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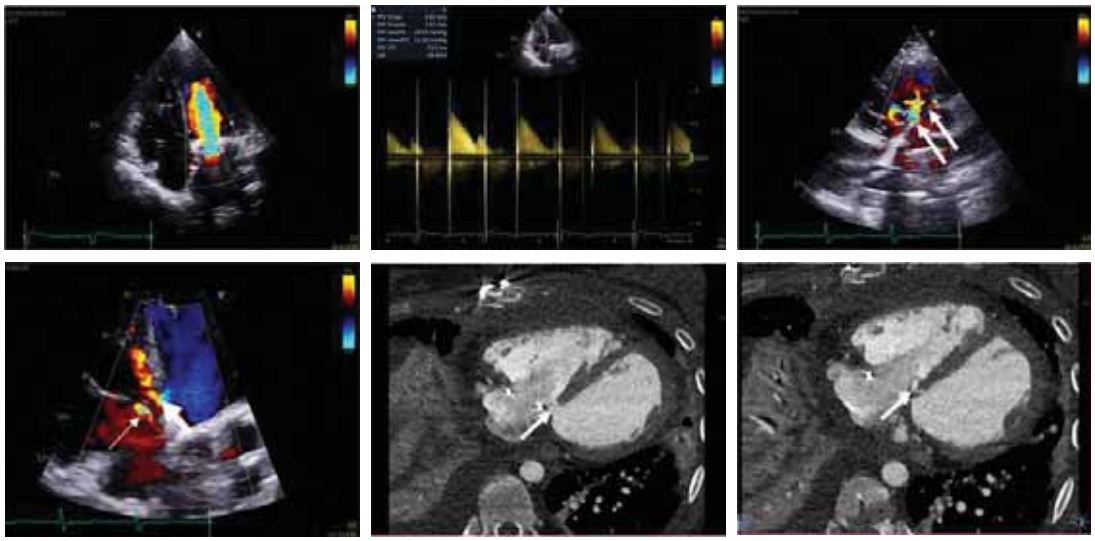

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Cardiac magnetic resonance imaging in heart failure: The added value of tissue characterization

William Watson, Madalina Garbi

Royal Papworth Hospital, Cambridge University Health Partners, Cambridge Biomedical Campus, Cambridge, United Kingdom

Related article
by Ojrzyńska-Witek et al.

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The article by Ojrzynska-Witek et al. [1] published in this month's edition of the journal showcases the abilities of cardiac magnetic resonance (CMR) in modern cardiology. The authors evaluate using CMR in heart failure of unknown etiology. A retrospective analysis of 243 patients referred for CMR for this indication resulted in a new diagnosis in nearly 40% of cases and changing management in 17%. Seven percent of patients were discovered to have myocarditis, 5% restrictive cardiomyopathy, 3% left ventricular non-compaction, and 3% end-stage hypertrophic cardiomyopathy. In 10% of patients, a previously undiagnosed myocardial infarction was discovered, and in 2%, a valvular heart disease.

Heart failure is a clinical syndrome due to a structural and/or functional abnormality of the heart [2]. The diagnosis of heart failure is based on the presence of clinical symptoms and signs; however, the diagnosis of the structural and/or functional substrate is based on cardiovascular imaging. The first-line imaging modality is echocardiography [3]. Echocardiography has the benefit of easy access; it is less expensive, more portable, available in more countries, and more tolerated by the patient. Echocardiography, therefore, makes an appropriate modality for emergency presentations, urgent assessments, screening, or the investigation of patients with concomitant valvular heart disease. CMR is an appropriate tool for non-urgent assessment, for subjects with challenging echocardiographic windows, and for the diagnosis of heart failure etiology in cases eluding echocardiography.

CMR has the advantage of allowing precise quantification of myocardial volumes and contractility, which is highly relevant when left ventricular ejection fraction is the parameter that most strongly guides heart failure interventions. It is a widely applicable technique, with the advantage of no ionizing radiation. However, technical limitations require scan times of 30 to 45 minutes and may cause difficulties in patients with arrhythmia. It is contraindicated in those with MR unsafe devices. CMR may be considered as a screening test, where precise volume quantification is useful to uncover subtle deficits in contractile dysfunction; however, its cost in comparison with an echocardiogram must be considered when it is used widely.

CMR's unique advantage is, however, that it interrogates myocardial tissue, for which there is an ever-expanding toolkit of techniques. Late Gadolinium imaging in CMR revolutionized the field: the pattern of enhancement allowed the differentiation of infiltration, infarction, edema, and other causes of myocardial dysfunction [4]. As a common pathway for different forms of heart failure is fibrosis, late gadolinium imaging would seem ideally suited to making a diagnosis, while location and burden of scar can predict mortality and heart failure hospitalizations. By gauging the volume of infarcted myocardium by late gadolinium imaging, myocardial viability for revascularization in the setting of ischemic cardiomyopathies can be assessed. Late gadolinium imaging together with assessment of inducible ischemia also play an important role

in diagnostic and prognostic evaluation of patients with heart failure with preserved ejection fraction [5].

In recent years, mapping techniques have further expanded the range of diagnoses that can be assessed with CMR [6]. T1 mapping and extracellular volume quantification allow evaluation of inflammatory or infiltrative conditions, aiding diagnosis and assessing prognosis or guiding treatment. T1 mapping can discriminate reliably between amyloidosis, Anderson-Fabry, or other infiltrative conditions affecting the whole myocardium without the need for contrast administration. Accurately determined left ventricular mass, together with late gadolinium imaging, detected fibrosis, and native T1 values predict prognosis in patients with heart failure with preserved ejection fraction [7]. T2 mapping is sensitive to edema, therefore, helpful in acute pathology; it can also help with the diagnosis of MINOCA or prognostic evaluation of acute myocarditis [8]. T2* mapping is sensitive to the iron content and can demonstrate myocardial iron deposition in hemochromatosis or acute myocardial hemorrhage in infarction, again guiding treatment and giving useful prognostic data.

Research is increasingly focused on methodology to make CMR scans quicker, improve processing, eliminate the need for contrast administration and remove limitations around breath-holding or arrhythmia, and the field continues to evolve. The introduction of artificial intelligence has allowed for more automation in the analysis process and, in the future, will allow nuancing of the analysis of mapping data beyond the capability of the human eye.

Ultimately, CMR's utility as a "one-stop shop", with the unique ability to offer myocardial tissue characterization in addition to accurate chamber quantification, detection of inducible ischemia, and valvular or structural heart disease, can save patients undergoing multiple diagnostic procedures. The key steps in heart failure diagnosis, the assessment of left ventricular systolic function and determination of etiology, can be reliably performed using one technique. The article by Ojrzynska-Witek et al. [1], as well as a wealth of emerging evidence, demonstrate that the added value of CMR in all types of heart failure (with reduced, mid-range, or preserved ejection fraction) derives from myocardial tissue characterization.

Article information

Conflict of interest: None declared.

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Role of cardiac magnetic resonance imaging in heart failure

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Heart failure (HF) is approaching global pandemic proportions, with at least 26 million people currently affected worldwide. Irrespective of HF phenotype, stratified according to left ventricular ejection fraction (LVEF), i.e. "reduced" — HFrEF, "mildly reduced" — HFmrEF, and "preserved" — HFpEF, and despite an expanding array of effective treatments including renin-angiotensin-aldosterone-system inhibitors, angiotensin-receptor-neprilysin-inhibitors, β-blockers, sodium-glucose-co-transporter-2 inhibitors and cardiac resynchronization (CRT) therapy, morbidity, and mortality remains high [1]. Worryingly, with an aging population, coupled with rising HF incidence and an increasing prevalence of comorbidities, it is projected that HF hospitalizations will rise by 50% over the next 25 years, significantly impacting global healthcare systems [1].

Prompt diagnosis of HF and assessing underlying etiology is therefore imperative. Whilst echocardiography is the traditional workhorse in the HF diagnostic pathway, cardiac magnetic resonance imaging (CMR) is a class 1C recommendation [1] in those with poor acoustic windows and in whom myocardial tissue characterization is paramount e.g. myocardial infarction (MI), infiltration (e.g. amyloidosis). Compared to echocardiography, CMR offers unlimited imaging planes, superior spatial resolution, and unrivaled tissue characterization properties, enabling further sub-categorization of HF into differing clinical etiologies with a high degree of accuracy [2].

In the recent issue of *Kardiologia Polska* (*Kardiol Pol*, *Polish Heart Journal*), Ojrzyńska-Witek et al. [3] sought to evaluate the role of CMR in identifying the underlying etiology of HF patients in whom preceding diagnostic workup (including clinical evaluation, echocardiography, and coronary angiography in those with cardiac risk factors for coronary artery disease [CAD]) had failed to elicit this. The authors reported the findings from a single-center, retrospective analysis of 243 CMR scans performed over 10 years. In summary, a new clinical diagnosis following CMR was observed in 38.7%. Such new CMR findings included dilated cardiomyopathy (DCM, 58.8%), myocarditis (7%), restrictive cardiomyopathy in 5.3% of which amyloidosis accounted for just over half, left ventricular (LV) non-compaction (2.9%), hypertrophic cardiomyopathy (1.2%), and Takotsubo cardiomyopathy (0.8%). Overall, CMR resulted in subsequently modified patient management in 16.9% of patients. While this study strongly advocates the value of CMR in HF and the authors should be applauded for their elegant work and study conduct, the findings also raise a number of key points for further consideration:

- The single-center study setting is not truly representative of the general HF population and is prone to referral bias. The baseline characteristics reveal a marked male preponderance (73%), and the mean age was only 44 years, which is in stark contrast to published epidemiological

data from HF populations whereby females typically account for more than 50% and the average age is a few decades older [1].

- The main HF phenotype studied was HFrEF (in 81%), again contrasting with the published literature [1], whereby HFmrEF/HFpEF account for nearly half of all HF cases. Furthermore, given the predominance of HFrEF and since subjects with CAD on angiography were excluded, a new finding of non-ischemic DCM is highly unsurprising.
- The CMR yield of new diagnoses (38.7%) is higher in comparison to another albeit, smaller (n = 150), prospective study [4] of HF patients comprising only HFrEF or HFmrEF, in which 30% had newly identified clinical pathologies. In both studies, the most common finding again was of non-ischemic DCM (58.8% vs. 24%). In our own single-center experience confined to HFpEF (n = 154; mean age, 72 years), similar new CMR findings were observed in 27% of cases [5]. We speculate that the overall CMR diagnostic yield would likely have been even greater if the proportion of HFpEF studied was higher because this particular HF phenotype is associated with increasing age and a heavy co-morbidity burden, including conditions such as obesity, atrial fibrillation, and lung disease, rendering traditional echocardiographic assessment challenging and increasing the influence of CMR in diagnosis [1].
- It remains unclear from the study description whether the same protocol was used throughout. For example, consistent use of parametric T1/T2/T2* mapping may have further enhanced the sensitivity to detect conditions such as amyloidosis, myocarditis, and iron-loading [2].
- Although the study did not report clinical outcome data related to the new clinical pathologies identified by CMR, a strong signal further supporting CMR usage in HF has recently been shown in a multi-center trial (OUTSMART-HF) [6] of 500 patients (mean age 59 years; HFpEF proportion 7%) who were randomized to either routine i.e. echocardiography plus CMR vs. selective CMR (only at the physician's discretion) in non-ischemic HF. While the study did not reveal any significant differences between the imaging arms in terms of specific HF diagnoses, CMR yet again increased the overall yield of such diagnoses (44%) above baseline echocardiography. Furthermore, patients with specific HF causes identified by CMR suffered more clinical events compared to non-specific HF causes (19% vs. 12% at 12 months; $P = 0.02$), demonstrating the potential prognostic value of CMR-guided HF assessment.
- Evidence on the cost-effectiveness of CMR in HF is still lacking.

Beyond the refinement of underlying clinical diagnosis, CMR may play a useful role as we enter an era of precision-based, personalized medicine. CMR has high diagnostic accuracy for detecting significant CAD following stress perfusion and is also the imaging gold standard for detection of both left atrial (LA) and right ventricular (RV) volumes and function, as well as focal (late gadolinium enhancement [LGE]) and diffuse fibrosis (T1 mapping/extracellular volume [ECV]). CMR allows further refinement of HF into key underlying pathophysiological substrates, enabling targeted therapies and further risk stratification. The first step in such prognostication is the detection of CAD with a high degree of accuracy by stress perfusion CMR and LGE [7, 8]. Ischemic HF confers a worse prognosis compared to non-ischemic HF (5-year survival 45% vs. 62%) [9]. Furthermore, MI is readily detectable by CMR with accurate information about localization and transmural extent, as well as predicting response to revascularization, LV recovery of dysfunctional myocardium, and ultimately survival [8]. Across the spectrum of HF, irrespective of LVEF, worse outcomes have been observed with CMR-derived RV dysfunction [10, 11], LA volumes and LAEF [12], focal fibrosis detected by LGE (MI [8] and non-MI [2,13]), and diffuse fibrosis (ECV) [14]. The presence of mid-wall focal fibrosis may further impact decision-making regarding device selection (CRT-P vs. CRT-D), guide LV ventricular lead placement in HFrEF, and predict responsiveness to CRT [15].

Article information

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Last before-death alert remote monitoring transmission in patients with heart failure with reduced ejection fraction. Much ado about nothing

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Related article
by Dyrbuś et al.

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Remote monitoring (RM) of cardiac electrical implantable devices (CIEDs) is the application of communication technology to patients wearing a pacemaker, implantable cardioverter-defibrillator, or cardiac resynchronization therapy device [1].

RM technology has undergone many developments in recent years, ranging from the original transtelephonic monitoring to the currently available CIEDs with wireless telemetry capabilities, from fax reports to a social network system service, from wired to wireless interrogation, and from one-way to two-way transmission [2, 3].

Taken together, these innovations have made it possible for RM, when applied to patients with heart failure with reduced ejection fraction (HFrEF), to reduce costs associated with follow-up of CIEDs [4], to detect arrhythmias early [5], and to reduce heart failure-related hospitalizations and, most likely, mortality [6] (Figure 1).

In this issue of *Kardiologia Polska* (*Kardiol Pol*, *Polish Heart Journal*), Dyrbuś et al. [7] show the results of a subanalysis of the COMMIT-HF registry regarding the last transmissions delivered by the remotely monitored CIEDs in a large cohort of patients with HFrEF.

The authors find that of the 1271 patients whose devices transmitted at least one message to the RM center, 198 (15.6%) had no alarm transmission, whereas 1073 (84.4%) had at least one alarm transmission. The respective mortality in patients with and without alarms during MRI was 29.7% and 12.6%. In patients without an alarm transmission, the

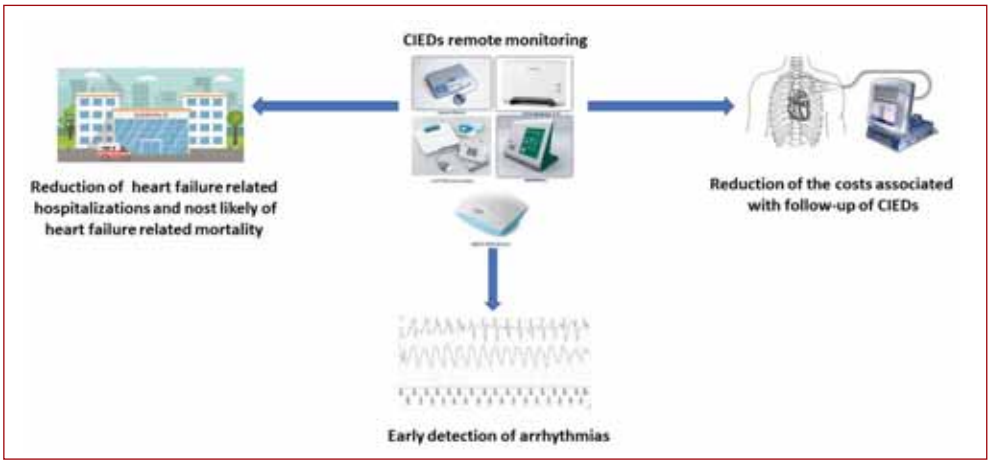

Figure 1. Benefits of using remote monitoring in patients with heart failure with reduced ejection fraction
Abbreviation: CIEDs, cardiac implantable electronic devices

last recorded transmission before death was scheduled in 166 patients and activated by an alarm in 152 patients. The most frequent alarm-activated last transmissions were atrial fibrillation/atrial flutter (39.4%) and ventricular tachyarrhythmias (26.8%).

Approximately 44% of ventricular tachycardias and 93% of cases of ventricular fibrillation were treated with the device, and 11 cases of transmitted arrhythmias met the criteria for an electrical storm.

Additionally, in 15 patients (10.6%) there was a reduction in biventricular pacing, and in 26 (18.3%) there were other causes of alarm transmissions, including indications of congestion.

Of the 142 patients in whom the last transmission was triggered by the alarm, 78 (58.2%) died in the hospital, whereas the remaining patients died elsewhere.

The results of this study are interesting and are worth some consideration.

First, most of the alarms were triggered by supraventricular arrhythmias (atrial fibrillation/atrial flutter) but did not generate a clinical reaction, either because such rhythms had already been known in the patient or because the patient had already been hospitalized. Therefore, these alarms did not lead to a change in clinical behavior on the part of the medical staff.

Second, the alarms for ventricular arrhythmias, which accounted for 26.8%, were in most cases associated with a delivery of therapy by the device, presumably with subsequent presentation of the patient in the emergency department or hospital. Even in this case, therefore, these alarms did not determine a change in clinical management.

Finally, 10% of the alarms were for a reduction in biventricular pacing, most likely due to an increase in the ventricular arrhythmic burden, in which case a change in drug therapy would have been desirable and likely useful for the patient.

Considering the above, it is my conviction that RM is futile during the end-stage phase of heart failure, in which the alarms (programmed or not) sent to the RM center add little to the stratification of the risk of death of the patient and do not modify clinical management at all.

In the future, the implementation and improvement of new risk scores that combine clinical and electrical parameters obtained by MRI, such as the SELENE score [8], will effectively improve the prognosis of patients with HFrEF, allowing medical staff to obtain useful tools for the management of these patients even in the terminal stages of the disease.

Article information

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REVIEW

Radiation-induced cardiac dysfunction: Practical implications

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ABSTRACT

Radiation-induced cardiac dysfunction is a critical healthcare concern facing survivors of thoracic cancers treated with radiation therapy. Despite cardiac-sparing advances in radiation therapy delivery, many patients with thoracic cancers receiving modern radiation therapy will still have incidental radiation exposure to the heart. Therefore, it is imperative that cardiovascular healthcare providers take appropriate measures to prevent, screen, and manage radiation-induced cardiac dysfunction in patients with a history of thoracic radiation therapy. In this review, we aim to provide healthcare providers with foundational information about radiation-induced cardiac pathophysiology and a chronology of advances in radiation technology. Subsequently, we provide an up-to-date review of treatment- and host-related factors that can influence a patient's risk for radiation-induced cardiac dysfunction. Finally, we culminate our discussion by detailing current screening and management guidelines to aid healthcare providers in caring for their patients with a history of thoracic radiation therapy.

Key words: cancer, cardiovascular disease, cardio-oncology, radiation, radiation-induced cardiac dysfunction

INTRODUCTION

Survival rates for patients with thoracic cancers have dramatically improved in recent decades due to advances in early detection and therapeutics. The expanding population of cancer survivors possesses a unique set of healthcare needs; integral among them is cancer treatment-induced cardiotoxicity. A number of cancer survivors treated with radiation therapy (RT) to the abdomen, chest, or neck (e.g. lymphomas, breast cancers, lung cancers, esophageal cancers) develop long-term radiation-induced cardiac dysfunction (RICD), as RT frequently results in incidental dose to the heart and/or vascular structures. Over the last 50 years, radiation oncologists have made great progress in reducing heart exposure from radiation treatments. However, up to one-third of thoracic cancer survivors receiving modern RT will present with one or more forms of RICD within 10 years of treatment [1]. Radiation-induced cardiac disorders observed in these patients range from coronary artery disease and valvular heart disease to pericarditis, arrhythmia, myocardial fibrosis, and cardiomyopathy (Figure 1). This review is intended to provide cardiovascular (CV) healthcare providers (e.g. cardiologists, cardio-oncologists, internists, etc.) with an overview of RICD pathophysiology, as well as current concepts in modern thoracic RT delivery. Furthermore, this review aims to provide CV healthcare providers with the most up-to-date guidelines for RICD screening and management in their patients.

MECHANISMS OF RADIATION--INDUCED CARDIAC DYSFUNCTION

Current evidence suggests that the cardiotoxic effects of radiation are imparted through both direct and indirect means (Figure 1) [2]. Radiation deposition directly damages nuclear DNA, which manifests as base damage, cross-linking, and single- and double-strand-

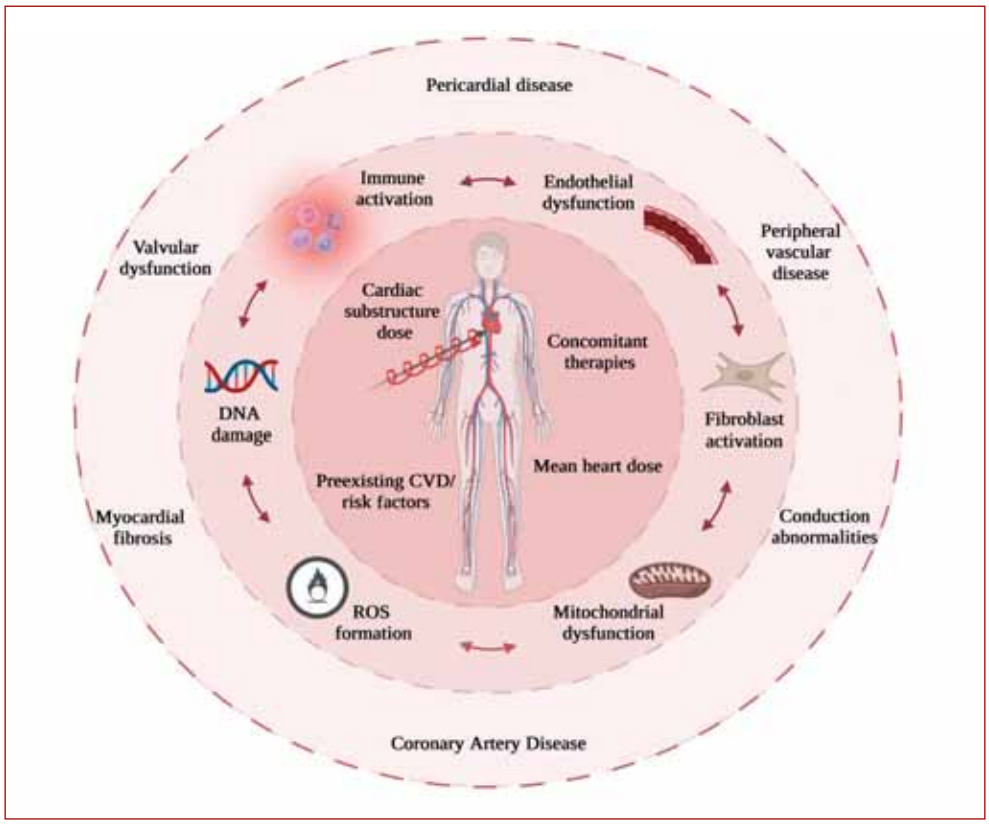

Figure 1. Interaction of mechanisms and factors contributing to radiation-induced cardiac dysfunction. Treatment- and host-related factors influence cardiac injury resulting from radiation therapy, including mean heart dose, dose to cardiac substructures, other cancer therapies, and preexisting CV risk (inner circle). These factors influence the degree and progression of radiation-induced cardiac damage, which is mediated by interactions among immune activation, endothelial dysfunction, fibroblast maturation, mitochondrial dysfunction, ROS formation, and DNA damage (middle ring). Radiation injury to the heart can ultimately lead to several forms of cardiovascular dysfunction, including pericardial effusion, peripheral vascular disease, conduction abnormalities, coronary artery disease, myocardial fibrosis, and valvular dysfunction (outer ring)

Abbreviations: CV, cardiovascular; CVD, CV disease; ROS, reactive oxygen species

ed breaks, with double-stranded breaks being most integral to lethal damage to cells after radiation [2]. In addition, radiation-induced hydrolysis of water and other cellular molecules yields reactive oxygen species (ROS), which can alter many cellular processes and preferentially degrade DNA telomeres and cellular organelles [3]. Radiation-induced destabilization of the mitochondria is particularly important, as disruption of oxidative metabolism can be both a cause and consequence of ROS production [4]. Following genomic damage, DNA repair systems are activated, and a network of genes encoding for cellular apoptosis and senescence are transcriptionally upregulated [5]. Many of the products of DNA repair act locally as danger-associated molecular patterns (DAMPs), inducing both pro-inflammatory and senescence-associated secretory phenotypes (SASP) in nearby cardiac cells [6]. Unresolved immune responses resulting from radiation injury are also likely critical drivers of late cardiac dysfunction [7].

Importantly, cardiac cells display differential sensitivity to radiation. As cardiomyocytes are terminally differentiated, postmitotic cells, they are relatively resistant to radiation damage [8]. Conversely, coronary endothelial cells, and in particular capillary endothelial cells, are highly radiosensitive [8]. Radiation-induced endothelial injury is thought to be a pivotal consequence of radiation, as disruption of the coronary microvasculature results in vascular insufficiency (Figure 1) [1]. Furthermore, maladaptive responses of the coronary vascular endothelial cells to radiation damage can contribute to a pro-thrombotic state over time [9].

ADVANCEMENTS IN RADIATION THERAPY — A BRIEF HISTORY

The main determinant of RICD development in patients with thoracic cancer is the dose of incidental radiation received by the heart [10]. In recent decades, advances in RT planning and delivery have dramatically decreased heart doses in many thoracic cancer populations, thereby improving the therapeutic ratio of RT in survivors. In the 1990s, traditional two-dimensional radiation field arrangements, which were based on simple x-ray imaging, were largely replaced by three-dimensional conformal radiation therapy (3DCRT) [11, 12]. Unlike its predecessor, 3DCRT relies on computed tomography (CT) imaging to deliver radiation to tumor volumes with a margin for both micro-

scopic tumor extension and uncertainties from the target's motion [11, 13]. This technique also allows accurate determination of the doses received by organs adjacent to the targets, such as the heart. By the end of the decade, even more technological advances were realized, including the wide availability of intensity-modulated radiation therapy (IMRT), owing to the development of computer-controlled multi-leaf collimators and inverse planning software [11, 13]. IMRT delivers multiple radiation beams with varying intra-beam intensities, allowing for radiation doses that conform to irregularly shaped tumor boundaries [11, 14]. Despite its non-tumor tissue sparing capabilities, especially with respect to minimizing high doses to organs at risk, IMRT requires a larger number of radiation beams than 3D-CRT, which substantially lengthens the RT treatment time. Thus, in the mid-2000s, volumetric modulated arc therapy (VMAT), a form of IMRT in which the entire dose volume is delivered in a single gantry arc, was introduced to improve IMRT treatment efficiency [14, 15]. Additionally, more recent technological advances include image-guided radiation therapy (IGRT), which can be used with both 3DCRT and IMRT and aids in the targeting of RT, and stereotactic body radiation therapy (SBRT). IGRT typically uses daily imaging before RT to recognize slight variations in tumor position across treatment fractions due to patient positioning or organ/target movement and uses this information to localize a radiation fraction appropriately [11, 16]. Unlike more traditionally fractionated RT regimens, SBRT precisely delivers highly conformal radiation doses to a small area in one to five large fractions [11, 14]. SBRT has been found to be particularly useful for ablative-type therapy in patients in whom surgical tumor resection is contraindicated, such as some patients with early-stage non-small cell lung cancer [17].

At present, there are several cutting-edge RT modalities at the forefront of cardiac-sparing treatment for patients with thoracic cancer. In pre-clinical models, the use of FLASH-RT has shown great promise in improving normal tissue tolerance [18]. Unlike traditional RT that delivers radiation dose over the span of minutes, FLASH-RT delivers a milliseconds-long, ultra-high radiation dose [18]. This instantaneous radiation delivery has been found to induce a protective metabolic response in non-tumor tissues, which may allow for higher radiation doses to be delivered to a tumor without additional normal tissue toxicity [18]. The first clinical trial implementing FLASH-RT began in 2020 to assess the feasibility and toxicities of this modality in cancer patients with bone metastases, but at this time FLASH-RT is not readily available outside of a clinical trial [18]. Proton therapy, which delivers positively charged particles rather than photons, is also a therapy with large cardiac-sparing potential [19]. However, the availability of proton centers in the US is limited, although the number of facilities has greatly increased over the past decade. Protons offer a physical advantage over photons due to their ability to be deposited at a specific tissue depth with little spread beyond this point [19]. Clinical trials in non-small cell lung cancer and esophageal cancers comparing mean heart dose (MHD) between photon (e.g. IMRT, SBRT) and proton therapies have demonstrated reductions in MHD with the use of protons. However, in the non-small cell lung cancer trial there was no reduction in lung toxicity or improved survival in the proton arm, while the esophageal cancer trial demonstrated a reduction in overall toxicities and a numerical decrease in cardiac toxicities, with no change in cancer outcome [20]. To date, the widespread implementation of proton therapy is limited due to expense and limited facilities offering this modality, which may change as more clinical trial data become available and more proton centers continue to open.

In addition to these technological developments, changes in patient setup and positioning during RT have helped to substantially reduce the heart dose. In breast cancer patients, alternative (e.g. prone vs. supine) positioning differentially displaces both the heart and breast tissue, which may distance the heart from the radiation field [21, 22]. Benefits derived from such positional changes in breast cancer patients appear to be in part dependent on tumor laterality and breast volume [22]. A large body of evidence supports the use of organ motion management techniques during cardiac sparing during RT. In particular, implementation of deep inspiration breath hold (DIBH) techniques in breast cancer patients receiving RT markedly reduces MHD (approximately 25%–67% reduction), as well as left anterior descending artery (LAD) dose (approximately 20%–73% reduction), compared to free breathing [23, 24].

MODERN RADIATION THERAPY — WHERE ARE WE NOW?

Collectively, the advancements discussed above have led to modern RT treatments that minimize, but often do not fully eliminate, incidental radiation received by the heart. Studies suggest that RICD can occur even with low levels of cardiac radiation exposure [25]. The cardiac-sparing capacity of current RT regimens varies among thoracic cancer populations, resulting in heterogenous RICD presentations. Additionally, it is important to recognize that these advanced techniques are not broadly available at all centers or appropriate for all patients. There also continue to be many survivors previously treated with RT who may have been exposed to higher doses than are seen using modern techniques.

In breast cancer patients treated with modern 3D-CRT, only a small percentage of the heart (e.g. anterior aspect) typically receives radiation, although left-sided breast tumors place the heart closer to the radiation field [23, 26]. Despite reductions in MHD, breast cancer survivors treated with RT are still at risk for developing late manifestations of RICD, such as myocardial fibrosis and coronary artery disease [27–29]. These chronic complications, in particular, are mechanistically linked to radiation-induced coronary microvascular destruction and consequent vascular insuf-

ficiency (discussed above) [27]. In contrast, patients with lung, esophageal, and gastric cancers frequently receive high doses of fractionated RT to small regions of the heart, leading to more acute forms of cardiac dysfunction (~2 years post-RT) [1, 30, 31]. Importantly, radiation dose to critical cardiac substructures may be more predictive of RICD development than MHD alone [12, 23]. For example, radiation exposure to the LAD and left ventricle has been found to associate with adverse cardiac outcomes in breast cancer survivors [31, 32]. In esophageal cancer patients, associations have been reported between radiation dose to the pericardium rim and risk of pericardial effusions, which is the most frequently observed form of RICD in this population [33, 34]. Finally, in patients with early-stage lung cancer, RT exposure to substructures, such as the left atrium, superior vena cava, LAD, heart base, and bilateral ventricles, has been linked to all-cause mortality during the survivorship period [30, 35–37].

INTERACTION OF RT WITH CONCOMITANT THERAPIES AND PATIENT FACTORS

Concurrent and/or sequential cancer therapies

A number of systemic cancer therapies, including immunotherapy, many types of chemotherapy, and endocrine therapy, have been independently associated with cardiac dysfunction in thoracic cancer survivors [35, 38, 39]. RT is frequently administered concomitantly or sequentially with these therapies, begging the question of whether treatments with both RT and cardiotoxicity systemic therapies produce additive or synergistic cardiotoxic effects. Concomitant RT and immune checkpoint inhibitor (ICI) therapy is relatively uncommon, although sequential therapy can occur in non-small cell lung cancer. Several clinical and pre-clinical studies report enhanced anti-tumor efficacy of combination RT and ICI therapy compared to ICI alone [5, 40]. Indeed, radiation may sensitize tumor cells to immunotherapy and expand the temporal window of immunotherapy efficacy by reducing tumor growth before latent immunotherapeutic effects [41]. More than 40% of cancer patients in the US are eligible for treatment with ICI (e.g. CTLA-4 inhibitors, PD-1 inhibitors, PD-L1 inhibitors), and ICI treatment is rarely associated with fulminant myocarditis. ICI treatment also has been associated with accelerated atherosclerosis [42–44]. PD-1 blockade after RT appears to enhance cardiac inflammation, which may be due to activation of shared immune pathways in the heart [45, 46].

Chemotherapeutic treatment, especially anthracycline treatment, also increases the risk for cardiac dysfunction in thoracic cancer patients. The risk ratios for cardiomyopathy in anthracycline-treated patients compared to non-treated individuals reveal that this cardiotoxicity is dose-dependent [47]. Typically, anthracycline-induced cardiotoxicity manifests as sub-clinical left ventricular dysfunction progressing to congestive heart failure [48]. Combination RT and chemotherapeutic treatment are widely reported to have a synergistic cardiotoxic effect. Recent analysis of over 36 000 childhood cancer survivor patients treated with combinations of RT and chemotherapy demonstrated the highest and earliest onset of ischemic heart disease compared to individuals treated with one or no therapeutic modality [49].

Pre-existing cardiometabolic risk factors

When assessing patients at risk for RICD, the context of traditional CV risk factors, including hypertension, hyperlipidemia, smoking, diabetes mellitus, age, and preexisting CV disease (CVD) must be considered. Traditional CV risk factors and established CVD increase the risk of adverse CV events in cancer patients undergoing RT, though the relative impact of these baseline risk factors across various cancer subtypes and adjunctive treatments continues to be elucidated. In a study of 963 patients with breast cancer who received RT, baseline traditional CV risk factors were associated with increased rates of ischemic coronary disease, with diabetes, smoking, and obesity corresponding to 3.23, 1.87, and 1.5-fold higher risks of CVD, respectively [25]. In addition, a history of prior ischemic heart disease was associated with a 7-fold increased rate of coronary events after RT [25]. Another study examining 1460 patients enrolled in breast cancer clinical trials found that baseline hypertension and diabetes were each associated with a 2-fold increased risk of cardiac events, while baseline coronary artery disease (CAD) was associated with a nearly 3-fold increased risk [50]. In a case-control study of patients with a history of Hodgkin Lymphoma treated with mediastinal RT, baseline hypertension was associated with an increased risk of CV events (odds ratio [OR], 1.81; 95% CI, 1.26–2.59), as were diagnoses of hyperlipidemia (OR, 2.17; 95% CI, 1.67–1.82) and diabetes mellitus (OR, 1.92; 95% CI 1.38–2.67) at baseline or during follow-up [51]. Similarly, in patients with non-small cell lung carcinoma (NSCLC) treated with thoracic RT, pre-existing CAD, heart failure (HF), peripheral vascular disease (PVD), or stroke were associated with an increased risk of CV events, with a relative risk of 7 (95% CI, 3.2–15.3) [30].

Coronary artery calcification (CAC) on cardiac gated and non-gated computed tomography (CT) of the chest identifies patients with underlying coronary artery disease who are at higher risk for CV events in the setting of RT [52]. In one retrospective study examining non-gated CT imaging in breast cancer patients, the presence of CAC was associated with post-cancer treatment CV events with an odds ratio of 4.9 [53]. Another study of patients with breast cancer found a similar correlation, with a 4.95 increased risk in patients with intermediate or high CAC scores prior to RT [54]. Indeed, vascular calcifications on baseline imaging may serve as a better predictor of future risk for CV events than traditional risk stratification based on laboratory and

Table 1. Imaging modalities and screening intervals for assessment of radiation-induced cardiac dysfunction

	Coronary artery disease	Cardiomyopathy	Valvular disorders	Constrictive pericarditis
Initial imaging modality and screening interval	CCTA/ CAC Within 5 years of RT, then every 5 years	TTE Within 6-12 months of RT[a], then every 5 years	TTE Within 5 years of RT, then every 5 years	TTE Within 5 years of RT, then every 5 years
Characteristic findings	CCTA: calcified or noncalcified plaque CAC: calcified plaque	Impaired GLS > –18% Reduced LVEF <50% Diastolic dysfunction[b]	Valve leaflet and annulus calcification Valve stenosis and/ or regurgitation	Ventricular septal shift Annulus reversus[c] Diastolic flow reversal in hepatic vein on expiration
Strengths	Early identification of CAD	Can identify CV dysfunction prior to HF symptoms	Accurate gradient assessment with Doppler	Noninvasive High specificity
Weaknesses	CAC on non-gated imaging may lead to false negatives	Limited views in some patients Cannot identify myocardial fibrosis	Limited views in some patients MV not as well assessed as TEE	Invasive hemodynamics may be needed to differentiate constriction vs. restriction

[a]Baseline screening is recommended at 6–12 months in high-risk patients; otherwise, initial screening within 5 years of RT is reasonable; [b]Measures of diastolic dysfunction include E/A reversal, E/A >2, reduced medial and lateral mitral annulus tissue Doppler velocities (medial e' <7, lateral e'< 10); [c]Annulus reversus is characterized by medial > lateral mitral annulus tissue Doppler velocity; alternatively, a medial e' of >9 cm/s in the setting of ventricular septal shift is 87% sensitive and 91% specific for constriction [61]

Abbreviations: CAC, coronary artery calcification; CAD, coronary artery disease; CCTA, coronary computed tomography; CV, cardiovascular; E/A, E wave/A wave; GLS, global longitudinal strain; HF, heart failure; LVEF, left ventricular ejection fraction; MV, mitral valve; RICD, radiation-induced cardiac dysfunction; RT, radiation therapy; TEE; transesophageal echocardiogram; TTE, transthoracic echocardiogram

demographic data, as it objectively categorizes existing atherosclerotic burden, is readily obtainable, and does not rely on prior evaluation and diagnosis of traditional CV risk factors.

Cancer survivors receiving RT, especially survivors of childhood cancers, are also at increased risk for developing CV risk factors that can further impact the risk for future CV events. In pediatric cancer survivors, hypertension, diabetes, dyslipidemia, and obesity were more prevalent and were found to disproportionately increase the risk of adverse CV events compared to sibling controls with similar traditional CV risk factors [55]. In a large retrospective study of childhood cancer survivors who underwent thoracic RT, post-treatment hypertension was strongly associated with the risk of developing any CV event (risk ratio [RR], 37.2; 95% CI, 22.2–62.3), most notably CAD, HF, and valvular heart disease, which had the highest relative excess risk due to interaction with RT. Diabetes, obesity, and dyslipidemia also conferred excess CV risk in these patients, though to a more modest extent [55]. Notably, cancer survivors with a history of childhood cranial RT involving the hypothalamic-pituitary axis have been found to develop metabolic syndrome at a higher rate. In a study of childhood survivors of acute lymphoblastic leukemia patients receiving hypothalamic-pituitary axis-involved RT were more likely to have a higher body mass index and insulin dysregulation [56]. Thus, in survivors of childhood cancers, in particular, RT may potentiate the early development of traditional cardiometabolic risk factors, increasing the risk for CV events in adulthood.

SCREENING AND MANAGEMENT GUIDELINES

Clinical assessment of patients at risk for or with suspected RICD

CV management of patients with a history of RT will always start with prevention. CV risk factors should be assessed and optimized at baseline and throughout survivorship to reduce the risk for subsequent RICD. Importantly, patients undergoing thoracic RT for staging or cancer therapy will have baseline CT chest imaging that should be reviewed for the presence of CAC to screen for evidence of atherosclerosis. The recent consensus statement from the International Cardio-Oncology Society (ICOS) emphasizes the importance of reviewing available CT chest imaging at baseline and in follow-up for all patients undergoing thoracic RT to identify patients with asymptomatic CAD who may benefit from preventative medical therapy [10]. Following RT, an annual CV history and physical exam form the basis of screening and prevention. At that time, CV risk factors can be assessed and optimized, available CT scans can be reviewed for CAC, and patients can be screened for signs and symptoms of ischemic heart disease, peripheral vascular disease (e.g. subclavian stenosis), heart failure, and valvular disorders.

Cardiac imaging used in the screening and diagnosis of RICD includes echocardiography, cardiac magnetic resonance imaging (MRI), CV CT, functional imaging (stress echocardiogram or myocardial perfusion imaging), and left heart catheterization (Table 1). Choosing the optimal imaging study depends on the specific pathology investigated, as well as patient-specific factors, including body habitus, presence of a defibrillator/ pacemaker, baseline heart rate, and coexistent arrhythmias or renal dysfunction. There is also a general appreciation for limiting further radiation exposure, when possible, e.g. stress echocardiogram would be preferred to myocardial perfusion imaging, when feasible when a functional ischemic test is indicated. ICOS and other major society guidelines all recommend cardiac imaging within 5 years after thoracic RT, with imaging as early as 6 months post-RT in high-risk patients [23]. Those at high risk include (1) younger patients less than 50 years old; (2) those receiving high doses of cumulative radiation (>30 Gy); (3) those receiving high doses of radiation fractions (>2 Gy/dose); (4) those with tumor(s) involving the heart or nearby adjacent tissue; (5) patients treated with

a lack of cardiac shielding; (6) patients receiving concomitant cardiotoxic chemotherapy; (7) those with traditional CV risk factors; and (8) patients with pre-existing CVD [10].

Transthoracic echocardiogram (TTE) remains the mainstay in evaluating cardiac dysfunction, pericardial disease, and valvular disorders in patients who have received thoracic RT. Assessment of systolic function includes quantification of left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS) measurement. GLS measurement is an emerging technique to detect subclinical CV toxicity. In a meta-analysis of 21 studies of patients with breast cancer and hematologic malignancies, a portion of whom underwent RT, GLS provided strong prognostic value for cancer therapy-related cardiac dysfunction [57]. A study of breast cancer patients undergoing RT demonstrated a reduction in GLS at 12-month follow-up despite no change in LVEF [58]. In these patients, GLS reduction was most pronounced in the anterior, anteroseptal and anterolateral walls, which received the highest RT doses. While GLS may detect subclinical cardiomyopathy and be a signal for future heart failure, more research is needed as to whether therapy targeted at an early change in GLS will affect CV outcomes.

TTE is also the primary tool for evaluating RT-related valvular heart disease due to its ready availability, comprehensive cardiac evaluation, and favorable side-effect profile [58]. Characteristic findings include aorto-mitral curtain calcification, as well as calcification of valve leaflets and the subvalvular apparatus, leading to either stenosis or regurgitation [59, 60]. TTE may also assess RT-related pericardial disease, including pericardial effusion and constriction. Mitral and tricuspid inflow variations of 25% and 40%, respectively, are commonly used thresholds to identify hemodynamically significant pericardial effusions [61]. A plethoric inferior vena cava is commonly seen with a hemodynamically significant pericardial effusion or constriction. On the other hand, annulus reversus (mitral annulus medial e' >lateral e'), respiration-related ventricular septal shift (due to ventricular interdependence), and hepatic vein diastolic flow reversal in expiration are characteristic of constriction [62].

In addition to being the gold standard for LVEF assessment, cardiac MRI provides additional detailed tissue characterization and may specifically evaluate for RT-associated fibrosis with gadolinium enhancement, T1 mapping, and extracellular volume quantification [63]. Cardiac MRI can be especially useful in patients with poor acoustic windows on echocardiograms and can also aid in the evaluation of pericardial disease and valvular disorders [64].

CAC on non-gated CT chest imaging represents an immediately available means of assessing for underlying coronary artery disease in patients with a history of chest RT, and evidence supports a good correlation between CAC assessment on cardiac gated and non-gated imaging, though there remains a 9% false-negative rate on non-gated imaging owing to larger CT slice thickness [65]. CAC on both gated and non-gated imaging enhances the estimation of pretest probability of obstructive CAD. Dedicated CAC measurement is indicated to aid in risk stratification for asymptomatic patients not otherwise on preventive therapy, who are at intermediate risk for CV events, as well as CV risk stratification in low-risk patients with chest pain [66].

Coronary computed tomography (CCTA) allows for noninvasive anatomic assessment of the coronary arteries and can identify both calcified and noncalcified plaque, as well as quantify the degree of stenosis. When available, calculation of fractional flow reserve (FFR) by CTA can also estimate lesion-specific ischemia [66]. The radiation dose for CCTA (2.7–5.1 mSv) is significantly less than myocardial perfusion imaging (12.8 mSV), though notable higher than CAC (1.0 mSv) and stress echocardiogram (no radiation). CCTA is indicated to evaluate for nonobstructive and obstructive CAD in patients with chest pain who have intermediate to high pretest likelihood for CAD [66].

Functional stress testing also continues to remain an option to evaluate for obstructive CAD in asymptomatic patients with a history of RT. Specific tests include stress echocardiography and stress nuclear myocardial perfusion imaging. As in the general population, functional testing provides the advantage of assessing exercise capacity, which adds prognostic value, in addition to evaluating for ischemic CVD. Recent ICOS recommendations deemphasize the role of functional testing in asymptomatic patients in favor of anatomical evaluation, as the former may not capture patients with nonobstructive CAD who will benefit from primary prevention with medical therapy [10]. Additionally, the recent ISCHEMIA trial showed no benefit for an initial revascularization strategy, compared to optimal medical therapy alone, in patients with stable coronary artery disease and moderate to severe ischemia on stress testing [67]. Whether clinical outcomes are better in those who receive an invasive intervention plus medical therapy than in those who receive medical therapy alone is uncertain. These results further highlight the multiple prior trials that support optimal medical therapy and prevention strategies as a first-line approach, especially in an asymptomatic patient [68].

In patients that ultimately require left heart catheterization, intravascular ultrasound (IVUS) may help further characterize RT-associated coronary lesions, which may manifest with heavy calcification or neointimal hyperplasia with negative remodeling [69]. In patients with RICD undergoing left heart catheterization who may be candidates for coronary artery bypass, care should be taken to evaluate the native internal mammary artery, which may become fibrosed or atretic, as the superior internal mammary nodal region is often a target of regional nodal RT in breast cancer patients [70, 71].

Biomarkers remain understudied in RICD, but current evidence does not support their routine use in the screening of subclinical disease. Recent ICOS guidelines suggest that N-terminal pro-B-type natriuretic peptide (NT-proBNP)

is reasonable to screen asymptomatic patients at risk of HF, based on population data, but studies have not consistently shown that rise in cardiac markers specifically after RT can otherwise predict future cardiovascular outcomes [10]. In a study of 87 patients who underwent thoracic RT for multiple cancer types, NT-proBNP and high sensitivity troponin T did not significantly change pre- and post-RT. Placental growth factor (PIGF) and growth differentiation factor 15 (GDF-15) were found to be elevated post-RT in a small subgroup of 27 patients with lung cancer and lymphoma; however, these changes did not correlate with new clinical or echocardiographic findings [72]. In a study of 129 patients with breast cancer undergoing RT, NT-proBNP, troponin, and C-reactive protein were not found to significantly change pre- and post-RT. However lipopolysaccharide-binding protein (LBP) was found to correlate with MHD and post-RT diastolic dysfunction on TTE in a study of 129 patients, a finding that awaits confirmation in larger studies [73].

A yearly history and physical exam are recommended to monitor patients with a history of cardiovascular RT exposure, and a screening interval of approximately 5 years is generally felt to be appropriate for repeat imaging to evaluate radiation-associated CAD, cardiomyopathy, valvular disorders, and/or pericardial effusion and constriction, depending on a patient's specific risk factors and comorbidities [10]. There is a paucity of data to guide specific reassessment intervals, but there should be a low threshold to investigate clinical changes, as the time course of RICD presentation is highly variable. Additional research is needed to determine the appropriate timing of reassessment after baseline imaging and biomarkers are obtained. Throughout survivorship, however, there should be a continuous focus on CV risk factor optimization and appropriate preventative therapy.

Management of RICD

Optimal medical therapy, including statin treatment and consideration for aspirin therapy, should be initiated in patients identified as having asymptomatic CAD on screening imaging. Patients with a history of RT and symptoms of acute or chronic chest pain should be managed according to the current guidelines. For patients requiring intervention for obstructive CAD, percutaneous intervention (PCI) is often favored over coronary artery bypass graft (CABG) due to the higher risk of surgery in patients with a history of thoracic RT, though diffuse disease is often encountered in this patient population, and PCI may be technically difficult [74]. Similarly, surgical valve intervention carries a high risk of morbidity and mortality compared to non-RT-exposed controls [60]. Calcification and fibrosis of the aortomitral curtain may complicate single valve replacement and can necessitate combined aortic and mitral valve replacement with extensive reconstruction (also known as a "commando" procedure). Transcatheter aortic and mitral valve replacement (TAVR, TMVR) may be preferred in patients at high risk for perioperative complications, and assessment by a multidisciplinary valve team is recommended to determine the optimal approach. In a retrospective study of 110 patients undergoing TAVR and surgical aortic valve replacement (SAVR) after mediastinal RT, TAVR was associated with lower 30-day mortality [75].

Guideline-directed medical therapy is recommended for RT-associated cardiomyopathy presenting as HF with reduced or preserved ejection fraction (HFrEF, HFpEF), though data are needed to best understand optimal therapeutics in this specific population. Importantly, restrictive and constrictive physiology should be considered in patients presenting with HFpEF. For patients with symptomatic constrictive pericarditis who fail to improve with medical therapy, pericardiectomy may be considered, though this procedure carries a high postoperative mortality rate approaching 20%, as reported in a retrospective study of 97 patients with chronic pericarditis (9 of whom had prior thoracic RT) [76]. When pericardiectomy is indicated, there may be some improvement in outcomes when the procedure is done earlier in the course of the disease.

CONCLUSIONS

The therapeutic ratio of RT for thoracic cancers has dramatically improved in recent decades, with modern RT retaining potent anti-cancer effects and improving upon the ability to spare non-tumor tissues. Despite RT advancements, many patients with thoracic cancers still receive radiation exposure to the heart, which damages cardiac tissue through both direct and indirect mechanisms. As a result, RICD is still a critical health concern facing patients who have received RT of the thorax, and the development of RICD in these patients is dependent upon numerous host- and treatment-related factors, including concomitant anti-cancer therapies and pre-existing CV risk factors. It is incumbent upon CV healthcare providers to conduct appropriate RICD screening and management measures to improve the quality of life and survival of patients treated with thoracic RT.

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REVIEW

Specific characteristics of STEMI in COVID-19 patients and their practical implications

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ABSTRACT

ST-elevation myocardial infarction (STEMI) is one of the cardiac emergencies whose management has been most challenged by the COVID-19 pandemic. Patients presenting with the "lethal combo" of STEMI and concomitant SARS-CoV-2 infection have faced dramatic issues related to the need for self-isolation, systemic inflammation with multi-organ disease and difficulties to obtain timely diagnosis and treatment. The interplay between these and other factors has partly neutralized the major advances in STEMI care achieved in the last decades, significantly impairing prognosis in these patients. In the present review article, we will provide an overview on mechanisms of myocardial injury, specific clinical and angiographic characteristics and contemporary management in different settings of STEMI patients with COVID-19, alongside the inherent implications in terms of in-hospital mortality and short-term clinical outcomes.

Key words: STEMI, COVID-19, myocardial injury, in-hospital death, fibrinolysis

INTRODUCTION

More than two years after it was first described, much remains to be discovered about Coronavirus Disease 19 (COVID-19) caused by Severe Acute Respiratory Syndrome-Corona-Virus 2 (SARS-CoV-2). While initially identified as atypical pneumonia, it is now evident that COVID-19 is rather a multi-organ disease with a wide variety of clinical presentations. Consistently, several hypotheses on patterns of myocardial injury in patients infected with SARS-CoV-2 have been advanced, including myocarditis, stress cardiomyopathy, and ischemic injury among others [1–4].

ST-elevation myocardial infarction (STEMI) is the most acute manifestation of ischemic heart disease and one of the most life-threatening cardiovascular emergencies [5, 6]. A hypothesis of an association between respiratory diseases and myocardial infarction (MI) had already been proposed during earlier epidemics, such as SARS caused by SARS-CoV-1 and Middle East Respiratory Syndrome, when the incidence of adverse cardiovascular events, including MI and death, was higher among those infected [7–9]. Also, the recently published IAMI (Influenza Vaccination Against Myocardial Infarction) trial demonstrated that influenza vaccination administered immediately after an acute MI was protective against ischemic events recurrence [10].

Patients presenting with STEMI at the time of the COVID-19 pandemic have been described to present poorer outcomes with higher in-hospital mortality, and multiple factors might contribute to this trend [11–13]. First, logistical challenges related to extensive health systems re-organization and patients' reluctance to seek medical attention for the fear of catching the infection could have contributed to worse quality of care. Secondly, the presence of symptomatic or asymptomatic SARS-CoV-2 infections might trigger myocardial infarction occurrence and precipitate its course.

Despite the diffusion of various tools for primary prevention and treatment, COVID-19

continues to represent a major health issue worldwide. Therefore, gaining a deep understanding of organ damage associated with COVID-19 is essential to limit its prognostic burden and reach a condition of coexistence with the virus.

This review aims to summarize the current evidence on the "lethal combo" between COVID-19 and STEMI, ranging from pathophysiology of acute myocardial injury associated with SARS-CoV-2 to clinical characteristics, management, and outcomes for patients presenting with STEMI and a SARS-CoV-2 infection.

MYOCARDIAL INJURY AND COVID-19

Cardiac injury has been shown to be quite common in COVID-19, with up to 40% of hospitalized patients presenting elevated cardiac biomarkers including troponin and brain natriuretic peptides [14, 15]. Myocardial injury associated with COVID-19 has also been described as a determinant of adverse prognosis, and higher troponin levels have been linked to higher rates of in-hospital death [15–17]. The dramatic independent prognostic role of troponin increase is well known. In a recent meta-analysis of 12 262 patients, a rise in troponin was associated with an almost five-fold mortality increase, irrespectively of age, gender, hypertension, diabetes, and coronary artery disease (CAD) [18]. However, whether myocardial injury represents a direct consequence of SARS-CoV-2 infection rather than just a systemic manifestation of the associated acute respiratory distress syndrome (ARDS) is still controversial.

Metkus et al. compared intubated patients with COVID-19 with a historical ARDS cohort, showing that myocardial injury in severe COVID-19 was related to baseline comorbidities and multiorgan failure but was not an independent predictor of mortality at multivariable regression analysis [19]. Most importantly, COVID-19-related ARDS was associated with a lower risk of myocardial injury compared with non-COVID-19-related ARDS [19]. In a similar study of 156 critically ill patients requiring mechanical ventilation in Europe, myocardial injury was more common in non-COVID-19 ARDS, unlike thromboembolic events which were significantly higher in patients with COVID-19 [20].

While such evidence places myocardial injury in COVID-19 in the context that is generally observed in ARDS, several hypotheses of a specific pathogenetic role of SARS-CoV-2 in cardiomyocyte damage have been postulated. These include (1) direct cytotoxic effect by coupling to angiotensin-converting enzyme 2 (ACE-2) receptor expressed in the myocytes [21]; (2) endothelial damage to blood vessels, caused either by a direct link of the virus to the ACE2 receptor or by hypercytokinemia-associated vasculitis, with exposure of tissue factor that promotes a hypercoagulability state [22]; (3) coronary microvascular damage from diffuse thrombogenicity [23, 24]; and (4) coronary atheromas destabilization [25].

All these mechanisms might explain various manifestations of cardiac damage reported in COVID-19 patients, such as acute MI, myocarditis, arrhythmias, and acute heart failure [2, 25]. In terms of MI, SARS-CoV-2 infection might most likely trigger three of the types defined by the Fourth Universal Definition: type 1, type 2, and type 4b (Figure 1) [26]. Type 1 MI is caused by atherothrombotic CAD. During COVID-19, systemic vasculitis, microvascular dysfunction, platelets activation and spreading inflammation determine a higher thrombotic burden leading to atherosclerotic plaque instability, as discussed below [27]. Type 2 MI is defined by a mismatch between coronary oxygen supply and demand, which is enhanced by cytokine storm and ARDS-associated hypoxemia. Also, metabolic acidosis is usually observed in severe COVID-19, leading to a rightward shift of oxygen-hemoglobin dissociation curve and worsening of hemoglobin affinity to oxygen [28]. On the other hand, fever and inflammatory states raise the metabolic needs of organs and tissues. Type 4b is a subset of percutaneous coronary intervention (PCI)-related MI characterized by stent/scaffold thrombosis. In COVID-19 positive patients, this event might be triggered by the consistent systemic thrombotic burden, as SARS-CoV-2 infection was independently associated with a 5-times higher risk of in-hospital definite stent thrombosis [27, 29], but a role could also be played by suboptimal stent delivery due to emergency revascularizations in more hemodynamically unstable patients.

HOSPITAL ADMISSIONS FOR MYOCARDIAL INFARCTION DURING THE COVID-19 PANDEMIC

The COVID-19 pandemic has put severe pressure on health systems worldwide. Increasing numbers of patients admitted to emergency departments for COVID-19 resulted in rapid saturation of hospitals and intensive care units (ICU) capacity. New emergency hospitals have been built all over the world to allow prompt treatment of a larger number of critically ill patients. On the other hand, a decreasing rate of hospitalizations from other acute conditions has been described, also including MI [30, 31]. In the United Kingdom, by the end of March 2020, the rate of hospital admissions for acute coronary syndromes fell by 40% compared to the same period in 2019 [32]. Similarly, a 48.8% decrease in acute MI hospitalizations was observed in an Italian nationwide study [33]. This trend becomes even more alarming if we consider the high degree of myocardial injury and MI among patients infected with SARS-CoV-2, as previously described.

Several factors might have contributed to this data. The first and more reasonable hypothesis is the allocation of most healthcare resources, including hospital staff and equipment, to contain the pandemic leading to a lower capacity of dealing with other medical emergencies [34]. Secondly, the pandemic had a psychological impact on patients, generating the fear of in-hospital contagion. This is supported by the observation of a greater reduction in non-ST elevation MI (NSTEMI) admissions compared to STEMI [35]. Moreover, in an observational study con-

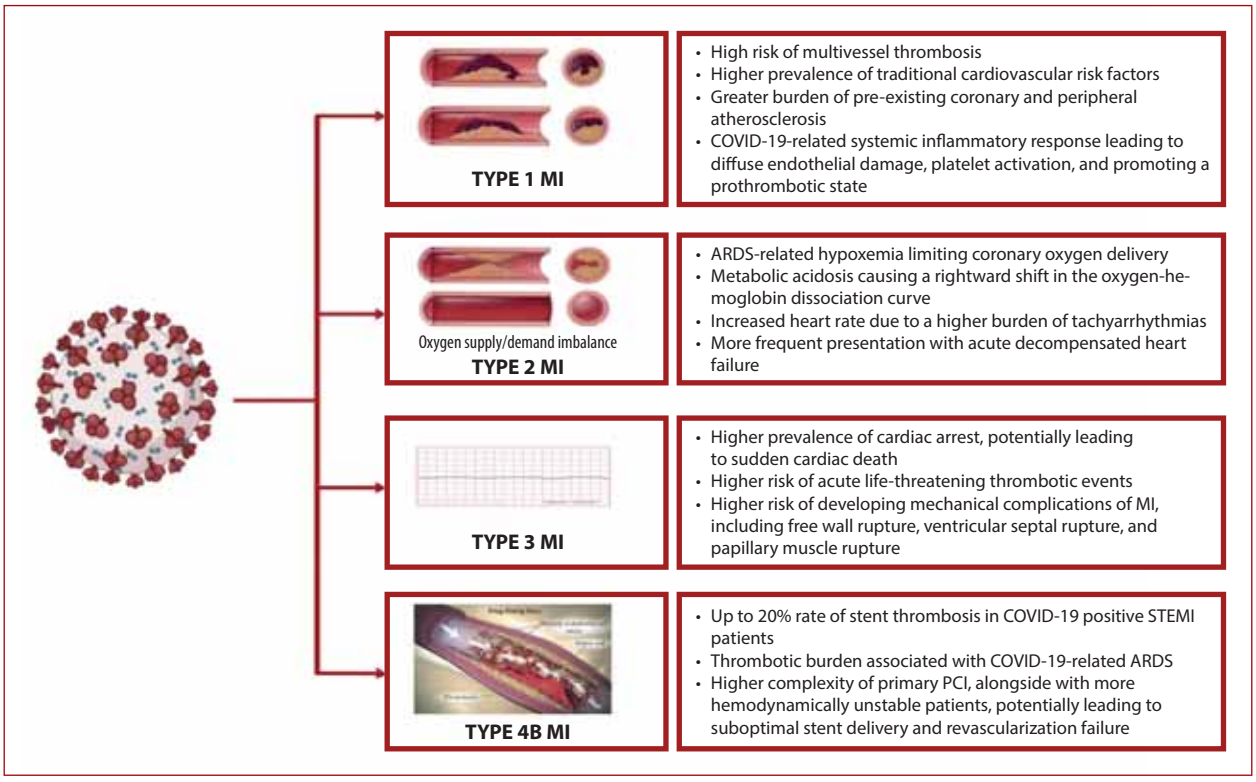


Figure 1. Patterns of myocardial infarction potentially associated with COVID-19

Abbreviations: ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 19; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

ducted in Italy in a non-epicenter area with relatively low pressure on the healthcare system, the incidence of STEMI was lower than expected and a U-shaped phenomenon with the nadir of hospital admissions during the first COVID-19 outbreak was observed [36]. Indeed, it should also be noted that infarct-related symptoms such as chest discomfort and dyspnea could be misinterpreted as being related to respiratory infection and targeted as respiratory symptoms in patients with COVID-19. Another interesting hypothesis is the paradoxically beneficial effect of social containment. A more relaxed lifestyle under lockdowns, compared to stressful daily living and sports activities, might have determined a lower incidence of MI, providing short-term protection to those carrying vulnerable coronary plaques [37].

CLINICAL FEATURES OF STEMI PATIENTS WITH AND WITHOUT COVID-19

Since the first phases of the pandemic, all patients presenting to the emergency department with a STEMI have received a nasopharyngeal swab RT-PCR testing and have subsequently been classified as either COVID-19 positive or negative. In other cases, a STEMI might have occurred in patients who were already hospitalized or quarantined at home with a prior diagnosis of COVID-19. A summary of real-world studies comparing STEMI patients with and without COVID-19, mainly published during the first wave, is reported in Table 1 [27, 29, 38–41].

Two studies conducted in the US demonstrated consistent ethnic disparities, with African American STEMI patients more likely to be COVID-19 positive compared to other ethnicities. While the present pandemic is often regarded as a social equalizer, affecting people from all over the world, ethnic minorities have been reported to suffer disproportionately from COVID-19 [42, 43]. Causes for higher rates of SARS-CoV-2 infection among African Americans might include a limited ability to practice social distancing at home or the higher probability of being part of the "essential workforce" that cannot work from home[44, 45]. The African American ethnicity has also been described as a risk factor for hospitalizations for COVID-19, but it was not related to death rates or the need for invasive ventilation [46]. It is, therefore, presumable that ethnicity itself is not a predisposing factor for worse outcomes and STEMI occurrence and that ethnic disparity is broken down when it comes to receiving hospital care.

STEMI patients with COVID-19 did also more frequently present cardiovascular risk factors, except for smoking, and other relevant comorbidities (chronic kidney disease, prior stroke, prior CAD), compared to their negative counterparts. Arterial hypertension and diabetes have been the two most common comorbidities associated with COVID-19 in the early data from the epicenters [47, 48]. The main point of interaction between SARS-CoV-2 and hypertension is probably the ACE-2 receptor, to which the spike protein (S) of the virion binds to facilitate viral

Table 1. Clinical characteristics of STEMI patients with and without COVID-19

	Choudry et al. [27], JACC 2020	Rodriguez-Leor et al. [29], Eurointervention 2021[b]	Case et al. [38], Am J Cardiol 2021	Kite et al. [39], JACC 2021	NACMI registry [41], JACC 2021	Saad et al. [40], JAMA 2021
Study period	March 2020 – May 2020	March 2020- April 2020	March 2020 – June 2020	March 2020 – July 2020[c]	January 2020 – December 2020[e]	January 2019 – December 2020
Country	UK[a]	Spain	US	Global[d]	US and Canada	US
Enrolment strategy	Consecutive patients	Consecutive patients	Consecutive patients	Patients whose data were uploaded on a web-based system	Prospective, investigator-initiated registry	Consecutive patients
Type of MI	STEMI	STEMI	STEMI and NSTEMI	STEMI	STEMI	STEMI (Out-of-hospital)
Prevalence of COVID-19, n (%)	39 (34)	91 (9)	86 (6)	Not assessed (n = 144)	Not assessed (n = 230)	565 (0.7)
Age, years, mean ±SD	61.7 ± 11.0 vs. 61.7 ± 12.6, $P = 0.63$	64.8 ± 11.8 vs. 62.5 ± 13.1, $P = 0.95$	70.8 ± 14.7 vs. 66.5 ± 14.6, $P = 0.008$*	63.1 ± 12.6 vs. 65.6 ± 13.4, $P = 0.018$*	$P > 0.05$ for comparison between age groups	$P > 0.05$ for comparison between age groups
Male gender, %	84.6 vs. 75, $P = 0.34$	84.4 vs. 78.4, $P = 0.18$	55.8 vs. 55.1, $P = 0.9$	77.8 vs. 72.2, $P = 0.14$	71 vs. 68, $P = 0.38$	69.9 vs. 70.3, $P = 0.85$
Afroamerican race, %	56.4 vs. 44.7, $P = 0.25$	—	64 vs. 48.2, $P = 0.005$*	—	Not assessed in control group (24% in Covid+ STEMI)	16.8 vs. 11.4, $P<0.001$*
Obesity	BMI (kg/m^2): 26.7 (24.8–30.7) vs. 26.87 (22.6–29.4), $P = 0.36$	—	Weight (kg): 80.5 ± 22.7 vs. 86.1 ± 38.2, $P = 0.08$	BMI (kg/m^2): 27.3 ± 4.5 vs. 27.8 ± 5.5, $P = 0.18$	BMI (kg/m^2): 29.3 ± 7.6 vs. 29.5 ± 6.4, $P = 0.7$	BMI (kg/m^2): 25.5 vs. 21.5, SMD = 0.09
Hypertension, %	71.8 vs. 42.1, $P = 0.003$*	51.7 vs. 53.3, $P = 0.28$	47.7 vs. 57.8, $P = 0.07$	64.8 vs. 44.8, $P <0.001$*	73 vs. 69, $P = 0.16$	79.1 vs. 74.8, SMD = 0.1
Dyslipidemia, %	61.6 vs. 36.8, $P = 0.02$*	48.4 vs. 46.9, $P = 0.27$	58.1 vs. 59.3, $P = 0.83$	46 vs. 28.9, $P <0.001$*	46 vs. 60, $P = 0.001$*	66 vs. 67.2, SMD = 0.02
Diabetes mellitus, %	46.2 vs. 26.3, $P = 0.04$*	23.1 vs. 20.9, $P = 0.06$	57 vs. 39.7, $P = 0.002$*	34 vs. 20.9, $P <0.001$*	46 vs. 28, $P <0.001$*	48 vs. 33.9, SMD = 0.29
Smoking, %	61.6 vs. 46.1, $P = 0.17$	18.7 vs. 45.5, $P<0.001$*	—	31.7 vs. 33.7, $P = 0.77$	44 vs. 59, $P <0.001$*	15.9 vs. 31.6, SMD = 0.38
Chronic kidney disease, %	—	—	44.2 vs. 26.1, $P <0.001$*	9.9 vs. 3.6, $P <0.001$*	—	20.7 vs. 15.7, SMD = 0.13
Lung disease, %	—	—	Asthma: 3.5 vs. 5.3, $P = 0.47$	11.8 vs. 13.4, $P = 0.78$	—	COPD: 11.7 vs. 14.9, SMD = 0.09
Prior stroke, %	—	—	16.3 vs. 8.6, $P = 0.02$*	7.6 vs. 5.7, $P = 0.11$	10 vs. 9, $P = 0.8$	6.7 vs. 6.1, SMD = 0.02
History of CAD, %	Previous PCI: 23.1 vs. 6.6, $P = 0.02$*	15.6 vs. 13, $P = 0.04$*	51.2 vs. 65.7, $P = 0.006$*	Previous PCI: 13.9 vs. 10.2, $P = 0.03$*	24 vs. 31, $P = 0.05$*	85.8 vs. 88.8, SMD = 0.09
History of heart failure, %	—	—	44.2 vs. 34.9, $P = 0.08$	19 vs. 2.8, $P<0.001$*	16 vs. 9, $P = 0.01$*	17.5 vs. 19.7, SMD = 0.06
Troponin T, ng/l, %	1,221 (179–4,143) vs. 369 (78.5–1,109), $P = 0.003$	—	22.9 ± 52.8 vs. 22.1 ± 43.7, $P = 0.91$*	2224.0 (58.0–7,449.5) vs. 899.0 (100.0–3,745.0), $P = 0.15$	—	—

[a]A total of 115 consecutive STEMI patients admitted to Barts Heart Center (London, UK) were included in the analysis. [b]9% of COVID-19 positive and 0.7% of COVID-19 negative STEMI patients in this group were already hospitalized at the time STEMI occurred. [c]Patients in the control group were taken from a pre-COVID-19 (2018–2019) database (n = 24 961). [d]75.3% of the included patients were from Europe, 11.1% from South America, 6.6% from Asia, 4.7% from Africa, and 2.2% from North America. [e]Patients in the control group were taken from a pre-COVID-19 (2015–2019) database and were sex and age matched to the 230 COVID-19 positive STEMI patients (2:1 ratio of control patients to COVID-positive patients)

Abbreviations: BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; COVID-19, Coronavirus Disease 19; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; SMD, standardized mean difference; STEMI, ST-elevation myocardial infarction; UK, United Kingdom; US, United States

entry in the respiratory district, thereby leading to its degradation [49]. ACE-2 downregulation leads to increased angiotensin II levels, which are responsible for enhanced arterial vasoconstriction and increased blood pressure [50–52]. The association between arterial hypertension and inflammation favors microvascular dysfunction and hypertensive end-organ damage, of which MI is one of the manifestations [53, 54]. Similarly, diabetic patients have higher ACE-2 levels than the general population, which predisposes to the infection, as well as lower innate and adaptative immunity activation; also, high blood glucose concentrations directly increase viral replication[55]. Notably, overexpression of reactive oxygen species and some inflammatory cytokines, such as interleukin-6, accelerate MI occurrence and is triggered both by diabetes and SARS-CoV-2 infection [56, 57]. Dyslipidemia has been shown to predict severe COVID-19 development in various studies and meta-analyses [58, 59]. A proposed mechanism involves the high arterial and venous thrombogenicity of COVID-19, which is particularly evident in patients with hypercholesterolemia and seems to be prevented by statin therapy [60]. Conversely, a significantly lower prevalence of smoking habits has been found among SARS-CoV-2 positive STEMI patients, which might seem counterintuitive considering the strong impact of cigarette smoking on both coronary atherosclerosis and respiratory illness. This finding is in line with larger reports on patients diagnosed with COVID-19 [61] but, while a protective immunomodulatory effect of nicotine was initially proposed to justify the reduced risk of SARS-CoV-2 infection, it is now common belief that this result is subject to several biases [62, 63].

Pre-existing coronary or cerebrovascular atherosclerosis was more frequent in COVID-19 STEMI in most of the examined studies. Both a systemic inflammation in response to the virus and the procoagulant and hemodynamic effect of the infection might indeed favor a vulnerable atherosclerotic plaque rupture with subsequent thrombus formation and acute ischemia [22, 64].

Finally, there seemed to be no gender differences between STEMI patients with and without COVID-19, even though women were consistently under-represented. While systemic inflammatory response related to the viral infection might enhance traditional cardiovascular risk factors and trigger coronary atherosclerosis, women often display a different pattern of ischemic heart disease, which might be influenced to a lower degree by SARS-CoV-2 infection [65, 66]. Further studies on COVID-19-related MI in female patients are warranted to help elucidate this point.

IN-HOSPITAL PRESENTATION AND ANGIOGRAPHIC CHARACTERISTICS

Several peculiarities in the spectrum of symptoms and angiographic findings across COVID-19 STEMI patients have been widely reported, and it has been questioned whether this variability only depends on logistic issues or is rather a consequence of intrinsic characteristics of the viral infection.

In regard to clinical presentation, the NACMI (North American COVID-19 Myocardial Infarction) registry reported a higher prevalence of atypical symptoms, including dyspnea and syncope, rather than chest pain in a cohort of 230 COVID-19 positive STEMI patients compared to a historical control group [41]. Considering the higher frequency of pulmonary infiltrates on chest X-ray observed in patients with COVID-19 in the same study, this suggests respiratory symptoms might mask the classical red flags of STEMI and cause a diagnostic delay. The coexistence of STEMI with SARS-CoV-2 infection might also translate into a higher percentage of heart failure on in-hospital arrival, as observed in a Spanish nationwide registry, in which 31.9% of COVID-19 positive STEMI vs. 18% of negative patients had signs of congestion ($P = 0.002$), with a significant trend towards higher Killip classes in the first group [29].

At coronary angiography, a higher thrombus burden in COVID-19 positive STEMI patients was highlighted by several reports. In the observational study conducted by Choudry et al. [27] at Barts Heart Centre (London, UK), subjects infected with COVID-19 displayed substantially higher rates of stent thrombosis (10.3% vs. 1.2%; $P = 0.054$), greater incidence of multiple thrombotic culprit lesions (17.9% vs. 0%; $P < 0.001$), higher thrombus grade (75% vs. 31.4% with grade 4–5; $P < 0.001$), and more frequent need for glycoprotein IIb/IIIa inhibitors (59% vs. 9.2%; $P < 0.001$) and aspiration thrombectomy (17.9% vs. 1.3%; $P = 0.002$). Interestingly, D-dimer levels correlated with the myocardial blush grade and dosage of heparin required during primary PCI (PPCI) [27]. Similar findings were observed in the registry by Rodriguez-Leor et al. [29] (mechanical thrombectomy was necessary in 44% vs. 33.5% of cases, $P = 0.05$, and glycoprotein IIb/IIIa in 20.9% vs. 11.2%, $P = 0.007$), in which there was also a lower usage of P2Y12 inhibitors pretreatment among COVID-19 positive patients. In both these European studies, there were no differences in terms of time to hospital admission, door-to-balloon time, and reperfusion strategy, suggesting that increased thrombogenicity is a direct effect of the SARS-CoV-2 infection. Another small registry (n = 78) conducted in 4 hospitals in Italy, Lithuania, Iraq, and Spain reported an alarming 21% prevalence of stent thrombosis [67]. Besides the prothrombotic state induced by COVID-19, which mainly causes venous thromboembolism [68], SARS-CoV-2 infection might trigger arterial thrombosis through platelet activation, vasoconstriction, and endothelial dysfunction [69]. Of note, the influenza virus itself was associated with a higher incidence of MI in a pre-COVID study [70].

Other reports, mainly conducted in the US and China, described a substantial delay in myocardial reperfusion, that did at least in part explain the higher rate of thrombotic complications. In a study by Xiang et al. [11], which collected data on almost 30 000 STEMI registered in China before and after the pandemic, patients admitted for STEMI

during the COVID-19 outbreak presented significantly longer time from symptom onset to first medical contact and from first medical contact to angioplasty/thrombolysis, with these differences being more marked in Hubei province (the epicenter). The NACMI registry observed a significant 13-minute difference in door-to-balloon time (79 vs. 66 min; $P = 0.008$); COVID-19 STEMI patients were also more likely to have a door-to-balloon ≥90 min (42% vs. 27%; $P = 0.006$), to receive no angiography (22% vs. 0%; $P < 0.001$), and to be treated with fibrinolysis or medical therapy rather than with PCI or coronary artery bypass grafting [41]. In a retrospective cohort study by Saad et al. [40], based on a US STEMI database, patients with COVID-19 did less frequently undergo coronary angiography (81.9% vs. 86.2%) and were more commonly treated with fibrinolytics only (1.9% vs. 0.2%); such gap was even more pronounced among those with in-hospital STEMI, of whom fewer than one third underwent angiography and fewer than one-fourth PPCI. Recommendations from Chinese and American scientific societies, which suggested considering thrombolysis in the first instance during the first outbreak to prevent hospital contagion, might justify the above-mentioned findings [71, 72]. However, even in the international COVID-ACS registry, in which 75% of patients were from European hospitals, significantly longer times from symptom to admission (173 vs. 339 min; $P < 0.001$) and door-to-balloon (83 vs. 37 min; $P < 0.001$) were described, as compared to national pre-COVID-19 databases [39].

In terms of culprit coronary lesions, it has been proposed that COVID-19 patients are more prone to present myocardial infarction with non-obstructive coronary artery disease (MINOCA). The incidence of this condition consistently varied among studies, reaching up to 56% in a case series from New York City [73], 39.3% in a case-series from Lombardy [13], 54.5% in a single-center French prospective study (vs. 6.9% in COVID-negative patients; $P < 0.001$)[74], and 23% in the American NACMI registry (vs. 1% in the control group; $P < 0.001$) [41]. MINOCA is an umbrella for several cardiac conditions, including Takotsubo syndrome, myocarditis, transient thrombosis, and type 2 MI, and this might explain differences in incidence across studies conducted at different times of the pandemic and with heterogeneous inclusion criteria [75]. On the other hand, it can be argued that SARS-CoV-2 potentially associates with several patterns of myocardial injury which mimic STEMI, thus requiring a careful diagnostic assessment in STEMI patients with COVID-19.

MORTALITY AND PERI-PROCEDURAL ADVERSE EVENTS

Historically categorized as a life-threatening cardiovascular emergency, mortality of STEMI has decreased drastically over the last decades, largely due to a substantial reduction in-hospital mortality [76]. The current 30-day mortality rate of patients with STEMI is between 2.5% and 10% according to several observations [77–79]. The association between STEMI and SARS-CoV-2 infection has led to a tremendous prognostic impact among patients presenting with what has been defined as the "lethal combo". Table 2 lists the main studies reporting short-term outcomes in STEMI patients with COVID-19. In-hospital mortality ranged from 15% to 40%, with consistent variability across different populations, and subjects who tested positive for SARS-CoV-2 also presented higher rates of cardiogenic shock (CGS), cardiac arrest, prolonged ICU stay, mechanical ventilation, major bleeding and stroke. Several causes, including delay in seeking medical care, longer door-to-balloon time (due to the need of activating specific hospital pathways), higher thrombotic burden, higher rates of baseline comorbidities and coexistence of respiratory distress, systemic inflammation, and multi-organ damage, might lie beyond this trend, and the most suitable etiologic model is likely to be multifactorial. Notably, in the study by Rodriguez-Leor et al. [29], COVID-19 was associated with a significant increase in both cardiovascular and non-cardiovascular mortality among STEMI patients. To assess the effect of different pathogenic factors on in-hospital outcomes, Kite et al. [39] performed a multivariable propensity-based analysis, showing that: (1) SARS-CoV-2 infection was an independent predictor for death (hazard ratio [HR], 3.33; 95% confidence interval [CI], 2.04–5.42) and CS (HR, 1.48; 95% CI, 1.27–1.72); (2) prolonged ischemia times were associated with poorer outcomes, with a 10% increase in mortality for every 10-minute delay; (3) in patients with CGS, CGS rather than COVID-19 was the major determinant of mortality. Even though the direct correlation between longer time to revascularization and occurrence of CGS was not explored, it is evident that patients' medical education and prompt activation of dedicated cath labs are pivotal to reducing clinical complexity and improving overall survival.

Additionally, patients with MI associated with COVID-19 might be at higher risk of developing mechanical complications, such as free wall rupture, ventricular septal rupture, and papillary muscle rupture [80, 81]. In a recently published large STEMI registry, the occurrence of mechanical complications was independently associated with both SARS-CoV-2 infection and pre-hospital delay, reaching an incidence of 5% in those presenting after 36 hours from symptom onset [82].

MANAGEMENT OF STEMI PATIENTS ACCORDING TO DIFFERENT SCIENTIFIC SOCIETIES

The best way to balance cardiovascular emergencies management — mainly acute MI — and COVID-19 control has been one of the most challenging issues created by the pandemics, especially during its first outbreak. At first, since the majority of patients needing cardiovascular care are not infected, it is essential to maximize their safety and that of medical personnel and at the same time to provide every patient the most advanced available care [83, 84]. The insti-

Table 2. Outcomes for STEMI patients with COVID-19

Study	Country	N. of COVID+ STEMI	N. of COVID- STEMI	Mortality, %	ICU admission	Stroke, %	Major bleeding, %	CGS, %	Mechanical ventilation, %
Stefanini et al. [13]	Italy	28	—	39.3	—	—	—	—	—
Choudry et al. [27]	UK	39	76	17.9 vs. 6.5, $P = 0.10$	28% vs. 5%, $P = 0.003$[e]	—	—	Cardiac arrest: 28.2 vs. 9.2, $P = 0.01$*	—
Rodriguez-Leor et al. [29]	Spain	91	919	Overall: 23.1 vs. 5.7, $P < 0.001$* CV mortality: 13.2 vs. 5.1, $P = 0.002$* Non-CV mortality: 9.9 vs. 0.5, $P < 0.001$*	—	—	3.3 vs. 1.5, $P = 0.21$	9.9 vs. 3.8, $P = 0.007$*	4.4 vs. 1.6, $P = 0.06$
Case et al. [38][a]	US	86	1 447	27.9 vs. 3.7, $P < 0.001$*	64%	—	—	—	33.7
Hamadeh et al. [67]	Lithuania, Italy, Spain, Iraq	78	—	—	—	Ischemic: 4; hemorrhagic: 6	—	Need for resuscitation: 17	18
Popovic et al. [74]	France	11	72	27.3 vs. 5.6, $P = 0.02$*	—	—	—	36.4 vs. 4.2, $P = 0.03$*	—
Kite et al. [39]	Global[b]	144	24 961[c]	22.9 vs. 5.7, $P < 0.001$*	33.9%	2.1 vs. 0.14, $P = 0.002$*	2.8 vs. 0.26, $P < 0.001$*	20.1 vs. 8.7, $P < 0.001$*	11.6 vs. 0.4, $P < 0.001$*
NACMI [41]	US and Canada	230	460[d]	33 vs. 4, $P < 0.001$*	Length of stay (days): 3 (1.0–10.0)	3 vs. 0, $P = 0.017$*	—	18 vs. 10, $P = 0.002$*	—
Saad et al. — OOH [40]	US	565	75 869	15.4 vs. 9, $P < 0.001$*	Length of stay (days): 1.0 (0.0, 3.0) vs. 1.0 (0.0–2.0), $P = 0.06$	Death + stroke: 18.2 vs. 10.5, $P < 0.001$*	9.7 vs. 6.9, $P = 0.007$*	18.2 vs. 16.8, $P = 0.38$	21.2 vs. 13.9, $P < 0.001$*
Saad et al. — IH [40]	US	359	3 656	79.9 vs. 38.8, $P < 0.001$*	Length of stay (days): 7.0 (1.0–15.0) vs. 3.0 (1.0 – 8.0), $P < 0.001$*	Death + stroke: 82.5 vs. 44.8, $P < 0.001$*	27 vs. 25.9, $P = 0.64$	25.3 vs. 27.2, $P = 0.45$	77.7 vs. 46.1, $P < 0.001$*

[a]This study included both patients with STEMI and with NSTEMI. [b]75.3% of the included patients were from Europe, 11.1% from South America, 6.6% from Asia, 4.7% from Africa, and 2.2% from North America. [c]Patients in the control group were taken from a pre-COVID-19 (2018–2019) database (n = 24 961). [d]Patients in the control group were taken from a pre-COVID-19 (2015–2019) database and were sex and age matched to the 230 COVID-19 positive STEMI patients (2:1 ratio of control patients to COVID-positive patients). [e]Crude data were not reported and have been interpolated from a study figure

Abbreviations: CGS, cardiogenic shock; CV, cardiovascular; ICU, intensive care unit; IH, in-hospital; OOH, out-of-hospital; other — see Table 1

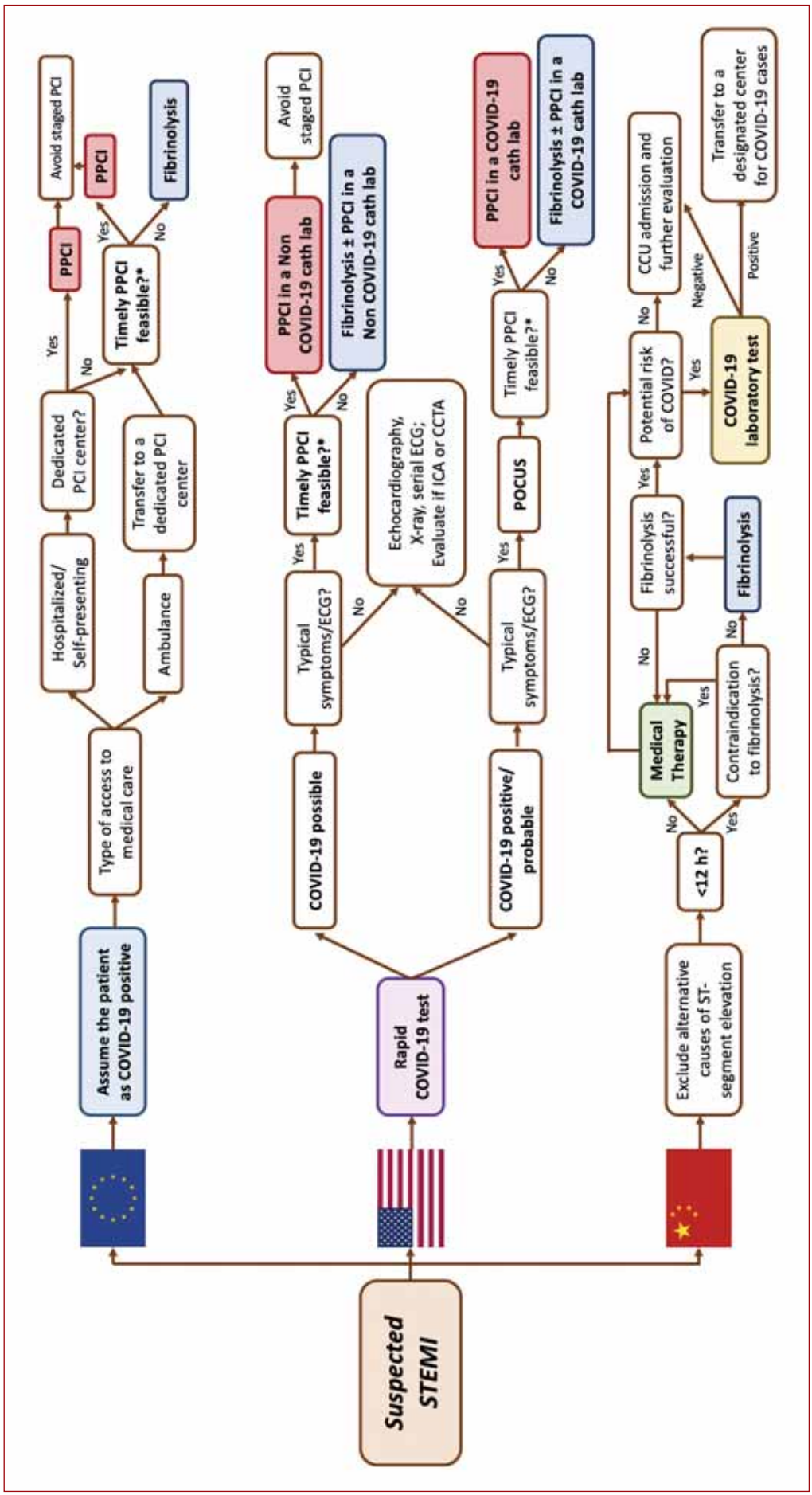
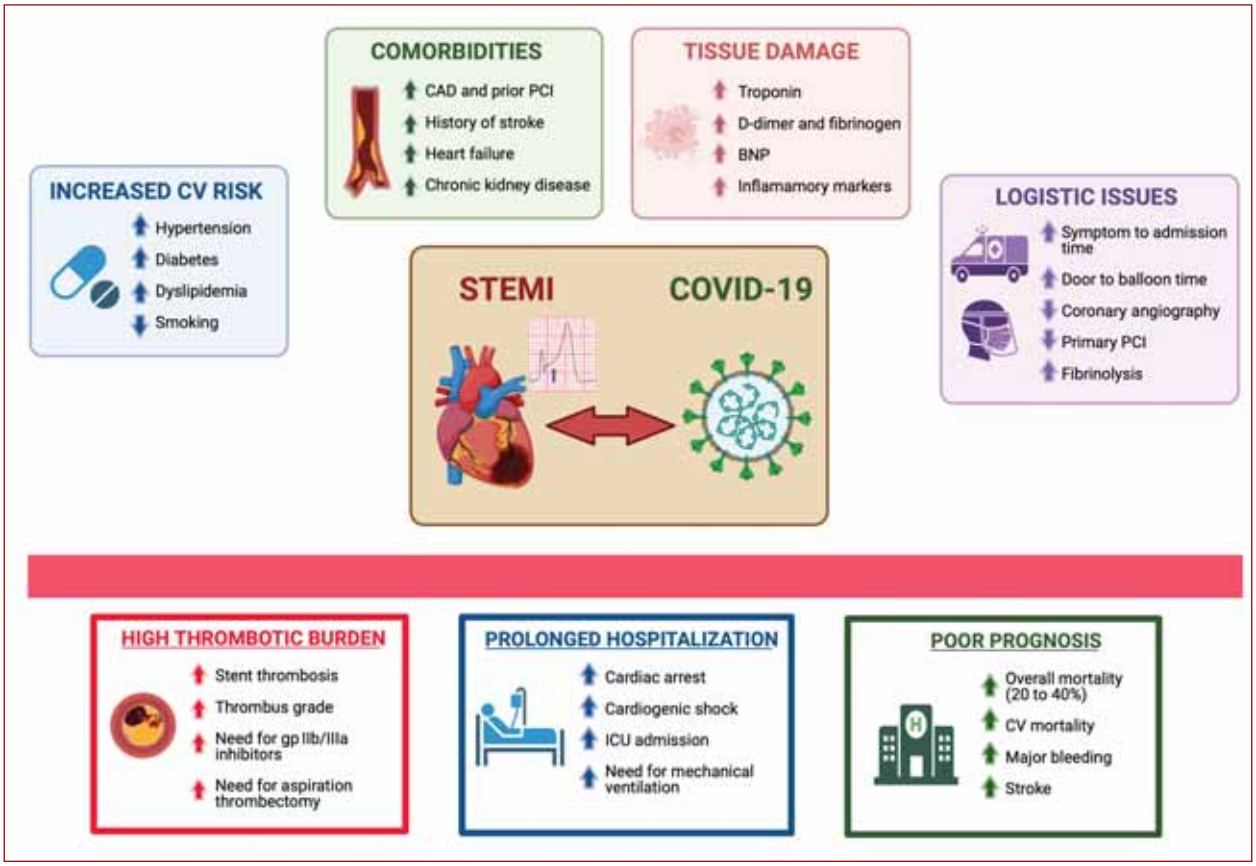


Figure 2. Recommended management of suspected STEMI during the COVID-19 pandemic according to European, American, and Chinese consensus documents. Main recommendations for the management of patients with suspected STEMI according to the European College of Cardiology (European flag), American College of Cardiology/Society for Cardiovascular Angiography and Interventions/American College of Emergency Physicians (American Flag), and the Peking Union Medical College Hospital (Chinese flag) are summarized. *If in a PCI center, the ability to perform timely PPCI depends on staff, dedicated cath lab, and personal protective equipment availability. In a non-PCI center, clinical status, transfer time, and team-specific details should be considered

Abbreviations: CCTA, coronary computed tomography angiography; CCU, coronary care unit; COVID-19, coronavirus disease 19; ICA, invasive coronary angiography;POCUS, point-of-care ultrasound; PPCI, primary percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction



Central illustration. Specific characteristics of STEMI in COVID-19 patients and their practical implications

Abbreviations: BNP, brain natriuretic peptides; CAD, coronary artery disease; COVID-19, Coronavirus Disease 19; CV, cardiovascular; gp IIb/IIIa, glycoprotein IIb/IIIa; ICU, intensive care unit; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction

tution of referral centers for PCI and cardiac emergencies has been helpful in terms of limiting overall in-hospital contamination, at the cost of increasing times from symptom onset to coronary revascularization in STEMI patients [11, 39–41].

Several scientific societies have developed an algorithm for suggested management of patients with clinical suspicion of STEMI, which did reflect local epidemiological curves (Figure 2) [72, 85–88]. The Peking Union Medical College Hospital, in China, posed the minimization of total ischemia time as its primary goal. As such, fibrinolysis was recommended as the first-line therapy for almost all patients, while immediate transfer to a cardiac catheterization lab could be considered just in the case of low risk of COVID-19 where a collection of samples for nucleic acids detection was not required [72]. A joint consensus document from the American College of Cardiology (ACC), Society for Cardiovascular Angiography and Interventions (SCAI), and the American College of Emergency Physicians (ACEP) advocated to (1) perform ultrarapid COVID-19 testing and, if not available, consider all patients with suspected STEMI as potentially positive; (2) perform additional non-invasive imaging tests before treatment (ultrasound in every patient) to exclude "STEMI mimickers", thereby taking into account longer door-to-balloon times; (3) regard PPCI as the standard of care as far as it can be timely provided [86]. Similar recommendations have been provided in a recently updated and published guidance from the European Society of Cardiology (ESC), which, however, stressed the goal of a maximum 120 minutes delay from diagnosis to reperfusion allowing PPCI without fibrinolysis [88, 89]. In the case of multivessel CAD on coronary angiography, treatment of non-culprit lesions and complete revascularization at the time of PPCI are also suggested by both the European and American guidelines, to limit further medical staff exposure.

CONCLUSIONS

STEMI care in the era of COVID-19 has represented a major health issue, with alarming rates of related in-hospital complications and mortality. This is, at least in part, a collateral damage of lockdown and health systems reorganization, which have often not allowed prompt diagnosis and timely reperfusion. However, specific COVID-19 features including increased thrombogenicity, ARDS-related hypoxemia, and the likelihood of affecting patients with more cardiovascular comorbidities, might contribute to further impaired prognosis of STEMI patients with COVID-19. While lessons learned from the first wave will hopefully allow us to better manage these patients in case of future outbreaks, further research elucidating potential mechanisms of interaction between SARS-CoV-2 and coronary atherosclerosis is warranted.

Article information

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Role of cardiac magnetic resonance in heart failure of initially unknown etiology: A 10-year observational study

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Editorial
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ABSTRACT

Background: The heart failure (HF) population is estimated to be 64.3 million people worldwide and continues to grow. Identifying the underlying cause of HF is crucial for patient management and prognosis.

Aims: We sought to evaluate the role of cardiac magnetic resonance (CMR) imaging to identify the etiology of HF and to evaluate the impact of CMR on diagnosis and patient management.

Methods: We retrospectively reviewed the medical charts of 8630 consecutive patients referred for CMR in a large tertiary center between 2008 and 2017 (10 years). In this study, we only included patients referred for CMR due to HF of unknown etiology whose diagnostic workup had not revealed suspicion of any specific cardiac disease leading to HF. We also analyzed changes in patient management that were guided by the CMR findings, which were defined as changes in treatment and/or the necessity of further tests.

Results: The study sample included 243 patients: 173 (71.2%) patients were male, and the mean (SD) age was 44.0 (15.2) years. All patients underwent contrast-enhanced CMR. Late gadolinium enhancement (LGE) was detected in 74.9% of cases. In 94 patients (38.7%), CMR led to a new diagnosis. In 41 patients (16.9%), patient management was changed by CMR. The latter group comprised patients with coronary artery disease, amyloidosis, valvular disease, and cardiomyopathies other than dilated, namely hypertrophic, restrictive, and left ventricular noncompaction.

Conclusions: Our study strongly suggests that CMR imaging is a valuable tool for determining the etiology of HF and affects patient management.

Key words: cardiac magnetic resonance, heart failure, heart failure of unknown etiology, late gadolinium enhancement

INTRODUCTION

Heart failure (HF) is a clinical syndrome caused by structural or functional cardiac abnormalities. It is associated with significant morbidity and mortality [1] and affects 1%–2% of the adult population [2]. In 2020, the HF population was estimated to be 64.3 million people worldwide, and it continues to grow [2]. In Poland, 1.24 million people (3.2% of the population) live with HF [3]. In Europe (particularly in Eastern European countries, including Poland [2, 4]), coronary artery disease (CAD) is the most common cause of both chronic and acute HF.

The identification of the underlying cause of HF is valuable because the outcomes for HF patients vary greatly depending on the etiology [5, 6]. Cardiac magnetic resonance (CMR) imaging is a diagnostic tool used to determine the etiology of HF and is recommended by

WHAT'S NEW?

To our knowledge, this is the first study evaluating the impact of cardiac magnetic resonance (CMR) imaging in the management of patients with heart failure of unknown etiology. We retrospectively reviewed all consecutive patients referred for CMR imaging due to heart failure of unknown etiology in a large tertiary center over a period of 10 years. In a group of 243 patients, we compared pre-CMR diagnosis (diagnosis of exclusion) with post-CMR diagnosis and analyzed its impact on clinical management. In our cohort, CMR led to a new diagnosis in 38.7% of cases and impacted patient management in 16.9% of the cases.

the European Society of Cardiology (ESC) guidelines [1] for patients with a poor acoustic window and for those suspected to have myocardial tissue disease. Because of its unique ability to noninvasively evaluate the myocardium, CMR imaging provides deeper insight into the mechanism leading to cardiac dysfunction and/or dilatation. Consequently, it enables the initiation of the causal treatment of diseases leading to HF. However, studies that demonstrate the true impact of CMR on diagnosis and management in a group of patients with heart failure of unknown etiology are lacking. Thus, we aimed to assess the value of CMR in a cohort of patients in a tertiary reference center.

METHODS

Study design

We retrospectively reviewed all medical charts of 8630 consecutive patients referred for CMR in a large tertiary center between 2008 and 2017, selecting for CMR studies performed due to HF. Then, we analyzed all available medical data to select patients with HF of unknown etiology. Only patients with no specific pre-CMR initial diagnosis were included. Patients whose referring physician suspected myocarditis, cardiomyopathy, a present or a previous myocardial infarction or advanced stable coronary disease (based on clinical signs and symptoms, patient and family history, or all pre-CMR studies) or any specific disease leading to HF were omitted from our analysis. In addition, patients with a family history that indicated possible cardiomyopathy or patients with a clinical presentation suggestive of cardiac amyloidosis, sarcoidosis, or peripartum cardiomyopathy were also excluded. Thus, we included only patients with diagnostic workups that did not reveal suspicion of any specific cardiac disease leading to HF.

All patients with risk factors for CAD had undergone previous invasive coronary angiography and/or computed tomography angiography to exclude CAD as the etiology of HF. Either no obstructive coronary disease was present in those patients or a single vessel disease was found that was not consistent with severe systolic function impairment.

All patients underwent echocardiography, and some patients were diagnosed with valvular disease. CMR imaging was performed in individuals with severe HF symptoms not correlated with the severity of valvular disease as determined by echocardiography.

The study was conducted in accordance with the Declaration of Helsinki. The project was approved by the Bioethics Committee of the National Institute of Cardiology (no. IK-NPIA-0021-16/1686/18). All participants gave written informed consent for the CMR study.

CMR protocol

All CMR studies were performed on a 1.5 Tesla scanner (Avanto or Avanto^{fit}, Siemens, Erlangen, Germany) using breath-hold cine in long-axis planes and sequential short-axis slices.

A gadolinium-based intravenous contrast agent was administrated to all patients, and the presence of late gadolinium enhancement (LGE) was evaluated. The LGE images were acquired 10–15 minutes after injection of the contrast agent. The imaging protocol encompassed all commercially available and clinically indicated sequences required for patients with HF due to an unknown etiology based on current guidelines and recommendations.

Left ventricular end-diastolic and end-systolic volumes were calculated using MASS software (MASS 6.2.1 or later, Medis, Leiden, The Netherlands). Endocardial and epicardial contours were delineated manually in the end-diastolic and end-systolic phases. The anatomy and function of the great vessels and valves were also assessed. The imaging protocol was left to the discretion of the physician supervising the study, as well as a team comprised of a cardiologist and a radiologist. The final CMR imaging-based diagnosis was obtained by a consensus between at least two skilled operators.

The diagnosis based on the CMR results was recorded. Subsequently, we analyzed changes in patient management guided by the CMR results.

Statistical analysis

The Kolmogorov-Smirnov test was used to test whether the data were normally distributed.

Continuous variables are expressed as the mean (standard deviation [SD]) or the median (interquartile range [IQR]). Left ventricular end-systolic (LVESV) and end-diastolic volumes (LVEDV) were normalized to the body surface area. The Student's t-test was performed to analyze continuous and normally distributed variables; otherwise, the Mann-Whitney test was used to test the differences between the groups. The Kruskal-Wallis test was used to make comparisons among the four groups with the most common diagnosis. The post hoc Conover test was applied for statistically significant

Table 1. Patient characteristics

	All patients	Men	Women	*P*-value (men vs. women)
N (%)	243	173 (71.2)	70 (28.8)	
Age, years, mean (SD)	43.9 (15.2)	44.0 (14.3)	46.2 (16.0)	0.29
LVEF, %, mean (SD)	28.3 (11.9)	25.9 (10.8)	33.3 (11.9)	<0.0001
LVEDV, ml/m^2, mean (SD)	162.4 (59.7)	172.9 (59.5)	135.0 (40.8)	<0.0001
LVESV, ml/m^2, mean (SD)	121.1 (59.3)	132.2 (59.1)	93.2 (41.0)	<0.0001
LGE, n (%)	183 (75.3)	131 (75.7)	51 (72.9)	0.86
Subendocardial	35 (14.4)	28 (16.2)	7 (10.0)	
Midwall	153 (63.0)	113 (64.7)	41 (58.6)	
Subepicardial	21 (8.6)	15 (8.7)	6 (8.6)	
Transmural	33 (13.6)	26 (15.0)	7 (10.0)	

Abbreviations: LGE, late gadolinium enhancement; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume

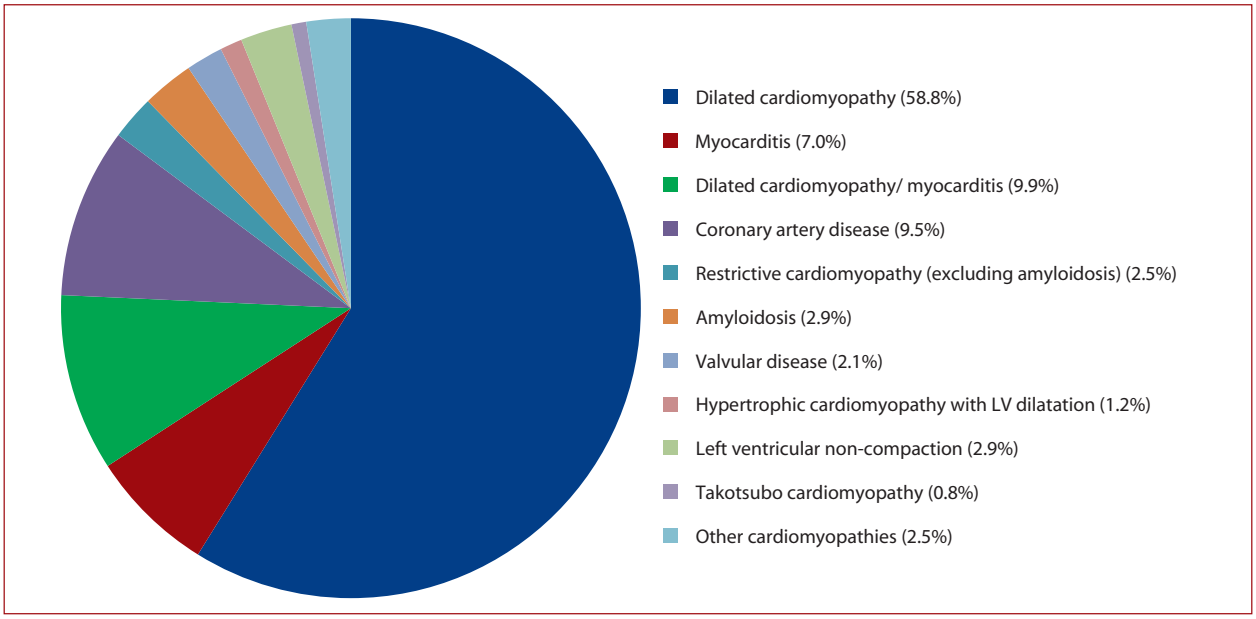

Figure 1. Final diagnoses

Abbreviations: LV, left ventricle

differences. Categorical variables were compared using the χ^2 test. A two-tailed *P*-value of less than 0.05 indicated statistical significance. Statistical analyses were carried out using MedCalc software (MedCalc 12.1.4.0, Ostend, Belgium).

RESULTS

Study cohort

Between January 2008 and December 2017, a total of 246 patients were referred for CMR study because of HF of unknown etiology. Of these, 1 patient was not included in the analyses due to poor-quality CMR images. Two other patients were excluded for the following reasons: 1 patient was excluded due to a significant improvement in cardiac function (normal left ventricular ejection fraction [LVEF] by CMR but poor left ventricular systolic function by the previous echocardiogram), and 1 patient was excluded due to a history of acute decompensated HF secondary to hyperthyroidism. In 5 cases (2.0%), the tests were shortened due to the critical condition of the patients.

The final cohort included 243 individuals, 71.2% (n = 173) of whom were male. The mean (SD) age of the patients was 43.9 (15.2) years. The mean (SD) LVEF was 28.3 (11.9)%. All patients underwent contrast-enhanced CMR. LGE was detected in 75.3% of the patients: 76.3% of men and 72.9% of women. A midwall pattern of LGE was detected in 63.0% of cases. The subendocardial, transmural, and subepicardial patterns of LGE were present in 14.4% and 8.6% of cases, respectively. Table 1 shows the baseline characteristics of the study cohort.

There were statistically significant differences in LVEDV, LVESV, and LVEF between men and women. There was no significant difference in age.

Final diagnoses

The final diagnosis distribution is shown in Figure 1. More than half of the patients (n=143; 58.8%) were diagnosed with dilated cardiomyopathy (DCM) (Figure 2A–C). In 17 patients (7.0%), CMR revealed a characteristic pattern of myocarditis, that met the Lake Louise criteria [7] (Figure 2D–F).

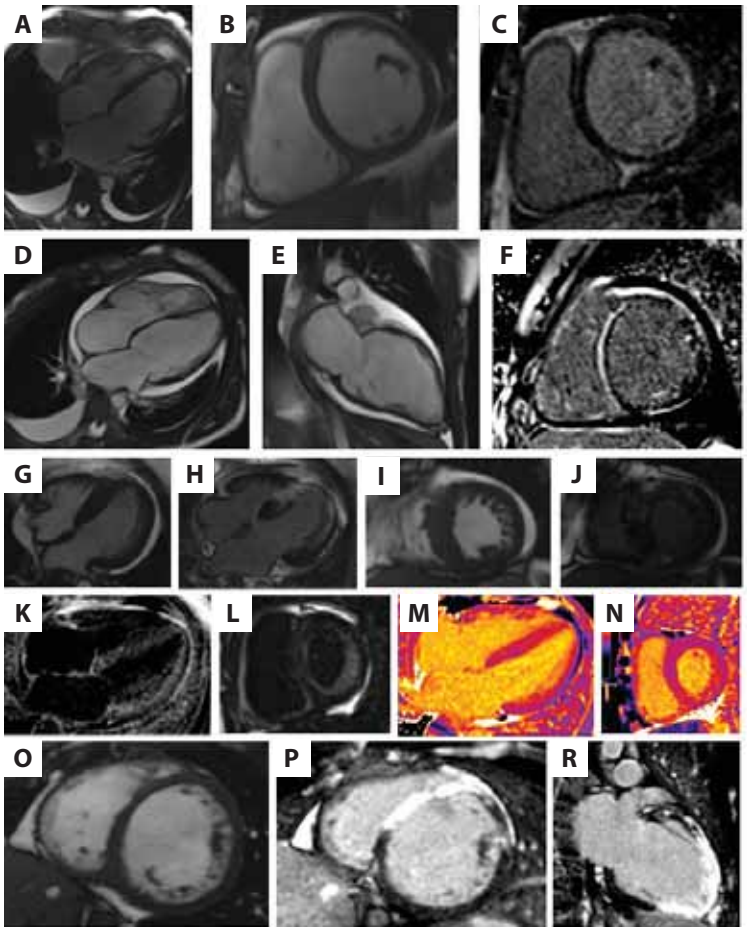

Figure 2. Examples of various new diagnoses and late gadolinium enhancement (LGE) patterns. **A–C.** Dilated cardiomyopathy. Biventricular dilatation (**A, B**) and midwall LGE in the interventricular septum and both right ventricular insertion points (**C**). **D–F.** Myocarditis. Biventricular dilatation (**D, E**) and subepicardial LGE in the interventricular septum, and in the anterolateral and posterior walls (**F**). **G–J.** Hypertrophic cardiomyopathy with left ventricular dilatation. Midwall to transmural LGE in hypertrophied segments (**H, J**). **K–N.** Amyloidosis. Typical global diffuse LGE patt ern (**K, L**). T1 mapping with increased T1 time (**M, N**). **O–R**. Coronary artery disease. Left ventricle dilatation (**O**). Transmural LGE in the septum, anterior wall, posterior wall and apex (**P–R**)

In 24 cases (9.9%), CMR-based diagnosis was unclear, and it was not known if these patients had myocarditis or DCM.

Other cardiomyopathies (qualified under the American Heart Association classification [8]) were less frequent: restrictive cardiomyopathy was found in 13 cases (5.3%), left ventricular noncompaction was found in 7 cases (2.9%), end-stage hypertrophic cardiomyopathy with left ventricular dilatation was found in 3 cases (1.2%) (Figure 2G–J) and stress cardiomyopathy (Takotsubo cardiomyopathy) was found in 2 cases (0.8%). Other cardiomyopathies were diagnosed in 6 cases (2.5%): hypokinetic non-dilated cardiomyopathy (HNDC) [9] was diagnosed in 4 patients, tachyarrhythmic cardiomyopathy was diagnosed in 1 patient, and storage cardiomyopathy was diagnosed in 1 patient.

In 53.8% of the restrictive cardiomyopathy (RCM) cases (7 patients, 2.9%), CMR showed a typical amyloid LGE pattern (Figure 2K–N).

In 23 cases (9.5%), the pattern of subendocardial to transmural enhancement and wall motion abnormalities indicated the presence of a previous undetected infarction (Figure 2O–R).

Five patients (2.1%) were diagnosed with valvular diseases responsible for HF. Three of these patients were found to have aortic valve disease: aortic stenosis in two cases and combined aortic stenosis and insufficiency in one case. One patient was diagnosed with right ventricular HF due to right-sided pathology caused by tricuspid insufficiency. In one case, mitral valve prolapse was previously missed by echocardiography, which led to HF.

Late gadolinium enhancement

There were no statistically significant differences between patients with LGE diagnosed by CMR and patients without LGE on CMR imaging when comparing age (median [IQR], accordingly 45.0 [43.0–56.0] years; 43.0 [34.8–54.3] years; $P = 0.72$) and volumes: LVEF (mean [SD], accordingly 27.4 (11.5)%; 29.8 (11.7)%; $P = 0.52$), LVEDV (median [IQR], accordingly 156.0 [110.0–194.0] ml/m^2; 140.5 [116.0–190.0] ml/m^2; $P = 0.39$), LVESV (median [IQR], accordingly 114.0 [79.9–160.8] ml/m^2; 97.0 [72.0–146.0] ml/m^2; $P = 0.25$).

The presence, type, localization, and extension of LGE were crucial in determining the final diagnosis (as presented in Figure 2).

Heart failure with reduced, mildly reduced, or preserved ejection fraction

Based on the ESC guidelines [1], all patients were stratified by their LVEF as having HF with reduced (HFrEF), mildly reduced (HFmrEF), or preserved (HFpEF) ejection fraction (as shown in Table 2). The heart failure with reduced ejection fraction (HfrEF) group was the largest and included 81.5%

Table 2. Patients subdivided into subgroups with HFrEF/HFmrEF/HFpEF

	HFrEF (n = 198)	HFmrEF (n = 36)	HFpEF (n = 5)	LVEF unknown (n = 4)
Dilated cardiomyopathy	130 (65.7%)	12 (33.3%)	0	1 (25.0%)
Myocarditis	13 (6.7%)	4 (11.1%)	0	0
Dilated cardiomyopathy/ myocarditis	17 (8.7%)	7 (19.4%)	0	0
Restrictive cardiomyopathy (excluding amyloidosis)	2 (1.0%)	2 (5.6%)	1 (20.0%)	1 (25.0%)
Hypertrophic cardiomyopathy with LV dilatation	3 (1.5%)	0	0	0
Left ventricular noncompaction	7 (3.5%)	0	0	0
Takotsubo cardiomyopathy	0	1 (2.8%)	1 (20.0%)	0
Coronary artery disease	16 (8.1%)	5 (13.9%)	0	2 (50.0%)
Valvular disease	3 (1.5%)	1 (2.8%)	1 (20.0%)	0
Other cardiomyopathies	3 (1.5%)	3 (8.3%)	0	0
Amyloidosis	4 (2.0%)	1 (2.8%)	2 (40.0%)	0

Abbreviations: HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LV, left ventricle; other — see Table 1

Table 3. Most frequent diagnoses

	Dilated cardiomyopathy	Myocarditis	Dilated cardiomyopathy/myocarditis	Coronary artery disease	*P*-value
LVEDV, ml/m^2, median (IQR)	159.0 (127.8–191.8)	151.0 (111.3–245.5)	145.0 (121.5–203.8)	162.0 (121.0–211.0)	0.93
LVESV, ml/m^2, median (IQR)	118.0 (86.8–155.5)	111.0 (79.8–199.0)	85.0 (75.3–175.3)	119.0 (79.8–167.0)	0.84
LVEF, %, median (IQR)	26.9 (18.8–33.1)	25.8 (18.1–40.0)	30.9 (16.8–41.2)	29.5 (20.2–36.2)	0.65
LVSV, ml/m^2, median (IQR)	40.0 (33.0–47.0)	41.0 (29.0–45.8)	44.0 (30.5–49.0)	39.0 (37.8–48.5)	0.80
Age, years, median (IQR)	43.0 (32.3–54.8)	35.0 (22.5–44.8)	35.0 (26.0–50.0)	51.0 (41.0–56.0)	0.005

Abbreviations: LVSV, left ventricular stroke volume; other — see Table 1

(n = 198) of the patients. Thirty-six patients (14.8%) were diagnosed with mildly reduced LVEF.

The heart failure with preserved ejection fraction (HfpEF) group involved 5 patients. Three of these patients were diagnosed with restrictive cardiomyopathy, with 2 cases caused probably by amyloidosis. One patient in the HFpEF group was found to have Takotsubo cardiomyopathy, and the fifth patient had mitral valve prolapse. In these 5 cases, the left ventricular end-diastolic and end-systolic volumes were not calculated due to poor-quality CMR images.

Most frequent diagnoses

The majority of patients were diagnosed with DCM, CAD, myocarditis, or had an ambiguous diagnosis: DCM/myocarditis. We performed statistical analyses among these groups (Table 3), and the volumes and LVEF exhibited no differences (Figure 3). There was a significant age difference, and the myocarditis and DCM/myocarditis groups were younger than the patients with DCM or CAD (Figure 4).

Change in the diagnosis and the impact on patient management

The diagnoses of exclusion in the HFrEF and HF with mid-range ejection fraction (HFmrEF) groups were DCM and HNDC, whereas, in patients with HFpEF, the diagnosis of exclusion was diastolic dysfunction. We compared the final and pre-CMR diagnoses (Figure 5). Changes in the diagnoses were reported in 94 cases (38.7%).

We also analyzed changes in patient management as guided by the CMR results, which were defined as changes in treatment and/or the necessity of further tests. Changes in the pre-CMR diagnosis were judged crucial and led to therapeutic consequences in 41 patients (16.9%) with CAD, amyloidosis, valvular disease, and other cardiomyopathies.

DISCUSSION

CMR is a non-invasive method used to assess cardiac function, volumes, and the great vessels, and provides deep insight into the myocardial structure (in terms of focal or diffuse fibrosis). Cine CMR has become the gold standard for the quantification of ventricular volumes and ejection fractions [10].

Echocardiography is the first-line imaging technique in patients with HF [10], whereas according to the ESC guidelines on acute and chronic HF [1], CMR is recommended for patients with technically limited echocardiographic images, and when there is a suspicion of the presence of disease affecting the cardiac muscle.

According to the American College of Cardiology Foundation (ACCF), American College of Radiology (ACR), American Heart Association (AHA), North American Society for Cardiovascular Imaging (NASCI), and Society for

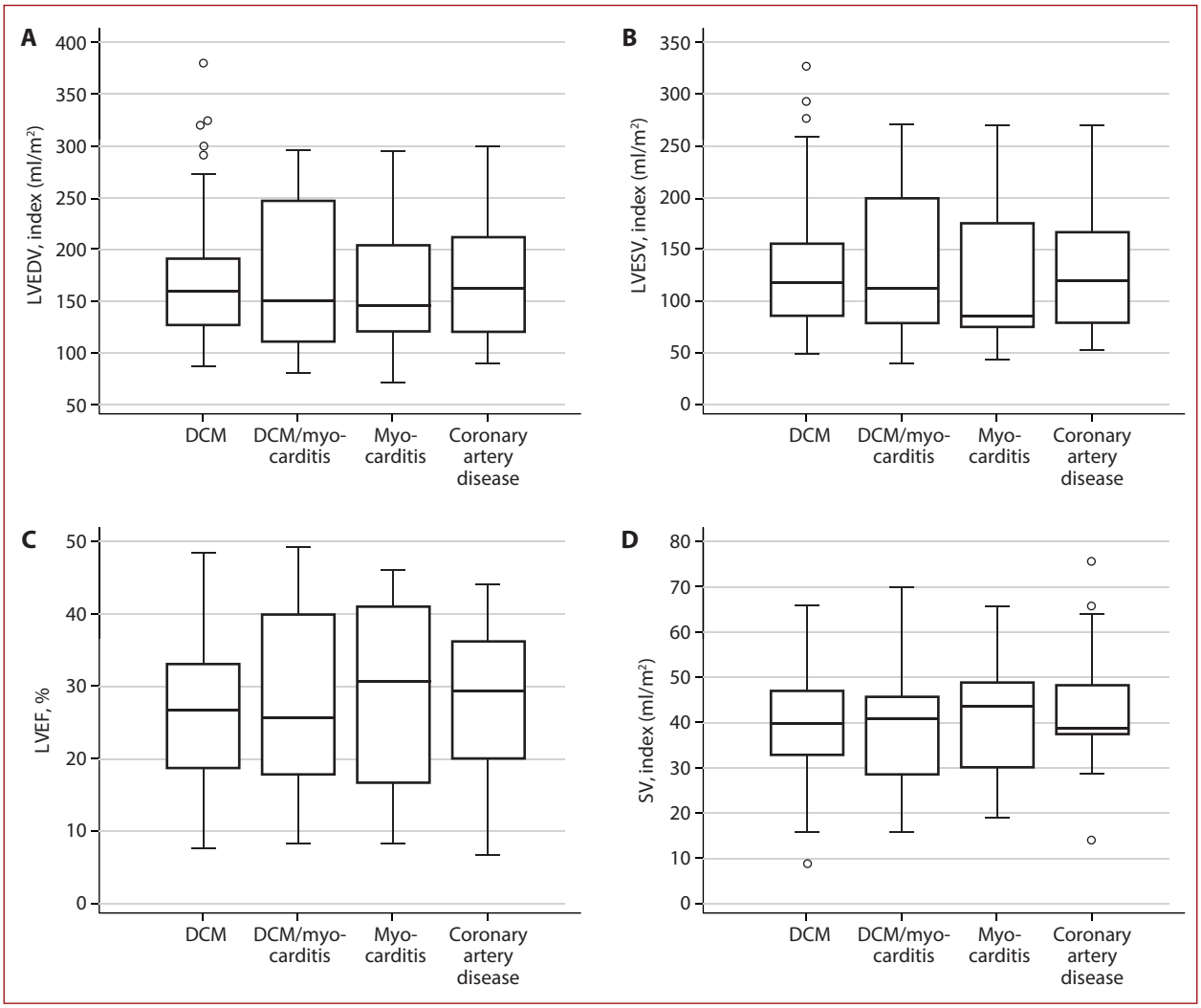

Figure 3. Left ventricular end-diastolic, left ventricular end-systolic volumes, left ventricular ejection fraction, and stroke volume of patients with the most common diagnoses. Box plot with median and IQR, whiskers are the minimum and the maximum, dots represent outliers

Abbreviations: DCM, dilated cardiomyopathy; IQR, interquartile range

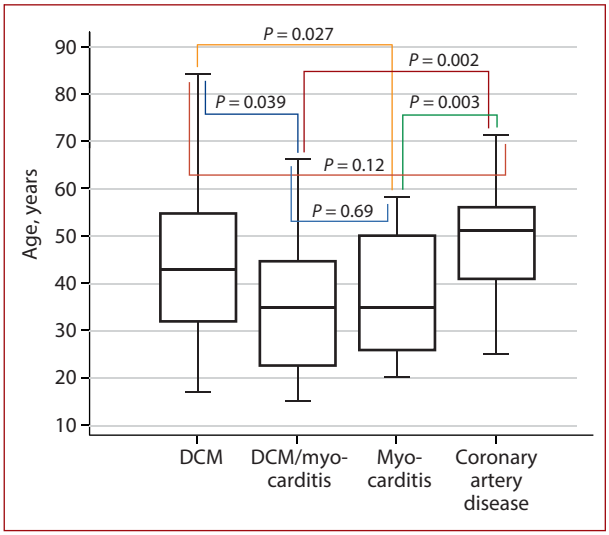

Figure 4. Ages of patients with the most common diagnoses. Box plot with median and IQR whiskers are the minimum and the maximum

Abbreviations: see Figure 3

Cardiovascular Magnetic Resonance (SCMR) consensus document [11], CMR imaging may be used to assess the biventricular size, function, and morphology and to evaluate the myocardium to determine the etiology of HF. CMR allows us to distinguish between ischemic and non-ischemic etiology in patients with HF [11, 12] and can be used to identify the underlying cause of non-ischemic cardiomyopathies [13].

The Heart Failure Association of the ESC recommends CMR imaging in etiological workups in patients with HFpEF [14]. Although echocardiography is the primary imaging technique of choice in the HFpEF group [15], CMR imaging also provides information on diastolic function [16].

Our study aimed to evaluate the role of CMR in identifying the underlying cause of HF due to an initially unknown etiology as well as its impact on patient management.

The final diagnosis was different from the pre-CMR diagnosis in 38.7% of patients and led to serious therapeutic consequences in 16.9% of cases. Consequently, the findings from the CMR study also impacted patient prognosis.

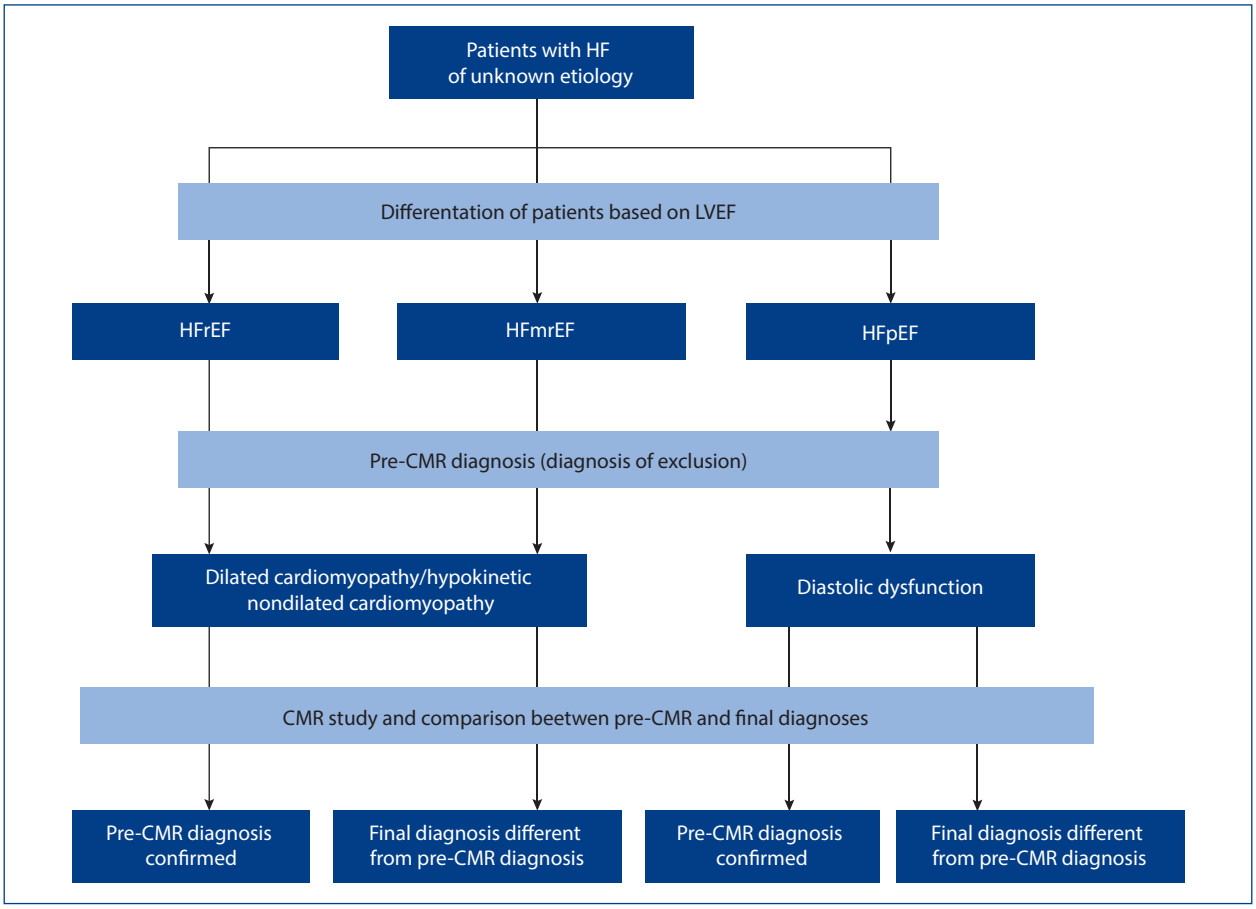

Figure 5. Definition of a change in the pre-CMR diagnosis

Abbreviations: CMR, cardiac magnetic resonance; HF, heart failure; other — Figure 1 and Table 2

In the EuroCMR registry, in more than 27 000 consecutive patients, CMR-based diagnosis differed from the pre-CMR diagnosis in 8.7% of patients and impacted patient management in 61.8% of cases [17]. Abassi et al. [18] reviewed CMR studies of 150 consecutive patients with LVEF ≤50% and studied the clinical impact of CMR defined as a new diagnosis or change in management. In their study, CMR impacted 65% of patients, led to a new diagnosis in 30% of cases, and impacted management in 52% of patients. Kangala et el. evaluated the impact of CMR on the diagnosis and prognosis in a group of patients with HFpEF [19]. In 27% of patients, CMR led to the identification of a previously undetected pathology that correlated with a worse prognosis.

Lin et al. [20] reported that non-ischemic cardiomyopathy was significantly less likely to be misdiagnosed in patients who underwent CMR before cardiac transplantation than in patients who did not undergo CMR.

To our knowledge, this is the first study to evaluate the impact of CMR in patients with an initially unknown etiology. Our study strongly confirmed the notion that CMR imaging is a valuable tool for determining the etiology of HF. Having studied a large real-life population, we provided evidence that CMR should be considered in all patients with unexpected and newly diagnosed HF, particularly if other tests cannot determine the etiology.

Study limitation

First, this study was conducted as a retrospective study. Patients were referred for CMR study by primary-care physicians. We analyzed only the data that was available in the medical records. Second, the patient cohort consisted only of Caucasians, and 99.2% of the patients were of Polish origin. Third, we have no follow-up data. Moreover, the HFpEF group included only 5 patients (2.1%), while the HFpEF group was estimated to include approximately 50% of all HF patients [16].

CONCLUSIONS

Our study highlights the usefulness of magnetic resonance imaging in determining the etiology of HF in patients in whom a diagnostic workup did not reveal the cause of impaired cardiac function. The study also suggests that CMR imaging significantly affects patient management.

Article information

Conflict of interest: None declared.

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Is the last before-death alert remote monitoring transmission in patients with heart failure life-threatening?

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Editorial
by Masarone

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ABSTRACT

Background: Remote monitoring (RM) of cardiac implantable electronic devices (CIED) allows for a regular analysis of the occurrence of arrhythmias and functioning of the devices.

Aims: To date, no study investigated the characteristics of the alert-triggered ultimate transmissions before death, which was the aim of the present analysis.

Methods: Patients monitored remotely in our center, whose baseline characteristics were obtained from the COMMIT-HF Registry (NCT02536443) were analyzed and divided according to the occurrence of alert transmissions during the RM. In patients who had an alert transmission, the last transmission was analyzed. All RM data were obtained from the software provided by four RM manufacturers.

Results: Of 1271 patients with CIEDs which transmitted at least one message to the RM center, 198 (15.6%) had no alert transmissions, while 1073 (84.4%) had at least one alert transmission. Respective mortality in patients with and without alerts during RM was 29.7% and 12.6%, respectively. In patients who had ever an alert, the last recorded transmission before death was scheduled in 166 patients and alert-triggered in 152 patients. The most frequent alert-triggered last transmissions were atrial fibrillation/flutter (39.4%) and ventricular tachyarrhythmias (26.8%). The median period from the last alert-triggered transmission to death was 10 days.

Conclusion: This is the first analysis of the ultimate RM transmissions delivered by CIEDs before death. In approximately 85% of RM patients with CIEDs, at least one alert transmission occurred during the RM, and in patients who had ever an alert, almost half of the last transmissions before death were alert-triggered.

Key words: remote monitoring, implantable cardioverter–defibrillators, cardiac resynchronization therapy, heart failure, last transmission

INTRODUCTION

Despite significant improvements in healthcare organization and treatment modalities, the prognosis in patients with heart failure (HF) remains poor [1–3]. Due to the high risk of sudden cardiac death, a certain percentage of patients with HF have indications for implantable cardioverter–defibrillators (ICDs) or for implantable cardioverter–defibrillators (CRT-D) used in cardiac resynchronization therapy [4–6]. Although in specific groups of patients, implantation of ICD or a CRT-D increases survival, the percentage of patients who die with the devices remains considerable [7].

Remote monitoring (RM) of patients with ICDs and CRT-Ds allows one to gather detailed information concerning the functioning of the device on the regular basis, without the necessity of patients to present themselves for in-person examinations [8–12]. Moreover, RM allows to continuously measure various vital parameters of the patient, such as the arrhythmia burden, the percentage of biventricular pacing, and thoracic congestion indicators, which have been proven to predict HF decompensation and worsen the patient's prognosis. In the large meta-analysis of randomized controlled trials, RM was asso-

WHAT'S NEW

To date, this is the first analysis of the last transmissions delivered before death by remotely monitored implantable cardioverter–defibrillators and cardiac resynchronization therapy implantable cardioverter-defibrillators. In approximately 85% of remotely monitored patients with heart failure and cardiac electronic implantable devices, at least one alert-triggered transmission occurred during the median of almost 5 years of remote monitoring. In patients with at least one alert delivered by the devices from the enrollment into remote monitoring, 48% of the last before-death transmissions were alert-triggered, while the remaining 52% were scheduled transmissions. In patients in whom the last transmission was alert-triggered, its most frequent causes were atrial fibrillation or flutter episode, ventricular tachyarrhythmia, or reduction in the percentage of biventricular pacing, and the median time from the last transmission to death was 10 days.

ciated with a significant reduction in the rate of in-person examinations [11]. On the contrary, the data on mortality reduction are inconsistent. In the IN-TIME trial, a significant reduction in mortality of patients monitored remotely was observed; however, it was not demonstrated in the other large trials conducted to date [8, 13, 14].

One of the possible explanations of these discrepancies in the results of the trials evaluating the efficacy of RM could have been related to differences in the organizational scheme of the RM centers, including the frequency and types of transmissions generated by the devices, the contents of the alert-triggered transmissions, and the type and timing of the clinical reactions undertaken [15].

To date, no study investigated the characteristics of ultimate messages obtained from the RM of ICD/CRT. Moreover, data on the percentage of patients having conditions requiring alert transmissions during the RM period are scarce.

Therefore, the present study aimed to examine the type and contents of the ultimate transmissions in the cohort of remotely monitored patients and to summarize the causes of the alert-triggered ultimate transmissions occurring before death.

METHODS

The details of the Contemporary Modalities In Treatment of Heart Failure Registry (COMMIT-HF) registry have already been described [7, 16]. In brief, COMMIT-HF is a single-center, ongoing prospective registry (NCT02536443), with patient-based data collection. Consecutive patients hospitalized with a diagnosis of systolic HF (left ventricular ejection fraction [LVEF] ≤35%) not caused by an acute coronary syndrome (ACS) at index hospitalization in the tertiary cardiovascular centers are prospectively enrolled in the Registry. The Registry encompasses detailed patient demographic characteristics, prior medical history, and complete data from the index hospitalization, including the type of implantable device and medications administered at discharge. The study protocol was approved by an appropriate institutional review board and ethics committee.

During the duration of the study, RM was assigned to consecutive patients depending on the reimbursement limitations and device availability in our hospital. Each patient, who had an implanted device eligible for RM and who declared willingness to adhere to the schedule of remote transmissions, received a transmitter compatible with the implanted device. The Central Remote Monitoring Office of our center involves two physicians (a cardiology consultant and a resident) and two electrophysiology nurses, who on weekdays analyze data derived from RM online systems and undertake adequate actions if indicated. The RM office provides surveillance of transmissions from all four major devices and RM manufacturers (Merlin.net™ of St. Jude — now Abbott, CareLink® of Medtronic, Latitude™ of Boston Scientific, and Home Monitoring® of Biotronik). Transmitted data are recorded and stored in the RM online software of all four major RM manufacturers. The undertaken clinical reactions, along with their results are archived in the paper and electronic databases. In general, the standard measured preset parameters transmitted remotely to the RM facility vary slightly according to the manufacturer and are described in detail in Supplementary material, *Table S1*.

The long-term RM data concerning the type of transmissions (scheduled or alert-triggered) and their contents, with particular emphasis on the occurrence of adequate or inadequate antiarrhythmic interventions of the devices, have been obtained from the investigator-initiated single-center RM database. In the database, the clinical course of RM is summarized for each patient on the yearly basis and includes the number, the type of alert-triggered transmissions, and the most clinically relevant programmed parameters.

All transmissions are initially labeled as unscheduled or scheduled by the RM system, however, for the registry, all transmissions were individually assessed by the authors of this study and classified accordingly to their content. In the cases of uncertainties about the contents or significance of the ultimate transmissions, representatives of the respective manufacturers were contacted for their verification.

At the time of the transmission, all therapeutic interventions were performed according to the current clinical situation of each patient based on the contents of the transmission and phone calls to patients or authorized relatives performed, when necessary, by the employees of the RM center. All interventions adhered to the European Society of

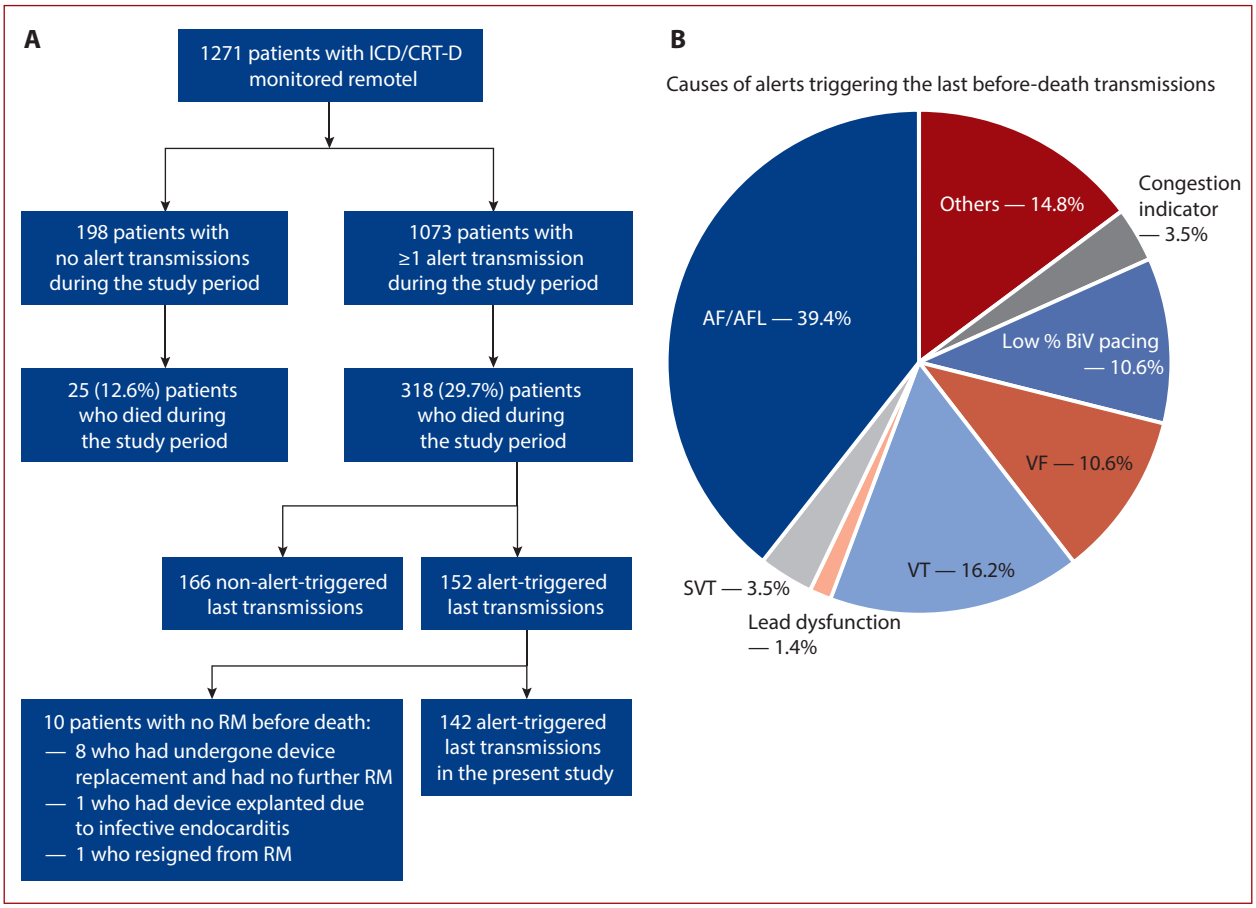

Figure 1. The study flowchart is presented on the left. The characteristics of the ultimate alerts are presented on the right

Abbreviations: AF, atrial fibrillation; AFL, atrial flutter; BiV, biventricular; CRT-D, cardiac resynchronization therapy, implantable cardioverter-defibrillator; ICD, implantable cardioverter-defibrillator, RM, remote monitoring; SVT, supraventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia

Cardiology (ESC) guidelines for Heart Failure, along with the ESC guidelines for Cardiac Pacing and Cardiac Resynchronization Therapy [17, 18]. The possible interventions included a referral for an in-person visit in the general practitioner's (GP) office or the outpatient specialist clinic, referral for an urgent or planned hospitalization, or modification in the patient's pharmacotherapy. In general, if a sustained ventricular tachyarrhythmia occurred, patients were always contacted, and if no reversible cause of arrhythmia had already been identified, most patients were referred for urgent hospitalization. The general scheme of clinical interventions undertaken in response to the alert-triggered transmissions is summarized in Supplementary material, *Figure S1*.

The long-term follow-up data were obtained from the National Health Fund, the only Polish healthcare provider. Based on this source, the causes of in-hospital deaths were available, established according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10). The list of all causes of death with respective ICD-10 codes in the analyzed population is presented in Supplementary material, *Table S2*.

Statistical analyses

This was an explorative study using the methods of descriptive statistics. The continuous variables were presented as mean (SD) for normal distribution or as median (interquartile range [IQR]) for non-normal distributions. Categorical variables were expressed as the absolute numbers and relative proportion (percentage) of patients with the respective attribute. The normality of distribution was verified using the Shapiro–Wilk test. All analyses were conducted using the Statistica 10 software (StatSoft, Inc., Tulsa, OK, US).

RESULTS

Between January 2009 and December 2017, 1271 patients were enrolled in the RM program after implantation of an ICD or CRT-D in our facility, and their devices transmitted at least one message. Of those, 198 (15.6%) generated no alert-triggered transmissions, while in the remaining 1073 (84.4%), there was at least 1 alert-triggered transmission, as presented in Figure 1A and Supplementary material, *Table S3*. The percentage of patients with any alert-triggered transmission during RM were 68.7%, 73.7%,

Table 1. Device parameters and manufacturers in patients with last alert-triggered transmission

Device parameters	All (n = 142)
Implantation due to the secondary prevention of sudden cardiac death, n (%)	37 (26.1)
ICD, n (%)	71 (50.0)
Single-chamber	34 (23.9)
Dual-chamber	37 (26.1)
CRT-D, n (%)	71 (50.0)
Device manufacturers	**All (n = 142)**
Biotronik, n (%)	4.9 (5.2)
Boston Scientific, n (%)	10 (7.0)
Medtronic, n (%)	13 (9.2)
St. Jude (Abbott), n (%)	112 (79.6)

Abbreviations: CRT-D, cardiac resynchronization therapy — implantable cardioverter-defibrillator; ICD, implantable cardioverter-defibrillator

and 79.6% in the first, second, and third years of monitoring, respectively. Of the 198 patients with scheduled-only transmissions, 25 (12.6%) died during the RM period, while among 1073 patients with at least one alert, there were 318 (29.7%) deaths. In patients who had ever had an alert, 166 of the last transmissions sent by the devices were scheduled, while 152 were alert-triggered. In 8 patients, the last alert-triggered transmission was followed by the device replacement, 1 had the device explanted due to infective endocarditis, and 1 resigned from RM. Therefore, these patients were excluded from the present analysis, which eventually included 142 patients, in whom the last transmission sent before death was alert-triggered.

Among those individuals, there were 71 patients with ICDs (50.0%) and 71 with CRT-D devices (50.0%). The vast majority of patients received a St. Jude device (79.6%), while the remaining devices were manufactured by Medtronic, Boston Scientific, and Biotronik as described in Table 1. More than a quarter of devices were implanted due to secondary prevention of SCD.

The baseline characteristics of the 142 patients, in whom the last remote transmission was alert-triggered are presented in Table 2. Women constituted approximately 20% of the studied group and the median age at implantation was 64 years. The ischemic cardiomyopathy was the primary indication for implantation of the devices (68.3%). At implantation, 35.9% of patients were in New York Heart Association (NYHA) functional class II and 52.1% in the NYHA class III. The mean left ventricular ejection fraction (LVEF) was 23% and the median left ventricular end-diastolic diameter (LVEDD) was 68 mm. At discharge, 95.1% of patients were prescribed a beta-blocker, 89.4% were administered a loop diuretic, and 74.0% an angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB), as described in Table 3.

Table 2. Baseline demographic and clinical characteristics of patient with last alert-triggered transmission

Demographics	Alert-triggered (n = 142)
Female, n (%)	32 (22.5)
Age at implantation, years, median (IQR)	64 (57–73)
Baseline characteristics	
Indication for implantation	
Ischemic cardiomyopathy, n (%)	97 (68.3)
Non-ischemic cardiomyopathy, n (%)	45 (31.7)
Arterial hypertension, n (%)	71 (50.0)
Atrial fibrillation, n (%)	54 (38.0)
COPD, n (%)	21 (14.8)
Dyslipidemia, n (%)	64 (48.6)
Smoking, n (%)	42 (33.1)
Prior stroke, n (%)	4 (2.8)
Prior MI, n (%)	77 (54.2)
Prior PCI, n (%)	61 (43.0)
Prior CABG, n (%)	26 (18.3)
Anemia, n (%)	39 (27.5)
Hemoglobin at implantation, g/l, mean (SD), (n/N)	140 (17.7) (122/142)
Diabetes, n (%)	62 (43.7)
NYHA class	
II, n (%)	51 (35.9)
III, n (%)	74 (52.1)
IV, n (%)	13 (9.1)
WBC, $\times 10^3$/µl, median (IQR), (n/N)	7.2 (5.8–8.6) (122/142)
PLT, $\times 10^3$/µl, median (IQR), (n/N)	188 (154–224) (122/142)
GFR ≤60 ml/min/1.73 m^2, n (%)	55 (38.7)
Serum creatinine, µmol/l, median (IQR) (n/N)	102 (84–121) (122/142)
BMI, kg/m^2, median (IQR), (n/N)	26.8 (23.5–30.8) (84/142)
LVEF, %, mean (SD)	23 (5)
LVEDD, mm, mean (SD), (n/N)	68 (10) (138/142)
LVESD, mm, median (IQR), (n/N)	57 (50–64) (138/142)

Abbreviations: BMI, body mass index; CABG, coronary artery bypass graft surgery; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MI, myocardial infarction; NYHA, New York Heart Association, PCI, percutaneous coronary intervention, PLT, platelet count, RBC, red blood cell count; WBC, white blood cell count

Table 3. Pharmacotherapy after baseline hospitalization for device implantation

Pharmacotherapy at discharge	All (n = 142)
Oral anticoagulant (any), % (n/N)	38.0 (54/142)
Antiplatelet drugs, % (n/N)	66.2 (94/142)
ACE-I/ARB, % (n/N)	74.0 (105/142)
Beta-blocker, % (n/N)	95.1 (135/242)
Loop diuretics, % (n/N)	89.4 (127/142)
Other diuretics, any, % (n/N)	14.8 (21/142)
Mineralocorticoid receptor antagonist, % (n/N)	83.8 (119/142)
Digitalis, % (n/N)	27.5 (39/142)
Other antiarrhythmic drugs, any, % (n/N)	19.0 (27/142)

Abbreviations: ACE-I, angiotensin convertase enzyme inhibitors; ARB, angiotensin receptor blockers

Table 4. Types of the last alert-triggered transmissions

Cause of alert	All alert-triggered transmissions (n = 142)
AF/AFL episode, n (%)	56 (39.4)
Permanent/persistent AF	33 (58.9)
New-onset AF, n (%)[a]	2 (3.6)
SVT episode, n (%)	5 (3.5)
Lead dysfunction suspicion, n (%)	2 (1.4)
Ventricular tachycardia, n (%)	23 (16.2)
Treated with ATP/HV, n (% of all VTs)	10 (43.5)
Ventricular fibrillation, n (%)	15 (10.6)
Requiring ATP/HV, n (% of all VFs)	14 (93.3)
Ventricular tachyarrhythmias fulfilling criteria of ES, n (% of all VT/VFs)	11 (28.9)
Biventricular pacing percentage reduction, n (%)	15 (10.6)
Others	26 (18.3)
Congestion monitor indications, n (%)	5 (3.5)
Patient triggered[b]	7 (4.9)

[a]New-onset AF, n (%)[a] — although the threshold for AF detection was ≥5 minutes, both episodes lasted ≥2 hours; [b]Patient triggered — alert with no signs of hardware/software device malfunctions and/or device indications

Abbreviations: AF, atrial fibrillation; AFL, atrial flutter; ATP, antitachycardia pacing; ES, electrical storm; HV, high-voltage therapy; SVT, supraventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia

Table 5. The clinical reactions to the last alert-triggered transmissions

Clinical reaction	Alert-triggered transmission (n = 142)
Any clinical reaction, n (%)	89 (62.6)
Telephone consultation, n (%)	36 (25.3)
Referral to the GP or outpatient specialist clinic visit, n (%)	13 (9.2)
Referral for hospital admission, n (%)	18 (12.7)
Pharmacotherapy modification, n (%)	2 (1.4)
Reaction not changing patient's condition, n (%)	20 (14.1) • 4 patients who died during/immediately after transmission • 12 patients who were already admitted to the hospital • 3 patients deemed critically ill in whom no action could bring a benefit • 1 patient who did not answer the phone despite numerous contact attempts

Abbreviation: GP, general practitioner

The median (IQR) time from implantation to death in patients with last alert-triggered transmission was 3.24 (2.01–4.36) years. The most prevalent type of the ultimate alert-triggered transmission was an atrial fibrillation/atrial flutter episode, which occurred in 56 (39.4%) of patients, as presented in Table 4 and Figure 1B. Two (3.6%) of those were new onsets of atrial fibrillation and 33 (58.9%) of patients had persistent/permanent AF. There were 38 transmissions triggered by ventricular tachyarrhythmias, of which 23 were ventricular tachycardia (VT) and 15 were ventricular fibrillation (VF) episodes. Approximately 44% of VTs and 93% of VFs were treated with the device and in 11 cases, the transmitted arrhythmias fulfilled the criteria of an electrical storm (ES). In 15 patients (10.6%) a reduction in biventricular pacing occurred, and in 26 (18.3%) other causes of alert transmissions occurred, including the indications of a congestion monitor. There were 7 patient-triggered transmissions, in which no hardware- or software-related issues were detected. In only 12 patients, the cause of the last alert-triggered transmission occurred for the first time, and in the remaining population, it had occurred during monitoring, as described in detail in Supplementary material, *Table S4*.

The clinical reactions of the RM center were undertaken in 62.6% (n = 89). The median time (IQR) from an alert-triggered transmission to the clinical reaction was 1 (0–2) day. There were 36 telephone consultations, 13 referrals to the GP or specialist clinics for in-patient visits, and 18 referrals for the urgent hospital admission. In 20 patients with alert-triggered last transmission, the clinical reaction, although undertaken, did not let change their condition. The most prevalent cause for such a state was that the patient had already been taken to the hospital and the transmission signal was generated from the hospital, or the patient died in an immediate period before transmission, as described in detail in Table 5. The median (IQR) time from the last alert-triggered transmission to death was 10 (2–26) days.

Finally, based on the administrative data, patients who died in the hospital were identified. In the analyzed population of 142 patients, in whom the last transmission was alert-triggered, data were available for 134, of whom 78 (58.2%) died in the hospital while the remaining patients died elsewhere. Worth noting is that in the 90 days preceding death, the median (IQR) number of hospital admissions of these patients was 1 (0–2), as was the number of visits in the outpatient clinics. The clinical causes of death in that group are summarized in Supplementary material, *Table S5*.

DISCUSSION

The main findings of our study are: (1) our analysis was the first to specifically examine the ultimate transmissions delivered by the CIEDs in patients with HF who were remotely monitored at the tertiary cardiovascular center; (2) during the RM period, the alert-triggered transmissions occurred in approximately 85% of the whole population of patients; (3) in patients who had had at least 1 alert-triggered transmission, the ultimate transmission was alert-triggered in 48% while the remaining transmissions were scheduled; (4) in patients in whom the last before-death transmission was alert-triggered, the most frequent causes of alerts were atrial fibrillation or flutter, ventricular tachyarrhythmias or a significant reduction in the biventricular pacing percentage; (5) the median (IQR) period from the last alert-triggered transmission to death was 10 (2–26) days.

Due to the concomitant presence of multiple risk factors predisposing to the development of patient- or device-related events, the risk of alert-triggered transmissions is higher than in the overall population of patients with implanted CIEDs [19] In the recent analysis by O'Shea et al. [21], the alert-triggered transmissions occurred in 45.7% of patients with ICDs. However, it should be noted that that study analyzed one calendar year, between November 2018 and November 2019. In our analysis, the monitoring period was substantially longer, as in some patients the RM, monitoring continued for more than 8 years. Therefore, the duration of the analysis period could explain a higher percentage of patients with alert-triggered transmissions [20].

In patients who had ever an alert condition, more than 50% of the last transmissions were scheduled — suggesting that at that time there were no indications of worsening of patients' conditions. One of the possible explanations for that high percentage of scheduled last transmissions is that less than half of all deaths in HF are due to sudden cardiac causes [21–23]. Hence, in the case of most patients who do not die due to non-cardiovascular causes or non-sudden cardiac death, even if their clinical condition significantly deteriorates, no arrhythmical abnormalities can be recorded in their last transmissions.

In those, whose ultimate transmission before death was alert-triggered, the most frequent cause of alert was an atrial flutter or a fibrillation episode, which constituted almost 40% of the ultimate alerts. Ventricular tachyarrhythmias constituted more than 25% of alerts, while reduction of biventricular pacing was responsible for more than 10% of all ultimate alerts. The presence of each of those conditions substantially worsens prognosis in HF, and a wide variety of mechanisms has been defined through which their occurrence could lead to a significant, abrupt deterioration of patient's conditions and decompensation of HF, often leading to death.

Although in approximately one-third of cases no clinical reaction has been performed, one has to acknowledge that in some cases the ICDs/CRTs generate alerts that are repeatable and consistent with the patient's history, such as the high AF burden in a patient with permanent AF or a persisting reduction of the biventricular pacing percentage. In our analysis, more than 90% of patients with either AF or reduction of the biventricular pacing percentage, had such alerts during the prior course of RM, and only in 4 subjects, such events occurred for the first time. In the trial by Crossley et al. [24] which randomized 1997 patients to RM or standard care, 62% of automatically triggered alerts were considered clinically meaningful, and therefore, required a reaction. In the IN-TIME trial, out of an average of 4.0 alerts delivered to the RM facilities per patient-year, patients were contacted in a mean of 2.1, thus the rate of reactions to alerts was 53% [15].

Limitations

The present analysis has a few limitations, mostly regarding its retrospective character. First of all, although all data have been transmitted to a single, tertiary center with more than 10-year experience in remote-monitoring of patients with ICDs and CRT-Ds, the use of four different manufacturers and software with different transmission schedules and settings could potentially influence the contents of the final transmission and its interpretation.

Second, the analyzed population, although highly specific, is not numerous and the generalization of data should be performed cautiously because baseline characteristics, adherence to the therapy and other external factors could potentially bias the results. Third, no exact information on the specific cause of death derived from autopsy has been obtained, therefore, no adjudicated classification of deaths has been possible. Moreover, no post-mortem analyses of the implantable devices were performed. If any patients remained in the distance from the transmitters disallowing the generation of the transmission, their data was available only through post-mortem examination of the device. Consequently, those data were not included in the present analysis.

Finally, despite a thorough analysis of data, the study was performed retrospectively and investigated the real-life practice. Hence, although most of the data were scrupulously archived in either a paper or electronic form, results of some clinical reactions, such as phone calls to patients, could be not saved for future examination.

CONCLUSIONS

This is the first analysis of the last-before-death transmissions delivered in the remotely monitored patients with heart failure and an ICD or a CRT-D. The alert-triggered transmissions occurred in approximately 85% of the whole population of patients under remote monitoring. In patients who had had at least 1 alert transmission, the ultimate transmission was alert-triggered in 48% while the remaining transmissions were scheduled. In patients, in whom the last before-death transmission was alert-triggered, the most frequent causes of alerts were atrial fibrillation or flutter, ventricular tachyarrhythmias, or a reduction in the biventricular pacing percentage.

Supplementary material

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

Article information

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Plaque morphology effect on periprocedural asymptomatic cerebral embolism in carotid artery stenting using first-generation carotid stents: A diffusion-weighted magnetic resonance imaging study

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ABSTRACT

Background: Silent cerebral embolism with carotid artery stenting (CAS) may contribute to dementia and cognitive decline. Moreover, clinically silent embolism is an important index of peri-procedural stroke risk.

Aims: The purpose of this study was to compare the periprocedural asymptomatic cerebral embolism rates of CAS procedures performed for noncalcified and calcified carotid artery plaques using diffusion-weighted magnetic resonance imaging (DW-MRI).

Methods: Five hundred and seventy clinically uncomplicated patients who underwent CAS at our center from December 2010 to June 2020 (mean [standard deviation, SD] age 69.3 [8.2 years]) were analyzed retrospectively. The patients were divided into 2 groups with noncalcified (268 patients) and calcified (302 patients) plague. Cerebral DW-MRI was performed for the patients before and after CAS and compared. The presence of periprocedural new ipsilateral diffusion limitations detected on cerebral DW-MRI was noted as a significant finding. Ipsilateral diffusion limitations of the non-calcified and calcified plaque groups detected on cerebral DW-MRI were compared.

Results: The presence of periprocedural asymptomatic ipsilateral DW-MRI lesions was higher in patients in the noncalcified plaque group (45 [16.8%]) than in patients in the calcified plaque group (31 [10.3%]; $P = 0.02$).

Conclusion: This study demonstrated that the rate of ipsilateral asymptomatic cerebral embolism detected on cerebral DW-MRI was higher in the CAS procedures performed for noncalcified carotid artery plaques than in those performed for calcified plaques.

Key words: carotid artery stenting, diffusion-weighted magnetic resonance imaging, embolism, new ischemic cerebral lesions, plaque morphology

INTRODUCTION

With the development of interventional devices and techniques, carotid artery stenting (CAS) has become an alternative to carotid endarterectomy (CEA) for the treatment of carotid artery stenosis [1]. The most important complications of carotid artery stenting include new ischemic cerebral lesions associated with distal embolization and neurological symptoms [2]. Silent cerebral embolism associated with CAS has been demonstrated to cause dementia, cognitive decline [3], and even ischemic stroke [4, 5].

Cerebral diffusion-weighted magnetic resonance imaging (DW-MRI) is a very sensitive method to detect silent brain lesions formed during CAS [6, 7]. The use of embolic protection devices (EPD) in CAS has decreased the incidence of new cerebral ischemic lesions associated with the procedure and detected through DW-MRI [8]. Therefore, EPD is strongly recommended during CAS procedures [9].

WHAT'S NEW

Carotid artery stenting (CAS) plays an important role in the preventive treatment of ischemic stroke, which is one of the top causes of disability and mortality. Asymptomatic cerebral embolism, best detected by diffusion-weighted magnetic resonance imaging, is an index of peri-procedural stroke risk, and it may enhance cognitive decline. We have evaluated, for the first time in a patient series exceeding 500, the relationship between plaque morphology and CAS-related asymptomatic cerebral embolism. With our routine use of first-generation (single-layer) carotid stents under transient cerebral protection, we found that the risk of cerebral embolism was larger in the case of soft, non-calcified plaques. Our findings suggest that patients at increased risk of CAS-related cerebral embolism, in particular, might benefit from novel plaque-sequestrating carotid stent systems that require further research.

Even though the CAS procedure is performed with the use of EPD, cerebral embolism may yet develop. New ischemic cerebral lesions caused by distal emboli that occur during CAS may develop due to several factors. Some of these factors include the cerebral status of patients, their vasculature, aortic arch type, devices used, the experience of operators. There is increasing recognition of the role of plaque morphology in the risk of cerebral embolism with CAS [10, 11]. Hence patients, lesions, and appropriate material selection play an important role in decreasing distal emboli associated with CAS.

Vulnerable atherosclerotic plaques are more likely to get ruptured and cause thrombotic and embolic effects [12]. Studies with small series demonstrated that carotid plaques with a noncalcified morphology resulted in more cerebral embolism in CAS compared to fibrocalcific plaques [13]. Except for carotid artery plaque nature, carotid ultrasound indices (carotid intimamedia thickness, extramedia thickness, intraabdominal thickness, and the combined PATIMA index) may play an important role in decision-making for coronary revascularization in patients with high cardiovascular risk [14, 15]. The purpose of our study was to compare the periprocedural asymptomatic cerebral embolism rates in CAS procedures in patients with noncalcified and calcified carotid artery plaques using DW-MRI.

METHODS

We obtained the approval of the ethics board of our center for this study (no. 2020-321). We included 570 clinically uncomplicated patients (mean [standard deviation, SD] age, 69.3 [8.2] years) who were admitted to our center from December 2010 to June 2020 and referred for CAS after consultation in the multidisciplinary carotid council consisting of neurology, cardiology, cardiovascular surgery, and radiology clinics. The patients were divided into 2 groups: the noncalcified (268 patients) and calcified (302 patients) plaque groups. Symptomatic patient (284 patients [50%]) was defined as one that had a history of the ischemic cerebrovascular event with or without sequela, transient ischemic attack (TIA), amaurosis fugax in the previous six months. Patients who were symptomatic and had more than 50% stenosis on digital subtraction angiography (DSA), according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) formulation, and those who were asymptomatic and had more than 80% stenosis were included in the assessment. All patients who had a glomerular filtration rate (GFR) greater than 60 ml/min/1.73 m^2 underwent computed tomography angiography (CTA) for the carotid after carotid Doppler ultrasonography (CDUS). The nature of patients' carotid artery plaques was determined using imaging techniques. The medical follow-up, CAS or CEA, was decided by the multidisciplinary team depending on the clinical features, comorbidities, and characteristics of carotid artery lesions of the patients. Table 1 shows the inclusion and exclusion criteria in our study. Table 2 shows the patients who were considered to be at risk for CAS and referred

Table 1. Inclusion and exclusion criteria

Inclusion criteria
Symptomatic ICA stenosis ≥50% on DSA
Asymptomatic ICA stenosis ≥80% on DSA
The ipsilateral external carotid artery is not totally occluded
Patent contralateral ICA
A complete circle of Willis (assessed by CTA)
Filter able to pass through the lesion without the need for predilatation (assessed by CTA)
Presence of adequate landing zone for the filter (4 cm) (assessed by CTA)
Informed consent form for the procedure signed by patients
Exclusion criteria
Symptomatic complications (23 patients)
Periprocedural hemodynamic instability (>10 minutes) (17 patients)
Distal ICA spasm (14 patients)
>30% residual stenosis (12 patients)
Procedure time >45 min (11 patients)
Diffusion limitation in the watershed area of the collateral carotid artery on cerebral DW-MRI after CAS, bilateral diffusion limitation and watershed diffusion limitation (26 patients)
Need for repeated pre/postdilatation (10 patients)
Balloon dilatation under an atmosphere pressure 20% greater than the nominal balloon pressure (5 patients)
CEA restenosis, history of radiotherapy, routine use of anticoagulants (37 patients)
Type III aortic arch (88 patients)
Ischemic stroke in the past 48 hours (15 patients)
Poor image quality of cerebral DW-MRI, contraindication for DW-MRI (pacemaker, claustrophobia) (23 patients)
History of rheumatic diseases (11 patients)
Diagnosis of cancer (14 patients)

Abbreviations: CAS, carotid artery stenting; CEA, carotid endarterectomy; CTA, computed tomography angiography; DSA, digital subtraction angiography; DW-MRI, diffusion-weighted magnetic resonance imaging; ICA: internal carotid artery

Table 2. Patients who were at risk for carotid artery stenting and thus underwent CEA

Patient or lesion characteristics
• Femoral access problem
• Arcus aorta is severely atherosclerotic or calcified
• Common carotid artery is severely tortuous
• Carotid artery lesion length >40 mm
• Diameter of carotid artery closer to the bifurcation > 10 mm
• Dense calcification in the carotid artery in the area of stenosis (Gray-Weale type IV)
• Carotis artery plaque is severely ulcerated or densely thrombotic
• GFR <30 ml/min/1.73 m^2
• Resistance to acetylsalicylic acid and clopidogrel

Abbreviations: GFR, glomerular filtration rate; other — see Table 1

for CEA. The criteria shown in Table 2 were based on our center's experience. In the cases excluded by the criteria outlined in Table 2, a stent procedure was applied to the carotid artery stenosis.

Preparation of patients for carotid artery stenting

Patients were informed about the details of CAS and signed informed consent forms. Antihypertensive, antihyperlipidemic, and antiplatelet medications that the patients had been taking were regulated. The procedure was initiated after their blood pressure values were regulated down below 135/80 mm Hg. We made sure that the patients had been taking dual antiplatelet therapy consisting of 100 mg acetylsalicylic acid (ASA), in particular, and 75 mg clopidogrel at least for 7 days. Otherwise, additional loading dose (ASA 300 mg, clopidogrel 600 mg), and maintenance antiplatelet therapy were planned. A resistance test was performed on venous blood for both antiplatelet agents in the morning of the procedure. CAS was performed after a loading dose of 2 tablets of 90 mg ticagrelor and 2 × 1 maintenance regimen if they had resistance only to clopidogrel.

Carotid artery stenting procedure

All procedures were performed by 2 operators: an invasive cardiologist and an interventional vascular neurologist. They were performed under local anesthesia with percutaneous transfemoral access. The patient's oxygen saturation, electrocardiographic, and blood pressure parameters were monitored throughout the procedure. The procedure was initiated with a femoral 8 F sheath. A 9F sheath was used when proximal protection was preferred as an embolic protection method. After the sheath was placed, all patients were given 75 IU/kg unfractionated heparin. Depending on the arcus aorta type of the patient evaluated in the council, a 5 F hydrophilic headhunter or sim 1.2 diagnostic catheter was used. CAS was performed with the anchor method in most of the patients. The telescopic method was used only in a few patients. Following bilateral carotid and cerebral DSA, we determined the embolic protection method, balloon and stent diameters, and if predilatation/postdilatation would be performed. The stent design was not selected according to either the lesion or vascular structure. The available stent design was placed in the stenotic carotid artery. For predilatation, 3.0–5.0 × 20 mm balloons (Invader; Alvimedica, Simpass; Simeks) were used. For the postdilatation procedure after carotid stent, 5.0–5.5 × 20 mm balloons (Viatrac; Guidant) were preferred. The balloon diameter for predilatation was calculated as around 1 mm smaller than the diameter of the distal intact ICA. When the residual stenosis was <30% after stenting, postdilatation was not performed. Tapered stents were used for all patients. The self-expandable stent diameter was adjusted so it was 20% larger than the diameter of the carotid artery measured digitally. The stent designs used at our clinic so far are closed-cell stent (20%), Xact carotid stent (Abbott, Santa Clara, CA, US), open-cell stents (67%); Sinus-carotid-conical RX stent (Optimed, Ettlingen, Deutschland), RX Acculink stent (Abbott), protege RX stent (Ev3, Medtronic, Plymouth, MN, US), a hybrid-cell stent (13%), and Cristallo idealE SE stent (İnvatec, Medtronic). In the following lesion groups, the proximal blockage system (Mo.MA®) was preferred as EPD. In the case of symptomatic and >90% carotid artery stenosis, ICAs after bulbous area are tortuous, the lesion was ulcerated and slightly thrombotic. For the other lesions, a distal protection method (filter [Emboshield, Filterwire, spider FX]) was used. Patients with a heart rate of <60/min were administered 1 mg atropine intravenously (IV) before carotid ballooning. Atropine was given to other patients if their heart rate went below <60/min after ballooning/stenting. To make sure if there had been distal embolization associated with CAS, bilateral cerebral DSA was performed and compared with pre-CAS scans. For all patients who did not undergo coronary artery angiography (CAG) beforehand, CAG was performed after CAS.

Follow-up after carotid artery stenting

All patients were followed up for hemodynamic and clinical parameters at the coronary intensive care unit for 24 hours following CAS. Cerebral DW-MRI was performed to be able to see possible asymptomatic cerebral DW-MRI lesions in patients 3–7 days before and 12–24 hours after the CAS procedure (Figure 1). A routine cardiac enzyme test was not made. The patients were followed up by the vascular neurologist for minor and major neurological complications for 24 hours following the procedure. On discharge, all patients were prescribed dual antiplatelet and statin therapy (if low-density lipoprotein [LDL] cholesterol was >70 mg/dl). Dual antiplatelet therapy was continued for 6–12 months if the patients did not have any other specific conditions.

Carotid plaque characterization

Carotid artery stenosis was first evaluated by CDUS and then by CTA. Plaque morphology, which is defined as predominantly fibrolipid (noncalcified) or fibrocalcific, and the degree of stenosis were initially determined through a sonography/DUS evaluation and CTA of supra-aortic vessels during the inclusion period. All lesions were eval-

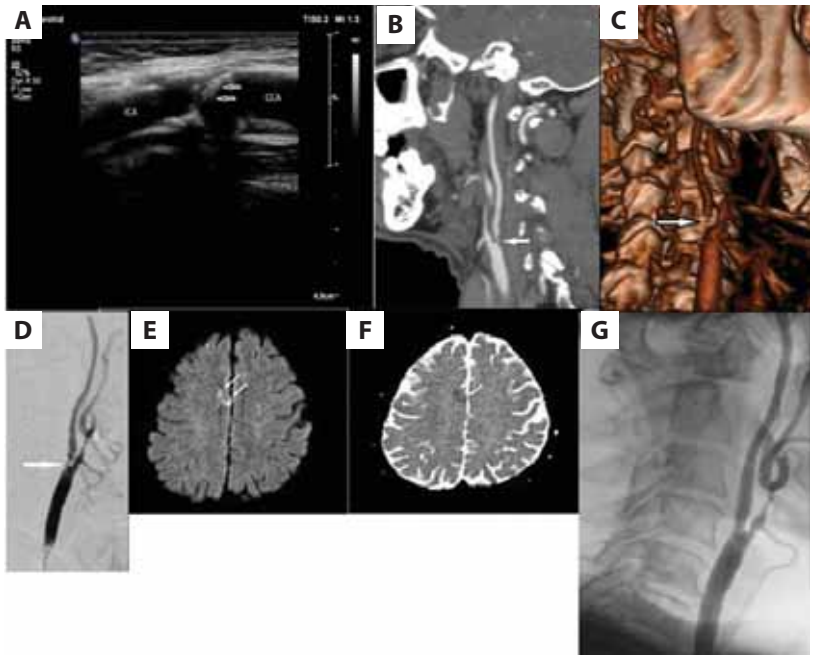

Figure 1. Noncalcified plaque-causing severe stenosis in the internal carotid artery (arrow). B-mode sonography (**A**), computed tomography angiography (**B**) 3D computed tomography angiography (**C**), and digital subtraction angiography (**D**). Postinterventional cerebral diffusion-weighted magnetic resonance imaging (**E**) shows the anterior cerebral artery territory high-signal intensity lesion (arrow). On ADC map (**F**), the lesion shows low-signal intensity (arrow) indicating its acute nature. Digital subtraction angiography after stenting (**G**)

uated with CDUS and CTA. Plaque morphology defined by CDUS was confirmed by CTA in lesions with severe stenosis in CDUS according to flow rate. Final plaque morphology before CAS was decided according to CTA findings. CDUS examination was performed using the Esaote SpA MyLab-Class C (Esaote SpA, Florence, Italy) device with the linear array probe, which allows the selection of frequencies between 3 and 11 MHz. The severity of carotid stenosis was evaluated by measuring the peak systolic velocity (PSV), with angle correction, at the narrowest point of stenosis. If PSV was in the range of 125–240 cm/s, carotid stenosis was considered to be 50%–70%. Stenosis was classified at more than 70% if PSV was more than 240 cm/s. The classification of Gray-Weale [16] was used for ultrasonography plaque characterization as follows: Type I, predominantly echolucent plaque with a thin echogenic cap; Type II, substantially echolucent lesions with small areas of echogenicity; Type III, predominantly echogenic lesions with small areas of echolucency; and Type IV, uniform echogenic lesions (equivalent to homogeneous). Type I and Type II were predominantly soft plaques with fibrolipid structure; Type III and Type IV were predominantly fibrotic and partly calcified plaques (hard plaques). In our study, Types I and II were classified as noncalcified plaque (Figure 1), and Type III as calcified plaque (Figure 2). Patients with Type IV plaque (dense calcification) were excluded from the study.

CTA examination was performed using the Philips Brilliance 64 detector CT (Holland) device (Philips Healthcare, 5680 DA Best, The Netherlands). After venous access was established through the antecubital vein and 80 ml nonionic contrast agent was administered at a rate of 4.5 ml/sec, axial-plane computed tomography images of the carotid and cerebral arteries were obtained using the tracking method. Acquired slices were transferred to the Workstation (Philips IntelliSpace Portal, Philips Healthcare) and multiplane images, maximum intensity projection, and volume rendering 3-dimensional images were developed by postprocessing the original slices via appropriate software (AVA). Plaque type was classified according to attenuation measurements from the previously reported criteria [17]. Predominantly lipid or fibroid plaques were defined as soft intermediate plaques with a median attenuation of ≤130 HU (Figure 1). Calcified plaques consisted of lesions having a median attenuation >130 HU (Figure 2). When there was a disagreement in plaque characterization between CTA and DUS, we used the data obtained by CTA. The stenosis caused by plaques as detected using CDUS was assessed according to the criteria developed by the Internal Carotid Artery Stenosis Criteria Consensus Committee. The severity of stenosis detected on CTA was evaluated according to the criteria of the NASCET.

DW-MRI

Cerebral DW-MRI images were obtained using a 1.5 Tesla Magnetom Sonata (Siemens, Erlangen, Germany). Cerebral MRI (DWI and ADC [apparent diffusion coefficient]) maps of patients were compared before and after CAS by an experienced interventional neurologist (ESG). New ipsilateral hyperintense DW-MRI lesions not seen before CAS were considered silent cerebral embolisms. The diffusion-weighted sequence was acquired with three different *b*-values (b = 0.500, and 1000 s/mm^2). A positive DWI scan

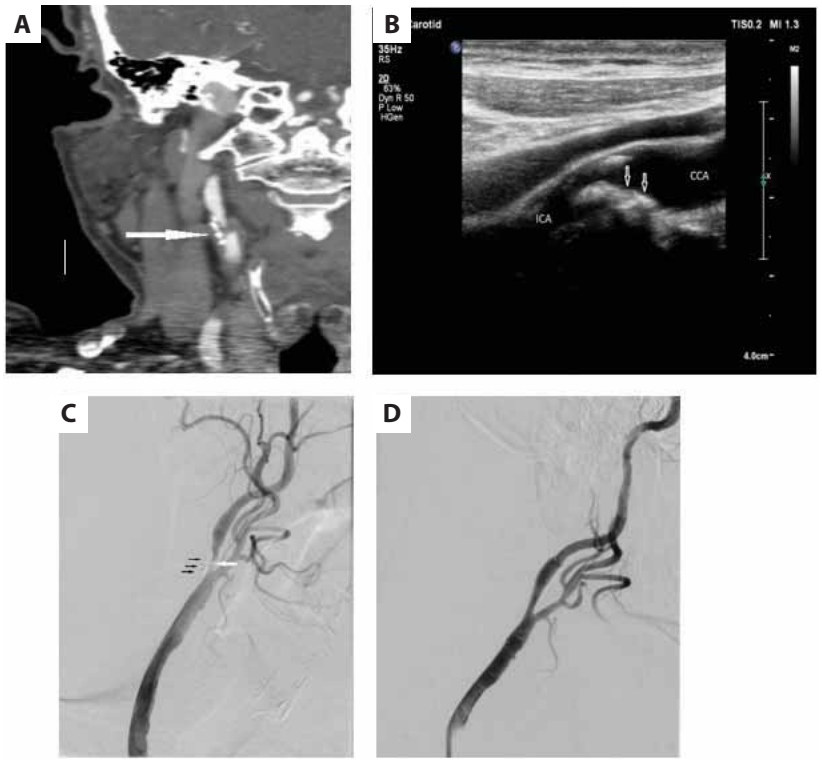

Figure 2. Calcified plaque-causing severe stenosis in the internal carotid artery (arrow). B-mode sonography (**A**), computed tomography angiography (**B**), and digital subtraction angiography before stenting (**C**), after stenting (**D**)

was defined as a high signal on the b1000 image. In the cases with a lesion on DWI, we also reviewed the ADC map and noted whether high-signal areas on the b1000 image showed low, high, or normal signal on the ADC map when comparing the affected area to the corresponding contralateral area. Furthermore, we assessed whether the lesions visible on DWI were also present on the T2 image.

Statistical analysis

The data obtained in this study was recorded with SPSS 24.0 (IBM Corp., Armonk, NY, US) software. The categorical variables were expressed as numbers and percentages while continuous variables were expressed as means and standard deviation. The Shapiro-Wilk test was used to analyze the concordance of the continuous variables with the normal distribution. For inter-group comparison, the Student's t-test was used for normally distributed parameters while the Mann-Whitney U test was used for other parameters that did not have the normal distribution. To analyze the categorical variables, the χ^2 test or Fisher's test was used. P <0.05 was considered to be statistically significant.

RESULTS

When the baseline characteristics of the noncalcified and calcified groups were compared, the mean age of the patients in the calcified group was found to be statistically significantly higher (mean [SD] age in the noncalcified and calcified groups, respectively, was 68.10 [9.9] vs. 70.86 [9.1] years; P <0.001). The rate of smokers was statistically significantly higher in the noncalcified group (the number of smokers in the noncalcified and calcified groups, was 110 [41.0%] vs. 93 [30.8%] respectively, P =0.011). No difference was found between the two groups as regards the other clinical characteristics (Table 3).

As for the procedural characteristics, balloon postdilatation was performed statistically significantly more in the calcified group (the number of patients undergoing balloons postdilatation in the noncalcified and calcified groups, was 96 [35.8%] vs. 137 [45.4%], respectively, P = 0.021). As for the other procedural characteristics, both groups were similar (Table 4).

When the two groups were compared for periprocedural asymptomatic ipsilateral cerebral DW-MRI lesion, which was the primary endpoint of our study, the lesion was detected in 45 (16.8%) patients in the noncalcified group and 31 (10.3%) patients in the calcified group. Periprocedural asymptomatic ipsilateral cerebral DW-MRI lesion was detected more often in the noncalcified plaque group than in the calcified plaque group, which was statistically significant (P = 0.022) (Table 5).

DISCUSSION

In this study, periprocedural ipsilateral cerebral DW-MRI lesion rates of calcified and noncalcified carotid plaques associated with CAS were compared with cerebral DW-MRI findings. The findings of this study demonstrated that carotid stents implanted into the noncalcified plaques were associated with a higher rate of periprocedural

Table 3. Clinical characteristics of the study groups

Variables	Noncalcified plaque (n = 268)	Calcified plaque (n = 302)	*P*-value
Age, years, mean (SD)	68.10 (9.9)	70.86 (9.1)	<0.001
Male, n (%)	209 (78.0)	230 (76.2)	0.605
Hypertension, n (%)	189 (70.5)	223 (73.8)	0.377
Diabetes mellitus, n (%)	108 (40.3)	119 (39.4)	0.828
Coronary artery disease, n (%)	180 (67.2)	222 (73.5)	0.097
Peripheral artery disease, n (%)	13 (4.9)	14 (4.6)	0.904
Smoking, n (%)	110 (41.0)	93 (30.8)	0.011
Chronic renal failure, n (%)	11 (4.1)	7 (2.3)	0.223
Symptomatic ICA stenosis, n(%)	134 (50.2)	151 (50.2)	0.996
LDL, mg/dl, median (IQR)	105.0 (77.2–136.0)	107.0 (83.7–136.2)	0.757
Statin intake, n (%)	249 (92.9)	274 (90.7)	0.345
Drug resistance, n (%)			
Absent	236 (88.1)	275 (91.1)	0.080
ASA	5 (1.9)	5 (1.7)	
Clopidogrel	27 (10.1)	18 (6.0)	

Data are expressed as median (interquartile range [IQR]) for non-normal distributed data and percentage for categorical variables

Abbreviations: ASA, acetylsalicylic acid; LDL, low-density lipoprotein; other — see Table 1

Table 4. Procedural characteristics of the study groups

Variables	Noncalcified plaque (n = 268)	Calcified plaque (n=302)	*P*-value
Stent length, n (%)			
30 mm	130 (48.5)	128 (42.4)	0.143
40 mm	138 (51.5)	174 (57.6)	
Stent diameter, n (%)			
6&8, 6&9, 7&9	114 (42.9)	119 (39.4)	0.404
7&10, 8&10	152 (57.1)	183 (60.6)	
Filter/ MoMA®, n (%)			
Protected	22 (8.2)	12 (4.0)	0.078
MOMA	99 (36.9)	126 (41.7)	
Filter	147 (54.9)	164 (54.3)	
Stent type, n(%)			
Open-cell	179 (66.8)	202 (66.9)	0.932
Closed-cell	54 (20.1)	58 (19.2)	
Hybrid-cell	35 (13.1)	42 (13.9)	
Predilatation, n (%)	172 (64.2)	197 (65.2)	0.793
Postdilatation, n (%)	96 (35.8)	137 (45.4)	0.021
Debris, n (%)	55 (20.6)	55 (18.2)	0.472

Abbreviations: MoMA, proximal embolic protection device; other — see Table 1

Table 5. Periprocedural ipsilateral cerebral DW-MRI lesion of all groups

	Noncalcified plaque, n (%)	Calcified plaque, n (%)	Total, n (%)	*P*-value
DW-MRI lesion absent	223 (83.2)	271 (89.7)	494 (86.7)	0.022
DW-MRI lesion present	45 (16.8)	31 (10.3)	76 (13.3)	
Total	268	302	570 (100)	

Abbreviations: DW-MRI, diffusion-weighted magnetic resonance imaging

asymptomatic ipsilateral DW-MRI lesions compared to the calcified plaques.

In the ACST-2 (second asymptomatic carotid surgery trial) study, which was published in 2021, procedure-related complications and long-term results were found to be similar between CAS and CEA in asymptomatic carotid stenosis [18]. Despite these large-scale randomized trials, the safety of CAS is still controversial [1, 19]. Stroke and transient ischemic attack after CAS are rare complications observed at high-volume and experienced centers [20]. Symptomatic or asymptomatic periprocedural cerebral embolism is one of the most important limitations of CAS [21, 22]. Silent cerebral embolism associated with CAS was demonstrated to cause dementia, cognitive decline [3], and even ischemic stroke in the subsequent years [4].

DW-MRI is a very sensitive method to detect cerebral lesions that develop during CAS [6, 7]. The rate of silent cerebral embolism associated with CAS and detected on DW-MR was reported to be up to 40% in some series [2, 23]. Thirty percent of these embolic events are observed in the contralateral hemisphere [24]. Unless an embolic protection method is used (unprotected), the rate of cerebral

embolism is 45%, which can be reduced to 33% with an embolic protection method [2, 10].

There is a need to find the cause of silent cerebral embolism, which is still common and clinically significant in protected CAS procedures and to reduce the incidence of embolism. In a study [10], age, hypertension, lesion eccentricity, and type III aortic arch were shown to cause cerebral ischemic lesion associated with CAS with the use of DW-MRI. Xiaoyu Xu et al. demonstrated in the study they conducted in 2020 that diabetes mellitus, ipsilateral calcified plaque, ulcerated plaque, predilatation, and use of open-cell stent were independent risk factors for silent cerebral lesions during CAS [25].

Some variables in CAS may increase the risk of embolism in the brain tissue fed by the stented carotid artery and some others may increase the risk of bilateral cerebral embolism. Long-term periprocedural hemodynamic instability may lead to bilateral cerebral embolism and especially watershed infarcts. Type III aortic arch, severely atherosclerotic and calcified aortic arch, inappropriate catheter use prolong the procedure time and increase the risk of bilateral embolism [26]. Severely tortuous carotid artery, severe ICA spasm, complex carotid plaques (long, ulcerated, thrombotic plaques), and the use of inappropriate antiplatelets increase the risk of embolism on the same side with the stent. In our study, to determine the risk associated with the nature of carotid artery plaque-causing cerebral embolism, we determined several exclusion criteria such as symptomatic complications, hemodynamic instability during the procedure, difficult and risky arcus aorta, severely tortuous carotid arteries, severely ulcerated, heavily thrombotic and heavily calcified circular carotid artery plaques, watershed infarcts, and a history of repeated ballooning. The goal was to find significant associations between these brain emboli fed by the stented artery and the nature of calcified and noncalcified plaques. Our study is different from other studies because statin was initiated for most of the patients before CAS and dual antiplatelet therapy was adjusted according to the antiplatelet resistance test results. A multidisciplinary team is crucial to decide on the right patients, right lesions, and the right procedure. The fact that all CAS procedures recommended by the multidisciplinary team were performed by the same operators and with the same method using similar materials is considered to be the main factor that kept the procedure-associated cerebral embolism rate at a very low level (13.3%) and increased the reliability of our results.

The most important step in implementing CAS to decrease cerebral embolism is to use an embolic protection device. Most of the studies investigating cerebral embolism with DW-MRI used the distal protection method. Contrary to these studies, we used the proximal blockage method for embolic protection in 39% of the study group. Before the proximal blockage system was used, intracerebral blood circulation was assessed, and a balloon intolerance test was performed. The PROFI trial demonstrated that the proximal blockage system was more advantageous than the distal protection method to reduce cerebral embolism in CAS [24]. If filters are smaller than the diameter of the vessel, distal particle embolization may occur between the vessel wall and filter. If it is larger than the vessel diameter, it may lead to spasm in the distal carotid artery. Filters cannot hold particles that are smaller than the pore sizes. Besides, they may also pour back their content if the technique is not used properly while retracting the filters. All the above-mentioned reasons may lead to diffusion limitation in the brain tissue on the distal side of the stented artery. Such risk associated with filters can be minimized at high-volume and experienced centers.

The mean age of the patients in the calcified plaque group was found to be statistically significantly higher. Calcification of vessel walls is known to increase with age [27]. We do not think that a higher mean age in the calcified group than in the noncalcified group would affect the result of our study.

The rate of smokers was found to be statistically significantly higher in the noncalcified group. Smoking is a general risk factor for vascular atherosclerosis. Studies with small series (33 patients) have demonstrated that smoking is an independent risk factor for stent restenosis [28]. In light of this information, we do not know to what extent smoking could affect the results of our study.

Balloon postdilatation after CAS increases the likelihood of periprocedural cerebral embolic events [29]. Predilation with high atmosphere before carotid stenting and avoiding post-stent postdilation may reduce the incidence of periprocedural cerebral embolism [30]. The number of patients undergoing balloon postdilatation after carotid stenting was higher in the calcified group than in the noncalcified group in our study. This might slightly increase the rate of cerebral embolism in the calcified group.

In our study, first-generation self-expandable carotid stents were used. In the literature, studies are investigating cerebral embolism using DW-MRI regarding different protection methods and mesh-covered stents. Each stent and protection method has a certain risk of periprocedural cerebral embolism. Currently, the ideal stent in terms of silent cerebral embolism risk has not been determined yet [31–33]. In the study by Karpenko et al. [34] in 2021, it was shown that CAS procedures performed with MicroNet-covered stents significantly reduce both periprocedural and first 30-days' cerebral embolism compared to first-generation stents. Another important result from the same study is that the cerebral DW-MRI quantitative volume analysis is extremely important in detecting and interpreting CAS-related cerebral embolisms [34].

The clinical effects of calcified atherosclerotic plaques were analyzed with pathological and imaging methods. Calcium hardens atherosclerotic plaque and makes it resistant to rupture [35]. Hunt et al. [36] showed with endarterectomy materials that calcified carotid plaques in symptomatic and asymptomatic carotid patients were

associated with fewer cerebrovascular events compared to noncalcified plaques. Neutrophilia to lymphocyte rate, which is an inflammatory marker, was found to be higher in the symptomatic and noncalcified carotid plaques with a stenosis of 50%–70% while it was lower in asymptomatic and calcified plaques [37, 38]. Echo-rich carotid plaques detected on CDUS typically have more calcium and fibrous tissue while echolucent plaques have more lipid content. Using these criteria, the Tromso trial revealed that echo-rich plaques were at a lower risk for neurological symptoms [39]. Therefore, more unstable noncalcified carotid plaques may cause more cerebral embolisms in CAS procedures. It may be useful to use intravascular ultrasonography (IVUS) to reveal the nature of the carotid plaque more clearly and to optimize the placement of the stent on the carotid artery wall [40].

Our study had certain limitations. It was a retrospective and single-center study. A total of 170 patients who may be at high risk of cerebral embolisms, such as symptomatic complications after CAS (23 patients), were excluded from the analysis for various reasons (Table 2). CEA, not CAS, was performed on 88 patients with target artery access difficulties. Quantitative volume analysis could not be performed for new embolic lesions detected in DW-MRI after CAS. Carotid lesions with circular heavily calcified plaques were not included in the study. IVUS could have been performed to determine the carotid artery plaque morphology more clearly and rule out the complications associated with stent location. Cerebral DW-MRI cross-sections could have been thinner.

CONCLUSIONS

The rate of periprocedural asymptomatic ipsilateral cerebral embolism detected on cerebral DW-MRI is higher in CAS performed for noncalcified carotid artery plaques compared to the calcified plaques. There is a need for further prospective, multi-center studies with a higher number of patients to validate the results of this study.

Article information

Conflict of interest: None declared.

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Managed Care after Acute Myocardial Infarction (MC-AMI) improves prognosis in AMI survivors with pre-existing heart failure: A propensity score matching analysis of Polish nationwide program of comprehensive post-MI care

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ABSTRACT

Background: Despite improvement in acute myocardial infarction (AMI) treatment, post-discharge mortality remains high. The outcomes are supposed to be even worse in patients with post-MI heart failure (HF), as only a half of patients with newly diagnosed HF survive four years.

Aims: The study aimed to analyze whether managed care after acute myocardial infarction (MC-AMI) is associated with better survival in AMI survivors with a pre-existing diagnosis of HF.

Results: The study included 7228 patients with a pre-existing diagnosis of HF who survived the hospitalization for AMI in Poland between November 2017 and December 2020, of whom 2268 (31.4%) were referred for the MC-AMI program. The median follow-up was 1.5 (0.7–2.3) years. In the unmatched analysis, patients without MC-AMI had more than twice higher 12-month mortality (21.8% vs. 9.9%; *P* <0.01) than MC-AMI participants. The difference remained significant after propensity score matching (16,8% vs. 10.0%; *P* <0.01). In multivariable analysis, participation in MC-AMI was an independent factor of 12-month survival. MC-AMI participants had a lower stroke rate (1.5% vs. 3.0%; *P* <0.01) and fewer hospital admissions due to HF (22.9% vs. 27.6%; *P* <0.01).

Conclusions: After propensity score matching, participation in MC-AMI was associated with lower rates of stroke, HF hospitalizations, and all-cause mortality in the 12-month follow-up and was an independent factor of 12-month survival in AMI survivors with pre-existing HF.

Key words: acute myocardial infarction, heart failure, managed care, survival

WHAT'S NEW?

The post-discharge period, also called the transition phase, is the most vulnerable in heart failure (HF) patients. For that reason, we aimed to analyze whether managed care after acute myocardial infarction (MC-AMI) is associated with better survival in AMI survivors with a pre-existing diagnosis of HF. Our study proved in propensity score matching analysis that participation in MC-AMI was associated with lower rates of stroke, HF hospitalizations, and all-cause mortality in a 12-month follow-up and was an independent factor of 12-month survival in AMI survivors with pre-existing HF.

INTRODUCTION

In recent years, an improvement in the treatment and in-hospital prognosis of myocardial infarction has been observed. However, the post-discharge mortality remains high, especially in patients with post-MI heart failure (HF), as only half of patients with newly diagnosed HF survive four years [1, 2]. The post-discharge period, also called the transition phase, is the most vulnerable in HF patients [3]. For that reason, the proposed interventions aimed to improve survival, including out-patient visits scheduled in the first days after discharge or early post-discharge multidisciplinary team management [1, 4]. It has already been demonstrated in previous studies from our database that managed care after acute myocardial infarction (MC-AMI) improves 12-month survival [5, 6]. Other studies on managed care programs after AMI revealed different results [7, 8]. For that reason, we aimed to analyze whether MC-AMI is associated with better survival in AMI survivors with pre-existing HF.

METHODS

The study is a retrospective analysis of data from the SILesian CARDiovascular (SILCARD) registry. General information on the SILCARD database was previously reported [9, 10]. The database contains records from all hospitals (n = 310) in the Silesian Province — a large administrative region in Southern Poland with 4.57 million citizens. The SILCARD database enrolled all consecutive Silesian adults admitted to the cardiology, cardiac surgery, vascular surgery, diabetology units for any reason, or hospitalized in the internal medicine or intensive care units with the principal diagnosis of cardiovascular disease (CVD). CVD was defined as R52 or J96 or any "I" code according to the 10th revision of the International Classification of Disease (ICD-10).

MC-AMI is Poland's National Health Fund and Ministry of Health program implemented to improve hospital and post-discharge care in AMI patients. The program was designed as a comprehensive plan composed of four core modules: I — hospitalization and acute intervention according to ESC guidelines, II — cardiac rehabilitation, III — implantation of implantable cardioverter defibrillators (ICD) or chronic resynchronization therapy (CRT-D) in eligible subjects, and IV — post-discharge scheduled out-patient cardiology care (at least four visits over 12 months).

The study included consecutive adult patients hospitalized due to AMI in Silesia between November 2017 and December 2020 and pre-existing diagnosis of HF, who survived ten days after discharge. The ten days were chosen because of the median time from hospital discharge to MC-AMI to exclude patients who died before the onset of the MC-AMI program. The follow-up was measured from the hospital discharge in patients who were discharged alive. Patients were divided into two groups: participating in MC-AMI and subjects in a control group. The control group included AMI patients hospitalized in the same period who did not consent for participation in MC-AMI.

The Bioethics Committee of the Medical University of Silesia approved the SILCARD database analyses (PCN/0022/KB/49/21).

Statistical analysis

The normality of the continuous variables was tested using the Shapiro-Wilk test. Variables with normal distribution were presented as means and SD and those with skewed distribution as medians and interquartile ranges (IQR). Categorical variables were shown as percentages. Baseline characteristics, medical history, and in-hospital interventions were compared using Student's t-test (for normally distributed variables), the nonparametric Mann-Whitney U test for continuous variables without normal distribution, and the $\chi 2$ test for categorical variables data with Yates' correction if applicable. After 1:1 propensity score matching, two groups of patients were also compared. Multivariable analysis was also performed to identify independent risk factors for all-cause death in a 12-month follow-up from the beginning of the MC-AMI program. The forward stepwise regression was used with all available parameters included in the model, and statistical significance was defined as $P < 0.05$. The Kaplan-Meier plots were drawn to visualize the survival curves. All statistical analyses were performed using TIBCO Statistica 13 software.

RESULTS

The study included 7228 patients with AMI and pre-existing diagnosis of HF, of whom 2268 (31.4%) were referred for MC-AMI treatment. The median follow-up was 1.5 (0.7–2.3) years.

Compared to the control group, patients in the MC-AMI program were younger, more often had a history of PCI and PCI and bleeding during the current hospitalization but less often a history of stroke and atrial fibrillation in the past (Table 1). In the unmatched analysis, patients without MC-AMI qualification had more than twice higher 12-month mortality (21.8% vs. 9.9%; $P < 0.01$) (Figure 1). The difference remained significant after propensity score

Table 1. Baseline characteristics regarding qualification for MC-AMI before and after matching

	Before matching			After matching		
	MC-AMI – n = 4960	MC-AMI + n = 2268	*P*-value	MC-AMI – n = 2221	MC-AMI + n = 2221	*P*-value
Age, years, mean (SD)	74.9 (10.2)	71.7 (9.7)	<0.01	72.2 (9.9)	72.0 (9.4)	0.67
Follow-up, years, median (IQR)	1.5 (0.6–2.3)	1.4 (0.7–2.1)	0.28	1.6 (0.7–2.4)	1.4 (0.7–2.1)	<0.01
Female sex, n (%)	2208 (44.5)	850 (37.5)	<0.01	843 (38.0)	840 (37.8)	0.95
STEMI, n (%)	944 (19.0)	480 (21.2)	0.04	461 (20.8)	464 (20.9)	0.94
History of hypertension, n (%)	4636 (93.5)	2140 (94.4)	0.16	2,100 (94.6)	2095 (94.3)	0.79
History of diabetes, n (%)	2644 (53.3)	1195 (52.7)	0.64	1188 (53.5)	1176 (52.9)	0.74
History of MI, n (%)	1965 (39.6)	925 (40.8)	0.36	915 (41.2)	906 (40.8)	0.81
History of pulmonary edema, n (%)	269 (5.4)	98 (4.3)	0.06	93 (4.2)	95 (4.3)	0.94
History of PCI, n (%)	1752 (35.3)	873 (38.5)	0.01	859 (38.7)	849 (38.2)	0.78
History of BMS implantation, n (%)	417 (8.4)	185 (8.2)	0.76	189 (8.5)	184 (8.3)	0.83
History of DES implantation, n (%)	1198 (24.2)	607 (26.8)	0.02	609 (27.4)	587 (26.4)	0.48
History of CABG, n (%)	452 (9.1)	235 (10.4)	0.1	226 (10.2)	231 (10.4)	0.84
History of valvular surgery, n (%)	123 (2.5)	51 (2.2)	0.61	54 (2.4)	49 (2.2)	0.69
History of PM implantation, n (%)	342 (6.9)	121 (5.3)	0.01	117 (5.3)	121 (5.4)	0.84
History of ICD implantation, n (%)	252 (5.1)	92 (4.1)	0.07	92 (4.1)	90 (4.1)	0.94
History of CRT-P/CRT-D, n (%)	75 (1.5)	27 (1.2)	0.33	26 (1.2)	27 (1.2)	0.99
History of ablation, n (%)	55 (1.1)	22 (1.0)	0.68	23 (1.0)	21 (0.9)	0.88
History of AF, n (%)	1469 (29.6)	589 (26.0)	<0.01	606 (27.3)	582 (26.2)	0.44
History of VT/VF/cardiac arrest, n (%)	180 (3.6)	78 (3.4)	0.74	75 (3.4)	77 (3.5)	0.93
Other arrhythmias, n (%)	2025 (40.8)	848 (37.4)	<0.01	851 (38.3)	837 (37.7)	0.69
History of COPD, n (%)	1179 (23.8)	517 (22.8)	0.38	509 (22.9)	511 (23.0)	0.97
History of asthma, n (%)	924 (18.6)	423 (18.7)	0.99	427 (19.2)	415 (18.7)	0.67
History of CKD, n (%)	784 (15.8)	307 (13.5)	0.01	292 (13.1)	302 (13.6)	0.69
History of RRT, n (%)	133 (2.7)	43 (1.9)	0.05	47 (2.1)	42 (1.9)	0.67
History of stroke, n (%)	801 (16.1)	290 (12.8)	<0.01	286 (12.9)	290 (13.1)	0.89
History of PAD, n (%)	236 (4.8)	91 (4.0)	0.18	81 (3.6)	90 (4.1)	0.53
History of cancer, n (%)	2068 (41.7)	990 (43.7)	0.12	964 (43.4)	967 (43.5)	0.95
Coronary angiography, n (%)	4012 (80.9)	2.254 (99.4)	<0.01	2,207 (99.4)	2,207 (99.4)	0.85
PCI, n (%)	2800 (56.5)	2012 (88.7)	<0.01	1970 (88.7)	1965 (88.5)	0.85
IABP, n (%)	64 (1.3)	19 (0.8)	0.12	41 (1.8)	18 (0.8)	<0.01
PM implantation, n (%)	109 (2.2)	28 (1.2)	<0.01	54 (2.4)	27 (1.2)	<0.01
ICD implantation, n (%)	52 (1.0)	5 (0.2)	<0.01	19 (0.9)	5 (0.2)	<0.01
CRT-P/CRT-D implantation, n (%)	16 (0.3)	6 (0.3)	0.85	4 (0.2)	6 (0.3)	0.75
Valvular surgery, n (%)	48 (1.0)	6 (0.3)	<0.01	13 (0.6)	6 (0.3)	0.17
Hospitalization in ICU, n (%)	392 (7.9)	91 (4.0)	<0.01	157 (7.1)	91 (4.1)	<0.01
Bleeding requiring blood transfusion, n (%)	662 (13.3)	153 (6.7)	<0.01	245 (11.0)	150 (6.8)	<0.01

Abbreviations: AF, atrial fibrillation; BMS, bare metal stent; CABG, coronary artery bypass Grafting; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; DES, drug-eluting stent; HF, heart failure; IABP, intra-aortic balloon pump; ICD, implantable cardioverter defibrillator; ICU, intensive care unit; MC-AMI, managed care after acute myocardial infarction; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PM, pacemaker; RRT, renal replacement therapy; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction; VF, ventricular fibrillation; VT, ventricular tachycardia

matching (16.8% vs. 10.0%; *P* <0.01) (Table 2). Participation in the MC-AMI program was an independent factor of 12-month survival in multivariable analysis (Table 3). MC-AMI has also been associated with a reduction in the rates of stroke and hospital admission due to HF.

DISCUSSION

We showed that participation in MC-AMI is associated with better 12-month survival in patients after AMI with pre-existing HF. A reduction in mortality rates was associated with a reduction in stroke and HF hospitalization rates. Interestingly, during the 12-month follow-up, there were no differences in coronary angiography, PCI, and ICD implantation rates between the groups. For that reason, the possible explanations of the positive impact of MC-AMI were improved ambulatory care (number of AOS visits) and rehabilitation after discharge. Participation in MC-AMI was also associated with a higher cost of treatment during the 12-month follow-up. Higher costs of hospital stay in MC-AMI participants might suggest that the course of AMI could be more complicated, influencing the costs of post-discharge care. To the best of our knowledge, our

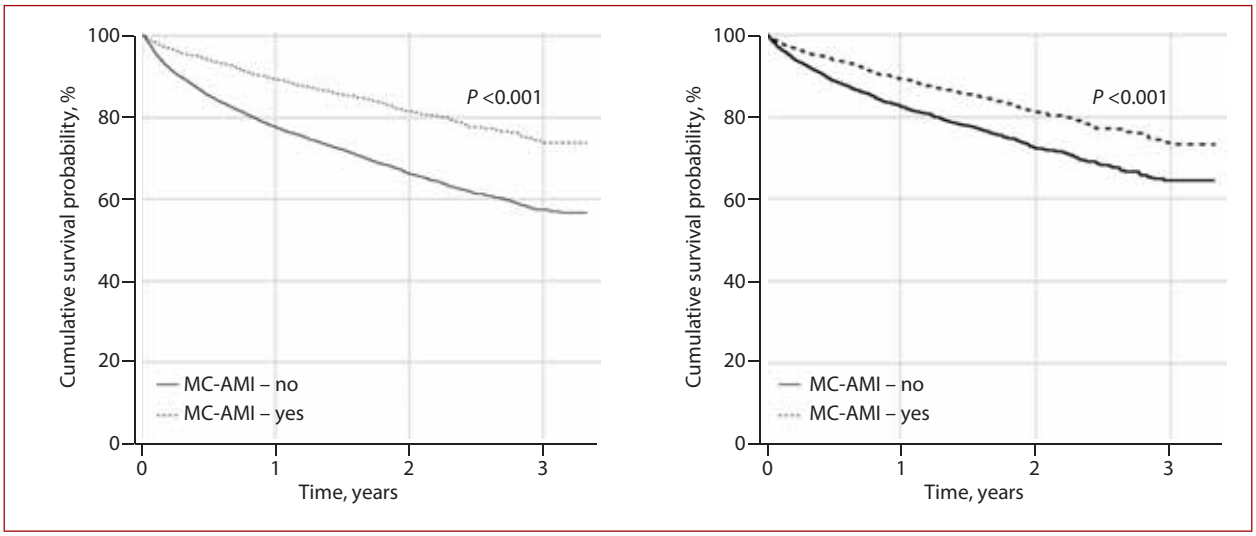

Figure 1. Comparison of survival in MC-AMI and non-MC-AMI groups before (left) and after (right) propensity score matching — Kaplan-Meier curves

Table 2. Events and outcomes in a 12-month follow-up regarding the MC-AMI attendance before and after matching

	Before matching			After matching		
	MC–AMI – n = 4960	MC–AMI + n = 2268	*P*-value	MC-AMI – n = 2221	MC-AMI + n = 2221	*P*-value
All-cause death, n (%)	886 (21.8)	165 (9.9)	<0.01	304 (16.8)	164 (10.0)	<0.01
Coronary angiography, n (%)	682 (16.8)	351 (21.0)	0.06	386 (21.3)	338 (20.6)	0.06
PCI, n (%)	485 (11.9)	272 (16.2)	<0.01	293 (16.2)	259 (15.8)	0.13
Stroke, n (%)	120 (2.9)	25 (1.5)	<0.01	54 (3.0)	24 (1.5)	<0.01
Rehabilitation, n (%)	822 (20.2)	1096 (65.4)	<0.01	461 (25.5)	1,076 (65.5)	<0.01
Hospitalization due to HF, n (%)	1215 (29.9)	378 (22.6)	<0.01	499 (27.6)	375 (22.9)	<0.01
Atrial fibrillation, n (%)	576 (14.2)	196 (11.7)	<0.01	239 (13.2)	194 (11.8)	0.03
PM implantation, n (%)	64 (1.6)	42 (2.5)	0.02	35 (1.9)	42 (2.6)	0.26
ICD implantation, n (%)	142 (3.5)	79 (4.7)	0.03	92 (5.1)	78 (4.8)	0.71
CRT-D implantation, n (%)	66 (1.6)	52 (3.1)	<0.01	33 (1.8)	51 (3.1)	0.02
GP visits per patient per year, median (IQR)	10 (5–16)	9 (5–14)	<0.01	10 (6-16)	9 (5-14)	<0.01
OHC visits per patient per year, median (IQR)	0 (0–2)	3 (1–5)	<0.01	1 (0-2)	3 (1-5)	<0.01
Cost of hospitalization, PLN, median (IQR)	9610 (0–13 342)	10679 (9718–15 227)	<0.01	10 571 (9610–14 943)	10 679 (9718–15 227)	<0.01
Cost of treatment during the 12-month follow-up, median, PLN, median (IQR)	316 (0–3610)	5547 (2276–8371)	<0.01	445 (36–4004)	5546 (2233–8351)	<0.01
Bleeding requiring blood transfusion, n (%)	662 (13.3)	153 (6.7)	<0.01	245 (11.0)	150 (6.8)	<0.01

Abbreviations: see Table 1

Table 3. Multivariable analysis of 12-month post-discharge mortality

	HR (95% CI)	*P*-value
RRT	1.85 (1.45–2.35)	<0.01
History of pulmonary oedema	1.43 (1.20–1.70)	<0.01
History of PAD	1.38 (1.14–1.67)	<0.01
History of diabetes	1.34 (1.22–1.47)	<0.01
Female gender	1.27 (1.15–1.40)	<0.01
MC-AMI	1.25 (1.09–1.42)	<0.01
STEMI	1.24 (1.11–1.40)	<0.01
History of CKD	1.20 (1.06–1.36)	<0.01
History of stroke	1.20 (1.07–1.35)	<0.01
Age, (per 5 years increase)	1.15 (1.12–1.18)	<0.01
History of COPD	1.15 (1.03–1.27)	0.01
PCI	0.61 (0.54–0.68)	<0.01
Rehabilitation after discharge	0.51 (0.45–0.58)	<0.01

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

study is the first one that showed the benefits of managed care in AMI survivors with pre-existing HF.

In our previous studies, participation in MC-AMI was associated with the reduction of MACE and MACCE rates in a 3- and 12-month follow-up, respectively, and lower all-cause mortality in 12-month observation [6, 11, 12]. Different approaches to post-discharge care in AMI patients were implemented in other countries. In Germany, nurse-based management among elderly patients after AMI had no significant impact on the mortality rate in a one-year follow-up [8]. In another trial, the disease management program improved the adherence to guideline-recommended medication, health care expenditures, and survival [7]. More evidence regarding post-discharge care is available in HF. According to the recent HF guidelines of the European Society of Cardiology, patients with HF should be enrolled in a multidisciplinary care management program to reduce the risk of HF hospitalization and mortality [1]. Reduced left ventricular ejection fraction is diagnosed in 18%–20% of patients discharged after AMI [13]. Thus, early post-discharge care is essential to reduce mortality and the probability of recurrent AMI and hospitalizations for acute HF. Patients after AMI with pre-existing HF seem to be at the highest risk of death or rehospitalization. Participation in MC-AMI resulted in the reduction of hospital readmission and mortality in our cohort. We have no data to present the importance of the particular MC-AMI components (education, ambulatory care, rehabilitation, and primary prevention of sudden cardiac death) in achieving the overall result. A decrease in the prevalence of stroke was an additional observation. It might be explained by better detection of atrial fibrillation in patients in MC-AMI and possibly better drug compliance in patients with more ambulatory visits. The atrial fibrillation rate after AMI was about 10% lower while the prevalence of stroke was 50% lower in the MC-AMI group.

Study limitations

Our study was designed as a retrospective analysis of a large, nationwide registry, which does not provide data on blood test results and pharmacological treatment during hospitalization and after discharge. Thus, propensity score matching did not include these parameters.

To conclude, participation in MC-AMI was associated with lower rates of stroke, HF hospitalizations, and all-cause mortality in a 12-month follow-up and was an independent factor of 12-month survival in AMI survivors with pre-existing heart failure.

Article information

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Very long-term follow-up of patients with coronary bifurcation lesions treated with bioresorbable scaffolds

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ABSTRACT

Backgrounds: The data concerning the use of bioresorbable vascular scaffolds (BVS) in coronary bifurcation lesions are limited.

Aims: The objective of the study was to evaluate the early and very long-term clinical outcomes of bifurcation stenting with ABSORB BVS.

Methods: One hundred consecutive patients with coronary bifurcation lesions treated with BVS were included. A total of 124 BVS were implanted. Provisional side branch stenting was performed in 66 patients, distal main stenting in 14 patients, systematic T stenting in 2, and T with minimal protrusion (TAP) in 5 patients. Side branch ostial stenting was performed in additional 12 patients.

Results: The procedural success was achieved in 98% of patients. In long-term follow-up, the rate of cardiac death was 4.0%, target vessel myocardial infarction was 5.0%, and target vessel revascularization (TVR) was 11%. The cumulative incidence of definite/probable scaffold thrombosis (ST) was 2% at long-term follow-up. Comparison with the historical drug-eluting stents (DES) group revealed higher mortality and major adverse cardiac events rate in the ABSORB group.

Conclusions: Stenting of coronary bifurcation lesions of low-to-moderate complexity with BVS was feasible with good acute performance and acceptable results. However, the risk of death and major adverse cardiovascular events was higher as compared with DES.

Key words: bifurcation lesion, bioresorbable scaffolds, percutaneous coronary intervention

INTRODUCTION

Coronary artery bifurcation stenting has always been a challenging procedure in interventional cardiology. In the bare-metal stents era, the results were unsatisfactory, mainly due to the increased risk of periprocedural complications, high rate of restenosis, and repeat target lesion revascularization (TLR) [1–3]. Significant improvement has been observed with the advent of drug-eluting stents (DES), primarily because of the restenosis and TLR reduction [4, 5]. Nevertheless, even in the current era, bifurcation stenting, compared with percutaneous coronary interventions (PCI) for the non-bifurcation stenosis, is associated with a higher rate of periprocedural complications and stent thrombosis at follow-up [6–8].

Suboptimal treatment outcomes after implantation of metallic DES [9, 10] resulted in the development of the bioresorbable vascular scaffold (BVS) technology, with the potential long-term benefit after complete scaffold resorption [11, 12]. Although Abbott Vascular has withdrawn ABSORB BVS (Abbott Vascular, Santa Clara, CA, US) from commercial use, the idea of "leaving nothing behind" is still attractive. BVS could prevent permanent obstruction of a side branch (SB) in bifurcation lesions, reducing the risk of its closure and improving access if future treatment was needed.

WHAT'S NEW?

We report on very long-term clinical outcomes of bifurcation lesions stenting with everolimus-eluting bioresorbable vascular scaffolds (BVS). We have shown that stenting of coronary bifurcation lesions of low-to-moderate complexity with bioresorbable everolimus-eluting scaffolds was feasible with good acute performance and acceptable results. However, the risk of death and major adverse cardiovascular events was higher as compared with the second-generation drug-eluting stents. To our knowledge, this is the longest follow-up of patients after bifurcation stenting with everolimus-eluting BVS.

Since the benefits of BVS had been expected after scaffold disappearance, a very long-term observation time is necessary for the ultimate validation of this technology. The data concerning the use of BVS in coronary bifurcations are limited. Given the complexity of the procedure and the potential risk of struts' damage, it is imperative to evaluate the efficacy and long-term safety of BVS in such lesions.

METHODS

Study design, objectives, and patient selection

The study is a prospective, nonrandomized clinical registry of patients with coronary bifurcation lesions treated with everolimus-eluting BVS [16]. One hundred consecutive patients with stable coronary artery disease (SCAD) or acute coronary syndromes (ACS) were enrolled between October 2012 and December 2016. The study excluded patients with lesions deemed too complex to be treated with scaffolds (e.g., extreme tortuosity, severe calcifications, diffuse disease), concomitant serious, life-shortening illnesses, patients unable to receive prolonged dual antiplatelet therapy (DAPT), or requiring chronic oral anticoagulation therapy. Bifurcation lesion was defined and classified according to the European Bifurcation Club definition and Medina classification [13, 14].

The study group was compared with a historical control group of 107 patients undergoing coronary bifurcation stenting with a new generation DES (Xience™, Promus™, Endeavor™) between October 2006 and January 2009. Patients were selected from another prospective, nonrandomized clinical registry of patients treated with second-generation DES [15].

The main objective of the present study was to evaluate the long-term efficacy and safety of ABSORB BVS in coronary bifurcation lesions. The secondary outcome of interest was to compare the long-term performance of BVS with the second-generation DES.

The follow-up was calculated as the period from the procedure to the last contact with the patient, by phone or in-person during planned or urgent hospitalization.

The study was performed according to the provisions of the Declaration of Helsinki and good clinical practice and was approved by the local Ethics Committee (protocol no. 1015/13). All patients gave written informed consent to participate.

Procedure description

One day before planned PCI, all aspirin-, and clopidogrel-naive patients received a loading dose of both drugs, 300 mg each. Patients with ACS were loaded with 600 mg clopidogrel and 300 mg aspirin on admission. The PCI procedure was performed via the radial or femoral approach, according to the operator's preference. After vessel puncture, patients were given a bolus of unfractionated heparin in a dose of 100 U per kilogram. Intravascular ultrasound (IVUS) or optical coherence tomography (OCT) imaging were used at the operator's discretion but are strongly recommended in all complex cases. The procedure was regarded successful if the final thrombolysis in myocardial infarction (TIMI) 3 flow was obtained both in the main vessel (MV) and the side branch (SB), and the final MV diameter stenosis was below 30%. On discharge, all patients were advised to remain on DAPT for 12 months and then lifelong on aspirin alone. Clopidogrel was the only P2Y12 inhibitor used until March 2014 (66 patients) when the drug was replaced with ticagrelor after a few cases of BVS failures in other patients.

Bifurcation treatment strategy and techniques

The provisional approach was strongly recommended. In the first few months, we sized the MV scaffold according to distal reference diameter with high-pressure deployment (≥14 atm) and proximal optimization technique (POT) with a balloon diameter of 0.25–0.5 mm larger than the size of the scaffold (16 patients). In the later period, a proximal vessel maximum diameter (Dmax) was used to size the scaffold, with implantation pressure below 14 atm. Pre-dilatation and POT were also strongly recommended for all cases. Only T or T with minimal protrusion (TAP) techniques were allowed if a two-stent strategy was needed. All operators were strongly discouraged from using any complex techniques that might result in scaffold damage, e.g. culotte, crush, or simultaneous kissing stenting. If the final kissing-balloon post-dilatation (FKB) was required, low-pressure inflation (8 atm) was performed with a minimal protrusion of SB balloon into MV lumen (the mini kissing or snuggle technique). As no data were available on using BVS in this indication, all patients were scheduled for planned coronary angiography after 12 months post procedure. Quantitative coronary analysis (QCA) was performed after the procedure by two independent oper-

ators. Measurements were performed in three segments: the proximal and distal MV segment and SB.

Study endpoint and definitions

The primary clinical study endpoint was a device-oriented target vessel failure (TVF), defined as the combination of cardiac death, target vessel myocardial infarction (MI), or clinically driven target vessel revascularization (TVR). The primary procedural outcomes were device success, defined as successful delivery and deployment of the scaffold at the intended target lesion, and procedure success, defined as <30% residual stenosis in MB and TIMI 3 flow in both vessels, with no major periprocedural complications.

The secondary outcome of interest was the frequency of major adverse cardiac events (MACE), composed of death, myocardial infarction, ST, and target lesion revascularization (TLR), as well as the incidence of ST, classified according to the Academic Research Consortium criteria [17]. Both periprocedural and spontaneous MIs were defined according to the universal definition [18].

To compare BVS with DES II, we assessed the following endpoints: death and the composite endpoint of death, MI, and TLR.

Statistical analysis

All continuous variables were presented as means (standard deviation [SD]) for normal distribution or medians (interquartile range [IQR]) for non-normal distribution. The normality of the distribution of variables was tested using the Kolmogorov-Smirnov test. Categorical variables were presented as counts and percentages or frequencies. The significance of differences between the mean values of the continuous data consistent with the normal distribution was assessed using the Student's t-test. The Mann–Whitney U test was used to compare the continuous data inconsistent with the normal distribution. Categorized variables were compared using the χ^2 test.

The Gehan-Breslow-Wilcoxon test was used for survival analysis. In addition, the analyses were repeated, stratifying patients by cardiovascular high-risk groups. The prognostic relevance of different variables regarding the prediction of endpoints was estimated using univariable logistic regression analysis. The multivariable logistic regression model included the variables with the value of P <0.1 in the univariable model. We used PQStat Software (PQStat v.1.8.0.476, Poland) for statistical analysis.

RESULTS

Patient population and lesion characteristics

Between October 2012 and December 2016, one hundred patients with bifurcation lesions were treated with the implantation of one or more ABSORB BVS. Two patients received additional metallic stents during PCI because of major dissection of the main vessel after BVS implantation. The clinical follow-up was available for all survivors, at a median (IQR) of 1434 (1126–1969) days, with the follow-up at one year available in all patients. The baseline demography and clinical characteristics are presented in Table 1. The mean age was 62 (10) years, 76 patients were males (76%), 30 had diabetes mellitus (30%), and 13 had chronic kidney disease (13%). The majority of subjects had stable angina (82%). Supplementary material, *Table S1* summarizes vessel and lesion characteristics. True bifurcation lesion (Medina 1,1,1 / 1,0,1 / 0,1,1) was found in 27 patients, and ostial side branch lesions (Medina 0,0,1) in 13. About 90% of lesions were classed as type B2 or C according to the American College of Cardiology and American Heart Association. In 10% of cases, the lesion was diagnosed as MV chronic total occlusion (CTO). Twenty-one lesions comprised the left main coronary artery (LMCA). On QCA, the median of proximal and distal MV reference diameters were 3.4 (3.1–3.7) mm and 3.0 (2.5–3.3) mm, respectively, whereas the median of lesion length and diameter stenosis was 10.5 (8.0–16.0) mm and 70 (30–80)%. The median of SB reference diameter was 2.3 (2.0–2.55) mm, SB lesion length 5.0 (3.0 – 10.5) mm, and lesion diameter stenosis 20 (10–70)%.

Table 1. Baseline demographics and clinical characteristics of the study group

Variable	Patient-based
Age, years, mean (SD)	62 (9.7)
Male sex, n (%)	76 (76.0)
Previous MI, n (%)	47 (47.0)
Hypertension, n (%)	78 (78.0)
Diabetes mellitus, n (%)	30 (30.0)
Insulin-treated diabetes mellitus, n (%)	8 (8.0)
Current smoker, n (%)	41 (41.0)
Chronic kidney disease (eGFR < 60 ml/min), n (%)	13 (13)
PVD, n (%)	8 (8.0)
History of PCI / CABG, n (%)	54 (54.0) / 4 (4.0)
Clinical presentation, n (%)	
Stable angina / silent ischemia	82 (82.0)
Unstable angina / non-ST-elevation MI	15 (15.0)
ST-elevation MI	3 (3.0)
Left ventricular ejection fraction, %, median (IQR)	60.0 (50–60)
Multivessel disease, n (%)	39 (39.0)

Abbreviations: CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; IQR, interquartile range; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vessel disease; SD, standard deviation

Procedural details

Complete procedural data are presented in Table 2. Lesion pre-dilatation was performed in 90% of procedures, whereas a high-pressure post-dilatation only in 59 patients (59%). A simple approach with single scaffold implantation was applied in 92, whereas the technique with two scaffolds in eight patients: systematic T stenting in two, TAP in five, and crush in one of them. Among 66 patients treated with provisional stenting, scaffold struts were crossed with a balloon towards SB in 20 cases. A potential scaffold deformation was then corrected with FKB (or mini-KB) and POT in eleven cases, whereas in the remaining nine, only POT was applied. All complex procedures were finished

Table 2. Procedure characteristics

Variable	Patient-based
Radial approach, n (%)	78 (78.0)
Guiding catheter 6 F, n (%)	98 (98.0)
Simple technique (single stent used), n (%)	92 (92.0)
Provisional SB stenting	66 (66.0)
Side branch ostial stenting	12 (12.0)
Distal main stenting	14 (14.0)
Systematic T stenting, n (%)	2 (2.0)
TAP, n (%)	5 (5.0)
Crush, n (%)	1 (1.0)
Pre-dilatation, n (%)	90 (90.0)
High-pressure post-dilatation, n (%)	59 (59.0)
POT, n (%)	59 (59.0)
SB post-dilatation, n (%)	20 (20.0)
Ballon diameter, mm, median (IQR)	2.5 (2.0–2.5)
Balloon pressure, atm, median (IQR)	10 (10–15)
MB Scaffold diameter, mm, median (IQR)	3.0 (3.0–3.5)
MB Scaffold length, mm, median (IQR)	18 (18–28)
MB Scaffold implantation pressure, atm, median (IQR)	16 (14–16)
SB Scaffold diameter, mm, median (IQR)	2.5 (2.5–3.0)
SB Scaffold length, mm, median (IQR)	18 (18–28)
SB Scaffold implantation pressure, atm, median (IQR)	16 (14–16)
Final kissing/snuggle, n (%)	19 (19.0)
IVUS / OCT, n (%)	38 (38.0)
Device (scaffold) success (lesion based), n (%)	100 (100)
Procedure success, n (%)	98 (98.0)
Fluoroscopy time, min, mean (SD)	12.2 (8.0)
Contrast use, ml, mean (SD)	157.7 (75.2)

Abbreviations: IVUS, intravascular ultrasound; LAD, left anterior descending; LCX, left circumflex; LMCA, left main coronary artery; OCT, optical coherence tomography; OM, obtuse marginal branch; POT, proximal optimization technique; RCA, right coronary artery; TAP, T, and protrusion; other — see Table 1

with FKB and POT. The median MV scaffold diameter and length were 3.0 (3.0–3.5) mm and 18 (18–28) mm, respectively, with the median implantation pressure of 16 (14––16) atm. In SB, the median scaffold diameter and length were 2.5 (2.5–3.0) mm, 18 (18–28) mm, and the median implantation pressure was 16 (14–16) atm. IVUS was used in six, whereas OCT in thirty-two patients. The device and procedure success rates were 100% and 98%, respectively.

Clinical outcomes

The in-hospital stay was clinically uneventful in all patients. Periprocedural MI was diagnosed in two subjects: as a consequence of SB occlusion in one case and in the course of a septal branch closure in another. An isolated, asymptomatic elevation of troponins more than five times above the limit was observed in one more patient, without any ECG changes. At 30 days, two deaths were observed: one sudden and unexplained death in a 53-year-old male, nine days after ostial LCX stenting (Medina 0,0,1) with a 3.5 × 18 mm scaffold. The second patient died during an ischemic stroke. In another patient, target-vessel MI occurred due to a scaffold thrombosis five days after stenting of the ostial lesion (Medina 0,0,1) in an obtuse marginal branch with a 2.5 × 18 mm scaffold (Figure 1). Final OCT examination during baseline procedure revealed scaffold protrusion into MV, with no signs of any strut fracture (Figure 1C). All three patients remained on aspirin and clopidogrel during the events. In a long-term follow up three more cases of cardiac death and four MI were observed. Target vessel failure was finally diagnosed in 5 patients

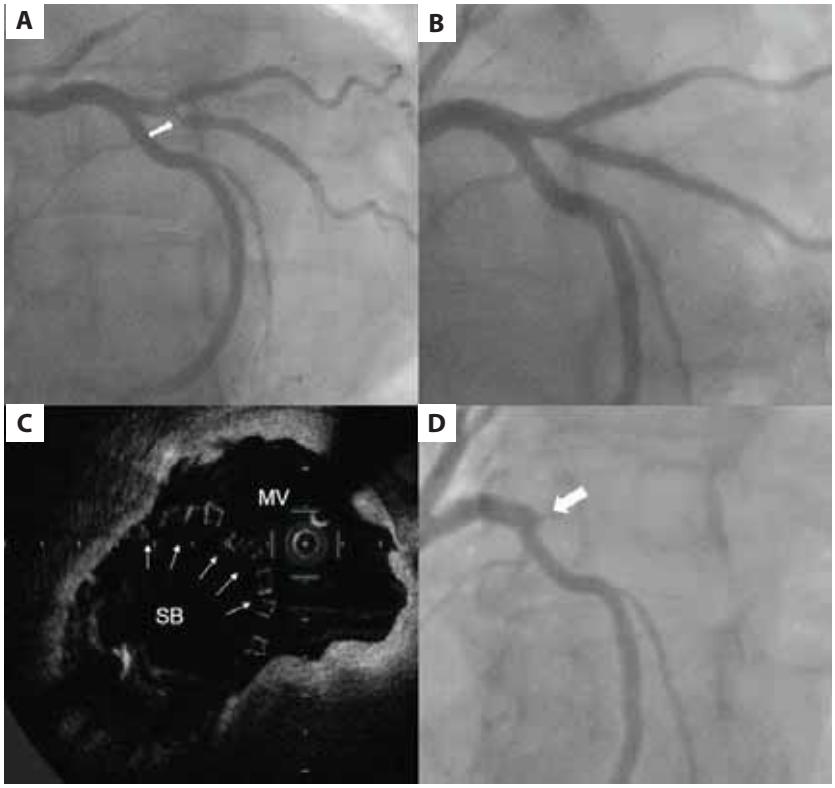

Figure 1. A case of side branch ostial stenting with BVS. **A.** Medina 0,0,1 lesion in the obtuse marginal branch. **B.** Final result after BVS 2.5 × 18 mm implantation and FKB with two 2.5 balloons. **C.** OCT image showing scaffold protrusion into MV. **D.** MV thrombosis five days after the procedure

Abbreviations: BVS, bioresorbable vascular scaffold; FKB, final kissing balloon; MV, main vessel; OCT, optical coherence tomography

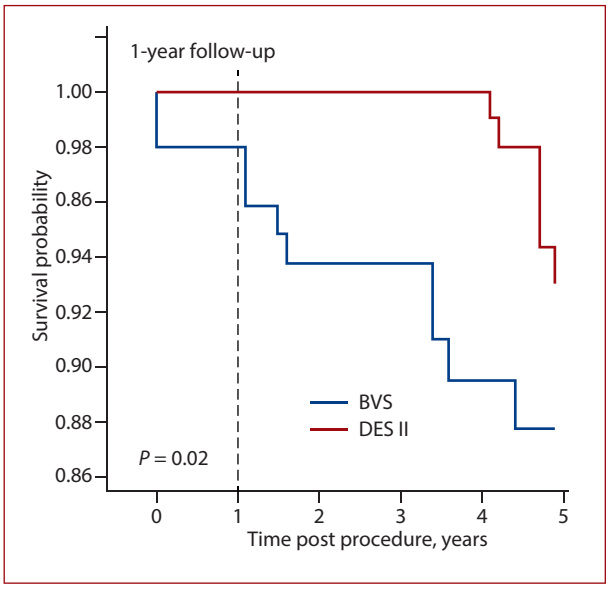

Figure 2. Kaplan-Meier curves for overall survival

Abbreviations: DES, drug-eluting stent; other — see Figure 1

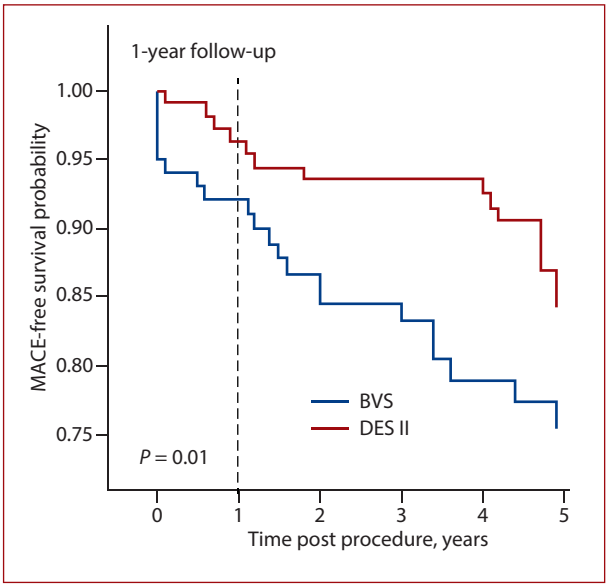

Figure 3. Kaplan-Meier curves for MACE

Abbreviations: MACE, major adverse cardiac events; other — see Figure 1

within 30 days after the procedure and 15 patients in the long-term follow-up. Data on 30-day and long-term clinical outcomes are presented in Table 3.

Angiographic follow-up

The angiographic follow-up, 12 months post the index procedure, was scheduled for all patients. Ultimately, the examination was performed in only 68 of them, mainly due to patients withdrawing their consent. The median time of coronary angiography was 372 (183–412) days. Among patients who underwent coronary angiography, the incidence of scaffold restenosis was 11.8% (8 patients), of which 7 occurred in the main vessel (treated with provisional stenting technique) and one in the side branch (treated with SB ostial stenting technique). There was no vessel occlusion in the implanted BVS. In 26 patients, OCT was performed, which showed the average main vessel diameter stenosis of 15 (10–22.7)% and late lumen loss (LLL) of 0.68 (0.18) mm.

Table 3. Clinical outcomes

Variable	30 days	Long-term
Death, n (%)	2 (2.0)	11 (11.0)
Cardiac death	1 (1.0)	4 (4.0)
Non-cardiac death	1 (1.0)	7 (7.0)
Any MI, n (%)	2 (2.0)	5 (5.0)
Target vessel MI, n (%)	1 (1.0)	5 (5.0)
TVR, n (%)	1 (1.0)	11 (11.0)
TVF, n (%)	5 (5.0)	15 (15.0)
MACE, n (%)	7 (7.0)	26 (26.0)
Scaffold thrombosis, n (%)	2 (2.0)	2 (2.0)
Definite	1 (1.0)	1 (1.0)
Probable	1 (1.0)	1 (1.0)
Ischemic stroke, n (%)	2 (2.0%)	4 (4.0%)

Abbreviations: MACE, major adverse cardiac events; TVF – target vessel failure; TVR, target vessel revascularization; other — see Table 1

Comparison with patients having bifurcation lesions treated with the second-generation DES (historical group)

The baseline demography and clinical characteristics of both study groups are presented in Supplementary material, *Table S2*. There was no significant difference in age, sex, and major cardiovascular risk factors. The Gehan-Breslow-Wilcoxon test revealed that bifurcation treatment with BVS was associated with significantly higher 5-year mortality compared to DES II ($P = 0.02$) (Figure 2). Moreover, the stratified analysis showed significantly higher mortality in the BVS group compared to the DES II group in patients with arterial hypertension ($P = 0.02$), diabetes mellitus ($P = 0.03$), after myocardial infarction ($P = 0.01$), with multivessel coronary artery disease ($P = 0.004$) and left main disease ($P = 0.01$).

Moreover, MACE was also observed significantly more often in the ABSORB BVS group compared to DES II in the long-term follow-up (26.0% vs. 14.0%; $P = 0.03$) (Figure 3). The stratified analysis revealed a significantly higher rate of MACE in the BVS group compared to the DES II group in patients with hypertension ($P = 0.01$), previous myocardial infarction ($P < 0.001$) and a history of PCI ($P = 0.01$), multi-vessel coronary disease ($P = 0.009$), left main disease ($P < 0.001$), and moderate/severe calcifications ($P = 0.02$). In addition, a multivariable logistic regression analysis was included in the supplement to identify independent risk factors for death and MACE (Supplementary material, *Tables S3, S4*).

DISCUSSION

We reported on the clinical outcomes of one hundred patients with bifurcation lesions treated with the implantation of the ABSORB BVS. Our population comprised medium-risk

patients, mostly with SCAD and preserved left ventricle function, with simple or moderately complex bifurcation lesions. Combined MV and SB involvement was found in only 27% of cases, and the majority of them were treated with single scaffold deployment. Given the nature of lesions, the early and long-term results were acceptable and comparable to previous studies [19, 20]. Overall mortality was 11% during the entire follow-up period. Four patients died of cardiovascular causes, all of them within a year of the procedure. The design of ABSORB BVS has been evaluated in multiple trials, mostly with a low number of patients and relatively simple lesions. None of them was dedicated to bifurcation lesions. On the contrary, most patients with such lesions were excluded. The only study reporting on "real world" patients treated with BVS was the GHOST-EU registry [21]. A total of 1189 patients were enrolled, including more than 300 subjects with bifurcation lesions. Although no distinct analysis for this lesion subset was performed, bifurcation lesion was not found to be an independent predictor of target lesion failure (TLF). At six months, the rate of cardiac death was 1.0%, target vessel myocardial infarction 2.0%, TLR 2.5%, and TVR 4.0%. The cumulative incidence of definite/probable ST was 1.5% at 30 days and 2.1% at six months. Importantly, 16 out of 23 cases of ST occurred within 30 days after index PCI. GHOST-EU was the first study, showing the higher rate of ST, mostly clustered within 30 days after the procedure. This observation was consistent with our results, where both cases of ST occurred within the first days after the procedure.

Two major issues should be addressed regarding scaffold thrombosis: the learning curve and appropriate antiplatelet therapy. The retrospective studies highlighted the importance of predilatation, proper sizing of the scaffold (optimally based on intracoronary imaging), and post-dilatation, summarizing all components as a pre-dilatation, sizing and post-dilatation (PSP) technique. In May 2015, a group of European experts published a consensus that contained recommendations on the PSP technique as the optimal technique of BVS implantation [22]. The effectiveness of the above strategy was confirmed in the MICAT registry (the Coronary Slow-flow and Microvascular Disease Registry), in which the optimization of BVS implantation was associated with a significant reduction of in-scaffold thrombosis [23]. Since 2015, we have modified our BVS implantation technique according to the PSP technique. In all subsequent patients, pre-dilation and the high-pressure scaffold post-dilatation with the use of a non-compliant balloon, 0.25–0.5 mm larger than the scaffold diameter, was performed. In none of such cases, did we find any signs of strut fractures on the intravascular examination. In line with the recommendations, we have also significantly increased the use of OCT to select the scaffold size and optimize the procedure.

Since thick struts malapposition increases stent thrombogenicity [24], we changed scaffold sizing according to proximal MV reference diameter, using lower inflation pressure (10–14 atm) to avoid major carina shift and SB flow compromise. In case of flow compromise, a scaffold strut could have been easily crossed with a balloon in the majority of patients. Careful FKB was safely performed, but required low inflation pressure and minimal protrusion of SB balloon. Most of the FKB cases in our group were controlled with OCT, and we found no signs of scaffold damage. If SB stenting was needed, a scaffold or metallic DES could be used. The T or TAP technique was preferable. In the whole analyzed group, only one patient required DES that was implanted into the side branch using the TAP technique. We did not observe any complications with such an approach. Importantly, in each case of the two-stent technique, the use of imaging (preferably optical frequency domain imaging, OFDI) was highly recommended, to optimize the outcomes of the procedure and, during the control coronary angiography, to confirm the bioresorption process [25].

Interestingly enough, both cases of scaffold thrombosis occurred in patients with Medina 0,0,1 lesions after ostial SB stenting. This technique implies some scaffold overhang into the MV lumen. Due to scaffold elastic recoil, such protrusion may not be fully corrected with FKB. Hence, we cannot recommend using a scaffold for such lesions.

Based on our experience, at some point in the study, we decided to modify antiplatelet treatment after BVS implantations [26]. Since December 2014, we have recommended ticagrelor instead of clopidogrel for at least three months after the procedure. Following that change, we have not observed any more scaffold thrombosis in patients treated with BVS in our institution. It seems, therefore, that both the implantation technique and optimal DAPT significantly contribute to improving the safety of PCI with the use of BVS.

Comparing ABSORB BVS with the historical DES II group using the Gehan-Breslow-Wilcoxon test showed significantly higher mortality in the ABSORB group. The data also showed a significantly more frequent occurrence of MACE in the ABSORB BVS group compared to DES II. The presence of comorbidities increased both the risk of death and MACE.

The ABSORB II study compared ABSORB BVS with its everolimus-eluting metallic counterpart, Xience, but also excluded complex lesions such as bifurcation, CTO, and LMCA [27]. In a 3-year observation, device-orientated composite endpoint (DoCE) occurred significantly more often in the ABSORB BVS group, mainly due to the increased frequency of myocardial infarction associated with the treated vessel. Moreover, the expected improvement in vasomotor function was not demonstrated, and the late vascular lumen loss was significantly greater in the ABSORB group. The end of the ABSORB BVS technology was brought by the results of a 3-year follow-up of the randomized multicenter ABSORB III study, which compared ABSORB with Xience stents [28]. A 3-year follow-up revealed a higher incidence of the primary endpoint (cardiac death, target

vessel myocardial infarction, repeat revascularization due to ischemia) in the BVS group compared to the EES (13.4% vs. 10.4%; $P = 0.06$). However, the greatest concern was the significantly higher risk of stent thrombosis after BVS implantation compared to the EES (2.3% vs. 0.7%; $P = 0.01$).

The unfavorable results of studies with ABSORB BVS ™ prompted the European Society of Cardiology to change the recommendations for using bioresorbable scaffolds to class III, which was associated with their withdrawal from everyday clinical practice and allowing implantation only as part of research [29]. However, due to the potential benefits of BVS, the development of this technology is still ongoing. The current direction of research is focused mainly on the reduction of biodegradation time and struts thickness, which largely determines the healing process. Undoubtedly, all bioresorbable technologies require further intensive research, and the experience gained from very long observations of the use of ABSORB BVS ™ is a very valuable source of knowledge, setting the direction for the improvement of the future platforms.

A major limitation of the study is a nonrandomized, observational, single-center design with a small number of patients. The angiograms were not reviewed by the central angiographic core lab. Patients' selection might also play a role, with less complex lesions having been favored for enrolment. Clinical results were compared with a historical group of patients treated with second-generation DES.

CONCLUSIONS

Stenting of coronary bifurcation lesions of low-to-moderate complexity with bioresorbable everolimus-eluting scaffolds was feasible with good acute performance and acceptable results. However, the risk of death and major adverse cardiovascular events was higher as compared with the second-generation drug-eluting stents, especially in patients with comorbidities and multivessel or left main disease. In the future, the possible widespread use of new generation bioresorbable scaffolds will require careful clinical evaluation also in complex coronary lesions.

Supplementary material

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

Article information

Conflict of interest: Maciej Lesiak has received payments as an individual for advisory board and speaker's honoraria from Abbott Vascular, AstraZeneca, Biotronik, Boston Scientific, and Tryton Medical. Stefan Grajek has received payments as an individual on the advisory board and speaker's honoraria from Astra-Zeneca, Servier, Pfizer, Sandoz, Adamed, and Polpharma. Aleksander Araszkiewicz has received payments as an individual for the advisory board and speaker's honoraria from Abbott Vascular. None of the other authors has any conflicts of interest to declare.

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Survival analysis of patients with acute coronary syndrome receiving comprehensive coordinated care after myocardial infarction (KOS-Zawał)

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ABSTRACT

Background: This study aimed to analyze survival rates among patients with acute coronary syndrome (ACS) covered and not covered by the National Comprehensive Care after Myocardial Infarction (KOS-Zawał) program.

Methods: A total of 179 972 patients after myocardial infarction (MI) were enrolled in KOS-Zawał program between October 2017 and March 2020 and were included in the comparative analysis with survival analysis. A group of 24 496 (13.61%) patients received KOS-Zawał services, while a group of 155 476 (86.39%) were not covered by the KOS-Zawał program. The time points for observation of the incidence of death were set at 30, 180, and 365 days from the end of the first hospitalization.

Results: There was a lower incidence of death in favor of the KOS-Zawał group relative to the non-KOS-Zawał group both in hospital and at 30, 180, and 365 days after the end of hospitalization, respectively: 0.19% vs. 6.55%; 0.80% vs. 8.39%; 2.92% vs. 10.74%; and 6.35% vs. 13.40%. Survival analysis revealed a statistically significantly lower (P <0.0001) probability of death in the KOS-Zawał group compared with the non-KOS-Zawał group. Also, logistic regression analysis confirmed that patients in the KOS-Zawał group had a significantly lower risk of death than those in the non-KOS-Zawał group (odds ratio, 0.710; 95% confidence interval, 0.554–0.908; P = 0.007).

Conclusions: The KOS-Zawał comprehensive care program reduces the risk of death in the first year after MI by 29%. There are indications of a biased interpretation of the data due to the initial better clinical status of post-MI patients covered by the KOS-Zawał program.

Key words: acute coronary syndrome, KOS-Zawał limitations**,** KOS-Zawał program, mortality risk, myocadiac infarction

INTRODUCTION

Acute coronary syndrome (ACS) is a broad term that encompasses ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), and unstable angina (UA). These events are frequent in Poland and worldwide [1]. In 2019, 1 246 700 people with a principal diagnosis of ischemic heart disease (I20-I25 according to the ICD, International Classification of Diseases) were provided with healthcare services in Poland. As many as 228 100 of these patients had to be hospitalized. Medical care was mainly required for those with chronic ischemic disease. However, it can be noted that between 2014 and 2019, the percentage of patients who received services due to a diagnosed ACS increased. According to the information on publicly funded benefits, 102 700 people with the diagnosis of ACS were hospitalized in 2019 [2].

In 2019, the reimbursement value of health services provided in Poland due to ACS amounted to about 49% of the value

WHAT'S NEW?

Despite significant advances in the diagnosis and treatment of cardiovascular disease, mortality from myocardial infarction (MI) remains a major challenge for modern cardiology. The implementation of a nationwide program of comprehensive coordinated care after myocardial infarction (KOS-zawał) was expected to result in a longer life expectancy for patients. Our study showed that patients in the KOS-Zawał group were significantly less likely to die than those in the non-KOS-Zawał group. Promising results were presented, showing that the KOS-Zawał program reduces the risk of death for patients after MI by 29%. A potential limitation of the KOS-Zawał program regarding a biased interpretation of results was also pointed out, due to the possibility that patients in a better clinical condition at baseline, presenting with a more favorable prognosis after MI, may have been eligible for the KOS-Zawał program.

of all services (962.7 million PLN) to treat ischemic heart disease (IHD). Compared to 2014, these benefits increased by approximately 6%. ACS inpatient costs (I20.0, I21 by ICD) accounted for 61.4% of total IHD inpatient costs in 2019. As hospitalization costs amounted to 93% of the funds devoted to IHD, one may conclude that hospital treatment of myocardial infarction (MI) consumes a significant amount of money and shows an upward trend [2].

Special attention should be paid to the unfavorable trend of mortality within 12 months of 10.1% of patients who were discharged from health care facilities after acute coronary syndrome. The reasons for such a significant percentage of out-of-hospital mortality are considered to include patients' failure to make beneficial lifestyle modifications, failure to adhere to therapeutic recommendations, and difficult or insufficient access to specialized cardiac care [3].

Thanks to the development of modern diagnostics and treatment of cardiovascular diseases, including interventional cardiology techniques, a significant decrease in in-hospital mortality has been observed in Poland in recent years. Unfortunately, despite this, annual mortality after MI treated with interventional therapy (i.e. the most effective of all currently used methods) exceeds 12% [4]. This is why it became so important to implement the KOS-Zawał program, which is comprehensive care after myocardial infarction aiming to reduce death and disability due to heart failure and to enable rapid recovery and return to work [5]. Taking into account the causes of morbidity and mortality of patients after MI in Poland, the team of experts from the Polish Cardiac Society and the Agency for Health Technology Assessment and Tariffication developed an innovative concept of organization of post-MI care in Poland [6]. The experts proposed a model of coordinated care under which patients after MI are provided with easier access to cardiac surgical treatment, cardiac rehabilitation, and specialist cardiac care.

The proposed KOS-Zawał concept was eventually included in the regulations of the Minister of Health and Ordinances of the President of the National Health Fund (NFZ) and was implemented in Poland in the fourth quarter of 2017 as coordinated care after MI. The KOS-Zawał program is characterized in the NFZ reporting data by code 03.4100.500.02. Services under this scope started to be reported in October 2017 [7].

The primary objectives of developing and implementing the new healthcare organization were to improve the quality of medical care, increase patient satisfaction, and reduce the risk of subsequent cardiovascular events. A particularly important goal was to prolong the life of patients after MI by increasing the frequency and speed of full myocardial revascularization, increasing the frequency and speed of implantation of implantable devices (if indicated), increasing access to cardiac rehabilitation programs, especially those performed on an outpatient basis, facilitating access to cardiac consultations and reducing delays in the execution of individual procedures [8].

The presented study aimed to compare the survival of patients with acute coronary syndrome included in the comprehensive care after MI (KOS-Zawał) compared with patients not included in this program.

METHODS

Study design and participants

The described data were collected and reported by the National Health Fund (NFZ). Data in the comprehensive care after MI (KOS-Zawał) started to be collected and reported from October 2017.

The present study analyzed the data from 2017 to 2020 on 182 526 patients with acute coronary syndrome and other cardiovascular diseases, among whom there were 155 476 (85.18%) patients treated without the KOS benefit and 27 050 (14.82%) patients who were included in the KOS-Zawał program. The control group consisted of patients treated without the KOS-Zawał benefit, among whom there were 99 769 (64.2%) men and 55 707 (35.8%) women. In contrast, the study group consisted of patients covered by the KOS-Zawał program, which included 18 514 (68.4%) men and 8 536 (31.6%) women (Table 1).

The number of patients by year and quarter of initiation of treatment under the KOS-Zawał program is presented in Supplementary material, *Table S1*. A cross-section of the place of residence of patients who received KOS-Zawał benefits between October 2017 and March 2020 is shown in Supplementary material, *Figure S1*. The highest

Table 1. Demographic characteristics of patients covered by the KOS-Zawał benefits

Sex	N	Age, year, mean (SD)	Age group, years									
			<44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–84	>85
Male	18 514	64 (10.8)	5%	5%	9%	14%	20%	20%	12%	8%	5%	2%
Female	8 536	69 (10.7)	2%	3%	5%	9%	15%	20%	16%	13%	12%	6%

proportions of patients treated under the KOS-Zawał benefit came from the Silesian, Lower Silesian, and Lublin voivodeships.

Characteristics of treatment modules

The KOS-Zawał program provides patients with access to comprehensive cardiac rehabilitation, which includes treatment in four treatment modules. Module I is the treatment of the acute phase of MI (invasive treatment of ACS, angioplasty, interventional diagnostics of ACS, arterial bypass grafting, conservative treatment, follow-up visit within 14 days after discharge). Module II includes cardiac rehabilitation in an inpatient setting, in a center or day unit, and telerehabilitation. Module III includes electrotherapy (i.e., implantation of a cardiac assist device), and Module IV includes specialized cardiac care during the 12 months following ACS. Module IV concludes with a balance-of-care approach, which is the performance of laboratory tests and specialized counseling that includes a summary of the patient's clinical condition and/or the issue of a certificate of fitness to work.

Statistical analysis

Statistical analysis was conducted using R software version 3.6.1 (R Foundation, Vienna, Austria). Descriptive data were presented as the number of observations and percent or means and standard deviations (SD). The distribution of data was analyzed by the Kolmogorov-Smirnov test and the equality of variance by Levene's test. The χ^2, Student's t- and t-Welch tests were used for comparison of data. Comparative survival analyzes were performed by the Log-Rank test for two groups and the Log-Rank test for more than two study groups. Survival analyzes were shown using Kaplan-Meier survival curves.

To verify the impact of independent variables (demographic parameters, clinical parameters describing the patients' treatment history, the type of treatment applied, and the completion of cardiac rehabilitation within 60 days from the date of hospitalization, participation in the KOS-Zawał program) on the annual mortality of patients, a statistical model was created. Modeling was carried out in two stages. In the first stage, the propensity score matching (PSM) method was used, in which each patient covered by the KOS-Zawał program was matched with at least one patient not covered by KOS-Zawał but identical in terms of other independent variables. In the second stage, a logistic regression analysis was performed, where the dependent variable was the patient's death within 365 days from the date of the onset of hospitalization for MI. *P*-values <0.05 were assumed as statistically significant.

Table 2. Provision of benefits under the different modules of KOS-Zawał

Module	Number of patients, n (%)
Module I	23 724 (99.5)
Module IV	18 523 (77.7)
Module II	17 199 (72.2)
Module III	448 (1.90
Total	23 837 (100)

RESULTS

Clinical characteristics of patients receiving KOS-Zawał benefits

The structure of principal diagnoses at a patient's first KOS-Zawał hospitalization is shown in Supplementary material, *Table S2*, while *Table S3* presents the structure of comorbid diagnoses at the first hospitalization of patients qualified for the KOS-Zawał program.

The highest proportion of patients included those with acute MI (Supplementary material, *Table S2*), and the most common comorbidities were primary hypertension and the presence of other cardiovascular implants and grafts (Supplementary material, *Table S3*).

Description of the treatment provided to patients receiving KOS-Zawał benefits

The treatment applied to patients covered by the KOS-Zawał program was analyzed based on the treatment modules used. Table 2 shows data on patients who were treated at least once under a given treatment module (data obtained for n = 23 837). The highest percentage included patients treated under Module I (99.5%), Module IV (77.7%), and Module II (72.2%).

These results are confirmed in Table 3, which presents the variants of use of each module by patients covered by the KOS-Zawał benefit. The highest proportion of patients (64.3%) included those treated under Module I, Module IV, and Module II.

Survival analysis of patients with myocardial infarction

Only patients hospitalized for MI were included in the survival analysis (n = 24 496) and the total number of patients decreased to 179 972 patients (baseline n = 182 526).

Table 3. Options for the use of individual modules by patients covered by the KOS-Zawał service

Module I	Module II	Module III	Module IV	Number of patients (n)	Percentage of patients, %	Deaths within 30 days of first contact under KOS, %	Age, years, mean (SD)
1	1	0	1	15 319	64.3	0.0	64 (10.8)
1	0	0	0	3 839	16.1	4.0	68 (11.4)
1	0	0	1	2 684	11.3	0.0	67 (11.1)
1	1	0	0	1 435	6.0	2.0	66 (11.2)
1	1	1	1	373	1.6	0.0	68 (9.3)
0	0	0	1	53	0.2	0.0	69 (13.2)
1	0	1	1	50	0.2	0.0	69 (8.9)
0	1	0	1	44	0.2	0.0	64 (9.4)
0	1	0	0	15	0.0	0.0	67 (13.2)
1	1	1	0	13	0.0	0.0	69 (12.9)
1	0	1	0	11	0.0	0.0	69 (8.7)
0	0	1	0	1	0.0	0.0	55 (0.0)

Uses KOS-Zawał benefits = 1, does not use KOS-Zawał benefits = 0

The results are presented considering the rate of death within the first 30 days of starting the KOS-Zawał benefit and the age of the patients

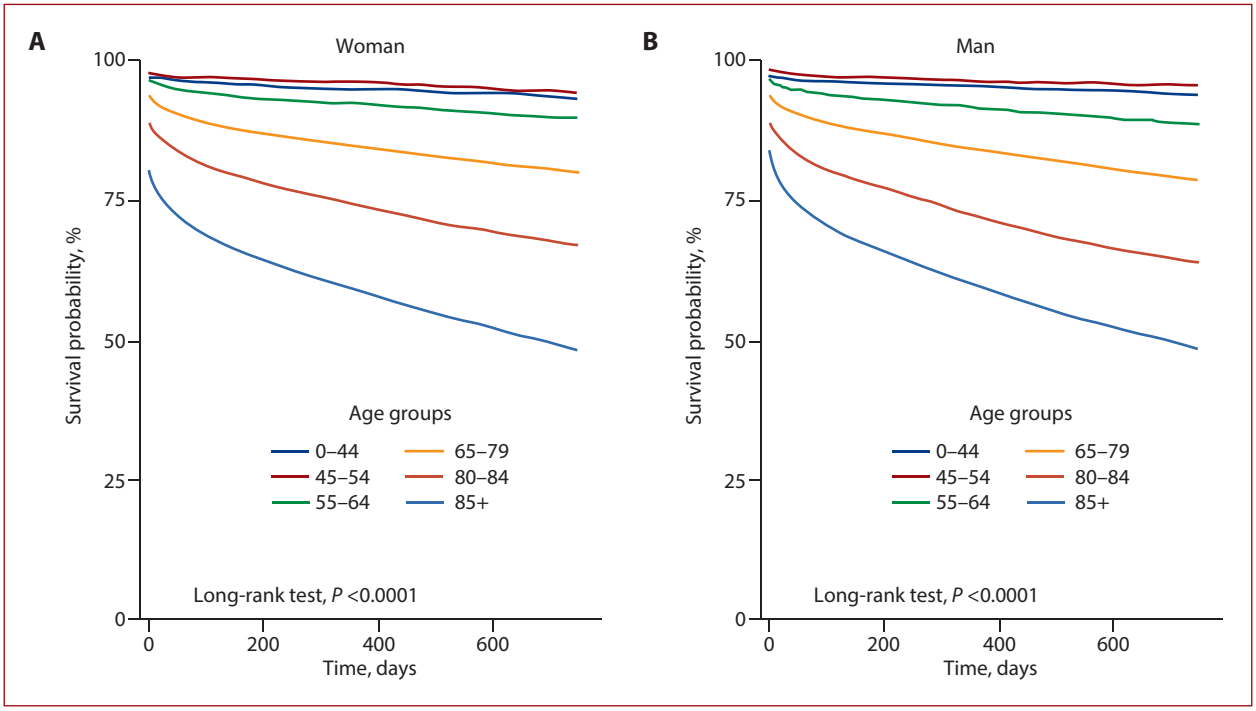

Figure 1. Kaplan-Meier survival curves for the total group of MI patients (n = 179 972) who were divided into two subgroups according to the "sex" parameter and six subgroups according to "age".

Notes: Comparative analysis was performed by the general Log-Rank test for more than two study groups

Figure 1 shows the survival probabilities calculated for the total group of patients (n = 179 972) hospitalized for MI according to sex and age group. It shows that in both male and female groups, the probability of survival significantly decreases with the increasing age of patients (in both cases P <0.0001).

Table 4 presents the results of comparative analyses for 4 time measurements: death in hospital, death within 30 days after hospitalization, death within six months, and death within one year after hospitalization. There were statistically significant higher survival rates for patients covered by the KOS-Zawał program compared with patients not covered by the program in all 4-time intervals.

Survival analysis of patients covered by KOS-Zawał (n = 24 496) by sex and age groups was also performed. There was a significant relationship between increasing age and the probability of death for patients, with men over 85 years of age having a 65% probability of survival and women of the same age having a higher 75% probability of survival (Figure 2).

Table 4. The incidence of deaths of patients who received a benefit due to myocardial infarction between October 2017 and March 2020 in the group of patients covered by the KOS-Zawał benefit and in the group of patients not covered by the benefit

KOS-Zawał / Time of death	Death at hospital, %	Death within 30 days, %	Death within 180 days, %	Death within 365 days, %
Total	6.74 (n = 179 972)	9.19 (n = 179 972)	13.66 (n = 173 783)	19.75 (n = 143 437)
Patients covered by KOS-Zawał benefits	0.19 (n = 24 496)[a]	0.80 (n = 24 496)	2.92 (n = 23 371)	6.35 (n = 16 889)
Patients not covered by KOS-Zawał benefits	6.55 (n = 155 476)	8.39 (n =155 476)	10.74 (n = 150 412)	13.40 (n = 126 548)
P-value	<0.0001	<0.0001	<0.0001	<0.0001

Measurements were made at 30 days, 180 days, and 365 days after the end of the first hospitalization. The number of patients against which the death rate was calculated is given in brackets

[a]The number of patients covered by the KOS-Zawał service is slightly lower than in previous statements because not every patient treated under KOS was hospitalized for a heart attack

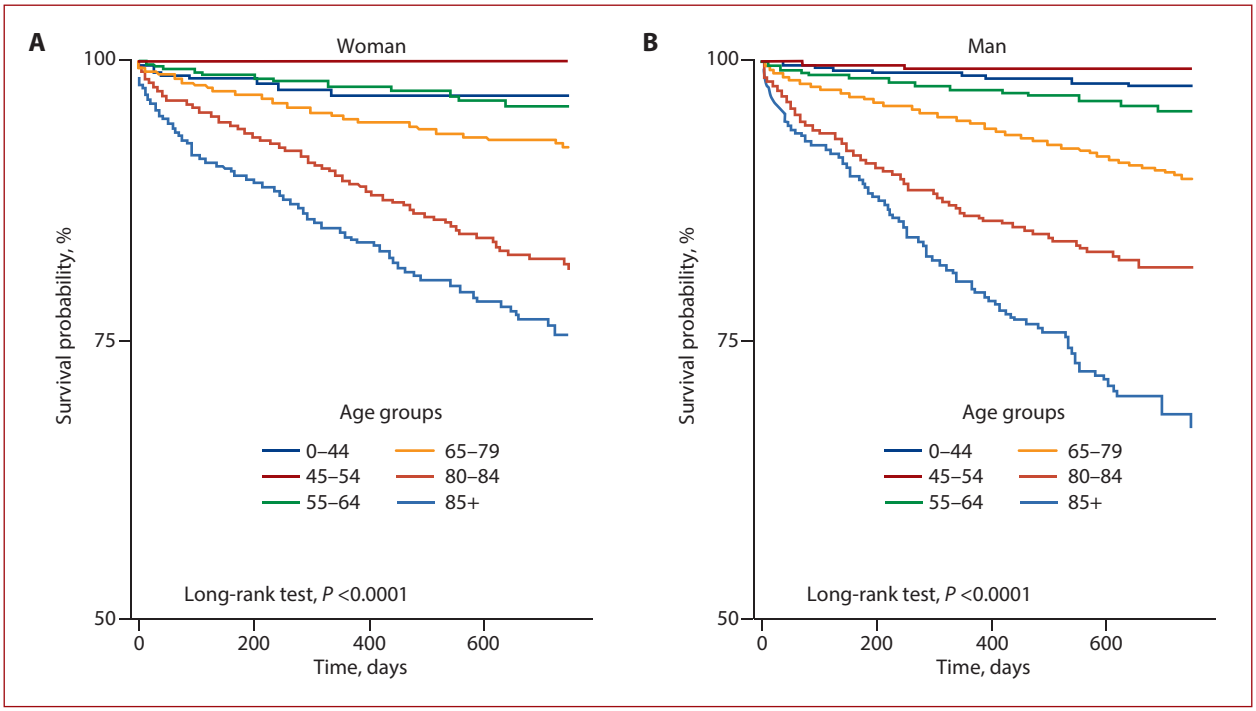

Figure 2. Kaplan-Meier survival curves for MI patients with KOS-Zawał (n = 24 496) by sex who were divided into six subgroups based on age

Notes: Comparative analysis was performed by the general Log-rank test for more than two study groups

Impact of selected independent variables on the mortality risk within 365 days from the date of the onset of hospitalization due to myocardial infarction

In the performed analyses, the number of patients covered or not by the KOS-Zawał program was reduced because the analyzed patient population was restricted to those who survived 60 days from the date of the onset of hospitalization for MI. This selection of the study samples is because one of the explanatory variables was that the patient's cardiac rehabilitation started within 60 days from the date of hospitalization.

Table 5 presents a comparative analysis of demographic parameters, clinical parameters describing the patients' treatment history, the type of treatment applied, and the completion of cardiac rehabilitation within 60 days from the date of hospitalization in patients covered by the KOS-Zawał program and those not covered by the program. It was shown that the frequencies of almost all analyzed parameters (except the variables "renal failure", "cancer," and "COPD") were statistically significantly different in the two study groups.

To determine which of the analyzed variables could be significant predictors of the risk of patient death within 365 days from the date of the onset of hospitalization for MI, logistic regression analysis was performed, and the results are shown in Table 6. Most of the variables studied were predictors of the risk of patient death, especially dialysis treatment (odds ratio [OR], 4.049; *P* <0.001), the presence of cancer as a comorbidity (OR, 2.113; *P* <0.001), and heart

Table 5. Characteristic of selected demographic and clinical variables, and variables describing patient's treatment, type of treatment, and cardiac rehabilitation within 60 days of hospitalization in the model constructed with using propensity score matching (PSM)

Variables	Total population n = 120 974 (100%)	Patients with KOS n = 16 957 (14%)	Patients without KOS n = 104 017 (86%)	*P*-value
Age, years	68.06 (11.6)	65.49 (10.9)	68.49 (11.6)	<0.001
Sex				<0.001
Male	78 355 (64.77)	11 622 (68.54)	66 748 (64.17)	
Female	42 619 (35.23)	5 335 (31.46)	37 269 (35.83)	
Kidney failure	4 549 (3.76)	639 (3.77)	3 911 (3.76)	0.953
Heart failure	17 408 (14.39)	1 901 (11.21)	15 499 (14.90)	<0.001
Hypertension	68 338 (56.49)	9 272 (54.68)	59 050 (56.77)	<0.001
Stroke	1 307 (1.08)	209 (1.23)	1 103 (1.06)	0.049
COPD	6 932 (5.73)	990 (5.84)	5 939 (5.71)	0.510
Diabetes	28 925 (23.91)	3 822 (22.54)	25 099 (24.13)	<0.001
AF and flutter	9 170 (7.58)	1 078 (6.36)	8 082 (7.77)	<0.001
Cancer	6 956 (5.75)	961 (5.67)	5 991 (5.76)	0.632
CABG	302 (0.25)	78 (0.46)	229 (0.22)	<0.001
PCI	10 440 (8.63)	674 (9.87)	8 769 (8.43	<0.001
Dialysis	387 (0.32)	76 (0.45)	312 (0.30)	0.002
MI with STEMI	41 797 (34.55)	6 978 (41.15)	34 856 (33.51)	<0.001
PCI during MI hospitalization	91 977 (76.03)	15 292 (90.18)	76 765 (73.80)	<0.001
CABG during MI hospitalization	1 548 (1.28)	304 (1.79)	1 248 (1.20)	<0.001
Cardiac rehabilitation within 60 days of the start of MI hospitalization	39 631 (32.76)	12 984 (76.57)	26 888 (25.85)	<0.001

Descriptive data were presented as mean (SD) or number (%)

Abbreviations: COPD, chronic obstructive pulmonary disease; AF, atrial fibrillation; CABG, coronary artery bypass grafting; PCI, percutaneous coronary interventions; MI, myocardial infarction; STEMI, ST-Elevation Myocardial Infarction; KOS-Zawał, comprehensive coordinated care after myocardial infarction

Table 6. Logistic regression analysis of prediction of risk of death in the total population of patients with myocardial infarction (n = 120 974)

Variable	OR (95% CI)	*P*-value
Age, years	1.058 (1.055–1.059)	<0.001
Male sex	1.217 (1.161–1.276)	<0.001
Kidney failure	1.334 (1.218–1.460)	<0.001
Heart failure	1.974 (1.868–2.084)	<0.001
Hypertension	0.776 (0.738–0.815)	<0.001
Stroke	1.8 (1.515–2.138)	<0.001
COPD	1.492 (1.379–1.612)	<0.001
Diabetes	1.358 (1.293–1.425)	<0.001
AF and flutter	1.052 (0.982–1.127)	0.149
Cancer	2.113 (1.968–2.268)	<0.001
CABG	1.184 (0.766–1.830)	0.447
PCI	0.899 (0.830–0.972)	0.008
Dialysis	4.047 (3.186–5.137)	<0.001
KOS-Zawał	0.710 (0.554–0.908)	0.007
MI with STEMI	1.123 (1.065–1.184)	<0.001
PCI during MI hospitalization	0.587 (0.559–0.616)	<0.001
CABG during MI hospitalization	0.834 (0.659–1.055)	0.131
Cardiac rehabilitation within 60 days of the start of MI hospitalization	0.345 (0.320–0.371)	<0.001

Abbreviations: OR, odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; AF, atrial fibrillation; CABG, coronary artery bypass grafting; PCI, percutaneous coronary interventions; MI, myocardial infarction; STEMI, ST Elevation Myocardial Infarction; KOS-Zawał, comprehensive coordinated care after myocardial infarction.

failure (OR, 1.974; *P* <0.001). In contrast, the risk of death within 365 days after MI of patients covered by the KOS-Zawał program was significantly lower than in patients not covered by the program (OR, 0.710; *P* = 0.007). The KOS-Zawał comprehensive care program reduced the risk of death in the first year after MI by 29%.

DISCUSSION

The results of studies conducted in Poland before the introduction of KOS-Zawał indicated that patients after MI are not always treated optimally [9]. Often the primary goals of secondary prevention were not achieved. It was indicated that, on average, one year after hospitalization for acute coronary syndrome or myocardial revascularization, 20% of patients smoked, 80% were overweight, 47% had too high blood pressure, and 73% had LDL cholesterol ≥1.8 mmol/l. In addition, one in ten patients did not take any antiplatelet drugs [9].

Among many factors responsible for this situation were insufficient availability of cardiac education and rehabilitation programs and inadequate access to outpatient cardiac care. Coordinated healthcare has become very popular in recent years because it means that healthcare is no longer focused on the provision of individual medical services and procedures but is centered around the patient. Coordinated care providers stop dividing up services and focus on solving a specific health problem. The provider focuses on solving a specific health problem, while the payer finances the whole treatment, rather than its individual stages.

Recently, KOS-Zawał, one of the first and most widely implemented coordinated care frameworks after MI, has also aroused considerable interest in Poland. The results of the program announced in 2020 were very satisfactory: the risk of death from all causes among people receiving care under the program was reduced by around 30%, which can be fully explained by improved access to specialized care, cardiac rehabilitation, as well as other cardiac procedures [10].

A recent study by Jankowski et al. [11] among patients hospitalized for acute MI in Poland between October 1, 2017 and December 31, 2018 shows that the annual all-cause mortality rate was 4.4% among KOS-Zawał participants and 6.0% in the group of patients not participating in the KOS-Zawał program. MI or stroke occurred in 10.6% and 12.0% (P <0.01), while all-cause death or cardiovascular hospitalization occurred in 42.2% and 47.9% (P <0.001) among KOS-Zawał and non-KOS-Zawał participants, respectively.

The results of our study, where a 29% reduction in the risk of death after MI was achieved (OR, 0.710; 95% confidence interval [CI], 0.554–0.908; P = 0.007), correspond with the results of the study by Jankowski et al. [10, 11].

It is also important to note that the care provided under the KOS-Zawał program is very well evaluated by patients. According to 96% of participants receiving care under this program, their health has benefited, and 99% thought that the KOS-Zawał program provided them with a sense of security [12]. The system of care for patients after MI, implemented at the end of 2017, ensures continuity of care for 12 months after discharge from the hospital, makes the timing of invasive procedures independent of administrative requirements, reduces delays in procedures, and allows the quality of medical care to be assessed.

Limitations

The KOS-Zawał program has undeniable clinical benefits for patients after MI, cardiovascular events, and stroke, resulting in a lower risk of death and shorter hospitalization. Despite the promising results of the KOS-Zawał program in Poland, which has been running for 4 years, its limitations, which translate into the presented survival analysis results, should be mentioned. Patients qualified for the KOS-Zawał program are those with a better baseline clinical condition and a more favorable prognosis after MI. This fact may contribute to a biased interpretation of the results. Further research on the effects of the KOS-Zawał program should be conducted taking into account baseline patients' characteristics.

CONCLUSIONS

The KOS-Zawał comprehensive and multidisciplinary care program reduces the risk of death in patients after MI by 29%. Although the results of the KOS-Zawał program should be treated with caution, it should be emphasized that it has significant clinical benefits for patients after MI.

Supplementary material

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

Article information

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Right atrial phasic function and outcome in patients with heart failure and reduced ejection fraction: Insights from speckle-tracking and three-dimensional echocardiography

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ABSTRACT

Background: Atrial phasic function can be assessed using speckle-tracking and three-dimensional (3D) echocardiography. The extent and role of right atrial (RA) dysfunction in left-sided heart failure (HF) is incompletely understood. We aimed to characterize RA phasic function in HF with reduced ejection fraction (HFrEF) and to assess its prognostic significance.

Methods: We prospectively enrolled 60 patients with HFrEF and 29 normal controls. RA phasic function was assessed using strain curves derived from speckle-tracking echocardiography and 3D volumetric analysis. Patients were followed for a composite endpoint of cardiac death or rehospitalization for HF.

Results: After a mean follow-up of 19 (9) months, 33 patients reached the primary endpoint. Patients with HFrEF and adverse outcomes showed an impairment of both reservoir, conduit, and booster pump RA function when compared to controls. After adjustment for age, left ventricular systolic and diastolic function, right ventricular systolic function and pulmonary artery pressure, RA maximal and minimal volumes, as well as passive emptying fraction, remained independent predictors of death or rehospitalization (hazard ratio [HR], 3.207; 95% confidence interval [CI], 1.288–7.984; $P = 0.012$; HR, 2.362, 95% CI, 1.004–5.552; $P = 0.049$; and HR, 2.367; 95% CI, 1.066–5.259; $P = 0.034$, respectively).

Conclusion: All three components of RA phasic function are impaired in left-sided HF. 3D RA maximal and minimal volumes, as well as 3D RA passive emptying fraction, are independent predictors of adverse outcomes in HFrEF.

Key words: right atrium, heart failure with reduced ejection fraction, atrial phasic function, atrial strain, 3D atrial volumes

INTRODUCTION

Both atria are highly dynamic chambers, with three mechanical functions which are related to the phases of the cardiac cycle: a reservoir function, serving as a storage for venous return during the ventricular systole; a conduit function, passively transferring the blood to the ventricle during the early ventricular diastole; and a booster pump function, actively forcing the blood into the ventricle during the late ventricular diastole [1]. Left atrial (LA) dysfunction is a well-established predictor of adverse outcomes in various clinical conditions [2–6], particularly in heart failure (HF) with either reduced or preserved ejection fraction (EF), and LA reservoir and contraction strain showed a good correlation with LA pressures [7]. However, the extent of right atrial (RA) dysfunction in HF and its prognostic significance remain to be clarified. Novel techniques such as three-dimensional (3D) and speckle-tracking echocardiography (STE) [8] allow a more refined evaluation of atrial phasic function.

WHAT'S NEW?

Right atrial geometry and function can be assessed with modern echocardiographic techniques such as speckle-tracking and three-dimensional (3D) echocardiography, but the role of this chamber in left-sided heart failure has been mostly neglected. In our study, we evaluated the morphology, function, and prognostic significance of the right atrium (RA) in patients with heart failure and reduced ejection fraction (HFrEF). We found that RA reservoir, conduit, and booster pump functions are all impaired in left-sided heart failure and that 3D RA maximal and minimal volumes, as well as 3D RA passive emptying fraction, are independent predictors of cardiac death and rehospitalization in HFrEF.

This study aimed to characterize the RA phasic function in HF with reduced EF (HFrEF), using 3D echocardiography and two-dimensional (2D) longitudinal strain derived from STE, and to assess the prognostic role of RA remodeling and mechanism in patients with HFrEF.

METHODS

Study population

We prospectively screened eighty-five consecutive outpatients with HFrEF who were referred to our echocardiography department between July 2018 and December 2018. The diagnostic of HFrEF [9] was based on the following criteria: symptoms and/or signs of HF and left ventricular (LV) EF <40% measured by the 2D Simpson biplane method. Exclusion criteria were atrial fibrillation or other significant arrhythmias which would have hampered 3D acquisitions (n = 9); a poor acoustic window, which would have made echocardiographic measurements unreliable (n = 7); inability to hold the breath (n = 3); the presence of comorbidities with life expectancy less than one year (n = 3); and significant respiratory diseases such as COPD (n = 2), and obstructive sleep apnea (n = 1). Sixty patients were thus eligible to form the final study population. They were clinically and hemodynamically stable, with no change in diuretic dose for at least 2 weeks before enrollment. Twenty-nine subjects with similar age and sex, referred for echocardiographic evaluation between July 2018 and December 2018, with no signs/ symptoms of HF, no structural heart disease, and normal left ventricular ejection fraction (LVEF) at echocardiography formed the control group. Recorded clinical data included cardiovascular risk factors, arterial blood pressure, and the New York Heart Association (NYHA) class, as well as brain natriuretic peptide (BNP) levels, when available. The study protocol complied with the Declaration of Helsinki, and it was approved by the ethics committee of our hospital; all participants provided written informed consent.

Echocardiography

An experienced sonographer performed 2D and 3D echocardiographic acquisitions according to current international recommendations [10], using a Vivid E9 (GE Vingmed, Horten, Norway) ultrasound machine equipped with a 2.5 MHz 2D matrix array transducer and a 4V probe. Offline data analysis was done using dedicated software (EchoPAC BT 12).

RA transversal diameter and RA area were measured at end-systole in the apical 4-chamber view. For 2D RA strain, we selected the apical 4-chamber view in which the free wall of the RA was best visualized. We performed high frame rate acquisitions (50–70 frames per second), and we used vendor-specific software originally designed for the LV (EchoPAC — Q Analysis package). The endocardial border of the RA was manually traced, beginning and ending at the tricuspid annulus, and the width of the region of interest (ROI) was manually adjusted to include the whole endocardium, but not the pericardium, as recommended [11]. A visual revision was performed, and readjustments of the ROI were done when needed. The zero-strain reference point was set at the time of the QRS complex (end-diastole) [11]. The software automatically divided the RA wall into six segments and provided an averaged strain curve of these segments, which was used to measure the reservoir RA strain (RASr), measured as the maximal longitudinal displacement at end-systole (having a positive value), and the contraction RA strain (RASct), measured as the difference between strain at ventricular end-diastole and strain at the time of atrial systole (having a negative value, as recommended [11]) (Figure 1).

Similarly, we traced the right ventricular (RV) endocardial border to measure RV strain, while the software divided the RV free wall and the interventricular septum (IVS) into three segments each, providing a six-segment model. The global longitudinal strain of the RV (GLS-RV) was measured as the average of the six segmental values, and the longitudinal strain of the RV free wall (RVFW-LS) as the average of the three segmental values of the free wall. The severity of the tricuspid regurgitation (TR) was graded using qualitative Doppler criteria, such as color flow jet area and the shape and density of the TR jet envelope [12]. Pulmonary artery systolic pressure (PASP) was estimated using the sum of the peak TR gradient — obtained from the continuous-wave Doppler spectrum of the TR jet — and the estimated RA pressure, based on the inferior vena cava (IVC) diameter and respiratory changes [10].

For 3D RA volumes, we used six-beat full-volume acquisitions from the apical 4-chamber view, with electrocardiographic gating during breath holding and 8–22 frames per second. The pyramidal volume of the RA was displayed in

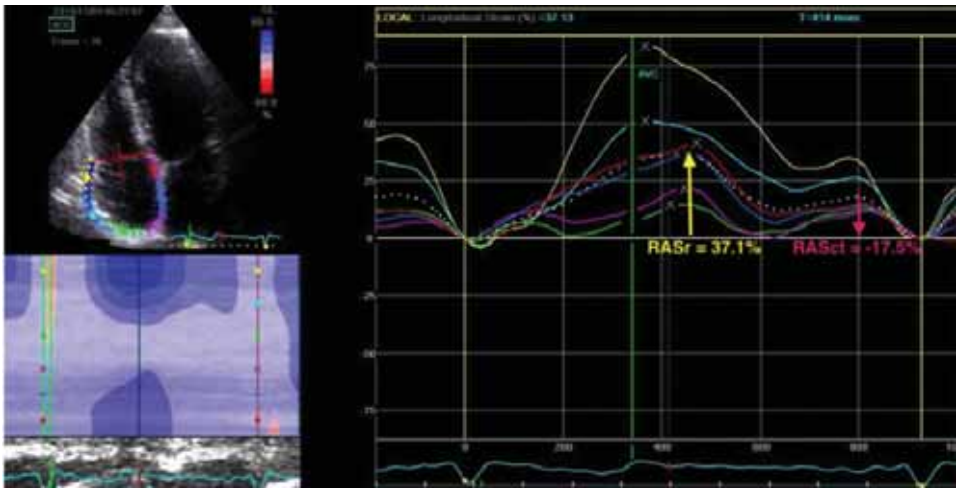

Figure 1. Measurement of RA strain using STE in the apical 4-chamber view. The six colored curves represent strain curves for six different segments of the RA. The dotted curve represents the average strain which was used to measure RAS_r (having a positive value) and RAS_{ct} (having a negative value)

Abbreviations: STE, speckle tracking echocardiography; other — see Table 1

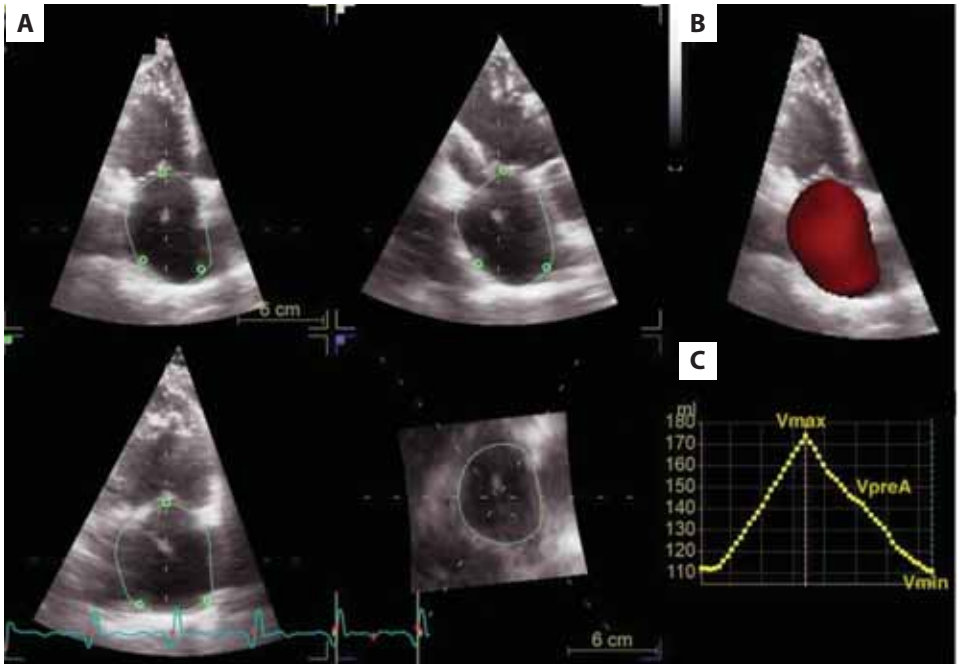

Figure 2. 3D assessment of the RA. Tracking of the RA border is manually readjusted in longitudinal and transverse views (**A**) to determine the 3D RA reconstruction superimposed on the greyscale 3D data set (**B**). The time-volume curve (**C**) depicts RA volume changes during the cardiac cycle and allows measurement of V_{max}, $V_{preA,}$ and V_{min}

Abbreviations: see Table 1

three orthogonal long-axis and one short-axis plane. The RA plane was tilted and translated to have the long axis of the RA in the centerline, and manual landmarks were set in the apical views, two markings at the tricuspid annulus, and one marking at the base of the RA in each plane. The software automatically reconstructed the 3D endocardial surface of the RA — which was manually readjusted if needed — and provided the RA minimum volume (RAV_{min}), at ventricular end-diastole, RA preA volume (RAV_{preA}), at the peak of the P wave on ECG, and RA maximum volume (RAV_{max}), at ventricular end-systole (Figure 2), which were all indexed for body surface area. From these volumes, we calculated:

- The total emptying volume (EV), as the difference between RAV_{max} and RAV_{min}, reflecting RA reservoir function;
- The passive EV, as the difference between RAV_{max} and RAV_{preA}, reflecting RA conduit function;
- The active EV, as the difference between RAV_{preA} and RAV_{min}, reflecting RA booster function;
- The corresponding emptying fractions (EmF): the total EmF = total EV/RAV_{max}, the passive EmF = passive EV/RAV_{max}, and the active EmF = active EV/ RAV_{preA}.

Table 1. Reproducibility of measurements for RA strain and volumes

Variable	Intraobserver ICC (95% CI)	Interobserver ICC (95% CI)
RAS_r	0.983 (0.933–0.996)	0.975 (0.900–0.994)
RAS_{ct}	0.881 (0.533–0.970)	0.816 (0.312–0.953)
RAV_{max}	0.969 (0.883–0.992)	0.962 (0.859–0.990)
RAV_{min}	0.974 (0.904–0.993)	0.951 (0.825–0.987)
RAV_{preA}	0.968 (0.755–0.993)	0.938 (0.781–0.983)

For abbreviations see text

Abbreviations: ICC, intraclass coefficients; RA, right atrial, RASr, reservoir RA strain; RASct, contraction RA strain; RAV_{min}, RA minimum volume; RAV_{preA}, RA_{preA} volume, RAV_{max}, RA maximum volume

We also measured another parameter of RA reservoir function, the 3D RA expansion index (RAEI), which represents the relative RA volume increase during the RA reservoir phase [13] and is calculated as 100 × total EV/RAV_{min}, as previously described for the LA [14].

Reproducibility

To test the intraobserver reproducibility of RA strain, as well as 3D RA volumes, measurements were repeated two weeks apart in 10 randomly selected patients from the study group. To test the interobserver reproducibility, the same 10 patients were measured by a second researcher, blinded to the prior measurements. We then calculated the intraclass coefficients (ICC) in a two-way mixed-effects model. Reproducibility results are presented in Table 1.

Follow-up

Patients were prospectively followed to ascertain the occurrence of any major adverse cardiovascular event (MACE). For the current study, we used a primary composite endpoint of cardiac death and any rehospitalization for HF. Cardiac death was defined as either sudden death, death resulting from an acute coronary syndrome, fatal arrhythmia, or acute exacerbation of HF. Follow-up was conducted for 19 (9) months, through check-up visits, when applicable, or phone contact otherwise.

Statistical analysis

The Kolmogorov-Smirnov test was used to check the normality of distribution. Continuous data were reported as mean and standard deviation or as median and interquartile range, depending on the distribution. Categorical data were displayed as numbers and percentages. To compare patients' characteristics, we used test or Fisher's exact test for categorical variables and the one-way ANOVA or Kruskal-Wallis tests (as dictated by distribution), with a pairwise posthoc Tukey test for continuous variables. Correlations between continuous variables were assessed using Pearson's correlation coefficient.

To compare the accuracy of RA parameters to predict adverse outcomes, receiver operating characteristic (ROC) curves and the respective area under the curve (AUC) were used, while cut-off values were chosen based on the highest sum of sensitivity and specificity. We performed Cox proportional hazards regression to determine the prognostic value of these parameters. Results were reported as hazard ratios (HR) with 95% confidence intervals (CI). The multivariable model was constructed using age and well-established MACE predictors in left-sided heart failure, such as parameters of LV systolic and diastolic function, parameters of RV function, and PASP. Kaplan-Meier analysis was used for event-free survival and the log-rank test was used to compare survival curves. We used the SPSS version 20.0 statistical software package for all analyses. Statistical significance was defined as a two-tailed p-value <0.05.

RESULTS

Clinical characteristics

Mean age was 61 (14) years in the study group and 57 (9) years in the control group ($P = 0.10$), and in both groups, the majority were men (67% and 66%, respectively). Baseline demographic and clinical characteristics are summarized in Table 2. The etiology of HF in the study group was as follows: 28.3% ischemic heart disease, 25% valvular heart disease, 8.3% post-myocarditis, 13.3% familial cardiomyopathy, and 25% idiopathic dilated cardiomyopathy.

During a mean follow-up of 19 (9) months, 33 patients (55%) reached the primary endpoint: there were 7 cardiac deaths (11.7%) and 26 readmissions (43.3%) for exacerbation of HF. There were no significant differences in age, sex, or comorbidities between patients with and without MACE.

Echocardiographic findings

Echocardiographic measurements are summarized in Table 3. The extent of LV systolic dysfunction did not significantly differ between patients with MACE and without MACE. However, patients with MACE had significantly higher LA filling pressures and higher LA maximal volume than patients without MACE, reflecting a more severe diastolic dysfunction. Patients in our study group had RV involvement, as GLS-RV and RVFW-LS were both impaired in comparison with controls, and they were both significantly more impaired in patients with MACE. According to the normal cut-off of -20% for RVFW-LS recommended by guidelines [15], 66% of the patients in the study group had RV longitudinal dysfunction. While PASP was more elevated in the study group, it did not differ significantly between patients with and without MACE. More than mild TR was found in 13 (22%) patients from the study group, 2 of whom (3%) had severe TR.

Right atrial phasic function

In our study group, both RAS_r and RAS_{ct} were impaired while compared with controls; however, only RAS_r differed significantly between MACE and no MACE groups, being significantly more impaired in the former. 3D assessment of the RA showed significantly higher RA indexed volumes (maximal, minimal, and preA) in patients with adverse

Table 2. General characteristics of study participants

Variables	Control group (n = 29)	MACE (n = 33)	No MACE (n = 27)	*P* for all
Age, years, mean (SD)	57 (9)	61 (14)	60 (14)	0.32
Male sex, n (%)	19 (66)	23 (70)	17 (63)	0.86
Comorbidities				
Hypertension, n (%)	13 (45)	21 (64)	20 (74)	0.07
Diabetes mellitus, n (%)	3 (10)	7 (21)	4 (15)	0.50
Smoking, n (%)	15 (52)	10 (30)	18 (67)[c]	0.02
NYHA class				
Class I, n (%)	N/A	0 (0)	2 (7)	0.01
Class II, n (%)	N/A	10 (30)	17 (63)	
Class III, n (%)	N/A	19 (58)	7 (26)	
Class IV, n (%)	N/A	4 (12)	1 (4)	
Medication				
ACE-I/ARB/ARN-I, n (%)	8 (28)	32 (97)[a]	27 (100)[a]	<0.001
β-blockers, n (%)	13 (45)	32 (97)[a]	27 (100)[a]	<0.001
MRA, n (%)	0 (0)	31 (94)[a]	27 (100)[a]	<0.001
Loop diuretic, n (%)	1 (3)	27 (82)[a]	14 (52)[a, d]	<0.001
Aspirin, n (%)	13 (45)	20 (61)	21 (78)[b]	0.04
BNP levels, pg/ml, median (IQR)	88 (68–99)	703 (403–1000)[a]	378 (199–503)[b, d]	<0.001

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

[a]*P* <0.001 vs. control group. [b]*P* <0.05 vs. control group. [c]*P* <0.01 vs. MACE group. [d]*P* <0.05 vs. MACE group

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARN-I, angiotensin receptor neprilysin inhibitor; BNP, brain natriuretic peptide; MACE, major adverse cardiac events; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association

Table 3. Echocardiographic findings

Variables	Control group (n=29)	MACE (n=33)	No MACE (n=27)	*P* for all
Left heart parameters				
LVEF, %	56 (4)	25 (7)[a]	27 (7)[a]	<0.001
Mitral E/A ratio	1.34 (0.30)	1.53 (0.72)	1.05 (0.90) *	0.03
Mitral E/E' ratio	6 (5–8)	16 (11–20)[a]	11 (7–14)[a, d]	<0.001
LA maximal volume, ml	45 (39–54)	79 (67–117)[a]	59 (41–88)[d]	<0.001
Right heart parameters				
RV diameter, mm	34 (32–37)	37 (34–45)[b]	34 (31–37)[f]	0.006
GLS-RV, %	–21.3 (1.4)	–10.5 (4.7)[a]	–13.1 (4.6)[a, e]	<0.001
RVFW-LS, %	–28.7 (2.7)	–12.6 (10.3)[a]	–17.4 (7.4)[a, f]	<0.001
RA diameter, mm	34 (7)	42 (10)[b]	36 (7)[f]	<0.001
RA area, cm^2	15 (13–17)	15 (14–23)	14 (12–16)	0.13
Tricuspid E/A ratio	1.07 (0.27)	1.37 (0.36)[b]	1.09 (0.38)[e]	<0.001
Tricuspid E/E' ratio	6.2 (1.5)	6.3 (3.2)	5.1 (2.4)	0.16
RAS_r, %	29.0 (8.8)	15.6 (9.8)[a]	21.9 (11.9)[c, f]	<0.001
RAS_{ct}, %	–14.1 (5.6)	–8.8 (7.4)[c]	–12.1 (6.5)	0.006
3D RAV_{max} index, ml/m^2	18 (17–24)	27 (22–46)[a]	20 (17–33)[f]	0.002
3D RAV_{min} index, ml/m^2	9 (8–12)	17 (11–32)[a]	12 (8–16)[e]	<0.001
3D RAV_{preA} index, ml/m^2	14 (12–18)	22 (16–38)[a]	15 (13–22)[f]	<0.001
3D Total EV, ml	20 (7)	22 (13)	19 (10)	0.47
3D Total EmF, %	52 (49–56)	38 (26–45)[a]	43 (34–49)[a, f]	<0.001
3D Passive EV, ml	11 (9–15)	9 (6–13)	8 (6–13)	0.36
3D Passive EmF, %	28 (7)	18 (8)[a]	24 (9)[f]	<0.001
3D Active EV, ml	9 (7–11)	8 (5–14)	7 (4–12)	0.26
3D Active EmF, %	32 (8)	21 (11)[a]	24 (11)[b]	<0.001
3D RAEI	110 (22)	61 (29)[a]	79 (37)[a, f]	<0.001
More than mild TR, n (%)	2 (7)	10 (30)[c]	3 (11)	0.03
PASP, mm Hg	21 (19–24)	39 (28–51)[a]	34 (26–41)[a]	<0.001

Data are expressed as mean (standard deviation [SD]) or median (interquartile range [IQR])

[a]*P* <0.001 vs. control group. [b]*P* <0.01 vs. control group. [c]*P* <0.05 vs. control group. [d]*P* <0.001 vs. MACE group. [e]*P* <0.01 vs. MACE group. [f]*P* <0.05 vs. MACE group

Abbreviations: E/A, ratio between early mitral/tricuspid inflow velocity (E wave) and late velocity corresponding to atrial contraction (A wave) derived from pulsed-wave Doppler; E/E', ratio between early mitral/tricuspid inflow velocity E derived from pulsed-wave Doppler and early mitral/tricuspid annulus velocity E' derived from tissue Doppler imaging; EmF, emptying fractions; EV, emptying volume; PASP, pulmonary artery systolic pressure; RAEI, RA expansion index; TR, tricuspid regurgitation; other — see Table 1

Table 4. AUC and optimal cut-off value for RA functional parameters to identify patients with MACE

Parameter	AUC (95% CI)	*P*-value	Cut-off value	Sensitivity, %	Specificity, %
RAS_r	0.662 (0.522–0.803)	0.032	19.1%	75.8	63
RAS_{ct}	0.655 (0.515–0.795)	0.040	–9.3%	60.6	74.1
3D RAV_{min} index	0.709 (0.578–0.840)	0.006	16 ml	63.6	77.8
3D RAV_{max} index	0.686 (0.550–0.821)	0.014	22 ml	75.8	63
3D RAV_{preA} index	0.700 (0.569–0.831)	0.008	19 ml	66.7	63
3D Total EV	0.571 (0.424–0.718)	0.345	14 ml	75.8	40.7
3D Total EmF	0.641 (0.500–0.782)	0.062	42%	72.7	55.6
3D Passive EV	0.538 (0.387–0.688)	0.619	9 ml	69.7	55.6
3D Passive EmF	0.684 (0.545–0.822)	0.015	18%	66.7	74.1
3D Active EV	0.599 (0.455–0.743)	0.189	6 ml	69.7	44.4
3D Active EmF	0.562 (0.415–0.709)	0.414	23%	66.7	48.1
3D RAEI	0.641 (0.500–0.782)	0.062	73	72.7	55.6

Abbreviations: AUC, area under the curve; see Tables 1, 2, and 3

Table 5. Cox regression analysis for parameters of RA phasic function as predictors of MACE

Variables	Unadjusted		Adjusted[a]	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
2D RAS_r	2.792 (1.255–6.213)	0.012	1.883 (0.787–4.506)	0.155
2D RAS_{ct}	2.475 (1.228–4.986)	0.011	1.980 (0.910–4.311)	0.085
3D RAV_{max} index	3.544 (1.577–7.966)	0.002	3.207 (1.288–7.984)	0.012
3D RAV_{min} index	3.188 (1.556–6.533)	0.002	2.362 (1.004–5.552)	0.049
3D RAV_{preA} index	2.424 (1.164–5.048)	0.018	1.937 (0.828–4.534)	0.127
3D Total EV	1.836 (0.823–4.096)	0.138	1.655 (0.694–3.948)	0.256
3D Total EmF	2.124 (0.986–4.576)	0.055	1.686 (0.731–3.887)	0.220
3D Passive EV	2.036 (0.967–4.287)	0.061	2.040 (0.945–4.403)	0.069
3D Passive EmF	2.716 (1.311–5.625)	0.007	2.367 (1.066–5.259)	0.034
3D Active EV	1.659 (0.788–3.493)	0.182	1.300 (0.582–2.904)	0.522
3D Active EmF	1.404 (0.681–2.897)	0.358	1.554 (0.716–3.370)	0.265
3D RAEI	2.124 (0.986–4.576)	0.055	1.686 (0.731–3.887)	0.220

*Adjusted for age, LVEF, mitral E/E' ratio, RVFW-LS, and PASP

Abbreviations: see Tables 1, 2, and 3

outcomes, both in comparison to the control group and to the HF patients without MACE at follow-up. Patients with MACE had lower total EmF, lower passive EmF, and lower RAEI than both patients without MACE and controls, reflecting RA reservoir and conduit dysfunction in patients with adverse outcomes. Patients in the study group also had RA booster pump dysfunction (namely, lower active EmF) when compared with controls, but with no significant difference between patients with and without MACE.

RAS_r showed a negative correlation, while RAS_{ct} showed a positive correlation with GLS-RV (r = –0.53; P <0.001 and r = 0.35; P = 0.006, respectively) and PASP (r = –0.33; P = 0.01 and r = 0.38; P = 0.003, respectively). All three RA volumes had a modest positive correlation with PASP (r = 0.37; P = 0.004 for all), while RAV_{min} and RAV_{preA} were also weakly correlated to GLS-RV (r = 0.26; P = 0.040 and r = 0.25; P = 0.049, respectively). None of the RA phasic volumes or emptying fractions were correlated to PASP (P >0.05 for all). However, there was a modest negative correlation between GLS-RV and total EmF (r = –0.38; P = 0.002), passive EmF (r = –0.32; P = 0.01), active EmF (r = –0.26; P = 0.04), and RAEI (r = –0.39; P = 0.002). RA strain and volumes showed no correlation with indices of RV diastolic function, but the tricuspid E/A ratio was weakly correlated with active EV (r = 0.31; P = 0.02), and the E/E' ratio was weakly correlated with total EmF (r = –0.31; P = 0.02), passive EmF (r = –0.26; P = 0.04), and RAEI (r = –0.27; P = 0.03).

Prognostic role of the right atrium

In ROC analysis, all three RA indexed volumes and passive EmF showed the best AUC, while cut-offs for event prediction and their corresponding sensitivity and specificity are shown in Table 4. RA volumetric and functional indices were tested using the Cox proportional hazards model for their ability to predict MACE. In univariable analysis (Table 5), RAS_r, RAS_{ct}, 3D indexed RAV_{max}, RAV_{min}, and RAV_{preA}, and passive EmF were significant predictors of adverse events (P <0.05 for all), reflecting that greater impairment of RA reservoir, conduit, or pump function determine an increased risk of adverse outcome. In unadjusted Kaplan-Meier analysis, the difference in event-free survival was greater when stratified by indexed RAV_{max} and RAV_{min} (Figure 3).

The multivariable model was constructed to be as simple as possible, to avoid overfitting while including

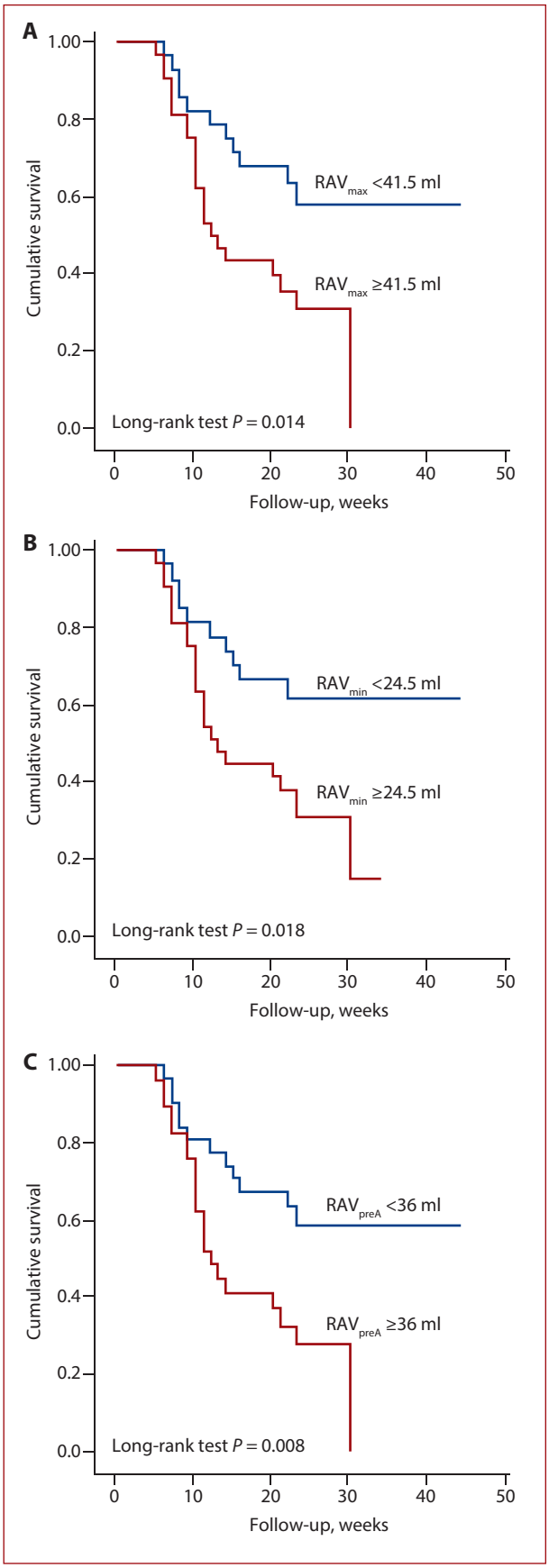

Figure 3. Kaplan-Meier survival curves stratified by the optimized cut-off value of RAV$_{max}$ >41.5 ml (**A**), RAV$_{min}$ >24.5 ml (**B**), and RAV$_{preA}$ >36 ml (**C**)

Abbreviations: see Table 1

established MACE predictors, such as age and parameters reflecting LV systolic and diastolic function, RV function, and the degree of pulmonary hypertension. In multivariable analysis, passive EmF, indexed RAV$_{max,}$ and indexed RAV$_{min}$ remained independent predictors of MACE after adjustment for age, LVEF, mitral E/E' ratio, RVFW-LS, and PASP (Table 5). An indexed RAV$_{max}$ larger than 22 ml was associated with a more than 3-fold risk for MACE, while an indexed RAV$_{min}$ larger than 16 ml and a passive EmF less than 18% determined a more than 2-fold risk for events. BNP levels were not included in the multivariable analysis since they were not available for all patients. The degree of TR was not included in the model because it was not a significant predictor of adverse outcomes in univariable analysis (P = 0.06).

DISCUSSION

In this study, we assessed the RA volumes and phasic function among patients with HFrEF and evaluated the prognostic role of RA dysfunction in these patients. Our findings can be summarized as follows: (1) all RA volumes were significantly larger in patients with HFrEF and MACE when compared with both normal subjects and with HF patients without MACE; (2) patients with HFrEF and MACE have impaired RA reservoir (RAS$_{r}$, total EmF, and RAEI), conduit (passive EmF) and booster pump function (RAS$_{ct}$ and active EmF) in comparison to controls; (3) indexed RAV$_{max}$, RAV$_{min,}$ and passive EmF are independent predictors of outcome in HFrEF after adjustment for age, LVEF, mitral E/E' ratio, PASP, and RVFW-LS.

While the prognostic role of RV dysfunction [16, 17] and LA phasic function [6] in HFrEF are well recognized, the role of the RA in diseases of the left heart is frequently overlooked. Conventional evaluation of the RA includes measurement of RA diameter and area, while 2D volumetric assessment is not routinely recommended [15]. Since RA remodeling is often asymmetrical, 3D measurements can assess the atrial size more accurately than 2D echocardiography [18]. STE and 3D echocardiography are useful tools for the characterization of RA phasic function and remodeling, and both RA reservoir strain [19] and 3D RA volumes [20] were found to be good diagnostic tools for identifying elevated RA pressure. While RA function has been studied in pulmonary arterial hypertension using innovative echocardiographic techniques [21, 22] and cardiac magnetic resonance (CMR) [23, 24], data regarding the phasic function of the RA in left-sided HF are scarce.

Normal reference values for RA strain indices and 3D volumes have been previously defined [18, 25]; however, this is the first study so far that assesses the RA size and function with both STE and 3D echocardiography in patients with HFrEF. In our study, all 3D RA volumes were larger, and all 3D emptying fractions, as well as RA strain indices, were lower in patients with MACE than in normal controls. Previous research reported altered RA reservoir strain in HF patients [26], while Jain et al. found in their

CMR study that HFrEF patients have an alteration of both RA reservoir and conduit function [27]. To our knowledge, our study is the first one to report impairment of all three components of RA phasic function in patients with HFrEF.

The RA maximal volume index (RAVI) assessed with 2D echocardiography was previously found to be an independent predictor of death, heart transplantation, and/or HF rehospitalization in patients with chronic systolic HF [28]. Similar results were reported by Proplesch et al. [29], who found that RAVI, but also RA total EmF, were predictors of death or 12-month rehospitalization in a cohort of patients with HF. Furthermore, a CMR study also found that RAVI is an independent mortality predictor in HFrEF [30], providing an additional contribution to the mortality risk stratification. Consistent with these previous findings, our study is the first, so far, to report the independent predictive value of both 3D indexed RAV_{max} and RAV_{min} in patients with HFrEF. An enlarged RAV_{max} was associated with a more than 3-fold, while an enlarged RAV_{min} was associated with a more than 2-fold hazard of adverse events in patients with HFrEF. We also found that a passive RA EmF < 18% determined a more than 2-fold hazard of MACE, reflecting the importance of RA conduit dysfunction in determining adverse outcomes. As it has been previously stated [31], atrial reservoir and pump functions have a greater contribution to ventricular stroke volume in the initial stages of cardiac disease, while conduit function becomes most important in advanced stages when ventricular diastolic pressure rises and the role of the other two phasic functions diminishes.

The RA and RV have a complex interplay throughout the whole cardiac cycle. On the one hand, the RA is more than just a blood receptacle, acting as a dynamic modulator of RV performance by redistributing RV filling and ejection force among reservoir, conduit, and booster functions. The atrial compliance directly influences the filling of the ventricle, and atrial phasic dysfunction will impair ventricular performance and reduce cardiac output [32]. On the other hand, the RV is subject to increased afterload in left-sided HF, which will determine RV remodeling and hypertrophy, increase RV pressure, and result in subsequent elevation of RA pressure. However, in our study, RA volumes and passive EmF remained independent outcome predictors even after adjusting for PASP and RV systolic function, which reinforces the idea that the RA is not a passive transit chamber but an active cavity allowing dynamic energy transfer to the ventricle [33], modulating the ventricular performance and having prognostic implications. While the severity of functional TR is highly dependent on loading conditions, the degree of TR did not predict events in our study. A probable explanation is that our cohort included stable outpatients, the majority with mild TR, with stable doses of diuretics. This suggests that the RA functional impairment and its predictive role in our study are related to an intrinsic alteration of the RA mechanics rather than to the degree of functional TR.

While some authors suggest that RA size is merely a surrogate of RV diastolic function [34], we found no correlations between RA volumes and tricuspid E/A and E/E' ratios in our study. A possible explanation for this is that RV diastolic function and RV filling pressure are related not only to RA size but also to its stiffness and contractility. This implies that RA mechanics has an independent pathophysiological role in left-sided HF, an idea that has been previously suggested [35]. Our results highlight that RA assessment in left-sided HF should not be neglected and that measuring just the currently recommended end-systolic dimensions might not be enough.

Study limitations

This study should be interpreted in the context of several limitations. While it has the advantage of being a prospective study, its main limitation is the small sample size and the relatively short follow-up period. Second, we excluded patients with a poor acoustic window, which brings a potential selection bias. More importantly, we did not include patients with atrial fibrillation to avoid stitch artifacts in 3D echocardiography, and since atrial fibrillation determines changes in atrial size and function, it is uncertain whether our results apply to patients with HFrEF and atrial arrhythmias. Last but not least, for RA assessment we used vendor-specific software that was initially designed for the LV; hence, the cut-off values we reported in ROC analysis might not apply to other software.

CONCLUSION

Our study is the first one to report a comprehensive assessment of phasic RA function, using STE and 3D echocardiography, in patients with HFrEF, including evaluation of its prognostic value. We found that all three RA volumes and all three components of RA mechanics were impaired in patients with HFrEF and adverse outcomes. Moreover, we found that 3D RA maximal and minimal volumes, as well as 3D passive EmF, were independent predictors of major adverse events, irrespective of well-established demographic and echocardiographic risk factors. Further studies are needed to evaluate if RA phasic function retains its prognostic value in long-term follow-up. However, these results reinforce the idea that the RA is not just a passive transit chamber, and its evaluation should not be overlooked in patients with left-sided HF.

Article information

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Long-term outcomes in patients after left atrial appendage occlusion: The results from the LAAO SILESIA registry

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ABSTRACT

Background: The benefits of oral anticoagulation (OAC) therapy are undeniable. However, such treatment is contraindicated in 2%–10% of patients. According to the latest guidelines, percutaneous left atrial appendage occlusion (LAAO) may be considered in stroke prevention.

Aims: We analyzed the data of patients from the Polish population, who had undergone LAAO procedures in the Silesian Province based on limited reports.

Methods: The data from the SILCARD database of all patients who underwent LAAO between 2006 and 2019, and the data from the databases of the centers performing the procedures in the Silesian Province were included in the LAAO SILESIA registry. We analyzed the efficacy and safety of the procedure and its relationship with the occurrence of stroke and bleeding in the post-hospital follow-up.

Results: We analyzed 649 patients with the mean values of CHA2DS2-VASc and HAS-BLED scores of 4.1 and 3.2, respectively. The predominant indication for LAAO was a history of bleeding during OAC. The most frequent in-hospital major adverse cardiac events were anemia, which required blood transfusion (5.5%), and pericardial effusion, which was treated either conservatively (0.9%) or interventionally (1.2%). During hospitalization, stroke was detected in 4 patients and three patients died of any cause. LAAO reduced the annual risk of stroke by 84% and the annual risk of bleeding by 27%.

Conclusions: Based on a "real-life" cohort of patients from the Silesian Province, we concluded that LAAO is related to low in-hospital major cardiovascular adverse events. In the long-term follow-up, LAAO reduced the rates of stroke and bleeding.

Key words: atrial fibrillation, left atrial appendage occlusion, stroke

INTRODUCTION

Atrial fibrillation (AF) is the predominant cardiac arrhythmia whose prevalence increases with age. In addition to clinical symptoms, a diagnosis of AF is associated with a higher risk of stroke and a poorer prognosis [1, 2]. Many papers and study results demonstrate that anticoagulant therapy is effective in reducing the risk of ischemic stroke and overall mortality in patients with AF [3, 4]. Although the benefits of oral anticoagulation (OAC) therapy are undeniable, such treatment is contraindicated in 2%–10% of patients [5, 6]. In the light of the above, according to the latest guidelines of the European Society of Cardiology (ESC) and the 2016 and 2020 guidelines of the Polish Cardiac Society, percutaneous left

WHAT'S NEW?

The benefits of oral anticoagulation (OAC) therapy are undeniable. However, such treatment is contraindicated in some patients. According to the latest guidelines, percutaneous left atrial appendage occlusion (LAAO) may be considered in stroke prevention. Evidence for the benefits of this form of therapy is provided by subsequent studies. Among these studies, the analyses based on patient data from the Polish population are limited. Therefore, we analyzed details of patients undergoing LAAO with the unique methodology of SILCARD registry with data from the centers in which such procedures were performed. We found LAAO to be associated with low in-hospital major cardiovascular events, and reduce rates of stroke and bleeding in the long-term follow-up

atrial appendage occlusion (LAAO) may be considered in stroke prevention [3, 4].

Since the introduction of the first LAAO procedures in the early 2000s, clinical experience and knowledge in this field have increased [7–9]. Various studies have shown that LAAO is associated with good short- and mid-term results regardless of the type of device used [8, 10–17].

Among these studies, the analyses based on patient data from the Polish population are limited. This prompted us to analyze patients undergoing LAAO in the Silesian Province using the unique methodology of the SILCARD registry completed with data from centers performing such procedures. The specific aim of our study was to analyze the efficacy and safety of the procedure and its relationship with the occurrence of stroke and bleeding in the post-hospital follow-up in a "real-life" cohort of patients.

METHODS

Data source

The data utilized in our registry were collected as part of the Silesian Cardiovascular Database (SILCARD) (ClinicalTrials.gov identifier, NCT02 743 533; https://clinicaltrials.gov/ct2/show/NCT02743533). General information on SILCARD was previously reported [18]. Briefly, the database contains records from all hospitals (n = 310) in the Silesian Province, which is a large administrative region in southern Poland with a population of 4.57 million people (approximately 12% of the total population of Poland), including 3.80 million adults. The Silesian Province provides a well-developed hospital network with two tertiary cardiology hospitals, three cardiac surgery departments, and 20 catheterization laboratories. The National Health Fund (NHF), which is the only public health care provider in Poland, has supplied all data to the database since 2006. The inclusion criteria were as follows: each hospitalization in the departments of cardiology, cardiac surgery, diabetology, or vascular surgery and hospitalization with a cardiovascular diagnosis in the department of internal medicine or intensive care. The exclusion criteria were hospitalizations of patients living outside of the Silesian Province and patients younger than 18 years on admission. The collected data included information on initial hospitalization with a diagnosis of cardiovascular disease (CVD) with a potential transfer to another department or hospital, other hospitalizations, and data from outpatient visits. If the patient was rehospitalized for CVD within 24 hours, both hospitalizations were considered one admission. According to the applicable rules, hospitals are obliged to report to the NHF on the principal diagnosis with up to two comorbidities defined by the International Classification of Disease, 10th Revision (ICD-10), and on medical procedures defined by the ICD-9 classification. CVD was defined as R52, J96, or any "I" code based on the ICD-10. The hospital registry number and the national identification number (PESEL) were used to match the information on each patient. All data were anonymized. The SILCARD registry was approved by the local Bioethics Committee.

The selected parameters of baseline characteristics and in-hospital course were completed from the databases of the centers performing the procedures (Silesian Center for Heart Diseases in Zabrze; Upper-Silesian Medical Center in Katowice; American Heart of Poland — Medical Center in Bielsko-Biała).

Study population

The analysis included all patients from the SILCARD database from January 1, 2006 to December 31, 2019 with atrial flutter or atrial fibrillation coded according to the ICD-10 as I48 who underwent percutaneous LAAO with the principal procedure coded according to the ICD-9 (international classification system for surgical, diagnostic, and therapeutic procedures, 9th Revision) as 37.4901. The exclusion criteria included residency outside of the Silesian Province and age under 18 years at the time of LAAO. As a result, the patient registry became known as the LAAO SILESIA.

Study data

Data available from the NHF included the total number of patients who had undergone percutaneous LAAO, their sex, age, comorbidities, hospitalization, and mortality. Screening for comorbidities was performed in hospital settings. Data were reported to the NHF using the ICD-10 and ICD-9 codes as primary or coexisting diagnoses. For the study, variables were defined as indicated in Table 1. Based on these baseline characteristics, stroke risk was calculated using the CHA2DS2-VASc clinical risk scale.

Table 1. Analyzed variables according to the ICD-9 and ICD-10 diagnostic codes

Analyzed parameters	Adopted ICD-10 codes
Arterial hypertension	I10–I13, I15
Bleeding, including bleeding from the gastrointestinal tract, genital tract, urinary tract, and respiratory tract	K62.5, K92.0, K92.1, K92.2, N02, R31, N93, R04.2, R04.8, R04.9
Chronic coronary syndrome	I25, I20.1, I20.8, I20.9
Chronic kidney disease	N17–N19
Death	I46.1, R96.0, I46.9, R96.1, R99
Diabetes mellitus	E10–E14
Hematopoietic system disease	D60, D61, D63, D64, D68, D69
Heart failure	I50, I42
Hemorrhagic shock or hemorrhage	R57.1, R58
Intraocular bleeding	H35.6, H43.1, H44.8, H45.0
Myocardial infarction	I21–I22
Pericardial effusion treated conservatively	I31.3, I31.2
Peripheral artery disease	I65–I67, I70.0, I70.1, I70.2, I70.8, I70.9, I77–I79
Ischemic, hemorrhagic, and undetermined stroke	I60–I64
Systemic arterial embolism	I74.0, I74.1, I74.2, I74.3, I74.4, I74.5, I74.8, I74.9
Transient ischemic attack	G45
Unstable angina	I20.0, I24.0, I24.8, I24.9
Analyzed procedures	**Adopted ICD-9 codes**
Blood transfusion requirement	99.04
CRT device implantation	00.50, 00.51, 00.52, 00.53, 0054, 37.792, 37.997
Coronary artery bypass grafting	36.11, 36.12, 36.13, 36.14, 36.15, 36.16, 36.17, 36.19
ICD implantation	37.941-944, 37.961, 37.962, 37.97, 37.991, 37.996
Percutaneous coronary intervention	00.45, 00.46, 00.47, 00.48, 00.661, 00.662, 36.06, 36.07, 36.09, 36.10
Pericardial effusion treated interventionally or surgically	37.0, 37.123
Pacemaker implantation	37.8

Abbreviations: CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator

From the databases of the centers performing the procedures, the additional detailed in-hospital data were included (1) the major bleeding risk score according to the HASBLED score; (2) a history of bleeding during oral anticoagulation therapy without a reversible cause; (3) periprocedural successful implant deployment; and (4) the anti-platelet/anti-thrombotic drugs at the discharge.

The following follow-up data were collected: (1) bleeding, including the need for blood transfusion; (2) transient ischemic attack (TIA), stroke, including fatal and non-fatal stroke; (3) systemic embolism; and (4) all-cause mortality.

Statistical analysis

Continuous variables were summarized using the arithmetic mean with standard deviation (SD) for normal distribution or the median with interquartile range (IQR) for non-normal distribution. Normality of distribution was verified using the Shapiro-Wilk test. Categorical variables were summarized using frequency tables.

The event-free survival probability (stroke and bleeding) after discharge was presented using the Kaplan-Meier method. The time to occurrence of the event (i.e. stroke and bleeding) was calculated after the discharge. If the events did not occur until February 1, 2020, this date was considered the end of the follow-up for all patients.

The patient annual risk of stroke was recorded based on the subject's CHA2DS2-VASc score, and then the average risk score for the study population was calculated. The annual risk of stroke and bleeding was then extrapolated from the published literature [19] and related to risk score estimation to determine the influence of LAAO on risk reduction in the analyzed group.

The calculations were performed using STATISTICA PL version 10 (StatSoft, Inc., Tulsa, OK, US).

RESULTS

The group we analyzed, included 649 patients. The number of procedures per year reached 25 in 2011, 6 in 2012, 8 in 2013, 62 in 2014, 71 in 2015, 92 in 2016, 116 in 2017, 124 in 2018, and 145 in 2019. The following number of LAAO procedures was performed per center in the analyzed period: (1) Silesian Center for Heart Diseases in Zabrze — 325; (2) Upper-Silesian Medical Center in Katowice — 208; (3) American Heart of Poland — Medical Center in Bielsko-Biała — 116.

Baseline characteristics

The mean (SD) age of patients eligible for LAAO was 73 (8) years. The mean (SD) values of CHA2DS2-VASc and HAS-BLED scores were 4.1 (1.9) and 3.2 (1.0), respectively. A history of bleeding on OAC without a reversible cause was the main indication for the LAAO procedure (81% of patients). In 17% of patients, a contraindication to OAC therapy was listed as an indication for LAAO. However, it was not specified. In addition, the ineffectiveness of long-term optimal anticoagulation in 9 patients and hematological disorders in 3 patients were reported. In most patients, chronic coronary syndrome, chronic heart failure, and hypertension were diagnosed. Baseline characteristics are listed in Table 2.

In-hospital course

The deployment of the occluder was successfully performed in 99.1% of patients. Postprocedural dual anti-platelet therapy with aspirin and clopidogrel was the primary treatment. Table 3 shows other important in-hospital course data, including the in-hospital need for blood transfusion in 36 patients (5.5%). In 8 patients, interventional or surgical treatment was necessary due to pericardial effusion, and stroke was reported in 4 patients. Two adverse events were reported in 3 patients, whereas 3 adverse events were observed in one patient during an in-hospital stay. In a 71-year-old female, pericardiocentesis followed by surgical treatment was necessary due to periprocedural tamponade. During hospitalization, 3 patients died of any

Table 2. Baseline characteristics

Characteristics	
Age, years, mean (SD)	73 (8)
Sex, male, n (%)	378 (58.2)
Atrial fibrillation, n (%)	649 (100)
CHA2DS2-Vasc score, mean (SD)	4.1 (1.9)
HASBLED score, mean (SD)	3.2 (1.0)[a]
Hypertension, n (%)	443 (68.3)
Heart failure, n (%)	274 (42.2)
Coronary artery disease, n (%)	361 (55.6)
Peripheral artery disease, n (%)	147 (22.7)
Diabetes mellitus, n (%)	154 (23.7)
Chronic kidney disease, n (%)	54 (8.3)
Previous MI, n (%)	110 (16.9)
Previous UA, n (%)	137 (21.1)
ACS until 12 months before LAAO, n (%)	76 (11.7)
Previous PCI, n (%)	192 (29.6)
Previous CABG, n (%)	37 (5.7)
Previous TIA, n (%)	40 (6.2)
Previous stroke, n (%)	145 (22.3)
Previous ischemic stroke, n (%)	109 (16.8)
Previous hemorrhagic stroke, n (%)	45 (6.9)
Previous bleeding, total, n (%)	431 (80.9)*
Previous systemic embolism, n (%)	8 (1.2)
Hematopoietic system disease, n (%)	75 (11.6)
Implanted PM/CRT-P, n (%)	116 (17.9)
Implanted CRT-D/ICD, n (%)	64 (9.9)

[a]Data available for 533 patients

Abbreviations: ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; LAAO, left atrial appendage occlusion; MI, myocardial infarction; PCI, percutaneous coronary intervention; PM, pacemaker; SD, standard deviation; TIA, transient ischemic attack; UA, unstable angina

Table 3. In-hospital course data

Characteristics	
Successful implant deployment, n (%)	528 (99.1)[a]
Drugs at discharge	
Aspirin, n (%)	530 (99.4)[a]
Clopidogrel, n (%)	529 (99.2)[a]
In-hospital adverse events	
Pericardial effusion, conservative treatment, n (%)	6 (0.9)
Need for blood transfusion, n (%)	36 (5.5)
Pericardial effusion, interventional/surgical treatment, n (%)	8 (1.2)
TIA, n (%)	3 (0.5)
Stroke, total, n (%)	4 (0.6)
Non-fatal stroke, n (%)	3 (0.5)
Fatal stroke, n (%)	1 (0.2)
In-hospital death, n (%)	3 (0.5)

[a]Data available for 533 patients

Abbreviation: TIA, transient ischemic attack

cause. Pericardial effusion and multiorgan failure leading to death were observed in a 74-year-old male on day 29 after LAAO. On the first day after the procedure, a 77-year-old female died due to a stroke. After successful surgical removal of the occluder directly after LAAO in a 51-year-old female, multiorgan failure developed, which resulted in the patient's death on the same day.

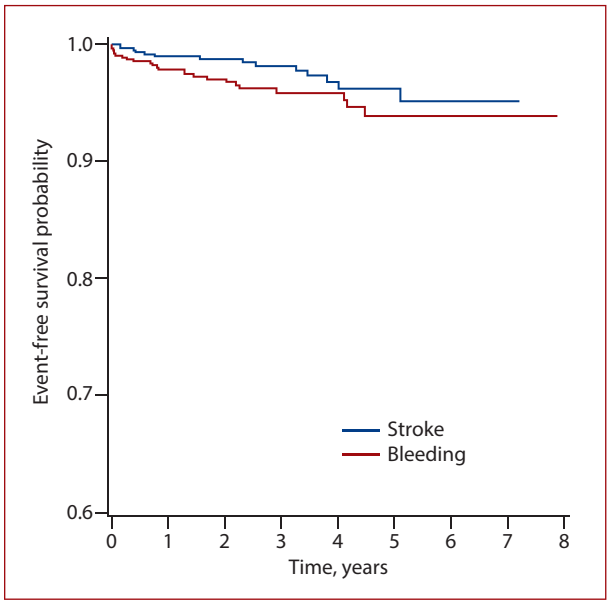

Figure 1. Freedom from stroke (the blue curve) and bleeding (the red curve) after discharge presented by the Kaplan-Meier curve

Follow-up data

In a long-term follow-up with a median (interquartile range, [IQR]) of 777 (339–1324) days, TIA was diagnosed in 9 (1.4%) patients and stroke in 14 (2.2%) patients, including one subject who died due to a stroke. Among patients with stroke, 13 subjects were diagnosed with ischemic stroke and 1 with hemorrhagic stroke. Bleeding was reported in 25 patients (3.9%), including 9 patients (1.4%) who required blood transfusion. Systemic embolism was observed in 4 patients.

In a 12-month follow-up, ischemic stroke was reported in 5 patients (0.8%), whereas bleeding in 14 patients (2.2%). Considering the above and based on CHA2DS2-Vasc and HASBLED scores, LAAO reduced the annual risk of stroke by 84% and the annual risk of bleeding by 27% (Figure 2). Among the group of patients discharged from the hospital, 132 (20.4%) subjects died of any cause in the long-term follow-up (Table 4).

DISCUSSION

The presented data of patients who underwent percutaneous LAAO were obtained from a large regional registry. We analyzed baseline characteristics, selected in-hospital and long-term follow-up parameters, and information related to adverse events and death of any cause. Based on the results, we can presume that LAAO is safe and is associated with promising long-term efficacy to prevent stroke in AF patients with poor compliance to OAC.

LAAO was performed mainly in elderly patients (mean age, 73 years) with a high risk of stroke estimated by the CHA2DS2-Vasc scale — 4.1 (1.9). Both outcomes were similar to most results obtained from available registries [12, 16, 20, 21]. In a few registries, such as in the multicenter Amplatzer Cardiac Plug (ACP) registry [11], the mean age of patients who underwent the procedure was even higher, and the

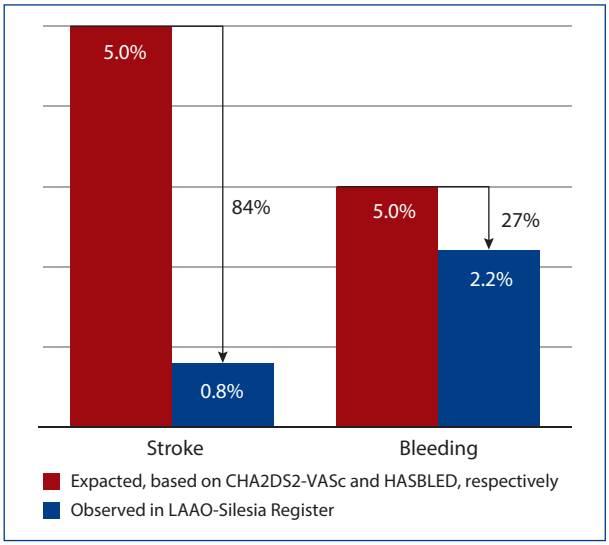

Figure 2. Effectiveness of LAAO in a 12-month reduction in ischemic stroke and bleeding after discharge

Abbreviations: see Table 2

Table 4. Analyzed follow-up data

Characteristics	N (%)	Median time to event in days (IQR)
Follow-up duration, days	646 (99.5)	777 (339–1324)
TIA	9 (1.4)	253 (106–802)
Stroke, total	14 (2.2)	493 (218–1177)
Ischemic stroke	13 (2.0)	547 (250–1187)
Non-fatal stroke	11 (2.0)	714 (155–1272)
Fatal stroke	3 (0.5)	1348 (184–1525)
Bleeding, total	25 (3.9)	302 (74–809)
Bleeding requiring blood transfusion	9 (1.4)	83 (25–246)
Systemic embolism	4 (0.6)	1115 (341–1989)
Death, any cause	132 (20.4)	579 (213–1071)

Abbreviations: see Table 3

percentage of patients >75 years of age constituted 55% of the group. In addition, patients were usually affected by multiple diseases, including chronic coronary syndrome, chronic heart failure, and hypertension. Compared to the above registries, a significant difference in the collected data was related to a high percentage of heart failure (42.2%) and a proportionally low percentage of patients with chronic kidney disease (8.3%). It can be related to an increasing number of patients with heart failure in the Polish population [22] or the exclusion of this group of patients from the previous analyses [8, 10, 23, 24]. The obtained results may also be affected by the registry restriction, arising from a limited number of diagnoses reported to the NHF.

Notably, the predominant indication for LAAO in the Silesian population was bleeding related to OAC, which was reported in 80.9% of cases (including the incidence rates of hemorrhage or hemorrhagic shock, hemorrhagic stroke, or ocular hemorrhage). These indications are consistent with the consensus document prepared by the Association of Cardiovascular Interventions and the Heart Rhythm Section of the Polish Cardiac Society [25]. It is a rather high percentage compared to other European registries, where bleeding was the indication for LAAO in 42%–80% of patients [11, 16, 17, 20, 21]. These discrepancies are even greater when compared with the results of the analyses based on German registries. In the prospective LAARGE [17] registry, the frequency of major bleeding was low and occurred in 28.9% (bleeding was defined as severe in the case of transfusions, surgical treatment, intracranial hemorrhage, and/or hemodynamically unstable patients requiring urgent medical support) and was even lower (18%) in a study based on a single-center registry published by Kleinecke et al. [26]. Therefore, it may suggest that more different indications for LAAO are considered in the above-mentioned countries.

Interestingly, the percentage of successful implant deployment during LAAO was high and reached 99.1% in our population. The high percentage of successful implantations was previously reported [7, 10], and it increased with the experience of operators. Their expertise has an impact on the reduction of adverse events [8], particularly pericardial effusion and the need for blood transfusion. These data were confirmed by the Italian registry [27]. In our observation, the in-hospital prevalence of pericardial effusion depending on the treatment strategy (conservative or interventional) affected 6 (0.9%) and 8 (1.2%) patients, respectively. This percentage of pericardial effusion is comparable to the previous data from the ACP registry [11] where tamponade was diagnosed in 1.24% of patients or in the LAARGE registry [17] where pericardial effusion requiring intervention was reported in 2.3% of cases.

Interpretation of the comparative analysis of bleeding is difficult due to the dissimilarity of selected definitions of major bleeding for each study. In our analysis, the major bleeding was defined as the in-hospital need for blood transfusion and affected 36 patients (5.5%). The LAARGE prospective registry [17] reported the incidence of major in-hospital bleeding at 1.1% (seven patients). On the other hand, in the EWOLUTION registry [12], major bleeding occurred in 11% of patients within 30 days of the procedure.

Unfortunately, 3 patients (0.5%) died in the in-hospital period in the analyzed group. Two patients developed multiorgan failure after interventional treatment of pericardial effusion, and another patient died of a stroke. The risk of in-hospital death related to LAAO was low in the available registry data and ranged between 0.2% and 0.7% [12, 17, 20, 21]. In the ACP registry [11], three periprocedural deaths were reported. They were due to intracranial bleeding, cardiac tamponade, and embolization with a device, respectively. Other deaths occurred postoperatively due to arrhythmia, cardiac tamponade leading to multiorgan failure, an acute ST-elevation myocardial infarction (STEMI), device embolization on day 6 after the procedure, and pneumonia. In turn, Betts et al. [16] reported one death related to pericardial tamponade after transseptal puncture and advancement of the delivery sheath into the LAA. In the EWOLUTION registry [12] and long-term patient outcomes, including bleeding and

incidence of stroke/transient ischemic attack (TIA) three deaths were reported, none of which was directly related to the procedure (right ventricular failure on the day of the procedure, respiratory insufficiency on day 4, and cardiac death on day 6 postoperatively).

The possibility for cessation of OAC without increasing thromboembolic complications is the essence of the LAAO procedure. In our database, in a long-term follow-up of 777 days, TIA and stroke occurred in 9 (1.4%) and 14 patients (2.2%), respectively. Bleeding was reported in 25 patients (3.9%), 9 (1.4%) of whom required blood transfusion (Figure 1). Based on the above findings, an 84% reduction in the incidence of ischemic stroke and a 27% reduction in the incidence of bleeding were observed compared to the estimated value [19] (Figure 2). As we mentioned above, a detailed comparison of the prevalence of TIA, stroke, and bleeding episodes is problematic due to differences in reporting methods [11, 14, 17, 20, 21, 28]. However, the confirmed reduction of the occurrence of these adverse events should be indicated. The above registries report the annual risk of stroke after LAAO at 1.2%–2.2% [17, 20, 21, 28] ranging from 0.9% (ACP registry) [11] during a 13-month follow-up to 4.2% (Korean study) [14] during a 21.9-month follow-up. In large registries, the annual risk of major bleeding was estimated at 0.4-2.0% [17, 21, 28]. In turn, in the analysis of Kleinecke et al. [26], bleeding with varying degrees of severity occurred in 8 patients, which constituted 16% of the observed group.

In our cohort of patients, after a median follow-up of 777 days, more than 20% of patients died of any cause. This percentage seems to be high. As we mentioned above, patients undergoing LAAO represented the elderly Silesian population, often with many comorbidities that increase the risk of death. Compared to the international registries, the percentage of deaths increased with a higher mean age of patients and ranged from 5.2% during a 21.9-month follow-up to 11.5% during a one-year follow-up of the prospective registry [14, 17, 29]. Notably, the risk of death was independent of the type of occluder used for LAAO [21].

Limitations of the study

The above analysis was retrospective, with the typical limitations of this method. The LAAO-SILESIA registry based on the electronic database of a single healthcare provider is limited to core variables, coded according to ICD-9 and ICD-10, such as demographic data, comorbidities, in-hospital events (need for blood transfusion, TIA/stroke, in-hospital death, pericardial effusion depends on the method of treatment) and major cardiac events in a follow-up (death, bleeding, TIA/stroke). It does not cover data on laboratory results, echocardiographic parameters, fluoroscopy data, or the cause of death during the follow-up, which represents a major limitation of the study. The quality of data may be challenged by differences in the quality of data reported by different centers. The study does not account for patients who moved to another Province.

CONCLUSIONS

Based on a "real-life" cohort of patients from the Silesian Province, we conclude as follows:

The LAAO procedure is related to low in-hospital major adverse cardiac events.

LAAO reduced the rates of stroke and bleeding in a long-term follow-up.

Article information

Conflict of interest: None declared.

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Prevalence of heart rhythm disorders in patients with end-stage heart failure referred to qualification for heart transplantation

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INTRODUCTION

Heart failure (HF) affects 1%–2% of the adult population [1]. Notwithstanding substantial improvements in therapy, heart transplantation (HT) remains an accepted treatment option in end-stage HF [2, 3]. Heart rhythm disorders (HRD) are more common in patients with HF and worsen their prognosis [4, 5]. Assessment of HRD epidemiology in patients subjected to qualification for HT could allow for an improvement in targeted therapy. Thus, the aim of this study was a qualitative and quantitative analysis of HRD in patients with HF considered for HT.

METHODS

Retrospective clinical data of consecutive 169 patients with severe HF, who underwent the qualification procedure for HT, were analyzed. All patients were hospitalized from 2018 to 2019 in the 3rd Department of Cardiology, the Medical University of Silesia, the Silesian Center for Heart Diseases in Zabrze, Poland. Patients with end-stage, symptomatic HF despite optimal medical therapy were included in the study. Both scheduled and urgent patients were included in the analysis. The only exclusion criteria were the lack of maximal HF therapy in accordance with the current guidelines by the European Society of Cardiology. HT qualification was performed following the local protocol. Information about HRD was obtained during hospitalization from resting electrocardiography, Holter monitoring, and cardiac implantable devices (CIEDs) checks. Additional data were also obtained from previous medical history if available. The study was approved by the ethical committee of the Medical University of Silesia.

Statistical analysis

The qualitative variables were expressed as absolute number and percentage and were analyzed with the χ^2 test (where numbers were anticipated to be less than 5, Yates correction for continuity was implemented). The normal distribution of continuous variables was confirmed using the Kolmogorov-Smirnov test. Continuous variables were expressed as mean and standard deviation (SD). The significance of differences between mean values was tested with Student's t-test. A *P*-value of less than 0.05 was regarded as significant. Statistical analysis was performed using Statistica software version 13 (TIBCO Software Inc., Palo Alto, CA, US).

RESULTS

The mean standard deviation (SD) age of examined patients was 55 (10) years, and most of them were men (88.8%). Almost half of the patients (45.6%) were in class III of the New York Heart Association (NYHA). The ischemic etiology of HF was more frequent (52.1%). The mean (SD) left ventricular ejection fraction (LVEF) was 21 (8)%. Arterial hypertension and dyslipidemia were the most common comorbidities. Several patients (43.2%) had a history of myocardial infarction. More than half of the group had mitral regurgitation (52.1%). Most patients (94.1%) had CIED; many were implantable cardioverter-defibrillators (ICDs, 50.3%). In the analyzed group, ventricular arrhythmias were present in 40.8% of patients,

and most of them were ventricular tachycardia (VT) and fibrillation (VF). More than half of the group (52.1%) had a history of atrial flutter or fibrillation (AF). Ablation of any kind was performed in 17.2% of patients. All data are summarized in Table 1. Additional data from subgroups analysis are presented in the Supplementary material (*Tables S1–S3*).

DISCUSSION

Our registry shows the significant burden of patients with HRD. The most common arrhythmia was atrial fibrillation, which affects almost half of the analyzed group. Previous studies showed that such high prevalence was present in patients in class IV according to the NYHA [6]. In our study, patients in that class constituted only 11.8%. AF worsens the long-term prognosis of patients with HF and is associated with a higher number of hospitalizations and their longer duration [7]. The way in which AF affects HF is complex. The loss of synchronized atrial contraction and/or a persistently higher heart rate may provide negative ventricular remodeling [8]. The presence of AF leads to impairment in myocardial perfusion and perfusion reserve in a mechanism of microvascular coronary dysfunction [9]. Irregular pulse may not only worsen coronary flow, but it also affects other arteries and results in endothelial dysfunction [10]. There is evidence that rapid atrial rates are associated with increased inflammation, thrombin generation, and platelet activation [11]. Those processes may be partially reversed by sinus rhythm restoration [8]. Catheter ablation of AF in patients with HF reduces both mortality and HF-related hospitalization rates [4]. In the analyzed population, only 4.1% of patients with AF underwent such therapy. It seems that those patients should be more often considered for ablation.

Ventricular arrhythmias represent a wide range of HRD. Their incidence rises with the severity of HF. Along with HF progression, they are the most common cause of sudden cardiac death (SCD) in this population [1]. In the analyzed group, 39.6% of patients had at least one episode of VT or VF. Some patients (4.1%) met the criteria for an electric storm (ES) and underwent catheter ablation. ES is associated with high mortality [12]. The most common CIED in the presented group was ICD, which was implanted in more than half of the patients (50.3%). Modern HF pharmacotherapy is considered to have been a cause of substantial reduction in SCD rates in recent years. Despite that, ICD implantation in selected patients is still an essential part of HF therapy. In the analyzed population, ICD or cardiac resynchronization devices (CRT-D) were implanted in 93.5% of the patients. CRT-D in appropriate patients reduces morbidity and mortality, and improves cardiac function [13]. In the studied population, it is worth noting the high percentage of patients with CRT-D (43.2%). It is more than twice as high as within the general HF population from the same center [14]. HRD, especially AF, may lead to loss of adequate biventricular pacing and, in consequence, exacerbation of HF. An intensive clinical follow-up is crucial to

Table 1. Clinical, electrophysiology characteristics and heart rhythm disorders and ablation procedures of patients with end-stage heart failure who underwent qualification procedure for heart transplantation in 2018–2019

Variable	N = 169
Clinical characteristics	
Mean age, years, mean (SD)	55 (10)
Male gender, n (%)	150 (88.8)
NYHA class, n (%)	
I	7 (4.1)
II	65 (38.5)
III	77 (45.6)
IV	20 (11.8)
HF etiology, n (%)	
Ischemic	88 (52.1)
Nonischemic	81 (47.9)
Mean LVEF, %, mean (SD)	21 (8)
Chronic kidney disease, n (%)	61 (36.1)
Diabetes, n (%)	53 (31.4)
Dyslipidemia, n (%)	113 (66.9)
Arterial hypertension, n (%)	88 (52.1)
Peripheral artery disease, n (%)	25 (14.8)
Chronic obstructive pulmonary disease, n (%)	10 (5.9)
Active smoking, n (%)	122 (72.2)
Stroke, n (%)	17 (10.1)
Transient ischemic attack, n (%)	6 (3.6)
Coronary artery disease, n (%)	99 (58.6)
Myocardial infarction, n (%)	73 (43.2)
ST-elevation myocardial infarction	58 (34.3)
Non-ST elevation myocardial infarction	26 (15.4)
Percutaneous coronary intervention, n (%)	78 (39.8)
Coronary artery by-pass graft, n (%)	26 (15.4)
Valvular heart disease (moderate or severe), n (%)	103 (60.9)
Mitral regurgitation	88 (52.1)
Mitral stenosis	2 (1.2)
Tricuspid regurgitation	62 (36.7)
Aortic stenosis	13 (7.7)
Aortic regurgitation	11 (6.5)
Mean VO2max, l/min, mean (SD)	15.8 (5.1)
Electrophysiology characteristics	
Cardiac implantable electric device, n (%)	159 (94.1)
PM	1 (0.6)
ICD	85 (50.3)
CRT-D	73 (43.2)
AVB, n (%)	13 (7.7)
I°	1 (0.6)
II°	4 (2.4)
III°	8 (4.1)
SND, n (%)	1 (0.6)
Heart rhythm disorders and ablation procedures	
Ventricular arrhythmias, n (%)	69 (40.8)
VT/VF	67 (39.6)
ES	7 (4.1)
Other	5 (3)
Atrial fibrillation, n (%)	84 (49.7)
Paroxysmal	43 (25.4)
Sustained	41 (24.3)
Atrial flutter, n (%)	19 (11.2)
Other SVT, n (%)	7 (4.1)
Ablation, n (%)	29 (17.2)
PVI	7 (4.1)
AVN	8 (4.7)
CTI	5 (3)
VT	7 (4.1)
Other	2 (1.2)

Abbreviations: AVB, atrioventricular block; AVN, atrioventricular node; CRT-D, cardiac resynchronization therapy defibrillator; CTI, cavotricuspid isthmus; ES, electric storm; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PM, pacemaker; PVI, pulmonary vein isolation; SND, sinus node dysfunction; SVT, supraventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia

avoid HF decompensations in this population [1]. Remote monitoring care of patients with HF and CIEDs improves their prognosis [15].

Sinus node disease and atrioventricular block may result in life-threatening bradycardia or asystole. In the presented population, those conditions were reported in 7.7% of patients. This number could be underestimated due to the high rate of other CIED implantations. Presumably, some patients could have indications for a prior upgrade to CRT-D due to a significant proportion of right ventricular pacing.

The main limitation of this study is its retrospective character. Further analysis of the long-term prognosis of patients with HRD who underwent HT would be essential.

Supplementary material

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

Article information

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Arterial stiffness increases in response to an acute arterial load challenge induced by an isometric handgrip in healthy individuals

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INTRODUCTION

Arterial stiffness plays an essential role in the development of cardiovascular disease and its complications, including mortality [1]. The Arterial Stiffness Index (SI_{DVP}) can be measured non-invasively by analyzing the arterial digital volume pulse (DVP) [2]. SI_{DVP} correlates well with resting blood pressure (BP) although it is unknown whether it changes with a BP elevation frequently occurring during the day in all people.

Various physiological provocations can cause temporary BP increases, including an isometric handgrip (IHG) stimulating the sympathetic nervous system and increasing arterial load, which represents an opposition that needs to be overcome during ejection by the left ventricle (LV). However, an IHG is also accompanied by acceleration of the heart rate (HR). Furthermore, it is unknown whether the potential effect of an increase in BP upon SI_{DVP} is independent of a changing HR.

We attempted to find out if a rapid change in BP, caused by an IHG, can influence SI_{DVP} and, if such an association exists, whether it depends on the effects of an accelerating HR in healthy people.

METHODS

A total of 22 healthy adult volunteers were recruited. The participants were informed about the study, and written consent was obtained. The local Ethics Committee approved the study protocol.

As for the inclusion criteria, none of the study subjects could be on any medication or suffer from chronic conditions. Out of 23 screened subjects, one was rejected due to high resting blood pressure (value >140/90 mm Hg).

Isometric handgrip exercise

Resting brachial BP was obtained using an oscillometric method (705 IT, Omron Healthcare Co. Ltd., Kyoto, Japan). Maximal IHG strength was measured in a sitting position using the Jamar hydraulic hand dynamometer (Sammons Preston Rolyan, Bolingbrook, IL, US). Subsequently, the participants were instructed to compress the dynamometer for 3 minutes and maintain 30% of their previously determined maximal compression pressure. Systolic (SBP) and diastolic (DBP) blood pressure, pulse pressure (PP), and the heart rate (HR) were assessed at rest and between 2.45 and 3.15 minutes after the beginning of the IHG. The IHG was performed with the dominant hand (right hand for all participants), BP and SI_{DVP} were estimated on the contralateral limb.

Stiffness Index by digital volume pulse analysis

The digital volume pulse waveforms were recorded at rest and between the 2.45-minute and 3.15-minute marks of the 30% maximal IHG using a finger photoplethysmograph (Pulse Trace 2000, MicroMedical, Rhymney, UK). SI_{DVP}, which is an estimate of pulse wave velocity and arterial stiffness of the large arteries, was obtained from the subject's body height (h) divided by the time between the systolic and diastolic peaks of the DVP. Measurement represents the mean SI_{DVP} of 6 consecutive beats during 10 seconds.

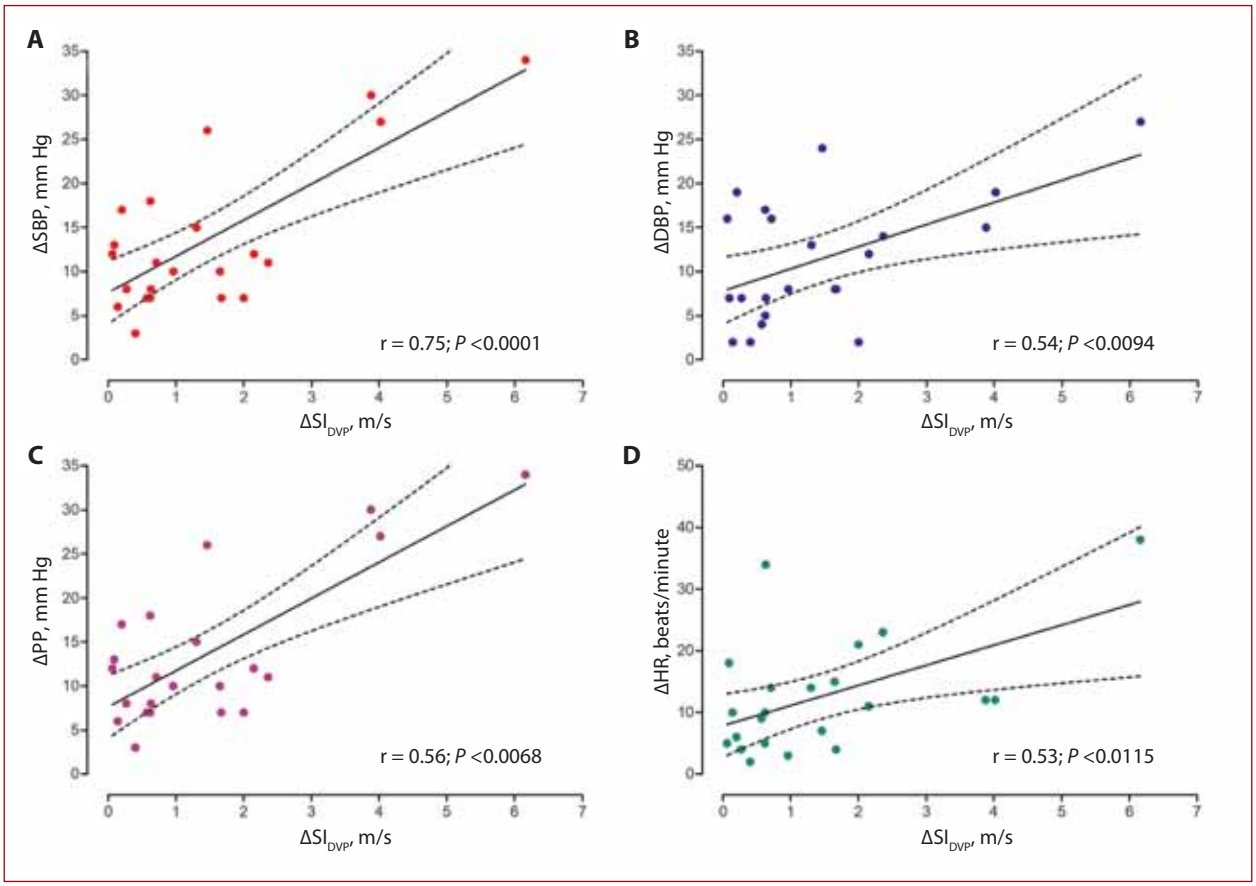

Figure 1. Correlation between the increase (Δ) in systolic BP, diastolic BP, PP pressure, heart rate, and the increase (Δ) in SI_{DVP} at the peak of handgrip exercise

Abbreviations: ΔSBP, increase in systolic blood pressure; ΔDBP – increase in diastolic blood pressure; ΔHR, increase in the heart rate; ΔPP, increase in pulse pressure; ΔSI_{DVP}, increase in the Stiffness Index

Statistical analysis

The continuous data distribution was normal (the D'Agostino-Pearson normality test); the results are reported as the mean (standard deviation [SD]). The rest-to-peak figures of the IHG measurements in respect of the SI_{DVP}, SBP, DBP, and HR were compared using paired t-tests. Correlations between the rest-to-peak of the IHG differences (Δ) of these parameters, i.e., ΔSI_{DVP} and ΔSBP, ΔPP or ΔDBP, or ΔHR, were analyzed through the Pearson correlation. Linear regression adjusted to the ΔHR was applied to study the relation between ΔSI_{DVP} and ΔSBP or ΔDBP. All statistical analyses were considered to be significant if $P < 0.05$. Analyses were conducted using MedCalc® statistical software version 20.014 (MedCalc Software Ltd., Ostend, Belgium).

RESULTS AND DISCUSSION

Clinical characteristics and results of the IHG are shown in Supplementary material, *Table S1*. The mean age of the studied subjects was 35.4 (12.3) years and there were 12 women. On average, the participants were slightly overweight, with a body mass index (BMI) of 26.0 (4.2) kg/m^2, and the maximal strength of the handgrip was 29.8 (7.9) kg.

The mean values in respect of the SBP, DBP, BPmean, PP, HR, and SI at rest and near the end of the IHG are presented and compared in Supplementary material, *Table S1*. All were within normal values. Compared to the rest, the IHG caused significant increases in all measured parameters.

Hemodynamic and Stiffness Index response to IHG maneuver

The initial study determined that the 3-minute IHG resulted in maximal hemodynamic response. Prolonging the IHG results in muscle weakness and diminished IHD. The increased SI_{DVP} and BP return to pre-exercise level within 1–3 minutes after cessation of the handgrip (data not shown).

Correlation of ΔSI_{DVP} with changes in SBP, DBP, PP, and HR during IHG

Figure 1 shows the results of the Pearson correlations between ΔSI_{DVP} and ΔSBP, ΔDBP, ΔPP, and ΔHR during the IHG. All correlations were positive and significant. Similarly, ΔBPmean was significantly correlated with ΔSI_{DVP} (data not shown).

Linear regression models adjusted for ΔHR show that ΔSI_{DVP} was significantly related to ΔSBP ($P = 0.0003$; adjusted model's R^2 0.61) and ΔDBP ($P = 0.0212$; adjusted model's R^2 0.40). In other words, ΔSI_{DVP} during the IHG was significantly correlated with ΔSBP or ΔDBP, regardless of the effects of ΔHR.

We demonstrate that an IHG-induced surge in BP increases arterial stiffness, regardless of the HR effects. An IHG is a physiological maneuver that stimulates the sympathetic nervous system, increases vascular resistance, and elevates BP. Consequently, raised SBP and DBP transfer the mechanical load from elastin to collagen fibers, distending and deforming the arterial walls and, thus, increasing arterial stiffness, which translates further into an increased LV arterial load.

Augmented arterial stiffness is a significant risk factor for cardiovascular events, particularly in elderly subjects, as well as in those suffering from diabetes, chronic renal disease, and hypertension [1]. The measurement of arterial stiffness is recommended in people with cardiovascular risk factors and diseases, particularly hypertension [3, 4]. Arterial stiffness is frequently described as segmental and local pulse wave velocity, or a general marker, such as the Stiffness Index. Prolonged exposure to hypertension results in adaptative structural changes in the arterial wall, which is difficult to reverse; therefore, acute decreases in BP do not reduce the markers of arterial stiffness. However, a long-term BP reduction decreases arterial stiffness.

In our study, the sustained (approximately) 3-minute increase in BP significantly augmented SI_{DVP}. Noteworthy is the fact that, on average, the increases in both SBP and DBP were within normal range values during the IHG. Nevertheless, these increases were sufficient to affect the distensibility of the arterial walls in healthy people.

Several investigators examined short-term vascular hemodynamics related to various forms of exercise in both young adults and the elderly [5–7]. However, BP and arterial stiffness were measured after a period of rest. In contrast, our study examines arterial stiffness at the peak of the IHG, during peak SBP and DBP. In patients with hypertension, an exaggerated response to exercise is frequently observed, resulting in higher arterial stiffness measures.

Blood pressure surges are commonly observed in healthy people and those with hypertension, e.g., during exercise, emotions, or after awakening [8]. Arterial stiffness measured during such events may likely differ from data acquired in different circumstances.

It was also noticed that an increase in sympathetic activity influences the mechanical properties of arterial vessels through various mechanisms, including the HR increase [9]. A positive relationship between the HR and high arterial stiffness was reported in normotensive and hypertensive individuals [10]. We have also noted similar findings, with the increase in the HR correlating positively with the increase in SI_{DVP}. However, the impacts of BP upon arterial stiffness appear to be unaffected by the potential influence of the HR. Nevertheless, it is currently difficult to separate the effect of BP and the heart rate on SI_{DVP}.

Study limitation

We studied only healthy subjects to evaluate whether arterial stiffness is a dynamic feature. Consequently, conclusions should not be extrapolated to patients with existing cardiovascular disease. Similar or even exaggerated responses could likely be observed in individuals suffering from hypertension. Nevertheless, this will require a separate study. Moreover, additional investigation is warranted in healthy populations, including improved sex balance and older subjects.

In summary, we showed that in healthy people a rapid increase in BP triggered by the 3-minute IHG elevates arterial stiffness, regardless of the change in the HR. As arterial stiffness depends on the current BP, it appears that the results of arterial stiffness measurements should be reported together with BP readings.

Supplementary material

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

Article information

Conflict of interest: None declared.

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Altered monocytic phenotypes are linked to a hypertension form: A clinical observational study

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INTRODUCTION

The past decade witnessed an explosion of research interest in the role of immunity in hypertension. Accumulating evidence suggests that immune cells infiltrate the key organs contributing to target damage [1]. Although it has become evident that T cells play an important role in experimental and human hypertension [1–3], the role of monocytes subsets remains to be elucidated. In humans, elevated blood pressure (BP) is related to the increased levels of inflammatory cytokines and activated monocytes [4]. Our study aimed to examine the exact phenotype of monocyte subsets in relation to various clinical pictures — established hypertension (HTN) and secondary form — primary hyperaldosteronism (PHA), compared to newly diagnosed hypertensives (NDH).

METHODS

Sixteen NDH, 14 HTN, and 15 PHA consecutive patients were recruited for the study. PHA was confirmed by a positive saline infusion test according to the Endocrine Society Guidelines [5]. HTN was defined as established hypertension treated with β-blocker, diuretic, angiotensin-II convertase enzyme inhibitor/angiotensin-II receptor blocker (ACEI/ARB), and calcium channel antagonist (CCA). In all HTN subjects, secondary causes of hypertension were excluded. NDH was defined as newly diagnosed, untreated hypertension. All patients were matched for sex, age, body mass index (BMI), and blood pressure levels on 24-hour ambulatory blood pressure monitoring (ABPM).

In all patients, clinical and biochemical evaluation, serum/plasma level of renin-angiotensin II (Ang II) — aldosterone, albuminuria in the 24-hour sample, 24-hour ABPM, echocardiography, duplex Doppler ultrasonography of carotid arteries, and monocytes characteristics were performed (Supplementary material, *Figure S1*).

This study was approved by the Local Bioethics Committee in the Institute of Cardiology in Warsaw (approval no. 1470). All procedures in the study were in accordance with the 1964 Declaration of Helsinki. Written informed consent was obtained from all patients.

Statistical analysis

The normality of variables distribution was checked with the Shapiro-Wilk test. Continuous variables with normal distribution were compared, among the 3 groups studied, using the ANOVA test. Continuous variables with non-normal distribution, including all 44 cell characteristics, were compared, among the 3 groups studied, using the Kruskal-Wallis test. Categorical variables were compared using the χ^2 test.

Linear regression analysis adjusted for age, sex, body mass index (BMI), and current smoking status was performed to test the effect of the PHA or HTN groups on selected monocyte subpopulations in relation to the

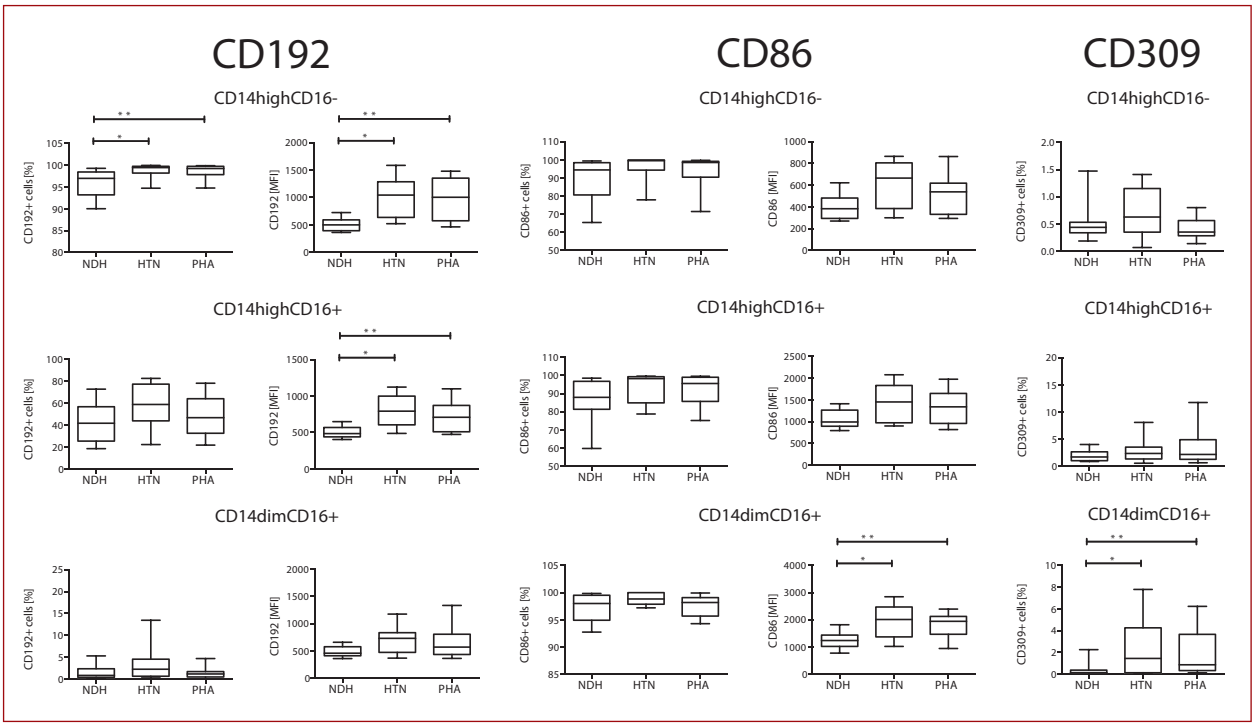

Figure 1. Expression of selected markers in monocyte subsets in patients with hypertension. The percentages of CD192, CD86, and CD309 positive cells within individual monocyte subsets including CD14highCD16-, CD14highCD16+, and CD14dimCD16+ cells are shown in patients with NDH, HTN, and PHA. MFI indicates mean fluorescence intensity. Boxes represent the 25th and 75th percentiles and horizontal lines the median

Abbreviations: HTN, hypertension; NDH, newly diagnosed hypertensives; PHA, primary hyperaldosteronism

NDH group. The false discovery rate (FDR) correction was applied while testing differences with respect to all 44 cell characteristics among all subgroups (Supplementary material, *Figure S2*).

RESULTS AND DISCUSSION

We assessed NDH, HTN, and PHA subjects matched for sex, age, BMI, and daily systolic and diastolic BP on 24-hour ABPM (Supplementary material, *Table S1*). Subjects with PHA were characterized by a significantly higher level of plasma aldosterone and a lower plasma level of Ang II as compared to NDH and HTN subjects. Diabetes mellitus (DM) 2 and ischemic heart disease (IHD) were observed more often in HTN and PHA compared to NDH. A higher left ventricular mass index (LVMI) was observed in the HTN and PHA groups as compared to NDH subjects (Supplementary material, *Tables S1, S2*).

We observed no differences in the content of total monocytes or their subsets including classical (CD14high-CD16-), intermediate (CD14highCD16+), and nonclassical (CD14dimCD16+) cells among the groups (Supplementary material, *Figure S1*). Our data are in line with results obtained by van der Heijden et al. [6] who did not observe significant differences in the peripheral monocytes subsets between PHA and NDH patients [6].

As monocyte chemoattractant protein-1 (MCP-1) is involved in monocyte infiltration into the inflamed tissue, we analyzed the role of its receptor — C-C chemokine receptor 2 (CCR2) among monocytes. We noticed that PHA and HTN subjects presented a higher percentage and mean fluorescence intensity (MFI) of CD192 among total monocytes, classical and intermediate subsets compared to NDH patients (Figure 1, Supplementary material, *Figure S2,* and *Table S3*). The multiple linear regression model showed that advanced forms of hypertension — HTN and PHA were linked to a higher percentage of CD14highCD16-CD192+ monocytes and higher surface expression of CD192 among classical and intermediate monocytes (Supplementary material, *Table S4*).

MCP-1 plays a key role in atherosclerosis and insulin resistance, and it is responsible for recruiting monocytes to the site of inflammation [7]. Infiltration of monocytes into the heart and vasculature in the course of hypertension depends on the CCL2 (C-C chemokine ligand)-CCR2 axis [1]. Pharmacological inhibition of CCR2 prevents the recruitment of monocytes into the aortic wall and heart [1]. Interestingly, Zaldivia et al. [8] have shown the reduction of classical monocyte activation in HTN patients after renal denervation procedure. Poor BP control might induce monocytes infiltration and progression of target organ damage (TOD) stated by albuminuria and higher LVMI and IMT. The chronic inflammatory state could create a vicious circle and further progression of TOD and the development of complications such as DM type 2 or IHD.

Secondly, we assessed CD309, known as vascular endothelial growth factor receptor 2 (VEGF-R2), which is expressed by endothelial cells and is a pro-angiogenic factor involved in neovascularization and atherosclerosis [9–10]. We proved that patients with HTN and PHA were characterized by a higher percentage of CD14dimCD16+ CD309+ monocytes in comparison to patients with NDH (Figure 1, Supplementary material, *Figures S1,* and *S2*). However, the result was not significant in the multiple linear regression model (Supplementary material, *Table S4*). We indicated that HTN and PHA subjects are characterized by higher intima-media thickness (IMT) which is considered a surrogate marker of atherosclerosis. *In vivo* models showed that VEGF induces the angiogenic cascade with hypoxia-inducible factor 1 (HIF-1). In hypertensive rats, VEGF expressed by macrophages and T lymphocytes stimulates endothelial cells to produce MCP-1, attracting monocytes and enhancing cell migration by increasing permeability of the endothelial layer [11]. There is evidence that VEGF induces migration and activation of monocytes through induction of MCP-1 [12]. Zhao et al. [13] have shown that VEGF acts as a mediator of Ang II-induced vascular inflammation. Stumpf et al. [12] have observed that young subjects with hypertension are characterized by higher plasma levels of VEGF and MCP-1. Elevated VEGF levels in hypertensive patients support the concept of abnormal angiogenesis in the pathophysiology of hypertension [14].

In the current study, we assessed CD86 expression as a key protein that provides the costimulatory signals necessary for T-cell activation and survival. The expression of CD86 was higher in the population of non-classical monocytes in HTN and PHA as compared to NDH subjects (Figure 1, Supplementary material, *Figures S1* and *S2*). The multiple linear regression model showed that patients with HTN and PHA were characterized by higher surface expression of CD86 among CD14dimCD16+ monocytes (Supplementary material, *Table S4*).

We observed a preactivated monocyte phenotype in hypertensives. This is consistent with other studies. Dorffel et al. have demonstrated the increase of interleukin (IL-1β) secretion from peripheral monocytes after Ang II stimulation in comparison to normotensive subjects [4].

The limitations of our study include the small sample size and the limited number of monocyte phenotypes analyzed. We also observed a high incidence of DM type 2 in PHA and HTN patients. Our observations were in line with results obtained in the JPAS and RESIST-POL registries (further discussed in Supplementary material, *Section S3*). Moreover, our study groups were treated with hypotensive drugs that could have influenced the phenotype of monocytes (Supplementary material, *Section S3*).

CONCLUSION

Monocytes isolated from patients with an advanced form of hypertension present features of increased cell activation measured as a higher percentage and surface expression of MCP-1 receptor among classical and intermediate subsets. Patients with poor hypertension control and features of TOD exhibit higher surface expression of costimulatory marker CD86 among nonclassical monocytes and a higher percentage of nonclassical cells positive for VEGF-R2.

Supplementary material

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

Article information

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Does sodium and potassium intake assessment by diet-related mobile applications do more harm than good?

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INTRODUCTION

Increased sodium intake is associated with elevated blood pressure (BP) and a higher risk of cardiovascular events while increased potassium intake appears to have opposite effects [1, 2].

Recent recommendations for cardiovascular prevention point to the need for reduced sodium intake and underline the positive role of potassium intake (e.g., with fruits or vegetables) [3].

About three-quarters of sodium are consumed with processed foods [4]. The estimation of the amount of sodium consumed with processed foods may be tedious. Thus, non-pharmacological intervention in the treatment of a particular patient remains difficult to assess, and a tool supporting low-sodium diet and education should be available.

It can be expected that patients will use the available mobile applications to monitor sodium intake [5]. Promising experience with only very few applications verified in clinical trials may lead both care providers and patients to an illusion about the benefits of using any of the available applications [6, 7]. Unfortunately, most of the available mobile applications have not been tested appropriately for medical purposes [8].

Thus, we aimed to validate four of the popular diet-related mobile applications for the assessment of sodium and potassium intake in processed food products.

METHODS

Among popular health-related mobile applications available in the Polish Appstore (*www.apple.com/pl/app-store/*), 4 mobile applications (App1=FatSecret 9.8, Secret Industries Pty Ltd, Caulfield North, Australia; App2=Yazio, Yazio 7.4.2. GmbH, Erfurt, Germany; App3==Fitatu 3.11.0, Fitatu Sp. z o.o., Poznań, Poland; App4=MyFitnessPal 21.22.5.36915, MyFitnessPal Inc., San Francisco, CA, US) were selected for the study.

A dietician performed a nutritional assessment of randomly selected two-day dietary recalls of 120 participants from the trial: "National Study of Nutrition and Nutritional Status of the Adult Polish Population in the Years 2017–2020" using the Polish reference method (RM), Dieta 6.0 software [9]. Sodium and potassium intake measured by selected mobile applications was compared with RM.

All quantitative values are presented using median values and interquartile range (IQR) or numbers followed by percentages. The comparisons of quantitative variables were performed using the Wilcoxon signed-rank test. Spearman's coefficients and scatterplots were used to present correlations between RM and results obtained by mobile applications. The agreement between methods was assessed using the Bland-Altman method. Detailed descriptions of mobile applications, dietary recalls selection, assessment, and statistical methods are available as Supplementary material.

Table 1. The comparison of daily median intake of sodium and potassium and the agreement between values obtained by the investigated mobile applications and the reference method (Bland-Altman analysis)

	Mobile application	Intake, mg	*P*-value	Bias, mg	Upper limit of agreement, mg	Lower limit of agreement, mg
Sodium	Reference method	3846 (2942–5235)	—	—	—	—
	App1	3520 (2439–4530)	<0.001	483 (278–687)	2697 (2347–3046)	–1731 (–2081–[–1382])
	App2	1745 (973–2642)	<0.001	2083 (1808–2357)	5060 (4589–5530)	–894 (–1365–[–424])
	App3	1942 (1234–2792)	<0.001	2010 (1765–2255)	4671 (4250–5091)	–651 (–1071–[–230])
	App4	247 (14–1112)	<0.001	3427 (3099–3755)	6981 (6419–7543)	–128 (–689–434)
Potassium	Reference method	3188 (2348–3914)	—	—	—	—
	App1	2910 (2062–3574)	<0.001	236 (84–387)	1880 (1620–2140)	–1409 (–1668–[–1149])
	App2	1244 (766–1784)	<0.001	1907 (1658–2157)	4615 (4187–5043)	-800 (–1228–[–372])
	App3	1985 (1128–2652)	<0.001	1256 (1038–1474)	3616 (3243–3989)	–1104 (–1477–[–731])
	App4	286 (11–684)	<0.001	2748 (2498–2999)	5467 (5037–5897)	29 (–400–459)

Sodium and potassium intake measured by reference method and each mobile application is presented as median values and interquartile range. Comparisons of values obtained by each mobile application with the reference method were made using the paired Wilcoxon signed-rank test with Bonferroni correction for multiple comparisons. Biases and limits of agreement with 95% confidence intervals for 120 subjects in each group

Abbreviations: App1, FatSecret; App2, Yazio; App3, Fitatu, App4; MyFitnessPal

RESULTS AND DISCUSSION

Clinical characteristic of the study group

Investigated dietary recalls were obtained from 60 females and 60 males. Median age and body mass indexes were 41 (28.8–54.0) years and 24.7 (22.4–27.7) kg/m^2, respectively. Considering dietary assessment, daily median energy intake was 2193 (1504–2767) kcal, protein intake 80 (55–100) g, carbohydrates intake 281 (198–339) g, and fat intake 76 (55–117) g.

Sodium intake measurements

According to the RM, daily median sodium consumption was 3846 (2942–5235) mg. Sodium consumption measured by mobile application was lower than measured by RM (Table 1). App4 showed no consumption of sodium (sodium intake = 0 mg) in 15 (12.5%) of the dietary records.

Sodium intake measured with App1 was strongly related to the RM, whereas App2 and App3 revealed moderate and App4 no correlation. Correlations are presented in Supplementary material.

The results of Bland-Altman analyses revealed relevant bias. The lowest bias was observed for App1, while App2 and App3 had similar intermediate biases, and the largest bias was observed for App4 (Table 1). Similarly, the lowest range between upper and lower limits of agreement was observed when App1 was used. Bland-Altman plots are available in Supplementary material.

Potassium intake measurements

Median potassium intake measured with RM was 3188 (2348–3914) mg. Potassium intake estimated with the mobile applications was lower than for RM (Table 1). App4 showed no consumption of potassium (potassium intake = 0) in 27 (22.5%) of the analyzed dietary records.

Potassium intake assessed by App1 and RM was strongly related, whereas the relations with App3 and App4 were moderate and with App4 weak. Correlations are presented in Supplementary material.

The results of Bland-Altman analyses showed relevant bias. The lowest bias was observed for App1, while App2 and App3 had similar moderate biases, and the largest bias was observed for App4 (Table 1). The range between lower and upper limits of agreement was lowest when App1 was used. Bland-Altman plots are available in Supplementary material.

We assessed daily sodium and potassium intake measured by mobile applications in comparison to the reference method in two-day dietary recalls from randomly selected 120 Polish citizens. Our results reveal that the four popular diet-related mobile applications do not agree with the RM. All applications underestimated sodium intake in most participants. This may give the users the false impression that their potentially excessive salt intake is normal. Also, potassium intake was underestimated in most of the participants. Among the products evaluated, the poorest results for both sodium and potassium intake were observed with MyFitnessPal (App4), where also a remarkable zero daily consumption of sodium and potassium was reported in >10 and >20%, respectively, of the participants, while FatSecret (App1) showed the least deviation from the RM.

Only a few small studies regarding the validity of popular mobile applications for the assessment of sodium intake have been published. Both FatSecret (App1) and MyFitnessPal (App4), among other mobile applica-

tions, against the United Kingdom reference method (Dietplan6) were unreliable in the assessment of sodium intake [10]. In a Belgian study, MyFitnessPal (App4) had a poor agreement with the reference method (Nubel) [11]. Moreover, the data from MyFitnessPal required cleaning before the analysis due to extremely high and likely erroneous values.

Despite poor results of validation studies, MyFitnessPal has been used in clinical trials aimed to decrease sodium intake; while sodium intake was reduced there was no significant BP reduction [12, 13]. FatSecret, Fitatu, or Yazio, have not been used in intervention studies aimed to reduce salt intake.

The mobile application Keenoa using an artificial intelligence algorithm underestimated potassium (and sodium as well) intake based on food images (photography) [14].

Important limitations of the study must be considered. First, mobile applications are continuously developing, and our results may become outdated. Second, the study was performed in the Polish population and may not be valid in other populations. Third, the study lacked assessment of urinary sodium and potassium excretions [15].

In conclusion, mobile applications may be easily accessible (depending, of course, on an individual's ability to use them); they are cheap and helpful tools. However, they must be properly validated before they are implemented for use. Currently, we cannot recommend any mobile applications for the assessment of sodium or potassium intake.

Supplementary material

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

Article information

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Daily behaviors regarding using smartphones in patients with high-voltage cardiac implantable electronic devices

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INTRODUCTION

The growth of the connectivity market in the 21st century, along with an increasing demand for new, more advanced appliances, has led to the situation when a vast majority of citizens have multiple "smart" devices. It is estimated that nowadays more than six billion people use smartphones [1]. The results of the European Heart Rhythm Association survey indicate that more than 80 000 implantable cardioverter-defibrillators (ICDs) and 50 000 cardiac resynchronization therapy (CRT) devices are implanted each year in patients with heart failure (HF) in Europe [2]. Therefore, the number of patients who have both an implantable device and a smartphone increases each year.

Already in the 1990s, evidence demonstrating interference of mobile phones with ICDs has grown, and in recent years more cases of significant malfunctions, including deactivation of life-saving therapies in patients with ICDs, due to the proximity of a smartphone have been reported [3–8]. Although the incidence of smartphone-induced interferences remains uncertain, it is important to assess that probability based not only on benchmark tests but also on the patients' perspective including the daily habits of smartphone users. Therefore, we undertook this analysis to examine the patients' behaviors regarding their use of smartphones.

METHODS

One hundred fourteen consecutive patients with an ICD or cardiac resynchronization therapy device (CRT-D) implanted according to the guideline-directed indications, who attended the device follow-up in our institution's department between the July 5, 2021 and August 15, 2021 were asked to participate in the study. Two patients declined participation. Among patients who agreed, a questionnaire consisting of 17 questions has been distributed. The first 11 questions concerned patients' daily behaviors were answered by patients while the remaining 6 about their demographics and device characteristics were filled by the nurse. Full details of the questionnaire, both in Polish and in the English translation, can be found in the Supplementary material.

The approval of the ethics committee and patient informed consent were not required for this study.

Statistical analysis

The categorical variables were presented as counts and percentages. The normality of distribution of continuous variables was examined with the Shapiro-Wilk test and, as all variables were distributed non-normally, they were reported as median (interquartile range [IQR]). STATISTICA 10 (StatSoft Inc., Tulsa, OK, US) was used for the calculations.

RESULTS AND DISCUSSION

Of 114 patients who answered the questionnaire, 77 (68.8%) had a smartphone. The median age of patients having a smartphone was 63 years, and women constituted 24.7% of all patients. The median time from implantation was 2.6 years.

More than three-quarters of patients (76.6%) had a smartphone for more than three years, and the most common locations to carry a smartphone were either handbags on the right hand (25.9% of the overall population)

Table 1. Characteristics of the population of patients with a smartphone and a high-voltage device

Characteristics of patients having a smartphone		Value
Age, years, median (IQR)		63 (58–71)
Male sex, n (%)		58 (75.3)
Type of device, n (%)	ICD-VR	25 (32.5)
	ICD-DR	20 (26.0)
	CRT-D	32 (41.6)
Pacing dependency, n (%)		5 (6.5)
Prevention of sudden cardiac death (primary; secondary), n (%)		72 (93.5); 5 (6.5)
Time from implantation, years, median (IQR)		2.6 (1.3–5.7)
Time since purchasing the smartphone, n (%)	More than 3 years	59 (76.6)
	1–3 years	13 (16.9)
	Less than 1 year	5 (6.5)
Most common location to carry the smartphone, n (%)	Handbag on the left hand	7 (9.1)
	Handbag on the right hand	20 (25.9)
	Trousers pocket	38 (49.4)
	Jacket pocket on the left	5 (6.5)
	Jacket pocket on the right	9 (11.7)
	Other	6 (7.8)
Most common location to hold the smartphone while talking, n (%)	Left ear	21 (27.3)
	Right ear	53 (68.8)
	Patient using loudspeaker	12 (15.6)
Average hours a day spent on talking on the smartphone, n (%)	For more than 3 hours	1 (1.3)
	For 1–3 hours	16 (20.8)
	For less than 1 hour	52 (67.5)
	Almost none	8 (10.4)
Mobile phone turned on during the night, n (%)	Yes, next to the bed	35 (45.4)
	Yes, although far from the bed	33 (42.9)
	No	9 (11.7)
Experience of interference ever experienced by the patient, n (%)	Yes, several times	2 (2.6)
	Yes, once	1 (1.3)
	No, never	74 (96.1)
Change in the most common location to carry the smartphone after device implantation, n (%)	None	52/76 (68.4)
	Yes, in total	24/76 (31.6)
	Yes, in the jacket pocket on the right	9/24 (37.5)
	Yes, in the trousers pocket	4/24 (16.6)
Change in the most common location to hold the smartphone while talking after device implantation, n (%)	None	58 (75.3)
	Yes, in total	19 (24.7)
	Yes, to the left ear	2/19 (10.5)
	Yes, to the right ear	13/19 (68.4)
	Yes, the patient now using a loudspeaker	3/19 (15.8)
Change in the average time spent on using the smartphone, n (%)	None	51 (67.1)
	Yes, more	22 (28.6)
	Yes, less	4 (5.2)
Knowledge on the interference due to proximity of the smartphone and a device, n (%)	Yes, since implantation	54 (70.1)
	Yes, long after implantation	9 (11.7)
	None	14 (18.2)

Abbreviations: CRT-D, cardiac resynchronization therapy; ICD-DR, dual-chamber implantable cardioverter-defibrillator; ICD-VR, single-chamber implantable cardioverter-defibrillator

or a trouser pocket (49.4%). The most common location used to hold a smartphone while talking was the right ear (68.8%) followed by the left ear (27.3%). Most patients used the phone for talking for less than an hour a day (67.5%) while 20.8% of patients used it for 1–3 hours a day. Three patients (3.9%) ever experienced interference with their device functioning associated with using the smartphone. Of those, two experienced multiple incidents, while one reported a single incident.

After implantation, almost one in three patients (31.6%) reported a change in the most common location used to carry a smartphone, with the most frequent location then being a jacket pocket on the right side of the chest. Similarly, almost one in four patients after implantation (24.7%) modified the most common location to hold their smartphones while talking, most frequently to the right ear. However, it should be noted that two patients changed the preferred location to the left ear. Finally, almost 20%

of patients having a smartphone did not know about the possibility of interference between the smartphone held too close to the device, while the further 11.7% had not obtained such information at the time of implantation, but later.

Our analysis is the first report demonstrating the present habits of patients with cardiac implantable devices and smartphones. The population of patients has been restricted solely to patients with an ICD or a CRT-D due to two factors. First, the prior reports regarding interferences of modern smartphones with implantable devices indicate inhibition of life-saving interventions in patients with high-voltage devices. Second, due to the high risk of all-cause and sudden arrhythmic death, it is those patients who are at the highest risk in case of device malfunction [9].

Our results indicate that almost 30% of all surveyed patients did not know of the possibility of interference between a smartphone and a high-voltage device at the time of implantation. With constantly increasing numbers of people having smartphones, the number of patients who are possibly prone to such interference will increase over time. Moreover, approximately 30% of patients hold their phones close to the left ear, contrary to the guidelines of ICD manufacturers, who advise against placing the smartphone closer than 15 cm from the implanted device and holding it close to the left ear [10, 11].

Although three patients reported interference with device functioning associated with using the smartphone, such percentage could significantly change over time, as the more advanced smartphones with quick charging capability and long battery longevity are being introduced into the market. Increasingly popular Apple iPhone MagSafe, which unlike conventional charging methods utilizes a wireless charging system, has been reported to inhibit high-voltage therapies of ICDs due to magnets embedded in the structure of new iPhones [4]. These findings were recently supported by the demonstration, both *in vivo* and *ex vivo,* that the placement of an iPhone 12 Pro Max over the device might induce clinically relevant magnet interference [5]. Similar observations were made about other "smart" devices, including headphones; however, the most compelling evidence has been growing regarding smartphones [4–8]. Therefore, identification of patients' habits and perspectives — along with similar studies in different areas — concerning the use of smartphones should be considered pivotal in order to implement strategies to allow patients to obtain benefit from both a life-saving cardiac device, and use all advantages offered by present smartphones [12]. In that context, our study is the first to demonstrate the possible gaps in patient knowledge requiring educational efforts to minimize the risk of potentially life-threatening interferences, especially in pacing-dependent patients or in those with a high probability of malignant arrhythmias, who might get the largest benefit from a properly functioning ICD or CRT-D.

Limitations

First, the small sample size should limit the generalization of the results into broader populations. Moreover, there may be differences regarding the percentage of the population possessing smartphones, as well as in the type of those smartphones. Furthermore, no specifications of the smartphones were registered; however, such an approach was adopted to reduce the complexity of the survey for often elderly patients, who could have been unaware of such information. Finally, no information has been gathered regarding the specification of the implantable devices in the analyzed population (apart from the type of the device) or details of interference reported by the patients. That is because the primary purpose of the study was not to examine this issue but rather to define the behavioral patterns of patients with high-voltage devices using smartphones. Therefore, no data from the implantable devices were extracted regarding the parameters of the devices or details of possible interference events reported by patients.

Supplementary material

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

Article information

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Impella-supported intracoronary lithotripsy of left main in-stent restenosis

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A 69-year-old man with the diagnosed non-ST-elevation myocardial infarction (NSTEMI) was transferred from a local hospital after coronary angiography because of the critical left main (LM) bifurcation in-stent restenosis (ISR) (Figure 1A). Twelve months earlier, the patient underwent NSTEMI complicated by a cardiogenic shock and cardiac arrest, treated with the percutaneous coronary intervention (PCI) of the LM bifurcation with the double kissing crush (DK crush) technique. The procedure result was assessed only by angiography, without using intracoronary imaging. Due to the optimal angiographic effect, no atherectomy was used. The patient's concomitant diseases included chronic heart failure (HF), previous myocardial infarction with a chronic total occlusion (CTO) of the right coronary artery (RCA), permanent atrial fibrillation, type 2 diabetes mellitus, chronic kidney disease stage 3, as well as anemia (hemoglobin, 6.1 mmol/l).

On admission, the patient manifested symptoms of decompensated HF (Killip-Kimball II) with deterioration to pulmonary edema. Echocardiography revealed a severely reduced left ventricular ejection fraction (LVEF) of approximately 20%. The patient was referred to the local Heart Team. Due to high operative risk (SYNTAX score, 47.5 points; EuroSCORE II, 10%), he was disqualified from the coronary artery bypass grafting (CABG) and qualified for high-risk rescue PCI with the use of Impella CP support (Abiomed, Denver, CO, US).

After pharmacological stabilization, we performed PCI by the left femoral approach using the EBU 3.5 Guide Catheter (7 F) (Medtronic Ireland, Galway, Ireland) with Impella CP support (flow, 3.2 l/min), inserted via the right femoral access (Figure 1B). Following the initial intravascular ultrasound (IVUS) evaluation (Figure 1C), we decided to perform shockwave intravascular lithotripsy (S-IVL) (Shockwave Medical Inc., Santa Clara, CA, US) because of the severely calcified plaques in the distal segment of LM and the proximal segment of the left circumflex artery (LCX). After 80 ultrasonic pulses, the S-IVL balloon (3.5 × 12 mm) was fully expanded. Following the pre-dilatation with the NC balloon (3.5 × 15 mm), the sirolimus-coated balloon (SCB) was successfully delivered (Magic Touch 3.5 × 25 mm). Because of the protruding calcium nodules in the distal segment of the LM (Figure 1D), we implanted the stent into the LM without covering the bifurcation (Figure 1E). The optimal final angiographic result was confirmed by IVUS (Figure 1F). The Impella was explanted directly after PCI while maintaining the patient's hemodynamic stability. The femoral artery was closed with two Perclose ProGlide devices (Abbott Vascular, Chicago, IL, US) and a 6-Fr Angio-Seal (St. Jude Medical, St. Paul, MI, US) device.

Following the PCI, the patient was monitored in the intensive care unit. Due to periprocedural blood loss, two units of red blood cells were transfused. The patient was discharged from the hospital six days after PCI.

The support of high-risk PCI procedures with Impella ensures hemodynamic stability and optimizes organ perfusion, improving crucial parameters such as renal function [1]. Patients without support from the second coronary artery due to its chronic total occlusion are particularly exposed to hemodynamic destabilization during the procedure. The safety and clinical efficacy of Impella's support in treating very high-risk populations have been demonstrated in several large registries and observational studies [2, 3]. Moreover,

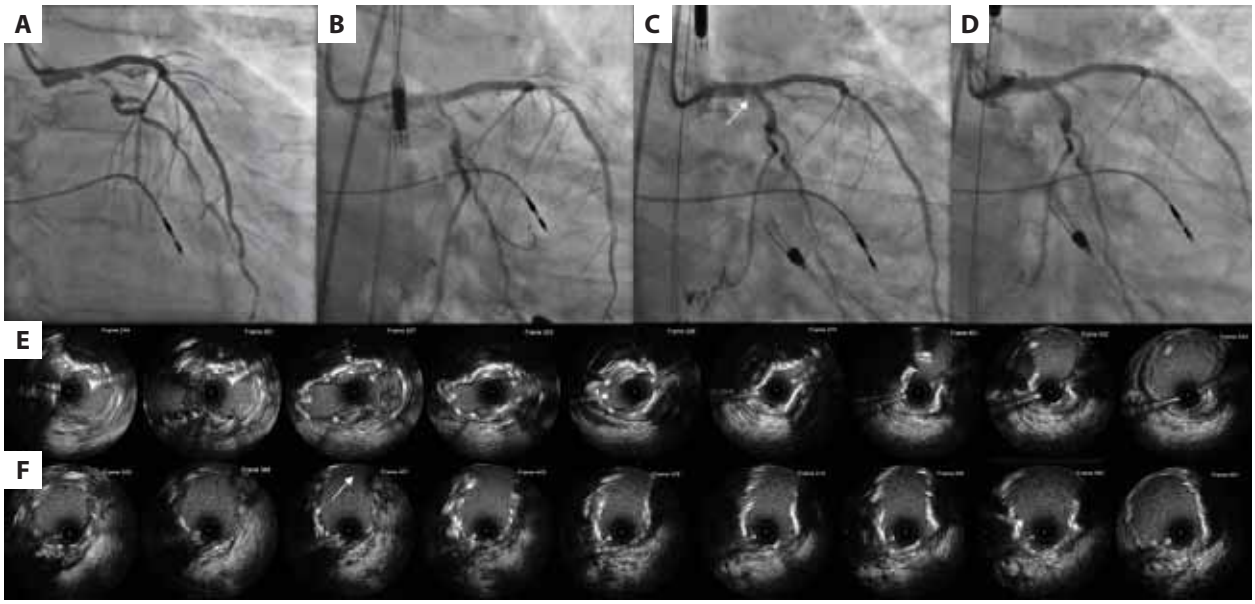

Figure 1. A. An anterior-posterior (AP) caudal angiographic view of the left coronary artery (LCA): significant stenosis of the left main and left circumflex arteries (LCX). **B.** AP caudal angiographic view of the LCA with Impella. **C.** Angiographic result after using a drug-coated balloon (DCB); protruding calcium nodules in the distal LM (the white arrow). **D.** Final angiographic view of the LCA after stent implantation. **E.** Intravascular ultrasound (IVUS) cross-sections of the LCX and the left main (LM) before shockwave intravascular lithotripsy (S-IVL). **F.** Final IVUS cross-sections of the anterior descending artery (LAD) in the proximal segment and the LM with a wide LCX ostium (the white arrow)

it should be emphasized that IVL seems to be currently the only effective and safe method of treating restenosis and/or under-expansion of stents implanted within highly calcified lesions [4].

Article information

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Successful shockwave intravascular lithotripsy of an under-expanded stent after a month from primary implantation

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We present a case of a 58-year-old male, with hypertension, hyperlipidemia, a past medical history of percutaneous coronary intervention (PCI) in the left anterior descending artery (LAD) in 2006, and with a history of inferior wall ST-segment elevation myocardial infarction (STEMI) one month before current hospitalization, treated with PCI in a regional Cardiology Department.

During the index procedure, coronary angiography (CA) revealed critical stenosis in the right coronary artery (RCA) and an additional lesion in the left circumflex artery (LCx). PCI-RCA with 3.0 × 30 mm drug-eluting stent (DES) implantation was performed successfully. Due to ongoing ischemia, a predilatation of LCx with a 2.0 × 15 mm non-compliant (NC) balloon at 12 atm was performed and followed by a 3.5 × 30 mm DES Resolute Onyx (Medtronic, Galway, Ireland) implantation at 16 atm. Due to significant stent under-expansion, unsuccessful optimization with a 3.5 × 15 mm NC at 22 atm was performed (significant "dog bone effect"). Additional postdilatation with an ultra-high-pressure 3.5 × 10 mm OPN-NC balloon at 35 atm was performed. Despite aggressive postdilatation, full stent expansion was not obtained. The patient was discharged with symptoms of angina, class II according to the Canadian Cardiovascular Society (CCS) scale.

One month later, the patient was referred to our Cardiology Department with exacerbation of angina symptoms (CCS class III). CA and fluoroscopic digital stent enhancement (DSE) revealed incomplete stent expansion in LCx (residual stenosis 80%) (Figure 1A). Additional evaluation in optical coherence tomography (OCT) revealed massive calcifications with coexisting impaired endothelialization on the under-expanded struts (Figure 1E and Supplementary material, *Video S1*). Initially, we performed unsuccessful postdilatation with a 3.5 × 15 mm NC balloon (20 atm) (Figure 1B). Therefore, we used the Shockwave Intravascular Lithotripsy (S-IVL) (Shockwave Medical Inc, Santa Clara, CA, USA) 3.5 × 12 mm balloon and after 40 ultrasonic pulses, we achieved full scaffold expansion (Figure 1C). Finally, we optimized the stent with a –3.75 × 15 mm NC balloon (16 atm). Control CA, DSE, and OCT confirmed adequate stent expansion without any residual stenosis (Figure 1D, 1F, and Supplementary material, *Video S2*). The patient was discharged two days after the procedure without any in-hospital complications.

In the presented case, at the primary PCI, the scaffold was implanted despite insufficient lesion preparation with an undersized balloon catheter, which resulted in significant post-PCI stent under-expansion and should not be part of contemporary practice.

Impaired stent expansion is associated with a higher risk of complications, mainly in-stent thrombosis and restenosis. To improve outcome, an appropriate lesion preparation before scaffold implantation with dedicated balloon-dependent devices (non-compliant, scoring, cutting, OPN) or atherectomy devices (rotational, orbital, laser) is fundamental [1, 2]. However, when the stent under-expansion occurs the armamentarium of treatment methods is limited [3, 4]. In our case, one of the major therapeutic options for stent

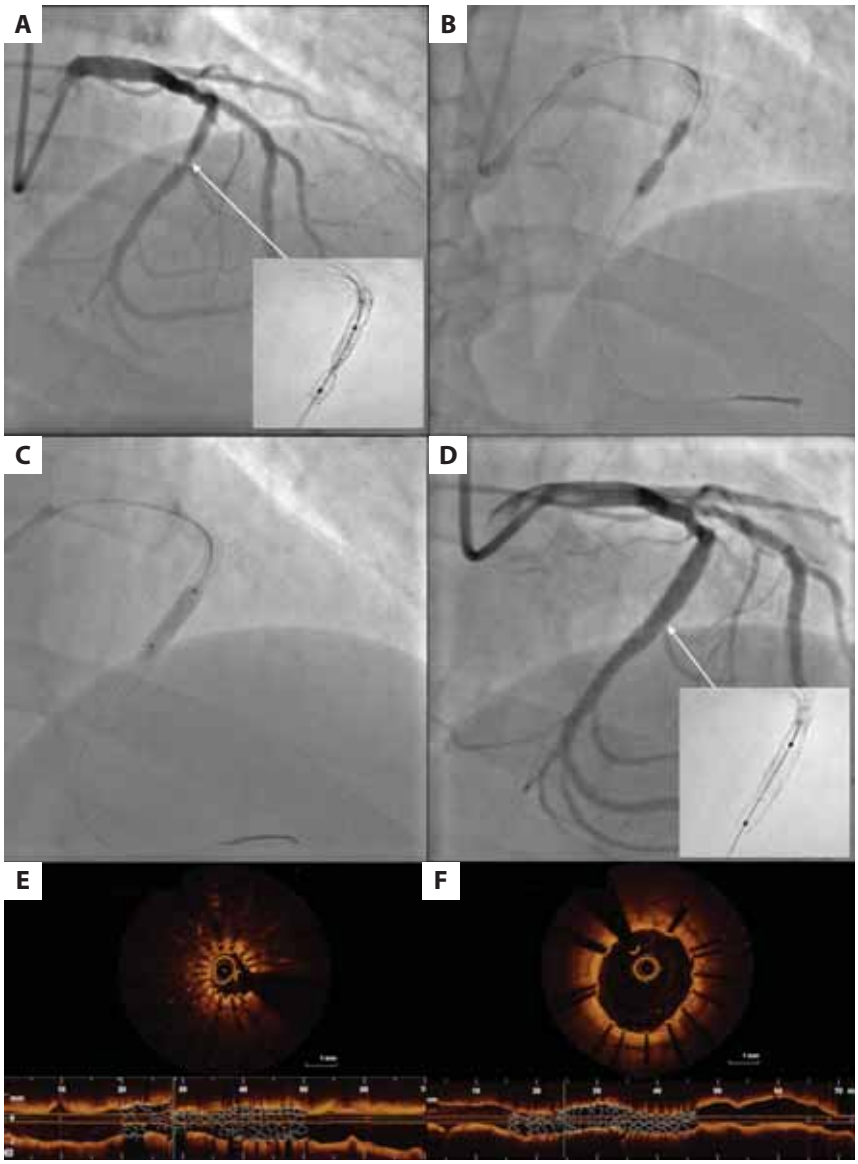

Figure 1. A. Coronary angiography of culprit lesion in the left circumflex artery and significant stent under-expansion visible in fluoroscopic digital stent enhancement. **B.** Significant under-expansion on the 3.5 mm non-compliant balloon catheter. **C.** Full expansion of the shockwave intravascular lithotripsy 3.5 × 12 mm balloon catheter. **D.** Final angiographic result of the procedure with adequate scaffold expansion visible in fluoroscopic digital stent enhancement. **E.** Initial lesion evaluated on optical coherence tomography. **F.** Final result confirmed on optical coherence tomography

under-expansion — postdiltation with the OPN balloon — turned out to be ineffective. Therefore, we used S-IVL as a bail-out technique. Although we did not observe any complications, the safety concerns are not unfounded — some data suggest that S-IVL may lead to disruption of scaffold integrity [5]. Nevertheless, in the presented case, the clinical benefits of the method outweighed its potential risk. We demonstrated that S-IVL with the additional support of OCT is a safe approach to a stent failure, even a month after the primary procedure.

Supplementary material

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

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Rupture of the membranous septum and aortic root perforation after transcatheter aortic valve implantation successfully treated by surgery

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Transcatheter aortic valve implantation (TAVI) has become a treatment of choice for aortic stenosis (AS) in patients at high and intermediate surgical risk [1, 2]. Emergency cardiac surgery after TAVI is rare (1%) and has a high mortality rate (67%). The most common causes are prosthesis dislocation/embolization, coronary occlusion, severe regurgitation, right ventricle (RV) or aortic annulus rupture, and aortic dissection [3]. A 70-year-old male was admitted with symptomatic severe AS (the New York Heart Association [NYHA] class III). Transthoracic echocardiography (TTE) showed a bicuspid aortic valve (BAV), maximal and mean gradients of 78 and 46 mm Hg, respectively, and of 50% left ventricular ejection fraction (EF). The patient was disqualified from surgical valve replacement due to high risk (EuroSCORE, 4.7%) and comorbidities (chronic obstructive pulmonary disease, diabetes, liver cirrhosis, chronic renal insufficiency). Based on multi-slice computed tomography (MSCT), the Heart Team recommended TAVI via the right femoral artery despite calcified stenosis of the right external iliac artery. The lithotripsy was attempted with a 6.5 × 60 mm Shockwave balloon but was unsuccessful, so transcarotid access was chosen as the next step. Under general anesthesia, Edwards-SAPIEN 3 Ultra 29 mm valve was implanted through the left carotid artery (Figure 1A) with satisfactory effect: mean gradient 14 mm Hg, EF 50%, no paravalvular leak. Three days after TAVI the patient developed hypotension (90/30 mm Hg) and oliguria. Hemodynamically significant fistula between the aortic root and the RV was visualized on transesophageal echocardiography (TEE) (Figure 1B). MSCT confirmed rupture of the membranous part of the interventricular septum (Figure 1C). Transcatheter closure of the fistula was unsuccessful because of the instability and dislocation of the 4 Amplatzer Valvular Plug III occluders in the pulmonary artery. Occluders were removed with a snare (Figure 1D). Due to progressive cardiogenic shock (blood pressure 80/10 mm Hg, metabolic acidosis, anuria), the patient was subjected to salvage surgery (EuroSCORE, 83.8%). During surgery, the fistula between the aorta and RV was closed with a pericardial patch (40 × 20 mm), and Hancock 25 (Medtronic, Minneapolis, MN, US) bioprosthesis was implanted (Figure 1E). The ruptured ascending aorta was replaced with the aortic prosthesis (JOTEC, Hechingen, Germany). The procedural time was 4 hours, and after 15 hours the patient was weaned from the ventilator. Three days after surgery a pacemaker was implanted due to advanced AV block. TTE showed preserved EF, proper function of the prosthetic valve, and no PVL. Post-sternotomy wound infection was successfully treated by vacuum-assisted closure therapy and antibiotics. Hospitalization time was 32 days. After

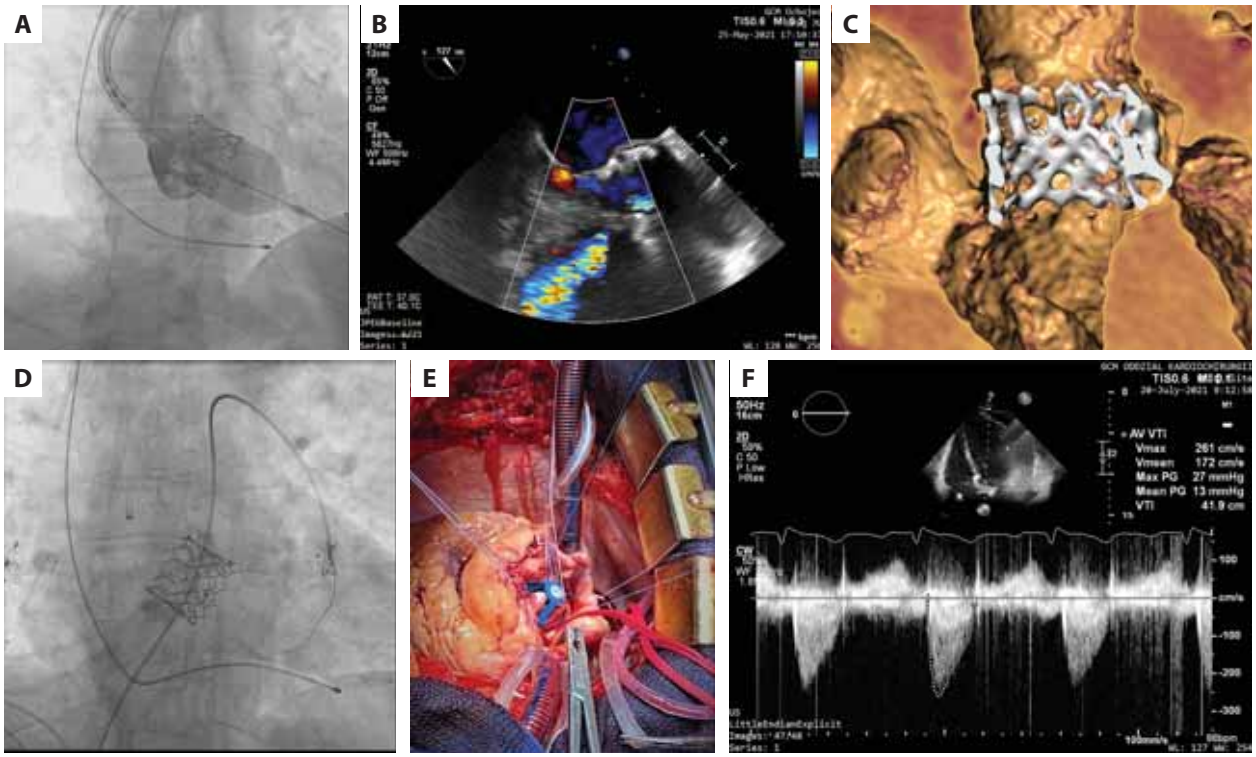

Figure 1. A. Fluoroscopy imaging of transcarotid transcatheter aortic valve implantation (TAVI) SAPIEN 3 Ultra 29 implantation. **B.** Echocardiography imaging of jet from the aortic root into the right ventricle. **C.** 3D imaging of the reconstruction rupture of ventricular septum after TAVI. **D.** Fluoroscopy imaging of attempts to close the ventricular septum rupture. **E.** Implantation of the Medtronic Hancock 25 valve. **F.** Echocardiography follow-up imaging

a 30-day follow-up, the patient remains stable (NYHA class I), and TEE results are reassuring (Figure 1F). The key to the success of the TAVI procedure is proper valve size selection and an optimal depth of implantation, especially in BAV. Recent consensus summarized the sizing and positioning of SAPIEN valves in BAV [4]. Bioprosthesis sizing based on the annulus diameter, rather than the circle method, may have contributed to the complication. Circle measurement at the inter-commissural aortic valve region suggests a downsized bioprosthesis could have provided safe anchoring and proper sealing. In case of such serious complications, only good cooperation of the Heart Team gives the patient a chance to survive.

Article information

Conflict of interest: None declared.

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Transcatheter treatment tricuspid regurgitation by valve-in-ring implantation with a novel balloon-expandable Myval® THV

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Transcatheter tricuspid valve-in-valve (TVIV) and valve-in-ring (TVIR) implantation procedures have emerged as important alternatives for high-risk patients [1].

A 59-year-old female patient, who first underwent closed mitral commissurotomy for mitral stenosis in 1989, was admitted to our department with complaints of dyspnea and edema in the legs and abdomen. The patient had a mitral valve replacement in 1991 and, in 2016, an aortic valve replacement and implantation of a 34-mm Edwards MC3 rigid partial ring (Edwards Lifesciences, LLC, Irvine, CA, US) were performed, together with tricuspid commissurotomy and patch augmentation. Transthoracic echocardiography (TTE) reported massive tricuspid regurgitation, increased tricuspid gradient (mean gradient 8 mm Hg), functional aortic and mitral prosthetic valves, and a preserved left ventricular ejection fraction (LVEF; 55%). Multislice computed tomography (MSCT) demonstrated the shape of the annuloplasty ring very well, and measurements of the ring area, circumference (933 mm), and diameter (30 mm) were performed in detail without thrombus and vegetation (Figure 1A).

After analyzing the literature evaluating Edwards MC3 34-mm Tricuspid annuloplasty partial ring and the echocardiography and MSCT findings, it was decided to implant the 32-mm Myval transcatheter heart valve (THV) system (Meril Life Sciences Pvt. Ltd., Vapi, Gujarat, India). As the right femoral vein was large, tortuous and edematous on examination, the procedure was performed under sedation in the left femoral vein with TTE. We crossed the valve with 6 Fr Multipurpose MPA1 via a 0.35-inch hydrophilic guidewire, and the Lunderquist Extra-Stiff Wire Guide (LES; Cook Inc., Bloomington, IN, US) was placed into the right ventricle. After an unsuccessful placing of a temporary pacing catheter via a jugular vein in the right ventricle, the system was prepared for rapid pacing over the stiff guidewire that would carry the valve system. Then the 32-mm Myval THV balloon-expandable valve was slowly implanted to avoid deforming the partial annuloplasty under the rapid pacing (180 bpm) in the precise position on fluoroscopy (Figure 1B, Supplementary material, *Video S1*). Incomplete rings lead to a higher risk of valve overexpansion, embolization, and paravalvular leaks, which can be avoided by a cautious and slow positioning of the THV. For the Myval positioning, detailed preparation was performed with multimodality imaging before the procedure, various positions were searched under the scope, and implantation was attempted by seeing the annuloplasty ring nearly at the same level. After Myval functions were observed to be good in hemodynamic, echocardiographic, and fluoroscopic controls, the procedure was terminated by applying an eight-shaped suture to the femoral vein (Figure 1C, Supplementary material, *Video S2*). The patient was discharged the next day without complications, with mild valve and mild paravalvular tricuspid regurgitation with a mean gradient of 3.5 mm Hg on TTE (Figure 1D, Supplementary material, *Video S3*).

Valve dysfunction or degeneration after tricuspid valve replacement or repair with annuloplasty ring is frequent. It increases the

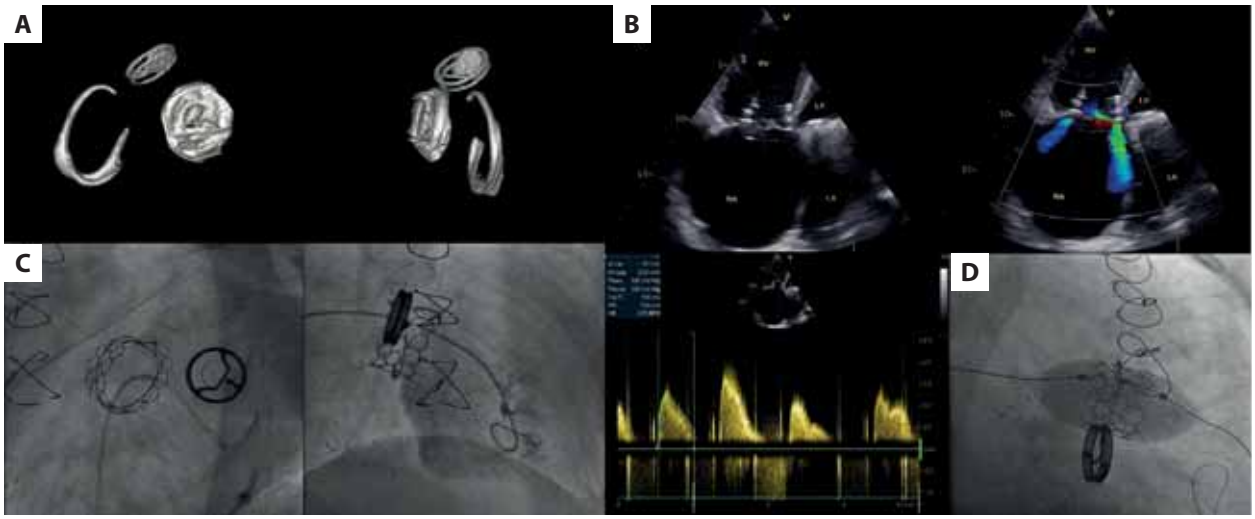

Figure 1. A. Cardiac computed tomography showed the ring shape and downward angle in the septal region. **B.** Echocardiographic images 2 days after transcatheter tricuspid valve-in-ring (TVIR). **C.** Angiographic images after transcatheter TVIR Myval implantation. **D.** Angiographic images of implantation of the 32-mm Myval transcatheter heart valve

morbidity and mortality of the patients and may require redo surgery. Currently, to overcome this dilemma, case series concerning transcatheter TVIV or TVIR have emerged due to the risk of redo surgery. Transcatheter TVIR is a more challenging procedure than transcatheter TVIV, and successful and unsuccessful cases with Edwards Sapien XT, SAPIEN 3 (Edwards Lifesciences, Irvine, CA, US), and Melody (Medtronic, Minneapolis, MN, US) THV systems have been described [2–5].

To our knowledge, this first case report showed that the novel balloon-expandable Myval THV system is suitable for transcatheter TVIR.

Supplementary material

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

Article information

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Ventricular septal rupture after mechanical mitral valve replacement

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Adults with congenital heart disease often require several cardiothoracic interventions throughout their lifespan, with each re-operation posing an additional risk of short- and long-term complications.

Here, we present the case of an 18-year-old female patient with congenital partial atrioventricular canal and parachute mitral valve. She underwent surgical closure of the atrial septal defect with an autologous pericardial patch in 2002. This was followed by a 21-mm St. Jude Medical mechanical mitral valve replacement due to severe mitral incompetence in 2004. She was admitted to our institution with heart failure symptoms, New York Heart Association (NYHA) class III. Echocardiographic examination revealed pannus-related mechanical prosthesis dysfunction causing severe mitral stenosis (Figure 1A, B). She was referred for the mitral valve replacement. The early postoperative period after a 25-mm St. Jude Medical Regent valve replacement was uneventful. During the third post-operative day, the patient presented with progressive dyspnea and hypotension requiring catecholamine infusion. A right pleural effusion was diagnosed and drained. Despite her stable condition, recurrent pleural effusions developed. The physical examination revealed a loud holosystolic murmur at the left sternal border with a thrill. Transthoracic echocardiography showed a rupture in the muscular part of the interventricular septum with two left-to-right shunts considered significant (Figure 1C, D). Cardiac computed tomography confirmed the diagnosis (Figure 1 E, F). The patient was referred for a redo operation. Ventricular septal rupture closure using a pericardial patch followed by a tricuspid valvuloplasty with a 26-mm Edwards ring were performed. In the early postoperative period, the patient required another pleural drainage. Laboratory investigations showed hypoalbuminemia, which was treated with intravenous albumin supplementation. Moreover, *Pseudomonas aeruginosa* wound infection was diagnosed. As targeted antibiotic therapy was ineffective, negative pressure wound therapy was implemented. All the applied treatment methods resulted in gradual improvement in the patient's condition. Eventually, she was discharged from the hospital, and after a 3-month follow-up period, remained free of heart failure symptoms.

Rupture of the left ventricle is a very rare and serious complication of mitral valve replacement [1]. It was described mainly in the area of the left ventricular posterior wall and classified into three types according to its localization: (1) at the atrioventricular groove; (2) at the base of the papillary muscles; or (3) between the base of the papillary muscles and atrioventricular groove [2]. After the first report by Zacharias et al. in 1975 [3], currently almost no new cases can be found in the literature. There are, however, reports of atrioventricular septal rupture causing left ventricle-right atrium shunt (Gerbode type) related to mitral valve replacement [4]. We support Beranek's hypothesis that similarly to rupture of other parts of the left ventricular wall, the rupture of the muscular part of the interventricular septum, as seen in our patient, could be potentially caused by excessive myocardial stretching. In turn, this could lead to cardiomyocyte apoptosis, secondary

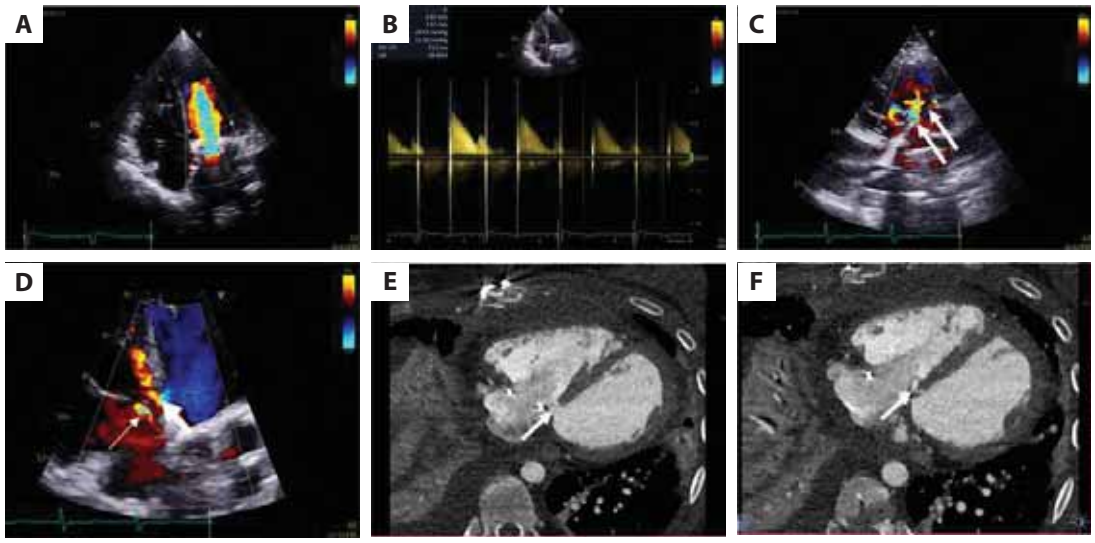

Figure 1. A. Transthoracic echocardiography. Apical four-chamber view. Color flow Doppler. Turbulent flow through mitral mechanical mitral prosthesis. **B**. Transthoracic echocardiography. Continuous flow Doppler signal. Elevated gradients through mechanical mitral prosthesis reaching 28.4 mm Hg of maximum and 11.2 mm Hg of the mean pressure gradient. **C.** Transthoracic echocardiography. Parasternal short-axis view. Two ruptures in the muscular part of the ventricular septum with left-to-right shunts (the arrows). **D.** Transthoracic echocardiography. Apical four-chamber view. Left-to-right shunt through one of the ventricular ruptures (wide arrow), tricuspid regurgitation (the narrow arrow). **E.** Cardiac computed tomography. Axial view. One of the ventricular septum ruptures (the arrow). **F.** Cardiac computed tomography. Axial view. The second of the ventricular septum ruptures (the arrow)

hemorrhage, and weakening of the ventricular wall [5]. Yet, the question of why precisely this part of the left ventricle ruptured remains unanswered.

Article information

Conflict of interest: None declared.

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Stereotactic arrhythmia radioablation in recurrent ventricular tachyarrhythmias

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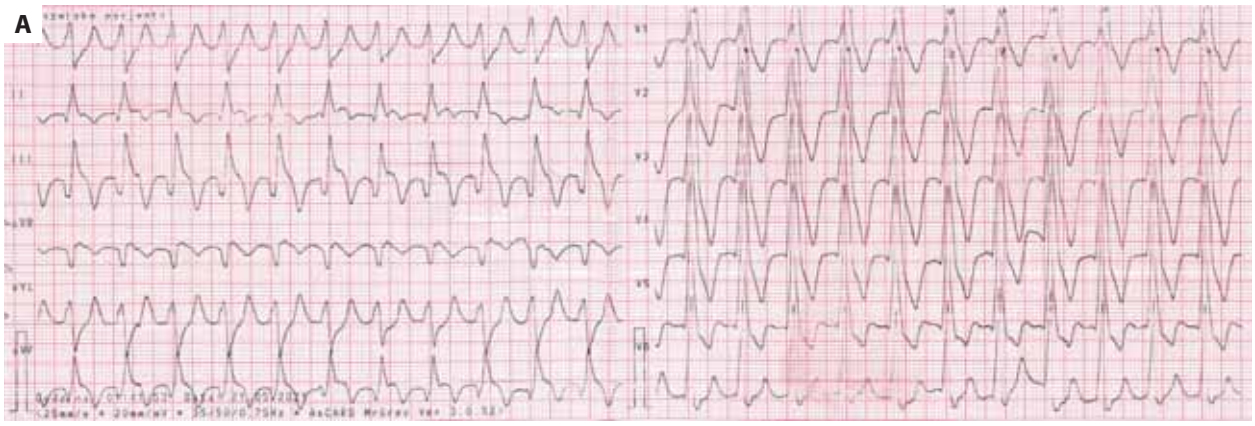
A 67-year-old male with a history of posteroinferior myocardial infarction in 1992, cardiac arrest, and single-lead implantable cardioverter-defibrillator (ICD-VR) implantation in 2015 was referred to the Department of Electrocardiology due to recurrent episodes of monomorphic ventricular tachyarrhythmias (VT) and electrical storms (Figure 1A). The patient had a history of paroxysmal supraventricular tachyarrhythmias (SVT) and post-amiodarone hyperthyroidism. In February 2021, he had undergone radiofrequency catheter ablation of the left ventricle (LV) arrhythmogenic substrate with little benefit (25 adequate high-voltage shocks until current admission).

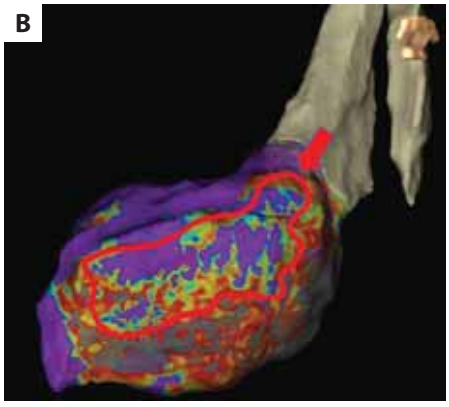
On admission, the patient was in sinus rhythm and euthyroid. The LV ejection fraction (LVEF) was 35% (Supplementary material, *Figure S1*). The coronary angiography showed chronic total occlusion of the right coronary artery with no significant progression of the coronary artery disease. Mexiletine was introduced to decrease the ventricular arrhythmia burden, with moderate effect.

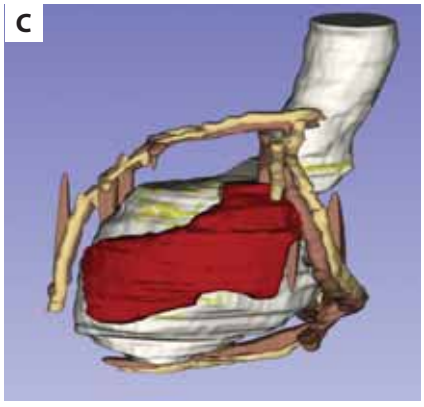
Rotational angiography and electrophysiology study (EPS) of the LV was performed using 3D EnSite™ Precision™ mapping system (Abbott Cardiovascular, Plymouth, MN, US; Supplementary material, *Video S1, S2*). During the procedure, five different morphologies of VT were identified. According to the literature [1], not only endocardial and left-sided substrates were possible. However, based on the arrhythmia morphologies, the left ventricular origin was most probable.

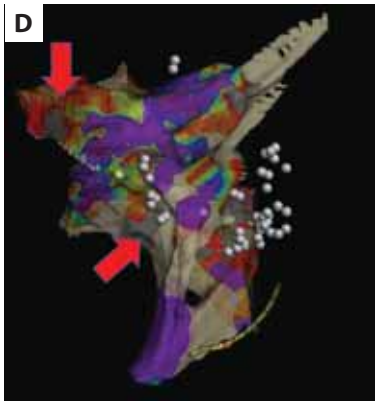
Fusion imaging of computed tomography (CT) and 3D electrophysiological mapping was used to delineate tissue scar with surrounding heterogeneous zone and define the target area for stereotactic arrhythmia radioablation (STAR; Figure 1B, C, Supplementary material, *Figures S2–S4*). The treatment was performed using the Varian EDGE™ radiosurgery system (Supplementary material, *Figure S5*) volumetric arc modulated radiotherapy (VMAT) to assure optimal dose distribution and the Deep Inspiration Breath Hold (DIBH) technique to account for respiratory movement during the irradiation. The cardiac motion was compensated by the internal target volume (ITV) approach based on available cardiac-gated CT data. Ablative energy was delivered transmurally using 6MV photons in one fraction of 25 Gy.

On the first day after the procedure, the patient experienced well-tolerated, incessant monomorphic VT of 105 bpm with occasional capture beats (Supplementary material, *Figure S6*), which was treated by electrical cardioversion. The ICD was reprogrammed to introduce anti-tachycardia pacing (ATP) up from 100 bpm — "Ramp" and "Ramp" + algorithms.









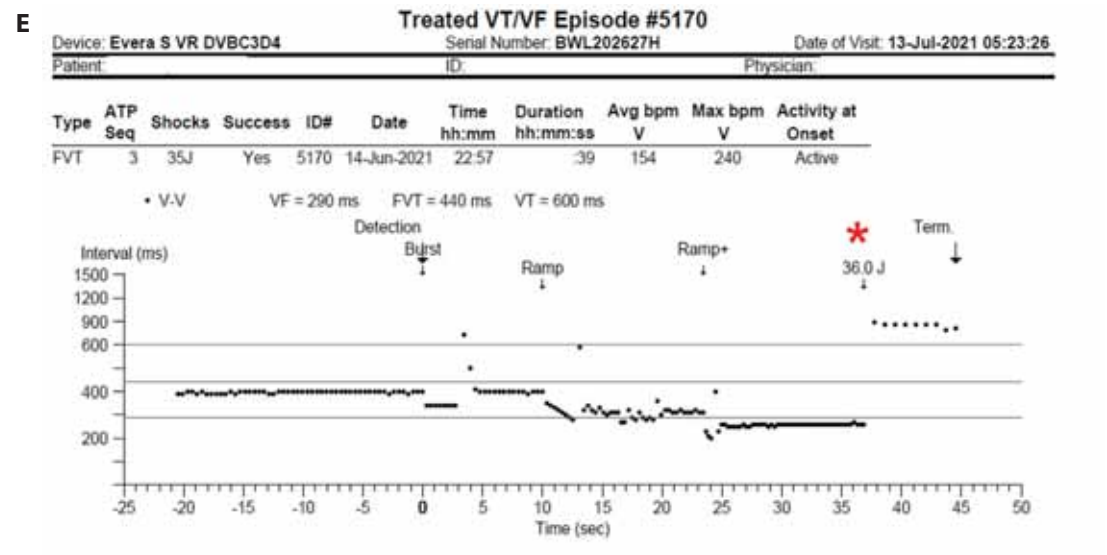


Figure 1. A. ECG of VT originating from the LV after the LV catheter ablation; **B.** The arrow shows scar and heterogenous zone in EPS; **C.** The arrows show the area covered by stereotactic radiotherapy infusion image of CT and EPS. **D.** EPS voltage map of the right atrium with ablation application markers (suboptimal effect due to low electrical activity) — the arrows show low voltage sites. **E.** ATP-triggered VT with subsequent high voltage (36J) shock (marked with an asterisk) as a result of SVT

Abbreviations: CT, computed tomography; ECG, electrocardiogram; EPS, electrophysiology study; LV, left ventricle; SVT, supraventricular tachycardia; VT, ventricular tachycardia

During the six-week post-ablation blanking period, the only VT detected by ICD was successfully terminated with ATP (Supplementary material, *Figure S7*). Moreover, ICD analysis revealed three episodes of paroxysmal SVT triggering VTs via ATP (Figure 1D, Supplementary material, *Figure S8*). Notably, a significant improvement in LV contractility was reported (LVEF ~50%; Supplementary material, *Figure S9*).

After consideration, the EPS was performed to treat the supraventricular arrhythmogenic substrate. Both atria revealed low electric activity (presumably post-ischemic; Figure 1E). Two ectopic foci were found in the right and the left atrium; nevertheless, only temporary termination of the arrhythmias was feasible. During programmed ventricular pacing no sustained VTs were induced.

The single-ventricle ICD was replaced three months after the STAR procedure due to elective replacement indicator (ERI). Up to this time, neither sustained nor non-sustained arrhythmias were recorded. The patient experienced significant clinical improvement. According to the literature and clinical experience, the device incorporating the FarFieldMD morphology discriminator algorithm was chosen [2]. Additionally, the patient was provided with a remote care transmitter.

The case shows multiple possibilities of arrhythmical foci and emphasizes the potency of cardiac implantable devices both in termination and triggering arrhythmias. With its transmural properties, STAR can become a potential challenger to complex epicardial ablation in the future. The reported excellent efficacy of STAR [3] was confirmed in the presented complex case and calls for further investigation.

Supplementary material

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

Article information

This clinical case is based on a medical history of a patient enrolled in the SMART-VT trial (Stereotactic Management of Arrhythmia — Radiosurgery in Treatment of Ventricular Tachycardia, NCT04642963).

Conflict of interest: None declared.

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Percutaneous coronary intervention combining rotational atherectomy and intravascular lithotripsy in two vessels with edge restenosis assisted by percutaneous left ventricular pump support

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A 61-year-old white man was admitted to the invasive cardiology department to have high-risk percutaneous coronary intervention (PCI) with percutaneous left ventricular assist device (pLVAD) support. Echocardiography demonstrated a decreased left ventricular ejection fraction of 15% with disseminated regional contractility abnormalities. Coronary angiography revealed multivessel disease with multifocal critical stenosis in the right (RCA) and left descending coronary arteries (LAD) (Supplementary material, *Figure S1A, B*). The patient was consulted by the Heart Team and qualified for multivessel disease (MVD) PCI with pLVAD support.

First, the Impella CP (Abiomed, Danvers, MA, US) was introduced into the left ventricle. Regarding heavy concentric calcifications located in the second segment of RCA, we decided to use rotational atherectomy (RA) (Boston Scientific, Marlborough, MA, US). The RotaWire Floppy was placed in the distal part of the artery supported with the FineCross microcatheter (Terumo Interventional Systems, Tokyo, Japan). Subsequently, rotablation with a 1.5-mm burr at 150 000 rotations per minute was performed. The pre-dilatation within the distal segment was carried out with 2.0 × 20 mm, 2.5 × 27 mm to 16 atm compliant balloons. Then, the Xience 2.5 × 12 mm drug-eluting stent (DES) was implanted with 16 atm. Pre-dilatation in the medial segment of RCA was unsuccessful due to rupture of the 3.5 × 20 mm, non-compliant (NC) super high-pressure balloon (Sis Medical, AG, Winterthur, Switzerland) inflated to 30 atm. Therefore, intravascular lithotripsy was performed with the 3.5 × 12 mm — 80 pulses Shockwave balloon (Shockwave Medical, Fremont, CA, US) allowing subsequent implantation of the 3.5 × 38 mm, 22 atm DES Xience. Post-dilatation with the 4.0 × 20 mm to 29 atm NC balloon catheter was conducted, and an optimal effect was confirmed via optical coherent tomography (OCT).

Following, a long calcified lesion in the proximal LAD with concomitant edge restenosis of the previously implanted stent was visualized by coronary angiography and confirmed in the OCT examination (Figure 1A, C). The 3.0 × 12 mm Shockwave balloon was used to apply 80 pulses within the stent and proximal segment of the LAD. Subsequently, pre-dilatation with the 3.0 × 20 mm, 20 atm NC balloon was done. Proximally to the previously inserted stent, the 3.0 × 28 mm and 3.5 × 15 mm DES Xience Sierra were implanted. Post-dilatation with 3.5 × 15 mm, 3.0 × 20 mm NC balloons inflated at 28–29 atm was performed. Good stent apposition and expansion were confirmed via OCT (Figures 1B, D).

The presented procedure is a rare use of lithotripsy in the treatment of long lesions with calcified edge restenosis with the support of pLVAD due to extreme reduction of left ventricular ejection fraction. Moreover, despite the presence of the cardiac resynchronization therapy defibrillator (CRT-D) and the necessity of pLVAD use, their function

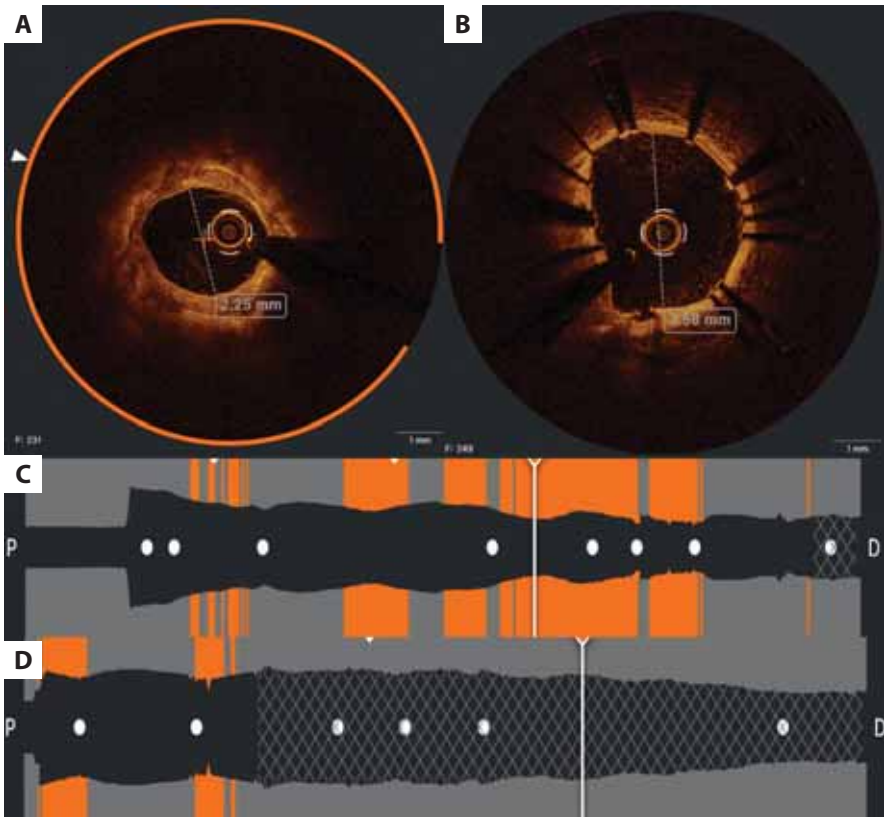

Figure 1. Optical coherent tomography of the left anterior descending artery. **A, C.** Longitudinal and cross-section showing a long, massively calcified lesion of 4 cm in length length reaching the proximal edge of the previously implanted stent. In most diseased parts, calcifications were circumferential (360 degrees) with thickness above 1 mm. **B, D.** Longitudinal and cross-section displaying good apposition of implanted stents

remained stable during lithotripsy implementation. Therefore, we suggest that this technology could be beneficial in many clinical scenarios, also complementary to the RA method in the treatment of complex calcified lesions.

Supplementary material

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

Article information

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Transcatheter tricuspid valve-in-valve replacement due to severe bioprosthesis dysfunction in a patient with endocardial leads

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The safety and efficacy of transcatheter valve-in-valve implantation have led to the rapid growth of this treatment strategy especially in high surgical risk patients with aortic valve prosthetic dysfunction [1]. Although less proven, transcatheter tricuspid valve-in-valve replacement has also good short-term outcomes. Performing such a procedure in patients with endocardial leads poses an additional risk. Potential concerns include the impact of the pacemaker lead on the valve deployment, the presence and the extent of the perivalvular leak along with the pacemaker lead, and the risk of jailed lead dysfunction during the procedure and in the long-term follow-up [2–5].

A 59-year-old female patient with Ebstein's anomaly, after surgical tricuspid valve replacement with a 31-mm Carpentier-Edwards bioprosthesis due to severe tricuspid regurgitation in 1987, after dual-chamber pacemaker implantation due to symptomatic second-degree atrioventricular heart block in 2003 was regularly followed-up in our outpatient clinic. From the beginning of 2021, she gradually started to present heart failure symptoms (exertional dyspnea with nausea and lower extremity edema) ultimately in class III according to the New York Heart Association classification. Laboratory tests revealed increased serum N-terminal prohormone for brain natriuretic peptide concentration of 1526 pg/ml (in comparison to 669 pg/ml a year before). Transthoracic echocardiographic examination demonstrated tricuspid bioprosthesis dysfunction with a mean transvalvular gradient of 14.5 mm Hg and a small perivalvular leak in the lateral part of the tricuspid ring, the enlarged right ventricle with a preserved systolic function, and severely enlarged right atrium (Figure 1A, B). Cardiac computed tomography confirmed the diagnosis (Figure 1C). Taking into consideration prior sternotomy, benign thrombocytopenia, and her new affiliation with Jehovah's witness group, the Heart Team decided to refer her for percutaneous valve-in-valve implantation with right ventricle lead jailing. Pre-procedural pacemaker interrogation showed 88% pacing with underlying sinus rhythm with second to third-degree atrioventricular block resulting in the heart rate of 40–65 bpm, dual-chamber pacing mode, and correct right ventricle lead threshold. The patient underwent tricuspid valvuloplasty with a 25-mm Edwards balloon followed by valve-in-valve 29-mm Sapien 3 bioprosthesis implantation via the right femoral approach. The procedure was complicated by a femoral vein bleeding with an extensive hematoma and a hemoglobin concentration decrease not requiring blood transfusion. There were no changes in the device function in the post-procedural interrogation. Multimodality imaging using transthoracic echocardiography and cardiac computed tomography revealed correct position and good function of the bioprosthesis with a mean transvalvular

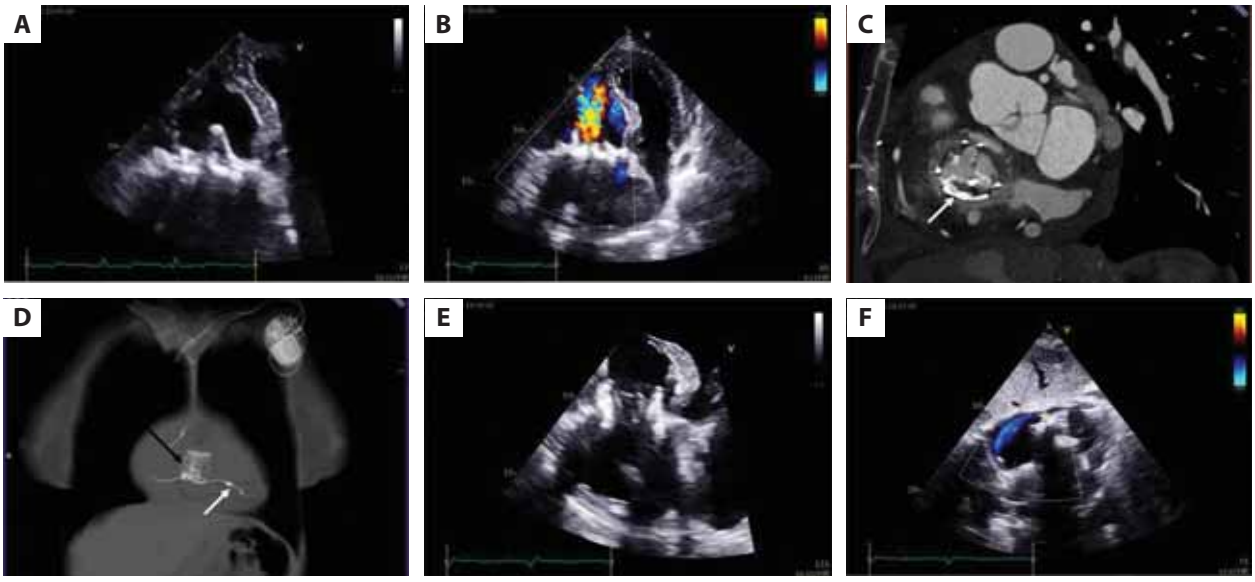

Figure 1. A. Transthoracic echocardiography. Four-chamber apical zoom view. Degenerated leaflets of the tricuspid bioprosthesis. **B.** Transthoracic echocardiography. Four-chamber apical view. Color Doppler flow. Turbulent flow through degenerated leaflets of the tricuspid bioprosthesis. **C.** Cardiac computed tomography. Multiplanar reconstruction, short-axis view. Bioprosthetic tricuspid valve degeneration (the arrow) — thickening and calcifications of the valve leaflets. **D.** Cardiac computed tomography after reimplantation of the tricuspid valve. Multiplanar reconstruction. Tricuspid valve bioprosthesis (the black arrow), pacemaker lead (the white arrow). **E.** Transthoracic echocardiography after the valve-in-valve procedure. Four-chamber apical zoom view. Correct position of the tricuspid valve-in-valve bioprosthesis. **F.** Transthoracic echocardiography after the valve-in-valve procedure. Substernal long-axis view. Color Doppler flow. Mild perivalvular leak in the lateral part of the tricuspid ring in the surrounding of the ventricular lead

gradient of 3.4 mm Hg and a mild perivalvular leak in the lateral part of the tricuspid ring in the surrounding of the ventricular lead (Figure 1D–F). At a three-month follow-up, the patient was free from heart failure symptoms, and her hemoglobin concentration was stable at the level of 13.3 g/dl.

Transcatheter tricuspid valve-in-valve implantation is a safe alternative to redo surgical tricuspid valve replacement, especially in high surgical risk patients. Reported data show that jailing of the right ventricle lead does not cause a severe perivalvular leak or pacemaker dysfunction in the short-term follow-up. Yet, more studies are required to evaluate long-term outcomes.

Article information

Conflict of interest: None declared.

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Public interest in cardiac arrest after Christian Eriksen's mid-football-game event was acute rather than chronic: The analysis of Google search trends

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Publicly witnessed cardiac arrest raises concern among its spectators, especially when it affects young and healthy individuals, such as professional sportsmen. They are typically subject to regular medical health checks, yet it does not protect them from sudden events of potentially fatal nature [1, 2]. Such an event happened during the European Football Championship EURO 2020 and was transmitted and watched worldwide. On June 12, 2021, during a match between Denmark and Finland, a Danish player Christian Eriksen had a cardiac arrest, with immediate life support from the medical services on-site. He was then transferred to a local department of cardiology, where he received the full treatment including an implantable cardioverter-defibrillator (ICD).

One of the possible measures of the increased public interest in any topic may be the increase of queries for specific keywords in web search engines. That phenomenon may be used to identify demand for knowledge and to use to educate the public. Our study aimed to analyze the temporal pattern of interest in cardiac arrest raised by the above-mentioned event in the Polish population to determine the time frame for an educational intervention. We used analytic tools provided by Google Trends to analyze searches performed in Poland during 12 months preceding the date of our data access (November 25, 2021). Keywords that were investigated are listed in the Supplementary material, *Table S1*. Trends of queries for all the keywords were reported as relative weekly rates for each of the 52 weeks. The value 100 corresponded to the maximum interest, while 0 corresponded to no interest.

We analyzed the correlations of temporal trends of searches for specific keywords. Detailed values for all correlations are presented in the Supplementary material, *Figure S1*. Our interest focused on the keywords with the highest correlation with the query "Eriksen," as we believed that it was the unfortunate event linked to that player that prompted people to search information about the player, the event itself, and all the health-related issues. We selected four keywords with statistically significant correlation ($P < 0.05$, correlation coefficient above 0.5, see Supplementary material, *Table S1*) and plotted them on the timeline along the search trend for the player's name to investigate the time relationships of the trends. That comparison is presented in Figure 1. Those four keywords in order of highest correlation were "heart attack", "resuscitation", "defibrillator", and "myocardial infarction". Based on the temporal relations, we consider that the spike in the relative search rate for those four keywords was related to the event described above. Noticeably, that interest was relatively short-lived and returned to the baseline during the third consecutive week.

As the immediate reaction of witnesses may improve prognosis [2, 3], it is crucial to use every opportunity for public education regarding cardiac arrest and resuscitation. According to our analysis, tragic news regarding sudden cardiac arrest during mass events may ignite interest in the general population and increase the demand for educational content.

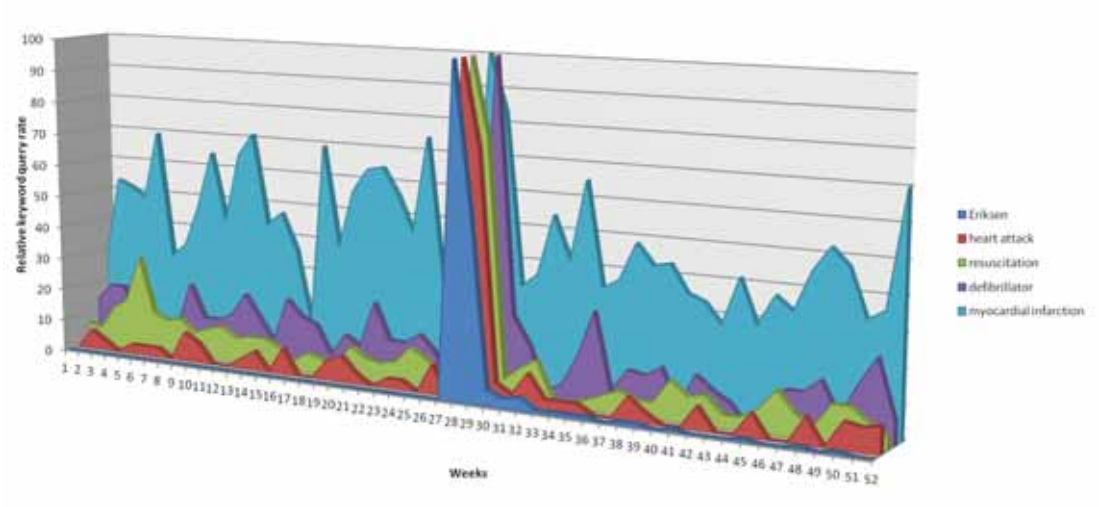

Figure 1. Temporal relations of the relative search rate for the four cardiovascular disease-related key words ("heart attack", "resuscitation", "defibrillator" and "myocardial infarction") most correlated with the search for "Eriksen" in the analyzed time frame (52 consecutive weeks, from November 25, 2020 to November 25, 2021)

However, meeting that demand with expert knowledge has to be prompt as the interest may peter out as soon as after several weeks.

Supplementary material

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

Article information

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Mobile aortic mural thrombus in a patient with small-cell lung cancer receiving cisplatin-based chemotherapy

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A 55-year-old man with right-sided small-cell lung cancer (SCLC) undergoing chemotherapy with cisplatin and etoposide was admitted to the hospital with a balloting thrombus located in a non-aneurysmal, non-atherosclerotic aortic arch.

The patient's SCLC (T4N3M0-IIIC) was diagnosed 2.5 months before admission with a Khorana score of 2, classified as intermediate-risk for thromboembolism, with the unclear benefit of routine anticoagulation in this subset of patients at the time. The oncology team did not start thromboprophylaxis in the absence of absolute indications. Past medical history was only significant for a 60 pack-year smoking history. On admission, laboratory tests revealed thrombocytosis (408×10^3/ul), and elevated D-dimer (625 ng/ml). Physical examination showed a significant reduction of vesicular sounds in the upper field of the left lung. Transthoracic echocardiographic (TTE) examination revealed the presence of a normoechogenic longitudinal balloting structure, 18 mm long and 5 mm wide, located at the base of the aortic arch (Figure 1, Supplementary material, *Videos S1* and *S2*). TTE also showed an enlarged left atrium and slight myocardial hypertrophy. No segmental left ventricular wall motion or valvular abnormalities were reported.

Immediately after confirmation of the presence of the aortic thrombus, the patient was anticoagulated with a therapeutic dose of enoxaparin 80 mg twice a day subcutaneously. Control TTE after 4 and 7 days of anticoagulation showed only a slight reduction of thrombus size (to 15 × 5 mm). No symptoms of embolism were reported by the patient during treatment. He was discharged on enoxaparin 80 mg twice a day, which resulted in complete clot resolution after 29 days of uninterrupted anticoagulation, followed by a continuation of treatment until the next chemotherapy.

The association between malignancy and hypercoagulability, leading to thromboembolic events such as venous thromboembolism (VTE) and arterial thromboembolism (ATE), is well recognized and extensively described in the literature. Aortic mural thrombus (AMT) is a rare form of ATE, where approximately 25% of patients have documented hypercoagulable states, and 10% were previously diagnosed with malignancy [1].

Currently, there are no explicit guidelines regarding the management of AMT in cancer patients receiving chemotherapy, with treatment strategies guided by evidence-based guidelines for venous thrombosis in cancer patients or analyses of the few previously described cases. Treatment modalities include pharmacological anticoagulation, thoracic endovascular aortic repair (TEVAR), and open aortic surgery. Pharmacological options for management of patients with cancer-associated VTE range from monotherapy with low molecular weight heparin (LMWH), unfractionated heparin (UFH), rivaroxaban, apixaban, or fondaparinux, and strategies based on a combination of warfarin with LMWH, UFH or fondaparinux, or combination of edoxaban with LMWH or UFH [2]. Treatment of AMT following cisplatin-based chemotherapy in the current literature differed between patients. All described cases implemented

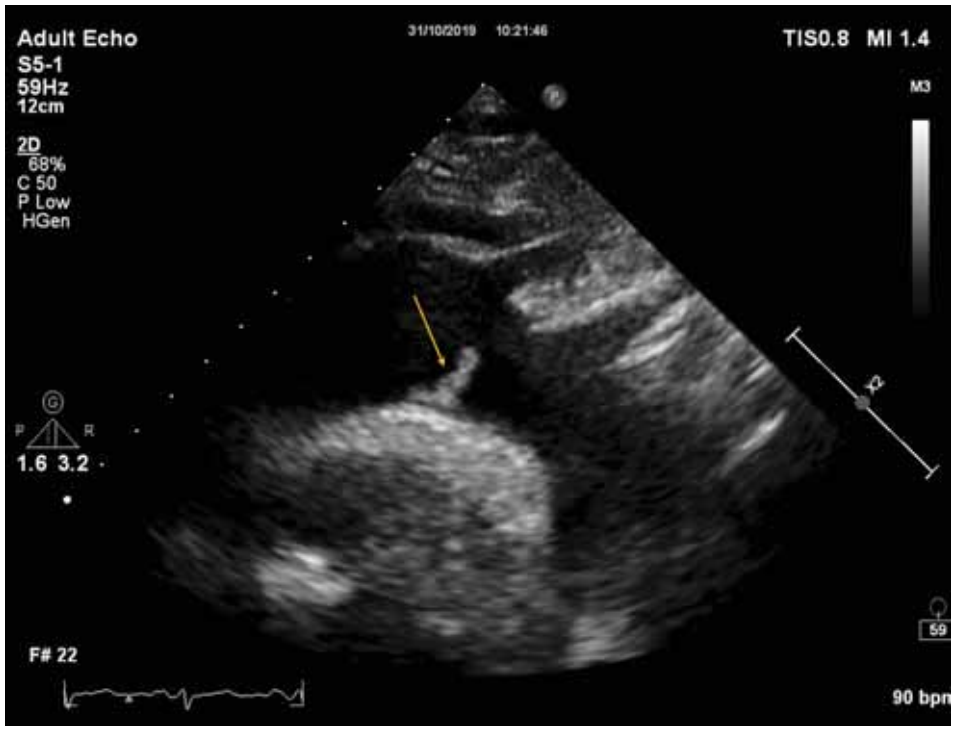

Figure 1. Normoechogenic longitudinal balloting structure at the base of the aortic arch on transthoracic two-dimensional echocardiography (the yellow arrow)

conservative management, varying from LMWH with acetylsalicylic acid followed by vitamin K antagonist (VKA) [3], UFH followed by VKA [4], to therapy with subsequent administration of UFH, LMWH, and rivaroxaban [5].

In conclusion, clinicians should be aware of the risk of AMT as a rare, but potentially fatal, complication of chemotherapy in cancer patients receiving chemotherapy. As no clinical guidelines are currently available, choosing the most appropriate treatment modality presents a challenge and should be individualized. In our case, the thrombus was successfully treated with enoxaparin, showing that monotherapy with LMWH could be a safe and effective strategy. However, further studies are needed to reach a definitive conclusion.

Supplementary material

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

Article information

Conflict of interest: None declared.

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Cardiac paraganglioma: A challenging diagnostic and treatment dilemma

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In their recently published clinical vignette, Redzek et al. [1] reported an interesting case of cardiac primary neuroendocrine tumor in a previously asymptomatic 38-year-old female, presenting with heavy chest pain, ST depression in inferolateral leads on electrocardiogram, and elevation of high-sensitive troponin I. Tumor's location (intrapericardial, near the right atrium, surrounding the right coronary artery), radiological features, and the absence of metastatic disease, as well as histopathology and immunohistochemistry findings, indicate paraganglioma (PGL) [1]. As cardiac PGLs are extremely rare, accounting for <0.3% of mediastinal tumors and 1%–3% of primary cardiac tumors, we would like to write a short comment [2].

Paragangliomas are uncommon neuroendocrine tumors that arise from chromaffin cells located outside of the adrenal gland. In the heart, PGLs either arise from branchiomeric paraganglia (in the roots of the great vessels including the pulmonary artery, pulmonary vein, vena cava, and aorta), or visceral autonomic paraganglia (the interatrial or interventricular groove) [3]. Although cardiac PGLs have been observed in all heart chambers, the most prevalent are left atrial PGLs, followed by aortic body tumors [2].

Clinical symptoms of PGLs are heavily influenced by the tumor's metabolic profile, which is most typically caused by mutations in predisposing genes. In a multi-institutional case series, it was reported that underlying mutations in the succinate dehydrogenase (SDH) B/C/D (SDHx genes) were implicated in around 77% of cardiac PGLs [2]. Redzek et al. [1] stated that the patient had no family history of PGL. Nevertheless, it should be emphasized that negative family history does not exclude the hereditary background of the disease because, in the case of *SDHD* gene mutations, the phenomenon of maternal imprinting occurs and there may also be incomplete disease penetration [4]. Therefore, patients with confirmed cardiac PGLs should be tested at the same time for predisposing germline mutations, particularly SDHx. Accordingly, we wonder whether the patient [1] had genetic testing. PGLs are either symptomatic or asymptomatic and may be biochemically active or inactive. In general, PGLs are classified into three biochemical phenotypes: noradrenergic, adrenergic, and dopaminergic. As cardiac PGLs are predominantly associated with SDHx mutations, they often present with the noradrenergic biochemical phenotype, with typical symptoms such as hypertension, sweating, diaphoresis, palpitations, headache, and dizziness. Only around 18% of patients present with chest pain or distress [2], which probably caused diagnostic difficulties in the reported case [1]. As the tumors are usually fed by coronary arteries, angina could be present as a result of coronary steal syndrome [4].

We would also like to draw attention to the metastatic potential of these tumors. Unfortunately, except for the existence of distant metastases, there are no exact histological features, immunohistochemical stains, or molecular criteria that point towards the diagnosis of malignancy [2]. The incidence of malignant cardiac PGLs is estimated at 6% [4]. Distant metastases may appear even after many years, and therefore these patients require a long-term follow-up in both imaging and hormonal examinations. The most notable predictor of aggressive clinical behavior is the presence of a germline *SDHB* mutation, as this mutation predisposes to familial para-

ganglioma-pheochromocytoma syndrome type 4 (PGL4), which is tightly associated with the extra-adrenal location of PGLs with high metastatic potential [5]. This is another strong argument in favor of all patients with cardiac PGL undergoing genetic testing.

Diagnosis of PGLs is mostly achieved with a multimodality approach including biochemical investigation, radiological and nuclear imaging. A biopsy is not recommended, especially in biochemically positive PGLs with a typical positivity of nuclear medicine imaging, due to extensive vascularity of cardiac PGLs, which makes the biopsy unsafe [2].

Surgery is the gold standard for treating cardiac tumors. However, PGLs can infiltrate cardiac tissues and coronary arteries, so resection may be difficult or even impossible, and cardiac transplantation may be necessary as the last option [2]. The authors should be commended for taking up this challenge and for successful surgery.

In conclusion, we would like to highlight that cardiac PGLs are rare tumors with significant surgical demands and that even though the complete surgical excision can be challenging, it remains the mainstay of treatment. We would also like to emphasize the importance of considering a genetic etiology in every case of cardiac PGL.

Article information

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Rare cardiac tumors represent an ultimate challenge for the whole Heart Team. Authors' reply

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We are very delighted that our recently published article in which we presented a peculiar case of a primary cardiac neuroendocrine tumor [1] drew the attention of the scientific community and wish to thank readers for their interest in our work. This uncommon disease, which has been encountered at our center for the first time, initially left our whole team confused. Nevertheless, the detailed multimodal imaging and precise diagnostics cleared the way for safe and successful surgical removal, which together with comprehensive postoperative pathohistology, immunohistochemistry analyses, and additional imaging workup, enabled the patient's appropriate overall management.

In their comment, Peczkowska et al. [2] provide a very practical and methodical overview of paragangliomas. It includes their pathogenesis and classification, with special emphasis on the potential genetic basis of the disease mainly due to the succinate dehydrogenase (SDH) mutation variants that can be identified in three-quarters of patients with cardiac paragangliomas [3]. The authors [2] highlighted the importance of genetic testing, particularly for SDH genes, for determining the hereditary background of the disease in such patients. Our local healthcare system currently does not have the resources that could provide the aforementioned genetic testing, so unfortunately it could not have been performed in our patient [1]. Based on the information taken at the time of admission, as well as detailed family history investigated subsequently after the final diagnosis, we could confirm that the patient's family history was negative. Nonetheless, we do acknowledge that the negative family history cannot exclude the hereditary background of the disease due to the variable penetrance of the mutations [4].

Regarding the metastatic potential of the tumor, as part of the systemic evaluation, our patient underwent comprehensive and detailed imaging including octreotide scan, computed tomography of the chest, and magnetic resonance imaging of the abdomen and small pelvis, which were all negative for other tumor foci. Some additional analyses that might have been considered include metaiodobenzylguanidine (MIBG) scan and hormonal examinations. However, these were not performed because the patient did not present any symptoms whatsoever that would be suggestive of excessive catecholamine production (i.e. hypertension, headaches, pallor, excessive sweating), nor any other abnormal hormonal activity such as carcinoid syndrome. To the present day, more than two years later and with regular periodic follow-up, there have been no signs of distant metastases or local disease recurrence in our patient.

We would like to emphasize that this challenging cardiac tumor could not have been managed properly without the remarkable cooperation and teamwork of a wide array of different medical specialties. The Heart Team, consisting of a cardiologist and a cardiac surgeon together with an anesthesiologist, was crucial for establishing the right approach and making the decision for surgical removal of the tumor. The surgery itself was performed in general endotracheal anesthesia through

total median sternotomy. Pericardiotomy revealed normal heart in sinus rhythm, situs solitus, with a large, pale pink tumor that was present on the lateral side of the right atrium and ventricle. Further surgery was performed on total cardiopulmonary bypass (total heparinization, selective bicaval to the ascending aorta, venting through the ascending aorta), using intermittent antegrade hyperkalemic solution (St. Thomas). The tumor sample was sent for *ex tempore* and imprint cytology analyses when the diagnosis of the neuroendocrine tumor was suspected. The tumor mass was then excided *in toto* from the heart walls and the right coronary artery around which it was wrapped. Total aortic cross-clamping time was 58 minutes, with a total bypass time of 80 minutes. Following the surgery, it was up to the pathologist, radiologist, nuclear medicine specialist, and oncologist to establish the final diagnosis and perform additional examinations and patient follow-up.

In essence, cardiac involvement is not unusual in patients with carcinoid syndrome due to systemic effects of neuroendocrine tumors (characteristically represented by carcinoid heart disease — a fibrous thickening of the endocardium, mainly involving the heart valves, leading to their malfunction) [5]. However, the primary localization of neuroendocrine tumors in the heart is extremely rare and requires the outstanding cooperation of different medical specialists for proper patient management and favorable outcome.

Supplementary material

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

Article information

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Acute cardiovascular conditions in the setting of multiple sclerosis relapse: Practical implications

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In clinical practice, chronic demyelinating syndromes including multiple sclerosis (MS) generally present with relapses and remissions and are well known to be associated with an increased risk for cardiovascular disease possibly due to a variety of factors including chronic inflammatory burden [1, 2], sedentary lifestyle, etc. In their recently published article, Łagosz et al. [1] have reported an interesting case of acute myocardial infarction (AMI) in a male patient during his MS relapse possibly triggered by a SARS-CoV-2 vaccination [1]. In this regard, we would like to comment on this case report and also highlight a variety of acute cardiovascular conditions in patients with an MS relapse.

First, it seems quite evident that a variety of MS and/or vaccine-related factors might have triggered the evolution of AMI in this case [1]. Certain cytokines including interleukin 2 (IL-2), etc. were previously suggested to account for pathogenesis, relapse, and progression of MS largely through autoimmune pathways [2]. In particular, heightened disease activity in MS might lead to acute increases in cytokine levels [2]. This potentially suggests a cytokine-related atherosclerotic plaque rupture in the patient during his MS relapse. Therefore, we wonder about the severity of systemic inflammation in the patient [1]. On the other hand, we hold the opinion that vaccine-related in-situ thrombus formation (associated with hypercoagulation [1] or autoimmune vasculitis) seems to be a more likely trigger of AMI in this context. This possibility might also warrant examination of a variety of arterial and venous structures (deep veins, cranial arteries, etc.) for subtle complications (including subclinical thrombosis, aneurysm formation) in the patient. In general, only histopathological examination (mostly performed during autopsy) can unveil the absolute mechanism of acute coronary occlusion in the presence of multiple triggers.

Second, an episode of takotsubo syndrome (TTS) (co-existing with AMI) might also be quite likely and might have been masked by AMI and acute neurological events in the patient [1]. In particular, MS and Bickerstaff's brainstem encephalitis might induce TTS episodes especially during their relapses through a variety of mechanisms, including involvement of the primary autonomic center (located in medulla oblongata), emotional stress, enhanced systemic inflammation, as well as paradoxical increments in orexin (a neuropeptide that has important pathogenetic implications in certain neurodegenerative diseases and has a substantial impact on adrenergic discharge) levels [3]. Interestingly, certain clinical features including systemic inflammation, old age and severe physical conditions (possibly consistent with the features of the patient [1]) might be particularly associated with the co-existence of TTS and acute coronary syndromes (ACSs) which might lead to worse outcomes [4]. Therefore, the presence of severe stenosis or total occlusion consistent with ACSs, as visualized on the coronary angiogram (CAG), could not safely rule out an accompanying TTS episode [4]. Accordingly, we wonder about findings of left ventriculogram (apical ballooning, etc.), if any, in the patient. Taken together we would like to underscore the potential likelihood of TTS occurrence in this case and in similar clinical scenarios (either in isolation or co-existing with ACSs).

Finally, the risk of idiopathic cardiac arrhythmias might also increase during an MS relapse as a consequence of cytokine impact and autonomic imbalance, etc. [2]. This possibly warrants close rhythm monitoring until the remission of neurological findings [2]. Therefore, we wonder whether the patient had any arrhythmic episodes [1].

In conclusion, a variety of acute cardiovascular conditions might be encountered during the course of MS relapses [2, 3]. However, these conditions might present with atypical or vague symptoms [1] or might be masked by the rampant neurological findings [3]. This warrants close supervision of cardiac symptoms [2] and routine evaluation of basic tests (troponins, echocardiogram, etc.), and where necessary, implementation of advanced modalities (including CAG) for prompt cardiovascular management in patients with an MS relapse.

Article information

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The interlinking background of multiple sclerosis and coronary artery disease. Authors' reply

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We appreciate readers' interest in the presented case and gladly take the opportunity to respond [1]. The comments on our article highlight key issues and bring an interesting perspective, for which we would like to thank. Since the clinical vignette form has its limitations, we were not able to fully report on the complex background.

As mentioned by Polat et al. [2], the complex pathophysiology with multifactorial etiology of acute coronary syndrome (ACS) does not allow us to establish a certain cause of myocardial infarction (MI) using standard diagnostic tools in each case. Finding the answer to the question about the triggering factor and mechanism of atherosclerotic plaque rupture could be unattainable. Expanding the diagnosis to include intravascular ultrasound or infrared imaging could bring new data, but both techniques have their restrictions and would not influence the treatment.

Growing evidence shows that vascular disease and multiple sclerosis (MS) share similar pathogenesis, which includes autoimmunity and pro-inflammatory pathways. Alterations to endothelial functions have been observed in other chronic immune-mediated diseases such as rheumatoid arthritis, psoriasis, and atopic eczema, most likely as a result of inflammatory activity. Endothelial dysfunction may be a precursor to lesions both in MS and atherosclerosis. Changes in endothelium cause increased adherence of immune cells that are involved in the formation of atherosclerotic plaques and enhancement of procoagulant properties due to platelet activation. Higher levels of lipoprotein-associated phospholipase A2 and homocysteine, linked with cardiovascular disease, are also common findings among MS patients. The local inflammatory component in atherosclerotic plaques plays a significant role in most cases, especially in active, unstable plaques; and while systemic inflammation may have contributed to plaque rupture, it does not appear to be the primary factor in the settings of the moderate inflammatory response (white blood count 11.38×10^3/μl, C-reactive protein 74 mg/l) [3]. Another aspect that should be taken into account is dysfunction of the autonomic nervous system and cardiac repolarization, which have been observed in several studies, and could contribute to increased prevalence of MI. Finally, the treatment of MS and its side effects cannot be ignored. Systemic glucocorticoids are the cornerstone of treating relapses and are associated with a significantly increased risk of stroke, MI, and atrial fibrillation. Cardiotoxicity has been reported for disease-modifying therapies (DMTs) such as interferons, mitoxantrone, natalizumab, and fingolimod, which are all used in the treatment of MS. Post-vaccination ACS and MS relapses have been observed in some cases, but the relationship between them is uncertain and requires further study, as mentioned in the original article. Perhaps, even if the histological examination was performed, the cause would still remain unclear. The overlapping burden of comorbidities makes this process even more difficult, and although many hypotheses could be made, pinpointing the exact cause would require a much broader investigation and would not necessarily provide a definitive answer.

Many reports on cases of Takotsubo syndrome (TTS) in the course of multiple sclerosis exacerbation have been published. Indeed, ACS associated with relapse of MS can present as TTS but is not in fact TTS. There have been reports of MI-induced TTS or TTS with secondary plaque rupture, but these conditions occur where acute regional wall motion abnormalities are more extensive than the culprit coronary arteries territory and correspond to the Takotsubo pattern. Coronary multivessel lesions, high troponin I levels, and presented echocardiography likely exclude this diagnosis [4]. However, the pathophysiology of MI is often associated with catecholamine release, microvascular spasm, metabolic impairment, and stunning, resulting in a Takotsubo-like pattern [5]. Perhaps these definitions may need to be changed in the future.

Finally, patients in the acute phase of a MI admitted to the cardiac intensive care unit are closely monitored within 48 hours as part of standard management. Although MS relapse is associated with arrhythmia risk, in this clinical situation, ACS and reperfusion are particularly predisposing, thereby longer surveillance could be considered for this sub-population. No arrhythmia was observed in our case, however, the important nature of these considerations should be borne in mind, as they empasize value of interdisciplinarity in the evaluation of patients. Regardless of progress, this shows how many limitations and unanswered questions remain in medicine.

Article information

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Management of patients after heart valve interventions. Expert opinion of the Working Group on Valvular Heart Diseases, Working Group on Cardiac Surgery, and Association of Cardiovascular Interventions of the Polish Cardiac Society

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INTRODUCTION

This document aims to systematize the recommendations for the management of adult patients after surgical and percutaneous valve interventions in acquired valvular heart disease. In recent years, the number of patients after transcatheter repair or implantation of the aortic, mitral, and tricuspid valves has increased significantly. At the same time, there has been considerable development of surgical techniques, including minimally invasive approaches. The number of patients undergoing these procedures is rising substantially as well. Greater accessibility of modern diagnostic and therapeutic methods, along with novel indications for interventions, also increases the patient population. Proper management of these patients after the procedure is essential to achieve the best possible long-term outcomes of interventional treatment of valvular heart disease.

Table 1. Echocardiographic parameters for the assessment of mitral/tricuspid valve after the valve repair procedure

- Length and height of the leaflets coaptation of the repaired valve, leaflet tenting area
- The presence and severity of regurgitation (quantitative methods: vena contracta, effective regurgitant orifice area (EROA) by proximal isovelocity surface area (PISA), regurgitant volume and a regurgitant fraction (2D/3D + Doppler)
- Evaluation of valve morphology (annulus and leaflets), artificial tendinous chords, the position of papillary muscles (depending on the procedural technique)
- Assessment of peak diastolic velocity as well as the mean gradient
- Assessment of left ventricular dimensions and ejection fraction (LVEF), as well as select right ventricular (R) dimensions and functional parameters, e.g. tricuspid annular plane systolic excursion (TAPSE)
- Calculation of right ventricular systolic pressure (RVSP) in the presence of tricuspid regurgitation

Table 2. Echocardiographic probability of pulmonary hypertension (PH)

Peak tricuspid regurgitation velocity, m/s	Other "pulmonary hypertension echo signs" present[a]	Echocardiographic probability of pulmonary hypertension
≤2.8 or not measurable	No	Low
≤2.8 or not measurable	Yes	Intermediate
2.9–3.4	No	
2.9–3.4	Yes	High
>3.4	Not required	

[a]Echocardiographic indices of pulmonary hypertension (at least 2 from different categories required). Category A: Right ventricle/left ventricle basal diameter ratio >1.0; Flattening of the interventricular septum in short axis parasternal wiev; Category B: Right ventricular outflow Doppler acceleration time <105 ms and/or mid-systolic notching; Early diastolic pulmonary regurgitation velocity >2.2 m/s; Category C: pulmonary artery diameter >25 mm; inferior vena cava diameter >21 mm with reduced respiratory collapse <50%; end-systolic right atrium area >18 cm^2

FOLLOW-UP OF PATIENTS AFTER CARDIAC VALVULAR INTERVENTIONS

Follow-up after surgical mitral and tricuspid valve repair

Patients undergoing mitral or tricuspid valve repair require intraoperative transesophageal echocardiography (TEE) and a subsequent transthoracic echocardiographic examination (TTE) before the hospital discharge. Considering long-term care of patients, it is critical to provide a detailed description of the procedural methods in the medical records, including information on the type and size of the annuloplasty ring [1] and all other surgical details relevant for follow-up imaging and possible future interventions. The armamentarium of surgical techniques for valve repair is wide and dependent, among others, on the type of pathology (i.e. whether the regurgitation is primary or secondary) and on the mechanism of regurgitation (type I — annular dilatation, leaflet perforation; type II — leaflet prolapse; type III — leaflet restriction). The techniques include implantation of an artificial valve ring or artificial tendinous chords, resection or plication of the leaflet, as well as suturing or percutaneous clipping of the leaflets [2–7].

The postoperative follow-up should be performed in the first 30 days at the cardiac surgery department, followed by early postoperative TTE within 2–3 months as part of visits at cardiology clinics.

During the first outpatient TTE examination after cardiac surgery, the pleural and pericardial cavities should be examined to assess the presence of fluid that may accumulate due to postpericardiotomy syndrome. Table 1 summarizes the most important post-procedural echocardiography parameters that should be assessed. An accurate assessment of cardiac chamber size and function is essential. A detailed description of the morphology and function of the mitral and tricuspid valve is required. If there is a residual regurgitation, it should be reported taking into account full quantification, i.e.: vena contracta (VC) measurements, calculation of effective regurgitation orifice area (EROA) by proximal isovelocity surface area (PISA), regurgitant volume (assessing the aortic flow vs left ventricular stroke volume) using either two- or three-dimensional (2D or 3D) evaluation.

The aim of the valve repair is to restore the largest possible leaflet coaptation surface. Therefore, the assessment of the leaflet coaptation by measuring the coaptation length, height, and leaflet tenting area, as well as implanted ring adherence to the native cardiac tissue with regard to possible dehiscence, is especially important. The echocardiographic probability of pulmonary hypertension should also be evaluated (Table 2).

Outpatient evaluations should be performed at least annually unless the patient's condition requires more frequent monitoring [8]. Patients with functional mitral regurgitation secondary to left ventricular enlargement and dysfunction, for whom optimization of guideline-recommended treatment of heart failure is essential for survival, require special attention. Similar rules apply to all patients with left or right ventricular dysfunction after cardiac surgery according to general recommendations. Patients requiring anticoagulant therapy should be monitored for blood cell counts, coagulation parameters, kidney, and liver function.

Echocardiographic signs suggesting pulmonary hypertension (PH) parameters from at least two different categories are needed to determine the probability of PH are:

- A category: right ventricular/left ventricular basal diameter ratio >1.0; flattening of the interventricular septum in parasternal short axis view;
- B category: right ventricular outflow Doppler acceleration time <105 ms; Early diastolic pulmonary regurgitation velocity >2.2 m/s; pulmonary artery diameter >25 mm
- C category: inferior vena cava diameter >21 mm with decreased inspiratory collapse <50%; right atrial area (end-systole) >18 cm^2.

Follow-up after surgical repair of the aortic valve due to chronic aortic regurgitation

The etiological factors of aortic regurgitation (AR) are leaflet dysfunction, abnormalities in the anatomy of the aortic

complex (aortic opening, aortic bulb, size of the sinotubular junction), and pathologies in the proximal part of the ascending aorta. In recent years, the number of valve repair procedures in chronic aortic insufficiency has increased. These procedures must be tailored to the type of pathology and, due to difficulty level, require vast operator experience. For this reason, current recommendations of the European Society of Cardiology propose that aortic valve repair (AVRep) should be considered only in specialized centers with extensive experience. This explains a lower class of recommendations as compared to the previous edition of the guidelines [8].

Despite downgrading the recommendation, experienced cardiac surgeons will continue to perform these procedures, and the number of patients requiring monitoring after such procedures is expected to increase. Monitoring an AVRep patient after surgery requires knowledge of the surgical procedure including the specific surgical technique. Of note, the choice of the procedure depends on the center's experience, the coexistence of aortic aneurysm, characteristics of the valve leaflets, expected survival time, and finally the possibility of using anticoagulant therapy. In experienced centers, complex aortic valve repair (e.g. subcommissural annuloplasty in type Ic aortic regurgitation, leaflet plication in type II aortic regurgitation, annuloplasty or ring placement in the case of aortic annulus dilatation) and replacement of the aortic bulb while preserving the patient's native valve are increasingly performed (David's procedure — valve reimplantation, Yacoub procedure — bulb remodeling) and offer excellent long-term outcomes [8, 9].

The intraoperative TEE examination after the restoration of circulation is mandatory. It determines the effectiveness of the procedure and helps predict the possible risk of regurgitation recurrence. In the intraoperative evaluation, the presence of asymmetric regurgitation, greater than trace (usually moderate or severe), obliges cardiac surgeons to reoperate. The type of reintervention depends on the direction of the regurgitant jet (consistent/opposite to the initial echocardiographic image). In the case of a residual central regurgitant jet found in the intraoperative examination, the degree of regurgitation should be determined — optimally in the TEE transgastric view. The presence of regurgitation, with EROA ≥10 mm^2 and VC width ≥3 mm, is an indication for reintervention. The choice of procedure depends on the size of the aortic annulus (>25 mm — annuloplasty is indicated) and possible restriction of the leaflets (re-repair or replacement of the valve) [9].

Echocardiographic parameters indicative of good immediate surgical outcome and predictive for durable AVRep, are

- Absence of residual regurgitation (or minimal central jet aortic regurgitation);
- Effective coaptation height ≥9 mm;
- Leaflet coaptation ≥4 mm;
- Aortic valve annulus <25 mm;
- No leaflet restriction;
- Mean transvalvular gradient <10 mm Hg [8, 9].

Cardiology associations did not recommend any specific schedule of follow-up echocardiographic examinations after AVRep. It seems reasonable to perform TTE monitoring like in patients with implanted bioprostheses — one month and 12 months after the procedure, and then annually. The new onset of symptoms indicative of valve dysfunction represents a specific urgent indication for an echocardiographic evaluation. An open international registry to evaluate medical and surgical outcomes of aortic valve insufficiency and ascending aorta aneurysm (AVIATOR) proposes a format for preoperative, intraoperative, and postoperative echocardiographic examination reports [10].

Patients who undergo thoracic endovascular aortic repair (TEVAR) without aortic valve intervention constitute a separate group. In these cases, the first clinical and imaging examination should take place one month after the procedure to exclude early complications. Subsequent evaluations are performed after 6 or 12 months, and then annually. In stable patients, after endovascular repair of the thoracic aorta due to aortic aneurysm, in the absence of endoleak in the first 24 months, the intervals between subsequent imaging examinations can be extended to 2 years. After aortic surgery, with a stable course of disease during the first year, longer intervals between follow-up examinations may be sufficient [8].

Chest computed tomography (CT) is the examination of choice for patients who underwent thoracic aorta surgery and the most widely used diagnostic tool, ensuring optimal visualization. Magnetic resonance imaging (MRI) also plays an increasingly important role. In patients with nitinol stent grafts, MRI must be supplemented with a chest X-ray to visualize the metallic stent struts. In the case of stainless-steel prostheses, MRI is associated with intense artifacts. TEE is reserved for patients with severe renal dysfunction [8, 11].

Follow up after surgical implantation of prosthetic cardiac valves

The follow-up of patients with prosthetic heart valves (PHV) should involve [1, 8, 12]:

- Assessment of the general condition with particular attention to blood pressure, presence of heart failure, heart rate, as well as identification of the occurrence of arrhythmias or conduction disturbances;
- Monitoring the quality of anticoagulant therapy (acenocoumarol or warfarin) with the international normalized ratio (INR) values (obligatory in patients with a mechanical prosthesis);
- Echocardiographic assessment of cardiac chambers as well as the structure and function of the prosthesis.

The outpatient evaluation should be performed within 30 days, and then annually unless the patient's condition requires more frequent monitoring. Clinical judgment dictates whether more frequent visits are required, particularly if the patient has comorbidities, heart failure during

cardiac surgery as well as in the case of patients undergoing emergency surgery in infective endocarditis (IE). The INR should be assessed frequently to ensure maintenance within the recommended target range, depending on the implanted prosthesis and patient clinical characteristics (every 4 weeks and 1 week after every change in drug dose).

Echocardiography should be performed within the first three months after surgery. The obtained detailed description of the prosthetic valve function, the assessment of the dimensions and function of the cardiac chambers, as well as evaluation of the other valves, should serve as a reference in the further follow-up. In the early postoperative period, up to 30 days, the presence of effusion in the pericardial and pleural cavities should be excluded.

TTE/TEE should be performed whenever symptoms and/or suspected valve dysfunction appear. In a patient with a surgically or transcatheter implanted bioprosthesis, it is recommended to perform a follow-up TTE after 1 year, and then every year, according to the European Society of Cardiology (ESC) 2021 guidelines. TEE is indicated in the case of a non-diagnostic TTE image and in each case of suspected valve dysfunction. There are currently no indications for regular TTE monitoring in asymptomatic patients with mechanical prostheses, although patients with an ascending aortic dilatation and after mitral valve replacement should be monitored annually to control tricuspid regurgitation and right ventricular function.

The evaluation of PHV function should take into account the type of prosthesis and its size, as well as the function of the heart chambers, in particular the left ventricular ejection fraction. Importantly, all available windows should be used to minimize the impact of acoustic shadowing from PHV structure (also related to Doppler flow signal), including TEE as needed. Elevated transvalvular gradients require a complete diagnostic workup of suspected PHV obstruction. In case of doubt, one should use the manufacturer's data for a specific type of the implanted prosthesis [12], which provides the value of effective orifice area (EOA). The measured EOA value should not differ from the reference value for a given size of the prosthesis by more than 0.25 cm^2. Significant PHV stenosis is characterized by EOA smaller than reference by more than 0.35 cm^2. Difficulties may arise in differentiating the valvular stenosis from the so-called patient-prosthesis mismatch (PPM) which occurs usually when a PHV that is too small for the patient's body size is implanted in the aortic position [12, 13]. EAVCI recommends echocardiographic indicators for differential diagnosis (Table 3), as well as performing exercise echocardiography in patients with elevated resting gradients [12, 14, 15]. It should be noted, however, that exercise stress testing is safe in asymptomatic patients and in those with biological PHV, whereas it is contraindicated in suspected endocarditis or blockage of the valve disc.

Table 3. Essential echocardiographic parameters in the comprehensive evaluation of prosthetic valve function

- Peak velocity, m/s
- Mean gradient, mm Hg
- Effective regurgitant orifice area (EROA) and indexed effective orifice area cm^2/m^2
- Doppler velocity index (DVI)
- Systolic acceleration time (AT) — evaluation of the aortic valve prosthesis
- Ejection time (ET) — evaluation of the aortic valve prosthesis
- Pressure half time in mitral valve assessment
- Regurgitant jet evaluation (transvalvular, paravalvular and "physiologic" regurgitation)

Echocardiography is essential to define the presence, location, and severity of PHV regurgitation. The echocardiographic evaluation must discriminate physiological from pathological regurgitant flow and define intra- or periprosthetic regurgitation. The origin and direction of the jets should be evaluated, with quantification of regurgitation.

TEE (preferably by 4D/4D color flow) should follow TTE to precisely diagnose and quantify PHV dysfunction in suspected valve leak or obstruction (e.g. due to thrombus, pannus, or vegetation). Cinefluoroscopy must be performed in suspected blockage of the mechanical valve disc. The interpretation of echocardiographic parameters of prosthetic aortic and mitral valve function at rest, during the exercise test, and in the long-term follow-up is presented in Table 4.

Follow-up after transcatheter edge-to-edge mitral valve repair (TMVR)

Currently, two transcatheter edge-to-edge repair systems (MitraClip, Abbott Vascular, Santa Clara, CA, US and PASCAL, Edwards Lifesciences, Irvine, CA, US) are available in

Table 4. Selected echocardiographic parameters of prosthetic aortic and mitral valve function

Position of the prosthesis	Parameter	Normal	Possible stenosis	Significant stenosis
Mitral position	Peak velocity, m/s	<1.9	1.9–2.5	≥2.5
	Mean gradient, mm Hg	≤5	6–10	≥10
	Exercise-induced increase in mean pressure gradient, Δmm Hg	<5	5–12	>12
	Increase in mean pressure gradient in long-term follow-up evaluation, Δmm Hg	<3	3–5	>5
Aortic position	Peak velocity, m/s	<3	3–3.9	≥4
	Mean gradient, mm Hg	<20	20–34	≥35
	Exercise-induced increase in mean pressure gradient, Δmm Hg	<10	10–19	≥20
	Increase in mean pressure gradient in long-term follow-up evaluation, Δmm Hg	<10	10–19	≥20

Poland. The principle of both procedures is similar. The aim of patient monitoring after the edge-to-edge repair is to assess both the early and late procedural success rate and effectiveness, as well as to monitor the progression of heart failure [8]. It is important to assess the position, orientation, and stability of the clip, the size of the iatrogenic atrial septal defect, as well as to determine residual/new regurgitant jets and evaluate the severity of tricuspid regurgitation and left and right ventricular function. It is also of utmost importance to assess the occurrence of single leaflet detachment. Intraoperatively, before the clip is released from the delivery system presence, significant mitral stenosis should be evaluated since it is associated with a poorer prognosis. In the long-term follow-up, the diastolic transvalvular pressure gradient and mitral valve orifice area are also assessed.

While the visual exclusion of mild regurgitation is not difficult, to assess severe regurgitation and/or multiple regurgitant jets it is necessary to integrate many quantitative and semi-quantitative parameters (PISA radius, VC width, regurgitant jet area, length, volume, E wave velocity, analysis of the mitral and pulmonary venous inflow patterns, the intensity of the continuous wave [CW], Doppler regurgitant jet signal, the forward stroke volume of the LV). This is because residual regurgitant jets run in many directions and planes and they often cross each other. Assessment of pulmonary venous flow is useful since flow reversal is an indirect sign of significant regurgitation. In practice, the EROA calculation is of little use in evaluating the regurgitation after MitraClip implantation. If the obtained echocardiographic measurements are unreliable, then TEE or magnetic resonance imaging should be performed.

Comparative echocardiographic assessment before, during, and after the MitraClip procedure, allows for the ongoing monitoring of the reverse cardiac remodeling. When assessing the severity of right ventricular systolic dysfunction and functional tricuspid regurgitation, the magnitude of pulmonary hypertension should be considered. For this purpose, it is reasonable to use tricuspid annular plane systolic excursion (TAPSE)/right ventricular systolic pressure (RVSP) ratio, reflecting the ventricular-pulmonary coupling. The values of the quotient <0.31 are associated with poor long-term prognosis, which should be taken into consideration when planning for the next stage of surgical treatment, e.g. clipping the tricuspid valve.

Postoperative ASD usually does not induce a relevant interatrial shunt. Left-to-right shunts are most common and typically bear no hemodynamically significant consequences. Right-to-left shunts, especially in patients with right heart dysfunction, are associated with an increased risk of paradoxical embolism. In some patients, especially with concomitant right ventricular dysfunction, iatrogenic ASD may be a significant clinical problem, exacerbating the symptoms of right ventricular failure (see: Management of complications after cardiac valve interventions). In these patients, the standard assessment should include Qp/Qs ratio measurements using Doppler (Qp — pulmonary blood flow, and Qs — systemic blood flow) or an invasive saturation monitoring. The echocardiography examination after edge-to-edge repair should be treated as an examination of a patient with severe compensated heart failure. Patients treated with transcatheter mitral valve repair (TMVR) should undergo a periodic echocardiographic evaluation with a similar frequency of visits and for the same indications as for patients with heart failure with reduced ejection fraction.

Patients after transcatheter procedures should be evaluated at discharge. Outpatient monitoring is recommended during one month after the procedure, with TTE examination (or TEE in some patients) after 1 year and then annually. The first post-operative examination performed within 30 days of MitraClip implantation should be the starting point for comparative evaluation performed during subsequent follow-up visits.

It is not uncommon for patients considered for edge-to-edge repair procedures to wear cardiac implantable electronic devices (CIED): implantable cardioverter defibrillator (ICD), cardiac resynchronization therapy-pacemaker (CRTP), or cardiac resynchronization therapy-defibrillator (CRTD). While assessing the right ventricular function and tricuspid regurgitation, attention should be paid to the potential CIED-mediated tricuspid regurgitation, and in the case of the febrile state, a potential lead-dependent IE. In patients with worsening heart failure, electrical storm occurrence or progression of ventricular dysfunction is important to assess cardiac chamber dimensions, the restriction of mitral leaflet motion and severity of residual mitral and tricuspid regurgitation, echocardiographic signs of volume/pressure overload (measurement of the inferior vena cava diameter), as well as to assess the unfavorable remodeling.

Follow-up after transcatheter aortic valve implantation (TAVI)

The patients after percutaneous transcatheter aortic valve implantation should be followed up regarding the prosthetic valve leak and obstruction/restenosis. The likelihood of paravalvular regurgitation after TAVI is low [8]. It has been further reduced to 0%–2% with newer transcatheter heart valve designs. While mild paravalvular leak (PVL) does not affect the prognosis of patients after TAVI, moderate/severe PVL is associated with a worse prognosis. Predictors of a paravalvular leak include undersizing, the presence of massive calcifications or incidence of the bicuspid aortic valve, and finally, incorrect positioning of the prosthesis. In the case of very low valve implantation, a supraskirtal regurgitation may occur, which is often difficult to differentiate from a typical leak. Transvalvular regurgitation can occur in the presence of valve malapposition, deformation, degeneration, thrombosis, perforation, or infective endocarditis (IE).

Both TTE and TEE remain the preferred methods of assessing the size of PVL, notwithstanding their limita-

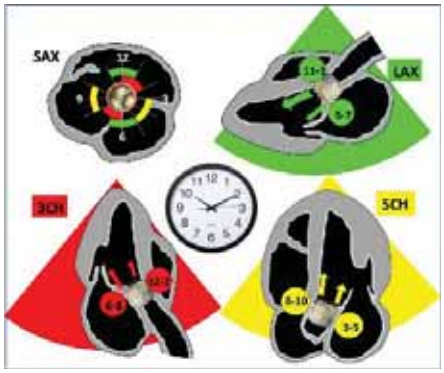

Figure 1. The methodology of paravalvular leak assessment in standard transthoracic echocardiographic examination projections after transcatheter aortic valve implantation procedure

Abbreviations: 3CH, apical three-chamber view; 5CH, apical five-chamber view; LAX, parasternal long-axis view; SAX, parasternal short-axis view

tions. When assessing PVL, attention should be paid to color-coded Doppler signals in standard transthoracic and transesophageal projections. It is necessary to visualize the prosthesis in all available projections to minimize the influence of the artifact on the quality of the color-coded Doppler signal. Anterior PVL is more visible in the apical 3-chamber view during TTE, while posterior PVL are best visualized in the mid-esophageal and transgastric view during TEE. The methodology of PVL assessment in 4 standard transthoracic views is presented in Figure 1. The PVL grading should be comprehensive and include quantitative and semi-quantitative measurements, including the assessment of diastolic flow in the descending aorta. A quick method of assessing the PVL significance is the evaluation of PVL circumferential extent, defined as the sum of PVL orifice circumference(s) divided by the valve circumference. If the extent exceeds >20% (a cutoff >30% is proposed in some sources) the PVL is severe. If the PVL has been assessed on echocardiogram as greater than mild and there are discrepancies between the clinical symptoms and the PVL severity, MRI may be necessary.

Echocardiographic examination after the TAVI procedure, besides the PVL assessment, should also report the resting transvalvular gradient, as well as the function of both ventricles and atrioventricular valves. Early post-TAVI TTE is crucial for follow-up evaluation of the implanted prosthesis, representing baseline hemodynamics. The increasing mean gradient in consecutive examinations may indicate valve thrombosis or degeneration. A comprehensive evaluation of the prosthesis failure mechanism can be performed using TEE and CT. The evaluation of transvalvular gradients should be supplemented with the calculation of the EOA and EOAi of the valve. The increase in the transvalvular gradient may be caused by valve thrombosis, leaflet degeneration, or IE. Notably, in the first months after surgery, the increase in transvalvular gradient may be due to improved LV systolic function and an increase in left ventricular output. In this situation, the opening of the valve, measured as EOA, is normal and stable. In the first years after TAVI, the increase in transvalvular gradients with a concomitant decrease in EOA is usually caused by valve thrombosis (which is uncommon after >3 years). Diagnostics should then be extended to include TEE and possibly CT. In later years, the increase in transvalvular gradients and the decrease in EOA are mainly due to valve degeneration.

After TAVI, the first follow-up examination should be performed at discharge, then after 30 days, 1 year, and then every 1–2 years after the procedure with specific evaluation of the prosthesis function, assessment of potential PVL, left ventricular (LV) function, and the severity of mitral regurgitation if present. In asymptomatic patients with adequate function of the implanted prosthesis, preserved LV systolic function without concomitant valvular disease, subsequent evaluations should be performed as in other patients with bioprostheses and in every case of patient-reported cardiac symptoms. More and more experts recommend TTE every 1–2 years based on the current data.

Echocardiography is an essential component of cardiac evaluation and therefore should be performed on all consecutive follow-up visits. Concomitant functional mitral regurgitation often regresses after TAVI, but its course in individual patients is difficult to predict, which should prompt a mitral regurgitation jet assessment at each subsequent visit. Mixed etiology mitral regurgitation may not be reduced after TAVI procedure, and therefore determining patients' eligibility for the next stage procedure — e.g. edge-to-edge repair — might be necessary. Patients with degenerative mitral valve disease and coexisting mitral stenosis will require more frequent visits to monitor the progression of the disease. If necessary, the decision for the next-stage surgical treatment is made.

MANAGEMENT OF COMPLICATIONS AFTER CARDIAC VALVE INTERVENTIONS

Complications of valve surgery — prevention and treatment

Complications associated with surgical treatment of valvular heart disease can be divided into two groups.

The first group includes complications that may follow any classic cardiac surgery procedure. These are associated with using cardiopulmonary bypass and surgical access. The use of extracorporeal circulation can initiate a systemic inflammatory response syndrome (SIRS), which in the case of prolonged surgery, may cause kidney and lung injury, intestinal ischemia, coagulation disorders, vascular endothelial dysfunction, and hemolysis.

To reduce the intensity of this unfavorable phenomenon, the duration of extracorporeal circulation should be shortened. Therefore, hybrid procedures facilitate minimally invasive approaches, where instead of complex procedures, such as e.g. surgical aortic valve replacement (SAVR)

and coronary artery bypass grafting (CABG), the treatment is divided into stages — the first is percutaneous coronary intervention and the next minimally invasive aortic valve replacement. In the case of CABG, it is possible to eliminate the extracorporeal circulation (Off-Pump Coronary Artery Bypass Grafting, OPCAB). Extracorporeal removal of inflammatory mediators is possible with adsorption filters. Infection and impaired wound healing are considered important complications of surgical access. Mediastinitis is known to be the most severe form of infection with a very high mortality rate. Minimally invasive accesses, for example, right-sided mini-thoracotomy for mitral valve surgery or upper mini-sternotomy for aortic valve interventions, as well as proper preprocedural preparation of the patient (elimination of inflammatory foci before the surgery), reduce the incidence of these complications.

The second group of complications include those directly related to a specific valve procedure, including conduction disturbances and a paravalvular leak.

Postoperative conduction disturbances

Postoperative atrioventricular block (AVB) after mitral valve procedures occurs in 24% of patients and intraventricular conduction disturbances occur in 15% of patients. Conduction disturbances in most cases resolve spontaneously before the patient's discharge from the hospital, but about 4% of patients after mitral valve surgery require implantation of a permanent pacemaker. Factors such as prolonged duration of myocardial ischemia, damage to the artery supplying the atrioventricular node, large size of implanted valvular prosthesis, and simultaneous ablation of the atrial fibrillation substrate are associated with an increased risk of conduction disturbances [16].

The risk of atrioventricular block after SAVR is over 10%, and the prevalence of intraventricular conduction disturbances is approximately 8.5%. Roughly 1.5% of patients require permanent pacemaker implantation. Risk factors associated with permanent pacemaker implantation include the history of cardiac arrhythmias, bicuspid aortic valve, aortic valve regurgitation, female sex, prolonged extracorporeal circulation, previous cardiac surgery, or myocardial infarction [17]. New-onset significant conduction disturbances are common after TAVI (see: Complications after transcatheter valve interventions) [18].

Tricuspid valve procedures are associated with a high risk of permanent conduction blocks. This is due to the anatomical proximity of the stimulus-conduction system. Twenty-one percent of patients after valve replacement surgery and over 9% of patients after repair surgery are qualified for permanent pacemaker implantation [19]. The factors increasing that risk are heart ischemia time exceeding 60 minutes and simultaneous operation on the mitral valve [20].

Implant the largest possible prosthesis to avoid the PPM phenomenon is a common risk factor for the occurrence of postoperative conduction disturbances, which is difficult to avoid. Patient-prosthesis mismatch (PPM) essentially is a concept of a relatively small effective orifice area in relation to the patient's body size. Severe PPM after aortic prosthesis implantation, defined as the indexed effective orifice area (EROAi) <0.65 cm^2/m^2, and PPM after mitral prosthesis implantation, defined as EROAi <1.2 cm^2/m^2, could have a possible adverse effect on long-term survival [21, 22].

Post-operative paravalvular leak

Paravalvular leaks (PVLs) have been shown to be a major complication that results from insufficient sealing between the native annular tissue and the outer aspect of the prosthesis. Based on the literature, the prevalence of PVL after surgical aortic valve replacement (SAVR) is 2%–10% and 7%–17% in the case of mitral prosthesis implantation. A significant leak can lead to heart failure, hemolytic anemia, as well as IE.

The configuration of the native aortic annulus, which consists of three deep interconnected arches, is a factor contributing to the incomplete valve adherence. PVLs are often the result of significant tension between the non-compliant ring of the prosthesis and the arches of the native aortic annulus. This problem can be mitigated by placing sutures through the aortic wall that secures the valve in a single plane. The choice of prosthesis is also important. Valve implantation due to IE is also a risk factor for a PVL. Patients with mechanical prostheses with a non-compliant metal ring bear the highest PVL risk. Some stented bioprostheses have a more compliant ring with marked arches, which reduces tension. Stentless bioprostheses eliminate the risk of PVL almost entirely. PVLs observed after surgical mitral valve interventions are most often a result of the injury to the delicate heart tissue caused by the sutures holding the valve. This is due to the much higher pressures affecting the valve in the left venous outlet and prior IE [23]. The indication for reoperation is any hemodynamically or hematologically significant PVL unless percutaneous closure is feasible.

Factors increasing the risk of PVL after transcatheter aortic valve implantation are valve undersizing, incorrect valve positioning, and massive calcification of the native valve [24].

Repeat valve surgery (reoperation)

Cardiovascular diseases are the leading cause of mortality in Poland. The occurrence of these diseases is undoubtedly related to the aging of the population and the increasing access of patients to diagnostic tools, health promotion programs, and specialist care.

Data from the Society of Thoracic Surgeons National Database report indicate that the number of patients receiving bioprosthetic valves increased to over 78% in comparison to mechanical valves [25]. Similar data were also obtained in Europe and in the Polish National Register of Cardiac Surgery Procedures, the relationship between the number of implanted mechanical and tissue valves has

changed over the decade in favor of bioprostheses [26]. Young patients with a more active lifestyle often choose biological valves, therefore, accepting the risk of future reoperation. Nevertheless, the dysfunction of the prosthesis does not only concern biological valves [26].

Common indications for valve reinterventions include

- Recurrence of the pathology after primary valve repair;
- Degeneration of the bioprosthesis — the most common cause for reoperation;
- Prosthetic valve dysfunction, prosthetic heart valve thrombosis, pannus (mechanical and biological prostheses);
- Significant paravalvular leak;
- IE.

The most important risk factors for reoperated patients are [26, 27]:

- The patient's age at the time of reintervention;
- Female sex;
- Infective endocarditis;
- Left ventricular failure;
- Reduced ejection fraction;
- Multivessel coronary artery disease;
- History of multiple valve surgery;
- Reoperation type (elective, urgent, emergency).

Median sternotomy remains the standard approach for reinterventions. Re-do sternotomy carries a risk of right ventricular trauma or intraoperative bleeding, as well as the risk of inadvertent trauma to a patent coronary graft. Reoperations require careful preparation, including not only the assessment of indications but also the development of a management strategy. Computed tomography of the chest remains indispensable for overall imaging of the chest; hence, it primarily assesses relationships between mediastinal structures and the sternum. If the right ventricle or the aorta adheres to the sternum, an alteration of the reoperation strategy and technique should be considered. In such patients, cardiopulmonary bypass before repeat sternotomy seems a valid option to render cardiac reoperation safer. This implies the need for peripheral cannulation. The femoral vascular access site is the most frequently used.

The development of minimally invasive techniques has also resulted in major changes in current surgical practices in cardiac reoperations. Minimally invasive procedures, such as mini-sternotomy or mini-thoracotomy, reduce the risk of pericardial and pleural adhesions. Thus, performing cardiac reoperation in patients with previous cardiac surgery using a minimally invasive technique reduces the procedural risk of reintervention. In patients with patent coronary grafts, it is possible to perform the reoperation via lateral mini-thoracotomy or using a thoracoscopic approach. In patients who have undergone valve surgery and are eligible for surgical revascularization, it is possible to perform the procedure using a minimally invasive technique through the left-sided lateral mini-thoracotomy approach (MIDCAB) [28]. Among other surgical strategies, a hybrid approach should also be considered, combining minimally invasive cardiac surgery and interventional cardiology. An example of this are percutaneous coronary interventions within coronary artery bypass grafts.

In the case of aortic bioprosthesis dysfunction in prohibitive surgical risk patients, with contraindications to reoperation, the technique of transcatheter valve implantation — TAVI valve-in-valve (ViV) is a new and preferred strategy [29]. It can be also performed in dysfunctional mitral and tricuspid bioprostheses.

Reoperation is recommended not only in patients with valve dysfunction but also in those affected by the progression of valve disease after previous cardiovascular surgery, most often coronary surgery. Despite the development of minimally invasive and endovascular techniques, reoperations are still high-risk procedures that require careful assessment of indications and the scope of surgery. The rapid growth of technology and diagnostic imaging decreases the risk of reintervention in many patients. A summary of the most important indications and recommendations on the management of prosthetic valve dysfunction according to the 2021 ESC/EACTS Guidelines for the management of valvular heart disease is presented in Table 1 [8].

Complications after transcatheter valve interventions

Complications after TAVI: The main goal of the TAVI procedure is to stretch and widen the valve orifice and improve blood flow into the aorta, which can be achieved in almost all patients. An effective treatment leads to a detectable improvement in the patient's condition including the improvement of exercise tolerance, reduction of dyspnea, elimination of syncope, relief of angina, and above all, improved survival and quality of life [1, 8, 30].

Due to the low invasiveness of the procedure, replacing general anesthesia with local anesthesia, and the fact that, unlike the surgical option, TAVI does not require opening the chest or use of extracorporeal circulation, the patient can be quickly mobilized and rehabilitated. The risk of periprocedural death is low and, in most patients, it does not exceed 1.0%–1.5%. The incidence of periprocedural myocardial infarction is extremely rare. The risk of conversion to open-heart surgery due to perioperative complications is low and does not exceed 0.3%.

Transcatheter aortic valve implantation (TAVI) is associated with a risk of periprocedural stroke (1.5%–4.0%); however, it is lower than that of Surgical Aortic Valve Replacement (SAVR). The risk of this complication appears to be reduced with the use of periprocedural cerebral vascular protection systems, especially in patients with a high risk of stroke associated with TAVI procedure (bicuspid valve, massive calcification of the aortic valve or the aortic arch, ViV procedures). An appropriate periprocedural pharmacotherapy with antiplatelet or anticoagulant agents seems to play an important role in patients with indications for anticoagulation, though that role requires further research.

Another life-threatening complication is cardiac tamponade, which may be caused by the left ventricular injury (due to guidewire) or aortic annular rupture. The risk factors include, inter alia, undersizing and massive native valve calcifications, especially in the area of the left coronary aortic valve leaflet and the aortic apparatus. If rapid ventricular pacing is used during the procedure, tamponade may be caused by the introduction of the pacing lead into the right ventricle.

Undersizing may result in the migration of the valve either into the left ventricle or to the ascending aorta. A rare but serious complication is damage to the mitral apparatus with rupture of papillary muscle or tendinous cords usually due to intraprocedural aortic valvuloplasty or careless manipulations in the left ventricle with guidewires or the delivery system. Another very rare serious complication is the formation of a ventricular septal defect.

Due to the nature of vascular access and the introducer diameters, vascular complications and the associated bleeding complications most commonly occur at the access site (3%–8%). As a consequence of the recent technological progress, a significant reduction of system size, as well as the contemporary percutaneous closure technologies and increasing experience of operators, such complications are less frequently observed. In the periprocedural period, conduction disturbances (left bundle branch block, atrioventricular blocks including complete block) may appear or increase, which in some patients (8%–25%) requires pacemaker implantation. The risk of pacemaker implantation is greater in patients with pre-existing conduction disturbances.

The technique of the procedure itself (the depth of prosthesis implantation), severe native valve calcifications, and the type of bioprosthesis used (higher risk for self-expanding bioprosthesis, lower for balloon-expandable valves) are also of immense importance in terms of the occurrence of this complication. New valve generations and improved implantation techniques have reduced the risk of PPM.

Contrast-induced nephropathy (CIN) is one of the leading causes of hospital-acquired, transient acute kidney injury (AKI), especially in patients with previous chronic kidney disease. Proper hydration of the patient in the periprocedural period, avoiding prolonged hypotension and the use of as little iso-osmolar contrast media as possible during the procedure minimizes the risk of this complication. The occurrence of periprocedural arrhythmias (mainly atrial fibrillation), although similarly to AKI observed less frequently than after SAVR, requires treatment following the current recommendations, as well as the implementation of an anticoagulant regimen. In less than 5% of patients, depending on the type of prosthesis, moderate or severe PVL is observed post-TAVI (see: Follow-up after transcatheter aortic valve implantation), which worsens the prognosis. Modern prostheses are designed to reduce the risk of this complication by the addition of external sealing skirts.

Complications after transcatheter mitral valve repair (TMVR)

Among several approaches to transcatheter mitral valve repair; in Poland, the most popular technique is transcatheter edge-to-edge-approach (TEER).

Determining patients' eligibility for TMVR should be consistent with the consensus recommendations developed in centers with expertise in both surgical and percutaneous treatment of mitral valve disease by experienced multidisciplinary teams. Notably, medical therapy must be optimized, and CRT-D use considered [1, 8, 31, 32].

Periprocedural complications of transcatheter edge-to-edge repair procedures with the MitraClip and PASCAL systems include periprocedural death (less than 1%), bleeding at the vascular access site of various severity (up to approximately 5%–8% in total), single leaflet detachment (less than 2%), complete clip detachment or embolization (<0.05%), leaflet perforation, mitral chordal rupture, cardiac perforation followed by pericardial tamponade (mainly the left atrium or its appendage), thrombus formation within the left atrium, stroke, and TIA, as well as kidney failure. Conversion to emergency cardiac surgery is extremely rare (<0.5%).

Clip placement requires an interatrial transseptal puncture, which due to the relatively large delivery system and guiding catheter creates an iatrogenic atrial septal defect (iASD). It may close spontaneously or remain patent after the procedure (incidence of 50%–85% after 30 days and <30% after 12 months). In the event of acute respiratory failure, it is recommended to close the iASD immediately after the TMVR procedure with an adequate, dedicated occluder. The long-term approach to postprocedural ASD is controversial. The data from the registries are contradictory and demonstrate both the beneficial effect of left atrial decompression on symptoms and prognosis, as well as an increased risk of worsening heart failure and poorer prognosis.

Complications of edge-to-edge procedures result from the procedural technique itself, and their incidence decreases significantly with a proper candidate selection by a multidisciplinary team, as well as with the increasing experience of the operators and centers.

Valve-in-valve — transcatheter valve implantation for failing surgical bioprostheses

Valve-in-valve (ViV) TAVI emerged in 2007 and since then has become an established treatment option for surgical bioprosthetic valve deterioration. The 2019 STS/ACC TVT Registry reported a significant increase in the number of ViV-TAVI procedures (over 4 500 procedures were performed in the USA) [33]. This is due to the more frequent use of biological prostheses in younger patients and an increased risk of reoperation in patients previously undergoing SAVR (comorbidity, presence of coronary bypass grafts). ViV procedures are most frequently performed on malfunctioning surgically implanted aortic valve bi-

oprostheses (stented and scentless valves, homografts), and more and more often, also on mitral and tricuspid bioprostheses (stented valves).

In the case of ViV procedures in the aortic position, transfemoral access is favored over alternatives. In ViV transcatheter mitral valve replacement the transseptal approach has emerged as the preferred option, but trans-apical access is also viable, whilst ViV tricuspid valve replacement is performed via internal jugular and femoral approaches [34].

The pre-procedural preparation process includes (1) TTE (assessment of the pathology mechanism; quantitative assessment of the gradient and/or degree of regurgitation; comparison of parameters obtained immediately after SAVR allows to distinguish prosthesis-patient mismatch [PPM] from degeneration); (2) TEE (PVL and infective endocarditis); (3) CT of the heart with contrast medium and CT angiography of the aorta (access assessment, accurate measurements of coronary height from the aortic valve annulus, aortic root dimensions, orientation of the bioprosthetic commissures and sizing of the prosthesis); (4) coronary angiography; (5) reviewing the SAVR procedural data (verification of the surgical technique, residual gradient after SAVR, as well as valve type and dimensions).

It is very important to establish the "true internal diameter," which depends on how the valve leaflets are mounted in the stent frame, as well as the type of animal tissue (bovine vs. porcine). The mechanism of bioprosthesis dysfunction is important, as in stented bioprostheses stenosis is dominant, while in stentless, regurgitation. The technique of the procedure is similar to TAVI in a native aortic valve, but prior knowledge of the characteristics of the previously implanted bioprosthesis is necessary (stent cells as the orientation point the top of the stent or a marker within the prosthesis) [35]. This information can be obtained from the "Valve in Valve App" developed by V. Bapat (ViV aortic and ViV mitral).

The most important limitation of ViV-TAVI procedures is a risk of an elevated residual gradient after transcatheter valve implantation in small size degenerated surgical bioprostheses. Depending on the initial anatomy of the aortic valve region (e.g., the depth, width, and height of the sinuses) and the type of bioprosthetic surgical aortic valve (e.g., externally or internally mounted leaflets), ViV-TAVI may be associated with an increased risk of coronary obstruction in some patients, as well as the consequent need for PPM implantation, which remain important issues. Therefore, pre-procedural planning with a thorough angio-CT analysis, with the measurement of the valve-to-coronary orifice distance (VTC) is crucial. In patients who are at risk of iatrogenic coronary obstruction (VTC < 4 mm), coronary protection of the coronary ostia and eventual stent implantation in case of coronary flow impairment, as well as BASILICA (Bioprosthetic or native Aortic Scallop Intentional Laceration to prevent Iatrogenic Coronary Artery obstructions during TAVR) procedure have been suggested as potential strategies for alleviating the risk.

Another issue is the preservation of future access to the coronary vessels after ViV-TAVI, which may be of particular importance in this group of patients due to the relatively long life expectancy compared to the general TAVI population. The appropriate orientation of the transcatheter aortic valve (TAV) in relation to the previously implanted surgical aortic valve is of great significance. There are numerous studies describing the self-expanding valves implantation technique that allows minimizing the phenomenon of commissural misalignment.

ViV-TAVI in degenerated surgical bioprosthetic valves has been performed in Poland since 2010 and constitutes approx. 2% of all TAVI procedures. Recently published data from the Polish Transcatheter Aortic Valve-in-Valve Implantation (ViV-TAVI) Registry from 14 participating centers and covering a total of 130 procedures showed high procedural effectiveness of ViV-TAVI, especially since second-generation transcatheter heart valves (bioprostheses that can be repositioned and/or with an additional sealing skirt) were introduced [36].

In summary, ViV TAVI procedures have emerged as a safe and effective alternative to SAVR reoperation, provided that patients are carefully selected, and the procedure is planned. A regular echocardiographic follow-up is necessary due to the possible degeneration of the bioprosthesis [8, 37].

Transcatheter management of paravalvular leaks

The PVL is found in several to over a dozen percent of patients with surgically implanted heart valve prostheses, and even in several dozen percent of patients with percutaneously implanted aortic valve prostheses (especially the first-generation valves, as the likelihood of paravalvular regurgitation has been reduced with newer heart valve designs) (see: Follow-up after transcatheter aortic valve implantation, and Post-operative paravalvular leak). The occurrence of PVL is directly linked to the presence of extensive calcifications of the native aortic annulus (the device landing zone) and/or inflammation-related destruction of the surrounding tissues, which prevents the prosthesis from adhering tightly to the annulus. A majority of PVLs occur within the first year from valve implantation; however, about 25% are discovered later, which may be due to the "smoldering" infection in the tissues surrounding the prosthesis. Reoperation is recommended if the paravalvular leak provokes heart failure symptoms and/or causes hemolysis requiring repeated blood transfusions [8, 38, 39].

When assessing a patient with a prosthetic valve in TTE, a careful examination technique is required to eliminate the limitations resulting from the presence of acoustic shadows that increase the risk of underestimating or even overlooking a PVL. An important indirect sign of a large PVL, especially in mitral valve prostheses, is a high transvalvu-

lar mean pressure gradient resulting from the increased transvalvular flow. TEE is helpful for definitive diagnosis. Irregular shape of the PVL channel with frequently oblique course, presence of multiple PVLs at the same prosthesis or coexistence of mitral and aortic PVLs in patients after double valve surgery necessitate multifactorial echocardiography assessment, in selected cases supplemented by cardiac magnetic resonance data (regurgitation fraction) [13, 40–42].

The role of transcatheter paravalvular leak closure (TPVLC) in the management of PVL is increasing, and it was granted class IIa recommendation in both the 2021 ESC [8] and 2020 American College of Cardiology and American Heart Association (AHA/ACC) guidelines [38]. Sealing PVL with occluders is performed from transvenous, transarterial, or transapical access (depending on the location of the PVL). The device is selected on the basis of echocardiographic (mainly 3-dimensional TEE) characteristics of the PVL channel [43] and in some cases, supplemented with CT data. Due to high surgical risk and frequent recurrence of PVL after surgical correction (up to 20% in long-term follow-up), the reoperation should be reserved for patients in whom PVL coexists with active IE, significant dysfunction or degeneration of the prosthetic valve, its mechanical instability or other concurrent indications for surgical treatment. Verification of TPVLC effectiveness should include both echocardiography and monitoring of hemolysis (reticulocytosis, unconjugated bilirubin, and lactate dehydrogenase [LDH]) to exclude the possibility of incomplete closure of PVL, which may exacerebate the hemolysis after TPVLC.

Pharmacotherapy after TPVLC is not standardized. In patients who require chronic anticoagulation therapy, the treatment is continued after the procedure, with the addition of antiplatelet drugs in some cases. In patients not receiving chronic oral anticoagulant treatment, dual antiplatelet therapy (aspirin + clopidogrel) is usually prescribed for 6 months.

MANAGEMENT OF SPECIFIC CLINICAL SITUATIONS AFTER CARDIAC VALVE INTERVENTIONS

Management of anticoagulant and antiplatelet therapy after prosthetic valve implantation

Over the past 50 years, around 4 million prosthetic heart valves have been implanted. Every year 300 000 prosthetic heart valve replacements are done worldwide, and the number is growing [44]. The surgical procedure remains the only effective treatment for the majority of patients with severe valvular heart disease.

Patients with mechanical prostheses

The latest guidelines for the management of valvular heart disease, published in 2021 and developed by the Task Force for the management of valvular heart disease of the ESC and the European Association for Cardio-Thoracic Surgery (EACTS), recommend lifelong treatment with VKA guided by the INR in all patients with mechanical prostheses (class IB). These guidelines are mainly based on observational data and expert opinion, as only a few randomized trials have been conducted so far. Factors influencing the prosthesis thrombogenicity include altered blood flow, activation of the blood coagulation caused by the surgical procedure, and exposure to artificial valve surfaces (sutures, components of the prosthetic heart valve). Currently, the most used VKAs are warfarin (half-life of 40 hours) and acenocoumarol (half-life of 8-11 hours). Attempts to use oral anticoagulants that are not-vitamin K antagonists have failed. Currently, the use of NOACs in patients with mechanical heart valves is contraindicated (class III B) [8].

VKA therapy in clinical practice is challenging as it is associated with several limitations, including the slow onset of action, prolonged activity after drug withdrawal, narrow therapeutic window, and variable dose response due to multiple interactions with other therapeutics or food. Treatment with VKA should be initiated on the first postoperative day in combination with bridging therapy with therapeutic doses of either unfractionated heparin (UFH) or off-label use of low-molecular-weight heparin (LMWH) until therapeutic INR is obtained.

INR is used to assess and monitor the effectiveness of VKA therapy. It is recommended to target a median INR value rather than a range to prevent viewing extreme values in the target range as a valid target INR. Target INR should be based not only upon prosthesis thrombogenicity but also on patient-related risk factors [8, 44]. Low-thrombogenicity mechanical heart valves are Carbomedics, Medtronic Hall, ATS, Medtronic Open-Pivot, St Jude Medical, Sorin Bicarbon, and high-thrombogenicity mechanical heart valves are Lillehei-Kaster, Omniscience, Starr-Edwards (ball-cage), Bjork-Shiley. Target INR in patients with mechanical prostheses without risk factors and with risk factors, such as a mitral or tricuspid valve replacement, previous thromboembolism, atrial fibrillation (AF), left ventricular systolic dysfunction, coagulation disorders, or older generations of prostheses are presented in Table 1 [8].

Patient education plays an important role in achieving stable anticoagulation. The guidelines emphasize the role of INR self-monitoring. The use of INR self-monitoring is associated with a lower rate of VKA-related complications in all ages. A study comparing the effectiveness of self-monitored vs in-clinic INR tested anticoagulation along with high patient compliance, demonstrated the safety of both methods after the implantation of the On-X mechanical heart valve in the aortic position. Hence, the guidelines recommend INR self-monitoring (class I B) for patients treated with VKA, provided that adequate training and quality control are performed. The addition of low-dose (75–100 mg) acetylsalicylic acid (ASA) to VKA may lower the incidence of thromboembolism at the cost of bleeding and may be occasionally necessary, usually in

Table 5. Recommendations on management of prosthetic valve dysfunction according to 2021 European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS) Guidelines for the management of valvular heart disease [8]

Thrombosis of mechanical prosthetic valve	Class	Level
Urgent or emergency valve replacement is recommended for obstructive thrombosis in critically ill patients without serious comorbidity	I	B
Fibrinolysis (using recombinant tissue plasminogen activator 10 mg bolus + 90 mg in 90 min with UFH or streptokinase 1 500 000 U in 60 min without UFH) should be considered when surgery is not available or is a very high risk, or for thrombosis of right-sided prostheses.	IIa	B
Surgery should be considered for large (>10 mm) non-obstructive prosthetic thrombus complicated by embolism.	IIa	C
Bioprosthetic valve thrombosis		
Anticoagulation using a VKA and/or UFH is recommended in bioprosthetic valve thrombosis before considering re-intervention.	I	C
Anticoagulation should be considered in patients with leaflet thickening and reduced leaflet motion leading to elevated gradients, at least until resolution.	IIa	B
Hemolysis and paravalvular leak		
Reoperation is recommended if a paravalvular leak is related to endocarditis or causes hemolysis requiring repeated blood transfusions or leading to severe heart failure symptoms.	I	C
Transcatheter closure should be considered for suitable paravalvular leaks with clinically significant regurgitation and/or hemolysis in patients at high or prohibitive surgical risk.	IIa	B
Decision on transcatheter or surgical closure of clinically significant paravalvular leaks should be considered based on patient risk status, leak morphology, and local expertise.	IIa	C
Bioprosthesis failure		
Reoperation is recommended in symptomatic patients with a significant increase in transvalvular gradient (after exclusion of valve thrombosis) or severe regurgitation.	I	C
Transcatheter, transfemoral valve-in-valve implantation in the aortic position should be considered by the Heart Team depending on anatomic considerations, features of the prosthesis, and in patients who are at high operative risk or inoperable.	IIa	B
Transcatheter valve-in-valve implantation in the mitral and tricuspid position may be considered in selected patients at high risk for surgical reintervention	IIb	B
Reoperation should be considered in asymptomatic patients with significant prosthetic dysfunction if reoperation is low risk.	IIa	C

Abbreviations: UFH, unfractionated heparin; VKA, vitamin K antagonists

the setting of acute coronary syndrome and arterial stent implantation. Thus, the addition of antiplatelets to VKAs should be reserved for rare and carefully selected patients at very high risk of thromboembolism where the benefits exceed the risks (class IIa C).

In case of VKA overdose, major or life-threatening bleeding, and in patients requiring urgent surgery, the VKA should be discontinued, and 10 mg vitamin K should be administrated by slow i.v. infusion and if needed, repeated every 12 hours. Until the anticoagulation effect is reversed, the administration of prothrombin complex concentrates (PCC) and/or fresh frozen plasma (FFP) should be initiated according to body weight and pre-treatment INR. The efficacy should be monitored by reassessment of INR at 30 min and every 46 hours until normalization. In asymptomatic patients with INR >10, VKA must be discontinued, and oral vitamin K should be administered, while the INR values must be monitored on a daily basis for 2 weeks. Multiple randomized controlled trials in patients with INR between 4.5 and 10 suggest no difference in the incidence of bleeding with vitamin K vs. placebo. Thus, in such patients, VKA should be stopped temporarily, and a low dose of oral vitamin K (1–2 mg) can be considered individually, balancing the risks. Asymptomatic patients with INR <4.5 require cautious dose reduction and/or omission of one or more doses [8].

The anticoagulation strategy should be carefully considered in patients with prosthetic valves before elective non-cardiac surgery. It is recommended that oral anticoagulant therapy should not be interrupted before minor, low-risk procedures, such as cataract surgery or teeth extraction. In major surgical procedures, it is recommended to temporarily discontinue VKA therapy until INR <1.5 is achieved with the use of unfractionated heparin bridging or the use of low molecular weight heparin (LMWH) monitored and titrated to therapeutic doses (class I C) [8].

Patients with surgically implanted bioprosthetic valves

The incidence of thromboembolic events in patients with biological prostheses appears to be highest in the first 3 months after surgery. Lifelong oral anticoagulation, after surgical implantation of a bioprosthetic valve, is recommended only in patients who have other indications for anticoagulant therapy. Recent studies have shown that NOACs are not inferior to VKA. According to current recommendations, VKA administration should be considered for the first 3 months after the procedure in all patients with mitral or tricuspid biological heart valves (class IIa B). Either ASA (75–100 mg/day) or VKA monotherapy should be considered for 3 months after surgical implantation of an aortic bioprosthesis (class IIa B). NOACs rather than VKAs are recommended 3 months after surgical bioprosthesis implantation in patients with atrial fibrillation (class IIb C) [8].

Patients with transcatheter bioprosthetic valves

Lifelong antiplatelet therapy with a single agent is recommended after TAVI in patients with no baseline indication

Table 6. Target international normalized ratio for mechanical prostheses

Prosthesis thrombogenicity	No risk factors	≥1 patient-related risk factor
Low	2.5	3.0
Medium	3.0	3.5
High	3.5	4.0

for oral anticoagulant therapy (class I B). This recommendation was based on (1) a meta-analysis of three studies where a significant increase in major or life-threatening bleeding was observed with administration of dual antiplatelet therapy (DAPT) compared to monotherapy; (2) the latest POPular TAVI trial, which has demonstrated a significant reduction in bleeding and thromboembolic complications with the use of ASA alone compared to DAPT strategy. Therefore, a single antiplatelet therapy is recommended unless there are concomitant indications for DAPT (ACS, stent implantation).

There is a lack of data on the management of antithrombotic therapy after the implantation of the transcatheter mitral valve, but due to the increased risk of thrombus on the valve leaflets, manufacturers recommend VKA for up to 6 months in the absence of other indications for anticoagulation [8].

Patients after surgical mitral and tricuspid valve repair

Observational data show a comparable risk of thromboembolism with ASA or VKA use after mitral valve repair, though randomized data are lacking. High incidence and recurrence of new-onset AF, increased tendency to the thrombosis on the components of the repair systems and a relatively high proportion of ASA-resistant patients make VKA the preferred therapeutic strategy in the initial 3-month postoperative period. VKA should be considered in the first 3 months after mitral and tricuspid valve repair — class IIa C [8].

Patients after surgical aortic valve repair and aortic reconstruction

Due to a small number of such procedures, there are no clear guidelines for the management of this group of patients. Isolated reports from the literature indicate that in patients with aortic regurgitation who underwent aortic valve replacement, whilst maintaining the native valve, anticoagulation was not routinely administered. Monotherapy with a low dose of ASA (75–100 mg/day) should be considered for the first 3 months after the abovementioned interventions — class IIa C [8].

Patients after transcatheter mitral and tricuspid valve repair interventions

Optimal anticoagulation protocol for patients after edge-to-edge valve repair has not been standardized. It is recommended to use a loading dose of clopidogrel before or immediately after the procedure. Instead of clopidogrel, ASA can also be administered in a loading dose of 325 mg. After the procedure, clopidogrel at a dose of 75 mg/day or ASA 75–100 mg/day should be used for at least 6 months [45, 46].

A significant percentage of patients eligible for transcatheter repair of the mitral and tricuspid valves have AF and, therefore, indications for oral anticoagulation. Depending on the risk of bleeding in these patients, it seems advisable to add single antiplatelet therapy or a dual therapy of short duration.

Optimal management after valve interventions in pregnancy

In 2018, the European Society of Cardiology updated its guidelines for the management of women with cardiovascular disease during pregnancy. Pregnant women with mechanical heart valves belong to class III of the modified classification of the World Health Organization (mWHO) with regard to their risk of cardiac events during pregnancy, which represents a significantly increased risk of maternal mortality or severe morbidity, with a maternal cardiac event rate of 19%–27% [8, 47]. Women with mechanical heart valves should receive pre-pregnancy counseling and should be managed by a multidisciplinary care team during pregnancy and childbirth., i.e. the Pregnancy Heart Team. Follow-up visits during pregnancy should be performed every 1 to 2 months in an expert center with a Pregnancy Heart Team.

Different anticoagulation regimens should be carefully discussed before pregnancy. The patient should be informed that the use of VKA is the most effective way to prevent valve thrombosis and is the safest treatment for the mother. The dose-related increased risk of embryopathy, fetopathy, fetal loss, and fetal bleeding associated with the use of VKA should also be presented [48]. It is also necessary to inform the patient about a higher risk of valve thrombosis associated with the use of LMWH. The patient should understand that strict adherence to therapeutic recommendations is essential for successful pregnancy outcomes, irrespective of the treatment regimen. The choice of an anticoagulant depends on the dose of VKA necessary to obtain the therapeutic INR value [8, 47, 49].

If the VKA dose is low (warfarin <5 mg/day, acenocoumarol <2 mg/day), the continuation of VKA therapy throughout the entire pregnancy should be considered. The INR check should be determined weekly or every 2 weeks. An intra-hospital conversion to LMWH may be considered during the 6th–12th week of pregnancy under close monitoring antyXa level and after full disclosure of the associated risks is provided to the mother. The treatment of LMWH in the first trimester should take place in the hospital.

In women taking high-dose VKA (warfarin >5 mg/day, acenocoumarol >2 mg/day) discontinuation of VKA be-

tween weeks 6 and 12 of pregnancy and replacement with adjusted-dose intravenous UFH with APTT monitoring or subcutaneous administration of LMWH with strict anti-Xa monitoring should be considered. Initial doses of LMWH enoxaparin are 1 mg/kg and 100 IU/kg in case of dalteparin, administered subcutaneously twice daily. Doses should be adjusted according to the anti-Xa level at the time of maximum drug effect. Measuring anti-Xa levels shortly before the administration of the next dose should be considered. It is recommended to monitor the anti-Xa level daily in a hospital setting until reaching the target anti-Xa level, followed by a weekly anti-Xa activity assessment. For patients with mechanical heart valve prosthesis, recommended peak anti-Xa levels are at 1.0–1.2 U/ml (mitral and right-sided valves) or 0.8–1.2 U/ml (aortic valves) after 4 to 6 hours since drug dose administration and anti-Xa level before the next drug dose should be at >0.6 U/ml [8, 50]. If UHF is administered, once stable APTT values have been achieved, the intensity of anticoagulation should be monitored by the APTT level weekly, aiming at a reference range at least 2 times greater than the control. However, the use of UHF infusion for 6 weeks is difficult for practical reasons (labile APTT values, the need for 24/7 infusion, and the risk of infectious complications). After the patient had provided written informed consent, continuation of VKA administration should also be considered. VKA is the preferred anticoagulant in the second and third trimesters.

Regardless of the dose, it is recommended to discontinue VKA at week 36 and initiate unfractionated heparin infusion which should be monitored with APTT or use low-molecular-weight heparin with anti-Xa measurements. It is recommended to start the infusion of unfractionated heparin and adjust the dose (based on the APTT) 36 hours before the planned cesarean section in all patients. The infusion should be stopped 4–6 hours before the delivery and then restarted 4–6 hours after delivery if no bleeding has occurred [8, 50]. It should be emphasized that adjustments in anticoagulation regimens in pregnant women with mechanical valve prostheses should be implemented in the hospital setting.

Management of valve thrombosis after prosthesis implantation

Hemorrhagic and thromboembolic complications in patients with implanted valve prostheses account for 75% of all postoperative complications. Increased risk of thromboembolic events, both in the perioperative period and in long-term follow-up, is observed in patients with at least one of the following factors: age over 65, atrial fibrillation, heart failure, and low cardiac output syndrome, previous stroke, as well as the presence of common comorbidities such as hypertension, diabetes, renal failure, cancer, anemia, and coagulation disorders [51].

Obstructive prosthetic valve thrombosis should be suspected in every patient who presents with recent dyspnea or a thromboembolic event regardless of the type of prosthetic valve. The diagnosis should be confirmed by TTE and TEE, fluoroscopy, or CT [13]. When the echocardiographic assessment of a mechanical prosthesis is challenging, fluoroscopy can be a very useful diagnostic tool to demonstrate reduced valve leaflet mobility or immobilization of the mechanical prosthesis disk.

Management of mechanical prosthetic valve thrombosis either with pharmacological or surgical strategy is associated with a substantial risk of complications. Anticoagulation is the first-line treatment and should be initiated immediately in all patients until the thrombus is resolved [8].

Fibrinolytic therapy carries a higher risk of bleeding, systemic embolism, as well as thrombosis recurrence than surgery [13]. Urgent valve replacement is recommended in obstructive prosthetic thrombosis in severe condition patients without contraindications to surgery. The management of nonobstructive mechanical prosthetic valve thrombosis depends on the presence of thromboembolic complications as well as the size of the thrombi. Surgery should be considered for large (>10 mm) non-obstructive mechanical prosthetic valve thrombus, complicated by embolism, or persistent thrombus despite optimal anticoagulation [8, 52]. Anticoagulation therapy with VKA and/or UFH is the treatment of choice in biological prosthesis thrombosis [8].

Patients' eligibility for non-cardiac procedures after valve interventions

Patients who underwent valvular interventions may be at increased risk of perioperative cardiovascular complications during non-cardiac surgery. The risk can vary depending on the type and effectiveness of prior valve procedures, as well as the type of non-cardiac surgery [53].

Routine classification of non-cardiac surgeries into three risk groups: (low risk: <1%, moderate risk: 1%–5%, and high risk: >5%) should also be used in patients who underwent valvular interventions [54, 55].

Clinical and echocardiographic evaluation is recommended for all patients who underwent valve intervention, undergoing elective non-cardiac surgery associated with intermediate or high risk [53, 54]. In the overall assessment of patients after valvular intervention, the main issues are the evaluation of hemodynamic stability, assessment of clinical symptoms and investigating their relation to prior valve intervention, the risk assessment of non-cardiac surgery, as well as cardiac complications depending on the type of non-cardiac procedure. In patients after valvular intervention, with symptomatic heart failure or arrhythmias, apart from clinical and echocardiographic evaluation, appropriate pharmacological treatment is recommended, if necessary, before non-cardiac surgery [55, 56].

In patients with a history of a previous surgical correction of a heart defect or implantation of an artificial valve, non-cardiac surgery can be performed without

additional risk unless there is evidence of valvular or ventricular dysfunction. In current practice, the main issue is the necessity to modify the anticoagulant treatment regimen in the perioperative period — oral anticoagulants are temporarily replaced by UFH or LMWH in therapeutic doses [53, 56].

In patients with mechanical prostheses, bridging with UFH or LMWH before non-cardiac surgery carries a risk of perioperative bleeding, while temporary discontinuation of anticoagulation leads to a significant increase in the risk of thromboembolic complications, including valve thrombosis [57]. Therefore, anticoagulant treatment in patients with mechanical prostheses undergoing elective non-cardiac surgery requires detailed individual evaluation supported by other specialists if necessary [57, 58]. Discontinuation of oral anticoagulant treatment is not recommended for minor surgical procedures (e.g. dental, cataract surgery, skin incisions). where bleeding is usually minor and can be easily controlled.

Major surgeries require temporary discontinuation of oral anticoagulant therapy to achieve an INR of <1.5 and bridging therapy with UFH or LMWH at therapeutic doses. Fondaparinux should not be routinely used for perioperative bridging therapy but may play a role in patients with a history of heparin-induced thrombocytopenia [58].

Coronary artery disease after valve interventions

In the immediate postoperative period after valve surgery, interventional treatment of coronary artery disease is limited only to urgent interventions, i.e. in the case of acute coronary syndromes. In such situations, percutaneous revascularization is favored. In selected patients, revascularization may be performed as the next stage of a planned hybrid treatment after the valve intervention [8].

In long-term management of patients after percutaneous valve procedures, due to the baseline characteristics of this group (often elderly patients with multiple comorbidities), a decision whether to perform coronary angiography must be made individually and often depends on the diagnosis of acute coronary syndromes. If revascularization is indicated, percutaneous coronary intervention is preferred. In certain situations, cardiac reoperation must be considered; however, it is associated with a high surgical risk.

In patients after percutaneous aortic valve implantation, catheter access to coronary arteries may be difficult. This is due to the design of the implanted valve and the anatomical conditions — valve stent may extend over ostia of the coronary vessels. Additionally, when percutaneous coronary intervention is required, coaxial positioning of the guide catheter may be challenging. Such patients may benefit from referral to an experienced center, where the intervention can be safely performed. The above-mentioned difficulties have become the reason for modifying the design of new-generation TAVI valves and improving the methods of their implantation.

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Professor Marian Zembala (1950–2022) In memoriam

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Professor Marian Zembala, MD, PhD — an outstanding Polish cardiac surgeon and transplant surgeon, scientist, long-time academic teacher and educator of young people, director, and also a great lover of music, poetry, theater, painting, and sailing. He was born on February 11, 1950, in Krzepice near Częstochowa. He graduated from the Medical University of Wrocław in 1974 with honors and received the Primus Inter Pares award of the Polish Minister of Health, with a possibility to choose the place of work. He chose the Heart Surgery Department of the Medical Academy in Wrocław, which was his dream. Alongside his clinical work, he developed his scientific interests. In 1979, at the age of 29, he defended his doctorate with honors. His work in the Wrocław Clinic also provided an opportunity to go for his dream internship abroad, e.g. to the hospital in Utrecht, the Netherlands, where he worked under the supervision of Prof. F. Hitchcock (1981–1985). During his stay in the Netherlands, he initiated the largest post-World War II program of Polish Heart Poolse hartpatientjes naar Nederland, under which more than 500 Polish children with severe congenital heart defects were operated on free of charge between 1981 and 1992. For this ambitious project, he received an honorary award from Utrecht University and an award from the Primate of Poland, Cardinal Józef Glemp.

He returned to Poland in 1985, accepting Prof. Zbigniew Religa's offer to work in the team in Zabrze. This was the beginning of the next stage of Prof. Zembala's professional life — together with his mentor, Prof. Zbigniew Religa, he co-created cardiac surgery and transplantology in Zabrze, which he successfully developed for the next 30 years, especially after taking over the chairmanship in 1999. Over the years, the Department has become a leading Polish center with the widest range of cardiac surgical procedures performed in adults and children. The achievements of Prof. Marian Zembala are imposing and very well known. The main

Figure 1. Prof. Marian Zembala

areas of his professional interests focused on modern treatment of valvular heart disease, ischemic heart disease, pulmonary embolism, heart failure, mechanical circulatory support, and heart and lung transplantation in adults and children. His deep belief that limits are there to be crossed made him a pioneer of many modern treatment methods, which he successfully introduced into clinical practice in Zabrze. He performed the first lung transplantation in Poland (1998) and simultaneous heart and lung transplantation (2001).

Prof. Marian Zembala was also active at the European and global levels for many years, including being the President of the European Society for Cardiovascular Surgery (ESCVS) from 2010 to 2012, and the first Polish scholar to be the President of the European Association of Cardiothoracic Surgeons (EACTS) (2017–2018). He was a member of many national and international societies, editorial boards, committees and commissions, and a corresponding member of the Polish Academy of Sciences. In 2018, he received the title of Doctor Honoris Causa of the Piast Silesian Medical University in Wroclaw, i.e. his alma mater. He was also an Honorary Professor of the Silesian Medical University in Katowice. Author and co-author of more than 2000 publications, IF: 638.596; H-index: 33. Professor Marian Zembala received many awards and distinctions. The most important ones include: Papal Medal Benemerenti "Pro Ecclesia et Pontifice" (2012), Commander's Cross Polonia Restituta (2011), Saint Camillus Award (for activities for the city of Zabrze, 2010), and the Order of the Smile (2005), which was one of the most important awards for him because it was granted by children. The relationship with the region was also important to Prof. Marian Zembala. Even though he was not a Silesian by birth, for over thirty years he has been actively involved in the life and development of the Silesian macro-region, which he considered his little homeland. Prof. Marian Zembala was very successful as an organizer of health care in Poland, holding such positions as chairman of the Scientific Council to the Minister of Health (2008–2015), national consultant in cardiac surgery (2011–2016), and others. In 2015, he was appointed as the Minister of Health of Poland; he was known for always looking for solutions across boundaries.

In 1993, he became the Director of the Silesian Center for Heart Diseases in Zabrze, a position he held until his death. The hospital became his second home. With the dynamic development of the hospital, the then modest headquarters turned out to be too limited, and he decided to change it. Today we are fully aware that the expansion of the Silesian Center for Heart Diseases in Zabrze is his life's work. Together with his associates, he created one of the best and most modern centers for treatment of cardiovascular diseases in Poland. His great dream came true. We all knew it. The greatest success, and at the same time the fruit of great determination in action is the newest building, which will be opened at the end of May this year. It will also be a kind of a closure that will cement Prof. Zembala's great life achievements.

Apart from medicine, sailing was one of the greatest passions of Prof. Zembala. As a young man, he worked with young people from correctional homes. He also introduced cardiologists and cardiac surgeons to the beauty of sailing, inviting them to the so-called Cruises for the Heart. He believed that sailing taught humility, which is also very important in the work of a physician.

Prof. Marian Zembala was also sensitive to art — he loved theater, music, and poetry. On the one hand, he was tireless and determined in pursuing his goals, on the other, he was extremely sensitive to human suffering. He devoted his professional life entirely to serving sick people. He was incredibly demanding not only of himself but also of others. He was an extraordinary and persistent man, but at the same time warm-hearted. He fought fiercely for each patient, sometimes making seemingly irrational decisions, which later proved to be right and saved not only the patients' lives, but often their families as well. He was also a great ambassador of Polish science and medicine, a master and a guide for those who treated and were treated. His career was full of enough achievements for several lifetimes. He was a titan of work, often forgetting that sometimes you need to eat and sleep. Above all, Prof. Zembala loved his family and patients, who responded to his love. In 2018, he suffered a massive stroke, which, despite confining him to a wheelchair, did not prevent him from continuing to work and fight for the well-being of patients. He also always said that he would never have achieved such success if it wasn't for the people he met along the way. An important part of his life was also the memory of the pioneers.

It was his dream to sail on a long voyage after his retirement. We deeply believe, Professor, that you have just set sail on that voyage, your last voyage. We will miss you very much.

Ahoy, Dear Professor! Ahoy Dear Friend!

We bid farewell to a Great Man, a Wonderful Physician, a Loving Son, Husband, Father and Grandfather.

Thank you for everything. You will always remain in our memory!

Community of the Silesian Center
for Heart Diseases in Zabrze

Article information

Conflict of interest: None declared.

nadciśnienie tętnicze praktycznie

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arterial hypertension

nadciśnienie tętnicze W PRAKTYCE

Żnin, 6–7 maja 2022 roku

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dr hab. n. med. Arkadiusz Niklas

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Konferencja jest skierowana tylko do osób uprawnionych do wystawiania recept lub osób prowadzących obrót produktami leczniczymi — podstawa prawna: Ustawa z dnia 6 września 2001 r. Prawo farmaceutyczne (t. j. Dz.U. z 2019 r. poz. 499).

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

Skrócona informacja o leku JARDIANCE®

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

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

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

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

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

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

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

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18. Zjazd Polskiego Towarzystwa Nadciśnienia Tętniczego

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Gdańsk, 20–22 października 2022 roku

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