Valve Academic Research Consortium: VARC-2 criteria) for severe AS from February 2013 to October 2017. All patients were Heart-Team qualified, the study complied with the Declaration of Helsinki; all signed informed consent, and the study was approved by the local ethics committee. Indications for the TAVR procedure were determined on the basis of the consensus of the multidisciplinary cardiac team. Data regarding baseline clinical characteristics and baseline and post-procedural echocardiographic measurements were prospectively gathered within the confines of the Polish Registry of Transcatheter Aortic Valve Implantation (POL-TAVI). Notably, dyslipidemia was defined as its previous history or current statin/fibrate treatment, whereas chronic renal disease was its previous diagnosis. At baseline, the measurements obtained using 2-dimensional TTE (Vivid S5/E95, General Electric, Boston, MA, US) included left ventricular ejection fraction (LVEF), maximal and mean aortic valve (AV) gradient, AV area, and PASP (using the maximal tricuspid regurgitation velocity and the estimated right atrial pressure). Patients with baseline PASP >36 mm Hg [6, 7] were considered to have PH. Post-procedural TTE evaluation included maximal AV gradient and grade of paravalvular leak (PVL) [8].

All patients underwent ECG-gated angio-MDCT (384-row SOMATOM® Definition Flash, Dual Source, SIEMENS, Forchheim, Germany) before TAVR for evaluation of (1) AV anatomy (tricuspid vs. bicuspid valve category and no/mild vs. moderate/heavy valve leaflet Rosenhek score calcification) [9]; (2) annulus dimension and calcification [5] (no/mild vs. moderate/severe); and (3) vascular access.

Twenty-eight patients (9.5%) were excluded from the current study because: (1) their MDCT images could not be found or were of poor quality (e.g. obtained without ECG gating, or with technical errors in acquisition); or (2) had missing information regarding baseline characteristics or follow-up.

In an off-line fashion using systolic image reconstructions with syngo.via (Siemens Healthcare GmbH, Erlangen Germany), a single experienced observer (blinded to the clinical data) measured PAD in the widest short-axis within 3 cm of the bifurcation and ascending aortic diameter (AoD) measured at the level of the PAD; the ratio of PAD/AoD was calculated. To assess interobserver variability, another experienced observer examined 25 randomly selected datasets that were also measured again by the first observer for the intraobserver variability >6 months after initial evaluation.

We chose baseline high-density lipoprotein cholesterol (HDL-C) and C-reactive protein (CRP) levels as valid measures of patient frailty; both were measured with the Cobas C 311 automated chemistry analyzer (Roche Diagnostics, Indianapolis, IN, US) and categorized accordingly for low HDL-C (≤46 mg/dl) and high CRP (≥0.20 mg/dl) [4].

The primary endpoint was all-cause death at 1-year after TAVR. Secondary endpoints were in-hospital outcomes collected in accordance with VARC-2. Survival status and date of death were obtained from both the National Registry of Population and the Valve Polyclinic.

The TAVR procedure was performed [10] with either a self-expandable supra-annular device — early generation CoreValve or newer generation Evolut-R/-Pro (CoreValve ReValving Technology, Medtronic, Inc., Minneapolis, MN, US); Acurate neo (Boston Scientific Corporation, Maple Grove, MN, US); or Engager (Medtronic, Inc., Minneapolis, MN, US); a balloon expandable early generation Edwards SAPIEN or newer generation SAPIEN XT/3 (Edwards Lifesciences, Irvine, CA, US); or new generation self-deployed

intra-annular Lotus Edge Aortic Valve System (Boston Scientific Corporation) [11]. TAVR procedural characteristics were prospectively collected.

Statistical analysis

Categorical data were compared with the χ^2 or Fisher exact tests. Normally distributed variables were compared using Student t-test and presented as the mean (standard deviation [SD]). The Mann-Whitney test was used for comparisons of variables with non-normal distributions, presented as the median and interquartile range (IQR). Interand intraobserver variability in PAD and AoD measurements were assessed with calculated respective intraclass correlation coefficients. Simple relationships between the relevant parameters were analyzed with bivariate correlation computing Spearman rho (*r*). The 1-year mortality predictive performance of PAD and PAD/AoD were analyzed separately using receiver operating characteristic curve (ROC) analysis. The maximum value of the Youden Index was used for cutoff point selection with the highest predictive performance, and respective areas under the ROC curve (AUC) were measured. Survival rates were assessed using Kaplan-Meier analysis and compared with the log-rank test. The 1-year all cause-mortality predictors were identified using Cox regression (100% of studied subjects accomplished 1-year follow-up). All baseline clinical variables with *P*-value <0.1 in the univariate analysis were entered in the multivariable model. *P*-value <0.05 was considered significant. Statistical analysis was performed using the PASW Statistics 18 (IBM Corporation, Armonk, NY, US).

RESULTS

The study included 266 patients treated with successful TAVR for *de novo* AS from February 2013 to October 2017. Median (IQR) patient age was 82.0 (78.0–85.3) years, the majority were female (n = 164; 61.7%), and most had surgical high-risk (n = 169; 63.5%) according to EuroSCORE I/II. The VARC-2 combined safety endpoint was recognized in 64 (24.1%) patients, with 30-day and 1-year mortality rates of 3.4% (n = 9) and 12.8% (n = 34), respectively.

Overall, mean PAD and mean AoD were 26.8 (4.7) mm and 35.1 (4.3) mm, respectively, with a mean PAD/AoD ratio of 0.76 (0.13). High interobserver and intraobserver agreement in PAD and AoD measurements was documented (Supplementary material, *Table S1*). Patients who died at 1 year had larger mean PAD and mean PAD/AoD compared with the survivors (28.9 [5.0] mm vs. 26.5 [4.6] mm and 0.81 [0.13] vs. 0.76 [0.13]; *P* = 0.005 and *P* = 0.02 respectively), but similar mean AoD (35.7 [4.3] vs. 35.2 [4.3] mm; *P* = 0.60). The optimal cutoff values for PAD and the PAD/AoD ratio to predict 1-year mortality were 29.3 mm (sensitivity, 50%; specificity, 77%; AUC, 0.65; 95% confidence interval [CI], 0.58–0.70) and 0.74 (sensitivity, 79.4%; specificity, 46.1%; AUC, 0.62; 95% CI, 0.56–0.68).

Patients with PAD >29.3 mm had higher body mass index (BMI), tended to have diabetes mellitus (DM) more frequently, and had substantially more prior stroke/transient ischemic attacks (TIA) (Table 1). Overall, at baseline there were 18.0% (n = 48) of subjects with low HDL-C and concomitant high CRP, indicating a frail patient population with similar distribution between the studied groups of patients with PAD >29.3 mm vs. PAD ≤29.3 mm (Table 1). Overall, median PASP was 40.5 (30.0–51.0) mm Hg and weakly correlated with a larger PAD (r = 0.290 and *P* <0.001). Patients with PAD >29.3 mm had higher PASP and had a more frequent tendency for PH (PASP >36 mm Hg; Table 1).

Landing zone calcification in the annulus region and AV leaflets was similar between patients with PAD ≤29.3 mm vs. PAD >29.3 mm (Table 2). Subjects with PAD >29.3 mm were treated with valves with larger nominal diameters (Table 3). On the other hand, intra-annular (balloon or mechanically expanded) valves were deployed more often among patients with severe annular calcification/heavily calcified AV leaflets (54.7% vs. 43.1% in other subjects, *P* = 0.04, respectively). These were used with similar frequency between patients with PAD ≤29.3 mm vs. PAD >29.3 mm (50.0% vs. 47.2%, respectively; *P* = 0.78).

In-hospital outcomes were alike in patients with PAD ≤29.3 mm vs. PAD >29.3 mm (Table 4). The PAD >29.3 mm group (n = 72; 27%) had higher 1-year mortality than other patients (23.6% vs. 8.8%, log-rank *P* = 0.001; Figure 1). Patients who died within 1-year were older and frailer; they suffered from more prior stroke/TIA, chronic obstructive pulmonary disease, and atrial fibrillation (AF). They had lower baseline maximal AV gradient and higher PASP and PAD/AoD but similar frequency of severe annular calcification or heavily calcified AV leaflets (Supplementary material, *Table S2*).

After adjustment for baseline clinical, echocardiographic, and angio-MDCT parameters, baseline PAD >29.3 mm was associated with increased mortality after first year (HR, 2.221; 95% CI, 1.038–4.753; *P* = 0.04) independently of other risk factors (presence of low HDL-C and high CRP) (Table 5).

DISCUSSION

The main findings of our study are as follows: (1) Apart from the detailed insight into the aortic root anatomy crucial for sizing and valve type selection, baseline angio-MDCT done before the procedure provided additional information about the long-term prognosis after successful TAVR derived from a simple and quick measure of the maximal absolute systolic PAD; (2) The optimal cutoff value of maximal PAD to predict 1-year mortality found in our study (29.3 mm) is consistent with the current guidelines on diagnosis and treatment of PH, indicating that MDCT may raise a suspicion of PH by showing an increased PA diameter of ≥29 mm [2]; (3) However, almost 45% of our patients with PAD >29.3 mm had corresponding PASP that was within normal limits (≤36 mm Hg), with MDCT-derived PAD and Doppler-measured PASP having only a weak correlation, and increased baseline PASP not providing independent

Table 1. Comparison of baseline demographic clinical characteristics and echocardiographic parameters (preand post-TAVR) between the studied groups

	All patients (n = 266, 100%)	Patients with PAD ≤29.3 mm (n = 194, 72.9%)	Patients with PAD >29.3 mm (n = 72, 27.1%)	*P*-value
Baseline demographic and clinical characteristics				
Surgical high-risk[a], n (%)	169 (63.5)	119 (61.3)	50 (69.4)	0.25
Age, years, median (IQR)	82.0 (23.9–85.3)	82.0 (78.0–85.3)	82.0 (78.3–85.6)	0.95
Female, n (%)	164 (61.7)	117 (60.3)	47 (65.3)	0.48
BMI, kg/m^2, median (IQR)	26.9 (23.9–30.0)	26.1 (23.4–29.4)	27.9 (25.9–32.0)	0.001
Diabetes mellitus, n (%)	99 (37.2)	66 (34.0)	33 (45.8)	0.09
Hypertension, n (%)	207 (77.8)	153 (78.9)	54 (75.0)	0.51
Dyslipidemia, n (%)	228 (85.7)	169 (87.1)	59 (81.9)	0.32
Chronic renal disease, n (%)	98 (36.8)	68 (35.1)	30 (41.7)	0.32
Previous stroke/TIA, n (%)	36 (13.5)	20 (10.3)	16 (22.2)	0.02
Peripheral vascular disease, n (%)	39 (14.7)	24 (12.4)	15 (20.8)	0.12
Chronic obstructive lung disease, n (%)	28 (10.5)	17 (8.8)	11 (15.3)	0.18
Previous cardiac surgery, n (%)	53 (19.9)	40 (20.6)	13 (18.1)	0.73
Previous percutaneous coronary intervention, n (%)	82 (30.8)	62 (32.0)	20 (27.8)	0.55
Previous myocardial infarction, n (%)	62 (23.3)	47 (24.2)	15 (20.8)	0.63
Atrial fibrillation, n (%)	73 (27.4)	48 (18.0)	25 (34.7)	0.12
Pacemaker implanted, n (%)	40 (15.0)	28 (14.4)	12 (16.7)	0.70
HDL-C, mg/dl, mean (SD)	52.9 (21.6)	53.1 (22.3)	52.5 (19.8)	0.84
CRP, mg/dl, median (IQR)	0.20 (0.10–0.46)	0.18 (0.09–0.45)	0.28 (0.10–0.54)	0.18
Low HDL-C and high CRP[b], mean (SD)	52 (19.5)	35 (18.2)	17 (23.1)	0.47
Echocardiographic parameters (baseline and post-TAVR)				
Baseline LVEF, %, median (IQR)	57.0 (41.0–73.0)	59.0 (41.0–75.0)	53.0 (38.8–67.8)	0.048
Baseline LVEF <50%, n (%)	53 (19.9)	36 (18.6)	17 (23.6)	0.39
Baseline maximal AV gradient, mm Hg, median (IQR)	80.0 (65.4–92.9)	82.0 (68.0–95.0)	75.5 (59.8–89.2)	0.06
Baseline mean AV gradient, mm Hg, median (IQR)	49.0 (40.0–60.0)	49.4 (40.4–60.0)	48.0 (38.1–61.0)	0.46
Bicuspid aortic valve, n (%)	37 (13.0)	30 (15.5)	7 (9.7)	0.32
Baseline AV area, cm^2, median (IQR)	0.70 (0.50–0.80)	0.70 (0.50–0.82)	0.60 (0.50–0.79)	0.11
PASP, mm Hg, median (IQR)	40.5 (30.0–51.0)	39.0 (30.0–50.0)	45.5 (30.3–59.8)	0.02
PASP >36 mm Hg, n (%)	148 (55.6)	101 (52.1)	47 (65.3)	0.07
Post-TAVR maximal AV gradient, mm Hg, median (IQR)	15.0 (11.0–20.0)	15.0 (11.0–20.0)	16.0 (10.6–19.8)	0.89
Mild paravalvular leak, n (%)	63 (23.7)	43 (22.2)	21 (29.2)	0.26

[a]Logistic EuroSCORE I ≥10% or EuroSCORE II ≥4. [b]HDL-C ≤46 mg/dl and CRP ≥0.20 mg/dl

Abbreviations: AV, aortic valve; BMI, body mass index; CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LVEF, left ventricular ejection fraction; PAD, pulmonary artery diameter; PASP, pulmonary artery systolic pressure; TAVR, transcatheter aortic valve replacement; TIA, transient ischemic attack

Table 2. Comparison of relevant baseline angio-MDCT measurements between the studied groups

Procedural characteristics	All patients (n = 266, 100%)	Patients with PAD ≤29.3 mm (n = 194, 72.9%)	Patients with PAD >29.3 mm (n = 76, 27.1%)	*P*-value
PAD, mm, mean (SD)	26.8 (4.7)	24.6 (3.0)	32.7 (3.2)	<0.001
AoD, mm, mean (SD)	35.3 (4.3)	34.6 (4.3)	37.2 (3.6)	<0.001
PAD/AoD index, mean (SD)	0.76 (0.13)	0.72 (0.11)	0.89 (0.11)	<0.001
Moderate/severe annular calcification, n (%)	60 (22.9)	45 (23.7)	15 (20.8)	0.74

[a]Rosenhek score = 3 or 4

Abbreviations: AoD, ascending aortic diameter; SD, standard deviation; other — see Table 1

prognostic information; (5) At the same time, baseline PAD >29.3 mm accompanied by a joint presence of more frequent AF, more AF-related cerebrovascular events, and lower maximal AV gradient and LVEF at baseline, appeared to be novel and clinically useful markers of a more advanced stage of LV deterioration (5). PAD >29.3 mm proved to offer prognostic information that was independent of that obtainable with frailty assessment.

Mean PAD measured in TTE among patients with PH (diagnosed upon invasive measure of mean pulmonary artery pressure [mPAP]), with measured in TTE mean PASP of 52 mm Hg, was 28.0 mm. This is in line with the current PAD cutoff point of 29.3 mm and corresponding PASP of 45 mm Hg [12]. The cutoff value of MDCT-measured PAD to identify PH (diagnosed with right heart catheterization) reported in previous studies ranges from 25 to 33.2 mm

Table 3. Comparison of procedural characteristics between the studied groups

Procedural characteristics	All patients (n = 266, 100%)	Patients with PAD ≤29.3 mm (n = 194, 72.9%)	Patients with PAD >29.3 mm (n = 76, 27.1%)	*P*-value
Transfemoral access, n (%)	218 (82.0)	156 (80.4)	62 (86.1)	0.53
Subclavian access, n (%)	16 (6.0)	13 (6.7)	3 (4.2)	0.53
Nominal valve diameter, mm, median (IQR)	26.0 (26.0–29.0)	26.0 (26.0–29.0)	29.0 (26.0–29.0)	0.005
Self-expanded supra-annular valve, n (%)	137 (51.5)	97 (50.0)	40 (52.8)	0.78
Newer valve generations, n (%)	183 (68.8)	134 (69.1)	49 (68.1)	0.88
Post-dilatation, n (%)	67 (25.2)	48 (24.7)	19 (26.4)	0.87
Contrast agent volume (ml), median (IQR)	200 (150–200)	200 (150–200)	200 (150–200)	0.24
Fluoroscopy time, min, median (IQR)	28.3 (21.1–38.0)	28.2 (21.0–37.1)	28.7 (21.9–40.4)	0.23
Radiation, mGy, median (IQR)	1269 (783–2181)	1229 (709–2118)	1537 (936–2476)	0.04

Abbreviations: see Table 1

Table 4. Comparison of in-hospital events between the studied groups

VARC-2 endpoints	All patients (n = 266, 100%)	Patients with PAD ≤29.3 mm (n = 194, 72.9%)	Patients with PAD >29.3 mm (n = 76, 27.1%)	*P*-value
Life-threatening/disabling bleeding, n (%)	16 (6.0)	12 (6.2)	4 (5.6)	1.0
Major bleeding, n (%)	43 (16.2)	32 (16.6)	11 (15.3)	1.0
Any red blood cell transfusion, n (%)	88 (33.1)	67 (34.5)	21 (29.2)	0.46
Major vascular complications, n (%)	44 (16.5)	32 (16.5)	12 (16.7)	1.0
Myocardial infarction but without coronary artery obstruction requiring intervention, n (%)	1 (0.4)	1 (0.5)	0 (0)	1.0
Stroke, n (%)	5 (1.9)	3 (1.5)	2 (2.8)	0.61
New permanent pacemaker, n (%)	33 (12.4)	22 (11.3)	11 (15.3)	0.41
In-hospital mortality, n (%)	9 (3.4)	5 (2.6)	4 (5.6)	0.26
VARC-2 combined endpoint, n (%)	54 (20.3)	45 (23.2)	19 (26.4)	0.63
1-year all-cause mortality, n (%)	34 (12.8)	17 (8.8)	17 (23.6)	0.003

Abbreviations: VARC, Valve Academic Research Consortium; other — see Table 1

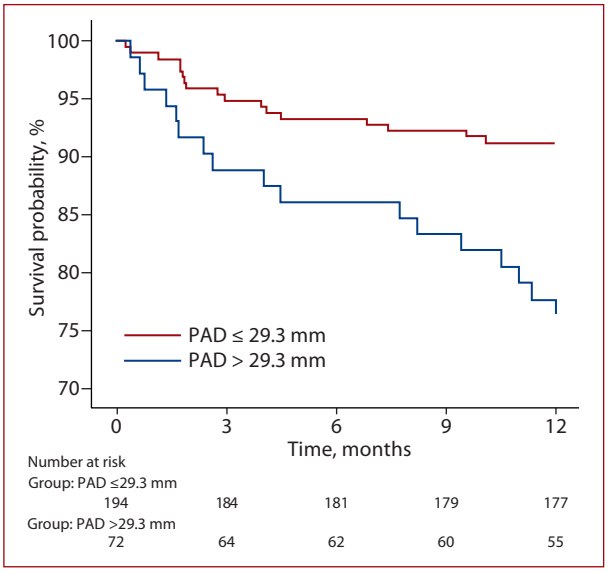

Figure 1. Subsequent mortality rates within 1-year after successful transcatheter aortic valve replacement were higher among subjects with pulmonary artery diameter ≥29.3 mm (log-rank $P = 0.001$), with median (interquartile range) 2.8 (1.7–7.8) months follow-up of those who died

Abbreviations: see Table 1

[13], and its corresponding correlation with mPAP ranged from r = 0.301 to r = 0.83 and it did not increase with larger PAD dimensions. Consistently, in our study, PAD correlated only weakly with PASP (r = 0.290). At least a 17% misdiagnosis rate (false positive) was also reported in the above studies. In our analysis, almost 45% of patients with PAD >29.3 mm had PASP ≤36 mm Hg (normal limit). Thus, an invasive measure of mPAP >25 mg was found in 75% of patients undergoing TAVR, with 82% of these having LV end-diastolic pressure (LVEDP) of >15 mm Hg [14], indicating postcapillary PH (a result of an increase in pulmonary venous pressure). On the other hand, a precapillary component of PH due to pulmonary vascular remodeling (identified with LVEDP ≤15 mm Hg or calculated diastolic PAP minus LVEDP of ≥7 mm Hg) was found in 32.3% of patients, which corresponds to the current 27.1% frequency of PAD >29.3 mm. Successful TAVR procedures lead immediately to a substantial decrease in mPAP. When compared with no PH, higher 1-year mortality rates were observed only among those with the precapillary element of PH. Hazard ratios of the precapillary and combined PH (joint presence of pre and postcapillary components) associated with increased subsequent mortality are similar to those

Table 5. Predictors of all-cause 1-year mortality

	Univariate		Multivariable	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age, years	1.061 (1.000–1.126)	0.05	1.049 (0.983–1.119)	0.15
Previous stroke/TIA history	2.463 (1.149–5.277)	0.02	2.130 (0.922–4.921)	0.08
Chronic obstructive lung disease	2.188 (0.953–5.026)	0.06	2.397 (0.879–6.536)	0.09
Atrial fibrillation	2.838 (1.449–5.561)	0.002	1.706 (0.793–3.670)	0.17
Baseline maximal AV gradient	0.976 (0.952–1.000)	0.046	0.991 (0.977–1.004)	0.17
PASP >36 mm Hg	2.007 (0.960–4.198)	0.06	1.704 (0.729–3.981)	0.21
PAD >29.3 mm	2.879 (1.470–5.641)	0.002	2.221 (1.038–4.753)	0.04
Low HDL-C and high CRP[a]	3.183 (1.519–6.667)	0.002	2.801 (1.328–5.910)	0.007

The multivariable model included all baseline clinical variables with *P*-value <0.1 in the univariate analysis

[a]HDL-C ≤46 mg/dl and CRP ≥0.20 mg/dl

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

found by us for PAD >29.3 mm (2.3 in precapillary and 3.15 in combined PH vs. the current 2.8, respectively). Thus, if PAD >29.3 mm is to reflect PH, it appears to indicate the presence of its precapillary component.

Baseline MDCT systolic PAD evaluation before TAVR is a noninvasive and simple measure with currently shown high inter and intraobserver accuracy, whereas invasive diagnosis is subjected to temporal changes in the relevant parameters (e.g. falsely normal LVEDP measure due to diuretics) that are crucial to specify a particular PH category to get the accurate prognostic information. Whereas mean AoD was similar, overall mean PAD in our study was substantially smaller than that measured among 707 consecutive patients treated with TAVR in Bonn (35.3 mm vs. 3.49 cm and 26.8 mm vs. 3.10 cm, respectively) [3]. However, the German authors did not perform inter- and intraobserver variability analyses. Importantly, our results of MDCT measurements of AoD and PAD, as well as the increased long-term mortality hazard ratios, are all in line with the recent large-scale study (n = 895) [15], which documented that patients with PAD ≥29.0 mm (41.2%) had 2.21 higher risk of 2-year mortality (95% CI, 1.44–3.39; *P* <0.001). Interestingly, in the above study absolute difference in average PASP between patients with PAD <29.0 vs. ≥29.0 mm was only 5 mm Hg (32 mm Hg vs. 37 mm Hg; *P* <0.001, respectively). Also, patients with PAD reduction on serial computed tomography (CT) studies compared to the no-reduction group had much better long-term survival (1.7% vs. 30.7%; *P* = 0.002 respectively).

The worse prognosis for patients with baseline PAD >29.3 mm observed currently after successful TAVR might be attributed to the natural course of the more frequent concomitant presence of DM with higher BMI and a trend toward twice more frequent chronic obstructive pulmonary disease, which is also in line with other observations among patients with dilated PAD or elevated pulmonary artery (PA) pressure [14, 15]. The above comorbidities are consistently associated with higher subsequent mortality despite successful TAVR and contribute also specifically to the progression of PH, thus their intensive treatment may also reduce severity of PH [16, 17]. At the same time, DM was shown to be associated with poor LV mass regression even after successful TAVR. Current results are in line with the prior observations linking dilatated PAD with features of more advanced and complex baseline LV dysfunction (abnormal myocardial structure with diastolic and systolic impairment) as signified by more frequent and longer AF history (more stroke/TIA complications) [18] and lower LVEF and baseline AV gradients. This further supports our hypothesis that the mechanism of worse prognosis of patients with PAD >29.3 mm is associated also with less LV recovery despite the successful AV replacement [19].

AoD indexed to body surface area (BSA; a measure of body size) appears a more patient-specific predictor of the risk of serious events than uncorrected AoD [19]. However, moderate or higher risk of subsequent events (≥8%/year) was seen with AoD <55.0 mm only among a few female subjects with height <150 cm. Further, there were a few male subjects with AoD >55.0 mm considered to be low-risk (~1%/year), with height ≥185 cm [20]. Indexing AoD for height was of similar predictive power compared to BSA [21].In our study, there was a weak correlation with BSA and PAD and with BSA and AoD ($r = 0.180$; $P = 0.003$ and $r = 0.224$; $P <0.001$, respectively), along with a weak correlation with PAD and AoD and none with BSA and PAD/AoD ($r = 0.316$ and $P <0.001$ and $r = 0.006$; $P = 0.927$, respectively). Similar results were obtained for BMI (estimate of total body fat). AoD in our study was significantly larger among patients with PAD >29.3 mm, but along with substantially bigger PAD/AoD index, indicating that the current increase in PAD is not just a simple measure of a larger dimension of the vessel parallel to bigger body size. Indexing PAD for height/BSA will not allow identification of patients with absolute PAD ≤29.3 mm but with increased risk of subsequent death. At the same time, it will not change the high-risk category of those with PAD >29.3 and bigger BSA/height.

Study limitations

This was a retrospective observational analysis subjected to the patient selection bias. The study is of a small scale with only a 1-year follow-up. PAD were measured on 2-dimensional axial images instead of 3-dimensional reconstructed images. We lacked data on the prior pulmonary embolism which might impact PAD and subsequent outcomes. Moreover, we did not have data on the right ventricular function and dimension, LV remodeling, or concomitant valvular insufficiencies, all of which are of potential prognostic importance [22].

CONCLUSIONS

Systolic PAD of >29.3 mm measured on baseline angio-MDCT is associated with increased subsequent 1-year mortality after successful TAVR regardless of the frailty measure. This measure is a suitable parameter for routine evaluation before TAVR and may be an important marker for patient prognosis to guide subsequent therapeutic actions.

Supplementary material

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

Article information

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Subclavian angioplasty during coronary interventions using radial approach

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ABSTRACT

Background: In the past years, the percentage of percutaneous coronary angiography and coronary interventions using radial access had significantly increased due to its higher safety, lower risk of major bleeding, and hence lower cardiovascular mortality. Subclavian artery stenosis is one of the challenges that may be met during transradial coronary interventions, which may necessitate femoral access crossover or conversion.

Aims: To evaluate the feasibility and safety of performing subclavian angioplasty *via* radial access during complex coronary interventions using the forearm approach.

Methods: A series of patients with complex radial approach due to subclavian stenosis received subclavian angioplasty during the procedure. We included 48 patients out of 22 500 procedures performed from February 2009 to February 2020. All patients did not have alternative vascular access due to extensive peripheral arterial disease (previous history of iliac stenting or distal aortic occlusion, which makes femoral access crossover difficult; also the contralateral radial/ulnar artery was very faint or not detectable at all).

Results: Mean age was 72 (10) years and 67% of patients were males. Subclavian angioplasty was successfully done in all patients *via* ipsilateral radial access; 44 patients (91.7%) required subclavian stenting, and 4 patients were treated by subclavian angioplasty without stenting. Coronary angiography or intervention was perfectly achieved through the revascularized subclavian artery; coronary stenting was successfully done in 36 patients as indicated.

Conclusions: It can be concluded that percutaneous subclavian artery angioplasty can be done safely and effectively to facilitate complex transradial coronary procedures with an acceptable immediate technical success, especially in patients without alternative vascular access. Also, we may conclude that subclavian angioplasty may be successfully performed in patients with symptomatic upper limb ischemia, *via* the radial approach.

Key words: percutaneous coronary intervention, peripheral intervention, transradial approach

INTRODUCTION

In the past years, the percentage of percutaneous diagnostic coronary angiography procedures and coronary interventions by radial or ulnar access had increased significantly. This increase is attributed to the reduction in mortality, major adverse cardiovascular events (MACE), and rate of major bleeding and vascular complications, hence the improved safety with the radial or ulnar approach [1, 2].

Diffuse atherosclerotic disease of the radial, ulnar or subclavian arteries, repeated procedures, iatrogenic dissection, and the need for intervention catheters with a larger diameter are the most encountered obstacles and the most frequent causes of femoral crossover or conversion [3–5].

Subclavian artery stenosis is associated with higher cardiovascular morbidity and mortality. It remains an important cause of

WHAT'S NEW?

The transradial approach is the routine access for percutaneous coronary procedures in most centers. However, there are still complex cases in which radial access may not be successful due to the presence of severe atherosclerotic disease or stenosis in the radial or subclavian artery. We present a series of 48 patients with a complex forearm approach due to subclavian stenosis, for which subclavian angioplasty was performed during the procedure. All the included patients did not have alternative vascular access. According to our knowledge, this is the first series in which subclavian angioplasty is performed *via* the radial route. We have found that percutaneous subclavian artery angioplasty can be done safely to facilitate complex transradial coronary procedures, especially in patients without alternative vascular access. Also, we can postulate that subclavian angioplasty may be successfully performed in patients with symptomatic upper limb ischemia, *via* the radial approach.

upper limb, brain, and cardiac ischemia [6]. Subclavian artery angioplasty is an alternative to femoral crossover in complex radial or ulnar access. Subclavian angioplasty procedures have been performed with success in symptomatic patients with critical upper limb ischemia; however, their use in patients undergoing transradial coronary procedures is still not known [7, 8].

This study aimed to underline the safety and efficacy of performing subclavian angioplasty *via* the transradial approach during coronary intervention procedures.

METHODS

We present a series of procedures with a complex radial approach due to subclavian stenosis, for which subclavian angioplasty was performed during the procedure. All patients had manifestations of ipsilateral upper limb ischemia in the form of claudication and difficult alternative vascular access due to diffuse and advanced atherosclerotic peripheral vascular disease. In all the included patients, the ipsilateral radial artery was palpated, but the contralateral side was faint or not palpable. We set goals of efficacy and safety that included the success rate of the procedure and the existence of radial/ulnar pulse at follow-up. Before performing the subclavian angioplasty, other strategies like sheathless catheters, 4–5 F catheters, and balloon-assisted tracking over angioplasty wire were tried without success [9]. All patients were on antiplatelet therapy, and immediately after the cannulation of the ipsilateral radial artery, the cocktail was administered through the introducer with 5000 IU of unfractionated heparin and 200 µg of nitroglycerin. In cases of suspicion of vasospasm, boluses with nitroglycerin or verapamil and sedatives were administered.

There were 48 cases of subclavian angioplasty, out of 22 500 coronary procedures, from February 2009 to February 2020. Patients presenting with the acute coronary syndrome (ACS) were excluded.

These were the steps of the procedure (Figure 1):

- Access through the radial route and advancing the 6 F introducer sufficiently to progress the catheters through the artery.
- Proceeding with a hydrophilic 0.035"guidewire or, if not possible, a 0.014"or 0.018"angioplasty guidewire trying to negotiate the stenosed subclavian artery.
- Progressing the peripheral over-the-wire (OTW) balloons and dilating the diseased segment.
- Proceeding with the coronary procedure and intervention as needed.
- Performing control injection at the end of the procedure to assess for residual stenosis or possible complications resulting from subclavian angioplasty and stenting of the diseased segment if needed.

The following data were collected: patients' demographics and risk factors, coronary angiographic data, subclavian angioplasty procedure details (wires used, balloons for predilatation or postdilatation, and subclavian stenting), and outcomes (success of subclavian angioplasty and success of coronary interventions).

Follow-up was performed at 1, 3, 6, and 12 months postprocedure. Clinical follow-up included recording of vital signs and palpation of the radial and ulnar pulses in all visits. An arterial duplex was performed at 6 and 12 months after the angioplasty procedure. Follow-up echocardiography was performed 1 month and 1 year after the coronary intervention.

Statistical analysis

Statistical analysis was conducted using Statistical Package for Social Sciences (SPSS version 25.0). Categorical variables are expressed as absolute values and percentages. Continuous variables were expressed as mean (standard deviation [SD]).

RESULTS

Patients' characteristics (Table 1)

Most of the patients were male (67%) with multiple cardiovascular risk factors (83% hypertensive, 75% dyslipidemic [low-density lipoprotein cholesterol, LDL-C, >160 mg/dl or triglycerides, TGs, >200 mg/dl], and 83% diabetic). Peripheral arterial disease (PAD) was previously documented in all patients; 36 patients had a previous history of iliac stenting,

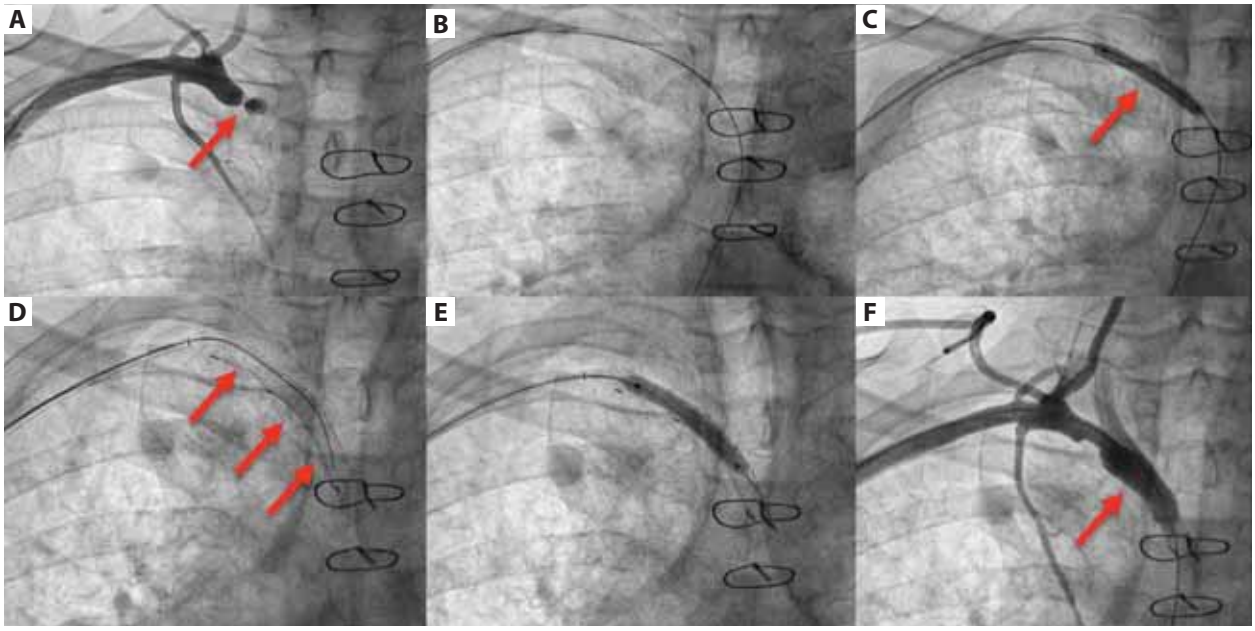

Figure 1. Angiogram showing: **A.** Severe stenosis in the right subclavian artery (the arrow). **B.** Crossing with a 0.018″ guide wire. **C.** Dilatation with a balloon 5 × 40 mm (the arrow). **D.** Two self-expandable stents 6 × 40 mm and 6 × 60 mm were deployed. **E.** Postdilatation with a 7 × 40 mm balloon. **F.** Good angiographic result (the arrow)

Table 1. Demographics and patients' characteristics

Age, years, mean (SD)	72 (10)
Male sex, n (%)	32 (67)
Active smoker, n (%)	24 (50)
Hypertensive, n (%)	40 (83)
Diabetes mellitus, n (%)	40 (83)
Atrial fibrillation, n (%)	5 (10.4)
Hyperlipidemic (LDL-C >160 mg/dl or TGs >200 mg/dl), n (%)	36 (75)
Peripheral artery disease, n (%)	48 (100)
Previous peripheral (iliac) stenting, n (%)	36 (75)
Prior ischemic heart disease (stable anginal symptoms or previous ACS or coronary revascularization), n (%)	32 (67)
Previous coronary intervention by the same approach, n (%)	8 (17)
BMI, kg/m^2	
Overweight, BMI, 25–29.9 kg/m^2, n (%)	26 (54.2)
Obese, BMI >30 kg/m^2, n (%)	5 (10.4)
Chronic kidney disease, eGFR <30 ml/min/1.73m^2, n (%)	4 (8)
Hemoglobin level, g/dl, mean (SD)	13.5 (2.1)
Serum creatinine, mg/dl, mean (SD)	1.0 (0.9)
Medications, n (%)	
Antiplatelets	44 (91.7)
NOAC	5 (10.4)
Statins	48 (100)

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; NOAC, non-vitamin K antagonist oral anticoagulants; TGs, triglycerides

4 patients had occluded distal aorta and 67% of patients had a previous history of coronary artery disease (CAD; stable anginal symptoms, or previous history of ACS, or coronary revascularization). Five patients (10.4%) had atrial fibrillation and were taking anticoagulation (non-vitamin K antagonist oral anticoagulants [NOAC], 3 patients were taking apixaban, and 2 patients were taking rivaroxaban). Statins were used in all patients, and 44 patients (91.7%) were taking antiplatelets. Mean hemoglobin concentration was 13.5 (2.1) g/dl, serum creatinine level was 1.0 (0.9) mg/dl. Twenty six patients were overweight (body mass index [BMI], 25–29.9 kg/m^2), and five patients (10.4%) were obese (BMI >30 kg/m^2).

Procedural data (Table 2)

Regarding angiographic data, severe arteriosclerotic stenosis of the subclavian artery was found in most of the included patients, and only four patients (8.3%) had a totally occluded subclavian artery which was successfully crossed with a steerable stiff 0.014-inch wire (e.g., ASAHI Confianza [Abbott Vascular, Santa Clara, CA, US]). Angioplasty was performed with different types of OTW peripheral balloons, the most commonly used balloon diameter was 6 mm. All cases were done with 6 F guiding catheters. Subclavian stenting was performed in 44 patients (91.7%), and 4 patients did not require stenting due to good luminal gain on control angiography performed at the end of the procedure. Balloon expandable stents were used in 50% of patients. Eight patients required 2 stents for treating subclavian stenosis. Destination introducer, to correct radial/brachial tortuosity, with a 6 F therapeutic catheter was used in eight patients. 75% of patients had significant CAD that was treated by coronary stenting, and 25% had non-significant CAD. For closure of the radial artery, a pneumatic brace system was used for 4–6 hours. Aspirin 75–100 mg was given to all patients, clopidogrel was used in 38 patients (79.2%), and ticagrelor in 5 patients (10.4%).

Table 2. Procedural data and follow-up

Multivessel coronary disease, n (%)	32 (67)
Angiographic severe coronary calcification, n (%)	16 (33)
Totally occluded subclavian artery, n (%)	4 (8)
Right subclavian artery disease, n (%)	32 (67)
Wires used, n (%)	
0.014″	32 (67)
0.018″	16 (33)
Exchange to 0.035″ wire (after predilatation)	24 (50)
Balloon predilatation, n (%)	48 (100)
Predilatation balloon diameter, mm, mean (SD)	4.8 (1.5)
Predilatation balloon length, mm, mean (SD)	60 (34)
Subclavian stenting, n (%)	44 (91.7)
Patients requiring two stents, n (%)	8 (17)
Subclavian stent diameter, mm, mean (SD)	6.25 (0.9)
Subclavian stent length, mm, mean (SD)	59.7 (19.5)
Balloon postdilatation, n (%)	16 (33)
Postdilatation balloon diameter, mm, mean (SD)	7.0 (0.9)
Postdilatation balloon length, mm, mean (SD)	50 (11.5)
Vascular complications, n (%)	0
Coronary PCI, n (%)	36 (75)
Long sheath 90 cm, n (%)	8 (17)
Successful coronary intervention, n (%)	48 (100)
Medications, n (%)	
Aspirin	48 (100)
Clopidogrel	38 (79.2)
Ticagrelor	5 (10.4)
NOAC	5 (10.4)
Follow-up, n (%)	
Patency of ipsilateral forearm pulsations	48 (100)
MACE	0

Abbreviations: MACE, major adverse cardiovascular events; PCI, percutaneous coronary interventions; other — see Table 1

*Follow-up (*Table 2*)*

With follow-up at 1, 3, 6 months, and 1 year, ipsilateral radial and ulnar pulse were clearly felt in all patients. Arterial duplex showed patent ipsilateral peripheral circulation in all treated patients. Four patients required repeat coronary angiography, and the subclavian stent was found to be widely patent in all of them. Patients with atrial fibrillation were maintained on aspirin and anticoagulants for 6 months, then aspirin was stopped. No MACE (myocardial infarction, stroke, arrhythmia, or mortality) was recorded in any of the included patients.

DISCUSSION

Nowadays, the transradial approach in coronary angiography and percutaneous coronary interventions (PCI) is an attractive alternative to the femoral approach. The expanded use of the transradial approach originates from its high procedural success, reduced risk of major access site-related bleeding, lower mortality, increased patient comfort, and cost reduction [1, 2].

However, there are still complex cases in which radial access may not be successful due to the presence of severe atherosclerotic disease or stenosis in the subclavian artery [3–5].

The evolution of the transradial approach over the last few years brought about new procedural difficulties that should be overcome by evolving techniques. As in the above-described cases, atherosclerotic disease or stenosis of the subclavian artery is a major obstacle to a successful radial approach and may result in complications or conversion to a transfemoral approach. Radial access is routinely used in our center, and we try to overcome any difficulties in the access site before shifting to alternative access without causing harm to the patients. Subclavian artery angioplasty represents a useful technique to overcome this obstacle in symptomatic patients undergoing coronary angiography or PCI.

We included 48 cases of symptomatic subclavian artery stenosis, all patients had 1 or more risk factors for atherosclerosis and had a documented history of extensive PAD; which ruled out the possibility of using other vascular accesses or shifting to femoral access. In the included patients, the ipsilateral radial artery was palpated, but the contralateral side was faint or not palpable, which made shifting to the contralateral side impractical. Also shifting to femoral access was not feasible as all of the included patients had extensive lower limb arteriopathy and history of iliac intervention or distal aortic occlusion. When thoroughly analyzing the patients' history, we found that most of the patients had symptomatic upper extremity ischemic symptoms. All patients underwent successful subclavian angioplasty through the radial approach, with or without stent implantation.

In most published series [8], left subclavian artery angioplasty predominates over right, perhaps because of some reservations about angioplasty at a site near the right common carotid origin. However, in our series, most of the cases (32 out of 48) had right subclavian artery disease which was successfully treated percutaneously without complications.

For the treatment of symptomatic hand ischemia, endovascular treatment with percutaneous angioplasty is now considered the first-line therapy for above elbow arterial diseases. Surgical revascularization is reserved for difficult cases with anatomy unfavorable to the percutaneous approach. The risk of new neurological or ischemic sequelae following subclavian angioplasty is very low [7, 8, 10].

Although the primary aim of our procedure was to open the subclavian artery to continue the percutaneous coronary procedure, this may raise the possibility of adopting radial access or a route for performing ipsilateral subclavian angioplasty while percutaneously treating symptomatic subclavian stenosis. According to our knowledge, this is the largest series in which subclavian angioplasty was performed *via* the radial route using single ipsilateral access, unlike most of the published series [10–13], in which the femoral route was the standard access.

CONCLUSION

Percutaneous subclavian artery angioplasty through the radial route is a safe and effective tool in symptomatic patients during complex transradial coronary procedures. It has an acceptable immediate technical success, leading to a reduction in the need for femoral crossover which may not be feasible in all patients especially those at high cardiovascular risk or having extensive PAD. Also, we may conclude that subclavian angioplasty may be successfully performed in patients with symptomatic upper limb ischemia, *via* the radial approach.

Study limitations

The main limitation is the design of the study, which is retrospective and non-comparative. Further studies may be needed to validate and confirm the findings in our study.

Screening for subclavian stenosis was not routinely performed in all patients, it was only diagnosed when the percutaneous catheters or guidewires could not advance into the aorta; this may underestimate the prevalence of subclavian stenosis in the studied population.

The contralateral subclavian artery was not injected to look for contralateral subclavian disease.

Article information

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Acute kidney injury as the most important predictor of poor prognosis after interventional treatment for aortic stenosis

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ABSTRACT

Background: Aortic stenosis (AS) is the most common acquired valvular disease. There are two methods of interventional treatment: surgical aortic valve replacement (SAVR) and transcatheter aortic valve implantation (TAVI). The choice between SAVR and TAVI depends on the assessment of individual perioperative risk and long-term treatment outcomes. It is essential to identify factors that may influence the outcomes of the treatment to minimize their negative effects.

Aims: The study aimed to identify the most important risk factor which affects treatment outcomes in patients with AS undergoing SAVR/TAVI.

Methods: This study reviewed retrospectively patients with AS who underwent SAVR or TAVI. The primary outcomes included incidences of major adverse cardiovascular events (MACE) defined as cardiovascular death, stroke, and hospitalization for cardiovascular issues assessed over a one-year follow-up period. An occurrence of postprocedural AKI (acute kidney injury) was identified as an independent predictor of MACE.

Results: The study included 78 patients, with the same number of subjects in each group (SAVR/TAVI [n = 39]). Twenty-nine patients developed AKI. It was similar in both groups (SAVR [n = 15]; TAVR [n = 14]). In the SAVR group, 13 (33%) patients developed at least one MACE compared to 5 (13%) patients in the TAVI group. AKI and the type of procedure (SAVR) were shown to be significantly and independently associated with the development of MACE ($P = 0.01$ and $P = 0.03$, respectively) as shown in the Cox multivariable regression model.

Conclusions: Our study demonstrated that AKI is the strongest predictor of major adverse cardiovascular events after using both methods of aortic valve replacement (SAVR/TAVI).

Key words: acute kidney injury, major adverse cardiovascular events, severe aortic stenosis, surgical aortic valve replacement, transcatheter aortic valve implantation

INTRODUCTION

Aortic stenosis (AS) is the most common acquired heart defect among adults. The average prevalence of severe aortic valve stenosis is estimated to be 0.2% in patients between 55 and 64 years of age. It increases with age, reaching approximately 3% at 75–80 years of age and even 10% after 80 years of age [1]. Severe, symptomatic aortic stenosis is associated with death of at least half of patients within 2 years after the onset of first symptoms. Such patients should undergo aortic valve replacement. The most common surgical methods are surgical aortic valve replacement (SAVR) and transcatheter aortic valve implantation (TAVI) [2].

The surgical risk increases with age, and patients are at risk of developing serious concomitant diseases; therefore, TAVI becomes an alternative treatment for this group of patients [3–6].

Indeed, several randomized clinical trials compared those procedures and confirmed that TAVI was non-inferior and even superior to SAVR with regard to clinical outcomes [3, 7–9].

WHAT'S NEW?

In this article, we argue that acute kidney injury (AKI) is the strongest predictor of major adverse cardiovascular events (MACE) in patients with aortic stenosis (AS) who underwent surgical aortic valve replacement (SAVR) or transcatheter aortic valve intervention (TAVI) during one-year follow up. To the best of our knowledge, this study is the first that investigated impact of postprocedural AKI on the occurrence of MACE (including cardiovascular death, stroke, and hospitalization for cardiovascular problems) in both groups (SAVR and TAVI), during long-term follow-up.

Still, the final decision regarding the choice of the optimal treatment method should be made by the Heart Team after individual assessment of benefits and risks of the procedure and the patient's preferences [3, 5].

Chronic kidney disease (CKD) often coexists in patients with severe aortic stenosis, possibly due to similar etiology. Renal dysfunction provokes aortic valve calcification. Recent studies have shown that acute kidney injury (AKI) is a common complication after cardiac surgery and its frequency is significantly higher in patients with CKD [10]. Depending on the research, it occurs in 3% to 43% of SAVR and 3% to 57% of TAVI procedures. Several studies showed that postprocedural AKI is associated with poor prognosis [11, 12]. However, TAVI is a generally less invasive procedure, which might mitigate the negative impact of postoperative AKI.

The study aimed to identify the most important risk factor which affects treatment outcomes in patients with AS undergoing SAVR/TAVI.

METHODS

Study population

This retrospective cross-sectional study with active follow-up enrolled a total of 120 consecutive patients with severe aortic stenosis who underwent TAVI or SAVR between December 2018 and December 2019 in the Department of Cardiac Surgery. The decision on choice of treatment method in each case was made at a meeting of the Heart Team consisting of an attending cardiologist, cardiac surgeon, invasive cardiologist, and echocardiographer. Afterward, patients who qualified for conservative treatment or those who died before the planned procedure (TAVI/SAVR) were excluded from further analysis. The full exclusion criteria were incomplete medical documentation and lack of consent for the proposed interventional treatment. Besides, patients qualified for aortic balloon valvuloplasty or those who died before the planned aortic valve replacement (SAVR/TAVI), as well as patients with severe CKD (stage G5 according to Kidney Disease: Improving Global Outcomes [KDIGO] on the treatment of dialysis), were also excluded from the study.

Patients were divided into 2 groups based on the treatment method (TAVI/SAVR). The surgical protocol was a source of intraoperative information, and the postoperative course was assessed on the basis of daily observations made by physicians and available in the hospital database. We analyzed all available clinical data including laboratory test results and transthoracic echocardiography (performed twice: before the procedure and before the discharge in each case). The study protocol was approved by the Local Ethics Committee and the study followed the principles outlined in the Declaration of Helsinki.

Procedural details

The surgical aortic valve replacement (SAVR) was performed in the operating room under general anesthesia with extracorporeal circulation, from the classic median approach and median sternotomy. The procedure consisted of the removal of the native aortic valve and implantation of the prosthesis.

The TAVI procedures were performed in a hybrid operating room. The patients were under conscious sedation or general anesthesia. The choice of vascular approach (femoral/transapical/transaortic) depended on the anatomy and severity of atherosclerosis of the peripheral arteries and aorta, as assessed by computed tomography. During the procedure, the patients were continuously monitored with arterial blood pressure measurement and received a temporary cardiac pacing electrode. Depending on the valve morphology and the number of calcifications, aortic valve valvuloplasty was performed during rapid ventricular pacing. The valve was positioned under video-assisted control and echocardiographic guidance and then implanted.

Analyzed clinical parameters

During preparation for the procedure, the patients underwent transthoracic and transesophageal echocardiography and also coronary diagnostics (coronary computed tomography angiography [CCTA]/coronarography — the choice of method depended on the patient's age, symptoms, risk factors, and positive family history of ischemic disease) and, in the case of TAVI, also multislice computed tomography of the aorta. The study groups were subject to a detailed clinical assessment (severity of symptoms according to the New York Heart Association [NYHA] class, body mass index [BMI], concomitant diseases, i.e., diabetes, hypertension, atrial fibrillation, renal diseases), echocardiographic (left ventricular ejection fraction, aortic valve area, maximal and minimal transvalvular gradient, maximal aortic valve velocity), and biochemical (creatinine, glomerular filtration rate [GFR], N-terminal pro-B-type natriuretic peptide, hemoglobin). All patients had a surgical risk estimated based on common cardiac surgical risk scales: the European Cardiac Risk Assessment System (EuroSCORE II) or the Society of Thoracic Surgeons (STS) [3, 13].

Table 1. Types and sizes of valves used during the procedure

Type of valve	SAVR (n = 39)	Type of valve	TAVI (n = 39)
Medtronic Hancock II[a] size, mm (n)	21 (9) 23 (6) 25 (7)	Portico TM Valve[b] size, mm (n)	23 (1) 25 (2)
St. Jude Epic/Epic TM Supra[b] size, mm (n)	19 (1) 21 (2) 23 (4) 25 (4) 27 (1)	Evolut R[a] size, mm (n)	23 (1) 26 (5) 27 (4) 29 (4) 34 (1)
Medtronic Freestyle[a] size, mm (n)	21 (1)	Evolut PRO[a] size, mm (n)	25 (1) 26 (5) 29 (5) 34 (1)
Edwards Perimount[c] size, mm (n)	21 (1) 23 (1) 25 (1) 27 (1)	Edwards Sapien Lifesciences[c] size, mm (n)	23 (1) 26 (6) 29 (1)
		Core Valve[a] size, mm (n)	23 (1)

Producer: [a]Medtronic, Münchenbuchsee, Switzerland. [b]Abott, Chicago, IL, US. [c]Edward Lifesciences Corporation, Irvine, CA, US

Names of the valves: Core Valve, Edwards Perimount, Edwards Sapien Lifesciences, Evolut PRO, Evolut R, Medtronic Freestyle, Medtronic Hancock II, Portico TM Valve, St. Jude Epic/ Epic TM Supra

Abbreviations: SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation

The serum creatinine level was measured in each patient 24 hours before the procedure and every day after the procedure until discharge from the hospital.

The baseline renal function was estimated based on the patient's medical history and results of laboratory tests before the procedure. Chronic kidney disease was defined when the glomerular filtration rate (eGFR) was lower than 60 ml/min/1.73 m^2; stages were assessed according to the KDIGO [10, 14].

Acute kidney injury was diagnosed when serum creatinine level increased by ≥0.3 mg/ml (≥26.4 µmol/l) within 48 h or increased ≥1.5 times within 7 days compared with baseline (using the KDIGO), as recommended by the Valve Academic Research Consortium-3 (VARC-3) [14].

Follow-up and study endpoints

An occurrence of adverse events was evaluated within one year of the follow-up period. Major adverse cardiovascular events (MACE) were defined as cardiovascular death, stroke, and hospitalization for cardiovascular issues. According to VARC-3, hospitalization was defined as any admission to an inpatient unit or hospital ward for ≥24 h, including an emergency department stay due to cardiac or cardiovascular reasons [14].

All patients included in the study were observed during one-year follow-up. All MACE data were collected from the inter-hospital electronic database of patients. We collected follow-up data from all patients included in the study. In the case of more than one MACE in one patient, only the first event that occurred was considered in further MACE analysis.

Statistical analysis

Categorical variables are presented as numbers with a corresponding percentage. Categorical variables were compared using the χ^2 test or for a low number of counts (<5 in any cell of a frequency table) — the 2-way Fisher's exact test. Continuous variables are presented in the form of mean with standard deviation or median with interquartile range. The normality of distribution was verified by the Shapiro-Wilk test. Differences between the groups were assessed using the t-test or Mann-Whitney U test (depending on the normality of distribution). A survival analysis using the Kaplan-Meier curve and log-rank test was performed to compare the MACE-free survival time of patients with and without AKI. Univariable Cox regression was carried out to find factors associated with the occurrence of MACE. Subsequently, statistically significant variables were included in the multivariable Cox regression model built using the forward stepwise method. P-value below the level of 0.05 was considered statistically significant. All calculations were carried out in STATISTICA 13.3 software (TIBCO, Palo Alto, CA, US).

RESULTS

Overall, from 120 hospitalized patients with severe AS, 42 subjects met exclusion criteria, mainly due to qualification for conservative treatment (n = 30; 6 of them did not give consent to the proposed surgical treatment), qualification for balloon aortic valvuloplasty (n = 5), or death before performing the procedure — SAVR/TAVI (n = 7), and 78 patients were included in further analysis. Most of the 78 studied patients were females (male n = 34 [43.6%], female n = 44 [56.4%], mean age [SD]: 73.3 [10.52]). Thirty-nine patients underwent SAVR, and 39 patients underwent TAVI. The types of valves used for SAVR are presented in Table 1. None of the patients received a mechanical prosthesis. TAVI procedures were performed from the femoral (n = 25), transapical (n = 8), and transaortic (n = 6) approach.

Table 2. Study group characteristic

	All patients (n = 78)	SAVR (n = 39)	TAVI (n = 39)	*P*-value
Age, years, mean (SD)	73.3 (10.5)	66.7 (9.1)	79.9 (7.3)	<0.01
Male, n (%)	34 (43.6)	18 (46.2)	16 (41)	0.74
BMI, kg/m^2, mean (SD)	27.6 (5.1)	27.1 (4.3)	28 (5.7)	0.36
EuroSCORE, %, median (IQR)	2.7 (1.7–4.7)	2.2 (1.3–3.5)	3.6 (2.1–6.9)	0.01
STS, %, median (IQR)	2.5 (1.6–4.1)	1.9 (1.2–3.5)	3.6 (2.1–5.5)	<0.01
Diabetes, n (%)	21 (26.9)	11 (28.2)	10 (25.6)	1.00
Hypertension, n (%)	69 (88.5)	35 (89.7)	34 (87.2)	1.00
Pulmonary embolism in the past, n (%)	1 (1.3)	1 (2.6)	0 (0)	1.00
Myocardial infarction in the past, n (%)	18 (23.1)	7 (18)	11 (28.2)	0.42
Current smoking, n (%)	15 (19.2)	11 (28.2)	4 (10.3)	0.08
Atrial fibrillation, n (%)	30 (38.5)	13 (33.3)	17 (43.6)	0.49
PCI in the past, n (%)	7 (9)	2 (6.1)	5 (14.3)	0.43
Cardiostimulator implanted before intervention, n (%)	9 (11.5)	3 (7.7)	6 (15.4)	0.48
GFR (45–59), ml/min/1.73 m^2, n (%)	19 (24)	10 (26)	9 (24)	0.78
GFR (30–44), ml/min/1.73 m^2, n (%)	12 (15)	6 (15)	6 (15)	
GFR (15–29), ml/min/1.73 m^2, n (%)	3 (5)	1 (2)	2 (5)	
Hemoglobin, g/dl, mean (SD)	12.7 (1.8)	13 (1.8)	12.5 (1.9)	0.31
NT-proBNP, pg/ml, (n = 70), median (IQR)	2098 (775–5413)	1849 (843–4572)	2948 (772.5–7765.5)	0.34

Abbreviations: BMI, body mass index; GFR, glomerular filtration rate; IQR, interquartile range; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCI, percutaneous coronary intervention; SD, standard deviation; STS, Society of Thoracic Surgeons; other — see Table 1

Table 3. Comparison of echocardiographic parameters and stage of the NYHA class before and after intervention

	Total (n = 78)	SAVR (n = 39)	TAVI (n = 39)	*P*-value	Total (n = 78)	SAVR (n = 39)	TAVI (n = 39)	*P*-value
	Before procedures				After procedures			
Maximal valve gradient, mm Hg, mean (SD)	67 (22.4)	70 (21.6)	64 (23.1)	<0.01	24 (9.5)	29 (8.1)	18 (7)	<0.01
Mean valve gradient, mm Hg, mean (SD)	42 (14.9)	45 (14.1)	39 (15.2)	<0.01	13 (5.4)	16 (4.9)	10 (3.7)	<0.01
Maximal valve velocity, m/s, mean (SD)	4.1 (0.7)	4.1 (0.7)	4 (0.7)	<0.01	2.4 (0.5)	2.7 (0.4)	2.1 (0.4)	<0.01
Ejection fraction, %, mean (SD)	55.9 (10)	56.4 (9.6)	55.4 (10.7)	0.68	52 (10)	52.3 (9.2)	51.8 (10.8)	<0.01
NYHA stage I, n (%)	0 (0)	0 (0)	0 (0)	0.86	2 (3)	2 (5)	0 (0)	0.47
NYHA stage II, n (%)	12 (15)	6 (15)	6 (15)		66 (90)	30 (85)	36 (97)	
NYHA stage III, n (%)	63 (81)	33 (85)	30 (77)		3 (4)	2 (5)	1 (3)	
NYHA stage IV, n (%)	3 (4)	0 (0)	3 (8)		2 (3)	2 (5)	0 (0)	

Abbreviations: NYHA, New York Heart Association; other — see Tables 1 and 2

Basic demographic, clinical, echocardiographic, laboratory characteristics, and estimated surgical risk (based on EuroSCORE II/ STS) of the patients studied are presented in Tables 2 and 3. Apart from age, both groups did not differ significantly in terms of demographic parameters. The mean age of TAVI patients (mean [SD] = 79.9 [7.3]) was higher than the mean age of patients with SAVR (mean [SD] = 66.7 [9.1]) (P <0.01). In addition, EuroSCORE II (median [IQR] = 3.6 [2.1–6.9]) and STS scores (median [IQR] = 3.6 [2.1–5.5]) of patients undergoing TAVI were higher than EuroSCORE II (median [IQR] = 2.2 [1.3–3.5]) and STS scores (median [IQR] = 1.9 [1.2–3.5]) of patients treated with SAVR (P <0.05) (Table 2). Also, echocardiographic parameters measured before and after surgery were different between the groups (P <0.01) (Table 3). The SAVR group demonstrated a higher mean of maximal valve velocity and mean of maximal or mean valve gradient than the TAVI group (P <0.01). There were no significant differences in ejection fraction before surgery between the 2 groups.

Before surgery, CKD was assessed in 34 (44%) patients. The number of CKD was the same in each group (n = 17; 44%) (Table 2).

Acute kidney injury occurred in a total of 29 patients (37%), and 41% (n = 12) of them had been previously diagnosed with CKD. There was no statistically significant difference in the number of AKI cases between the SAVR group (40%; n = 15) and the TAVI group (36%; n = 14) (P = 0.86) (Table 4). We recorded 24 incidences of MACE in 18 patients during one-year follow-up: 15 incidences in the SAVR group and 9 incidences in the TAVI group (Tables 4 and 5). Eight patients died within a year after the procedure. The number of deaths after SAVR (n = 4) and

Table 4. Summary of the main endpoints

Characteristic	Total (n = 78)	SAVR (n = 39)	TAVI (n = 39)	*P*-value
AKI, n (%)	29 (37)	15 (40)	14 (36)	0.86
Number of patients with at least one MACE, n (%)	18 (23)	13 (33)	5 (13)	0.06
Number of all MACE events, n	24	15	9	NA

Abbreviations: AKI, acute kidney injury; MACE, major adverse cardiovascular events; NA, not applicable; other — see Table 1

Table 5. Summary of all MACE occurrences in patients after SAVR and TAVI with and without AKI

	AKI (yes) (n = 29)			AKI (no) (n = 47)		
MACE	Total n (%)	SAVR n (%)	TAVI n (%)	Total n (%)	SAVR n (%)	TAVI n (%)
Any	13 (100)	10 (77)	3 (23)	11 (100)	5 (45)	6 (55)
Death	5 (100)	4 (80)	1 (20)	3 (100)	0 (0)	3 (100)
Residual stroke	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)	1 (100)
Hospitalization for cardiac disorders	8 (100)	6 (75)	2 (25)	6 (100)	5 (83)	1 (100)
Hospitalization for vascular issues	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)	1 (100)

Both the choice of procedure and occurrence of AKI were significantly associated with MACE risk (P-value for SAVR 0.03, for AKI 0.01 — for details see Table 6). Singular MACE items were not analyzed statistically due to the low number of events

Abbreviations: see Tables 1 and 4

TAVI (n = 4) was the same. All patients who died following SAVR were diagnosed with postoperative AKI, while in the TAVI group only 25% of those who died had AKI. We noted 18% (n = 14) of rehospitalizations for cardiac disorders within a year. Seventy-eight percent (n = 11) of them were in the SAVR group (more than half [n = 6] of patients were diagnosed with AKI), and 22% (n = 3) were in the TAVI group (66% of patients were diagnosed with AKI) (Table 5).

In the SAVR group, two patients who died were also rehospitalized for cardiac disorders before death. In the TAVI group, the patients who died, also had other MACEs: one patient had a stroke after TAVI, and the remaining three were rehospitalized for cardiac disorders before death. One patient after TAVI, required hospitalization in the Vascular Surgery Department due to a complication associated with the femoral approach.

The Kaplan-Meier curve (Figure 1) presents the proportion of MACE-free survival against time, for patients with and without AKI. It implies that occurrence of AKI is significantly associated with the MACE-free survival time of patients who underwent AVR and TAVI (*P* log-rank = 0.01).

The univariable Cox model shows that the SAVR procedure and AKI are parameters significantly associated with a higher risk of MACE. These variables were taken into the multivariable Cox regression model, which shows that AKI is associated with a 3.75 higher risk of MACE, even after adjustment for type of treatment (SAVR) (HR, 3.75; 95% confidence interval [CI], 1.39–10.20; *P* = 0.01). The model shows that AKI was a risk factor for MACE independently of the type of procedure (Table 6).

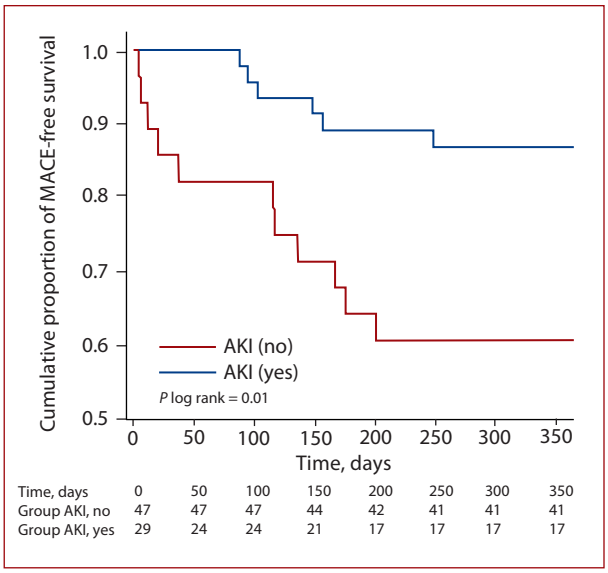

Figure 1. The Kaplan-Meier curve presenting the proportion of MACE-free survival against time for patients with and without AKI
P log-rank = 0.01

Abbreviations: see Table 4

DISCUSSION

In our study, we recorded 24 incidences of MACE in 18 patients during one-year follow-up: 15 incidences in the SAVR group and 9 incidences in the TAVI group. MACE was higher in the SAVR group (n = 15) than in the TAVI group (n = 9). SAVR is a more invasive procedure and is burdened with a high risk of complications. Therefore, even younger patients have a worse prognosis. Hence, less invasive methods need improvement as they are associated with a better prognosis, even in older and more burdened patients.

We identified AKI as the strongest predictor of poor prognosis in patients with aortic stenosis undergoing isolated aortic valve replacement, in the SAVR group and in the TAVI group. After that, we analyzed the impact of AKI on the occurrence of MACE during long-term clinical follow-up in both groups (SAVR/TAVI). Firstly, we observed no significant

Table 6. The univariable and multivariable Cox regression model for detecting factors associated with occurrence of MACE

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Sex (male)	1.3 (0.5–3.4)	0.61		
Age (for every 10 years)	0.9 (0.6–1.4)	0.63		
Procedure (SAVR)	2.9 (1.003–8.1)	0.049	3.2 (1.1–9.0)	0.03
EF (for every 5%)	1.0 (0.8–1.3)	0.89		
AKI (yes)	3.6 (1.4–9.9)	0.01	3.8 (1.4–10.2)	0.01
Creatinine level before surgery (for every 10 µmol/l)	1.1 (0.8–1.5)	0.56		
Diabetes	1.0 (0.6–1.8)	0.94		
Hypertension	1.0 (0.5–2.1)	0.96		
Myocardial infarction in the past	1.0 (0.6–1.9)	0.95		
Smoking currently	1.5 (0.6–4.2)	0.40		
Atrial fibrillation	1.0 (0.6–1.8)	0.93		
BMI, kg/m^2	1.0 (0.9–1.1)	0.62		
Hemoglobin, g/dl	1.0 (0.8–1.3)	0.93		
EuroSCORE (%)	1.1 (0.9–1.2)	0.32		
STS	1.0 (0.8–1.2)	0.69		
NT-proBNP, pg/ml	1.0 (0.99–1.0)	0.70		
GFR, ml/min	1.01 (0.99–1.03)	0.43		

Abbreviations: CI, confidence interval; EF, ejection fraction; HR, hazard ratio; other — see Tables 1, 2 and 4

difference in the occurrence of AKI in either group. In the PARTNER-1 trial and a study conducted by Thongprayoon et al. [15], there was also no difference in the incidence of AKI between TAVI and SAVR [2, 15]. A meta-analysis conducted by Shah et al. [16], showed lower rates of AKI after TAVI in comparison with SAVR but similar rates of AKI requiring renal replacement therapy. The discrepancy between the studies may be explained by a lack of standard definition of acute kidney injury and differences in the patient risk profile. Transcatheter aortic valve intervention is a generally less invasive procedure, which might suggest that it will be associated with a lower risk of postoperative AKI. However, this procedure is conducted in patients with concomitant diseases and involves pre- and postoperative administration of contrast agents and application of prolonged rapid ventricular pacing during valvuloplasty/valve positioning. Besides, the TAVI procedure might also be associated with bleeding which occurs due to vascular complications. All these factors might contribute to a higher risk of AKI than could be expected. SAVR is also associated with an increased risk of AKI because of many hemodynamic and inflammatory factors (such as cardiopulmonary bypass, transfusion, hypothermia, non-pulsed blood flow, and hemodilution) [16]. Our study shows that CKD was an important predictor of postoperative development of AKI. Studies conducted so far have also pointed out the same dependency [15, 17–20]. TAVI techniques (e.g. advances in 3D echocardiography, and the use of moderate sedation) are constantly being improved. Hence, this method, rather than SAVR, is likely to be a more modifiable factor in the reduction of postoperative renal function impairment [16, 21].

In addition, we observed that postprocedural AKI is a significant predictor of MACE.

During one-year follow-up, patients with AKI experienced more adverse events than those without AKI.

Death rates were the same in both groups. All patients who died after the SAVR procedure were diagnosed with postprocedural AKI, in contrast to the TAVI group in which only one patient who died had developed AKI. In the present study, we observed that SAVR patients were hospitalized significantly more frequently for cardiac disorders. More than half were diagnosed with AKI. A previous study shows that AKI plays the main role in predicting mortality in both groups [11, 20]. However, its role in predicting rehospitalization for cardiac disorders is less probable [22, 23]. A meta-analysis made by Bianco et al. [24] and a study conducted by Abbas et al. [25] show a significantly higher rate of rehospitalizations for cardiac disorders in patients who underwent TAVI. Kodali et al. [26] reported a similar rate of rehospitalizations for TAVI and SAVR (24.7% vs. 21.7%; $P = 0.41$). Danielsen et al. [27], in their meta-analysis, show a slightly higher rate of rehospitalizations after SAVR (17%) than after TAVI (16%). Neither of these studies assessed the impact of postprocedural AKI on the occurrence of MACE. It is crucial to perform further research focused on identifying AKI-related prognostic risk factors, as well as novel methods of prevention and treatment of AKI in patients after SAVR/TAVI.

Limitations

Our study has a few limitations which are mainly associated with its retrospective character. It is a single-center study, and its data are limited as they were obtained from one cardiology department. However, our center of cardiology and cardiac surgery is the only one performing TAVI procedures in the area of 2.5 million inhabitants (data from 30 June 2020). In addition, the study included quite a small number of patients. However, some patients who qualified for invasive treatment (TAVI/SAVR) refused to sign consent,

and some died before surgery. We did not include the urine output criterion for AKI diagnosis because of incomplete medical documentation.

CONCLUSION

Our study demonstrated that AKI is the strongest predictor of major cardiovascular adverse events after both methods of aortic valve replacement (SAVR/TAVI).

Article information

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Tetralogy of Fallot and bicuspid aortic valve: Rare coexistence

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INTRODUCTION

Bicuspid aortic valve (BAV) is one of the most frequent cardiovascular anomalies (prevalence 0.5%–2.0%) [1]. Briefly, multiple classifications and nomenclature have been previously proposed to describe the BAV types (Sievers, Schaefer, and Kang classifications). The recently published International Consensus Statement on Nomenclature and Classification of BAV distinguishes three types of BAV with specific phenotypes [2].

Tetralogy of Tallot (ToF) constitutes around 10% of all congenital heart diseases (CHD). The prevalence in general population is around 0.03% [3]. Recently Grzyb et al. [4] presented a very insightful analysis of the largest single-center cohort of 326 ToF fetuses.

Numerous papers have reported the association of BAV with other CHD, as well as extra-cardiac anomalies. However, only a few reports on the coexistence of BAV and ToF have been published so far. Most of them included pediatric patients and not adults (Supplementary material, *Table S1*), and usually did not have any details regarding the BAV type. Based on the very scarce data, the prevalence of BAV ranges between 0.2% and 2.4% in pediatric ToF cohorts and 2.0% in two cohorts of adult ToF patients (Supplementary material, *Table S1*).

Aim

We aimed to retrospectively identify BAV among the cohort of ToF patients.

METHODS

We retrospectively screened discharge summaries from an electronic database of a tertiary high-volume heart center. In the studied period (January 2008 to November 2020), 103 330 patients were hospitalized; among them — 564 ToF patients. The keywords: "tetralogy of Fallot" and "bicuspid aortic valve" (with their grammatical variants and abbreviations) were used to identify ToF and BAV.

Statistical analysis

Statistical analysis was limited to the simple calculation of the prevalence of BAV among all hospitalized ToF patients.

RESULTS AND DISCUSSION

Three patients (including one female) with ToF and BAV were identified. All of them underwent several transthoracic echocardiographic (TTE) examinations.

Patient 1 (MZ)

The first patient was a 40-year-old female after surgical correction of ToF (right ventricular outflow tract correction with a pericardial patch) at the age of three years, with ventricular arrhythmias treated with propafenone. She remained in functional class II according to the New York Heart Association. Her recent TTE revealed hypokinetic right ventricle (RV): tricuspid annular plane systolic excursion, 16 mm; RV, S' 7 cm/s, moderate pulmonary regurgitation (PR), dilated aortic root (44 mm),

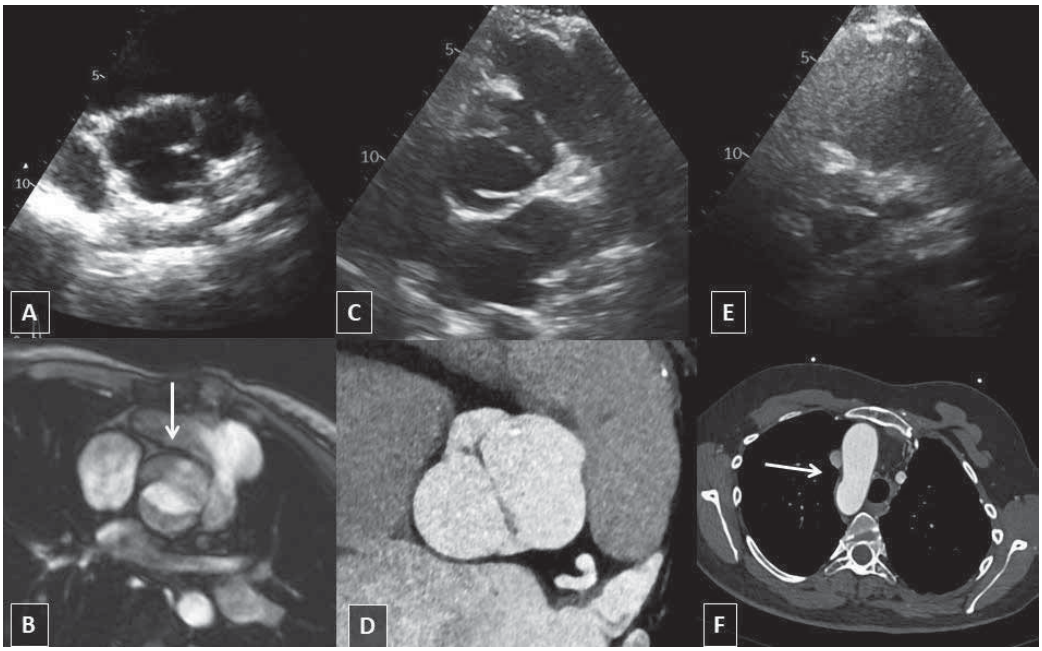

Figure 1. A, C, E. Patients 1–3, respectively. Echocardiography. The bicuspid aortic valve with fused coronary cusps. **B.** Patient 1. Cardiac magnetic resonance with focus on the bicuspid aortic valve (the white arrow). **D.** Patient 2. Chest computed tomography. The bicuspid aortic valve without raphe. **F.** Patient 2. Chest computed tomography. The right aortic arch (the white arrow)

and mild dilatation of the ascending aorta (AAo), 40 mm. Systolic function of the non-dilated left ventricle (LV) was preserved. The fused BAV type (right-left cusp fusion) was diagnosed (Figure 1A). Cardiac magnetic resonance (CMR) performed at the age of 32 years showed moderate to severe PR and a moderately enlarged RV with good contractility and confirmed the presence of BAV (Figure 1B). Peak oxygen uptake was 26 ml/min/kg (74% of value according to age and sex) on the cardiopulmonary exercise test. Conservative treatment was continued.

Patient 2 (ML)

The second patient was a 36-year-old male after total correction of ToF at the age of five years, with extreme hypoplasia of the left pulmonary artery, hypoplasia of the left lung (vascularized from the left internal thoracic artery, and bronchial and intercostal arteries), AAo dilatation, right-sided aortic arch (RAA) with a ductus diverticulum, persistent left superior vena cava, and paroxysmal supraventricular tachycardias. Recent TTE showed a dilated RV (RV inflow tract, 58 mm; RV outflow tract, 47 mm; RV area, 45 cm^2), significant PR, moderate tricuspid regurgitation (tricuspid regurgitation pulmonary gradient 49 mm Hg), enlarged right atrium (RA); area 29 cm^2, dilated both the aortic root (47 mm) and AAo (39 mm). Systolic function of both ventricles was preserved. The fused BAV type (right-left cusp fusion) was diagnosed and confirmed by chest computed tomography (CT) (Figure 1C). One year earlier, he had been offered a radio-frequency ablation of the arrhythmia substrate, to which he did not consent. No indication for the surgical correction of PR was established, and the limitation of exercise tolerance and paroxysmal dyspnoea were believed to be related to left lung hypoplasia.

Patient 3 (SW)

The third patient was a 48-year-old male after central pulmonary anastomosis at the age of 11 years and complete correction of ToF at the age of 32 years, with a significant shunt through re-ventricular septal defect with Qp/Qs 2:1 on the right heart catheterization, permanent atrial fibrillation, bifascicular block, and arterial hypertension. He was offered redo surgery. Preoperative TTE showed interventricular residual shunt in the lower part of the patch with a left-to-right gradient of 78 mm Hg, dilated and hypokinetic RV (RV inflow tract 59 mm, RV outflow tract 43 mm, RV S' 9 cm/s), mild tricuspid regurgitation (RV systolic pressure 93 mm Hg), enlarged RA (area 40 cm^2), dilated pulmonary trunk (27 mm), enlarged left atrium (area 38 cm^2), dilated both the aortic root (49 mm) and AAo (45 mm). The left ventricle was non-dilated with preserved systolic function. The fused BAV type (right-left cusp fusion) was diagnosed (Figure 1E). He underwent mechanical aortic valve implantation — St. Jude Medical Regent 27 mm (St. Jude Medical, Inc, St. Paul, MN, US) with closure of the re-ventricular septal defect using an artificial patch and surgery of the aortic root. The presence of BAV was confirmed intraoperatively. Postoperative TTE showed a reduction in the right ventricular systolic pressure (43 mm Hg).

Only small regurgitation of the aortic valve was visible in all these patients. In none of them, was trans-valvular gradient measured nor coarctation of the aorta diagnosed.

Firstly, all our patients presented with mild to moderate dilatation of the aortic root (40 mm, 47 mm, and 49 mm, respectively) and ascending aorta (40 mm, 39 mm, and 45 mm, respectively), without significant progression over time (Supplementary material, *Table S2*). Arterial hypertension (third patient) could contribute to AAo dilatation. Dilatation of the proximal AAo is frequent in BAV patients (20%–68%) [5]. Notably, most adolescents with repaired ToF and tricuspid aortic valve (TAV) show also significant dilatation of the aortic root and AAo [6, 7]. Assessment of AAo in ToF patients with BAV is limited to one study [7]. It revealed that aortic dissection did not occur in ToF patients with significant aortic aneurysms. Thus, AAo-diameter thresholds might be higher for ToF patients while considering prophylactic AAo surgery (taking into account the increased risk of re-operation). Already, all of our three patients underwent corrective surgery for ToF in the past. There was no availabe data about the risk of aortic dissection in ToF patients (usually after previous surgeries) with AAo-dilatation and BAV. Thus, the decision regarding prophylactic aortic surgery should be individualized.

Secondly, all our patients presented with the fused type of BAV, with right-to-left leaflet fusion. The quality of the echocardiographic examination in patients after previous cardiac surgeries may be suboptimal. Thus, accurate characterization of BAV morphology and the unambiguous assessment of the presence of raphe may be difficult. Other imaging modalities (CT, CMR) may give insight. A retrospective study of 156 adult patients has shown that right-to-left leaflet fusion was strongly associated with rapid aortic dilatation [5].

Thirdly, patient 2 presented with RAA (Figure 1F). The prevalence of RAA in the general population is very low (ranging between 0.04% and 0.1% [8, 9]); however, it is not a rare finding in ToF cohorts (around 20% [10]). Apart from ToF, the separate coexistence of BAV and RAA is a casuistic finding (Supplementary material, *Table S3*).

Finally, the prevalence of BAV among adult ToF patients (0.53%) is similar to the prevalence in the general population.

Limitations

Retrospective nature carries inherent limitations. We did not specifically analyze every imaging examination (echocardiography, chest CT, CMR) of ToF patients, but instead, we searched for specific keywords in our electronic database of discharge summaries. Secondly, two of three patients underwent surgical correction at an early age (in another hospital). Thus, we did not have a detailed report of the operation. Finally, the number of patients was small, and thus the statistical analysis was limited to the prevalence of BAV among ToF.

CONCLUSIONS

These three patients add to the very limited literature on BAV among ToF patients. The previous reports were focused on the casuistic coexistence of these two anomalies and mainly in the pediatric population. This paper presents the first systematic study of BAV among a large cohort of adult patients with ToF, providing additional new findings, namely the BAV type, as well as information on the prevalence of BAV among the ToF cohort.

Article information

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Myocardial perfusion in non-infarcted areas in acute coronary syndrome with ST-segment elevation assessed by SPECT perfusion imaging

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INTRODUCTION

Acute coronary syndromes (ACS) are associated with a global slowing of coronary perfusion [1, 2]. The sympathetic activity, increased in patients with myocardial infarction, impairs vasodilator responsiveness in the coronary circulation [2, 3]. A shift towards lactate metabolism in areas of the myocardium not affected by coronary occlusion was observed in animal models [4, 5].

We aimed to examine the myocardial perfusion and viability in non-infarcted areas in patients with first ACS with ST-segment elevation myocardial infarction (STEMI) as assessed by single photon emission computed tomography (SPECT) perfusion imaging, an imaging modality widely accepted for the diagnosis of cardiovascular diseases [6].

METHODS

This is a post hoc analysis of a trial on aspiration thrombectomy in STEMI patients performed between January 2005 and September 2008 [7].

The eligibility criteria were: (1) first STEMI within 12 hours from symptoms onset; (2) culprit lesion in the left anterior descending (LAD) or right coronary arteries (RCA); and (3) culprit Thrombolysis in Myocardial Infarction (TIMI) blood flow grade ≤2 [7]. The exclusion criteria included: (1) cardiogenic shock; (2) culprit in the left circumflex artery (LCX); (3) previous myocardial infarction; and (4) any chronic total coronary occlusion.

Following the angiography, the patients were randomized (1:1) to a group with aspiration thrombectomy or a group with standard primary percutaneous intervention (pPCI) of infarct-related artery (IRA). Immediately after and before the intervention all patients received an intravenous injection of ^{99m}Tc-sestamibi. An index SPECT examination (SPECT I) was performed within 3–5 hours after injection. Follow-up ^{99m}Tc-sestamibi imaging (SPECT II) was performed within 5–8 days after the intervention. Perfusion of the myocardium was assessed in 17 myocardial segments. LAD typically supplies 7 segments while RCA and LCX each supply 5 segments. We used a standard grading scale for visual assessment of perfusion where 0 indicates no perfusion impairment, 1 — mild, 2 and 3 moderate perfusion abnormalities, and 4 — lack of perfusion. The sum of perfusion segmental defect grades for each vessel territory and for the whole myocardium produced respective Summary Defect Score (SDS) indices. Separate SDS for LAD (SDS_{LAD}), RCA (SDS_{RCA}), and LCX (SDS_{LCX}) territories were calculated for SPECT I and SPECT II. Combined SDS for non-infarct-related territory was then calculated. Since in patients with culprit LAD there are 10 remote segments and in patients with culprit RCA there are 12 segments, we normalized the values, and hence normalized SDS for non-infarct-related territory ($SDS_{non\text{-}IRA}$) was either a product of (SDS_{RCA} + SDS_{LCX}) × 1.2 for the culprit LAD or SDS_{LAD} + SDS_{LCX} for the culprit RCA. To avoid bias related to the overlapping of blood supply in apical segments, we also calculated SDS for the basal LAD, basal RCA, basal LCX, and basal non-IRA segments (SDS_{LADBAS}, SDS_{RCABAS}, SDS_{LCXBAS}, and $SDS_{non\text{-}IRABAS}$ respectively). There are two basal segments for every coronary artery, and hence no normalization factor was needed. SPECT examinations were used for the assessment of left ventricular ejection fraction (LVEF).

The study was approved by the local Ethics Committee and was performed in accordance with the Helsinki Declaration. All patients participating in the trial signed informed consent.

Statistical analysis

Continuous data with normal distribution are presented as means with standard deviation while the non-normally distributed are presented as medians with interquartile ranges. Normality was assessed using the Shapiro-Wilk test. Correlations of continuous variables were assessed with the Spearman coefficient. A two-tailed paired sample t-test or Wilcoxon test were used to assess differences between continuous variables. All *P*-values below 0.05 were considered significant. Software MedCalc version 9.3.8.0 (MedCalc, Marierkerke, Belgium) was used for statistical analysis.

Results and discussion

There were 137 (5%) patients enrolled from 3030 patients with STEMI treated between January 2005 and September 2008 [7]. Paired SPECT I and SPECT II examinations with a full dataset enabling SDS evaluation were available for 124 (91%) patients (5 [4%] patients died before the second SPECT, 3 [2%] patients could not be transferred to the nuclear lab due to hemodynamic instability, and in 5 [4%] cases, SPECT data on SDS evaluation for separate segments were not available). There were 88 (71%) male patients with mean (SD) age of 62.9 (11.5) years. LAD was the culprit vessel in 41 (33%) and RCA in 83[67%] patients. Main comorbidities were hypercholesterolemia (n = 93, 75%), hypertension (n = 71, 57%), active smoking (n = 52, 42%), and diabetes mellitus (n = 19, 15%). Before the angiography, all patients received loading doses of acetylsalicylic acid (ASA) (300 mg) and clopidogrel (300–600 mg) (in 110 patients [89%] ASA, and in 91 patients (73%) clopidogrel was initiated before admission). Secondary lesions in non-culprit arteries were identified in 15 (12%) patients. The study results are summarized in Table 1.

Overall, median $SDS_{non\text{-}IRA}$ and $SDS_{non\text{-}IRABAS}$ improved between SPECT I and SPECT II examinations: median (interquartile range [IQR]), 9 (5–14) vs. 7 (4–11); $P < 0.001$ and 4 (2–8) vs. 4 (1–7); $P < 0.001$, respectively.

In subgroup analyses, we observed improvement in $SDS_{non\text{-}IRA}$ and $SDS_{non\text{-}IRABAS}$ between SPECT I and SPECT II both for patients with culprit RCA and patients with culprit LAD.

The median difference in normalized $SDS_{non\text{-}IRA}$ and $SDS_{non\text{-}IRABAS}$ between SPECT I and SPECT II (delta) was larger for culprit LAD than for culprit RCA: –2.4 (–6.3–[–1.2]) vs. –1 (–3–1); $P = 0.005$ and –1 (–3–0) vs. 0 (–1–0); $P = 0.001$ respectively. At SPECT I examination $SDS_{non\text{-}IRA}$

Table 1. Perfusion data at SPECT I and SPECT II examinations. Results are presented as median (interquartile range, IQR) or mean (standard deviation, SD)

Culprit	Perfusion data	SPECT I	SPECT II	*P*-value
Both (124)	$SDS_{non\text{-}IRA}$ median (IQR)	9 (5–14)	7 (4–11)	<0.001
	Normalized $SDS_{non\text{-}IRA}$ median (IQR)	9.8 (5–15.6)	8 (4–12)	<0.001
	$SDS_{non\text{-}IRABAS}$ median (IQR)	4 (2–8)	4 (1.5–7)	<0.001
	SDS_{LAD} median (IQR)	4 (1–20)	4 (2–13)	0.01
	SDS_{LCX} median (IQR)	4 (0–6)	2 (0–4)	<0.001
	SDS_{RCA} median (IQR)	12 (9–15)	8 (6–12)	<0.001
	SDS_{LADBAS} median (IQR)	1 (0–4)	1 (0–3)	0.04
	SDS_{LCXBAS} median (IQR)	2 (0–4)	1 (0–3)	<0.001
	SDS_{RCABAS} median (IQR)	8 (4–9)	6 (3–7.5)	<0.001
	SDS total median (IQR)	24 (16–34)	18 (12–26)	<0.001
LAD (n = 41. 33%)	$SDS_{non\text{-}IRA}$ mean (SD)	12.8 (4.6)	10.3 (5.0)	<0.001
	Normalized $SDS_{non\text{-}IRA}$ mean (SD)	15.4 (5.5)	12.3 (6.0)	<0.001
	$SDS_{non\text{-}IRABAS}$ median (IQR)	8 (4–11)	7 (3–9)	<0.001
	SDS total median (IQR)	36 (31–39)	28 (21–34)	<0.001
RCA (n = 83. 67%)	$SDS_{non\text{-}IRA}$ median (IQR)	7 (4–12)	6 (4–9)	0.01
	Normalized $SDS_{non\text{-}IRA}$ median (IQR)	7 (4–12)	6 (4–9)	0.02
	$SDS_{non\text{-}IRABAS}$ median (IQR)	3 (0–6)	3 (1–5)	0.02
	SDS total median (IQR)	21 (14–26.5)	15 (11–20)	<0.001
	Culprit	LAD	RCA	—
	SPECT I $SDS_{non\text{-}IRA}$ median (IQR)	13 (9.5–16)	7 (4–12)	<0.001
	SPECT I $SDS_{non\text{-}IRABAS}$ median (IQR)	8 (4–11)	3 (0–6)	<0.001
LAD (n = 41. 33%) vs. RCA (n = 83. 67%)	SPECT I normalized $SDS_{non\text{-}IRA}$ median (IQR)	15.6 (11.7–19.2)	7 (4–12)	<0.001
	SPECT II $SDS_{non\text{-}IRA}$ median (IQR)	10 (6.5–14)	6 (4–9)	<0.001
	SPECT II $SDS_{non\text{-}IRABAS}$ median (IQR)	7 (3–9)	3 (1–5)	0.001
	SPECT II normalized $SDS_{non\text{-}IRA}$ median (IQR)	12 (8.1–16.8)	6 (4–9)	<0.001
	Delta (S II – S I) normalized $SDS_{non\text{-}IRA}$ median (IQR)	–2.4 (–6.3–[–1.2])	–1 (–3–1)	0.005
	Delta (S II – S I) $SDS_{non\text{-}IRABAS}$ median (IQR)	–1 (–3–0)	0 (–1–0)	0.001

Abbreviations: BAS, basal; Delta (S II – S I), difference between SPECT II and SPECT I; IQR, interquartile range; IRA, infarct-related artery; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery; SD, standard deviation; SDS, Summary Defect Score; SPECT, single photon emission computed tomography

and $SDS_{non\text{-}IRABAS}$ medians were larger in patients with culprit LAD than with culprit RCA: 13 (9.5–16) vs. 7 (4–12) and 8 (4–11) vs. 3 (0–6); respectively P <0.001 for both comparisons. Also, SPECT II results showed larger $SDS_{non\text{-}IRA}$ and $SDS_{non\text{-}IRABAS}$ medians in patients with culprit LAD: 10 (6.5–14) vs. 6 (4–9); P <0.001 and 7 (3–9) vs. 3 (1–5); P = 0.001 respectively.

There was no difference in median SDS_{nonIRA} and median $SDS_{nonIRABAS}$ between patients with and without secondary stenosis in SPECT I: 8 (4–12.5) vs. 9 (5–14); P = 0.45; 6 (2.5–8) vs. 4 (2–8); P = 0.66, respectively, nor in SPECT II: 6 (2.5–12) vs. 7 (5–11); P = 0.59; 5 (1.5–7) vs. 4 (2–6); P = 0.64, respectively.

The median LVEF was 46% (37%–53%) at SPECT I examination and 45.5% (40%–53%) at the follow-up (P = 0.06). Overall, $SDS_{non\text{-}IRA}$ was inversely correlated with LVEF both at SPECT I and SPECT II examination (R = –0.398; P <0.001 and R = –0.41; P <0.001, respectively). Similar results were obtained for $SDS_{non\text{-}IRABAS}$ (R = –0.437; P <0.001 and R = –0.392; P <0.001, respectively).

Our study is the first to document the presence of global myocardial ischemia detected with SPECT imaging in STEMI patients. The main findings of the study are 1) perfusion in non-infarct-related territories is impaired in the acute phase of STEMI and improves within a week following pPCI; 2) STEMI with culprit lesion located in LAD has a larger impact on perfusion in non-infarct-related territories than inferior STEMI with culprit RCA.

Our data support reports demonstrating that non-culprit artery flow is impaired in patients with STEMI and suggest that slower blood flow impacts perfusion and causes global myocardial ischemia [1]. Gibson et al. [1] showed that thrombolysis improved coronary flow also in non-IRA. Our data extend these findings in relation to tissue perfusion to the patients treated with pPCI. The current report is in line with the data published by Uren et al. [3] who found with the use of positron emission tomography that vessel vasodilator response in patients with myocardial infarction is abnormal even in segments not supplied by the IRA. Moreover, this abnormality may be responsible for the extension of myocardial necrosis. Our findings are in concordance with the results of pathophysiological studies performed on dogs showing that LAD occlusion causes focal necrosis in the remote segments supplied by a patent artery [5].

The finding that STEMI with LAD occlusion is accompanied by especially pronounced perfusion impairment of non-infarct-related territories is similar to the results published by Gibson et al. who showed that STEMI with culprit LAD is associated with slower corrected TIMI frame count [1]. Our results and those presented by Gibson et al. demonstrate the impact of perfusion abnormalities in non-infarcted areas on left ventricular systolic function. Interestingly, we did not find a relation between secondary stenosis in non-IRA and perfusion impairment.

It should be added that currently, the routine use of an aspiration thrombectomy is not standard practice in STEMI patients, however, it does not influence the study findings.

Article information

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Incidental diagnosis of Brugada syndrome in two girls hospitalized for pediatric inflammatory multisystem syndrome related to COVID-19 (PIMS-TS)

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SARS-CoV-2-related pediatric inflammatory multisystem syndrome (PIMS-TS) is a novel syndrome first described in England in May 2020 [1]. It affects children 2–6 weeks after COVID-19 infection whether symptomatic or not. The course of the disease varies from mild to requiring Intensive Care Unit support, with a 2% mortality rate reported [2]. An inherent symptom of PIMS-TS is high fever. Cardiac evaluation is crucial in PIMS-TS patients as the involvement of the cardiovascular system determines the course of disease and prognosis.

We present 2 cases of girls aged 5 (Patient 1) and 7 years (Patient 2). They were both admited to hospital due to high unremitting fever, weakness, and mucocutaneous and gastrointestinal symptoms. Patient 2, presented with severe dyspnea and had a history of upper respiratory tract infection with a highly possible COVID-19 etiology 3 weeks earlier.

On admission, the girls presented with fever, polymorphic rash, and conjunctival redness. Patient 2 had hepatomegaly, pleural effusion, and cardiac enlargement on chest X-ray. Laboratory test results in both patients were typical of PIMS-TS with significantly elevated inflammatory parameters, cardiac biomarkers, lymphopenia, hyponatremia, and increased D-dimers. Following PIMS-TS diagnostic and treatment protocol, electrocardiography (ECG) and echocardiography were performed [3]. ECG showed abnormal repolarization with coved ST-segment elevation ≥2 mm, followed by negative T wave in V1 and V2 precordial leads. Such abnormalities are not characteristic of PIMS-TS.

The patients were treated for PIMS-TS in accordance with the Polish Pediatric Society recommendations [3]. Immunomodulating therapy (immunoglobulins and glucocorticosteroids) and acetylsalicylic acid were administered. Patient 2 developed symptoms of cardiogenic shock with severely reduced left ventricular ejection fraction and required inotropic medication. They both recovered without complications. Their ECGs normalized once the fever resolved.

With the aforementioned ECG recordings, both patients met the criteria for the Brugada type 1 ECG pattern [4]. Brugada syndrome phenocopies were excluded [5]. Patients and their first-degree relatives underwent a thorough cardiological screening according to the Heart Rhythm Society/European Heart Rhythm Association/Asia Pacific Heart Rhythm Society (HRS/EHRA/APHRS) expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes [4].

Patient's 1 family's cascade screening led to the patient's father being subjected to an ajmaline challenge, which revealed a typical Brugada syndrome pattern. Moreover, the index-case paternal grandfather suffered a sudden cardiac death. The girl's genetic test with Next Generations Sequencing (NGS) testing showed a variant of unknown significance in the SCN5A gene. No other family members shared the disease. No significant events were reported in patient's 2 family. They are currently being investigated to exclude the disease in first-degree relatives of the patient. NGS testing is in progress. Both patients were then given lifestyle change recommendations, according to the HRS/EHRA/APHRS expert consensus statement [4]. However, both

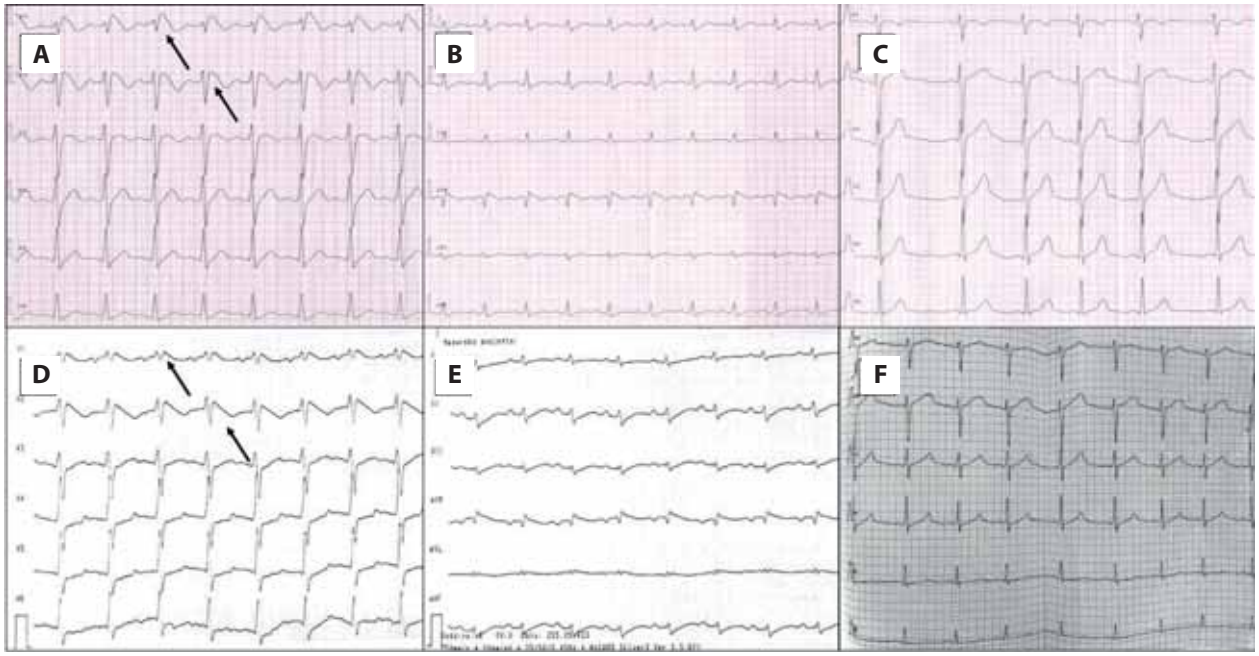

Figure 1. A, B. Patient 1 — ECG obtained during fever showing Brugada pattern (the black arrows) in the precordial leads. **C.** Patient 1 — normal ECG recording after defervescence, precordial leads. **D, E.** Patient 2 — ECG obtained during fever showing Brugada pattern (the black arrows) in the precordial leads. **F.** Patient 2 — normal ECG recording after defervescence, precordial leads

Abbreviations: ECG, electrocardiogram; PIMS-TS, pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2

families were reassured about the low risk of life-threatening arrhythmias in asymptomatic and incidentally diagnosed patients.

The two cases presented a typical but severe course of PIMS-TS. High and long-lasting fever occurring in PIMS-TS exposed the abnormal electrocardiographic repolarization pattern which led to the diagnosis of Brugada syndrome. In children, ECG in fever is rarely performed, however, as stated, it may lead to a correct diagnosis.

Article information

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When an interventional cardiologist needs an interventional radiologist: Efficient treatment of coronary perforation

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Coronary artery perforation is a life-threatening sequel complicating 0.2%–0.9% of percutaneous coronary interventions (PCI) [1]. Here, we present an example of fruitful cooperation between an interventional cardiologist and a radiologist in managing distal right coronary artery (RCA) perforation. A 76-year-old male with a history of dyslipidemia, type 2 diabetes mellitus, and prior PCI in the left circumflex artery was admitted for PCI in RCA with rotational atherectomy. The patient was on dual antiplatelet therapy (acetylsalicylic acid 75 mg and clopidogrel 75 mg). From the right radial approach, rotablation was performed with 1.5 mm and 1.75 mm burrs in the proximal and mid RCA segments (Figure 1A–B). After successful rotablation, a working guidewire was advanced (Sion blue with a J tip, Asahi Intecc, Irvine, CA, US), and two sirolimus-eluting stents Prolim (Balton, Poland) were deployed in the mid (3.5 × 25 mm) and proximal (4.0 × 29 mm) segments. Stents were optimized with a non-compliant balloon catheter (4.0 × 12 mm) under intravascular ultrasound imaging (Figure 1C). However, at the final checking, the contrast extravasation next to one of the posterolateral branches was disclosed (Figure 1D; Supplementary material, *Video S1*). Despite three prolonged balloon inflations, the leakage was not stopped. Echocardiography showed no signs of cardiac tamponade; therefore, no protamine sulfate was administered. After consulting with an interventional radiologist, five spiral coils were used: three 1 mm/3 cm MicroPlex Hydrosoft 3D (MicroVention, Aliso Viejo, CA, US) and two 2 mm/3 cm + 2.5 mm/6 cm Axium Prime coils (Medtronic, Minneapolis, MN, US) (Figure 1E). The perforation was successfully closed with no excessive fluid in the pericardium (Figure 1F; Supplementary material, *Video S2,* and *S3*). The patient was discharged after two days on dual antiplatelet therapy.

In some cases, prolonged balloon inflation may lead to hemostasis, but if pericardial bleeding continues, definitive treatment may be needed (covered stents or cardiac surgery) [2]. However, covered stents are not feasible for small vessels. In such cases, embolization may play a part. In our patient, the radiologist used coils designed to close intracranial aneurysms. When introduced, their successive loops change direction, evenly distribute themselves within the vessel, and efficiently close the perforation. Moreover, poly (glycolide-co-L-lactide) or nylon microfilaments reduce the flow and accelerate thrombosis [3]. Such an approach allowed the patient to avoid open heart surgery and enabled quick discharge.

Supplementary material

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

Article information

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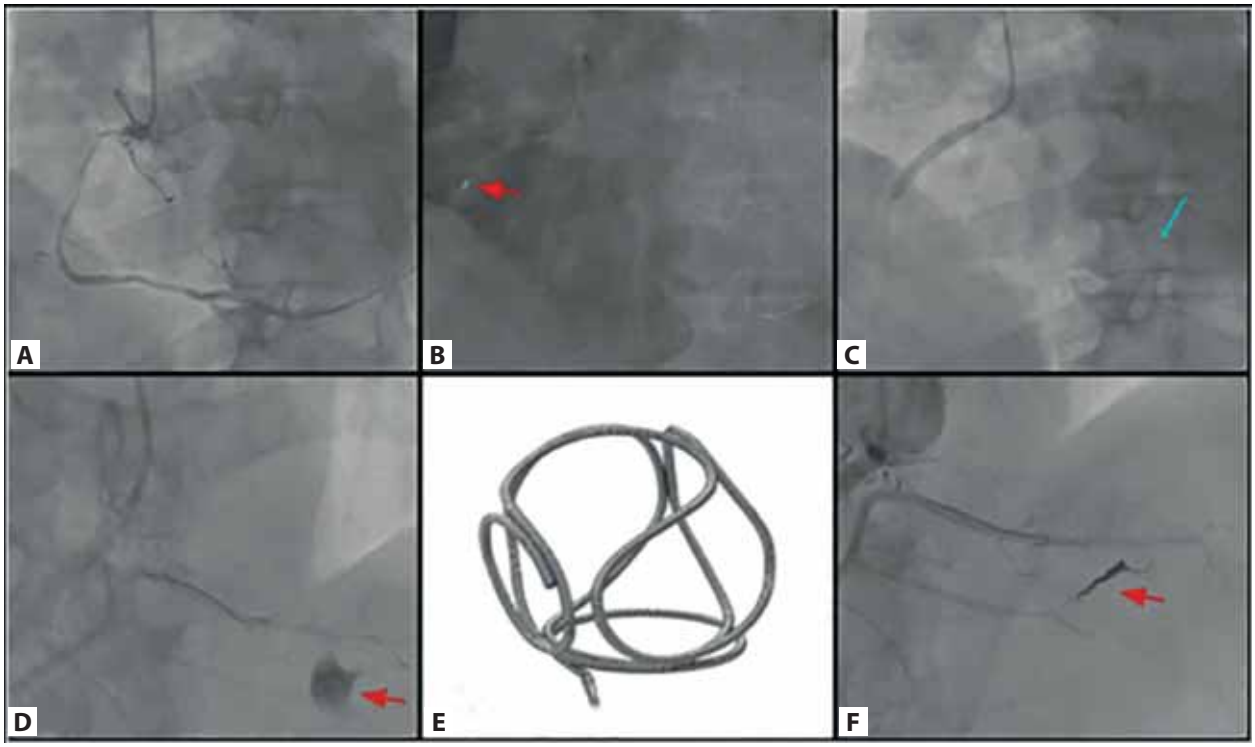

Figure 1. A. Significant long stenosis in the proximal and medial RCA. **B.** A rotablation procedure (the red arrow showing the burr). **C.** Stent optimization with deep location of the distal guidewire (the arrow showing the distal end of the guidewire). **D.** Contrast extravasation (the red arrow). **E.** An example spiral coils used to close the perforation. **F.** The final view with coils (the red arrow) implanted in the posterolateral branch of the RCA

Abbreviation: RCA, right coronary artery

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A large left atrial appendage thrombus revealed on transthoracic echocardiography as a cause of acute lower limb ischemia

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An 85-year-old female with hypertension, mitral stenosis (MS), and atrial fibrillation (AF) of undetermined duration, with suboptimal anticoagulation, was admitted due to exacerbation of heart failure. The treatment of heart failure and acenocoumarol therapy were optimized. Routinely performed transthoracic echocardiography (TTE) revealed moderate MS (mean gradient 6 mm Hg) (Figure 1A), signs of right ventricular overload, a slightly enlarged left atrium, and an abnormal highly mobile "soft" structure 25 × 14 mm in size (Figure 1B; Supplementary material, *Video S1*), fixed in the place of the left atrium appendage (LAA) (Figure 1C; Supplementary material, *Video S2*). A LAA thrombus was suspected. Unfortunately, two days after admission the patient presented severe pain in the right lower limb and signs of acute limb ischemia (ALI) such as pallor, cold limb, paresthesias, and pulselessness. On bedside TTE performed immediately, the previously detected additional

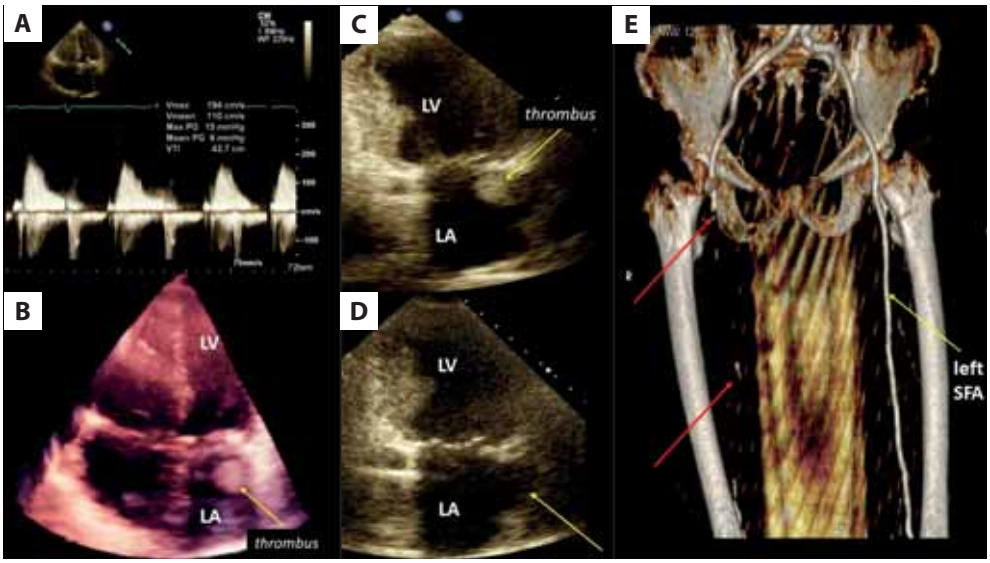

Figure 1. A. Transmitral mean gradient (6 mm Hg) indicating moderate mitral stenosis; continuous wave Doppler; **B.** Additional mass (thrombus) visible in the slightly enlarged left atrium (the arrow); 3D TTE, four-chamber view; **C.** Additional structure (thrombus) fixed in the place of the left atrium appendage (the arrow); 2D TTE, two-chamber view; **D.** Absence of pathological mass in the area of the left atrium appendage (the arrow); 2D TTE, two-chamber view; **E.** Lower-extremity computed tomographic angiography showing occlusion of the distal part of the right common femoral artery, right superficial femoral artery and deep femoral artery (red arrows). Normal flow in the left superficial femoral artery (yellow arrow)

Abbreviations: LA, left atrium; LV, left ventricle; SFA, superficial femoral artery; 2D TTE, two-dimensional transthoracic echocardiography; 3D TTE, three-dimensional transthoracic echocardiography

mass located in the LAA was not visualized (Figure 1D), which confirmed that the clot had detached from the heart.

Lower-extremity computed tomographic angiography showed occlusion of the distal part of the right common femoral artery, entire superficial femoral artery, and deep femoral artery (Figure 1E). The patient was urgently operated on by vascular surgeons, who removed thrombi from the occluded arteries, with a satisfactory treatment result.

ALI induced by acute peripheral arterial occlusion (APAO) is one of the most common causes of urgent interventions in vascular surgery [1], associated with a high risk of limb loss and increased mortality [2]. Most frequently ALI is caused by embolism, thrombosis, or rarely by dissection or trauma [1–3]. Importantly, embolism originating in the heart or aorta may lead not only to APAO but also to transient ischemic attack or stroke, with all their serious consequences. Valvular and non-valvular AF are common causes of cardioembolic events [4]. Al-Azzawi et al. [1] evaluated 120 patients with APAO on the upper (45 pts) and lower (75 pts) extremities, who underwent surgical embolectomy. TTE performed during the postoperative period detected a cardiac source of embolism in 62.4% of patients, including MS in 12.5% and AF in 33.3%. The prevalent source of cardioembolism are thrombi located in the LAA [4]. Transesophageal echocardiography is the imaging of choice for the LAA. It is also possible to identify thrombus on TTE, however, its sensitivity remains low [4].

In the described case, TTE, showing a large additional mobile mass in the LAA area, proved to be diagnostic for a cardiac source of embolism. Balloon embolectomy was urgently performed, as standard treatment of ALI caused by an embolus, in accordance with current recommendations [3]. It seems reasonable to perform at least TTE in patients with ALI, as soon as possible, to detect a potential cause of embolism. In exceptional situations, TTE is sufficient to make a diagnosis, as was the case in the described patient with very high embolic potential. In patients with non-valvular AF and unstable oral anticoagulation percutaneous LAA closure may be an alternative method for stroke prevention [5]; however, in our patient, the coexistence of AF and moderate mitral valve stenosis was confirmed.

Supplementary material

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

Article information

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Tetralogy of Fallot after palliative Blalock-Taussig shunt in a 50-year-old female: Complex medical and social challenge with fatal outcome due to COVID-19

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A 50-year-old female with tetralogy of Fallot, without regular cardiological follow-ups, was referred to a cardiologist at a district hospital by her general practitioner due to resting dyspnea. The patient, a mother of two healthy children, did not undergo surgical correction of the heart defect in infancy but had a palliative Blalock-Taussig operation with the creation of a shunt between the right subclavian artery and the ipsilateral pulmonary artery at the age of 7 years [1]. Physical examination showed signs of central cyanosis and body mass of 40 kg with a height of 159 cm (body mass index [BMI], 17.0 kg/m^2). Arterial blood saturation equaled 69.1%, hemoglobin reached 21.0 g/dl, hematocrit — 74.2%, and platelet count — 98 000/µl (n >150). A transthoracic echocardiogram showed a large ventricular septal defect, an overriding aorta, and increased maximum gradient through the stenotic pulmonary artery valve of 70 mm Hg, with mild pulmonary insufficiency. The pulmonary artery trunk was widened, and the right ventricle was slightly enlarged with a thickened free wall of 11 mm and impaired systolic function. Left ventricle size was within normal ranges with signs of concentric hypertrophy and a mildly compromised systolic function (left ventricular ejection fraction — 48%) [2]. Due to the patient's symptoms, elevated D-dimer (1005 µg/l [n <500]), troponin T (110.7 ng/ml [n <14]) and N-terminal pro-B-type natriuretic peptide (11833 pg/ml [n <125]) computed tomography angiography of the pulmonary arteries was performed which did not confirm the presence of a pulmonary embolism. The patient was referred to an invasive cardiology unit for cardiac catheterization and further diagnostics. Ergospirometry revealed low maximum oxygen consumption, and plethysmography showed a restrictive type of ventilation. Heart catheterization showed a right-left shunt at the level of ventricular septum defect and a left-right shunt at the level of Blalock-Taussig anastomosis, high pressure in the pulmonary circulation with estimated much increased vascular resistance (18–22 WU). The patient was disqualified from surgical treatment. Treatment with prostanoids and bosentan was unsuccessful due to serious side effects not accepted by the patient. The patient was next referred to the Grown-Up Congenital Heart Disease (GUCH) Outpatient Clinic in Krakow [3]. Due to limited access to the aforementioned clinic and the patient's poor clinical and economic condition, further follow-up was conducted at the department of cardiology at the District Hospital in Bochnia. The multidirectional actions, based on clinical experience and a case-by-case basis, comprised home oxygen therapy, recurrent phlebotomies, as well as dealing with malnutrition, supraventricular and ventricular arrhythmias, and an increased risk of coagulation abnormalities. This therapy resulted in the stabilization of the patient's condition. Social services were involved, and the patient received home hospice care. Medical recommendations included influenza and pneumococcal vaccinations. When the COVID-19 pandemic broke out, a recom-

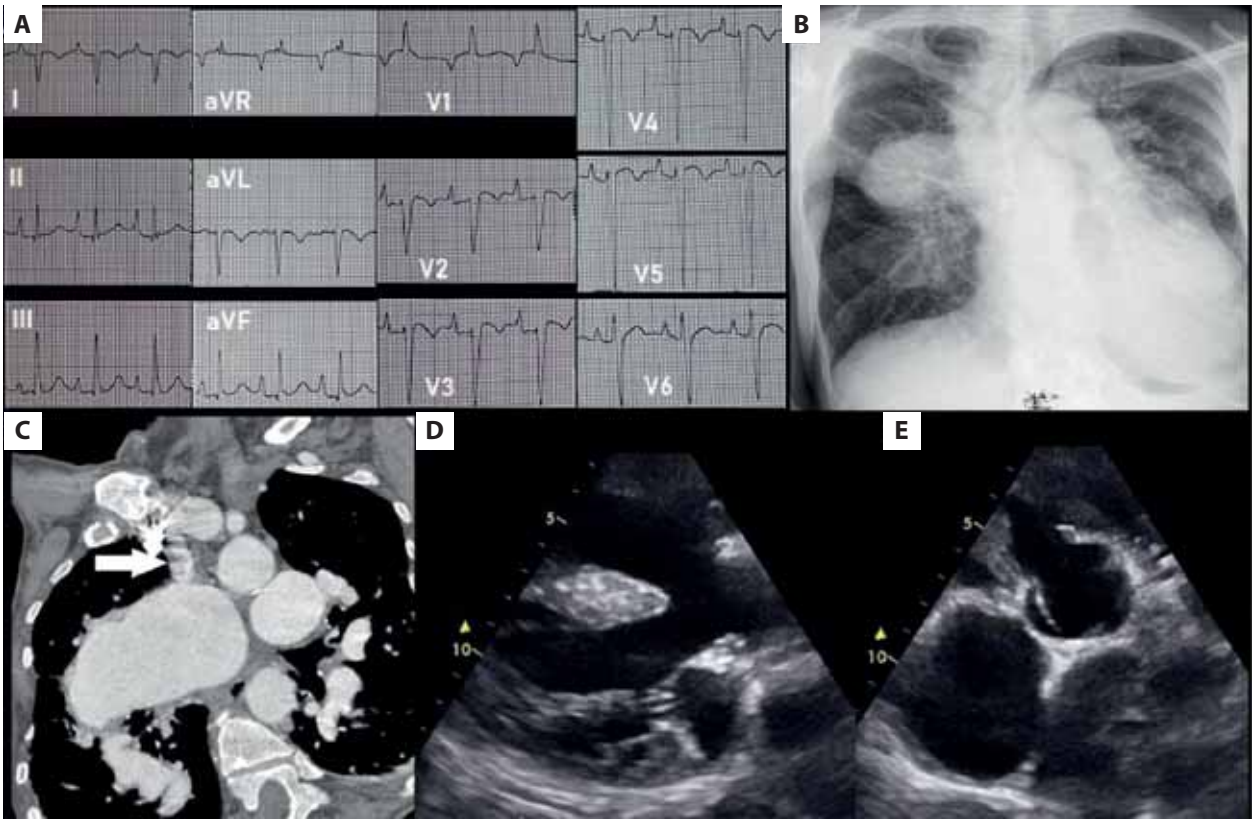

Figure 1. A. An electrocardiogram with sinus rhythm, features of both atria hypertrophy, right heart deviation, and signs of hypertrophy of both ventricules. **B.** Chest X-ray displaying enlarged heart silhouette with dilated right pulmonary hilum due to dilatation of the right pulmonary artery. **C.** A thoracic computed tomography scan showing a patent Blalock-Taussig shunt (arrow). **D–E.** A transthoracic echocardiogram with: **D.** A large ventricular septal defect. **E**. An overriding aorta

mendation to avoid gatherings was given. Unfortunately, before COVID-19 vaccines were developed, the patient's husband fell ill with COVID-19 and transmitted the virus to the patient who developed acute respiratory failure and later died. In conclusion, vaccinations for emerging infectious diseases and booster vaccinations for respiratory contagious disorders including COVID-19 should be highly promoted and considered both for patients with severe heart diseases, such as heart failure and congenital defects, and their household members [4, 5].

Article information

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Simultaneous pulmonary embolization and myocardial infarction with ST-segment elevation related to paradoxical embolization: Significance of patent foramen ovale

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Paradoxical embolism is the clinical condition in which the embolic material from the venous system is transmitted to the arterial system through an intracardiac shunt — a patent foramen ovale (PFO) or an ostium secundum atrial septal defect. Sometimes a thrombus may also get entrapped in a PFO creating a risk of a peripheral arterial embolism. It is a rare and unconventional source of acute arterial occlusion. It can cause a stroke, visceral vessel embolism, and in some cases a myocardial infarction [1, 2].

A 36-year-old man without significant cardiovascular diseases was admitted to the hospital with an acute anterior-inferior ST-segment elevation myocardial infarction (Figure 1A) resulting from an embolism in the left anterior descending artery (LAD) (Figure 1B). The dominant clinical symptoms were dyspnea, and chest pain. Vital signs were as follows: (1) oxygen saturation level: 92%; (2) blood pressure: 90/50 mm Hg; and (3) heart rate: 120/min. In laboratory tests, high D-dimer levels were detected (7454 ng/ml; norm: <500) and elevated cardiac troponin levels were found (>25 ng/ml; norm: <0.016). While performing a routine transthoracic/transesophageal echocardiography assessment, we found: (1) right ventricular enlargement (parasternal long-axis view): 3.9 cm; (2) elevated tricuspid regurgitation peak gradient >55 mm Hg; (3) flattening of the interventricular septum: D-shaped left ventricle (Figure 1D); and (4) a thrombus straddling the PFO (Figure 1D–E). The computed tomography pulmonary angiography confirmed a central pulmonary embolism with a thrombus formed in the right pulmonary artery and complicated by a thrombus straddling the PFO (Figure 1C). The coronary angiography demonstrated total occlusion of the LAD (Figure 1B). A percutaneous mechanical aspiration thrombectomy attempt to remove the thrombus from the LAD was unsuccessful. Only small fragments of the thrombus were removed.

The patient underwent cardiac surgery by sternotomy, with extracorporeal circulation, which involved atriotomy with the removal of all available thrombi from lobar and segmental pulmonary arteries, PFO, and the LAD artery (Figure 1F–G). The patient received therapeutic doses of unfractionated heparin monitored with activated partial thromboplastin time. Intraoperative venography of iliac veins and the inferior vena cava showed no thrombus. At the same time, a temporary inferior vena cava filter was used. Due to the patient's serious condition and emergency surgery, Doppler-ultrasonography of lower extremities was not performed.

Thrombolytic treatment was not used due to the risk of fragmentation of the thrombus stuck in the PFO. The patient died in the operating theater of cardiac arrest due to pulseless electrical activity despite successful revascularization of the LAD with the left internal mammary artery coronary artery bypass graft, as a result of concomitant pulmonary

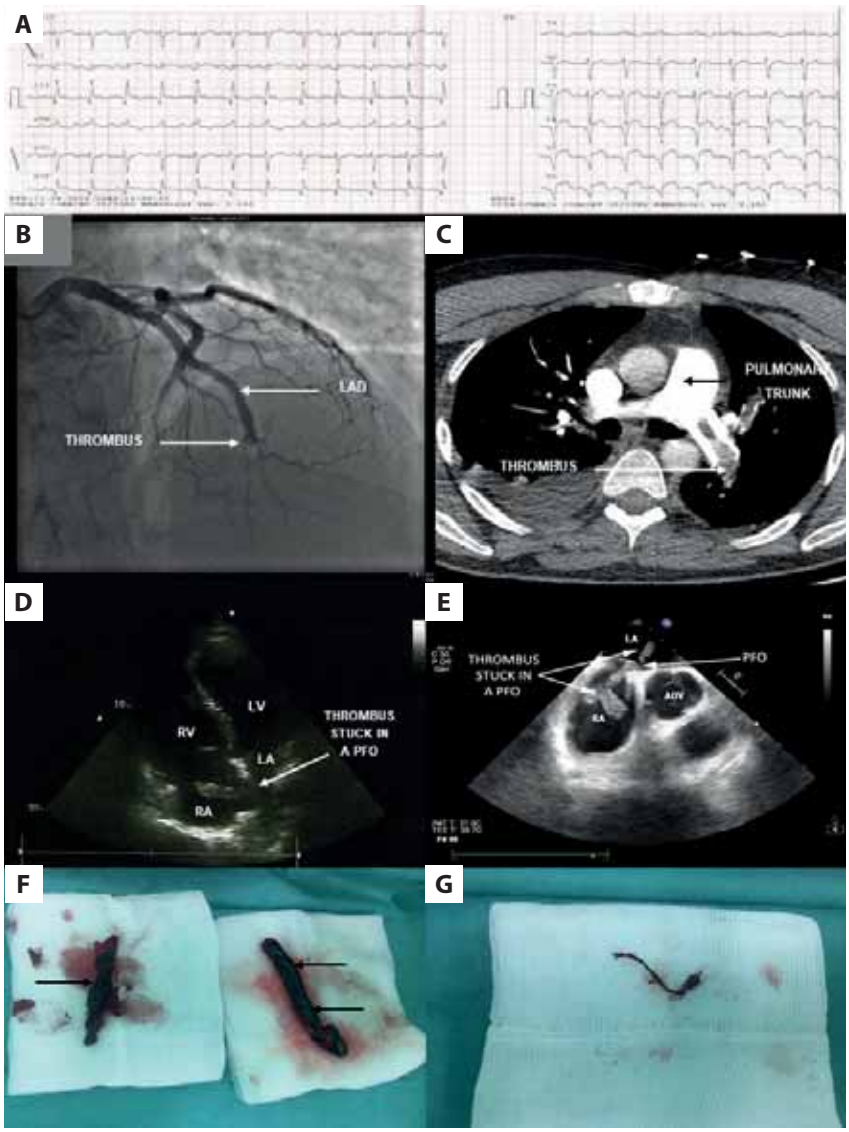

Figure 1. A. Electrocardiogram on admission: SR 120/min, right deviation of the heart electric axis, ST-segment elevation and pathological Q wave in precordial V4–V6 leads, slight ST-segment elevation and pathological Q wave in inferior leads II, III, aVF. **B.** Coronary angiography: massive thrombotic burden in the middle part (seventh segment) of the LAD (the arrow is pointing at the proximal part of the massive thrombus). **C.** Angio-CT image: a massive thrombosis of the pulmonary artery main trunk; the arrow is pointing at the thrombus (horizontal view). **D.** Transthoracic echocardiography: the thrombus trapped in a PFO extending into the RA and LA, enlarged RV; the arrow is pointing at the part of the thrombus in the RA and LA (modified apical four-chamber view). **E.** Transesophageal echocardiography: the thrombus stuck in a PFO with a mobile part in the LA; the arrows are pointing at the parts of the thrombus in the RA and LA (high transesophageal view). **F.** The thrombus removed from the PFO — single arrow; the thrombus removed from the lobar pulmonary artery — double arrows. **G.** The thrombus removed from the LAD

Abbreviations: CT, computed tomography; LA, left atrium; LAD, left anterior descending artery; LV, left ventricle; PFO, patent foramen ovale; RA, right atrium; RV, right ventricle; SR, sinus rhythm

embolism (PE) and massive embolic myocardial infarction. An intra-aortic balloon pump had no effect.

The mechanism of paradoxical embolism formation in PE patients is provoked by increased pressure in the pulmonary arteries, right ventricle, and right atrium resulting in a reversal of the blood shunt through a PFO [3]. The course of PE and paradoxical embolism can be multi-phased and may appear on consecutive days of hospitalization. A thrombus trapped in the PFO can be asymptomatic and can remain unnoticed, making it exceptionally difficult to take preventative measures and set an effective treatment.

A diagnosis of PE should lead to obligatory echocardiographic screening for the presence of both right heart/pulmonary arteries thrombus in transit and the presence of a PFO or thrombus stuck in the PFO [4]. When present, it is necessary to search for the symptoms of paradoxical embolism. Making the diagnosis at an early stage makes it possible to remove the thrombus and close the PFO by cardiac surgery, which constitutes a recommended procedure [5]. In the case of crossed embolism, taking a therapeutic approach (thrombolysis/cardiac surgery) should be individualized depending on the case because there are no direct guidelines for the treatment in such clinical situations [4, 5]. Rescue percutaneous aspiration thrombectomy of the coronary artery has limited effectiveness in the treatment of venous thrombus occlusion due to its size and structure (so-called red thrombus: erythrocyte-rich), as opposed to the well-documented high effectiveness of classic arterial thrombus aspiration in an unstable atherosclerotic plaque (so-called white thrombus: platelet-rich). Still, a vast armamentarium of interventional devices is left as a second-line treatment option and recommended mostly when systemic thrombolysis fails or is contraindicated. One of the promising options is the combined use of the AngioVac system (AngioDynamics, Inc., Latham, NY, US) and SENTINEL™ cerebral protection system (SCPS; Boston Scientific, Marlborough, MA, US) [5]. This device has a potential role in

percutaneous treatment of thrombus in transit, especially in patients with contraindications for thrombolysis and patients who may not be eligible for surgery [5].

The presence of PFO poses a risk of crossed embolism in patients with deep-vein thrombosis and PE. This is an important argument for prophylactic PFO closure or for administering chronic anticoagulant therapy [2, 5]. However, currently, PFO occlusion in patients with suspicion of cerebral or noncerebral embolism is neither clearly nor definitely established.

Article information

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Multivessel spontaneous coronary artery dissection as a cause of acute coronary syndrome: An often-forgotten differential diagnosis

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A 55-year-old female patient with no history of cardiovascular disease was admitted to our hospital with acute retrosternal chest pain. Her electrocardiogram showed ST-segment elevation in leads I, aVL, and V2–V4, with ST-segment depression in leads II, III, aVF, and V6. The patient was diagnosed with ST-segment elevation myocardial infarction, and urgent coronary angiography was performed. It showed multivessel spontaneous coronary artery dissection (SCAD) type 2a of the left anterior descending artery (LAD) and SCAD type 2b of the posterolateral branch from the right coronary artery (Figure 1A–C). Moreover, intravascular ultrasound was performed, which, aside from confirming dissection of the LAD, showed no signs of atherosclerosis. Her laboratory results demonstrated markedly elevated creatine kinase myocardial band and troponin-T levels and hypercholesterolemia.

Echocardiography showed akinesis of the apex and apical segments of all walls,

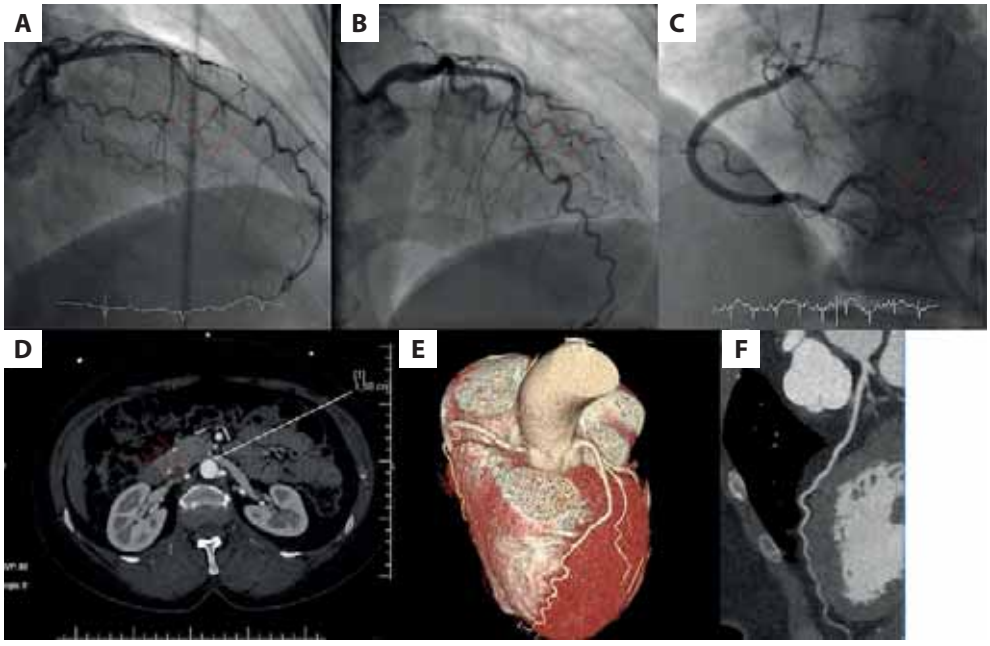

Figure 1. A–B. Coronary angiography showing spontaneous coronary artery dissection (SCAD) of the left anterior descending artery. **C.** Coronary angiography showing SCAD of the posterolateral branch from the right coronary artery. **D.** Computed tomography (CT) showing the right renal artery with morphology characteristic of fibro-muscular dysplasia. **E–F.** CT showing complete healing of coronary arteries

hypokinesis of medial segments of the anterior wall with hyperkinesis of basal segments, and a left ventricular ejection fraction of 45%–50%. Due to the presence of SCAD in coronary angiography and the patient's history of migraine headaches, additional imaging, including computed tomography of the cerebral, carotid, and vertebral arteries, was performed, in which dissection of intracerebral arteries was excluded, and a common origin of the left common carotid artery and the brachiocephalic trunk was revealed. Moreover, a Doppler-ultrasound examination of renal arteries showed no features of fibro-muscular dysplasia. The patient was treated conservatively with dual antiplatelet therapy, a statin, angiotensin-converting enzyme inhibitor, and beta-blocker. However, due to bradycardia, the beta-blocker was withdrawn. Control echocardiography showed an improvement in left ventricular systolic function, and she was discharged in good condition. During a follow-up visit, 3 months later, computed tomography was performed, which visualized the right renal artery with morphology characteristic of fibro-muscular dysplasia and complete healing of the coronary arteries (Figure 1D–E). Therefore, dual antiplatelet therapy was modified into single antiplatelet therapy with aspirin only.

This case shows multivessel SCAD as a cause of acute coronary syndrome. It highlights the importance of considering SCAD in the differential diagnosis of chest pain, particularly in middle-aged women and patients with few conventional atherosclerotic risk factors. Since a spontaneous recovery of the dissected artery is observed in the vast majority of patients, a conservative strategy is generally favored over revascularization [1, 2]. Diagnosing SCAD with the use of coronary angiography may be in some cases challenging, therefore, intravascular ultrasound or optical coherence tomography can be helpful [3]. Moreover, imaging of extra-coronary arteriopathies is advised in SCAD patients [2]. Although there is currently greater awareness of this condition, SCAD remains underdiagnosed and poorly understood, with few studies evaluating management strategies, assessing the presence and impact of predisposing and precipitating causes, or assessing its effects on shortand long-term cardiovascular prognosis [1, 2, 4].

Supplementary material

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

Article information

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When foe becomes a friend: Sequential balloon tamponade, coiling, and autologous fat particle embolization for the successful seal of a refractory distal coronary perforation during a percutaneous coronary intervention

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Coronary artery perforation (CAP) is a potentially severe complication of percutaneous coronary intervention (PCI) with an incidence of 0.71% which is managed conservatively in 73.3% of the cases, followed by the use of covered stents (24%), deployment of coils (0.7%), and fat embolization in 2% of cases [1]. Most large vessel perforations occur due to balloon or stent overinflation while distal vessel perforations are usually caused by the guidewire exit [2]. Furthermore, large vessel perforations are predominantly treated with covered stent implantation while distal and collateral perforations are typically amenable with coils or fat embolization, with both methods having inherent advantages and disadvantages [3–5]. CAP is associated with substantial mortality and morbidity as nearly 50% of patients require pericardiocentesis for tamponade, and up to 13% require emergency cardiac surgery for tamponade treatment [1]. Prompt recognition of CAP and immediate intervention during coronary angiography can significantly minimize the adverse consequences.

A 70-year-old man was admitted for an acute non-ST-segment elevation myocardial infarction. He had a history of arterial hypertension and chronic coronary syndrome as he had previously undergone PCI to the proximal circumflex (Cx) and mid-right coronary arteries seven and six years, respectively, before the current event. Cx stenosis was a culprit for his current presentation. The left main was engaged with a 6F catheter *via* the right radial artery, and the lesion was crossed with a workhorse wire. It was then pretreated with two semi-compliant (SC) balloons upon which delivery of a drug-coated balloon (DCB) was attempted without a success. Another wire was then introduced across the lesion as a "buddy wire" followed by an attempt to deliver DCB and then DES, however, with no success. A proximal Cx segment was again predilated with an SC 2.0 × 20 mm balloon and 2.5 × 18 mm DES was eventually implanted. However, late images showed Ellis type II perforation at the site of distal Cx (Figure 1A), and another occluding SC 2.0 × 20 mm balloon was inflated at 8 atm proximally to the perforation site (Figure 1B). Despite this intervention, the extravasation of the contrast was still active (Figure 1C) so an additional 6F XB 3.5 guiding catheter was introduced adjacent to the existing catheter in the LM *via* right transfemoral access by using the "ping-pong" technique. This allowed for the advancement of the FineCross 1.8 F microcatheter at the perforation site, and its position was securely fixed by the previously deployed and inflated SC balloon — the so-called "block & deploy" technique (Figure 1D). Three coils (2 mm × 4 cm) were then delivered by the microcatheter proximally to the perforation site followed by repeated inflation of the occluding balloon; however, without achieving stoppage of extravasation (Figure 1E). Finally, fat particles were harvested and prepared from subcutaneous tissue at the femoral artery puncture site (Supplementary material, *Video S1*). Then they were delivered through the microcatheter directly at the perfora-

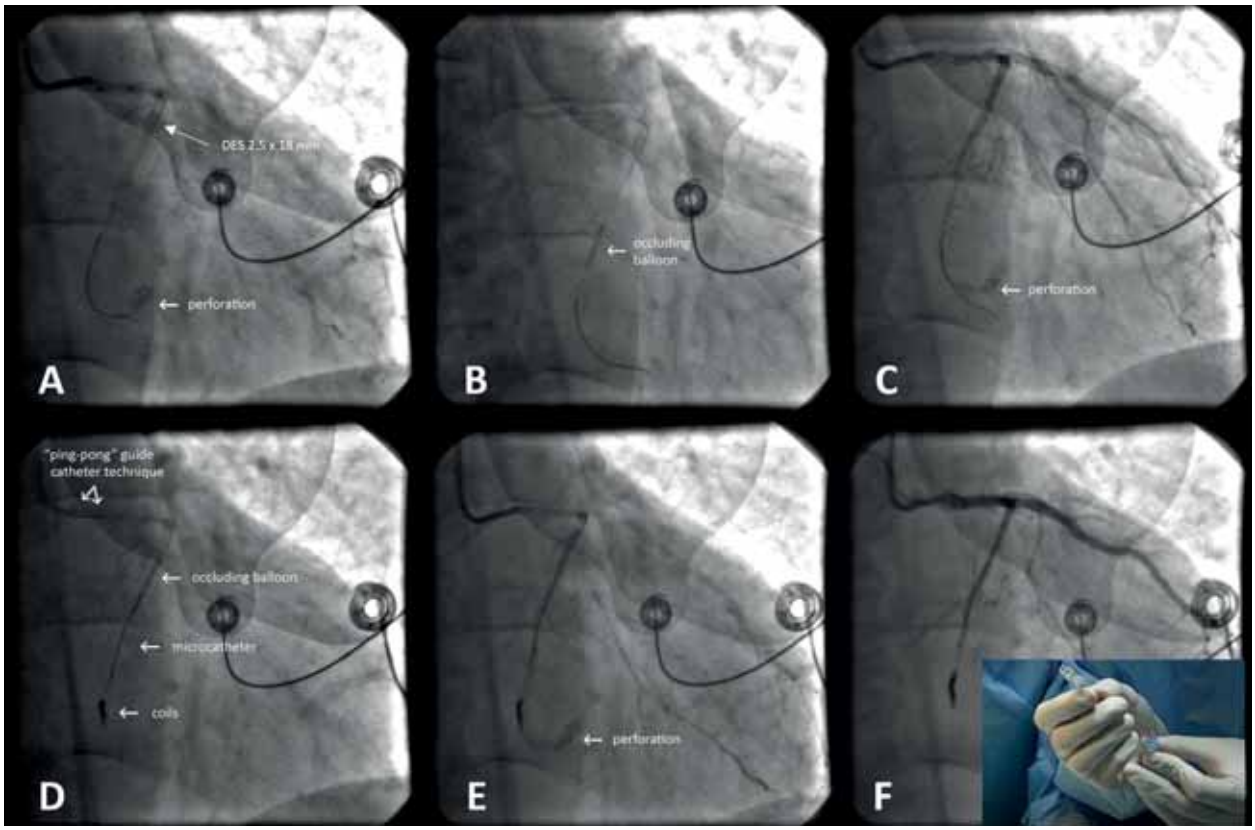

Figure 1. A. After successful drug-eluting stent implantation (2.5 × 18 mm), a perforation of the distal circumflex artery was observed (type II Ellis perforation). **B.** The occluding balloon was inflated twice (2 × 10 min) proximally to limit hemorrhage. **C.** Despite balloon inflations, an active contrast extravasation was still present at the distal vessel. **D.** Second 6 F catheter was inserted *via* femoral access engaging the left main with the previously deployed catheter by using the "ping-pong" technique. Deflation of the occluding balloon on the first catheter allowed for advancement of the microcatheter (1.8 F) to the perforation site and delivery of 3 coils (2 mm × 40 mm) by the modified "block & deliver" technique, which limited hemorrhage by inflating the occluding catheter again; **E.** Contrast extravasation was still observed despite deployment of 3 coils and repeated inflation of the occluding balloon again for 10 minutes. **F.** Fat particles were harvested from subcutaneous tissue near the femoral artery puncture site and were delivered to the perforation site through a previously positioned microcatheter — this intervention finally resulted in the successful closure of the perforation

tion site successfully sealing the perforation (Figure 1F). A post-procedural transthoracic echocardiogram showed small (2 mm) pericardial effusion without right ventricular compression while the patient remained asymptomatic with preserved hemodynamic stability both during and after the procedure.

In conclusion, we feel that the demonstrated technique, while well-known in interventional radiology should be added to the armamentarium of interventional cardiology. It presents a simple and efficient treatment option for refractory coronary artery that might not be amenable to graft stents or protamine infusions.

Supplementary material

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

Article information

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New-onset postoperative atrial fibrillation after coronary artery bypass graft surgery

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We have read with great interest the article by Smukowska-Gorynia et al. [1], entitled "Neopterin as a predictive biomarker of postoperative atrial fibrillation following coronary artery bypass grafting". First of all, we congratulate the authors for their valuable contribution to the literature. However, we would like to discuss some points about inflammatory biomarkers and postoperative atrial fibrillation (PoAF) after coronary artery bypass graft (CABG) operations.

This is a well-designed single-center study. And the reliability of the diagnosis of PoAF, which is a very important in PoAF studies, has been resolved by continuous telemetry follow-up in patients. In addition, patients who underwent elective surgery were included in the study, and patients with a history of atrial fibrillation or flutter were excluded [1]. In this study, which included prospectively planned elective surgery patients, was telemetry recording of at least 24 hours performed in the preoperative period? Could patients with preoperative atrial fibrillation have been missed?

Negative effects of thyroid dysfunctions on cardiac surgical operations are known [2]. In the current study, while patients with preoperative hyperthyroidism were excluded, a total of 10 patients with hypothyroidism were included in the study [1]. Why did the authors not exclude patients with hypothyroidism from the study? Low levels of the active thyroid hormone triiodothyronine are known to be associated with poor outcomes in cardiac surgery patients. The positive effects of triiodothyronine replacement therapy on clinical outcomes have been demonstrated in this group of patients [3].

In the current study, the authors investigated the role of the biological marker neopterin in predicting the risk of PoAF after isolated CABG operations. And neopterin blood levels were measured at three different times (before operation, on the 1st day after operation, and between the fifth and eighth day after operation). PoAF is frequently detected in the first five days after the operation and peaks on the second day [4]. Why did the authors measure neopterin between the fifth and eighth days of their study? Did they intend to predict the recurrence of PoAF? The recurrence of PoAF was detected in 10 patients in their study [1].

In their study, the authors stated that the multivariable models were divided into three models: preoperative (5 variables), surgical (2 variables), and echocardiographic (5 variables). Here, the patient groups were determined as 30 patients who developed PoAF and 71 patients who did not [1]. In two multivariable models, five variables were included in the analysis. Could this be the cause of overfitting [5]?

Article information

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New-onset postoperative atrial fibrillation after coronary artery bypass graft surgery. Authors' reply

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Referring to the letter from Engin et al. [1], we would first like to thank the authors for their interest in our manuscript. We are grateful for all words of appreciation, as well as interesting observations and questions.

Our study concerned new-onset postoperative atrial fibrillation (POAF) following elective coronary artery bypass graft surgery (CABG), hence patients with a history of atrial fibrillation were excluded. However, the exclusion criteria were based on medical records, and a 12-lead electrocardiogram and 24-hour heart rhythm monitoring were available immediately after surgery. We assumed that the probability of a new atrial fibrillation episode between admission and the surgery would be negligible.

The issue of functional thyroid disorders is well known to us, therefore, all patients with a history of hypothyroidism had to be euthyroid and adequately treated with triiodothyronine replacement [2]. Moreover, in our study, a history of hypothyroidism did not differentiate patients with POAF from patients without POAF [3]. Only patients currently being treated for hyperthyroidism were excluded from the study to avoid its influence on the development of POAF.

As we stated in the introduction, the study was designed to determine whether the preoperative or postoperative neopterin concentration was a better prognostic factor in POAF. Since neopterin was first evaluated as a predictive factor in POAF, we decided to test it before surgery and at two-time points after surgery, and, indeed, we also investigated its association with a possible recurrence of POAF.

Finally, there is the question of multivariable statistical models. One of the limitations of our study was the number of patients, which then limited the examination of all factors in one model. Therefore, we decided to divide many statistically significant potential predictors into three groups: preoperative, surgical, and echocardiographic. According to these analyses, apart from the higher preoperative concentration of neopterin, important factors were also: higher body mass index (BMI, kg/m^2), history of pulmonary disease, increased diastolic thickness of interventricular septum, and duration of operation [3].

Article information

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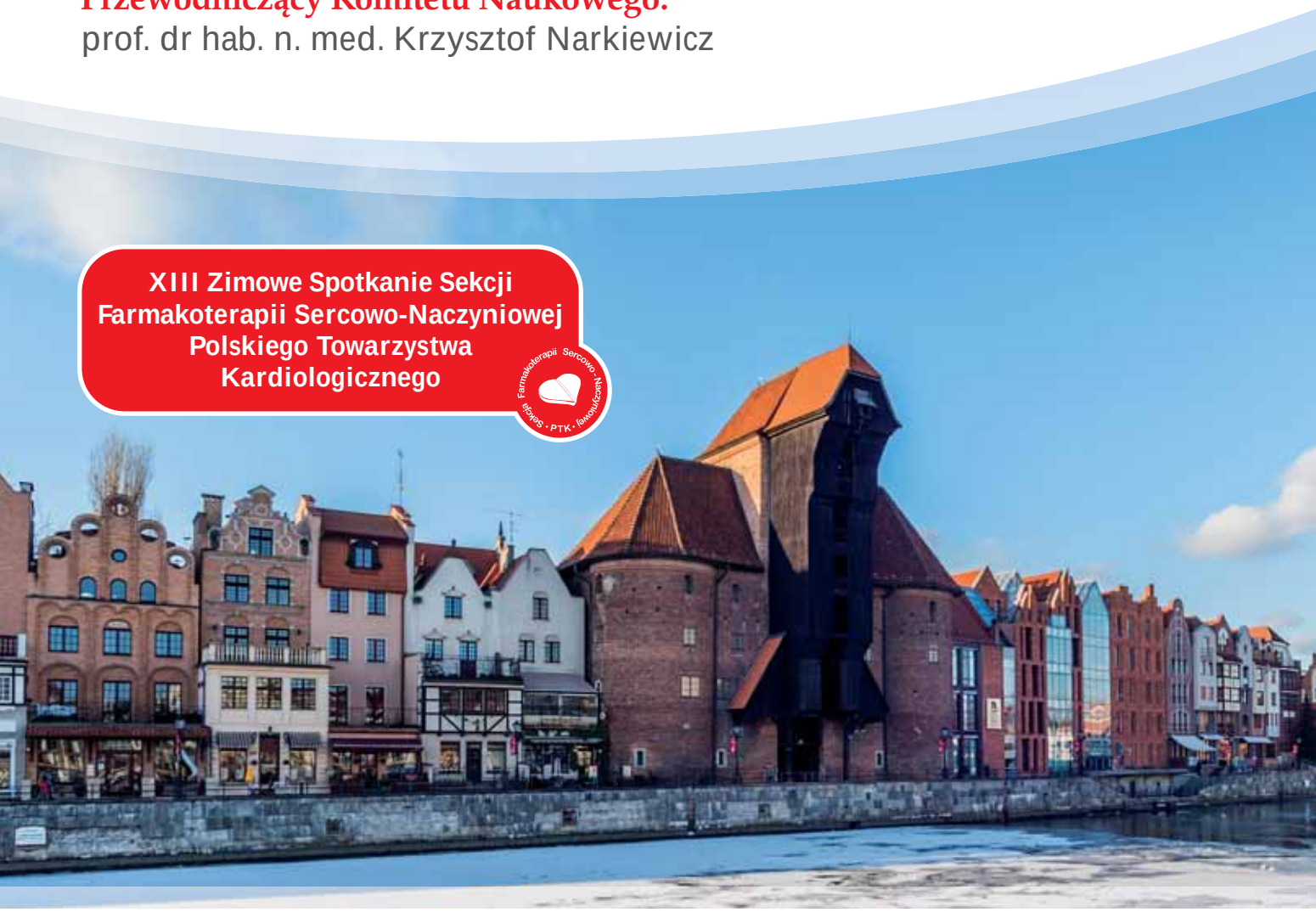

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