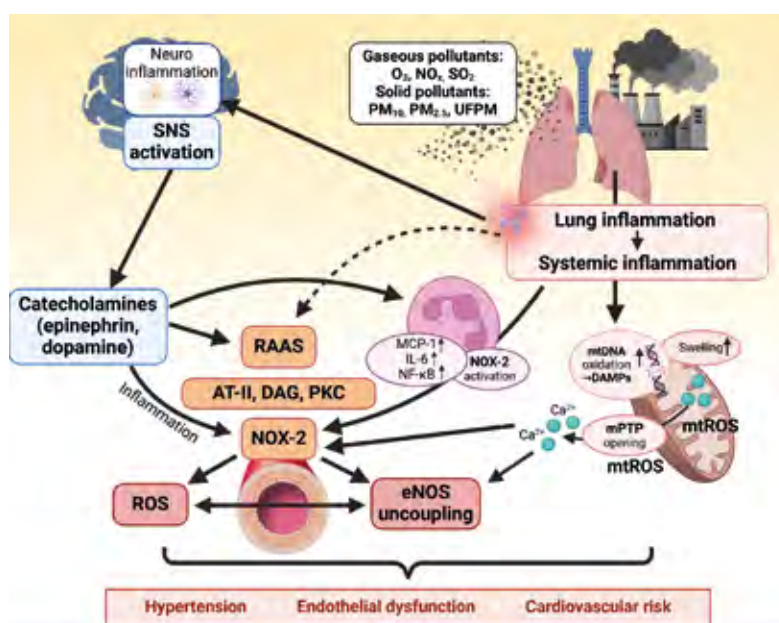




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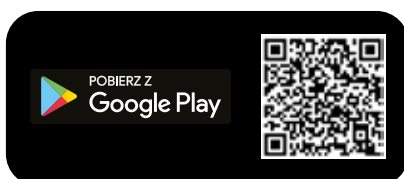
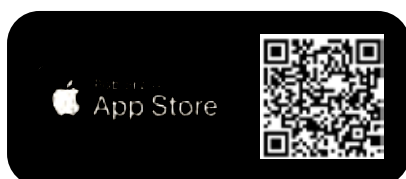


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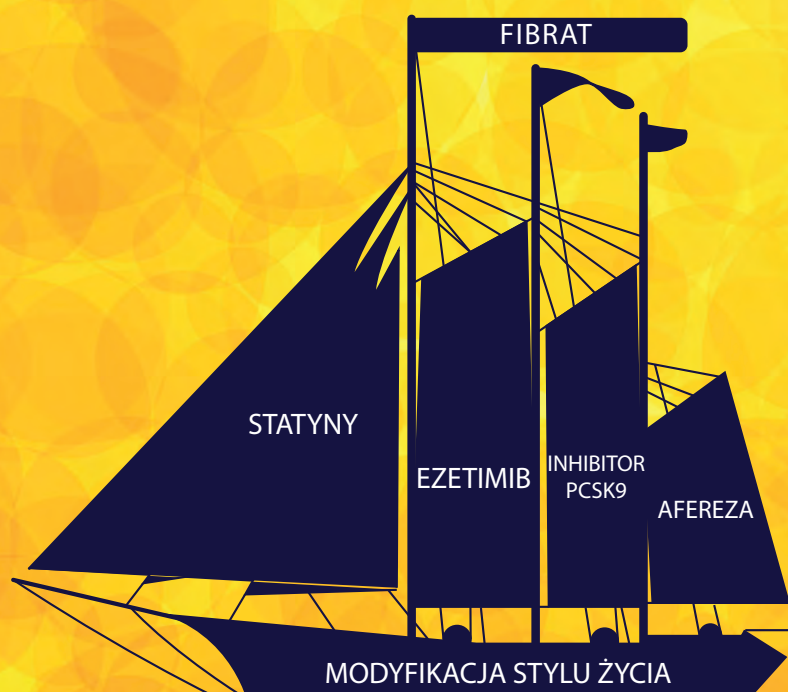
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Beyond the blanking period: Can biomarkers predict early AF recurrence after RFA?

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Radiofrequency ablation (RFA) is an established and widely used approach for the management of atrial fibrillation (AF), however, early recurrence of AF (ERAF) within the first three months remains a clinical challenge. The so-called blanking period, traditionally viewed as a phase of myocardial healing and transient arrhythmias, is a subject of ongoing debate. It is regarded as a “grace period” where recurrences do not necessarily indicate procedural failure, nevertheless ERAF may predict long-term recurrence and should not be dismissed [1]. Notably, an expert consensus statement has recently shortened the blanking period from three months to eight weeks, reflecting evolving perspectives on its clinical significance [2]. The study by Yin et al. [3], “Inflammation response post-radiofrequency ablation for atrial fibrillation: implications for early atrial fibrillation recurrence”, offers new insights into the role of inflammation in this critical period.

THE ROLE OF INFLAMMATION IN EARLY RECURRENCE OF ATRIAL FIBRILLATION

Yin et al. [3] analyzed 90 patients undergoing RFA, measuring four biomarkers at multiple time points before and after the procedure: high-sensitivity C-reactive protein and fibrinogen, reflecting inflammatory and prothrombotic processes, and creatine kinase isoenzyme and cardiac troponin I, indicating myocardial injury. Their findings showed a significant post-procedural increase in all biomarkers, highlighting the acute inflammatory response and myocardial stress induced by RFA.

The study further assessed the predictive value of the four biomarkers for ERAF. ERAF occurred in 38.9% of patients, underscoring its clinical relevance. They found that elevated levels of all four biomarkers were associated with ERAF in univariate analysis. However, after multivariable adjustment for age, history of hypertension, electric cardioversion, and RF ablation time, only high-sensitivity C-reactive protein remained an independent predictor. This finding strengthens the hypothesis that inflammation plays a key role in atrial remodeling and arrhythmogenesis [4].

IMPLICATIONS FOR POST-ABLATION MANAGEMENT

The study's findings suggest potential strategies for refining post-ablation management. First, given the association between inflammation and ERAF, targeted anti-inflammatory strategies — such as corticosteroids or colchicine — may help mitigate post-ablation inflammation [5, 6]. Biomarker-guided therapy could help identify patients most likely to benefit. Second, patients with persistently elevated inflammatory biomarkers may warrant intensified rhythm monitoring using wearable electrocardiogram technology or continuous telemetry. Third, while RFA remains the dominant strategy, alternative technologies such as cryoballoon ablation and pulsed-field ablation may offer advantages in reducing inflammation and myocardial injury. Pulsed-field ablation, in particular, is gaining attention for its ability to create precise lesions with minimal collateral damage. Comparative studies evaluating inflammatory responses

following different ablation modalities could provide valuable insights into optimizing procedural approaches [7].

Limitations

Despite its valuable insights, the study by Yin et al. [3] has limitations. The single-center design and relatively small cohort size suggest that these findings need to be validated in larger, multi-center studies. Additionally, standardized cutoff values for biomarkers are yet to be defined, which is critical for clinical implementation.

CONCLUSION

The study by Yin et al. [3] highlights inflammation as a key factor in post-ablation AF recurrence, challenging the conventional view of the blanking period as merely a phase of transient recovery. If inflammatory biomarkers can reliably predict ERAF, they may serve as critical tools for personalized patient management. Moving forward, large-scale prospective studies are needed to confirm these findings and to define how best to incorporate biomarker data into routine clinical practice.

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Cardiovascular prevention: The need for local strategies beyond guidelines

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Secondary prevention is an essential step in the management of ischemic heart disease because it saves more lives than acute care [1]. Jankowski et al. [2], in this issue of *Polish Heart Journal*, present a survey including 801 patients ≤80 years old, discharged after an acute coronary syndrome or myocardial revascularization procedure from 12 cardiology departments from 6 Polish departments during the period 2022–2023. This study reveals that at the end of follow-up less than 10% of patients had the main risk factors well controlled, which is consistent with previous European studies [3], despite the high prescription rate of recommended secondary prevention drugs at 6 and 18 months after discharge. Although part of these results may be explained by an artefact produced by the change over time in therapeutic targets in the European Society of Cardiology guidelines, the reasons for the discrepancy between good adherence to recommended treatments and such poor risk factor control are still unclear.

One potential explanation is suboptimal dose prescription. For instance, while the number of sold medicine packages of statins and ezetimibe as a fixed-dose combination increased tenfold in Poland in 2024 as compared with the 2020–2021 period, as many as 24% of physicians reduced the dose of statin while starting ezetimibe at the same time, probably resulting in delays to target attainment and unnecessary further exposure to low-density lipoprotein cholesterol [4]. Another potential explanation is low adherence

to secondary cardiovascular prevention therapies. The median time to discontinuation after the initiation of statin therapy, for instance, has been reported in 15 months [4]. In Poland, low adherence to other post-myocardial infarction therapies, such as clopidogrel, has also been described [5].

Several factors influence adherence, including system-based and individual factors. At the individual level, excessive work-related stress or lack of social support increase the risk of unhealthy behaviors and may be associated with worse self-care. Patients with low health literacy or socioeconomic status show a reduced therapeutic adherence due to limited understanding of the disease or the benefits of treatment. Financial barriers are, of course, important if pharmacological therapy is not fully covered, which is seldom the case. Mental health conditions, particularly depression, may further compromise adherence to healthy behaviors, better self-care, and pharmacological adherence. Higher prevalence of biological cardiovascular and behavioral risk factors, particularly smoking, is also more frequent among unemployed individuals, who also have worse mental health [6]. In the current study, Jankowski et al. [2] show how employment is one independent factor associated with better achievement of secondary prevention treatment goals. It is therefore essential to tailor secondary cardiovascular prevention recommendations and treatments to individual patient profiles, environments, and needs.

At a system level, the financial burden of pharmacological therapies on patients is significant. A Polish Cardiac Society survey showed that 65.8% of respondents were taking two or more fully paid medications a month, and 24.2% spent more than 500 PLN (equivalent to 115 EUR) per month on medications. Additionally, only 2 out of 17 cardiology treatments were reimbursed, including less than 50% of lifestyle disease treatments [7]. Inequities in access to care and therapies, especially innovative therapies, may also be relevant [7]. Lower education and income levels, as well as residence in more deprived areas, are associated with higher prevalence of cardiovascular risk factors [8].

Lack of access to cardiac rehabilitation and secondary prevention programs (CR) may also contribute to poor control of cardiovascular risk factors. CR improves post-myocardial infarction management and prevents future events, particularly if they finish the program. However, significant gaps in CR access and participation have been identified across Europe in general and in Poland in particular [9]. Low participation rates and regional variations in access have been described [10, 11]. The Polish Registry of Acute Coronary Syndromes and Acute Myocardial Infarction reported that CR was performed in only 19%–23% of cases [12] and short program durations. In addition, the average time per CR in Poland was approximately 12 hours, lower than other European countries (24.8 ± 26.0 hours on average) [9].

Strategies to enhance cardiovascular prevention in the general population and in the non-working and deprived groups in particular are needed. Local focused programs to improve outcomes, such as the Coordinated Care in Myocardial Infarction Program (KOS-MI), have proven effective in improving outcomes, although they are more focused on specialized care than primary care where long-term secondary prevention mainly lies [12]. National policies, such as the few available in European countries [13, 14], should have more impact by promoting multidimensional and interdisciplinary approaches, prioritizing both primary (disease prevention) and primordial (risk factor prevention) strategies to strengthen cardiovascular prevention as a whole. These strategies, provided they include the evaluation and integration of approaches based on social determinants of health, may be more effective in reducing the incidence of the classic risk factors for cardiovascular disease, such as those based on secondary prevention after acute coronary syndromes, where therapeutic inertia may be a more relevant problem. In that sense, the Polish National Cardiovascular Disease Program [15] will have to balance between reinforcing primordial and primary prevention and optimizing secondary and tertiary prevention. The recently approved European Plan on Cardiovascular Health [16] will be a unique opportunity to strengthen national policies on cardiovascular health and, hopefully, to secure funding for these plans.

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Air pollution and hypertension: Mechanistic and epidemiological insights

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ABSTRACT

Air pollution is an important environmental risk factor and, according to the Global Burden of Disease Study, a leading contributor to global morbidity and mortality. Hypertension, a major risk factor for cardiovascular diseases, has been increasingly associated with exposure to various air pollutants. This review aims to highlight key mechanistic and epidemiological findings underlying the relationship between air pollution and hypertension. On a mechanistic level, air pollution contributes to oxidative stress, systemic inflammation, endothelial dysfunction, and activation of the sympathetic nervous system, leading to impaired vascular function and elevated blood pressure. Epidemiological findings consistently demonstrate that both short- and long-term exposure to solid and gaseous pollutants are associated with increased blood pressure and a higher risk of hypertension. These findings are confirmed by meta-analyses across diverse populations, with evidence suggesting greater susceptibility among vulnerable groups, including the elderly and those with pre-existing cardiovascular conditions. Despite emerging evidence, important knowledge gaps remain regarding precise exposure assessment, the impact of specific air pollutants, and the synergy between air pollution and other environmental stressors. Targeting these gaps in future is necessary for effective development of public health interventions and policy measures to reduce the adverse health effects of air pollution on blood pressure regulation and hypertension risk.

Key words: air pollution, hypertension, epidemiology, pathophysiology

AIR POLLUTION AS A SUBSTANTIAL PUBLIC HEALTH THREAT

Air pollution, a ubiquitous environmental stressor, represents a critical contributor to the global burden of disease [1]. Humans inhale approximately 8.6 m³ of air daily [2], equating to over 250 million liters across a lifespan [3], highlighting the substantial exposure to airborne pollutants. Among these, fine particulate matter (PM_{2.5}, i.e., atmospheric particles with an aerodynamic diameter smaller than 2.5 µm) is recognized as particularly detrimental to health, with energy production and agriculture identified as primary sources in Europe [4]. In response to its profound

health impacts, the European Union (EU) has proposed a so-called zero pollution vision for 2050, aiming to significantly reduce pollution and mitigate its adverse effects on human health and the environment [5].

The Global Burden of Disease (GBD) Study underscores the substantial role of air pollution as a leading risk factor for global mortality, with cardiovascular disease being the leading cause, comparable to high blood pressure, smoking, and dietary risks [6]. In the recently published GBD Study, air pollution (level 2) was identified as the second leading risk factor for global mortality (after high blood pressure). Although estimates vary significantly [7], recent studies estimated and attributable

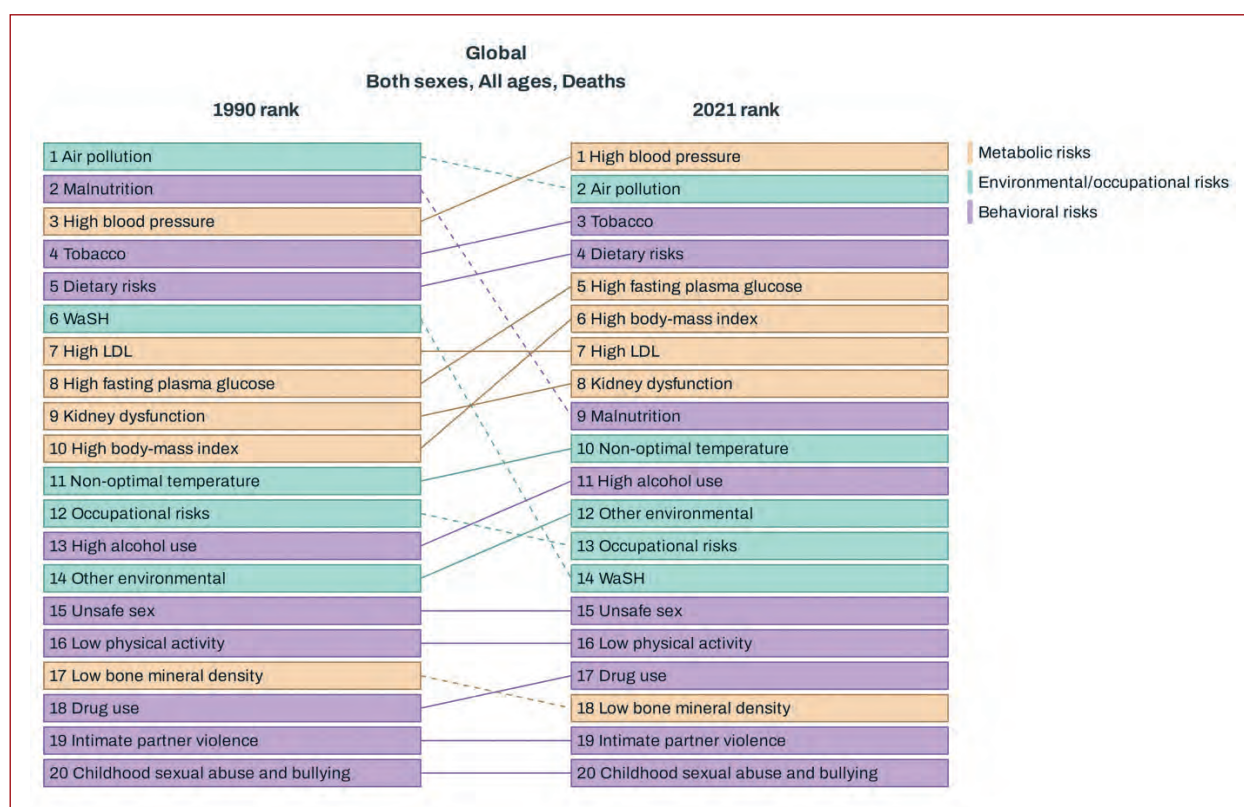


Figure 1. Key risk factors for global mortality: A comparison of total numbers between 1990 and 2021 based on the Global Burden of Disease Study. Obtained from [8] with permission

mortality to this risk factor of 8.08 million (uncertainty interval 6.71–9.48) deaths worldwide in 2021 [6, 8] (Figure 1). Within Europe, Poland bears a disproportionately high burden, with 33 965 (uncertainty interval 26 061–43 196) deaths attributable to air pollution in 2021, accounting for 6.56% of all deaths [8] (Figure 2). During this period, annual pollutant concentrations in Poland averaged 17 $\mu\text{g}/\text{m}^3$ for $\text{PM}_{2.5}$, 26 $\mu\text{g}/\text{m}^3$ for PM_{10} (i.e., atmospheric particles with an aerodynamic diameter smaller than 10 μm), 25 $\mu\text{g}/\text{m}^3$ for nitrogen dioxide (NO_2), and 45 $\mu\text{g}/\text{m}^3$ for ozone (O_3), with Kraków, Katowice, and Łódź emerging as the most polluted cities [9]. Indeed, recent studies from Poland indicate that air pollution contributes to the progression of coronary disease in diabetic patients [10] and increases the risk of hospital admission for both acute and chronic coronary syndromes [11], as well as for exacerbations of chronic obstructive pulmonary disease [12]. While less than 1% of the EU's urban population is exposed to $\text{PM}_{2.5}$ levels exceeding the EU standard of 25 $\mu\text{g}/\text{m}^3$, the European Environment Agency reports that 97% are subjected to concentrations surpassing the stricter 2021 World Health Organization (WHO) guidelines, which set an annual average limit of 5 $\mu\text{g}/\text{m}^3$ and restrict 24-hour averages to no more than 15 $\mu\text{g}/\text{m}^3$ on 3 to 4 days per year [13, 14]. Nevertheless, the WHO suggests that no firm threshold for $\text{PM}_{2.5}$ has been identified below which no damage to health is observed [15]. A recent study found that even at $\text{PM}_{2.5}$ levels below 5 $\mu\text{g}/\text{m}^3$, mortality increases supralinearly, indicating that

meeting the WHO updated guidelines could prevent an additional 1.5 million deaths globally each year [16] (Figure 3).

Recent epidemiological studies have highlighted a robust link between air pollution and both high blood pressure and hypertension [17, 18]. Given that hypertension is a leading cause of global disability and mortality, as identified by the GBD Study [6], understanding the contribution of air pollution to the development of hypertension is of critical clinical relevance. This review examines the association between air pollution and hypertension, with a focus on mechanistic and epidemiological insights. It will further examine interventional strategies and identify gaps in existing knowledge.

PATHOPHYSIOLOGY OF AIR POLLUTION AND BLOOD PRESSURE REGULATION

Different components of air pollution have different pathways by which they interact with the cardiovascular system. While gaseous components, such as NO_2 , O_3 , or sulfur dioxide (SO_2), can directly enter circulation, particulate matter (PM) mostly stays in the respiratory tract, with size-dependent penetration [18]. Only the ultrafine PM (i.e., atmospheric particles with an aerodynamic diameter smaller than 0.1 μm) can directly translocate into circulation [19]. Presence of PM in the lung causes an inflammatory reaction, mostly by activating resident macrophages and granulocytes [20]. These activated immune cells can enter circulation or release pro-inflammatory cytokines and dam-

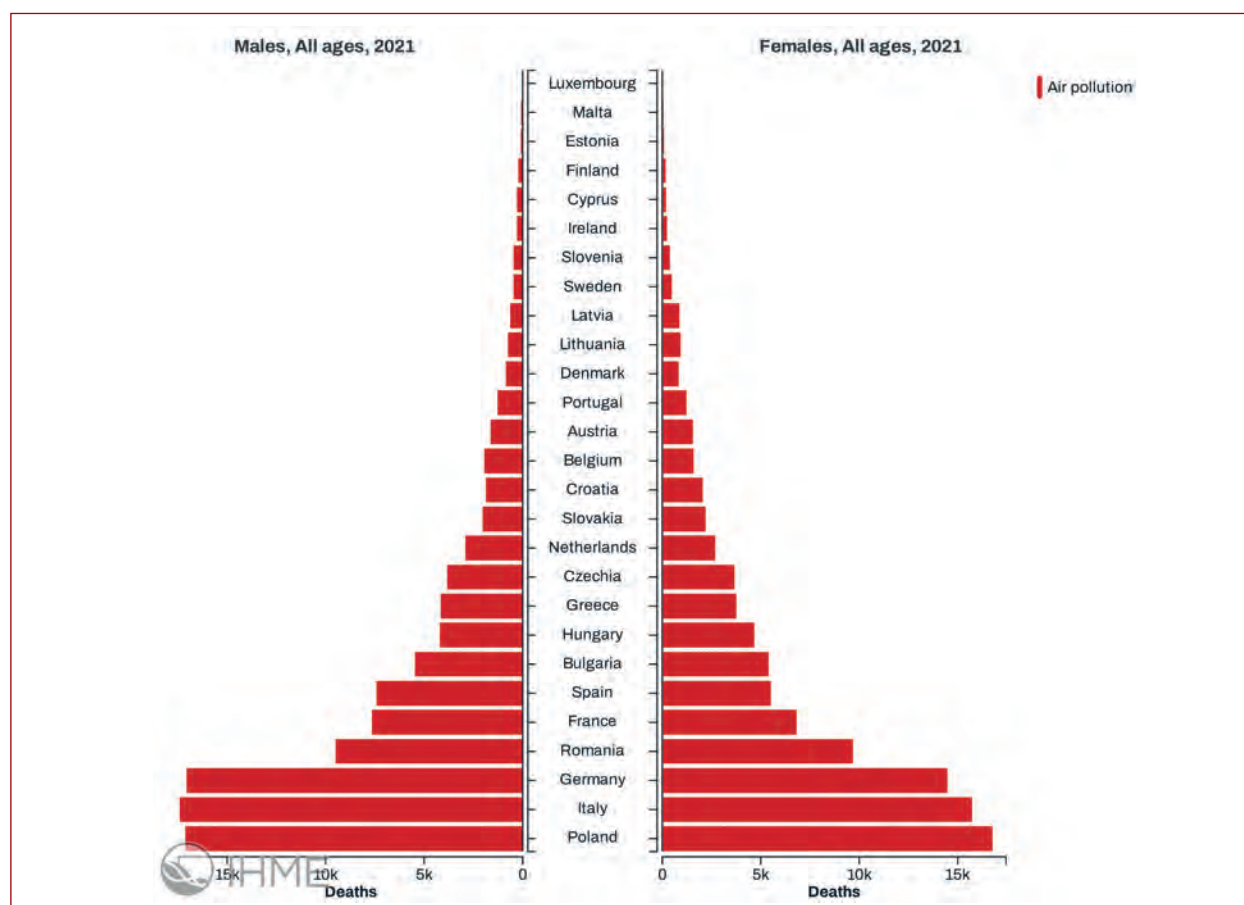


Figure 2. Air pollution-related deaths in 2021 across European Union countries according to the Global Burden of Disease study. Obtained from [8] with permission

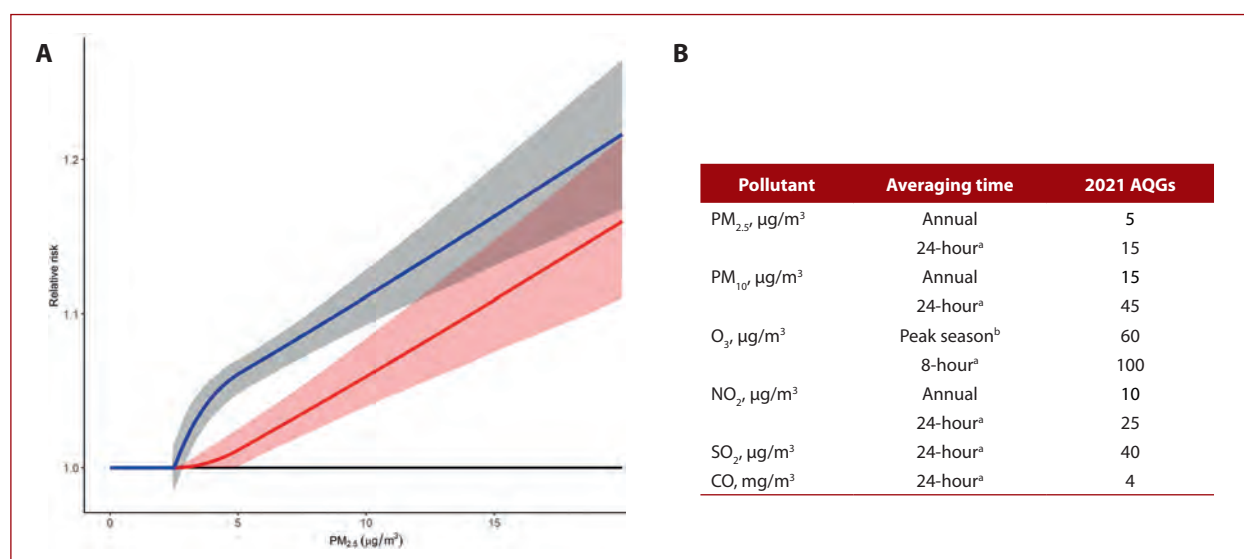


Figure 3. A. Concentration-response functions for outdoor PM_{2.5} and nonaccidental mortality. For low exposure (0–20 µg/m³), the blue line (with 95% CI) shows the refined function based on the Canadian Census Health and Environment Cohort, while the red line (with 95% CI) represents the current global function using a counterfactual concentration between 2.5 and 5 µg/m³. Obtained from [16] with permission. **B.** Recommended global World Health Organization Air Quality Guidelines. PM_{2.5}: particulate matter with a diameter smaller than 2.5 micrometers. PM₁₀: particulate matter with a diameter smaller than 10 micrometers. O₃: ozone. NO₂: nitrogen dioxide. SO₂: sulfur dioxide. CO: carbon monoxide ^a99th percentile (i.e., 3–4 exceedance days per year). ^bAverage of daily maximum 8-hour mean O₃ concentration in the 6 consecutive months with the highest 6-month running-average O₃ concentration. Annual and peak season is long-term exposure, while 24 hour and 8 hour is short-term exposure. Obtained from [14] with permission

Abbreviation: CI, confidence interval

age-associated molecular patterns, giving rise to systemic inflammation. In addition to systemic inflammation, PM can also activate the mechanoreceptors in the lung, which further activate the lung arc reflex and the sympathetic nervous system (SNS), promoting the release of catecholamines [21]. PM can carry reactive oxygen species on its surface, but the direct effects of these reactive oxygen species (ROS) have little impact on the redox balance in the body, and it is rather the defense mechanisms that promote the release of endogenous ROS [23]. General presence or ROS in the lungs, as well as the toxic load of the PM, such as reactive quinones and aldehydes, and transition metals, can deplete antioxidants like glutathione and ascorbate and cause oxidative stress [23, 24]. Inflammation and oxidative stress are key mechanisms by which air pollution exerts its negative effects on vascular function, promoting hypertension and atherosclerosis.

One of the most important mechanisms associated with vascular function and blood pressure regulation is endothelial nitric oxide (NO) signaling. Endothelial NO synthase (eNOS) produces NO in vascular endothelial cells, which then diffuses into smooth muscle cells of the vasculature, causing vasorelaxation through inhibition of calcium (Ca^{2+}) influx [25]. NO signaling is sensitive to oxidative stress, as superoxide radical ($\text{O}_2^{\cdot-}$) can scavenge NO, producing peroxynitrite (ONOO^-), which can further nitrate protein tyrosine residues, inhibiting eNOS activity [26]. In addition, eNOS is potentially sensitive to S-nitrosylation, further inhibiting its activity [27]. Superoxide can originate from many sources, such as nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase), mitochondrial electron transport chain, and interestingly, also from uncoupled eNOS. It is the NADPH oxidase that is most prominently associated with air pollution toxicity because it is an enzyme used by activated immune cells for host defense [28]. Studies in humans have shown that endothelial function is impaired in subjects exposed to higher levels of air pollution, mostly envisaged by the reduction in flow-mediated dilation [29, 30]. Interestingly, some studies have found that only PM, but not the gaseous compounds, causes endothelial dysfunction [31], while some also point to the ability of O_3 and NO_x to cause impairment in vascular function [32, 33]. Animal studies have confirmed the relationship between air pollution components and the impairment in vascular endothelial function [34, 35]. Specifically, the activation of the NADPH oxidase was a major contributor to the total burden of oxidative stress and endothelial dysfunction [36]. Some studies have shown that vascular tone changes associated with air pollution exposure are in part mediated by endothelin 1 (ET-1), a potent vasoconstrictor [37, 38]. Oxidative stress derived from NADPH oxidase can increase levels of ET-1, which then activate the ET-1/ ET_A -receptor signaling, further driving NADPH oxidase activation through protein kinase C activity [25]. Increased secretion of angiotensin 2 (AT-2) was also a hallmark of air pollution induced vascular dys-

function and increased blood pressure [34, 39]. An increase in AT-2 is, naturally, often associated with changes in angiotensin converting enzyme (ACE-2) expression [40, 41].

As mentioned above, the SNS can be activated through systemic inflammation or lung arc reflex, causing the release of catecholamines, which lead to the increase in blood pressure. In the analysis of the Multi-Ethnic Study of Atherosclerosis cohort, it was found that urinary epinephrine levels were positively associated with long-term NO_x and $\text{PM}_{2.5}$ exposure, pointing to activation of the SNS and increased catecholamine secretion [21]. An interventional study in healthy individuals directly observed an increase in muscle sympathetic nerve activity after diesel exhaust exposure, using microneurography of the peroneal nerve [42]. Activation of the SNS was shown to be present in $\text{PM}_{2.5}$ exposure studies in mice [43], where the observed increase in blood pressure was mitigated by pharmacological intervention with $\alpha_2\text{a}$ agonist guanfacine. Increased SNS activity was associated with systemic inflammation mediated through nuclear factor kappa B pathway.

Mitochondrial damage can have a direct impact on blood pressure because mitochondrial dysfunction is implicated in cardiac hypertrophy and function [44]. A study in mice and primates showed that O_3 exposure can cause pulmonary and aortic mtDNA damage [45]. Other studies pointed to air pollution-mediated mitochondrial dysfunction through oxidative stress, mtDNA damage, mitochondrial permeability transition pore opening, and mitochondrial swelling [46–49]. A link between air pollution-derived $\text{PM}_{2.5}$ exposure and cardiac hypertrophy was found to be caused by calcium overload-mediated mitochondrial dysfunction [50], showing the importance of this pathway. A summary of the mechanisms by which air pollution exerts negative effects on vascular tone and function is presented in Figure 4.

EPIDEMIOLOGICAL INSIGHTS INTO THE ASSOCIATION BETWEEN AIR POLLUTION AND HYPERTENSION

Comprehensive epidemiological findings have underscored a strong relationship between air pollution and hypertension, being the subject of numerous meta-analyses and observational studies. These findings consistently indicate that exposure to various air pollutants elevates the risk of hypertension and increases blood pressure across diverse cohorts globally.

Long-term exposure to air pollution has been linked to sustained blood pressure elevations and a higher prevalence and incidence of hypertension. Meta-analyses have provided robust evidence supporting these associations. Zhao et al. [51] found a relative risk of 1.21 (95% confidence interval [CI], 1.07–1.35) for incident hypertension and an odds ratio (OR) of 1.06 (95% CI, 1.03–1.09) for prevalent hypertension. Another meta-analysis from Niu et al. [52] confirmed that exposure to PM_{10} , $\text{PM}_{2.5}$, and PM_{10} significantly increased the risk of hypertension as well as systolic

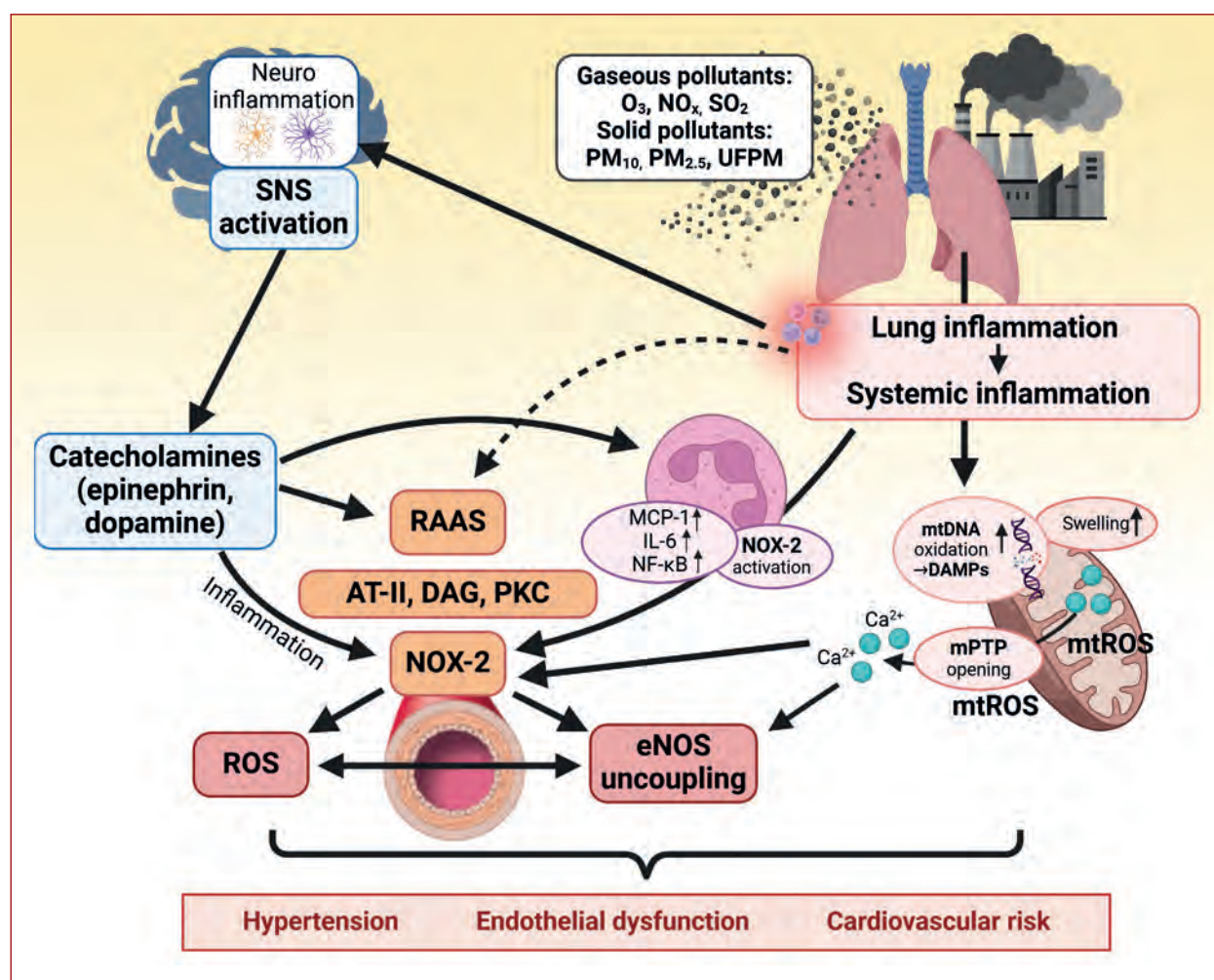


Figure 4. Mechanistic overview of the air pollution-mediated vascular tone and function. Air pollution components enter through the lung where the local immune system response gains a systemic character through release of pro-inflammatory cytokines and migration of activated immune cells. Systemic inflammation can cause oxidative stress at the level of vasculature but can also promote the activation of the SNS, driving further inflammation and vasoconstriction. Modified from [82] with permission. Created with BioRender.com

Abbreviations: AT-II, angiotensin 2; DAG, diacylglycerol; DAMPs, damage-associated molecular patterns; eNOS, endothelial nitric oxide synthase; IL-6, interleukin 6; MCP-1, monocyte chemoattractant protein 1; mPTP, mitochondrial permeability transition pore; NF-κB, nuclear factor kappa B; NOX-2, NADPH oxidase catalytic subunit; PKC, protein kinase C; RAAS, renin-angiotensin-aldosterone system; ROS, reactive oxygen species; SNS, sympathetic nervous system; UFPM, ultrafine particulate matter

and diastolic blood pressure. Meta-analytic evidence from Qin et al. also indicated that adult hypertension incidence was significantly influenced by exposure to PM_{2.5} (OR, 1.10; 95% CI, 1.07–1.14), PM₁₀ (OR, 1.04; 95% CI, 1.02–1.07), and sulfur dioxide (SO₂) (OR, 1.21; 95% CI, 1.08–1.36) [53]. Notably, weaker associations were observed in children. Nevertheless, the meta-analyses from Yan et al. [54] and Huang et al. [55] demonstrated that short- and long-term exposure to PM led to significant blood pressure increases among children and adolescents. Ma et al. investigated the association between PM_{2.5} exposure and hypertension risk in adult non-pregnant women. The findings revealed that a 10 µg/m³ increase in PM_{2.5} exposure was associated with a 23% higher risk of hypertension (hazard ratio (HR), 1.23; 95% CI, 1.08–1.40) and 7% higher odds ratio (OR, 1.07; 95% CI, 1.00–1.14) [56]. Subgroup analysis highlighted

menopause, non-White ethnicity, and diabetes as key risk factors for PM_{2.5}-induced hypertension

In a large American cohort of women, a positive association was found between long-term PM_{2.5} exposure and incident hypertension risk, with a HR of 1.06 (95% CI, 1.02–1.11) [57]. Similarly, research involving Spanish adults reported a significant association between higher exposure to PM_{2.5} and PM₁₀ and hypertension incidence [58]. Comparable findings have been observed in Chinese cohorts, including both children [59] and adults [60]. In India, heightened exposure to PM_{2.5} was associated with both an increased incidence of hypertension and elevated systolic blood pressure [61]. The multicenter PURE study, which examined data from 21 countries, demonstrated that exposure to PM_{2.5} was linked to increased odds of hypertension (OR, 1.04; 95% CI, 1.01–1.07) and significant

increases in both systolic and diastolic blood pressure [62]. Fu et al. [63] found in a cohort of Chinese adults aged 50 years and above that a $16.8 \mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ exposure corresponded to a 17% heightened risk of hypertension (HR, 1.17; 95% CI, 1.10–1.24) alongside significant increases in systolic (2.54 mm Hg) and diastolic (1.36 mm Hg) blood pressure. The population-attributable fraction of hypertension due to $\text{PM}_{2.5}$ was estimated at 23.44% (95% CI, 14.69–31.55).

Short-term exposure to elevated levels of $\text{PM}_{2.5}$ is consistently associated with immediate increases in blood pressure. An analysis involving 7108 non-hypertensive individuals from seven Chinese cities found a near-instantaneous blood pressure rise following $\text{PM}_{2.5}$ exposure, with effects gradually diminishing over 12 hours. An interquartile range increase of $33 \mu\text{g}/\text{m}^3$ in $\text{PM}_{2.5}$ led to cumulative increases of 0.58 mm Hg in systolic and 0.31 mm Hg in diastolic blood pressure [64]. In a Chinese cohort exposed to high levels of black carbon, a $1 \mu\text{g}/\text{m}^3$ increase in exposure levels over the preceding 10 hours was associated with a 0.53 mm Hg increase in systolic blood pressure (95% CI, 0.17–0.89) and a 0.37 mm Hg increase in diastolic blood pressure (95% CI, 0.10–0.65) [65]. Elevated heart rate variability indicative of heightened sympathetic activity was also observed.

Importantly, data from the SPRINT trial suggest that the cardiovascular benefits of intensive blood pressure lowering (systolic blood pressure <120 mm Hg) may be higher in individuals chronically exposed to higher levels of $\text{PM}_{2.5}$ [66]. The study found that intensive blood pressure control reduced cardiovascular risks more significantly among participants exposed to $\text{PM}_{2.5}$ levels above United States air quality standards ($>12 \mu\text{g}/\text{m}^3$) compared to those in cleaner environments.

INTERVENTIONAL STRATEGIES

Cities and urbanized areas are important contributors to air pollution due to dense population being accompanied by traffic and industrial activities. Urban planning strategies can mitigate the health impacts not only of air pollution but also of other prevalent environmental stressors, such as noise and extreme temperatures. These approaches were recently summarized under the concept of a so-called heart-healthy city design [67, 68].

Reducing emissions from traffic, which are major sources of PM and gaseous pollutants, through the promotion of electric vehicles, improvement of public transportation systems, introduction of vehicle-free zones, and implementation of congestion pricing can significantly contribute to lower air pollution levels. Additionally, supporting the use of hybrid mobility solutions such as e-bikes and the implementation of walking and cycling areas can support the shift from traditional combustion-engine vehicles toward more active forms of mobility [69].

Reducing residential emissions, particularly those from household heating, represents a critical intervention

strategy for mitigating $\text{PM}_{2.5}$ exposure and its associated health risks [70].

Creating green spaces has gained recent attention, and it can help to reduce air pollution through three main mechanisms: deposition, dispersion, and modification. Vegetation, particularly plant leaves, captures PM from the air, reducing pollutant concentrations. Green spaces can also enhance air dispersion, breaking up pollution hotspots, and modify airflows to reduce exposure to harmful pollutants [71]. Moreover, green spaces can enhance cooling effects and counteract heat island effects, indirectly contributing to blood pressure regulation through heat mitigation [72].

Transitioning to cleaner energy sources through regulations to limit emissions from industries and power plants is crucial for reducing population exposure to air pollution. Policies aimed at phasing out fossil fuels and promoting renewable energy sources align with both health and environmental goals as outlined by the zero pollution vision introduced by the EU [5]. In line with this, recently it has been estimated that an annual 5.13 million premature deaths globally are linked to ambient air pollution from fossil fuel use, which could be prevented by gradually eliminating these emissions. This represents 82% of the total number of air pollution-related deaths that could be avoided by controlling all human-made emissions [73].

Individuals can adopt measures to limit their personal exposure to air pollution. Closing windows during peak pollution periods, using home air filtration systems, and avoiding outdoor activities during high pollution episodes are discussed strategies. Wearing protective masks, such as N95 respirators, has been shown to reduce exposure to PM and may positively impact cardiovascular health, including blood pressure [74]. Lastly, pharmacological approaches such as antioxidants and anti-inflammatory drugs may mitigate oxidative stress and vascular inflammation induced by pollutant exposure [75].

GAPS IN KNOWLEDGE

Although comprehensive evidence on the association between air pollution and hypertension has emerged in recent years, several crucial gaps in knowledge exist, highlighting the need for further research efforts to enhance the understanding and to develop more effective interventions.

A primary shortcoming of epidemiological studies is the lack of accurate exposure assessment methodologies. Current approaches often rely on outdoor air pollution measurements based on the residential address, which may not accurately reflect individual exposure levels and their fluctuation. The development and validation of personal exposure monitoring technologies could provide more precise insights into actual exposure to air pollution over the course of the day, allowing for a more accurate examination of the association between air pollution and blood pressure changes [76].

The contribution of specific air pollutants and their components in causing hypertension remains not fully understood. While $PM_{2.5}$ has been comprehensively studied [17, 18], less is known about the effects of particulate size (such as UFP against larger particles) and particulate components (e.g., soot or nitrate-sulfate-ammonia). In addition, gas tracers should be further investigated, such as volatile organic compounds and gaseous pollutants like O_3 and NO_2 . Future studies should aim to identify which components are most harmful and investigate their specific mechanisms of action and interactions with blood pressure regulation [23].

It remains incompletely understood how rapidly blood pressure or vascular changes occur following exposure and how long these effects persist [77]. In addition, more research is needed to understand whether the impact of long-term air pollution exposure on blood pressure is reversible with improved air quality or if there are sustained vascular changes [78].

Identifying susceptible/vulnerable populations is of special importance for targeted interventions. While there are studies suggesting that some groups, such as the elderly [79], those with pre-existing cardiovascular conditions [80], as well as socioeconomically deprived individuals [81], may be more vulnerable to the hypertensive effects of air pollution, more research is needed to replicate these findings and to identify other at-risk populations. This is especially important considering that the aging population, particularly in Western countries, may increase vulnerability to air pollution-related health effects, even if pollution levels remain stable or decrease.

The interaction and synergy between air pollution and other environmental stressors that often co-exist in urbanized and densely populated areas, such as noise pollution and extreme temperatures, in causing hypertension is not well understood [82, 83]. Future studies should investigate potential synergistic effects and how these combined exposures impact blood pressure regulation.

While oxidative stress and inflammation have been implicated as key pathways underlying disease risk [84], a more comprehensive understanding of the pathways involved could lead to the development of targeted preventive strategies or pharmacological treatments.

CONCLUSION

The present review displays compelling evidence suggesting that air pollution is a significant contributor to the development of hypertension. Mechanistic studies demonstrate that oxidative stress, systemic inflammation, and endothelial dysfunction induced by various air pollutants are involved in the disruption of blood pressure regulation. Epidemiological findings consistently associate both short- and long-term exposure to solid and gaseous pollutants with an increased risk of hypertension. These findings underscore the importance of air pollution as a modifiable risk factor for hypertension. Effective mitigation strategies,

including reducing emissions, enhancing urban green spaces, and implementing public health policies, are essential to minimize exposure and its associated health effects. However, more research is warranted to improve exposure assessment, identify the most harmful pollutants, and examine interactions between air pollution and other environmental risk factors. This will help to develop targeted interventions and inform public health policies to reduce the burden of hypertension and associated cardiovascular diseases attributed to air pollution. Adhering to the air quality guidelines established by the WHO (Figure 3) is essential for the protection of public health, particularly for vulnerable populations.

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How to treat coronary in-stent restenosis? Recent advances and their practical implications: State-of-the-Art Review

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ABSTRACT

Percutaneous coronary intervention with stent implantation has revolutionized the treatment of coronary artery disease. However, a significant drawback of this approach is the risk of in-stent restenosis (ISR), which increases each year following stent placement. This review of the current literature aims to enhance our understanding of the mechanisms behind ISR and its treatment. To accurately evaluate these mechanisms, intravascular imaging should be utilized during all the steps of revascularization. In particular, multiple mechanisms of ISR can coexist in a single patient, each influenced by various clinical and angiographic risk factors. It is essential to focus on adequate lesion preparation, including plaque-modifying or plaque-ablative techniques, because these are crucial for achieving positive outcomes. In the contemporary era, advancements like new, thin-strut, drug-eluting stents and drug-coated balloons offer promising options for addressing ISR. In this review paper, we address the limitations and advantages of both technologies.

Key words: coronary artery disease, drug-coated balloon, drug-eluting stent, in-stent restenosis, percutaneous coronary intervention

INTRODUCTION

Coronary artery disease (CAD) is one of the leading causes of death and hospitalization worldwide. The introduction of percutaneous coronary intervention (PCI) with stent implantation was an important milestone in invasive cardiology, and it has been established as the preferred method of treatment for patients with obstructive CAD; however, stent implantation carries the risk of in-stent restenosis (ISR), which occurs in about 4% of patients within two years after receiving a drug-eluting stent (DES) [1].

The treatment of ISR, which accounts for 5%–10% of all PCIs, presents a significant challenge [2, 3]. However, achieving long-term success requires diagnosing all ISR mechanisms, adequately preparing the lesions, and utilizing optimal DES or drug-coated balloon

(DCB) strategy [4]. Intravascular imaging should be routinely used at each stage of the procedure, especially to evaluate the mechanism of ISR [5]. The complexity of these interventions often results in suboptimal clinical outcomes, with reported rates of target lesion revascularization (TLR) ranging from 38% to 58% over a 10-year follow-up period [6].

In this state-of-the-art review, we aim to discuss current evidence-based strategies for the executive of ISR in interventional practice.

CLASSIFICATION OF ISR

ISR is defined as a reduction of $\geq 50\%$ in the lumen diameter stenosis of a previously stented segment or within 5 mm proximally and distally to the stent, as visualized by coronary angiography [7, 8]. The most commonly used classification for ISR was proposed by

Table 1. Classifications of ISR

Mehran et al. [9] classification		Waksman et al. [10] classification			SCAI classification [11]	
Classification	Definition	Classification		Definition	Classification	Time interval
Focal ISR	Lesions that are 10 mm or shorter in length located at the unscaffolded segment, stent body, or the proximal or distal margins, or multifocal ISR	I	Mechanical	Stent underexpansion (type I A) Stent fracture (type I B)	Early	<30 days
Diffuse intrastent ISR	Lesions longer than 10 mm that occur within the stents and do not extend beyond the stent margins	II	Biologic	Neointimal hyperplasia (type II A) Neoatherosclerosis, non-calcified (type II B) Neoatherosclerosis, calcified (type II C)	Late	30 days to 1 year
Diffuse proliferative ISR	Lesions longer than 10 mm that extend beyond the margins of the stents	III	Mixed pattern	Combined mechanical and biologic etiology	Very late	>1 year
ISR with total occlusion	Characterized by a TIMI flow grade of 0	IV V	Chronic total occlusion >2 layers of stent			

Abbreviations: BMS, bare metal stent; ISR, in-stent restenosis; TIMI, thrombolysis in myocardial infarction

Mehran et al. [9], based on angiographic patterns. An alternative classification introduced by Waksman et al. [10] considers different disease processes. Additionally, the SCAI classification [11] takes into account time intervals and morphological substrates. These classifications are summarized in [Table 1](#).

MECHANISM OF ISR

Identifying the underlying mechanism is a critical step in the treatment of ISR. This understanding allows for the use of targeted techniques in lesion preparation, which improves the immediate effectiveness of the procedure and enhances long-term outcomes by lowering the risk of recurrent restenosis. It is also essential to understand that multiple ISR mechanisms can coexist in a single patient, influenced by various clinical and angiographic risk factors. Clinical factors include female gender, advanced age, obesity, and comorbidities such as diabetes mellitus (DM) and chronic kidney disease (CKD). Additionally, patients presenting with acute coronary syndrome after previous revascularization, also due to ISR, resistant to antiproliferative drugs, and hypersensitivity to stent components are at higher risk of recurrent restenosis.

The most significant angiographic factors include calcified and long lesions, bifurcation and ostial coronary disease, chronic total occlusion (CTO), small vessel disease, multivessel coronary artery disease, or the treatment of saphenous vein grafts (SVGs). These lesion characteristics can lead to suboptimal procedural outcomes and consequently increase the risk of ISR. The most important procedural factors include stent malapposition, stent underexpansion, geographical lesion miss, stent deformation or fracture, stent overlapping, stent gaps, distal edge dissection, and multiple stent layers. Furthermore, using bare metal stents (BMS) remains a substantial risk factor. The key principles and factors associated with ISR are depicted in [Figure 1](#). Consequently, a comprehensive treatment approach should tackle the underlying causes

of ISR and optimize systemic treatments to control clinical risk factors effectively.

Clinical factors

Comorbidities significantly affect peri-procedural and long-term prognosis, including increased incidence of ISR. The underlying mechanisms are complex and ultimately lead to the progression of atherosclerosis. One of the strongest independent predictors of restenosis is DM [12]. Endothelial damage is a major contributor to micro- and macrovascular complications mediated by hyperglycemia-induced oxidative stress [13]. Furthermore, the hyperactivity of vascular smooth muscle cells and impaired particular glycoproteins contribute to more aggressive and rapidly progressing atherosclerosis. According to the 2020 EXCEL trial comparing the efficacy of XIENCE (XIENCE PRIME™ or XIENCE V™ or XIENCE Xpedition™ or XIENCE PRO™; Abbott Vascular, Santa Clara, CA, US) and coronary artery bypass graft surgery (CABG) for left main revascularization, patients with DM are at an increased risk of undergoing multiple revascularization procedures, which have been shown to quadruple the risk of cardiovascular death.

Patients with CKD tend to have a higher frequency of other comorbidities and more complex CAD compared to those without CKD, including highly prevalent and more severe coronary artery calcification. Coronary calcification is influenced by a range of factors, including hyperphosphatemia, calcium-phosphate imbalance, uremic toxins, chronic inflammation, oxidative stress, and the activation of various signaling pathways in different cell types, such as vascular smooth muscle cells, macrophages, and endothelial cells. It independently predicts the risk of coronary heart disease and total cardiovascular disease more than traditional risk factors in the general population [14, 15].

Furthermore, the risk of ISR and adverse cardiovascular events remains increased in the CKD population compared to individuals without CKD. Moreover, in both DM and CKD patients, vessel trauma caused by stent implantation

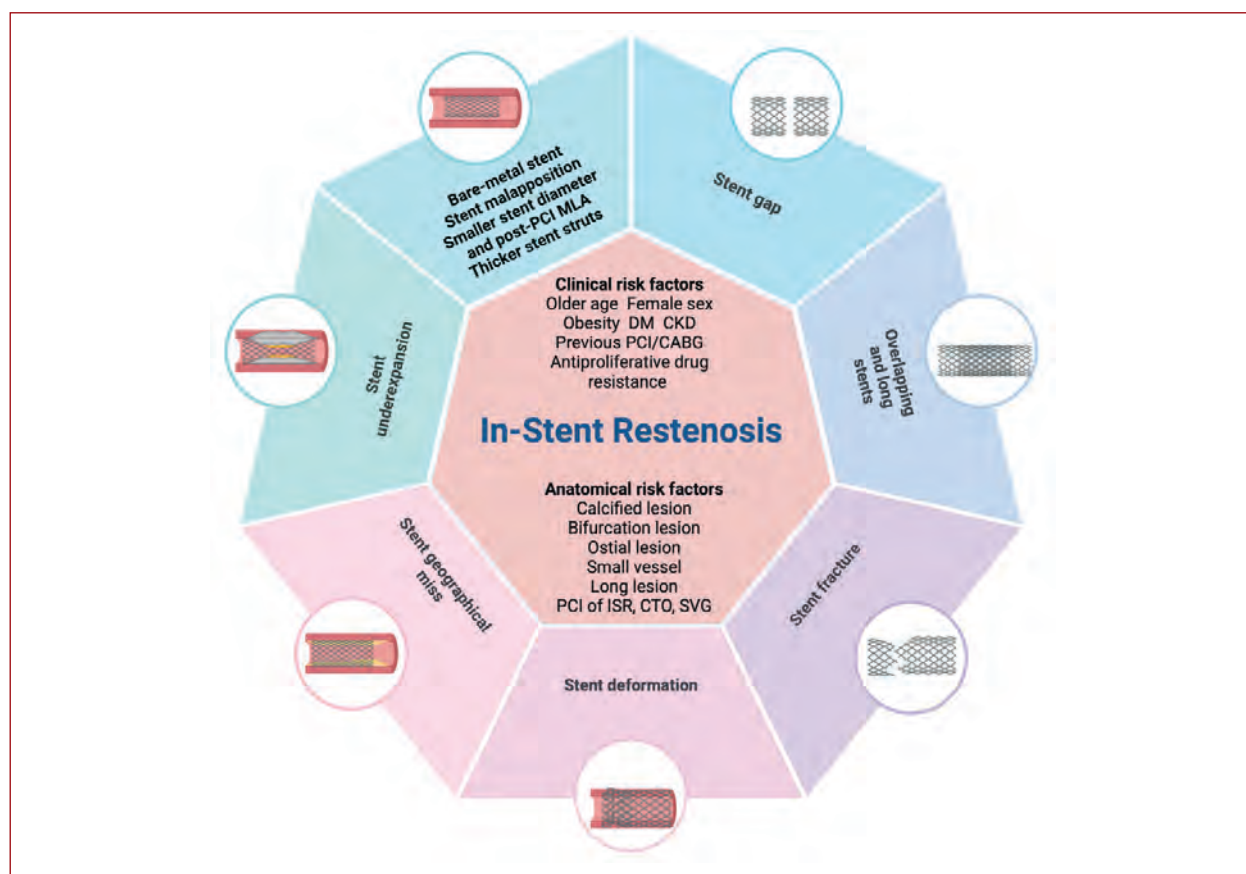


Figure 1. Clinical, procedural, and anatomical factors associated with ISR

Abbreviations: CABG, coronary artery bypass graft; CKD, chronic kidney disease; CTO, chronic total occlusion; DM, diabetes mellitus; ISR, in-stent restenosis; MLA, minimum lumen area; PCI, percutaneous coronary intervention; SVG, saphenous vein graft

promotes intimal hyperplasia, leading to luminal loss, reduced minimal luminal area, and subsequent TLR [16].

Antiproliferative drug resistance or hyporesponsiveness is not routinely assessed in patients undergoing PCI. One potential symptom is recurrent ISR following the implantation of DES that releases the same antiproliferative drug [17]. However, recent clinical trials have provided conflicting evidence regarding the impact of drug hyporesponsiveness on DES restenosis, complicating efforts to define the optimal treatment for these patients. In the RIBS-III study, Alfonso et al. [18] found that a “hetero-DES” strategy — switching to a different DES to manage restenosis — is superior to a “homo-DES” strategy, which involves using the same DES. The conclusion was based on both angiographic and clinical efficacy. Conversely, an earlier angiographic study by Cosgrove et al. [19] reported similar outcomes between those receiving the same or a switched strategy but had a limited angiographic follow-up rate of only 69%. Additionally, Garg et al. [20] found no differences in clinical events among a small observational cohort. Previous studies have indicated that hypersensitivity reactions induced by stent components may result in local inflammation and the formation of neointima, leading to long-term adverse cardiovascular events, including ISR [21]. Several studies have demonstrated an increased risk of restenosis

associated with nickel allergies [22], and this association has remained significant in patients treated with cobalt-chromium stents [23]. Additionally, data suggest that allergic reactions have been reported with the use of poorly biocompatible polymers found in first-generation DES [24].

Anatomical and morphological factors

Coronary artery calcification is a significant anatomical risk factor for ISR, particularly associated with calcified nodules (CN). CN is defined as a nodular calcification that protrudes into the coronary artery lumen and can be categorized into two subtypes: eruptive and non-eruptive, each with unique histopathological and prognostic characteristics. In the study by Teda et al. [25], CNs were identified in 4.9% of ISR lesions. Notably, CNs can progress with regrowth and reprotrusion into the vessel lumen even when lesions are properly prepared before stent implantation [26]. This process often occurs shortly after the stenting, with the rate of TLR increasing six months post-procedure [27, 28]. The other subtype of calcified lesions is severe circumferential coronary calcification, characterized by a 360-degree distribution that significantly affects both peri-procedural and long-term outcomes, including the rate of ISR. Inadequate preparation of lesions in segments with more than 180 degrees of calcium arc often results in stent underexpansion.

Preparing for this calcified lesion aims to create multiple calcium cracks. If DES is deployed without first addressing the circumferential calcification, patients face a long-term risk of ISR [29]. Therefore, the treatment strategy selection, especially for lesion preparation, should be based on an assessment of the severity and distribution of calcifications evaluated with intracoronary imaging.

The other anatomical risk factor for ISR is bifurcation lesions. Coronary artery bifurcation disease is found in at least 20% of coronary angiography patients [30]. Although multiple PCI techniques have been developed, including advanced bifurcation stenting techniques, clinical outcomes observed in several randomized controlled trials (RCTs) have shown a worse long-term prognosis for bifurcation lesions than non-bifurcation lesions [31]. Currently, the gold standard for treating significant *de novo* coronary artery bifurcation disease is PCI with DES implantation, with the single-stent provisional stenting technique being the first-line strategy (level of evidence I A) [5]. The two-stent technique is recommended only in selected patients with stenosis of large side branches (SBs) extending more than 10 mm beyond the vessel ostium. However, the Double Kissing Crush vs. Provisional Stenting Technique for Treatment of Coronary Bifurcation Lesions II (DKCRUSH-II) trial [32] found significantly lower angiographic restenosis rates at 8 months in the double kissing (DK) group compared to the provisional stenting group. Specifically, the rates of ISR for the main vessel were 3.8% vs. 9.7%, respectively ($P < 0.036$), and for SB they were 4.9% vs. 22.2%, respectively ($P < 0.001$). The DKCRUSH-V randomized controlled trial conducted by Chen et al. [33] showed that the rates of ISR in the main vessel at the 13-month angiographic follow-up were comparable between the DK crush strategy and provisional stenting. However, the ISR rate at the ostium of SB was 12.0% with provisional stenting, compared to 5.0% with the DK crush technique. Independent predictors of SB occlusion among patients undergoing repeated intervention for ISR were also identified. These included SB occlusion during initial stenting, diabetes, SB ostium involvement, baseline SB TIMI flow grade < 3 , and restenosis length [34]. In turn, the risk of SB restenosis, stent thrombosis, and major adverse cardiovascular events MACE can be reduced by optimizing the procedure with final kissing balloon inflation. ISR following provisional and two-stent strategies for bifurcation lesions remains a significant concern, with occurrence rates ranging from 5% to 15%. The evidence regarding the preferred treatment is still limited. It presents significant challenges due to increased technical complexity and a higher risk of procedural failure, especially in left main restenosis. In clinical practice, the operator's experience plays a significant role in selecting the appropriate procedural technique for bifurcation lesions. Optimizing procedures under the guidance of intracoronary imaging is highly recommended to improve outcomes [35].

Percutaneous recanalization of native coronary CTOs is also associated with a significantly higher rate of ISR during

long-term follow-up compared to the subset of lesions [36]. Several mechanisms contribute to this increased risk of re-occlusion. One factor may be stent undersizing, which can occur due to adverse remodeling, subintimal hematoma, or impaired blood flow. Additionally, increased vessel trauma, longer stented segments, and post-revascularization remodeling of the vessel also play significant roles in this process. In addition to the previously discussed risk factors, significant predictors of ISR in both CTO and non-CTO lesions include stent diameter and the subsequent minimal stent area (MSA). An analysis of the combined TAXUS IV, V, VI, and ATLAS Workhorse Trials involving 1580 patients showed that post-intravascular ultrasonography (IVUS) MSA greater than 5.7 mm² predicted 9-month angiographic stent patency [37]. In smaller vessels, a post-intervention optical coherence tomography (OCT)-assessed MSA of less than 3.5 mm² [38] was identified as a predictor of 9-month ISR and TLR following PCI with a 2.5-mm diameter everolimus-eluting stent (EES) [37]. In a CTO-specific study, Kim et al. [39] found that the minimal lumen diameter (MLD) and stent expansion ratio were independent predictors of ISR. Image-guided PCI in CTO lesions usually enables accurate vessel sizing, particularly in the presence of vessel dissection or hematoma. Intracoronary imaging helps to assess calcifications and select the method of modification to facilitate stent expansion. Moreover, optimizing the stent implantation based on intracoronary imaging enables the greatest MLD, MSA, and stent expansion ratio to prevent downstream stent thrombosis and ISR. Furthermore, if the CTO is located at the aorto-ostium or a bifurcation, the procedural complexity increases, resulting in a higher risk of long-term MACE and ISR [40].

Procedural factors

According to the expert consensus document of the European Association of Percutaneous Cardiovascular Interventions, stent expansion $> 80\%$ (MSA divided by average reference lumen area) should be obtained in routine clinical practice [41]. Stent underexpansion is often associated with early ISR, which defines the duration from stent implantation as less than one year, while neoatherosclerosis contributes more commonly to late ISR [42]. Thus, adequate lesion preparation with calcium cracks and adequate stent expansion are the primary factors affecting PCI outcomes, with stent underexpansion being the strongest predictor of ISR [43, 44]. The study by Kang et al. [43] showed that 42% of ISR lesions present stent underexpansion. The characteristics of underexpanded stent lesions differ from *de novo* atherosclerotic lesions. In underexpanded stents, the plaque often contains heavy, deep calcifications, including calcific nodules that resist dilatation through non-plaque modification techniques. Additionally, underexpanded restenotic stents treated with subsequent stent implantation may lead to new stent underexpansion and an increased event rate during follow-up. Subsequent stenting of a recurrent ISR lesion is associated with chronic

underexpansion and a high rate of adverse events if the cause of ISR is not adequately addressed [45].

Stent malapposition may coexist with underexpansion within the same implanted stent. It is usually linked to the use of undersized stents and the unique characteristics of the coronary arteries, which can make stent delivery and optimal implantation challenging. These characteristics include significant tortuosity and fluctuations in lumen diameter [41].

While acute malapposition, if not severe, has not been shown to increase the risk of stent-related adverse events [46], late (acquired) malapposition has been associated with a higher risk of DES failure, including thrombosis and restenosis [47]. Several mechanisms have been suggested to explain late stent malapposition. These include positive arterial remodeling, reduced plaque and media due to the dissolution of jailed thrombus, persistent incomplete stent apposition, and chronic stent recoil [48]. Risk factors for late malapposition include overlapping stents, longer stent lengths, and type C lesions. In addition, the risk of ISR increases with the number of stents implanted, their length and diameter, and the presence of tandem stenting. Using multiple stents enlarges the total contact area between the stent body and the vessel wall, which can lead to neointimal proliferation and a higher rate of restenosis. A reference diameter of less than 3 mm is a predictive factor for ISR [49, 50].

ISR TREATMENT

The optimal method for treating ISR lesions is still under discussion. Ultrathin strut DESs may enhance PCI efficacy by reducing the risk of target-lesion and target-vessel failures compared to other DESs. However, one potential limitation is the reduced radial strength, which could increase the risk of recurrent events if the lesion is not adequately prepared. DCBs have emerged as a promising alternative to DESs for treating ISR, primarily by delivering drugs directly to the lesion without the need for additional stent struts. By avoiding foreign materials in the vessel, the DCB minimizes inflammation and reduces the risk of restenosis, which helps maintain the minimum lumen area. The effectiveness of drug delivery to vascular tissue relies on the coating formulation and application techniques, leading to varying pharmacokinetic profiles. This protective lipophilic coating facilitates accelerated drug diffusion and penetration into the arterial wall during balloon inflation [51]. Currently, DCBs coated with either paclitaxel or sirolimus are available for clinical use. It is important to note that sirolimus-coated balloons operate through a different mechanism of action compared to paclitaxel-coated ones and have a broader therapeutic range.

Paclitaxel is known for its high lipophilic properties, allowing easy diffusion into the vessel wall upon contact with the intima, with fast uptake and long tissue retention [51, 52]. Furthermore, irreversible binding of paclitaxel to microtubules leads to prolonged presence in vascular cells

[53]. On the other hand, paclitaxel has a narrow therapeutic window, and excessive dosing may lead to toxic effects [54]. The paclitaxel-coated balloon has a drug dosage that ranges from 2 to 3.5 $\mu\text{g}/\text{mm}^2$ on the balloon's surface [55].

Sirolimus and its analogs recently emerged as an alternative due to their cytostatic properties and wide therapeutic window. Compared to paclitaxel, sirolimus is cytostatic and has a wider therapeutic range. It is a macrocyclic lactone that demonstrates cytostatic effects by primarily inhibiting the mammalian target of rapamycin, an essential serine/threonine kinase that plays a crucial role in cell growth, proliferation, and survival [56]. Delivering “-limus” drugs to the vessel wall is more difficult due to lower lipophilicity [56]. For DCB-based delivery of sirolimus, it was necessary to develop delayed-release technologies to overcome the above limitations and to ensure adequate antiproliferative treatment. Sirolimus is delivered into the blood vessel by encapsulating the drug in a lipophilic carrier utilizing Nanoluté technology (Magic Touch, Concept Medical, US) [57]. The drug is then released from the encapsulated nano-carrier into the vessel wall. Another method used to transfer the crystalline sirolimus formulation to the tissue involves the use of butylated hydroxytoluene as an excipient, which facilitates a sustained release of the drug (Sequent SCB) [58]. Sirolimus-DCB has a drug dosage that ranges from 1.27 $\mu\text{g}/\text{mm}^2$ to 4 $\mu\text{g}/\text{mm}^2$ on the balloon's surface [67].

Unlike DCB, the two-layer metal scaffold reduces the risk of elastic recoil and negative vessel remodeling. Furthermore, covering the lesion with a new stent layer eliminates the risk factors of ISR resulting from mechanical damage to the previously implanted stent (e.g., strut fracture). On the other hand, a DCB strategy allows the delivery of an antiplatelet drug without the need to implant a new metal platform. This is particularly beneficial for patients who have recurrent and multilayered ISR. Additionally, long-term studies have shown strong evidence supporting the use of DCB in patients experiencing first DES restenosis, demonstrating that this method is both safe and effective [59, 60]. The AGENT IDE trial led to the approval of the first DCB in the United States, showing the superiority of DCB vs. uncoated balloons concerning TLF, TLR, and target vessel-related myocardial infarction (TV-MI) at one year, with no differences in cardiac death [61]. However, according to the 2024 European Society of Cardiology (ESC) guidelines for chronic coronary syndromes, DES is recommended over DCB for treating DES-restenosis (class I A) [3, 6, 62, 63]. Giaccoppo et al. [62] demonstrated that patients treated with DCB had higher TLR rates than those treated with DES in cases of DES restenosis.

In contrast, the risk of safety endpoints was numerically lower in the DCB group at 3-year follow-up. The ten-year outcomes comparing DES and DCB have been presented in the ISAR-DESIRE 3 [6] trial, which showed no significant differences in clinical endpoints for DES-restenosis. In a meta-analysis by Elgendy et al. [63], DES and DCB therapies

carried the same risk of target vessel revascularization (TVR) at one year. However, the TVR and target TLR rates were higher in the DCB group than in the DES group at longer follow-up periods. It is essential to highlight that only a small number of patients in the cited studies underwent intravascular imaging during PCI to identify the underlying mechanisms of ISR.

While only DES stents are currently in use, some patients still have BMS implants from the past. The studies assessing BMS restenosis showed that DCB had much better clinical and angiographic outcomes than non-coated balloon angioplasty; however, the results are similar for first-generation DES [62, 64–66]. Based on randomized trial data from a large meta-analysis, DCBs are as effective as DES in reducing revascularization BMS restenosis [67].

For DES restenosis, DCBs similarly were shown to be superior to un-coated balloon angioplasty [64, 68, 69]. Studies comparing DCB and DES in instances of DES restenosis have reported inconsistent results. Similarly to the ISAR DESIRE 3 study, the PEPCAD China ISR trial demonstrated non-inferiority of DCBs vs. paclitaxel-eluting stents for DES-restenosis therapy [70]. Only a few studies have compared DCB with new-generation DES in DES restenosis. The RIBS IV [71] randomized clinical trial of 309 patients assessed the effectiveness of DCB compared to DES in patients with DES restenosis. The angiographic follow-up showed that EES was superior to DCB in terms of in-segment MLD during 6 to 9 months of follow-up (2.03 ± 0.7 mm vs. 1.80 ± 0.6 mm; $P < 0.01$), lower percent diameter stenosis ($23 \pm 22\%$ vs. $30 \pm 22\%$; $P < 0.01$) and binary restenosis rate (11% vs. 19%; $P = 0.06$). The superiority of EES over DCB in the rate of TLR was confirmed in another one-year clinical study (4.5% vs. 13.0%; $P = 0.007$). The results were maintained during the three-year follow-up, reaching a TLR rate of 7.1% for EES and 15.6% for DCB ($P = 0.015$). Mortality and MI rates did not differ significantly between the groups [72]. A recent meta-analysis of 10 RCTs that included both BMS and DES restenosis (DAEDALUS study) [67] showed that DCB therapy is slightly less effective than repeat DES stenting in reducing the need for TLR over a period of 3 years. However, it is crucial to note that the benefits of stenting are mainly observed in patients with DES restenosis. The composite endpoint rates, including all-cause death, MI, and target lesion thrombosis, were similar across both groups. Additionally, the rates for individual endpoints, such as all-cause mortality, did not show significant differences between the two groups. Again, only a small percentage of included patients underwent intravascular imaging-guided PCI.

While RCTs serve as the gold standard for comparative analysis, real-world data also play a crucial role in providing insights into the efficacy of ISR treatment approaches. The DEB-DRAGON Registry [73] analyzed consecutive patients experiencing their first incidence of DES restenosis, who underwent PCI with either paclitaxel-DCB or thin-strut

DES. The propensity score matching analysis showed no significant differences between the thin-strut DES group and DCB group regarding TLR (11.2% vs. 11.2%; $P = 0.707$), TVR (13.4% vs. 14.2%; $P = 0.523$), and the device-oriented composite endpoint (14.2% vs. 14.2%; $P = 0.667$) at 3-year follow-up. However the in long-term follow-up of chronic coronary syndrome patients undergoing PCI of ISR, the use of DES was associated with reduced rates of TLR (HR, 0.54; 95% CI, 0.33–0.88; $P = 0.013$), TVR (HR, 0.57; 95% CI, 0.41–0.80; $P = 0.009$), and device-oriented composite endpoints (HR, 0.65; 95% CI, 0.42–0.99; $P = 0.046$), compared with patients treated with DCB [74].

Newer data were published in 2024. Wańha and Iwańczyk et al. [75] presented a study comparing sirolimus-DCB vs. thin-strut DES in DES restenosis. A total of 1545 patients with 1679 ISR lesions were included in the pooled analysis. After propensity score matching, there were no significant differences in the rates of TLR (11.6% vs. 11.8%; $P = 0.329$), TVR (14.0% vs. 13.1%; $P = 0.822$), MI (7.2% vs. 4.5%; $P = 0.186$), all-cause death (5.7% vs. 4.2%; $P = 0.476$), and MACE (21.5% vs. 17.6%; $P = 0.242$) between DCB and thin-strut DES during a follow-up period of 2 years. Therefore, the potential clinical advantage of reducing strut thickness and the number of stent layers may be best reflected in the outcome of patients with ISR. The dilemma regarding whether to use a new scaffold or DCB in patients with DES restenosis remains unsolved. Furthermore, the results of ISR treatment also depend on the type of restenosis. A study conducted by De Filippo et al. [4] showed that ultrathin-strut DES was associated with a significantly lower risk of device-oriented composite endpoints compared to DCB and thin-strut DES. Additionally, ultrathin-strut DES also reduced the risks of TLR and TVR compared to DCB, whereas thin-strut DES did not show this benefit. No significant differences were observed in patients with focal DES restenosis. The advantages and disadvantages of DCB and DES in ISR treatment are shown in [Table 2](#).

Despite the downgrading of the DCB for treating ISR in the current ESC guidelines [3], many patients with ISR worldwide continue to be treated with the DCB strategy after careful lesion preparation and under intravascular imaging guidance. [Figure 2](#) presents an algorithmic approach for treating ISR.

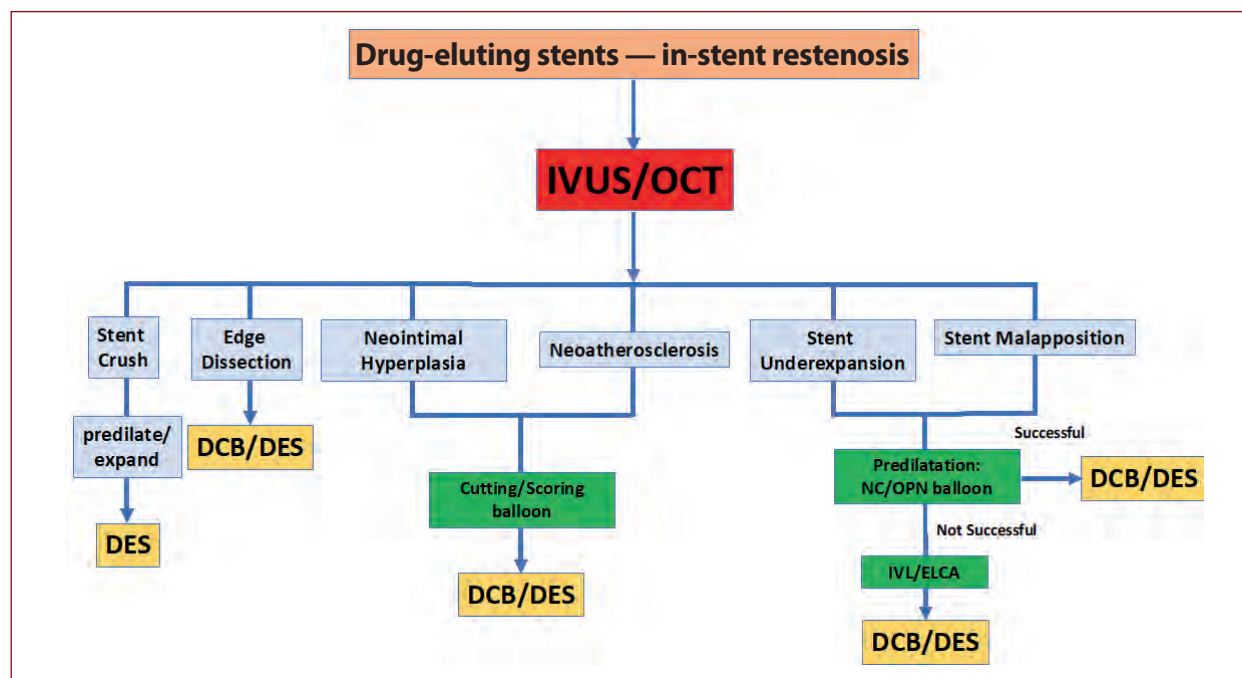
The bioresorbable vascular scaffold (BVS) is considered as a potential treatment option for ISR. Although scientific evidence for the safety and effectiveness of this strategy is limited, the available results are not encouraging. The RIBS VI study showed that late clinical results of DES are superior to those obtained with DCBs and BVS in patients with ISR. Beyond the first year, DCBs are safer and more effective than BVS [76].

The main previously published studies on ISR comparing DES and DCB are listed in Supplementary material, [Table S1](#).

Table 2. Advantages and disadvantages of DCB and DES in ISR treatment

	Advantages	Disadvantages
DCB	• Delivery of an antiproliferative drug without the implantation of a new metal platform • Reduction of inflammatory responses associated with DES • Reduction of the intensity and duration of the antiplatelet regimen — potentially preferred option for patients with at high risk of bleeding	• Higher risk of acute vessel closure and elastic recoil • Mandatory optimal lesion preparation before balloon inflation • In absence of IVI, suboptimal results (no interpretation of the cause for ISR)
DES	• Better acute angiographic results compared with DCB • Reduced risk of elastic recoil • Treatment of mechanical damage of previously implanted stent (e.g., strut fracture) • Ultrathin DES –reduction of TLR and TVR risk compared to thin-strut-DES	• Risk of inflammatory response and hypersensitivity to DES components • Reduced radial strength (ultrathin DES)

Abbreviations: DCB, drug-coated balloon; DES, drug-eluting stent; IVI, intravascular imaging; TLR, target lesion revascularization; TVR, target vessel revascularization

**Figure 2.** Algorithmic approach to ISR

Abbreviations: DCB, drug-coated balloons; DES, drug-eluting stents; IVUS, intravascular ultrasound, NC, non-compliant; OCT, optical coherence tomography; other — see Figure 1

LESION PREPARATION FOR ISR LESIONS

ISR PCI requires careful lesion preparation to ensure satisfactory long-term angiographic and clinical results. Lesion preparation guided by intravascular imaging modalities is strongly recommended, and the underlying mechanisms of ISR must be carefully considered before deciding on a DES- or DCB-based treatment [77].

Cutting/scoring balloons

Cutting balloon angioplasty (CBA) has emerged as an effective strategy to reduce the recurrence of ISR [78]. The core concept of CBA involves the incision of atherosclerotic plaque or neointimal tissue using 3 to 4 arthrotomes during balloon inflation. This process creates a controlled fracture line that enables larger luminal diameters at lower pressures and reduces acute elastic recoil in *de novo* lesions [79]. Therefore, applying CBA was an effective debulking method for an atherosclerotic plaque or neointimal

tissue if ISR occurred [80]. Thus, utilizing CBA for lesion preparation may improve the outcomes of DCB therapy for ISR. However, a limited number of studies have investigated the outcomes of combining CBA and DCB for ISR lesions. The randomized ISAR DESIRE 4 trial (Intracoronary Stenting and Angiographic Results: Optimizing Treatment of Drug-Eluting Stent In-Stent Restenosis 4) demonstrated that the strategy of scoring balloon angioplasty followed by DCB was superior to standard balloon angioplasty followed by DCB in reducing the rate of late lumen loss at 6 to 8 months [81]. There are also emerging data on the role of scoring balloons for lesion preparation before DCB use [82]. In general, plaque modification devices are preferred for neoatherosclerosis or fibrous plaque treatment. Controlled incisions of the plaque allow for expansion of the lesion, reducing the risk of elastic recoil, and possibly better absorption of the antiproliferative drug into the vessel wall.

Intravascular lithotripsy

Another treatment option for severe ISR calcifications is intravascular lithotripsy (IVL). The multicenter IVL-DRAGON registry described the safe off-label use of IVL to enhance stent expansion in a calcified plaque resistant to balloon angioplasty [83]. Additionally, the Rota-Tripsy combination in selected patients has been successfully used to treat stent restenosis caused by calcified neoatherosclerosis [84]. In recent years, there has been increasing interest in IVL as a device for debulking in treating ISR prior to DCB angioplasty and DES procedures. IVL emits localized shock waves from multiple emitters positioned on a specialized delivery catheter [85, 86]. The balloon is inflated at low atmospheres, allowing one or more cycles of sonic waves to be delivered, which induces the rupture of the calcifications, thereby facilitating subsequent dilation of the lesion. While favorable results have been reported in *de novo* coronary artery disease treatment, there are currently no randomized trials specifically addressing ISR. However, several case reports have highlighted the feasibility of using IVL for ISR, positioning it as a potential therapeutic option for calcium debulking [87, 88]. In summary, IVL should be considered for cases of neoatherosclerosis involving severe calcifications and underexpanded stents due to calcified lesion.

Excimer laser coronary atherectomy

Excimer laser coronary atherectomy (ELCA) is an atheroablative technique that precisely cuts coronary atheroma, including calcium, without causing thermal damage [45, 89]. IVUS has shown that the mechanism for lumen enlargement after ELCA on non-stented lesions is primarily due to tissue ablation (accounting for 76% of lumen enlargement) and vessel expansion (making up 24% of lumen enlargement). ELCA is commonly applied to various types of lesions, including thrombotic, diffuse, calcified, restenotic, and ostial lesions. Li et al. [90] demonstrated that ELCA may be a safe and effective technique in the treatment of ISR CTOs. The use of ELCA can achieve good immediate angiographic results without increasing peri-procedural complications or the incidence rates of 9-month MACEs. In a multicenter, retrospective observational study, ELCA appeared to be a safe method with acceptable long-term results for the management of recurrent ISR. Technical and procedural success were achieved in 92%, comparable to the control group in which ELCA was not used. Coronary perforation occurred in 2 patients as a result of distal wire perforation but was not ELCA-related. There was no in-hospital MACE [91]. Indeed, the multicenter IVL-ELCA DRAGON registry showed that both IVL and ELCA achieved similar success and safety outcomes in treating underexpanded stents [92]. Therefore, in centers experienced in ELCA treatment, the method may be applied for in-stent neoatherosclerosis or underexpanded stents when other interventions fail.

Rotational atherectomy

Rotational atherectomy (RA) for in-stent restenosis can effectively modify calcifications in new atherosclerotic plaque or ablate under-expanded stents; however, the success rate is variable with a high risk of procedural complications [93]. In a case study by Okamura et al. [94], stent ablation was performed to address restenosis lesions resulting from the crushing of a sirolimus-eluting stent. Their findings indicated that the size of the metallic particles generated during the rotational atherectomy of stent struts was $5.6 \pm 3.6 \mu\text{m}$, suggesting that this particle size was safe with no risk of issues as regards distal embolization. Tips for effective stent ablation include selecting the appropriate burr size, initially ablating only the stent struts, and then using a larger second burr to ablate the calcification behind the stent struts. However, due to an increased risk of burr entrapment during stent ablation, gentle handling with a gradual increase in burr size is essential, and this technique should be used only as a last resort.

IMPROVED IMAGING TOOLS

Stent enhancement

Digital stent enhancement (DSE) is an imaging technique designed to improve the visualization of stent struts. Several companies have utilized and validated DSE technology. However, the general methodology is consistent, primarily involving automatically detecting a balloon's proximal and distal markers in each frame from a cine run. DSE systems can provide relevant images for assessing deployment irregularities, stent expansion, stent fracture, and the gap between the stents, which is crucial in determining the mechanism of ISR [95]. In patients undergoing PCI with DSE, a reduction in late loss and binary restenosis was observed, as well as a lower rate of TLR at 6 and 12 months, respectively, compared to patients treated without DSE [96]. Individual studies have demonstrated that stent measurements obtained through DSE correlate well with intraluminal measurements acquired *via* IVUS, although they tend to overestimate the stent diameter [97, 98]. The primary limitation of the technique is its two-dimensional visualization, which can result in the oversight of an underexpanded stent, even when viewed in orthogonal planes. Moreover, DSE does not provide direct information about stent apposition on the vessel wall and is limited only to the stent evaluation without atherosclerotic plaque. Another limitation is the need for balloon markers inside the stent, which restricts the ability to visualize stents implanted during previous procedures without additional vessel instrumentation. Digital enhancement complements intravascular imaging rather than replacing it, improving the routine assessment of stent expansion and enabling visualization of stents in specific scenarios where IVUS or OCT cannot be used (Figures 3 and 4).

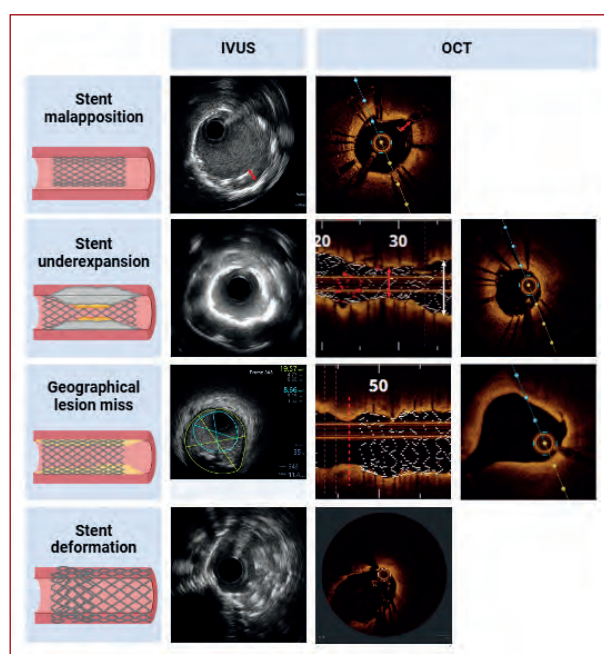


Figure 3. IVUS and OCT images demonstrating stent-related factors associated with in-stent restenosis

Abbreviations: see [Figure 2](#)

Intravascular imaging

Identifying the mechanisms contributing to in-stent restenosis is crucial for guiding subsequent treatment stages, enhancing both safety and effectiveness. Intracoronary imaging is an essential tool at each phase of the PCI procedure [99]. The IVUS or OCT analysis results inform treatment strategies, evaluate the methods' effectiveness, and optimize procedures. Utilizing intracoronary imaging at all stages of treatment improves the prognosis for patients with ISR. The European Society of Cardiology guidelines and a focused document from the European Association of Percutaneous Coronary Intervention recommend using intravascular imaging techniques for treating stent failures (class IIa) [5, 100]. While both methods have their unique strengths and limitations, they offer distinct capabilities.

Intravascular ultrasound

IVUS is a catheter-based imaging technique that provides high-resolution cross-sectional coronary artery images. Its axial resolution ranges from 100 to 200 μm , while the lateral resolution is approximately 250 μm [101]. The latest advancement, high-definition IVUS, utilizes a 60 MHz transducer to deliver superior image quality, achieving an axial resolution of 40 μm , reduced noise, and greater penetration depth. The sound waves produced by the transducers penetrate subsequent layers of the vessel and are reflected based on the acoustic properties of the tissue. IVUS allows for detailed measurements of both the luminal and vascular areas and offers insights into different types of plaque morphology, including fibrotic, calcific, and vulnerable plaques. Importantly, for assessing the mechanisms of

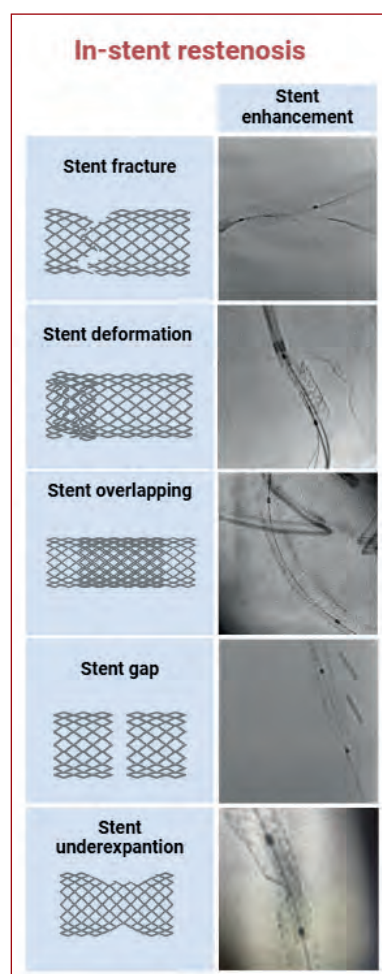


Figure 4. Digital stent enhancement factors associated with in-stent restenosis

ISR, IVUS may allow the identification of the causes of stent failure, such as neointimal hyperplasia, neoatherosclerosis, undersized stents, underexpansion of the stent, malposition of stent struts, and stent edge restenosis.

Optical coherence tomography

This is a catheter-based imaging technique that utilizes near-infrared interferometry to provide high-resolution images of the coronary arteries. Its axial and lateral resolutions are significantly higher than those of IVUS, reaching 15 and 20–40 μm , respectively. The imaging process involves emitting near-infrared light at a wavelength of approximately 1300 nanometers, with images produced by detecting backscattered light. Due to its enhanced spatial resolution, FD-OCT allows for superior visualization of intracoronary pathological features compared to IVUS [102] ([Figure 4](#)), especially identifying neo-atherosclerotic plaques and the presence of thrombus. Additionally, FD-OCT provides detailed images of stent architecture, strut apposition, and reliable characterization of neointima morphology. Automated analysis of OCT frames using artificial intelligence supports the detection of stent malposition and under-expansion. This technology assists operators

in assessing the mechanisms behind ISR and optimizing treatment strategies to minimize the risk of both the occurrence and recurrence of ISR.

However, OCT also has limitations: it requires administration of contrast agents for blood clearance before imaging, making it suboptimal for patients with chronic kidney disease; in patients with aorto-ostial lesions, optimal blood clearance can be difficult to achieve due to challenges in intubating the coronary artery with a guide catheter, resulting in poorer image quality; additionally, the penetration depth of FD-OCT is limited and cannot accurately assess larger, aneurysmal, or positively remodeled coronary arteries.

SPECIFIC CLINICAL SCENARIOS OF ISR

Recurrent ISR

Recurrent ISR refers to the occurrence of a second event of ISR after successful treatment of an initial restenosis lesion [103]. Data on R-ISR prevalence are limited, with at least 1.4% of all patients undergoing PCI [104]. This group has a high risk of cardiac events, especially repeated revascularizations; therefore, according to the guidelines, those patients should be considered for surgical revascularization [5]. The long-term outcomes following R-ISR revascularization are limited due to insufficient RCT in this area. Treatment of R-ISR with additional stent implantation is controversial, because implanting another metallic layer within the artery reduces the lumen area and causes progressive luminal stenosis. A study by Wolny et al. [105, 106] demonstrated that, over 3 years, the incidence of TLR after DES implantation for R-ISR was 20.9%, and 27.1% for patients treated with DCB. Another study reported a 27.7% TLR rate for DES and 38.3% for DCB over a two-year follow-up period [107]. A study involving a four-year follow-up of patients with R-ISR after the implantation of an additional stent layer for R-ISR treatment revealed a TLR rate of 27.6% [108].

Left main ISR

The left main coronary artery supplies a large area of heart muscle. Therefore, ISR in the left main coronary artery can lead to significant ischemia, which could be associated with high morbidity and mortality rates. ISR after DES placement in an unprotected left main artery continues to occur, with an incidence ranging from 9.7% to 17.6% [109, 110]. CABG is typically regarded as the standard treatment for LM-ISR. However, because there is a higher risk of perioperative complications and mortality, especially in high-risk patients, such as those with acute coronary syndrome, PCI may be a viable alternative for restoring blood flow. There are only a few studies that compare the outcomes of PCI and CABG for patients with unprotected LM-ISR. The results of the LM-Dragon [111] registry, which compared PCI with CABG in ISR, showed only a lower incidence of cardiac death in PCI compared with CABG in short-term

follow-up; however, during the long-term follow-up, patients treated with CABG less often required TVR; no other differences were observed. The results support the use of PCI in unprotected LM-ISR, demonstrating its safety and effectiveness in LM-PCI. The results of the PCI revascularization strategy in LM-ISR were highlighted in the FAILS study, which reported that major adverse cardiac events occurred in 26% of patients and TLR in 22% of patients at the 27-month follow-up [109].

ISR-CTO

ISR-CTO is the most severe type of restenosis, accounting for 5%–10% of all treated CTOs [112]. The treatment is challenging; however, compared to non-ISR CTOs, having a roadmap can help guide wires through the true lumen. Studies indicate that ISR-CTO can be recanalized with similar success rates as in-hospital MACE and *de novo* CTOs [112].

In-stent restenosis in the saphenous vein grafts

Lesions in SVGs present different morphological characteristics compared to native vessel atherosclerosis. Plaques are typically lipid-rich and softer, making them more prone to rupture than plaques found in native coronary arteries [113, 114]. The PCI of SVGs carries a higher risk of stent failure than in native arteries, with an ISR rate of 4.3% at one year [9, 115]. In these cases, various biological factors, such as inflammation or accelerated neoatherosclerosis, may influence ISR [116]. When deciding on the treatment for SVG-ISR, repeating PCI of the SVG using DES, DCB, or PCI on the native vessels should be considered.

FUTURE DIRECTIONS AND ONGOING STUDIES

Several studies are currently evaluating new-generation DCB and DES for the treatment of ISR. A crucial factor in effectively treating restenosis is the careful and precise preparation of the lesion, which is essential for achieving favorable long-term outcomes with both DCB and DES. A key distinction of DCB treatment is that it avoids adding another layer of a stent. Intravascular imaging is recommended during PCIs and should be utilized before the procedure and throughout each treatment step. Optimal lesion preparation involves advanced plaque modification techniques, which may include specialized high-pressure balloons or atherectomy [77]. Future studies on ISR treatment should focus on randomization conducted after lesion preparation, using intravascular imaging to assess the most suitable treatment device for ISR.

CONCLUSIONS

The mechanisms leading to ISR are often complex and require a careful assessment by intravascular imaging, whose parameters represent the best surrogates for predicting favorable outcomes, also because imaging should guide each step of ISR-PCI and help to select among dif-

ferent strategies, including the use of plaque-modifying or plaque-ablative techniques. Only after obtaining an optimal old stent improvement should the final decision be made between further stenting or DCB.

Supplementary material

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

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Inflammation response post-radiofrequency ablation for atrial fibrillation: Implications for early atrial fibrillation recurrence

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Editorial

by Hennings and Meyre

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ABSTRACT

Background: Inflammation is associated with early recurrence after atrial fibrillation (AF) ablation and is linked to stroke in AF.

Aims: The aim of this study is to investigate the time course of inflammatory biomarkers following radiofrequency ablation (RFA) for AF and its relation to early AF recurrence.

Material and methods: Ninety patients who underwent successful RFA for AF were enrolled. Blood samples were collected from the median cubital vein preoperatively and on postoperative days 1, 2, 3, 7, and 14 to measure levels of high-sensitivity C-reactive protein (hs-CRP), fibrinogen, creatine kinase isoenzyme (CKMB), and cardiac troponin I (cTnI). Follow-up evaluations of AF recurrence were conducted at weeks 1, 2, 3, and 4 and months 2 and 3 postoperatively.

Results: The hs-CRP levels significantly increased on postoperative days 2 and 3 compared to preoperative values, followed by a decline on days 7 and 14 ($P < 0.05$). The fibrinogen level peaked between postoperative days 2 and 7 ($P < 0.05$), and then declined by day 14. CKMB and cTnI levels peaked between postoperative days 1 and 3 ($P < 0.05$). The escalation of hs-CRP following RFA was identified as an independent risk factor for early AF recurrence (OR, 2.948; 95% CI, 1.892–4.602; $P = 0.004$).

Conclusions: The degree of inflammatory response following RFA serves as a predictive marker for early AF recurrence, and the significant inflammatory response and hypercoagulable state are evident within the first week post-RFA for AF, potentially explaining the heightened risk of early thromboembolic events.

Key words: atrial fibrillation, inflammation, myocardial injury, radiofrequency catheter ablation, recurrence of atrial fibrillation

INTRODUCTION

Atrial fibrillation (AF) is a prevalent form of rapid cardiac arrhythmia encountered in clinical practice, associated with heart failure, an increased risk of stroke, and heightened mortality and disability rates [1]. Radiofrequency ablation (RFA) is a crucial therapeutic approach used to restore sinus rhythm and manage AF [2]. Despite its benefits, this technique is often challenged by a high incidence of postoperative recurrence. Although early

AF recurrence does not fully reflect the procedural success, it is a significant predictor of late recurrence, which is critical for guiding clinical treatment strategies for AF [3, 4]. Therefore, attention must be directed towards this “blank period” following RFA for AF.

Recent studies have demonstrated a correlation between inflammatory responses and early recurrence following catheter ablation for AF [5]. However, the relationship between preoperative and postoperative inflammatory

WHAT'S NEW?

In our study, the extent of the inflammatory response escalation after radiofrequency ablation serves as a predictive indicator for early atrial fibrillation recurrence. Furthermore, high expression of prothrombotic markers at 1 week after radiofrequency ablation for atrial fibrillation might explain the increased risk of early thromboembolic events. The magnitude and specific alterations in postoperative elevation of inflammation after radiofrequency ablation for atrial fibrillation was investigated with the aim of helping guide the timing and regimen of postoperative interventions to prevent recurrence of atrial fibrillation.

responses and both early and late recurrence following ablation has produced inconsistent results [6–8]. Detailed research on the underlying mechanisms has shown that postoperative inflammation plays a significant role in the initiation and progression of AF [9]. Patients with AF undergoing ablation are at an increased risk of thromboembolic events, particularly within the first two weeks post-procedure, although the precise mechanisms remain unclear [10].

In this study, we aimed to investigate the specific temporal profile of inflammatory response following ablation, examining its relationship with prothrombotic risk and AF recurrence. By utilizing blood biomarkers as therapeutic targets, we seek to mitigate the inflammatory response after ablation, thereby providing theoretical evidence for evaluating operation outcomes and reducing early recurrences.

MATERIAL AND METHODS

General information

In this prospective study, 98 patients aged less than 75 years with AF were consecutively enrolled between March 2015 and May 2016. All patients successfully underwent a circumferential pulmonary vein isolation (CPVI) procedure. The exclusion criteria were acute or chronic infections, left ventricular dysfunction, left atrial diameter greater than 50 mm, atrial thrombosis, valvular heart disease, hyperthyroidism, history of AF ablation, previous prosthetic heart valve replacement, malignant tumors, blood disorders, contraindications to anticoagulation therapy, or inability to adhere to anticoagulant medication. This study was approved by the local Ethics Committee (Approval number: 2016122).

Operation procedure

Prior to the procedure, transesophageal echocardiography was performed to exclude left atrium thrombus. All antiarrhythmic agents were discontinued for five half-lives before the procedure. All patients underwent CPVI treatment following a standardized surgical protocol, without any additional ablation beyond the pulmonary veins unless they had been diagnosed with atrial flutter prior to the operation. A computed tomography scan of the left atrium and pulmonary veins was conducted preoperatively to assess their size and morphology.

During the procedure, under three-dimensional anatomical mapping (Carto 3, Biosense Webster), a pres-

sure-infused ablation catheter was inserted through the interatrial septum into the left atrium for RFA. A circular mapping catheter (Lasso® NAV eco, Biosense Webster) was utilized before, during, and after CPVI treatment to record pulmonary vein potentials. The standard approach involved creating an encircling lesion around two adjacent ipsilateral pulmonary veins as the endpoint for successful ablation. Following the achievement of entrance and exit block in pulmonary vein potentials, a monitoring period of 20 to 30 minutes was implemented before reassessing conduction status. If recovery was observed during this period, the ablation procedure was continued. If sinus rhythm did not resume despite achieving entrance block, unidirectional cardioversion was performed using a 360 J shock.

Sample collection

Blood samples were collected from the median cubital vein preoperatively and on postoperative days 1, 2, 3, 7, and 14. High-sensitivity C-reactive protein (hs-CRP), fibrinogen, creatine kinase-MB (CKMB), and troponin-I levels in peripheral blood were measured at each time point and were promptly analyzed. Hs-CRP was quantified using an immunoturbidimetric latex CRP assay, fibrinogen levels were determined using the STAR coagulation analyzer, CKMB concentrations were assessed using an immunoinhibition method, and troponin-I measurements relied on chemiluminescent immunoassay. The normal reference ranges for these biomarkers are as follows: hs-CRP 0–0.08 mg/l, fibrinogen 2.38–4.98 g/l, CKMB 0–24 U/l, and troponin-I 0–0.04 ng/ml. The extent of biomarker elevation is defined as the maximum value observed (between day 1 and day 14) minus the baseline value recorded preoperatively, such as hs-CRP elevation, fibrinogen elevation, CKMB elevation, and troponin-I elevation.

Postoperative care and follow-up

All patients received standard postoperative care, including immobilization, fluid therapy, and continuous cardiac monitoring for three days. Outpatient follow-up visits were scheduled at weeks 1, 2, 3, and 4 post-operation, and at months 2 and 3. Weeks 1–4 post-operation suggest four times of follow-up in the first month. After 1 month post-procedure, follow-up was conducted twice a month, and patients underwent electrocardiogram (ECG) examinations and 48-hour ambulatory ECG recordings to assess arrhythmia recurrence. AF recurrence was defined as any episode of atrial arrhythmia lasting ≥ 30 seconds. Early

recurrence was defined as any episode of atrial arrhythmia lasting ≥ 30 seconds within 3 months post-ablation based on ECG examination and ambulatory ECG recordings. Anticoagulation therapy with oral anticoagulant medication was continued for at least three months post-ablation. For patients with a CHADS₂ score ≤ 1 and no recurrence, oral anticoagulant medication was discontinued. The CHADS₂ scoring system includes congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and previous stroke/transient ischemic attack, and it is used to predict stroke risk in patients with non-valvular AF. For patients with a CHADS₂ score > 1 , anticoagulation therapy was continued for 12 months before considering discontinuation based on mutual agreement with the patient.

Statistical analysis

Data analysis was performed using SPSS 13.0 statistical software. Normally distributed continuous variables are presented as mean (standard deviation). Continuous variables that were not normally distributed are expressed as median (interquartile range). Categorical data are displayed as frequencies and percentages. The χ^2 test or Fisher's exact test was used to analyze categorical data. A significance level of $P < 0.05$ was considered statistically significant. Intra-group indicators following ablation were compared using a repeated measures mixed linear model. Logistic regression analysis models assessed the impact of various risk factors on early recurrence post-ablation. The Enter method in single-factor logistic regression analysis was utilized to calculate unadjusted odds ratios (OR) for initial screening of risk factors associated with early recurrence. Significant variables identified in the single-factor analysis, along with clinically relevant variables believed to impact early recurrence, were incorporated in the multiple-factor logistic regression analysis model to determine the risk factors for early recurrence.

RESULTS

General characteristics of baseline data

The baseline characteristics of the patients and procedural characteristics are summarized in Table 1. The CHADS₂ score was 1 (0–1). Among the 98 patients initially screened, two patients met the exclusion criteria (Figure 1). At least 90 patients were examined, six of whom failed to appear for more than one visit or Holter recording and were excluded from this study. The follow-up period was 3 months, during which 35 patients experienced recurrence, resulting in an early recurrence rate of 38.9%. Among the patients, 53 (58%) had paroxysmal AF, and 37 (42%) had persistent AF.

Table 1. Baseline information of the enrolled patients with atrial fibrillation

Characteristics	Patient cohort (n = 90)
Age, years	56 (11.6)
Male	42 (46.7%)
Comorbidities	
Hypertension	41 (45.6%)
Diabetes	7 (7.8%)
Coronary artery disease	12 (13.3%)
Previous stroke/TIA	8 (8.9%)
Low-density lipoprotein (mmol/l)	2.77 (0.62)
Blood creatinine (umol/l)	68.5 (11.2)
Baseline Hs-CRP	11.9 (6.5–17.8)
Baseline fibrinogen	0.8 (0.5–1.2)
Baseline CKMB	4.8 (2.8–7.1)
Baseline troponin-I	1.4 (0.9–1.6)
CHADS ₂ score	
0	32 (35.6%)
1	43 (47.8%)
2	8 (8.9%)
≥ 3	7 (7.7%)
CHADS ₂ score	1 (0–1)
Type of AF	
Paroxysmal AF	53 (58%)
Persistent AF	37 (42%)
Usual medications	
β -blockers	32 (35.6%)
Propafenone	30 (33.3%)
ACE inhibitors or ARB	33 (36.7%)
Echocardiographic parameters	
Left ventricular ejection fraction, %	62.5 (8.2)
RF ablation time, min	126.5 (22.6)

Results are mean (SD), median (interquartile range), or n (%)

Abbreviations: ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; CHADS₂, congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and previous stroke/TIA; RF, radiofrequency; SD, standard deviation; TIA, transient ischemic attack

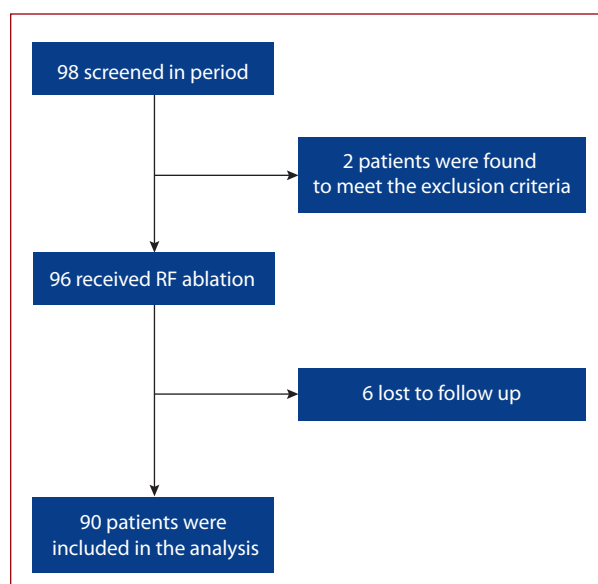


Figure 1. Flow diagram of the study

Abbreviation: RF, radiofrequency

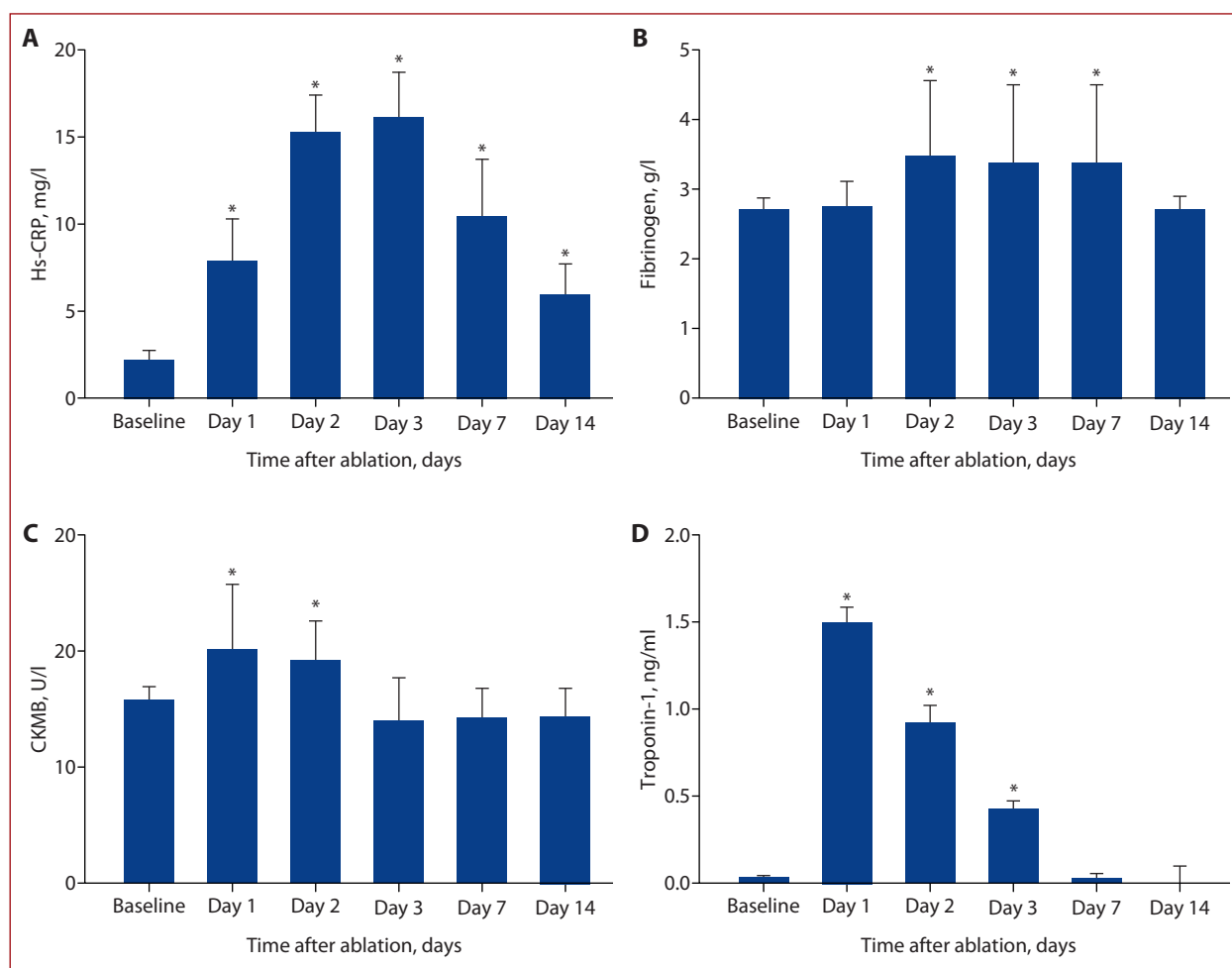


Figure 2. Duration with respect to variations in inflammatory markers following radiofrequency ablation for AF. **A.** High-sensitivity C-reactive protein (hs-CRP); * $P < 0.05$ (compared to baseline values). **B.** Fibrinogen; * $P < 0.05$ (compared to baseline values). **C.** Creatine kinase isoenzyme (CKMB); * $P < 0.05$ (compared to baseline values). **D.** Troponin-I; * $P < 0.05$ (compared to baseline values)

Changes in inflammatory biomarkers at different time points following RFA for AF

hs-CRP

Following RFA for AF, hs-CRP levels significantly increased over time compared to preoperative levels. The hs-CRP levels were significantly higher on postoperative days 1, 2, 3, 7, and 14 ($P < 0.05$), with peak levels observed on postoperative days 2 and 3 ($P < 0.05$). Subsequently, hs-CRP levels decreased but remained slightly elevated compared to preoperative levels on postoperative days 7 and 14 (Figure 2A).

Fibrinogen

Fibrinogen levels showed significant variations pre- and post-RFA on postoperative days 1, 2, 3, 7, and 14 ($P < 0.05$). There was a significant increase in fibrinogen levels on postoperative days 2, 3, and 7 compared to preoperative levels ($P < 0.05$), with a peak between days 3 and 7. By day 14, fibrinogen levels had returned to preoperative levels ($P > 0.05$) (Figure 2B).

CKMB

CKMB levels significantly increased on the first postoperative day, reaching a peak ($P < 0.05$). Levels then decreased from the second to the third postoperative day and returned to preoperative levels by day 3 ($P > 0.05$). This decreasing trend continued through the seventh and fourteenth days (Figure 2C).

Troponin-I

Troponin-I levels significantly increased on the first postoperative day, reaching their highest level. Levels gradually decreased during follow-up visits but remained higher than preoperative levels on the second and third postoperative days ($P < 0.05$). By the seventh day, levels had returned to preoperative values ($P > 0.05$), and a further reduction was noted by the fourteenth day (Figure 2D).

Follow-up and recurrence of AF

During the three-month follow-up period, patients attended outpatient appointments at specified intervals, includ-

Table 2. Predictor of early AF recurrence by multivariable analysis

Variable	P-value	OR	OR 95% CI	
			Lower limit	Upper limit
Age	0.081	1.031	1.012	1.441
Hypertension	0.201	0.506	0.427	0.801
electric cardioversion	0.159	3.071	1.056	8.938
RF ablation time	0.102	1.116	1.025	1.243
CKMB elevation	0.753	1.390	0.479	2.765
Troponin-I elevation	0.052	2.550	0.993	6.546
Fibrinogen elevation	0.097	1.176	0.856	3.256
Hs-CRP elevation	0.004	2.948	1.892	4.602

Abbreviations: CI, confidence interval; OR, odds ratio; other — see Figure 2

ing postoperative weeks 1, 2, 3, and 4, and at the second and third months. Of the 90 patients who underwent RFA for AF, 35 experienced early recurrence, resulting in an early recurrence rate of 38.9%. Univariate logistic regression analysis results indicated difference in age, hypertension, electric cardioversion, and RF ablation time in relation to early recurrence of AF ($P > 0.05$). However, elevations in inflammatory biomarkers such as CKMB, troponin-I, fibrinogen, and hs-CRP were identified as risk factors for early recurrence. The extent of elevation in CKMB (OR, 1.207; 95% CI, 1.020–1.428; $P = 0.029$), troponin-I (OR, 2.834; 95% CI, 1.116–7.196; $P = 0.028$), fibrinogen (OR, 3.564; 95% CI, 1.090–11.654; $P = 0.035$), and hs-CRP (OR, 2.864; 95% CI, 1.493–5.493; $P = 0.002$) showed a positive correlation with early recurrence of AF. Multivariable logistic regression analysis revealed that only the degree of elevation in hs-CRP was an independent predictor of early recurrence following RFA for AF (OR, 2.948; 95% CI, 1.892–4.602; $P = 0.004$) (Table 2).

Post-procedure complications

All patients recovered following treatment, with no withdrawals from the study. Two patients developed sinus bradycardia and required pacing. Four patients experienced mild fluid overload, necessitating diuretic therapy.

DISCUSSION

The efficacy of RFA in the treatment of AF is widely recognized. However, postoperative recurrence remains a significant clinical concern [11]. Several factors have been identified as being associated with the recurrence of AF following RFA, including left atrial diameter, body mass index, and inflammatory biomarkers. Specifically, there has been an increasing focus on inflammatory biomarkers. Most arrhythmias that occur within three months following ablation for AF can resolve spontaneously, likely due to procedure-induced inflammation [12]. Early recurrence of AF serves as a reliable predictor for late recurrence and is one of the most significant predictive factors [3, 4]. In our study, we applied a three-month post-ablation blanking period, though the recent expert consensus statement has shortened this period to two months [13]. Early recurrence may be attributed to secondary inflammation after the

ablation procedure but does not necessarily indicate treatment failure. Evaluation of operation outcomes should be conducted once inflammation has subsided. The aim of this study was to investigate the relationship between inflammatory changes following RFA for AF and early recurrence.

In this study, the levels of CKMB and troponin-I were observed to increase and reach their peak on the first day following ablation for AF. Subsequently, they exhibited a gradual decline after three days, returning to preoperative levels within the first week. These findings suggest mild myocardial injury after the procedure, attributed to cardiac tissue damage during ablation rather than myocardial ischemia [14]. Lim et al. [15] reported that the troponin-I level peaked on the first day following RFA for AF and continued to rise until the third postoperative day, while CKMB levels also peaked on the first day, consistent with our findings. Furthermore, the levels of CK-MB and potentially troponin I might be influenced to some extent by cardioversion. The magnitude of elevation in cardiac muscle proteins may be associated with the intensity of radiofrequency pulses delivered during the operation and the ablation site.

Our study showed that hs-CRP levels peaked on the second and third day following ablation and remained elevated for 14 days before gradually declining. Previous studies have demonstrated that localized myocardial tissue damage and edema occur after ablation for AF [16]. This results in an acute inflammatory response characterized by increased white blood cell count, hs-CRP levels, coagulation biomarkers, and other markers. Additionally, early post-ablation inflammation induces a prothrombotic state in patients undergoing ablation for AF within two weeks postoperatively, significantly contributing to complications such as thromboembolism associated with AF [17]. The results of this study revealed a notable elevation in fibrinogen levels from the second or third day post-operation, peaking on the third and seventh days, and persisting until the seventh day compared to preoperative levels. This phase of heightened coagulation marker expression coincides with most thromboembolic complications arising within two weeks following RFA, potentially explaining the increased risk of early thromboembolic events. Therefore, monitoring the timing and degree of anticoagulation after ablation for

AF may effectively prevent thromboembolic events and reduce anticoagulant costs and bleeding risk.

Emerging studies have demonstrated a close correlation between oxidative stress, inflammatory reactions, and the occurrence, progression, and maintenance of AF. Frustaci et al. [18] observed lymphocyte infiltration in atrial myocardium biopsies from patients with paroxysmal AF, accompanied by surrounding necrotic cardiac tissue, which provided pathological evidence supporting the presence of inflammation in AF development. Yuksel et al. [19] enrolled 427 patients undergoing isolated off-pump coronary artery bypass grafting in this retrospective observational cohort study and for the first time demonstrated that multi-inflammatory indices predicted new-onset AF after off-pump coronary artery bypass grafting. The mechanisms underlying AF recurrence following RFA are complicated and not fully elucidated. Previous studies have indicated that preoperative baseline hs-CRP levels independently predict AF recurrence following RFA [20]. This study revealed that the extent of postoperative rise in hs-CRP levels (defined as the difference between maximum postoperative value and preoperative level) is an independent risk factor for early AF recurrence. Koyama et al. [21] found that a higher inflammatory response following ablation for AF is associated with a greater rate of early AF recurrence, consistent with our findings. However, there is controversy regarding factors influencing early recurrences following ablation for AF. Richter et al. [22] found that recurrences within 48 hours of ablation cannot reliably predict late recurrences.

Studies have demonstrated that the use of corticosteroids and anti-inflammatory medications post-catheter ablation for AF can mitigate inflammation, thereby reducing the occurrence of early postoperative arrhythmias [23, 24]. Colchicine, a medication with anti-inflammatory, immunosuppressive, and antifibrotic properties, is primarily used to treat acute attacks of arthritic gout and has anti-carcinogenic properties. It exerts a potent cardioprotective effect by reducing the incidence of cardiovascular diseases through its anti-inflammatory action, such as minimizing in-stent restenosis in coronary arteries and decreasing the likelihood of pericardial effusion and pleural effusion following cardiac operations. Studies have shown that oral administration of colchicine for three months following RFA for AF reduces early recurrence rates [23]. Additionally, a three-day regimen of corticosteroid use following RFA for AF not only reduces early recurrences but also lowers the incidence of midterm arrhythmias [24]. However, an experimental animal study found that prophylactic steroids did not alter the systemic inflammatory response or lesion healing in pigs undergoing atrial ablation [25]. Furthermore, numerous studies have confirmed that inflammation is a significant contributing factor in the development of AF [9, 26].

Limitations

A limitation of this study is follow-up and recurrence of AF — the probing frequency following RFA might be low, failing to show the peak of fibrinogen levels. Thus, the extent of this biomarker may be underestimated. Inflammation presents a novel target for clinical treatment strategies aimed at combating AF development [27]. Further research is warranted to elucidate the complex mechanisms linking inflammation with AF [28].

CONCLUSION

In this study, the extent of the inflammatory response escalation after RFA serves as a predictive indicator for early atrial fibrillation recurrence. The results of our study revealed high expression of prothrombotic markers one week after RFA for AF, which may explain the increased risk of early thromboembolic events seen in other studies, which can guide the timing and degree of anticoagulation to effectively prevent thromboembolic events while reducing anticoagulant costs and bleeding risk. The results may assist in determining the optimal timing and regimen of postoperative interventions to prevent AF recurrence. They may also help mitigate the inflammatory response after AF ablation, providing theoretical evidence for evaluating procedural outcomes and reducing early recurrences.

Article information

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Implementation of cardiovascular prevention guidelines in clinical practice. Results from the POLASPIRE II survey

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Editorial

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ABSTRACT

Background: There is limited knowledge about the implementation of current guidelines in every-day clinical practice.

Aim: To describe risk factors management in patients with coronary artery disease through lifestyle modifications and the use of drug therapies to provide an objective assessment of the implementation of the current guidelines on cardiovascular prevention.

Methods: Twelve departments of cardiology in 6 regions participated in the study (conducted in 2022–2023). Patients (aged ≤80 years) were recruited and interviewed 6–18 months following hospitalization due to an acute coronary syndrome (68.7%) or a myocardial revascularization procedure (31.3%).

Results: A total of 801 patients (median age 66.4 years, 595 men and 206 women) were examined. The proportion of patients with high blood pressure was 66.5%, with high low-density lipoprotein cholesterol 79.8%, and with high HbA1c 16.0%; 19.5% of participants were active smokers, and 80.5% were overweight/obese. The proportion of patients taking at least one antiplatelet/antithrombotic agent was 92.8%, a β-blocker 84.7%, an angiotensin converting enzyme inhibitor or angiotensin II type 1 receptor blocker 79.8%, and a lipid-lowering drug 89.5% patients. Only 8.6% patients had all the 5 main risk factors well controlled, while 2.4% had all risk factors at recommended target and were prescribed an antiplatelet or an antithrombotic drug and an angiotensin converting enzyme inhibitor or angiotensin II type 1 receptor blocker.

Conclusions: There is considerable opportunity of further reduction of cardiovascular risk in Polish patients treated for coronary artery disease. A revision of the ongoing and more intensive endorsement of cardiovascular prevention programs is advisable.

Key words: cardiovascular risk, coronary artery disease, secondary prevention

INTRODUCTION

Coronary artery disease (CAD) is a leading cause of death worldwide [1]. In recent years, both pharmacological and invasive treatment methods for CAD have advanced significantly. However, in Poland, the annual mortality rate among patients who survive a myocardial infarction remains about 10% after discharge from hospital [2]. Studies have identified several causes for this high mortality rate, including insufficient implementation of lifestyle changes, inadequate control of risk factors, and suboptimal pharmacotherapy [3–9]. Recent research has shown a favorable trend for some risk factors, but not for all [9–12]. Although guidelines for the management of risk factors have recently been updated, there is limited knowledge about their impact on everyday medical practice in Poland [13–15].

The purpose of this study was to evaluate the implementation of current guidelines for the secondary prevention of CAD by assessing patients' lifestyle changes, the efficacy of major cardiovascular risk factor management, and the use of recommended pharmacotherapy.

METHODS

The study was conducted across 6 regions: 1 in the northern part of Poland, 2 in the eastern part, 1 in the central part, and 2 in the southern part of the country. In total, 12 cardiology departments from ten different hospitals participated in the study, including 3 municipal hospitals and 7 teaching hospitals.

At each center, the medical history of consecutive patients aged ≤ 80 years who had been hospitalized due to acute coronary syndrome (unstable angina, ST-segment elevation, and non-ST-segment elevation myocardial infarction), had undergone percutaneous coronary intervention, or were scheduled for coronary artery bypass grafting, was reviewed by centrally trained staff. Patients who died during hospitalization were excluded from the study. For individuals hospitalized more than once in 2021–2022 for

the reasons mentioned above, only data from the first hospitalization were considered.

Centrally trained research staff carried out data collection using standardized methods across all centers; they reviewed patient medical records, conducted interviews, and performed examinations of the participants. The data collection process followed identical procedures and methods, ensuring consistency across all research centers. Standardization covered both the measurement tools and the methods used for recording and storing data.

Patients were invited to participate in a follow-up examination 6 to 18 months after being discharged. These examinations were conducted in 2022–2023. During the interview, data regarding demography (age, sex, marital status, professional activity), CAD, tobacco products use status, blood pressure, prescribed medications, comorbidities, and lifestyle (having regular physical activity 30 min on average five times a week, diet) were obtained using standardized data collection forms. The specialization of the physicians who treated the study participants were defined according to the study participants' answers to the question "Whose care are you currently (in the last 3 months) under for your cardiac condition".

During the physical examination, patients were weighed and measured in a standing position, without shoes or heavy outer garments, using standard scales equipped with a vertical ruler. Body mass index (BMI) was calculated using the formula: $BMI = \text{weight [kg]} / (\text{height [m]})^2$. Waist circumference was measured with a metal tape placed horizontally along the mid-axillary line, midway between the lowest edge of the rib cage and the top of the hip bone, while the patient stood. All patients had their blood pressure measured at least twice on the non-dominant arm in a sitting position after resting for at least five minutes. If the systolic value differed by more than 20 mm Hg or the diastolic value by more than 10 mm Hg, the measurement was repeated.

WHAT'S NEW?

Despite substantial evidence on the benefits of lifestyle changes, risk factor management, and the use of cardioprotective medications following a cardiac event, this study demonstrates that the implementation of the current European Society of Cardiology guidelines in everyday clinical practice remains inadequate. Two out of three patients had blood pressure levels that were too high, four out of five had elevated low-density lipoprotein cholesterol levels, and 64% of patients continued smoking. Furthermore, only one in 3 patients with coronary artery disease made efforts to meet the recommended levels of physical activity. Additionally, the study suggests a decrease in prescription rates of cardioprotective medications following a cardiac event. These findings indicate the need for more intensive implementation of recommendations for secondary prevention, which could help reduce morbidity and mortality among Polish patients with coronary artery disease.

To assess lipid parameters and fasting blood glucose, a venous blood sample was taken in the morning after at least 12 hours of fasting. Smoking status was verified through the concentration of carbon monoxide in the breath using a smoker analyzer (Bedfont Scientific, Model Micro+).

Persistent smoking was defined as smoking at the time of the interview among those who smoked during the month before the index event. High blood pressure was defined as values $\geq 130/80$ mm Hg for patients under 70 years and $\geq 140/80$ mm Hg for those aged 70 years or older. High low-density lipoprotein (LDL) cholesterol was defined as LDL cholesterol levels ≥ 1.4 mmol/l, high HbA1c as HbA1c levels $\geq 7.0\%$, and high BMI as BMI ≥ 25 kg/m² [13]. Increased waist size was defined as ≥ 94 cm for men and ≥ 80 cm for women.

The secondary prevention coefficient was defined as the sum of points assigned for each controlled risk factor (non-smoking, blood pressure $< 130/80$ mm Hg for patients under 70 years and $< 140/80$ mm Hg for patients aged 70 years and older, LDL cholesterol < 1.4 mmol/l, HbA1c $< 7.0\%$, and BMI < 25 kg/m² — one point for each). Additionally, one point was given for taking an antiplatelet or antithrombotic agent, and one point for using an angiotensin converting enzyme (ACE) inhibitor or an angiotensin II receptor antagonist. Thus, the secondary prevention coefficient could range from 0 to 7.

The study protocol was approved by the institutional bioethics committees: the Bioethics Committee of the Center of Postgraduate Medical Education in Warsaw (approval numbers 72/2022 and 129/2022), the Bioethics Committee of the Jagiellonian University (approval number 1072.61.20.94.2021), the Bioethics Committee of the MSWiA Hospital in Warsaw (approval number 16/2022), and the

Bioethics Committee of the Medical University of Białystok (approval number APK.002.139.2022). All study participants signed the informed consent form.

Data management

All data were collected electronically *via* web-based entry using a unique identification number for each center and individual. The data were entered into an online database. The data management center was responsible for ensuring the completeness, internal consistency, and accuracy of the data.

Statistical analysis

Categorical variables are presented as percentages, while continuous variables are expressed as means with standard deviation or medians (interquartile ranges [IQRs]), as appropriate. The Shapiro–Wilk test was used to assess the normality of the distribution. The Pearson χ^2 test was applied to categorical variables. Normally distributed continuous variables were compared using Student's *t*-test, while the Mann–Whitney *U* test was used for variables without a normal distribution. A two-tailed *P*-value of less than 0.05 was considered statistically significant. A multi-variable, stepwise logistic regression analysis was used to assess factors independently related to the value of the secondary prevention coefficient. In the stepwise backward regression analysis, all variables described in Table 1 were included in the initial model, and subsequently those with the lowest value of the χ^2 statistics were eliminated in a stepwise approach to obtain the model containing variables significantly associated with the dependent variable only. All calculations were run using STATISTICA 13 software (TIBCO Software, Palo Alto, CA, US).

Table 1. Characteristics of the study population

	Men n = 595	Women n = 206	P-value	Total n = 801
Age, years, median (IQR)	66.0 (60.2–71.3)	68.1 (62.0–73.1)	<0.001	66.4 (61.0–72.1)
Duration of education ^a , years, median (IQR)	12 (11.0–15.0)	12 (11.0–14.0)	0.31	12 (11.0–15.0)
Event			0.16	
Myocardial infarction, n (%)	282 (47.4)	114 (55.3)		396 (49.4)
Unstable angina, n (%)	116 (19.5)	38 (18.4)		154 (19.2)
Percutaneous coronary intervention, n (%)	121 (20.3)	37 (18.0)		158 (19.7)
Coronary artery bypass grafting, n (%)	76 (12.8)	17 (8.3)		93 (11.6)
Prior hospitalization for cardiovascular reasons, n (%)	323 (54.3)	104 (50.5)	0.35	427 (53.3)
Employed, n (%)	226 (40.0)	36 (17.5)	<0.001	262 (32.7)
Married, n (%)	501 (84.2)	128 (62.1)	<0.001	629 (78.5)
Participation in a rehabilitation programme following the index hospitalization, n (%)	282 (47.4)	101 (49.0)	0.69	383 (47.8)
Specialization of the physician ^a				
Cardiologist, n (%)	519 (87.2)	186 (90.3)	0.24	705 (88.0)
General practitioner, n (%)	396 (66.6)	154 (74.8)	0.03	550 (68.7)
Diabetologist/endocrinologist, n (%)	73 (12.3)	41 (19.1)	<0.01	114 (14.2)
Other physician, n (%)	95 (15.0)	21 (10.2)	0.04	116 (14.5)
No regular check-ups, n (%)	10 (1.7)	2 (1.0)	0.47	12 (1.5)

^aAmong subjects who participated in the follow-up examination, as declared by the patients

Abbreviation: IQR, interquartile range

Table 2. Proportions of patients who did not reach treatment goals 6–18 months after discharge

	Men	Women	P-value	Total
Smoking, n (%)	113 (22.2)	25 (14.1)	0.02	156 (19.5)
Persistent smoking, n (%)	123 (66.8)	27 (54.0)	0.09	150 (64.1)
High blood pressure ^a , n (%)	407 (68.9)	122 (59.8)	0.02	529 (66.5)
High LDL cholesterol ^b , n (%)	385 (78.7)	145 (82.9)	0.24	530 (79.8)
High HbA1c ^c , n (%)	80 (15.9)	28 (16.3)	0.92	108 (16.0)
High BMI, kg/m ² ^d , n (%)	479 (81.6)	158 (77.5)	0.20	637 (80.5)
Increased waist ^e , n (%)	436 (74.1)	176 (86.6)	<0.001	612 (77.3)

^aAvailable in 795 cases. ^bAvailable in 664 cases. ^cAvailable in 674 cases. ^dAvailable in 791 cases. ^eAvailable in 792 cases

Abbreviations: BMI, body mass index; HbA1c, glycated hemoglobin; LDL, low-density lipoprotein

Table 3. Patients' lifestyles at the time of interview 6–18 months after discharge (as declared by the patients)

	Men	Women	P-value	Total
Persistent smokers having attempted to quit smoking since hospital discharge, n (%)	86 (69.9)	19 (70.4)	0.96	105 (70.0)
Overweight or obese patients having attempted actively to lose weight since discharge, n (%)	266 (62.3)	92 (63.4)	0.80	358 (62.6)
Patients having regular physical activity 30 min. on average 5 times a week, n (%)	210 (35.3)	64 (31.1)	0.24	274 (34.2)
Patients trying to reduce salt intake, n (%)	359 (60.3)	127 (61.7)	0.73	486 (60.7)
Patients trying to reduce fat intake, n (%)	409 (68.7)	142 (68.9)	0.91	551 (68.8)
Patients trying to reduce calories intake, n (%)	349 (58.7)	122 (59.2)	0.85	471 (58.8)
Patients trying to increase vegetables and fruits intake, n (%)	411 (69.1)	154 (74.8)	0.14	565 (70.5)
Patients trying to increase fish intake, n (%)	343 (57.6)	103 (50.0)	0.06	446 (55.7)
Patients trying to increase fat fish intake, n (%)	257 (43.2)	67 (32.5)	<0.01	324 (40.4)
Patients trying to reduce sugar intake, n (%)	361 (60.7)	126 (61.2)	0.90	487 (60.8)
Patients trying to reduce alcohol intake, n (%)	270 (45.4)	66 (32.0)	<0.01	336 (41.9)

RESULTS

In total, 982 patients were invited to participate in the study. Ninety-one patients did not respond to the invitation, 86 refused for personal or other reasons, and 4 patients died. Finally, 801 patients were included in the study (Table 1). Mean age of the study population was 66.5 (8.9) years. Female patients were older, less often professionally active, and less frequently married (Table 1). Overall, 49.4% of patients had been hospitalized for acute myocardial infarction, 19.3% for unstable angina, and 31.3% for myocardial revascularization. The median time from hospital discharge to the follow-up examination was 0.97 (0.76–1.17) years.

The proportions of patients who did not achieve treatment goals 6–18 months after discharge are presented in Table 2. Overall, 19.5% of the study participants were smokers, with a persistent smoking rate of 64.1%. Most of the persistent smokers attempted to quit following the index hospitalization (Table 3).

The median systolic blood pressure was 133.0 (121.5–146.0) mm Hg, and the median diastolic blood pressure was 80.5 (73.0–88.5) mm Hg. High blood pressure, defined as $\geq 130/80$ mm Hg for patients under 70 years and $\geq 140/80$ mm Hg for those aged 70 years or older, was observed in 66.5% of the study participants (Table 2). Blood pressure of $\geq 140/90$ mm Hg was found in 41.6% of participants (43.8% of men and 35.3% of women; $P = 0.03$), while blood pressure of $\geq 130/80$ mm Hg was noted in 71.8% of patients (73.8% of men and 66.2% of women; $P = 0.04$).

The median total cholesterol concentration was 3.71 (3.19–4.47) mmol/l, with LDL cholesterol at 1.97 (1.48–2.55) mmol/l, high-density lipoprotein cholesterol at 1.24 (1.06–1.48) mmol/l, and median triglycerides at 1.20 (0.93–1.63) mmol/l. Overall, 95.0% of participants had LDL cholesterol levels ≥ 1.0 mmol/l (95.3% in men and 94.3% in women; $P = 0.60$), while 56.5% (55.4% in men and 59.4% in women; $P = 0.36$) had LDL cholesterol levels ≥ 1.8 mmol/l.

The median fasting glucose concentration was 5.66 (5.11–6.50) mmol/l, with a median HbA1c concentration of 6.0% (5.6%–6.5%). Overall, 52.3% of participants (53.8% of men and 47.9% of women; $P = 0.16$) had fasting glucose levels of at least 5.6 mmol/l, while 18.7% (17.8% of men and 21.4% of women; $P = 0.27$) had fasting glucose levels of at least 7.0 mmol/l.

The median BMI was 28.8 (25.7–32.0) kg/m². A BMI of ≥ 25 kg/m² was observed in 80.5% of patients (Table 2), BMI ≥ 30 kg/m² in 40.6% of patients (41.9% of men and 36.8% of women; $P = 0.20$), BMI ≥ 35 kg/m² in 11.8% of patients (11.2% of men and 13.2% of women; $P = 0.45$), and BMI ≥ 40 kg/m² in 2.5% of patients (2.2% of men and 3.4% of women; $P = 0.34$). The median waist circumference was 94.5 (86.0–103.0) cm for women and 101.0 (93.0–103.0) cm for men. Waist circumference ≥ 80 cm and ≥ 88 cm was found in 86.3% and 71.6% of women, respectively. Waist circumference ≥ 94 cm and ≥ 102 cm was present in 74.1% and 48.0% of men, respectively.

Table 4. Proportion of patients taking cardioprotective drugs 6–18 months after discharge from the hospital

	Men	Women	P-value	Total
Antiplatelets, n (%)	515 (84.9)	186 (90.3)	0.12	701 (87.5)
Anticoagulants, n (%)	80 (13.4)	23 (11.2)	0.40	103 (12.9)
Antiplatelets or anticoagulants, n (%)	552 (92.8)	191 (92.7)	0.85	743 (92.8)
β-blockers, n (%)	501 (84.2)	178 (86.4)	0.37	679 (84.7)
ACE inhibitors/ARB, n (%)	480 (80.7)	158 (76.7)	0.29	638 (79.7)
ACE inhibitors, n (%)	401 (67.4)	117 (56.8)	0.01	518 (64.7)
ARB, n (%)	81 (13.6)	41 (19.9)	0.03	122 (15.2)
Sacubitril-valsartan, n (%)	5 (0.8)	2 (1.0)	0.86	7 (0.9)
Calcium antagonists, n (%)	176 (29.6)	52 (25.2)	0.25	228 (28.5)
Diuretics, n (%)	196 (32.9)	71 (34.5)	0.68	267 (33.3)
Loop diuretics, n (%)	134 (22.5)	42 (20.4)	0.51	176 (22.0)
Thiazide or thiazide-like diuretics, n (%)	71 (11.9)	30 (14.6)	0.28	101 (12.6)
Potassium sparing diuretics, n (%)	145 (24.4)	35 (17.0)	0.02	180 (22.5)
Lipid lowering drugs, n (%)	534 (89.7)	183 (88.8)	0.96	717 (89.5)
Statins, n (%)	521 (87.6)	180 (87.4)	0.76	701 (87.5)
Fibrates, n (%)	20 (3.6)	7 (3.4)	0.97	27 (3.4)
Ezetimibe, n (%)	87 (14.6)	35 (17.0)	0.35	122 (15.2)
PCSK9 inhibitors, n (%)	0 (0.0)	1 (0.5)	0.09	1 (0.1)
Omega-3 fatty acids, n (%)	5 (0.8)	5 (2.4)	0.07	10 (1.2)
Antidiabetic agents, n (%)	207 (34.8)	70 (34.0)	0.88	277 (34.6)
Insulin, n (%)	41 (6.9)	21 (10.2)	0.17	62 (7.7)
Metformin, n (%)	140 (23.5)	49 (23.8)	0.95	189 (23.6)
SGLT2 inhibitors, n (%)	86 (14.5)	26 (12.6)	0.59	112 (14.0)
GLP-1 analogs, n (%)	4 (0.7)	2 (1.0)	0.66	6 (0.7)
Sulphonylurea, n (%)	26 (4.4)	6 (3.0)	0.37	32 (4.0)
Other, n (%)	7 (1.2)	2 (1.0)	0.82	9 (1.1)

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; GLP-1, glucagon-like peptide-1; PCSK9, proprotein convertase subtilisin/kexin type 9; SGLT2, sodium-glucose co-transporter-2

Table 3 presents patients' lifestyle habits, as reported by the participants. A minority of patients declared achieving the recommended level of physical activity. Regarding dietary improvements, most patients reported attempting to integrate healthier habits, primarily focusing on reducing fat intake and increasing the consumption of vegetables and fruits. The smallest proportion of patients reported trying to increase their intake of fish (**Table 3**).

The proportions of patients taking cardioprotective drugs 6–18 months after discharge from the hospital are presented in **Table 4**. Altogether 7.2% of patients were taking neither antiplatelet nor antithrombotic agents at the time of interview, while 0.8% were taking both an ACE inhibitor and angiotensin II type 1 receptor blocker (ARB). Altogether, 80.7% of patients were taking an ACE inhibitor or an ARB or sacubitril/valsartan. β-blockers were taken by 84.7% of patients, calcium antagonists by 28.4%, and diuretics by 33.3%. In addition, lipid-lowering drugs were taken by 89.5% of patients and antidiabetic agents by 34.6%.

The mean number of main cardiovascular risk factors (smoking, blood pressure, LDL cholesterol, HbA1c, and BMI) at recommended target was 3.21 (0.99) with 8.6% of patients having all five and 39.1% at least four risk factors well controlled. Fewer than three risk factors at the recommended goal was found in 22.0% of the study participants. The mean value of the secondary prevention coefficient was 3.99 (1.19); 3.90 (1.12) in females vs. 4.02 (1.22) in males;

$P = 0.29$. Altogether, 2.4% of the patients had all five main cardiovascular risk factors well controlled and were prescribed an antiplatelet or an antithrombotic drug and an ACE inhibitor or an ARB (**Figure 1**). Age, professional activity, index hospitalization for acute coronary syndrome, and participation in the cardiac rehabilitation since discharge from the hospital were significantly related to the value of the secondary prevention coefficient (**Table 5**).

DISCUSSION

The study results show that there is a great potential to reduce cardiovascular risk in patients with established CAD in Poland. Recent evidence on the quality of the secondary prevention of CAD in Poland is scarce. The previous multicenter survey, the POLASPIRE I study (carried out in 2017–2018), showed a high proportion of patients with CAD with uncontrolled risk factors [6]. The proportions of patients with risk factors at recommended target were generally similar in participants of the POLASPIRE I and II surveys. On the other hand, the proportions of patients prescribed cardioprotective drugs tended to be lower among participants of the POLASPIRE II survey as compared to patients studied in the POLASPIRE I study, with the exception of ezetimibe (2.5% vs. 15.3%) [6]. For instance, the proportions of patients taking an antiplatelet agent were 92.9% and 87.5%, a β-blocker 89.4% and 84.7%, an ACE inhibitor or an ARB 85.9% and 79.8%, and a statin 89.8% and 87.4% among the participants of the POLASPIRE I and

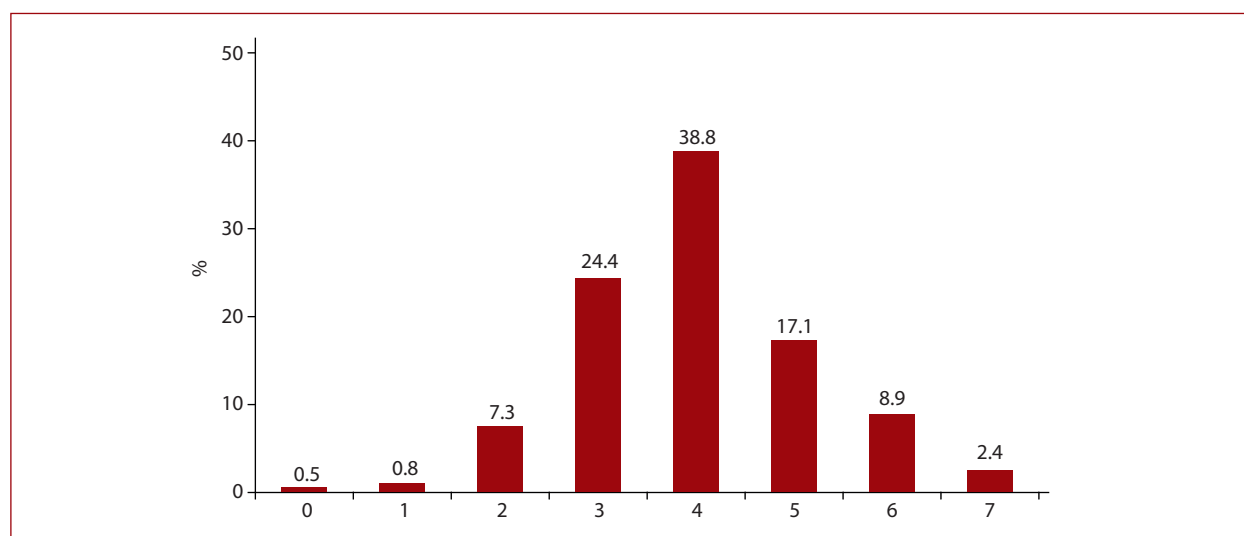


Figure 1. Distribution of the secondary prevention coefficient values

Table 5. Variables independently related to the secondary prevention coefficient value above 4

Variables	Odds ratio (95% confidence intervals)	P-value
Age, per 1 year	1.06 (1.03–1.09)	<0.001
Index hospitalization for acute coronary syndrome	2.16 (1.44–3.25)	<0.001
Professional activity	1.79 (1.14–2.80)	0.01
Participation in the cardiac rehabilitation since discharge	1.46 (1.01–2.09)	0.04

II surveys, respectively [6]. Compared to the post-myocardial infarction patients with left ventricular systolic dysfunction who participated in another multicenter study, the prescription rate of ACE inhibitors, beta blockers, and statins was similar, while that of antiplatelets was higher in the present survey [16]. Statins reduce cardiovascular events and mortality in patients with CAD or at high risk of cardiovascular disease. Despite this, not all patients with established CAD take them regularly. This has not changed in recent years [4, 6, 10, 13]. The study by Ramotowski et al. [9] showed that 66.8% of smokers undergoing coronary angiography were still smoking 6 months following hospitalization, a very similar figure to the present data. Another single-center analysis also provided evidence for low level of adherence to the guidelines for secondary prevention of CAD [8, 17]. The results of the POLASPIRE II survey are in accordance with earlier surveys on secondary prevention in Europe. Importantly, the recent EUROASPIRE V survey, which involved 81 centers from 27 countries, provided evidence for unhealthy lifestyles in terms of smoking, diet, and sedentary behavior, and insufficient treatment of hypertension, dyslipidemia, diabetes, and obesity among CAD patients [5]. Generally, the recommended secondary prevention targets were not achieved more often among the POLASPIRE II survey participants compared to patients studied in the EUROASPIRE V survey [5]. Similar conclusions could be drawn from a comparison of Polish patients with stable CAD with patients from the other European countries participating in the CLARIFY registry [18].

The study included patients aged ≤ 80 years only. The benefits of preventive interventions are well-established and evidenced in younger populations but are less clear in those over 80 years old. The management of cardiovascular disease in this group requires specific research. The unsuccessful implementation of cardiovascular prevention in individuals over 80 years old is a multifaceted issue that involves physical, cognitive, and systemic barriers. While prevention is still important in this age group, it should be adapted to their specific needs and limitations, focusing on measures that enhance quality of life and balance the risks and benefits of interventions [19, 20].

We did not find evidence for any major sex-based difference in the effectiveness of cardiovascular risk factors treatment following hospitalization for CAD. Sex was not significantly related to the value of the secondary prevention coefficient, neither in univariate nor after multivariate adjustments. These findings agree with some, but not all, of the studies [21–26].

We found a considerable decrease in the proportion of patients with blood pressure and LDL cholesterol level at the recommended targets compared to the results from the POLASPIRE I survey [6]. It should, however, be underlined that in the meantime the recommended targets were changed [13–15, 27, 28]. When we applied the previously recommended targets to the present data, we found very similar proportions of patients not achieving the goals (blood pressure 42% in POLASPIRE I and 42% in POLASPIRE II, LDL cholesterol 62% in POLASPIRE I and 56%

in POLASPIRE II) [6, 27–32]. These figures, along with no major difference in the proportion of smokers (17% vs. 19%) and the prevalence of obesity (42% vs. 41%), suggest that the quality of medical care in the field of secondary prevention has not improved in recent years [6]. Indeed, the patients' lifestyle as well as changes in prescription rates of cardioprotective medications (as compared with the POLASPIRE I survey results) may confirm this suggestion.

Limitations of the study

Participants of the present study do not represent the entire population of people with CAD: the data concern only those who underwent coronary artery bypass graft or percutaneous coronary intervention or were hospitalized for acute coronary syndrome, so the study results do not necessarily apply to all patients with chronic coronary syndromes. Moreover, only patients aged ≤ 80 years were included in the study; therefore, the results cannot be applied to older patients. It should be taken into account that patients may have taken medications irregularly; some studies indicate that up to 40% of patients who report that they regularly use the prescribed pharmacotherapy, it is not confirmed by objective tests [33–36]. Also, the study did not allow assessment of the impact of secondary prevention of CAD on the risk of cardiovascular complications. However, it is worth emphasizing that the study was based on direct contact with the patients and not only on a review of medical records. Furthermore, it was carried out using standardized methods and unified questionnaires, which allowed for a reliable assessment of the control of risk factors in patients, their lifestyle, and any secondary prevention management that has been enabled for them.

CONCLUSION

The data obtained in this multicenter study show the opportunity of further reduction of cardiovascular risk in Polish patients treated for CAD. This gives rise to the conclusion that a revision of on-going and more intensive endorsement of cardiovascular prevention programs is advisable.

Article information

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Cardiac pacemakers and implantable cardioverter-defibrillators without cardiac resynchronization capability: Impact on cardiac function in a median follow-up of 1-year

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ABSTRACT

Background: Current reports indicate that the presence of a lead in the right ventricle (RV) and chronic cardiac pacing may be associated with adverse clinical outcomes during a long-term follow-up.

Aims: The aim of the study was to evaluate outcomes of cardiac implantable electronic device (CIED) placement on the development of pacing-induced cardiomyopathy (PICM) as well as other unfavorable changes in cardiac structure and function.

Material and methods: In a single-center study we included patients after first-time implantation of a CIED without cardiac resynchronization therapy capability, with available electronic documentation of transthoracic echocardiography results up to 1 year before and at least 1 month after CIED placement. A detailed medical documentation review was performed.

Results: Among 94 patients with mean age 70 (range 65–79) years, including 29 (30.9%) women, after a median 12-month follow-up, PICM was observed in 11% of patients (all with atrial fibrillation and RV pacing percentage $\geq 20\%$), while mitral and tricuspid regurgitation progressed in 31.9% and 25.5% of patients, respectively. Older age and lower left ventricular ejection fraction (LVEF) before CIED implantation (hazard ratio [HR], 1.14; 95% confidence interval [CI], 1.02–1.29; $P = 0.03$ and HR, 0.93; 95% CI, 0.87–0.99; $P = 0.02$, respectively) were independently associated with development of PICM. There was no association of RV lead pacing site (RV outflow tract, septum, and apex) with this outcome.

Conclusions: Patients with atrial fibrillation, older age, expected substantial RV pacing, and decreased LVEF before CIED implantation should be considered for other approaches of pacing, rather than utilizing non-apical right ventricular lead placement to prevent PICM.

Key words: implantable cardioverter-defibrillator, left ventricular ejection fraction, mitral regurgitation, pacemaker, pacing-induced cardiomyopathy, tricuspid regurgitation

INTRODUCTION

Cardiac pacemakers (PMs) and implantable cardioverter-defibrillators (ICDs) are included in the list of cardiac implantable electronic devices (CIEDs) and play an important role in the rapidly developing modern cardiology. PMs are used to treat severe bradyarrhythmic disorders in symptomatic sick sinus syn-

drome, as well as in severe or symptomatic atrioventricular conduction disorders [1]. ICDs are commonly used in the prevention of sudden cardiac death due to life-threatening ventricular arrhythmias. These devices are utilized in primary prevention in patients with persistently reduced left ventricular ejection fraction (LVEF) (usually $\leq 35\%$) despite the

WHAT'S NEW?

The incidence of pacing-induced cardiomyopathy (PICM) and detailed factors related to the association of cardiac implantable electronic devices (CIEDs) with cardiac dysfunction remain to be clarified utilizing real-world patient data within a relatively short-term follow-up. This study shows that PICM is observed in 11% of patients during a median follow-up of 1-year after placement of a CIED with an endocardial lead in the right ventricle (RV), but without cardiac resynchronization therapy capability. All patients with PICM had atrial fibrillation and RV pacing percentage $\geq 20\%$. A lower left ventricular ejection fraction (but not RV lead pacing site) and increased age were independently related to the development of this adverse clinical outcome. Importantly, after the procedure, mitral and tricuspid regurgitation progressed in 31.9% and 25.5% of patients, respectively. These patients may benefit from alternative CIED modalities, such as conduction system pacing or cardiac resynchronization therapy as early as one year after CIED placement.

use of optimal pharmacological treatment for a period of at least 3 months. ICDs are also placed in the secondary prevention in patients after sudden cardiac arrest due to hemodynamically unstable ventricular tachycardia or ventricular fibrillation, in the absence of reversible causes of these arrhythmias [1, 2].

Classic CIEDs consist of a lead or leads that are implanted through the venous system into the cardiac cavities. Depending on the clinical circumstances, the distal part of the lead (typical pacing site) is placed in the right ventricle (RV), right atrium, and/or the coronary sinus, usually as part of cardiac resynchronization therapy (CRT). RV leads pass through the tricuspid valve, potentially causing or worsening tricuspid regurgitation (TR) or mitral valve insufficiency (MR) [3]. The tip of the transvalvular lead may be located in various pacing sites of the RV, i.e., the right ventricular apex (RVA), right ventricular septum (RVS), or right ventricular outflow tract (RVOT) considered as affecting cardiovascular outcomes.

There is increased effort to find novel markers, pathogenic pathways, to improve risk stratification, and treatment strategies in cardiovascular medicine [4–6]. According to the available data, the presence of leads in the heart and chronic RV pacing (RVP) affect the function and structural remodeling of the heart [7–9]. Several studies published so far have shown that a high percentage of RVP is associated with a reduction in LVEF in long-term follow-up [10].

Data on the relatively short-term impact of CIED, especially on real-world elderly patients' data with various RV leads placement sites is lacking, but it could enhance clinical counselling and decision-making. Therefore, the aim of the study was to assess the characteristics of patients after placement of a CIED without CRT capability and the incidence of pacing-induced cardiomyopathy (PICM), potential worsening of atrioventricular valvular regurgitation, and other cardiac structural and functional changes.

METHODS

Study population

In this retrospective study we included patients from a single cardiac center, undergoing first-time classical

implantation of a single- or dual-chamber CIED with transvenous RV lead, but without CRT capability. CIEDs included cardiac PMs and ICDs. We identified patients who had the CIED implantation procedure performed between May 5, 2016 and August 12, 2020. Baseline patient clinical and demographic data and medication history were obtained from a structured medical records review.

Included patients had the results of transthoracic echocardiography up to 1 year before and at least 1 month after CIED implantation in the available electronic medical documentation. The exclusion criteria were as follows: myocardial infarction, cardiac surgery, ablation, myocarditis or endocarditis, electrode replacement or device upgrade, and the initiation of significant pharmacological therapy during the follow-up period. Patients with hypertrophic, peripartum, and alcohol-induced cardiomyopathy were also excluded from the study. Consecutive patients who met the inclusion criteria and did not meet the exclusion criteria were included in the study.

Echocardiography

Patients underwent standard transthoracic echocardiography using the Doppler technique both before and after the CIED implantation. The study included assessment of LVEF, left ventricular end-diastolic dimension (LVEDD), left ventricular end systolic diameter, interventricular septum diameter, posterior wall thickness, tricuspid annular plane systolic excursion (TAPSE), RV diameter, measures of the RA and left atrium, and the presence of TR or MR [11].

Pacing-induced cardiomyopathy definition

Patients with dual-chamber devices were generally programmed with minimum basic rate of 60/min. Programming of the basic rate among patients with single (right ventricular)-chamber devices varied from 40 to 70/min. To define PICM we used two different criteria of drop in LVEF: (a) LVEF $\leq 40\%$ if baseline LVEF was $\geq 50\%$, or absolute reduction in LVEF $\geq 5\%$ if baseline LVEF was $< 50\%$; and (b) absolute reduction in LVEF $\geq 10\%$ regardless of baseline LVEF [12, 13]. PICM was diagnosed if at least one of these criteria of drop in LVEF was fulfilled and the RVP percentage was $\geq 20\%$ [12, 13].

Follow-up

The follow-up time was defined as time from CIED implantation to the transthoracic echocardiography after the procedure and encompassed the evaluation of drop in LVEF and PICM development (endpoints).

Statistical analysis

Continuous variables are depicted as means (standard deviations) or medians and interquartile ranges, depending on data distribution. Pearson χ^2 test or the Fisher exact test were used to evaluate categorical variables, which are presented as numbers and percentages. Student's t-test, the Mann–Whitney U test, and the Kruskal–Wallis test were used to assess differences between the study groups in terms of continuous variables, as appropriate. Related-samples Wilcoxon signed rank test and two-sided paired samples t test were used to compare continuous variables before and after CIED placement or between endogenous and paced QRS complex durations, depending on the normality of the tested variables. The McNemar test was used to compare the numbers of patients with defined stage of MR or TR before and after placement of CIED. To determine the optimal cut-off value of RVP percentage in the prediction of PICM, analysis of the receiver operating characteristics curve was performed and Youden's index was calculated. Multivariable Cox regression analysis was utilized to find independent variables affecting the development of PICM. We included preprocedural variables that were associated with PICM in comparative analyses. However, because all patients with AF and RVP $\geq 20\%$ had PICM, due to statistical reasons, modified variables were included into the multivariable model. In addition to these variables, we also incorporated the LVEF measured prior to the implantation of the CIED because this variable is well-established in the literature as a significant risk factor for the development of PICM. The Kaplan–Meier curves and the log-rank test were used to assess the event-free survival according to different RV lead pacing sites (RVOT, RVS, and RVA) in PICM patients and patients with a drop in LVEF. A *P*-value of <0.05 was considered statistically significant. Data were analyzed using SPSS statistical package, version 26 (IBM Corp., Armonk, NY, US).

RESULTS

The study group consisted of 94 patients aged 70 (65–79) years, and women constituted 30.9% ($n = 29$) of patients. Single-chamber and dual-chamber PMs were implanted in 31.9% and 28.7% of patients, while single-chamber and dual-chamber ICDs were placed in 14.9% and 24.5% of patients, respectively.

The clinical characteristics of the study patient group are presented in [Table 1](#). Most patients had arterial hypertension, dyslipidemia, and a history of atrial fibrillation (AF). Also, more than half of the patients took drugs from the group of beta-blockers, angiotensin converting

enzyme inhibitors, statins, diuretics, and aldosterone receptor blockers.

The tip of the ventricular lead was most often (62.8%) placed in the RVOT, while in 20.2% of cases, the ventricular lead was located in the RVA. The least frequent RVP site was the area of the RVS (17.0%). In our study 52% of the patients had LVEF $<50\%$, while 34% of the patients had LVEF $<40\%$.

The median time of follow-up from implantation to control echocardiography was 11.7 (5.9–20.0) months. During this time, the LVEF reduced (48.0 [31.5–60.0] vs. 45.0 [30.0–55.0]; $P = 0.021$) and the LVEDD increased (55.2 [9.6] vs. 56.7 [10.7]; $P = 0.019$) in the whole study group, while the incidence of PICM was 11%. On the other hand, TAPSE and RV diameter in a 4-chamber view did not differ after CIED placement ($P = 0.24$ and $P = 0.99$, respectively), and only a trend was observed for a change in RV diameter in parasternal long-axis view ($P = 0.07$). Moderate or severe TR was observed in 38 patients (40.4%) before CIED implantation, but in 42 patients (44.7%) after CIED implantation. In 25.5% of patients, we observed progression of TR by a minimum of one stage after CIED placement.

The median RVP percentage for all patients was 36.5% (range 1.5%–99.0%). As expected, patients with PICM had a greater RVP percentage when compared to patients without PICM (96.2% [40.0–100.0] vs. 23.5% [1.0–97.8]%; $P = 0.02$; [Table 2](#)). Receiver operating curve analysis revealed that the cut-off value for PICM development in terms of RVP percentage was 20.0% (Youden's Index = 0.488), with an area under the curve of 0.733 ([Figure 1](#)). As expected, we have shown a difference between endogenous and paced QRS complex duration (100.0 [90.0–120.0] ms vs. 160.0 [150.0–180.0] ms; $P < 0.001$).

Characteristics of the patients with and without PICM

Patients with PICM were older ($P = 0.01$) and more frequently had AF before CIED implantation when compared to patients without PICM (100% vs. 53.6%; $P = 0.005$; [Table 1](#)). We observed that 80% of PICM patients were ≥ 75 years old, while only 35.7% of patients without PICM were ≥ 75 years old ($P = 0.01$). Patients with PMs did not differ significantly from patients with ICDs regarding the presence of PICM (12.3% vs. 8.1%; $P = 0.74$). As expected, there was no association between non-cardiovascular comorbidities, including chronic kidney disease, between patients with and without PICM ([Table 1](#)).

Difference in echocardiographic parameters regarding patients with and without PICM

The change in LVEF during follow-up in patients with PICM, when compared to patients without PICM, was -5.5 (-10.0 to -0.75)% vs. 3.0 (-0.75 to 6.75), respectively; $P = 0.01$. Apart from that, there was no other difference regarding echocardiographic parameters when compared patients with and without PICM ([Table 3](#)). Similarly, we

Table 1. Baseline characteristics of the study patients with and without pacing-induced cardiomyopathy

Variables	Whole group (n = 94)	No-PICM (n = 84)	PICM (n = 10)	P-value
Demographic characteristics				
Age, years	70.0 (65.0–79.0)	69.3 (63.5–78.5)	77.8 (75.3–81.9)	0.01
Age ≥65 years, n (%)	69 (73.4)	59 (7.0)	10 (100.0)	0.06 ^a
Age ≥75 years, n (%)	38 (40.4)	30 (35.7)	8 (80.0)	0.01 ^a
Female sex, n (%)	29 (30.9)	27 (32.1)	2 (20.0)	0.72 ^a
Weight, kg	81.2 (72.5–94.8)	81.7 (73.9–95.0)	75.5 (58.0–86.3)	0.25
Height, m	1.68 (1.63–1.76)	1.68 (1.62–1.76)	1.64 (1.64–1.76)	0.95
Body mass index, kg/m ²	28.1 (25.5–33.2)	28.7 (25.5–33.3)	26.1 (21.6–27.8)	0.17
Cardiovascular diseases and risk factors, n (%)				
Atrial fibrillation	55 (58.5)	45 (53.6)	10 (100.0)	0.005 ^a
Type of atrial fibrillation				
Paroxysmal	5 (5.3)	4 (4.8)	1 (10.0)	0.04
Persistent	20 (21.3)	17 (20.2)	3 (30.0)	
Permanent	30 (31.9)	25 (29.8)	5 (50.0)	
Heart failure	50 (53.2)	45 (53.6)	5 (50.0)	1 ^a
Hypertension	75 (80.0)	66 (78.6)	9 (90)	0.68 ^a
Advanced atrioventricular block at the time of implantation	31 (33.0)	25 (29.8)	6 (60.0)	0.06
Coronary heart disease	53 (56.4)	47 (56.0)	6 (60.0)	1 ^a
Myocardial infarction	40 (42.6)	37 (44.0)	3 (30.0)	0.51 ^a
Peripheral arterial disease	52 (55.3)	47 (56.0)	5 (50.0)	0.75 ^a
Stroke/transient ischemic attack	12 (12.8)	12 (14.3)	1 (10.0)	0.36 ^a
Percutaneous coronary intervention	36 (38.3)	31 (36.9)	5 (50.0)	0.5 ^a
Coronary artery bypass graft surgery	18 (19.1)	16 (19.0)	2 (20.0)	1 ^a
Diabetes mellitus	31 (33.0)	28 (33.3)	3 (30.0)	1 ^a
Dyslipidemia	66 (70.2)	59 (70.0)	7 (70.0)	1 ^a
Hyperthyroidism	5 (5.3)	4 (4.8)	1 (10.0)	0.44 ^a
Hypothyroidism	12 (12.8)	12 (14.3)	0 (0.0)	0.35 ^a
Chronic kidney disease	17 (18.1)	15 (17.9)	2 (20.0)	1 ^a
Medications, n (%)				
Beta-blocker	75 (79.8)	66 (78.6)	9 (90.0)	0.68 ^a
Acetylsalicylic acid	40 (42.6)	38 (45.2)	2 (20.0)	0.18 ^a
ACE-I	63 (67.0)	54 (64.3)	9 (90.0)	0.16 ^a
ARB	14 (14.9)	14 (16.7)	0 (0.0)	0.35 ^a
CCB	18 (19.1)	15 (17.9)	3 (30.0)	0.40 ^a
Diuretic	71 (75.5)	63 (75.0)	8 (80.0)	1 ^a
Digoxin	9 (9.6)	8 (9.5)	1 (10.0)	1 ^a
Statin	71 (75.5)	62 (73.8)	9 (90.0)	0.44 ^a
Aldosterone receptor blocker	56 (59.6)	48 (57.1)	8 (80.0)	0.19 ^a
Propafenone	10 (10.6)	10 (11.9)	0 (0.0)	0.59 ^a
Ivabradine	2 (2.1)	2 (2.4)	0 (0.0)	1 ^a
Amiodarone	7 (7.4)	6 (7.1)	1 (10.0)	0.56 ^a

Data are presented as medians (interquartile ranges) or numbers (percentages)

^aFisher's exact test was used for assessing differences among categorical parameters

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor antagonist; CCB, calcium channel blocker; ICD, implantable cardioverter-defibrillator; PICM, pacing-induced cardiomyopathy; PM, pacemaker; RVA, right ventricular apex; RVOT, right ventricular outflow tract; RVS, right ventricular septum

did not note significant differences regarding the number of patients with a defined stage of mitral and tricuspid regurgitation before and after implantation of a CIED, but a trend towards increased severity of MR was observed (Table 4). The induction or progression of MR or TR after CIED implantation (minimum of one stage) was observed in 31.9% and 25.5% of patients, respectively. Patients with PMs had greater occurrence of TR (54.4% vs. 29.7%; $P = 0.02$) but not MR (47.4% vs. 43.8%; $P = 0.30$) compared to patients with ICDs.

Survival analyses and Cox regression models predicting the occurrence of PICM and drop in LVEF

In survival analysis, we considered not only PICM, but also the occurrence of drop in LVEF. There was no difference in event-free survival according to different RV lead pacing sites (RVOT, RVS, and RVA) both in patients with PICM (Figure 2A) and in patients with a drop in LVEF (Figure 2B).

Multivariable Cox regression analysis indicated that increased risk of developing PICM was observed, inde-

Table 2. Differences in laboratory, electrocardiographic, and cardiac implantable electronic device parameters regarding patients with and without pacing-induced cardiomyopathy

Variables	Whole group (n = 94)	No-PICM (n = 84)	PICM (n = 10)	P-value
Laboratory parameters				
Creatinine, $\mu\text{mol/l}$	95.0 (81.8–108.0)	92.0 (80.0–107.5)	105.5 (90.8–109.5)	0.22
Estimated glomerular filtration rate, ml/min/1.73 m^2	66.7 (20.3)	67.4 (20.9)	60.8 (13.9)	0.34
N-terminal pro-B-type natriuretic peptide, pg/ml	1480.5 (436.0–2793.5)	1495.0 (456.8–3284.5)	822.5 (44.5–1602.8)	0.18
Electrocardiographic parameters				
Native QRS, ms	100.0 (90.0–120.0)	100 (90–120)	105 (100–120)	0.92
Paced QRS, ms	160.0 (150.0–180.0)	160 (150–180)	160 (140–160)	0.28
CIED-related data				
Rate response, n (%)	15 (16.0)	15 (17.9)	0 (0.0)	0.36 ^a
Basic rate, bpm	60.0 (60.0–70.0)	60.0 (60.0–70.0)	65.0 (60.0–70.0)	0.29
Atrial pacing, %	33.7 (8.0–56.8)	20.0 (8.0–60.5)	32.0 (0.0–32.0)	0.77
Right ventricular pacing, %	36.5 (1.5–99.0)	23.5 (1.0–97.8)	96.2 (40.0–100.0)	0.02
$\geq 20\%$ of right ventricular pacing, n (%)	53 (56.4%)	43 (51.2%)	10 (100.0%)	0.004 ^a
Cardiac pacemaker, n (%)	57 (60.6)	50 (59.5)	7 (70.0)	0.74 ^a
Implantable cardioverter-defibrillator, n (%)	37 (39.4)	34 (40.5)	3 (30.0)	
Ventricular lead in RVOT, n (%)	59 (62.8)	53 (63.1)	6 (60.0)	0.97 ^a
Ventricular lead in RVA, n (%)	19 (20.2)	17 (20.2)	2 (20.0)	
Ventricular lead in RVS, n (%)	16 (17.0)	14 (16.7)	2 (20.0)	
Ventricular lead in apical position, n (%)	19 (20.2)	17 (20.2)	2 (20.0)	1.0 ^a
Follow-up time, months	11.7 (5.9–20.0)	11.2 (5.7–21.2)	16.0 (9.3–24.3)	0.23

Data are presented as medians (interquartile ranges) or means (standard deviations) or numbers (percentages)

^aFisher's exact test was used for assessing differences among categorical parameters.

Abbreviations: CIED, cardiac implantable electronic device; other — see Table 1

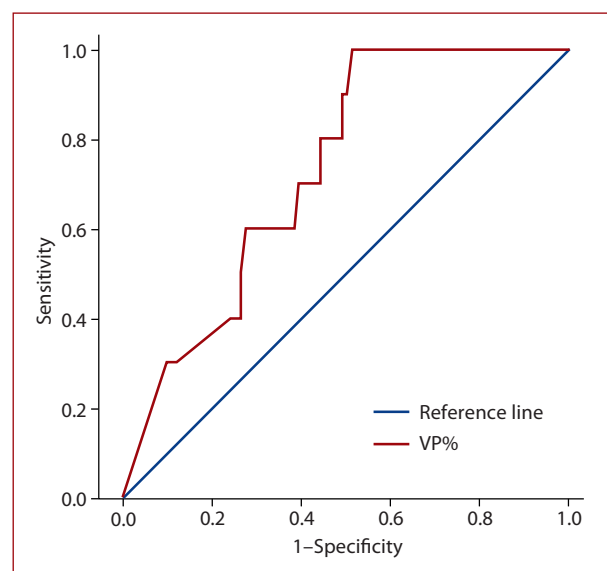


Figure 1. Receiver operating curve for ventricular pacing percentage in prediction of pacing-induced cardiomyopathy
Cut-off value = 20.0%, Youden's Index = 0.488

Abbreviation: VP %, right ventricular pacing percentage

pendently of RVP percentage and permanent or persistent AF, in older patients and subjects with lower LVEF before CIED implantation (HR, 1.14; 95% CI, 1.02–1.29; $P = 0.03$ and HR, 0.93; 95% CI, 0.87–0.99; $P = 0.02$, respectively; Table 5).

DISCUSSION

Interest in using markers and risk scores, as well as evaluating their clinical applicability in cardiovascular medicine, is growing [14–16]. Accurate risk of complications or adverse

outcome assessment is essential, especially in relation to common and life-saving cardiac procedures like CIED placement [17]. Some of these are associated with lead implantation, among others.

We have shown that as early as approximately one year after CIED implantation without CRT, with a ventricular lead located predominantly in the RVOT, a significant decrease in LVEF can be observed. A decrease in LVEF after implantation of CIED has already been described in a previous study on 43 patients during apical pacing (the only pacing site) during a median follow-up of 18 months [18]. Kachboura et al. [18] suggested that patients having a lead fixed into RV myocardium suffer from LV function deterioration, mainly due to interventricular mechanoelectrical dyssynchrony. Our study, evaluating different RVP sites and patients who underwent ICD placement, revealing a decrease in LVEF along with an increase in LVEDD and prolongation of QRS during RVP after CIED placement, is consistent with their results.

The LVEDD enlargement and increased ventricular dyssynchrony described in our research was also noticed by Xin et al. [19] on 61 patients who underwent replacement of dual-chamber PM and had third-degree atrioventricular block. Their results revealed that the mean LVEDD and QRS duration increased significantly in a 112.5-month follow-up compared with a control group (49.2 [5.9] mm vs. 46.4 [3.8] mm and 156.2 [29.8] ms vs. 97.1 [15.7] ms, respectively) [19]. These observations are similar to ours and underline the problem of left ventricular remodeling and dyssynchrony in patients after RV lead implantation and RVP. Interestingly, our results indicate no influ-

Table 3. Difference in echocardiographic parameters regarding patients with and without pacing-induced cardiomyopathy

Echocardiographic parameters — baseline	Whole group (n = 94)	No-PICM (n = 84)	PICM (n = 10)	P-value
LVEF, %	48.0 (31.5–60.0)	47.5 (30.0–60.0)	49.0 (34.3–55.3)	0.90
LVEDD, mm	55.2 (9.6)	55.6 (9.5)	52.2 (10.8)	0.30
LVESD, mm	40.0 (33.3–45.0)	40.0 (34.0–45.8)	40.5 (21.3–43.8)	0.46
IVS diastolic, mm	11.9 (3.1)	11.8 (3.2)	12.7 (2.2)	0.45
PWT diastolic, mm	11.0 (10.0–12.0)	11.0 (10.0–12.0)	11.0 (10.0–13.0)	0.43
TAPSE, mm	20.0 (17.0–22.5)	19.0 (16.0–23.0)	20.0 (20.0–22.0)	0.47
RV diameter in PLAX, mm	32.5 (27.0–36.0)	33.0 (27.0–37.0)	28.0 (26.5–33.5)	0.31
RV diameter in 4-chamber view, mm	40.0 (38.0–46.0)	40.0 (38.0–46.0)	39.5 (35.0–46.3)	0.69
RA area, cm ²	21.0 (18.0–26.0)	22.0 (17.0–26.0)	20.0 (19.0–23.5)	0.82
LA area, cm ²	27.7 (6.6)	27.9 (6.8)	26.1 (4.0)	0.45
Echocardiographic parameters — follow up	Whole group (n = 94)	No-PICM (n = 84)	PICM (n = 10)	P-value
LVEF, %	45.0 (30.0–55.0)	45.0 (30.0–55.0)	40.0 (37.3–61.3)	0.23
LVEDD, mm	56.7 (10.7)	56.8 (10.7)	55.5 (11.6)	0.72
LVESD, mm	43.0 (12.0)	43.3 (11.9)	40.7 (12.5)	0.52
IVS diastolic, mm	12.0 (9.0–13.9)	11.0 (9.0–14.0)	12.0 (10.0–12.0)	0.96
PWT diastolic, mm	10.0 (9.0–12.0)	10.0 (9.0–12.0)	11.5 (9.8–12.3)	0.20
TAPSE, mm	18.0 (16.0–22.3)	18.0 (16.0–21.3)	20.5 (15.3–25.8)	0.42
RV diameter in PLAX, mm	32.0 (28.0–38.0)	32.0 (28.5–38.5)	30.0 (28.0–35.5)	0.69
RV diameter in 4-chamber view, mm	40.0 (36.5–45.5)	40.0 (36.0–45.0)	45.0 (42.0–45.0)	0.23
RA area, cm ²	22.0 (18.0–28.0)	22.0 (18.0–28.5)	23.0 (18.1–23.7)	0.82
LA area, cm ²	27.0 (23.0–32.8)	27.0 (23.0–33.0)	26.0 (23.0–27.0)	0.43
EF difference, %	2.5 (–3.5 to 6.3)	3.0 (–0.75 to 6.75)	–5.5 (–10.0 to –0.75)	0.01

Data are presented as medians (interquartile ranges) or means (standard deviations).

Abbreviations: IVS, interventricular septum; LA, left atrium; LV, left ventricle; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; PLAX, parasternal long-axis view; PWT, posterior wall thickness; RA – right atrium; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; other — see Table 1

Table 4. Number of patients with a defined stage of mitral (MR) and tricuspid regurgitation (TR) before and after placement of cardiac implantable electronic devices (CIED)

MR stage before CIED implantation		MR stage after CIED implantation		P-value
Absence/mild	Moderate/severe	Absence/mild	Moderate/severe	
56 (59.5%)	38 (40.4%)	46 (48.9%)	48 (51.1%)	0.09
TR stage before CIED implantation		TR stage after CIED implantation		P-value
Absence/mild	Moderate/severe	Absence/mild	Moderate/severe	
56 (59.6%)	38 (40.4%)	52 (55.3%)	42 (44.7%)	0.5

Data are presented as n — number (percentage)

ence of RV leads and/or RVP on RV function and structure, as shown by no difference in TAPSE or RV diameters.

We observed progression of TR minimum of one stage after CIED implantation in one-fourth of the patients. These data seem consistent with Tatum et al. [20], who performed a meta-analysis concerning TR development in patients after CIED insertion. The percentage of patients with 0/1 grade of TR decreased significantly, whereas the percentage of patients with 2/3/4 grade TR increased significantly. However, our results on TR progression were not statistically significant, probably due to a relatively low number of patients. Importantly, Chodór-Rozwadowska et al. [21], in a group of patients undergoing CIED placement (including CRT), demonstrated that severe and massive TR occurred more often in patients with the non-RVA pacing site of the lead. There are several possible causes of TR worsening after CIED placement. First, interference between the RV lead and the tricuspid valve may result in disturbance

of the valve leaflet coaptation [3]. Other potential mechanisms range from leaflet perforation or entanglement to more prevalent pathologies like leaflet adherence or impingement [3]. Sadreddini et al. [22] postulated that electrical and, therefore, mechanical dyssynchrony derived from a non-physiological route of myocardial activation can lead to MR, and increased pressure in pulmonary capillaries and in RV, thereby triggering TR. They performed a study in which patients with CRT suffered less often from TR compared to patients without CRT. Another study conducted by Riesenhuber et al. [23] indicated MR as a risk factor of worsening TR in CIED patients. Regardless of the possible culprit of new-onset TR or TR worsening in patients after CIED implantation, it should be taken into consideration in all patients with symptoms of RV dysfunction who have undergone PM or ICD implantation. Importantly, as shown in previous studies, it is thought that certain changes in the tricuspid valve are irreversible because there may be no

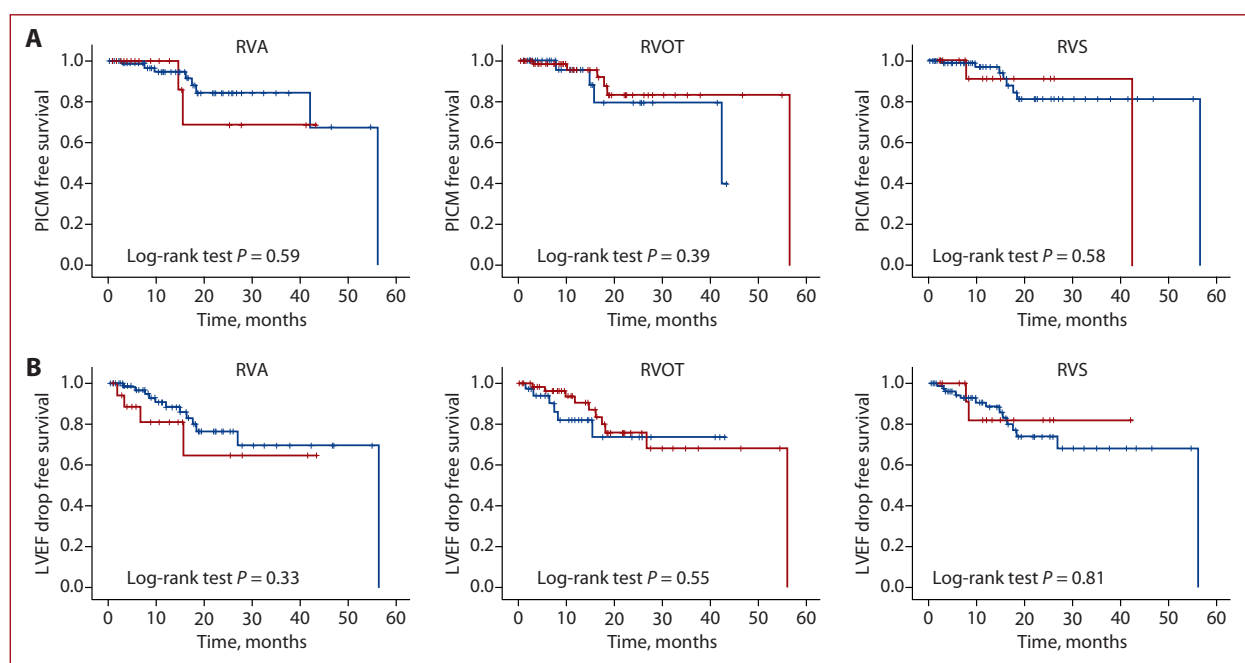


Figure 2. Kaplan–Meier curves showing the overall event-free survival probability according to different right ventricular lead pacing sites (right ventricular outflow tract, septum, and apex) in patients who developed pacing-induced cardiomyopathy (A) or drop in left ventricular ejection fraction (B)

Red color indicates patients with PICM (A) or drop in LVEF (B), while blue color indicates patients without these endpoints

Abbreviations: PICM, pacing-induced cardiomyopathy; RVA, right ventricular apex; RVOT, right ventricular outflow tract; RVS, right ventricular septum

Table 5. Multivariable Cox regression analysis model predicting occurrence of pacing-induced cardiomyopathy

Factors	Hazard ratio	95% confidence interval	P-value
Age	1.14	1.02–1.29	0.03
LVEF before CIED implantation	0.93	0.87–0.99	0.02
Percentage of right ventricular pacing	1.01	0.99–1.03	0.55
AF (permanent or persistent)	0.56	0.11–2.86	0.48

Abbreviations: AF, atrial fibrillation; other — see Tables 2 and 3

significant improvement in the degree of TR after removal of the RV lead [24]. Thus, careful RV lead introduction through the tricuspid valve should always be performed.

In our study all patients with AF and RVP $\geq 20\%$ had PICM, and therefore these variables are valuable predictors of PICM, but from a statistical and methodological point of view they could not be included in the final multivariable model. This highlights their importance in PICM development. To reduce the severity of cardiomyopathy we cannot only optimize pharmacotherapy, but especially in the case of PICM we should strongly consider qualifying patients for the most adequate type of device and lead placement, as well as to optimize the CIED programming to avoid unnecessary RVP, thus avoiding PICM. The use of new, more physiological cardiac pacing techniques, such as CRT, His-bundle, or left bundle branch area pacing, may prevent the negative consequences of chronic RVP [4, 25, 26]. However, performing these procedures should be considered in light of longer procedural duration and potentially increased risk of CIED infection [17]. To prevent collision of the RV lead with the tricuspid valve, in some cases, we can consider a leadless PM, which could be espe-

cially valuable for patients with lead-related complications in conventional transvenous CIED [27, 28]. In the case of indications for ICD implantation, the use of a subcutaneous ICD, which does not involve an intracardiac lead (but without the capability of permanent cardiac pacing), may also prevent some unfavorable changes or adverse outcomes [29].

Limitations of the study

It should be noted that the study was conducted in one clinical center and utilized strict exclusion criteria (which are the strengths of our study, eliminating potential bias); thus, the number of patients included and the number of endpoints are limited. The exclusion criterion of patients who underwent upgrade to CRT could lead to a decrease in PICM incidence in our study. However, occurrence of PICM requiring an upgrade to CRT in a median follow-up of 1-year seems to be rare and is probably reduced by appropriate qualification of high-risk patients to *de novo* CRT placement (e.g., patients with heart failure with reduced ejection fraction, who require ventricular pacing due to high-degree atrioventricular block [1]). The retrospective

nature of the study with a lack of full echocardiographic study, present in the electronic medical documentation of screened patients, is another limitation. Moreover, the time of follow-up and postprocedural echocardiography was different. However, we reduced this limitation by performing multivariable Cox regression analysis. Finally, we did not test the potential association of novel peripheral blood biomarkers on adverse clinical outcomes [16], which could be tested in another prospective study in the future.

CONCLUSIONS

Patients with AF, significant RVP percentage, advanced age, and lower LVEF are at increased risk of PICM development. After CIED placement, the MR and TR may progress in about one-third and one-fourth of patients, respectively, regardless of the presence of PICM. Patients at high risk of PICM development or valvular regurgitation onset or exacerbation should be considered for alternative CIED modalities including conduction system pacing, CRT, leadless PM, or subcutaneous ICDs.

Article information

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Conflict of interest: RK participated in educational activity, which was supported by GE. PTM participated in educational activities, which were supported by CIED manufacturers as well as Polpharma and received speech honoraria from Boehringer Ingelheim. Other authors declared no conflict of interest.

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Left and right atrial echocardiographic parameters and outcomes in patients with atrial fibrillation

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ABSTRACT

Background: This study evaluates the association between left atrial and right atrial (LA, RA) parameters and a composite endpoint (CEP) of all-cause death, thromboembolism, acute coronary syndrome, and heart failure hospitalization in atrial fibrillation (AF) patients.

Material and methods: Patients were prospectively enrolled. At baseline, the following echocardiogram parameters were measured: LA and RA antero-posterior diameter index (iLAAPD, iRAAPD), LA and RA volume index (LAVi, RAVi), LA and RA sphericity index (LASi, RASi), LA and RA emptying fraction.

Results: A total of 489 patients (61.3% males) with a median age of 75 (66–80) years and a median CHA₂DS₂VASc score of 3 (2–5) were enrolled (92.2% receiving anticoagulation). Permanent AF was present in 40.5% of the total cohort. After a median follow-up of 1114 (392–1384) days, 129 patients (26.3%) reached the CEP. The highest sensitivity for CEP was for LA emptying fraction <28% and iRAAPD >24 mm/m² (72% and 73%, respectively) while the best negative predictive values were for iLAAPD and LAVi (both 81%). Right atrial parameters were not associated with CEP. Discrimination analysis using net reclassification improvement (NRI) showed that iLAAPD and LAVi significantly improved patient reclassification compared to a null model without atrial parameters (iLAAPD NRI 0.30; *P* = 0.005; LAVi NRI 0.32; *P* = 0.002). Multivariate Cox regression analysis found that LA dimensions, volume, and function were associated with a higher risk of adverse outcomes and significantly improved risk prediction for the CEP.

Conclusions: LAVi and iLAAPD enhance discrimination and risk prediction for adverse outcomes in AF patients.

Key words: atrial cardiomyopathy, atrial fibrillation, atrial remodeling, echocardiography, outcome

INTRODUCTION

Atrial fibrillation (AF) poses a significant challenge to healthcare systems, especially in Western countries, due to the rising number of affected patients, associated adverse outcomes, and costs of care [1]. Research on AF pathophysiology has focused on the remodeling process of the left and right atria. AF and atrial remodeling share a bidirectional link, each being both a cause and effect of the other [2, 3]. In clinical practice, structural remodeling is commonly assessed by measuring atrial dimensions and function. Various imaging techniques, including echocardiog-

raphy and cardiac magnetic resonance (MR), are used to evaluate atrial remodeling and underlying atrial cardiomyopathy [4]. There is no consensus on the optimal parameter for assessing atrial remodeling. Left atrial (LA) volume indexed by body surface area (BSA) is the most commonly used measure in daily clinical practice [5]. LA enlargement is a known factor associated with progression to permanent AF, affecting up to 22% of patients with first-diagnosed or paroxysmal AF, as recently reported in a large European cohort. Adding moderate-to-severe enlargement of the left atrium to the HATCH score (hypertension,

WHAT'S NEW?

To our knowledge, this is one of the first studies to comprehensively evaluate the correlation between a broad set of both left atrial and right atrial echocardiographic parameters and outcomes (defined as a composite of all-cause death, stroke or systemic embolism, any acute coronary syndrome, and hospitalization for new/worsening heart failure) in a real-world cohort of atrial fibrillation patients. We found that atrial echocardiographic parameters, particularly those related to the left atrium, were associated with long-term adverse outcomes, thus highlighting the importance of a comprehensive echocardiographic evaluation in clinical practice, because this assessment may provide valuable insights into the extent of atrial remodeling and underlying atrial cardiomyopathy.

age ≥ 75 years, stroke or transient ischemic attack, chronic obstructive pulmonary disease, and heart failure [HF]) resulted in a significant improvement in predicting the progression to permanent AF compared to the HATCH score alone [6]. In the context of AF ablation, increased left atrial antero-posterior diameter (iLAAPD) indexed by BSA was a predictor of AF recurrence [7, 8]; however, conflicting results remain [9, 10].

Recently, three-dimensional (3D) echocardiography techniques have been introduced. Schaaf et al. reported that patients with paroxysmal AF had greater LA volumes and impaired LA function compared to patients without AF [11]. Moreover, LA strain has been studied as a marker of AF recurrence after catheter ablation [12, 13] and a predictor of new onset of AF in patients with HF with preserved ejection fraction [14] and risk of ischemic stroke [15]. Atrial remodeling can also be evaluated using the left and right atrial sphericity indices (LASI and RASI). In a study analyzing left and right atrial sphericity with MR, LA sphericity was found to be associated with AF pattern, while right atrial (RA) sphericity was correlated with AF recurrences after catheter ablation [16].

In daily practice, advanced echocardiographic and MR methods for assessing anatomical atrial remodeling are not easily available. Therefore, we aimed to compare LA and RA echocardiographic parameters, which can be obtained through a simple echocardiographic assessment, to identify the best predictors of outcome in an unselected cohort of AF patients.

METHODS

The Fibrillazione Atriale in Modena (FAMo) registry is a prospective single-center observational study conducted at the Cardiology Division of the tertiary-care University Hospital in Modena. From March 2016 to December 2021, we enrolled in- and outpatients with AF in our tertiary center. The enrollment criteria included the following: 1) age ≥ 18 years; 2) an electrocardiogram (ECG) (standard 12-lead ECG recording or a single-lead ECG tracing ≥ 30 seconds showing no discernible repeating P waves and irregular RR intervals) documenting an AF episode within 1 year; 3) written and informed consent; and 4) no participation in clinical trials at the time of enrollment. At enrollment, we collected demographic, clinical, laboratory, pharmacotherapy, and echocardiographic data. The

protocol was approved by the local Ethical Committee (approval number: 237/16), and the study was performed according to the European Union Note for Guidance on Good Clinical Practice (CPMP/ECH/135/95) and the Declaration of Helsinki.

Diagnosis and pattern of AF, EHRA score, CHA₂DS₂VASc, and HAS-BLED scores were assessed according to 2020 European Society of Cardiology guidelines [1, 17].

Valvular heart disease was defined as aortic, mitral, tricuspid, or pulmonary valve stenosis or regurgitation graded as at least moderate to severe. Chronic kidney disease (CKD) was defined as Chronic Kidney Disease Epidemiology Collaboration group (CKD-EPI) formula value < 60 ml/min/1.73 m². Anemia was defined by hemoglobin levels < 13 g/dl for males and 12 g/dl for females. Major and clinically relevant non-major bleedings were defined according to International Society of Thrombosis and Hemostasis criteria [18].

For this analysis, we included patients with available information concerning the echocardiographic parameters as detailed below. Therefore, all patients who did not have a complete echocardiographic evaluation, with high-quality echocardiographic images allowing the measurement of atrial parameters included in the present analysis, were excluded.

Echocardiographic parameters

The echocardiographic parameters considered included LA and RA volumes indexed by BSA (LAVi and RAVi), indexed LA and RA antero-posterior end-diastolic diameters (iLAAPD and iRAAPD), LA and RA emptying fraction (LAEF and RAEF), and LASI and RASI.

A complete transthoracic echocardiographic evaluation was performed within 3 months after enrollment, using a commercial ultrasound system (EPIQ CVx, Philips Healthcare) with a X5-1 transducer or an ACUSONSC200 (Siemens Healthineers) machine with a 4V1c transducer. All measurements were obtained over three different cardiac cycles for patients in sinus rhythm and over five beats for patients in AF, with the final value being the mean of these and then indexed by BSA where appropriate. iLAAPD and iRAAPD were both measured in B-mode, in parasternal long-axis and in 4-chamber view, respectively, at the end of ventricular systole (corresponding at the end of the QRS in the electrocardiographic trace), when their dimen-

sion is maximal, using the inner-to-inner edge method. iLAAPD was considered abnormal when greater than 22 mm/m². Using both apical 4- and 2-chambers views, LAVi was measured and calculated with the biplanar Simpson method, while RAVi was measured in the 4-chamber view using single plane disc summation [5]. LAVi was classified as normal up to 34 ml/m², mildly dilated at 35–41 ml/m², moderately dilated at 42–48 ml/m², and severely dilated at values greater than 48 ml/m² [19]. LAEF and RAEF were calculated using the following formula: [(maximum volume – minimum volume)/maximum volume] × 100 [20]. The sphericity indices were calculated as the ratio between the antero-posterior and longitudinal diameter, obtained in the 4-chamber view in B-mode.

In the absence of standardization, RA and LA parameters were grouped according to indexed tertile values, with the highest tertile considered abnormal (LASI, iRAAPD, RAVi, RASI). For LAEF and RAEF, the lowest tertile was considered abnormal. All echocardiograms were performed by expert physicians and reviewed offline by the echo-lab team leader (AB) if needed. A good interrater reliability, with an interclass correlation coefficient of 98.4%–99.1%, was previously proven in our echo-lab for the measurements of atrial parameters [21].

Follow-up protocol and endpoints

Data were collected through the hospital Electronic Healthcare Records (EHRs), during in-office consultations, or by phone calls for patients not attending scheduled visits. Patients were generally followed up after 1 month and every 6 months thereafter, unless clinically relevant events occurred. For this analysis, the date of censoring follow-up was May 2022.

The primary endpoint was defined as a composite endpoint (CEP) of all-cause death, stroke or systemic embolism, any acute coronary syndrome, and hospitalization for new/worsening HF. The secondary exploratory outcomes were the single components of the CEP. The aim of this *post hoc* analysis was to compare LA and RA parameters in predicting the CEP, and the secondary exploratory outcomes.

Statistical analysis

Numerical variables are presented as median and interquartile range, and they were analyzed with the Mann–Whitney test, while categorical variables are shown as count and percentage, and they were compared using the χ^2 test. Kaplan–Meier curves were built to describe the survival-free from the CEP based on different atrial parameters. We dichotomized atrial values according to literature standards (iLAAPD and LAVi) or by comparing the highest tertile values against the lowest and middle tertiles (LASI, iRAAPD, RAVi, RASI), while for LAEF and RAEF the lowest tertile was compared to the middle and highest tertiles. Then we performed multivariable Cox proportional regression analysis, and 2 adjusted models were built: Model 1 (the “null model”) was adjusted for CHA₂DS₂VASc score, AF type,

and oral anticoagulant therapy, while Model 2 included also for chronic obstructive pulmonary disease, smoking history (current or former), and CKD, as well as the same co-variables as in Model 1. The results are reported as adjusted hazard ratio (aHR) with 95% confidence interval (CI). Then we added each atrial parameter to the “null model”, one by one, to determine if it was an independent predictor of the outcome when adjusted for the variables in the “null model”. The models were compared using the likelihood ratio test (LRT), and we checked the proportional hazard assumption using Schoenfeld residuals.

We built receiver-operating characteristic (ROC) curves and calculated the area under the curve (AUC) to evaluate the discrimination power of each atrial parameter vs. the CEP. The AUCs were compared using the DeLong test [22], with the ROC curve analysis of LAVi used as a reference.

In accordance with the method described by Pencina et al. [23], we performed a reclassification analysis, with the “null model” as reference; then we added each atrial parameter in the analyses, in order to quantify the improvement offered by these atrial measurements. We calculated the integrated discrimination improvement (IDI) and the net reclassification improvement (NRI) for each atrial parameter included to assess their predictive ability to reclassify the risk of events.

Finally, we used multivariable restricted cubic splines (RCS) [24] with 3 knots to illustrate the association between each LA and RA parameter as a continuous variable and the hazard of reaching the CEP. Each model was adjusted for CHA₂DS₂VASc score, AF type, and oral anticoagulant therapy.

A two-tailed *P*-value <0.05 was considered significant. Statistical analysis was conducted using R v.4.1.2 and its interface RStudio using predictABEL, survival, survminer, pROC and rms packages.

RESULTS

From the 856 AF patients enrolled, 489 (57.1%) with complete data were included in the present analysis. The flow-chart of the study is shown in Supplementary material, Figure S1. The study cohort comprised 300 males (61.3%) with a median age of 75 (66–80) years, a median CHA₂DS₂VASc score of 3 (2–5) and a median HAS-BLED score of 1 (1–2). Among them, 451 (92.2%) were on anticoagulant therapy. The AF types were as follows: 87 (17.8%) patients had paroxysmal AF, 141 (28.8%) had persistent AF, 198 (40.5%) had permanent AF, and 63 (12.9%) had first-detected AF. The clinical characteristics of the study cohort are detailed in Table 1.

The thresholds for identifying the highest tertile were as follows: LASI >0.71, iRAAPD >24 mm/m², RAVi >32 ml/m², and RASI >0.82. The lowest tertile thresholds for LAEF and RAEF were <28% and <25%, respectively.

After a median follow-up of 1114 (392–1384) days, 84 (17.2%) patients died and 129 (26.4%) reached the CEP. These patients were older, more frequently enrolled in the

Table 1. Patients' characteristics according to the primary composite endpoint

	CEP no (n = 360)	CEP yes (n = 129)	P-value
Age, years, median (IQR)	73 (65–78.2)	78 (73–83)	<0.001
Age ≥75 years, n (%)	156 (43.3)	90 (69.8)	<0.001
Female, n (%)	145 (40.3)	44 (34.1)	0.259
Enrollment site, n (%)			
Outpatient	245 (68.1)	53 (41.4)	<0.001
Ward	115 (31.9)	76 (58.6)	
BMI, kg/m ² , median (IQR)	27 (24.1–29.7)	26.1 (23.4–29.4)	0.184
AF type, n (%)			
Paroxysmal	77 (21.4)	10 (7.8)	<0.001
Persistent	112 (31.1)	29 (22.5)	
Permanent	128 (35.6)	70 (54.3)	
First detected	43 (11.9)	20 (15.5)	
AF on baseline ECG, n (%)	205 (56.9)	105 (81.4)	<0.001
EHRA score, median (IQR)	1 (1–2)	1 (1–2)	0.339
CHA ₂ DS ₂ -VASC, median (IQR)	3 (2–4)	4 (3–5)	<0.001
HASBLED, median (IQR)	1 (1–2)	2 (2–3)	<0.001
Smoker, n (%)	125 (34.8)	60 (46.5)	0.025
Diabetes, n (%)	60 (16.7)	31 (24.0)	0.087
Dyslipidemia, n (%)	176 (48.9)	64 (50.4)	0.851
Hypertension, n (%)	259 (71.9)	99 (76.7)	0.347
CAD, n (%)	82 (22.8)	53 (41.1)	<0.001
Cardiomyopathy, n (%)	19 (5.3)	16 (12.4)	0.013
VHD, n (%)	81 (23.3)	57 (44.9)	<0.001
EF, %, median (IQR)	56 (50–60)	52 (38–60)	<0.001
EF<40%, n (%)	54 (18.4)	48 (42.5)	<0.001
HF (%)			
No	293 (81.4)	57 (44.2)	<0.001
NYHA I	20 (5.6)	16 (12.4)	
NYHA II	31 (8.6)	31 (24.0)	
NYHA III	15 (4.2)	22 (17.1)	
NYHA IV	1 (0.3)	3 (2.3)	
Stroke/SE, n (%)	45 (12.5)	21 (16.3)	0.354
Major or intracranial bleeding, n (%)	11 (3.1)	5 (3.9)	0.872
PAD, n (%)	46 (12.8)	27 (20.9)	0.037
CKD-EPI, ml/min/1.73 m ² , median (IQR)	75.7 (61.3–88.2)	58.8 (43.6–73.8)	<0.001
CKD, n (%)	84 (23.3)	66 (51.2)	<0.001
COPD, n (%)	27 (7.5)	19 (14.7)	0.025
Anemia, n (%)	70 (19.5)	64 (49.6)	<0.001
Liver disease, n (%)	9 (2.5)	9 (7.0)	0.041
Malignancy, n (%)	76 (21.1)	32 (24.8)	0.457
aMMSE, median (IQR)	27.7 (26–29)	26.7 (24.7–28.7)	0.025
CI, n (%)	39 (12.6)	28 (23.5)	0.008
CCI, median (IQR)	1 (0–3)	3 (2–5)	<0.001
AC pattern, n (%)			
None	20 (5.6)	1 (0.8)	0.008
APT only	10 (2.8)	7 (5.4)	
AC only	282 (78.3)	93 (72.1)	
AC+APT	48 (13.3)	28 (21.7)	
Appropriately anticoagulated (%)	328 (91.1)	121 (93.8)	0.442

Abbreviations: AC, anticoagulation; AF, atrial fibrillation; aMMSE, adjusted mini mental state examination; APT, antiplatelet therapy; BMI, body mass index; CAD, coronary artery disease; CCI, Charlson Comorbidity Index; CHA₂DS₂-VASC, congestive heart failure, hypertension, age ≥75 years, diabetes, stroke/transient ischemic attack, vascular disease, age 65–75 years, sex category; CI, cognitive impairment; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; EF, ejection fraction; EHRA, European Heart Rhythm Association; HF, heart failure; IQR, interquartile range; NYHA, New York Heart Association; PAD, peripheral artery disease; SE, systemic embolism; VHD, valvular heart disease

Table 2. Outcomes in patients according to left atrial dilation (no-mild vs. moderate-severe)

	No or mild LA dilation (n = 276)	Moderate to severe LA dilation (n = 213)	P-value
CEP, n (%)	53 (19.2)	76 (35.7)	<0.001
Death, n (%)	33 (12.0)	51 (23.9)	0.001
Thromboembolism, n (%)			
Stroke	3 (1.1)	5 (2.3)	0.575
TIA	1 (0.4)	0 (0)	
Peripheral embolism	1 (0.4)	1 (0.5)	
ACS, n (%)			
UA	6 (2.2)	6 (2.8)	0.722
NSTEMI	9 (3.3)	5 (2.3)	
STEMI	1 (0.4)	0 (0)	
HF hospitalization, n (%)	20 (7.2)	31 (14.6)	0.013
Follow-up days, median (IQR)	1133 (392–1399)	1077 (404–1371)	0.815

Abbreviations: ACS, acute coronary syndrome; CEP, composite endpoint; HF, heart failure; IQR, interquartile range; LA, left atrial; NSTEMI, non-ST elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischemic attack; UA, unstable angina

Table 3. Atrial parameters and the primary composite endpoint

	CEP no (n = 360)	CEP yes (n = 129)	P-value
iLAAPD, mm/m ² , median (IQR)	21 (18–24)	23 (20–26)	<0.001
iLAAPD >22 mm/m ² , n (%)	125 (35)	73 (57)	<0.001
LAVi, ml/m ² , ml/m ² , median (IQR)	37 (27–48)	46 (35–55)	<0.001
LA enlargement, n (%)			
No	161 (45)	29 (23)	<0.001
Mild	62 (17.2)	24 (18.6)	
Moderate	52 (14.4)	20 (15.5)	
Severe	85 (23.6)	56 (43.4)	
LASI, median (IQR)	0.66 (0.60–0.74)	0.67 (0.60–0.75)	0.353
LASI high tertile, n (%)	118 (32.8)	46 (35.7)	0.627
LAEF, %, median (IQR)	36 (27–48)	30 (19–39)	<0.001
LAEF <28%, n (%)	93 (27.8)	59 (46.5)	<0.001
iRAAPD, mm/m ² , median (IQR)	21 (18–24)	23 (20–27)	0.001
iRAAPD high tertile, n (%)	75 (27.3)	57 (52.3)	<0.001
RAVi, ml/m ² , median (IQR)	27 (20–35)	32 (26–44)	<0.001
RAVi high tertile, n (%)	84 (28.7)	56 (46.7)	0.001
RASI, median (IQR)	0.75 (0.67–0.84)	0.76 (0.69–0.84)	0.756
RASI high tertile, n (%)	92 (33.5)	35 (32.1)	0.895
RAEF, %, median (IQR)	33 (22–45)	31 (19–42)	0.043
RAEF <25%, n (%)	90 (32.3)	45 (38.5)	0.284

Abbreviations: CEP, composite endpoint; iLAAPD, indexed left atrial antero-posterior diameter; iRAAPD, indexed right atrial antero-posterior diameter; LA, left atrial; LAEF, left atrial emptying fraction; LASI, left atrial sphericity index; LAVi, left atrial volume indexed by body surface area; RAEF, right atrial emptying fraction; RASI, right atrial sphericity index; RAVi, right atrial volume indexed by body surface area

hospital setting, had permanent AF, higher CHA₂DS₂VASc and HAS-BLED scores, and more likely to have a history of coronary artery disease, valvular heart disease, and HF (all $P < 0.001$) (Table 1).

Crude rates of adverse events, according to LA dilation, are reported in Table 2. Patients with moderate-to-severe atrial dilation (based on LAVi categories) had a higher rate of death ($P = 0.001$), more frequent admissions for new/worsening HF ($P = 0.013$), and higher rates of CEP ($P < 0.001$) compared to those with no-to-mild dilation. Both atrial diameters and volumes, and reduced LAEF were significantly associated with a higher rate of the CEP (all $P < 0.001$) (Table 3). Conversely, RAEF < 25% and both sphericity indexes were not associated with a higher rate of CEP (Table 3).

Kaplan–Meier curves showed a lower survival free from the CEP for the vast majority of LA parameters (iLAAPD, LAVi, LAEF) and some RA parameters (iRAAPD and RAVi), as detailed in Figure 1, except for LASI, RASI, and RAEF (Supplementary material, Figure S2). Table 4 shows the results of multivariable Cox regression analysis for the CEP: iLAAPD (aHR, 95% CI, 1.78; 1.24–2.57), LAVi (1.50, 1.03–2.19), LAEF (1.74; 1.21–2.48), and iRAAPD (1.65; 1.10–2.47) were significantly associated with a higher risk of CEP, while, when adjusting also for chronic obstructive pulmonary disease, smoking, and CKD, these results were confirmed only for iLAAPD and LAVi (1.63, 1.14–2.34; 1.47, and 1.03–2.09, respectively). Concerning the secondary exploratory outcomes (Supplementary material, Table S1), iLAAPD (1.92, 1.23–3.00), LAVi (1.87, 1.20–2.92), LAEF (1.80,

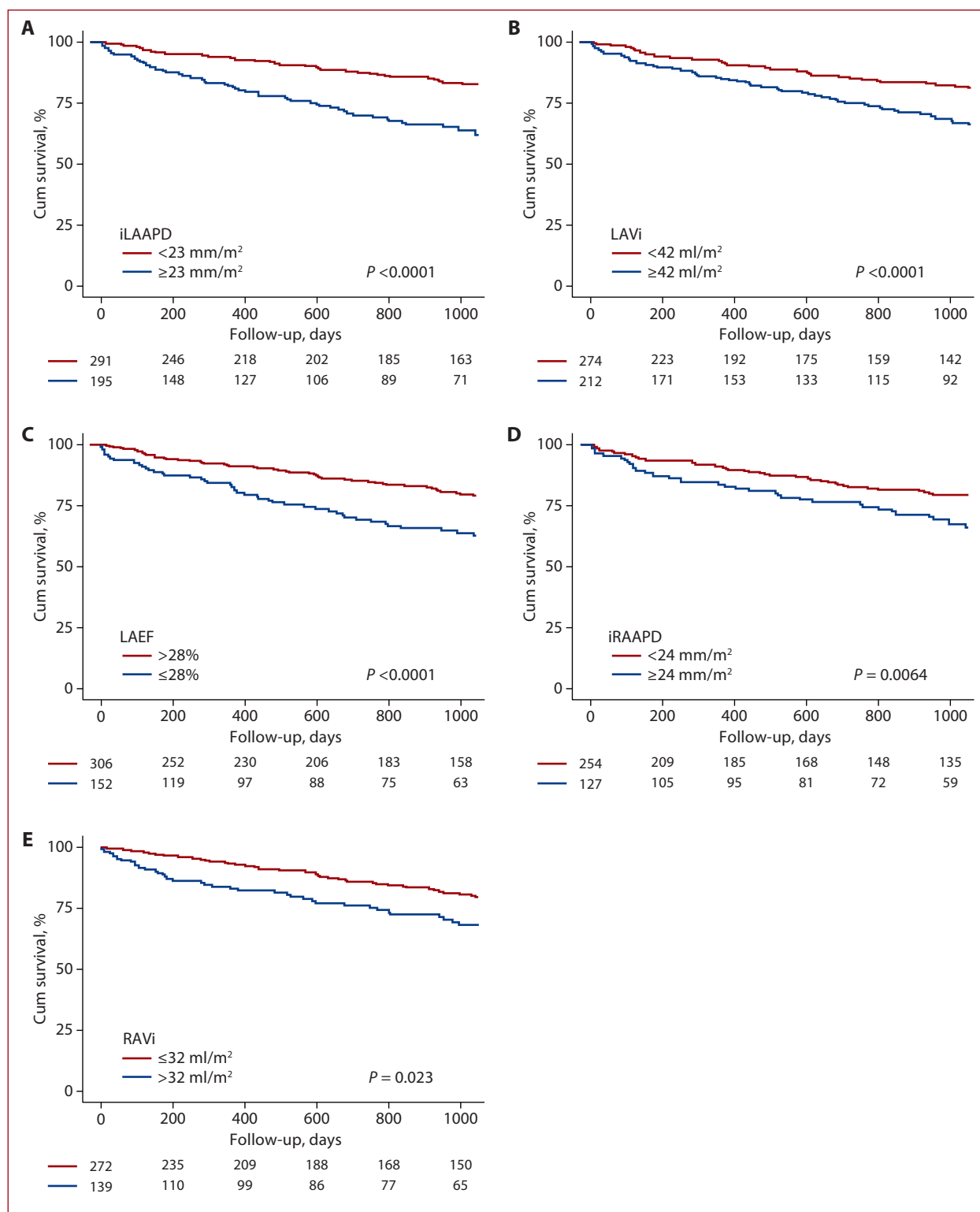


Figure 1. Kaplan–Meier survival curves for the primary composite endpoint. **A.** Kaplan–Meier curves for iLAAPD. **B.** Kaplan–Meier curves for LAVi. **C.** Kaplan–Meier curves for LAEF. **D.** Kaplan–Meier curves for iRAAPD. **E.** Kaplan–Meier curves for RAVi

Abbreviations: Cum, cumulative; iLAAPD, indexed left atrial antero-posterior diameter; iRAAPD, indexed right atrial antero-posterior diameter; LAEF, left atrial emptying fraction; LAVi, left atrial volume indexed by body surface area; RAVi, right atrial volume indexed by body surface area

Table 4. Multivariable Cox regression analysis and reclassification analysis

	aHR ^a (95% CI)	aHR ^b (95% CI)	P-value (LRT)	NRI (95% CI)	P-value	IDI (95% CI)	P-value
Null Model	–	–	ref	ref	ref	ref	ref
iLAAPD >22 mm/m ²	1.78 (1.24–2.57) 0.002	1.63 (1.14–2.34) 0.008	0.002	0.30 (0.09–0.50)	0.005	0.02 (0.01–0.04)	0.008
LAVi ≥42 ml/m ²	1.50 (1.03–2.19) 0.036	1.47 (1.03–2.09) 0.033	0.035	0.32 (0.12–0.53)	0.002	0.03 (0.01–0.05)	0.014
LASI >0.71	1.35 (0.93–1.95) 0.110	1.19 (0.81–1.73) 0.371	0.116	0.05 (–0.15 to 0.25)	0.640	0 (0–0)	0.525
LAEF <28%	1.74 (1.21–2.48) 0.003	1.37 (0.91–2.05) 0.130	0.003	0.26 (0.05–0.46)	0.014	0.01 (0.002–0.02)	0.021
iRAAPD >24 mm/m ²	1.65 (1.10–2.47) 0.015	1.01 (0.65–1.55) 0.972	0.015	0.16 (–0.07 to 0.39)	0.177	0.01 (–0.002 to 0.02)	0.098
RAVi >32 ml/m ²	1.41 (0.97–2.07) 0.074	1.54 (0.99–2.39) 0.054	0.074	0.21 (–0.01 to 0.42)	0.063	0.01 (–0.004 to 0.03)	0.128
RASI >0.82	0.84 (0.56–1.27) 0.420	0.93 (0.61–1.41) 0.739	0.415	0.05 (–0.17 to 0.28)	0.653	0 (0–0)	0.858
RAEF <25%	1.37 (0.94–2.00) 0.104	1.51 (1.01–2.26) 0.046	0.108	0.20 (–0.02 to 0.42)	0.073	0.01 (–0.003 to 0.03)	0.125

The P-value separately shown in the third column relates to the comparison of the atrial parameters' Cox regression model against the "null model" (our reference) using the LRT

^aThe analysis was adjusted for CHA₂DS₂-VASC, AF type and use of OAC. The number below the 95% CI refers to the multivariable Cox regression analysis p value. ^bThe analysis was adjusted for CHA₂DS₂-VASC, AF type and use of OAC, COPD, CKD, and smoking. The number below the 95% CI refers to the multivariable Cox regression analysis P-value

Abbreviations: AF, atrial fibrillation; aHR, adjusted hazard ratio; CHA₂DS₂-VASC, congestive heart failure, hypertension, age ≥75 years, diabetes, stroke/transient ischemic attack, vascular disease, age 65–75 years, sex category; CKD, chronic kidney disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; IDI, integrated discrimination index; iLAAPD, indexed left atrial antero-posterior diameter; iRAAPD, indexed right atrial antero-posterior diameter; LAEF, left atrial emptying fraction; LASI, left atrial sphericity index; LAVi, left atrial volume indexed by body surface area; LRT, likelihood ratio test; NRI, net reclassification improvement; OAC, oral anticoagulant; RAEF, right atrial emptying fraction; RASI, right atrial sphericity index; RAVi, right atrial volume indexed by body surface area

1.05–3.07), and RAVi (1.97, 1.09–3.55) were associated with a higher risk of death, and both LAEF (3.02, 1.27–7.17) and RAVi (6.44, 1.98–21.0) were associated also with a higher risk of hospitalization for HF. No statistically significant differences were observed regarding the other secondary exploratory outcomes (Supplementary material, Table S1).

The ROC analysis showed moderate power in discriminating patients who met the CEP (AUC always <0.7). However, LAVi ≥42 ml/m² and iLAAPD >22 mm/m² had better, though not optimal, negative predictive values (Supplementary material, Table S2).

At reclassification analysis, iLAAPD >22 mm/m² (NRI 0.30; 95% CI, 0.09–0.50; *P* = 0.005; IDI 0.02; 95% CI, 0.01–0.04; *P* = 0.008), LAVi ≥42 ml/m² (NRI 0.32; 95% CI, 0.12–0.53; *P* = 0.002; IDI 0.03; 95% CI, 0.01–0.05; *P* = 0.014), and LAEF <28% (NRI 0.26; 95% CI, 0.05–0.46; *P* = 0.014; IDI 0.01; 95% CI, 0.002–0.02; *P* = 0.021) were effective in reclassifying the hazard of reaching the CEP (Table 4) when added to the "null model". However, the sphericity indexes and RA parameters did not show significant reclassification ability.

Finally, Figure 2 and Figure S3 show the association between each atrial parameter, modelled as a continuous, non-linear variable, and the risk of CEP. Both iLAAPD and LAVi refined risk prediction. In detail, Figure 2A shows that for iLAAPD values above 21 mm/m² the risk of events of the CEP progressively and gradually increases until 27 mm/m², then tends to plateau for higher values. Figure 2B depicts

the relationship between LAVi and the risk of CEP: LAVi values higher than 40 ml/m² are associated with a progressive increase in the risk of CEP, which then plateaus for values above 60 ml/m².

DISCUSSION

The main finding of our study is that LA parameters, particularly iLAAPD, LAVi, and to a lesser extent LAEF, were significantly associated with an increased risk of the adverse cardiovascular (CV) events. Conversely, neither sphericity indexes nor RA parameters correlated with these adverse outcomes in AF patients.

To our knowledge, this is one of the first studies to comprehensively evaluate the correlation between a broad set of both LA and RA echocardiographic parameters and outcomes in a real-world cohort of AF patients. According to the literature, there is a lack of conclusive evidence regarding the predictive capability of atrial measurements obtained by transthoracic echocardiography in terms of clinical outcomes [9]. Previous studies primarily focused on fewer atrial parameters — mainly LA-related ones — and on outcomes following catheter ablation or predicting thromboembolic events [25]. Our study provides a holistic and broader assessment of atrial remodeling by exploring its implications not only for thromboembolic events but also for survival and major adverse CV events, which has considerable clinical value.

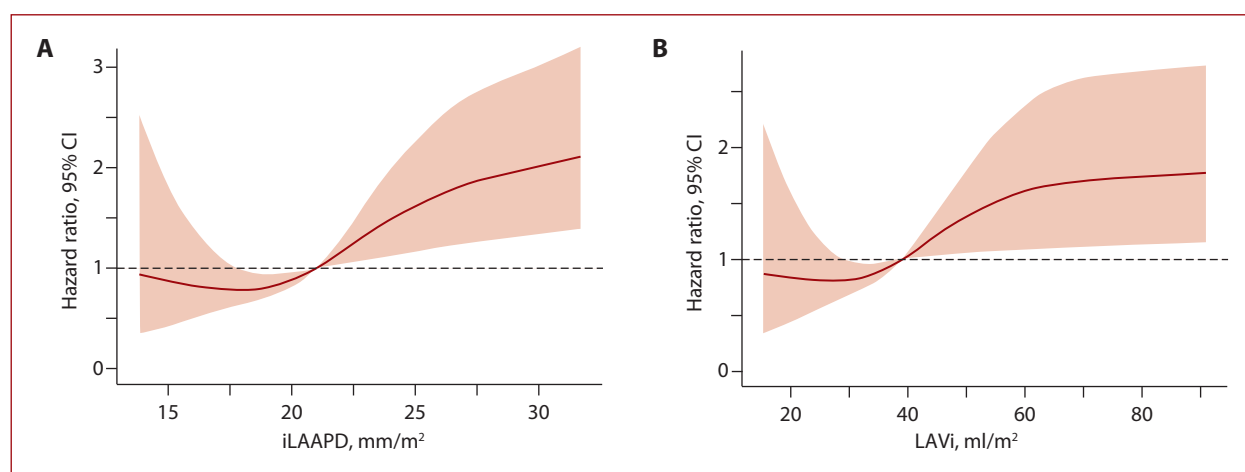


Figure 2. Multivariable Cox regression analyses plotted as restricted cubic splines curves using each atrial parameter as a continuous variable. **A.** iLAAPD modeled as a continuous variable. **B.** LAVi modeled as a continuous variable

Values over the dotted line indicate an increased hazard of CEP, while below indicate a reduced hazard. Panel **A.** shows that for iLAAPD values above 21 mm/m² the risk of events of the CEP progressively and gradually increases until 27 mm/m², then tends to *plateau* for higher values ($P=0.001$; P non-linearity = 0.258). Panel **B.** depicts the relationship between LAVi and the risk of CEP: LAVi values higher than 40 ml/m² are associated with a progressive increase in the risk of CEP, which then plateaus for values above 60 ml/m² showing a non-linear relationship ($P=0.003$, P non-linearity = 0.012). The analysis was adjusted for CHA₂DS₂-VASC, AF type, and use of OAC

Abbreviations: AF, atrial fibrillation; CEP, composite endpoint; CI, confidence interval; iLAAPD, indexed left atrial antero-posterior diameter; LAVi, left atrial volume indexed by body surface area; OAC, oral anticoagulant

The present analysis was focused on AF patients and allowed us to integrate prior knowledge by identifying LAVi, iLAAPD, and to a lesser extent LAEF as reliable predictors of adverse outcomes in AF patients. We found that an increase in iLAAPD and LAVi, simple atrial parameters, was statistically associated with adverse outcomes, likely reflecting chronic diastolic dysfunction and increased atrial filling pressures. Historically, LA size has been recognized as a predictor of CV outcomes in both AF and non-AF patients. Because AF can be considered a manifestation of atrial cardiomyopathy, and since LA remodeling is a well-known factor associated with AF progression, understanding atrial remodeling and its association with outcomes is crucial [26–31]. Tsang et al. [32] found that LAVi, considered the most reliable outcome predictor in sinus rhythm patients, poorly performed in predicting adverse CV events in AF patients. These preliminary results could be justified by the relatively small sample size and the complex nature of atrial remodeling, which goes beyond mere dilation. Of note, atrial dilation is not symmetrical — it spreads more in superior-inferior and medial-lateral directions. This asymmetry limits the utility of some bidimensional indices, such as sphericity indices, in capturing true atrial size and shape. Given the growing relevance of a deeper evaluation of the atria, a recent consensus statement revised the concept of atrial cardiomyopathy, which encompasses structural, electrical, and mechanical abnormalities of the atrial myocardium that extend beyond AF and result in changes in contractility, electrophysiology, and chamber architecture, potentially related to clinically relevant events [33]. This definition highlights the central interplay of structural and functional remodeling.

Similarly, LAEF, although less robust in our analyses, was associated with a higher risk of the composite endpoint, primarily driven by increased risks of death and HF hospitalization. Reduced LA ejection force, defined as the force exerted by the atrium in propelling blood into the ventricle during atrial systole, was associated with negative outcomes after ablation for paroxysmal AF, but LAEF did not seem to differ between recurrent and non-recurrent AF patients [34, 35]. A lower LAEF highlights negative atrial dynamics and can be considered as the result of the arrhythmia itself combined with an underlying atrial myopathy [36, 37]. In line with these results, the importance of LA function is emphasized especially in HF management, because its loss might lead to exacerbation of symptoms and might contribute to a refractory or worsening HF [38], particularly in patients with a history of AF.

Moreover, there is growing interest concerning the right heart structures and function and their association with AF, because recent evidence suggest that the RA shares the same substrate, electrical, and structural remodeling (e.g., patchy fibrosis, inflammation, vascular degeneration) as the LA [16, 39, 40]. However, to the best of our knowledge, no previous studies have extensively investigated their role in predicting adverse CV events. While we observed an association between RAVi and the composite endpoint on univariable analysis, this was not confirmed in multivariable models nor in reclassification analysis. Nonetheless, RAVi was associated with a higher risk of death and HF hospitalization, consistent with previous findings by Ko et al. [41]. Notably, RA enlargement may reflect a more advanced atrial remodeling, and most AF patients with increased RAVi had also LA dilation.

Our study has some limitations that should be highlighted. Firstly, this is an observational monocentric study with the intrinsic relatively short follow-up duration and limited granularity of available data (in particular, concerning concurrent medications and comorbidities), which may limit the generalizability of our findings. Given the observational design, our study should be considered as hypothesis-generating and reports associations rather than implying causality. Most of the echocardiograms were performed by the echo-lab team leader, who also took the majority of the measurements, minimizing inter-operator variability. Measurements by other physicians were reviewed by the team leader to ensure consistency [21]. Nonetheless, minor inter- and intra-operator discrepancies cannot be excluded and are acknowledged as a potential limitation of our study. Moreover, echo-parameters were not always obtained in the same rhythm for all patients, thus introducing heterogeneity in the evaluation. We did not use 3D imaging or LA strain evaluation, since they were not routinely employed in daily clinical practice, despite their potential role [42–45], and we focused on simple measurements, which can be easily obtained. One of the advantages of 3D echocardiography is a more detailed analysis of LA volumes in various phases of the cardiac cycle and the reservoir function [46]. Similarly, LA strain provides useful information concerning atrial function. Previous studies analyzed the role of LA strain and 3D LA volume in patients with embolic stroke of unknown origin, and in predicting the risk of stroke in patients with AF [47, 48]. The pathophysiological mechanisms are partially unknown; however, it has been hypothesized that there might be an association among reduced LA strain, LA fibrosis, and lower LA appendage flow velocity. Thus, the development of thrombi might be due to the reduced LA compliance during the LA reservoir phase, resulting in blood flow stasis in the atrium and increased risk of stroke [48, 49]. These advanced imaging techniques are particularly relevant for the characterization of atrial cardiomyopathy because these methods provide detailed insights into atrial structure and function (e.g., fibrosis, compliance, and reservoir function), which were not fully captured by mere dimension. For this reason, given the more widespread availability of these advanced echocardiographic techniques in recent years, incorporating these techniques in future research could improve risk stratification by identifying specific atrial dysfunction patterns contributing to adverse outcomes. Finally, despite controlling for many covariates, residual or unmeasured confounding in this analysis could not be excluded.

CONCLUSIONS

Atrial echocardiographic parameters, particularly those related to the LA, are associated with long-term adverse outcomes in AF patients. Our study highlights the importance of a comprehensive echocardiographic evaluation in clinical practice, because this assessment may provide valuable insights into the extent of atrial remodeling and

underlying atrial cardiomyopathy, and integrate clinical risk stratification and decision-making in AF patients.

Supplementary material

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

Article information

Conflict of interest: GB — small speaker fee from Boston, Boehringer Ingelheim, Bayer, Daiichi-Sankyo, Janssen and Sanofi, and he is Study Coordinator of ARISTOTELES (Grant from Horizon Europe — HORIZON-HLTH-2022-STAYHLTH-01 — Grant 101080189). The other authors declare no conflicts of interest. No conflict exists for any of the authors with regard to the data presented in the current study.

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The impact of previous VT substrate radiofrequency catheter ablation procedures for patients presenting with electrical storm

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ABSTRACT

Background: Ventricular tachycardias (VT) that appear after catheter ablation (RFA) may respond poorly to conservative treatment and increase mortality. Current evidence favors repeating RFA to reduce VT-burden and improve outcomes if recurrences are precluded. This has not exclusively been studied in electrical storm patients.

Aims: We sought to compare patient/procedural characteristics and long-term all-cause mortality and recurrences in single-RFA versus repeat-RFA patients.

Material and methods: This was a retrospective single-center analysis of consecutive electrical storm patients treated by RFA monitored for a mean of 32.8 (range 10–68) months. Inducibility of sustained monomorphic VT was assessed by programmed ventricular stimulation. We assessed differences in patient/procedural characteristics and compared all-cause mortality and recurrences in single-RFA versus repeat-RFA during the first year post-ablation.

Results: In total, 101 patients (mean age 59.69 [12.8] years, 32.7% non-ischemic cardiomyopathies, 34 cases of repeat-RFA) were included. Compared to single-RFA, repeat-RFA patients more frequently had non-ischemic cardiomyopathies (47.1% vs. 26.9%; $P = 0.04$), required more epicardial ablation (32.4% vs. 14.9%; $P = 0.04$), and more frequently had epicardial-access complications (14.8% vs. 1.6%; $P = 0.02$). All-cause mortality (repeat-RFA 10 deaths [29.4%] vs. single-RFA 21 deaths [31.3%]; $P = 0.99$) and recurrences (repeat-RFA 13 recurrences [38.2%] vs. single-RFA 23 recurrences [34.3%]; $P = 0.82$) were comparable during follow-up. All-cause mortality (log rank $P = 0.62$) and recurrences (log-rank $P = 0.65$) were similar in repeat-RFA vs. single-RFA during the first year after ablation.

Conclusions: Despite requiring more epicardial ablation and more non-ischemic myocardial substrate, repeat-RFA patients showed similar all-cause mortality and recurrences compared to single-RFA during the first year post-ablation.

Key words: all-cause mortality, electrical storm, programmed ventricular stimulation, recurrences, repeat ablation,

INTRODUCTION

Patients with a history of ventricular tachycardia (VT) catheter ablation (RFA) can develop recurrences that may respond poorly to conservative treatment and increase mortality [1, 2]. Although limited and derived from observational data, current evidence favors

the role of repeat-RFA to reduce VT burden and the potential to obtain outcomes similar to single-RFA cases, provided there are no VT recurrences after ablation [3–7].

Electrical storm (ES) aggravates outcomes of VT ablation [8–10]. Repeat-RFA procedures in the setting of ES episodes have only repre-

WHAT'S NEW?

Patients with a history of ventricular tachycardia ablation requiring redo procedures for electrical storm episodes were more frequently affected by non-ischemic structural heart disease, required more epicardial ablation, and developed more pericardial access-related complications. However, they achieved comparable rates of procedural success and all-cause mortality and ventricular arrhythmic recurrences during the first year after the procedure compared to patients undergoing first-time ablation at the time of electrical storm.

sented 30%–60% of studied populations in previous papers [3–7]. This study focused exclusively on ES patients and aimed to evaluate baseline patient and procedural characteristics and all-cause mortality and VT/VF recurrences in those with previous VT ablation procedures (“repeat-RFA”) in comparison to those undergoing first-time VT ablation at the time of ES (“single-RFA”).

MATERIAL AND METHODS

Study population

This was a retrospective longitudinal single-center analysis of consecutive implantable cardioverter defibrillator (ICD) patients treated by RFA between January 2014 and June 2023 for ES as defined in previously published papers and most recent consensus documents [11–13]: a minimum of three separate episodes of sustained ventricular monomorphic tachycardia (SMVT) treated by adequate

ICD therapies in a 24-hour interval refractory to medical antiarrhythmic treatment. Patients with exclusively polymorphic VT of ventricular fibrillation episodes (not preceded by SMVT) or patients with isolated SMVT episodes (<3 episodes/24 hours) were excluded from this analysis (Figure 1). Furthermore, RFA was not performed in ES patients demonstrating reversible causes (e.g., active ischemia, severe electrolyte abnormalities, drug toxicity) that achieved VT suppression after trigger correction. If subjects were previously naive to VT substrate ablation procedures and underwent first-time ablation at the time of study enrolment, they were defined as single-RFA subjects; otherwise, if at least one VT substrate ablation procedure had been performed prior to the moment of the reference ablation and study enrolment, they were defined as repeat-RFA patients. Previous VT substrate ablation procedures were performed either in other centers or in the study center.

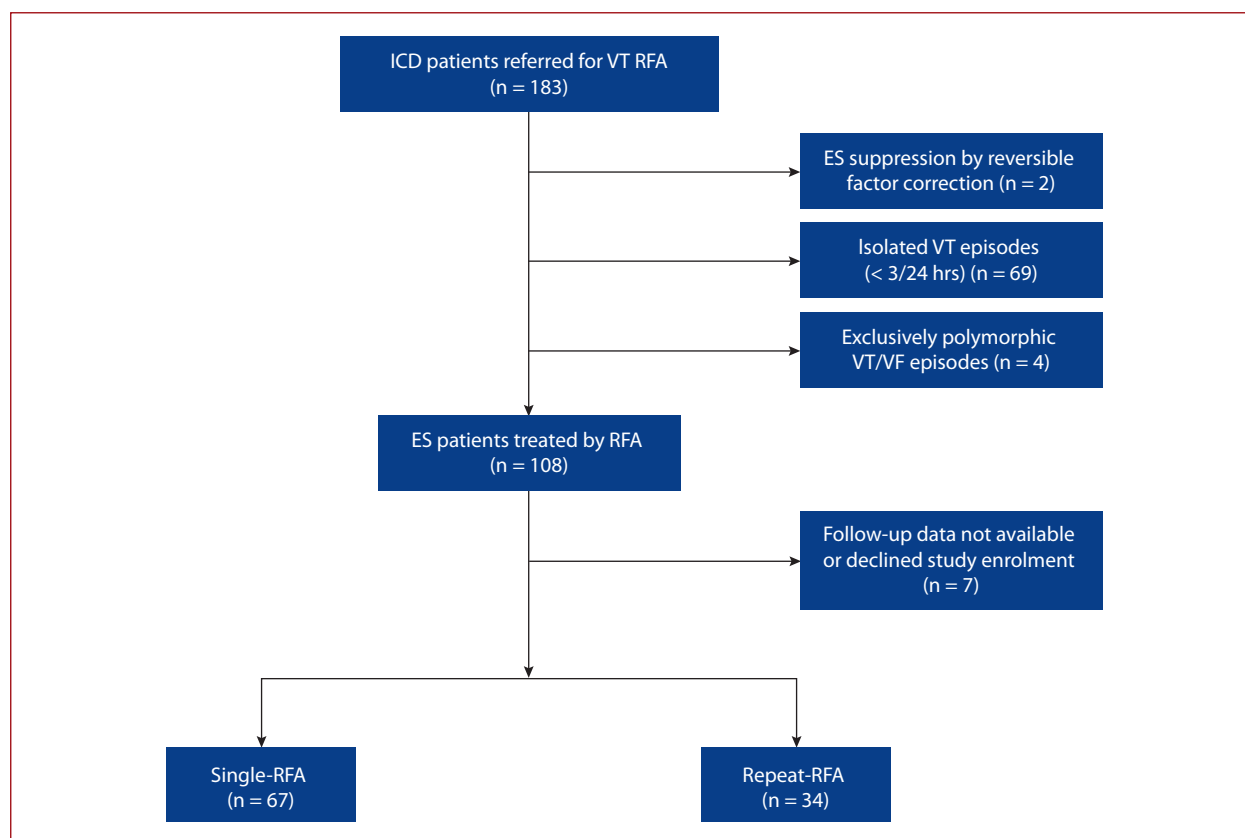


Figure 1 Flowchart detailing the selection process of the final study population

Abbreviations: ES, electrical storm; ICD, implantable cardioverter-defibrillator; RFA, radiofrequency catheter ablation; VF, ventricular fibrillation; VT, ventricular tachycardia

Imaging, electrophysiology study, and ablation strategy

Electrophysiological study and ablation were performed in fasting state under analgesia and conscious sedation. Electrogram recording and analysis was performed using the Boston Scientific LabSystem PRO EP Recording System v.2.7.0.16. High-density electroanatomical mapping with CARTO-3™ (Biosense Webster, Diamond Bar, CA, US) (>1800 points emphasizing the scar area and its border zone [BZ]) was performed in sinus rhythm with 16–500 Hz signal filtering. Right ventricle catheterization was obtained by transfemoral access; whereas, the left ventricle was instrumented by trans-septal or retrograde aortic approach. The pericardial space was accessed by fluoroscopy-guided anterior subxiphoid puncture. Epicardial mapping and ablation were performed if the electrocardiogram SMVT morphology (either preprocedural electrocardiogram or induced by programmed ventricular stimulation [PVS] after endocardial ablation) was considered to indicate an epicardial origin. Remote magnetic navigation (RMN) (Niobe II, Stereotaxis Inc., St. Louis, MO, US) and/or multielectrode catheter mapping (decapolar or duodecapolar) was used

at the electrophysiologist's case-specific discretion. Mitral regurgitation severity and biplane Simpson-based left ventricular ejection fraction (LVEF) on transthoracic echocardiography was based on previous recommendations for diagnosis [14, 15]. Ischemic cardiomyopathy (ICM) was defined by a previous myocardial infarction. Only characteristics from each patient's most recent ablation procedure were reported.

Normal myocardium was considered if the local electrogram amplitude was >1.5 mV (bipolar), >8.3 mV (unipolar LV), or >5.5 mV (unipolar RV), whereas dense scar and BZ myocardium were defined by endocardial bipolar signal amplitude <0.5 mV and 0.5–1.5 mV, respectively, in endocardial mapping. In epicardial mapping, bipolar electrogram amplitude >1 mV defined normal myocardium. Similarly to previously published analyses, a standard scar-de-channeling protocol eliminating conduction channel entrances [16] using open-irrigated ablation catheters (35–50 W, 45°) was used. The procedural workflow protocol is summarized in Figure 2. If hemodynamically tolerated, activation/entrainment was performed for any spontaneously induced VTs during mapping. After conduction

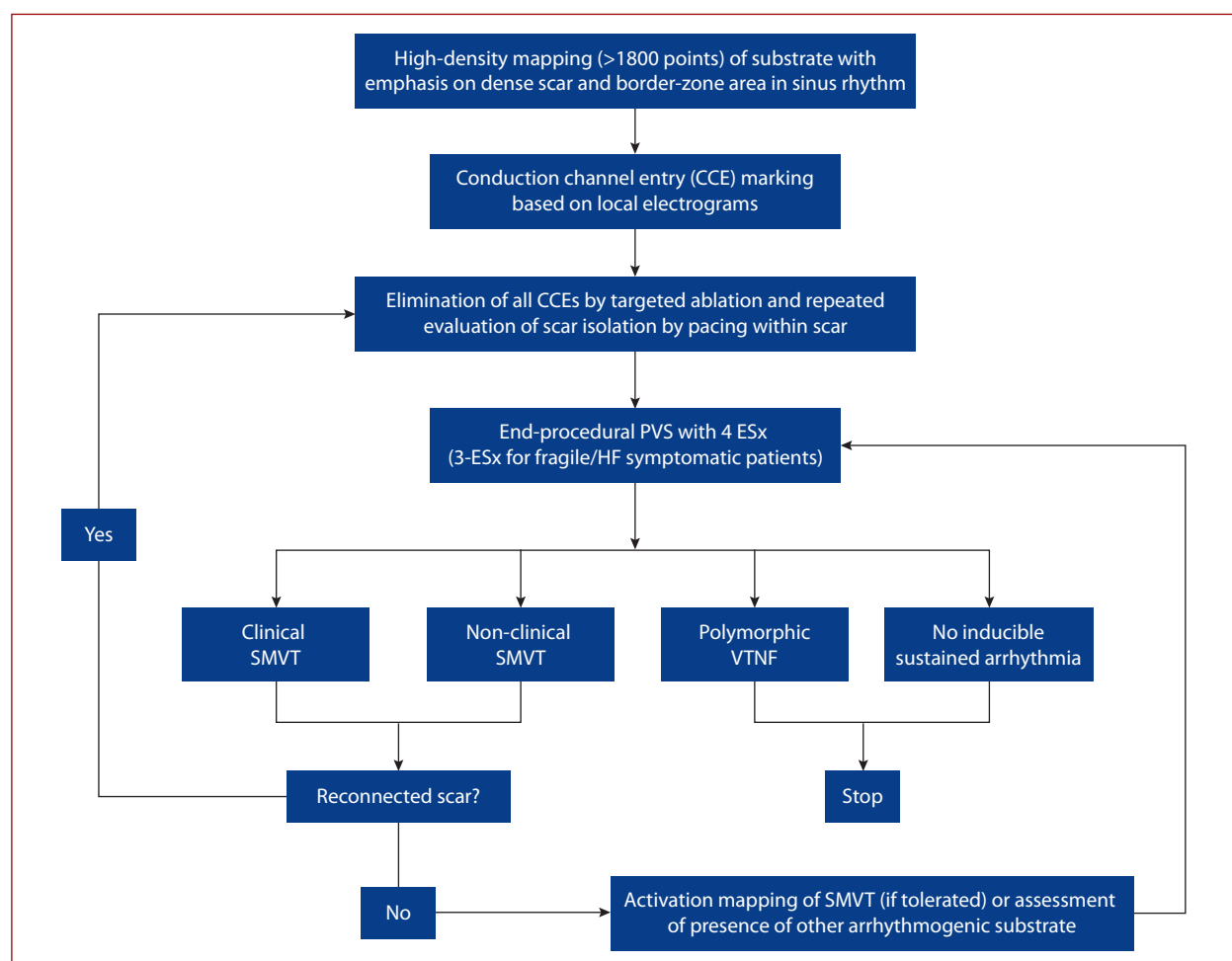


Figure 2. Flowchart detailing the ablation protocol applied for electrical storm patients

Abbreviations: CCE, conduction channel entry; ESx, extrastimuli; HF, heart failure; SMVT, sustained monomorphic ventricular tachycardia, other — see Figure 1

channel entry elimination, PVS was routinely performed with at least 2 drive cycle lengths (CLs) and 4 extra stimuli (ESx) (3 ESx in patients with severe heart failure symptoms at rest or extreme frailty) (at a minimum of 200 ms or until ventricular refractoriness) from two sites (medially and laterally to the scar) to test for residual inducible arrhythmia (as previously described [12]). For inducible SMVTs with CLs ≥ 250 ms [17], scar reconnection was assessed using a previously validated protocol [18] to demonstrate core isolation; high-output pacing (20 mA at 2 ms pulse width) was applied at multiple (≥ 3) sites inside the scar that had previously demonstrated capture and had not been targeted by ablation. If scar reconnection was demonstrated, the scar de-channeling protocol was repeated. If scar isolation was demonstrated, other potential substrate sites were emphasized by mapping, guided by the morphology of the persistently inducible VT. Clinical SMVT was interpreted by 12-lead electrocardiogram QRS morphology or by ICD-derived intracardiac electrograms with similar (± 20 ms) CLs.

A positive PVS was defined by persistently inducible sustained monomorphic VT (irrespective of clinical or non-clinical SMVT morphology) at testing, whereas the absence of any sustained monomorphic VT was considered a negative PVS. A positive PVS was further defined in relation to the type of residually inducible sustained monomorphic VT: *partial success* — elimination of clinical sustained monomorphic VT, with residually inducible sustained monomorphic VT; *failure* — residually inducible clinical sustained monomorphic VT.

Follow-up protocol

All follow-up data were analyzed in relation to the most recent ablation. All patients were scheduled for routine recurrent 6-month interval ICD interrogation visits after ablation at the study center or at other institutions by certified electrophysiologists to detect recurrent arrhythmic episodes. Symptomatic patients (palpitations, syncopal episodes, or ICD discharges) were scheduled for prompt ICD interrogation. We periodically assessed all-cause mortality by a 6 month-interval routine check-up of each patient's status using the National Health Insurance website. The exact date of the patient's death was subsequently confirmed by the patient's family or referring physician *via* telephone. For study analysis, scheduled ICD interrogation was performed in all patients that were alive in June 2023.

All-cause mortality rates were retrospectively analyzed after the moment of the most recent ablation, irrespective of cardiovascular and non-cardiovascular causes of death. Recurrences were defined by SMVT or polymorphic VT/VF episodes adequately treated by ICD intervention (either antitachycardia pacing or shock). ICD detection intervals were programmed to allow detection of any ventricular arrhythmia that was previously spontaneously present induced at PVS (-20 bpm relative to the slowest known VT).

The study protocol adhered to the principles of the Declaration of Helsinki and was approved by the human research committee of the Emergency Clinical Hospital of Bucharest Ethics Committee (12521 — 01/04/2022).

Statistical analysis

Continuous data were expressed as mean (standard deviation) for normally distributed data and median (interquartile range) for non-normally distributed data. Categorical data was expressed as percentage (count). The normality of data was evaluated using the Kolmogorov–Smirnov test. Categorical variables were compared using Fisher's exact test/ χ^2 analysis, and continuous variables were compared using Student's t-test (or one-way ANOVA test for comparison of more than two groups) if normally distributed and non-parametric tests (Mann–Whitney U test or Kruskal–Wallis 1-way for comparison of more than two groups). Subjects without previous VT ablations were attributed to the single-RFA subgroup, whereas those with a history of at least one VT ablation were attributed to the repeat-RFA subgroup. Cox proportional hazards analyses were used to specifically assess the association between the first occurrence of time-dependent outcome events (all-cause mortality and VT/VF recurrences, respectively) and repeat-RFA status during the first year after ablation. Furthermore, univariate Cox regression analysis was used to test the association between previously established predictors of events after ES ablation and the first occurrence of death or VT/VF recurrences during the first year after ablation; subsequently, all variables with significant effect were introduced in the multivariate model to test independent prediction of the composite end-point of death or VT/VF recurrences during the first year after ablation. Kaplan–Meier analysis was used to assess event-free survival during follow-up, and the log-rank pairwise comparison test was used to compare differences in survival curves of single-RFA vs. repeat-RFA patients within each of the following strata: PVS result (non-inducibility of any sustained monomorphic VT vs. residual inducibility of sustained monomorphic VT), etiology (ICM vs. NICM), and LVEF subgroup (LVEF $\leq 40\%$ vs. LVEF $> 40\%$) during the first year after ablation. A 2-sided *P*-value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 23 (IBM Corp., Armonk, NY, US) software and Prism 9 Version 9.5.0 (GraphPad Software, LLC).

RESULTS

A total of 101 patients were retrospectively included in this study. **Table 1** summarizes relevant patient and procedural characteristics. There were 34 patients attributed to the repeat-RFA subgroup, whereas 67 patients were attributed to the single-RFA subgroup. The repeat-RFA group consisted of 28 (82.5%) patients with two procedures, 5 (14.7%) with three procedures, and one (2.9%) patient with four procedures in the repeat-RFA group. Twelve patients (35.2%) in the repeat-RFA group had a history of previous

Table 1. Demographic, clinical, and procedural characteristics of patients (overall and repeat procedures vs. single procedure subgroups)

	Overall	Repeat-RFA	Single-RFA	P-value
Number of cases	101	34	67	
Age, years, mean (SD)	59.69 (12.8)	59.9 (14.7)	59.5 (11.8)	0.89
Males, n (%)	87 (86.1)	31 (91.2)	56 (83.6)	0.37
T2DM, n (%)	26 (33.7)	9 (26.5)	17 (25.4)	0.99
Active smoking, n (%)	20 (19.8)	8 (23.5)	12 (17.9)	0.75
Dyslipidemia, n (%)	62 (61.4)	21 (61.8)	41 (61.2)	0.99
Hypertension, n (%)	63 (62.4)	20 (58.8)	43 (64.2)	0.66
Overweight/obesity, n (%)	35 (34.7)	10 (29.4)	25 (37.3)	0.51
Beta-blocker before ablation, n (%)	83 (82.2)	27 (79.4)	56 (83.6)	0.59
Amiodarone before ablation, n (%)	68 (67.3)	22 (64.7)	46 (68.7)	0.82
CRT before ablation, n (%)	15 (14.9)	6 (17.6)	9 (13.4)	0.56
NYHA III/IV at admission, n (%)	29 (28.7)	8 (23.5)	21 (31.3)	0.49
Moderate or severe MR at admission, n (%)	33 (32.6)	16 (48.5)	17 (25.4)	0.025
AF at admission, n (%)	13 (12.9)	4 (11.8)	9 (13.4)	0.99
Type of AF — paroxysmal	24 (23.8)	9 (26.5)	15 (22.4)	0.67
Type of AF — persistent	8 (7.9)	4 (11.8)	4 (6)	
Type of AF — permanent	8 (7.9)	2 (5.9)	6 (9)	
LVEF, mean (SD)	32 (11.6)	32.9 (12)	31.5 (11.5)	0.56
Days of hospitalization, median (IQR)	6 (4–10)	10 (5.2–19.5)	5 (4–8)	0.07
NICM, n (%)	34 (32.7)	16 (47.1)	18 (26.9)	0.04
Endoepicardial ablation, n (%)	21 (20.8)	11 (32.4)	10 (14.9)	0.041
Remote magnetic navigation ablation, n (%)	79 (78.2)	27 (79.4)	52 (77.6)	0.99
Total scar/total map area, mean percentage (IQR)	20.7 (10.8–28.8)	20.3 (9.1–34.5)	20.9 (11.1–27.2)	0.86
Border-zone/total scar area, mean percentage (IQR)	60.6 (41.7–77)	60.1 (45.6–74.2)	63.4 (41.3–79.7)	0.91
Number of SMVTs induced during the procedure, median (IQR)	2 (1–3)	2 (1–3)	2 (1–3)	0.77
Substrate-based ablation strategy, n (%)	96 (95)	33 (97.1)	63 (94)	0.66
Activation mapping-based strategy, n (%)	62 (61.4)	23 (67.6)	39 (58.2)	0.39
Partial success, n (%)	32 (31.7)	12 (35.3)	20 (29.9)	0.65
Negative PVS, n (%)	55 (54.5)	19 (55.9)	36 (53.7)	0.99
Procedure duration, min, median (IQR)	185 (146–246.5)	180 (141–267.5)	185 (145–236)	0.35
Ablation-related non-vascular access-related complications, n (%)	9 (11.5)	6 (24)	3 (5.7)	0.027
Vascular access hematoma, n (%)	3 (3.1)	2 (6.3)	1 (1.5)	0.24
Beta-blocker after, n (%)	87 (86.1)	29 (85.3)	58 (86.6)	0.99
Amiodarone after, n (%)	72 (71.3)	25 (73.5)	47 (70.1)	0.81

Abbreviations: AF, atrial fibrillation; CRT, cardiac resynchronization therapy; IQR, interquartile range; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NICM, non-ischemic cardiomyopathy; NYHA, New York Heart Association; PVS, programmed ventricular stimulation; repeat-RFA, repeat procedures; SD, standard deviation; single-RFA, single-procedures; SMVT, sustained monomorphic ventricular tachycardia; T2DM, type 2 diabetes mellitus

ablation for electrical storm, whereas the other 22 (64.7%) had a history of ablation only for VT episodes. Twelve subjects (35.2%) were previously treated and referred from other centers, whereas the other 22 (64.7%) underwent previous VT ablation procedures in our center. For patients with repeated ablations, the previous procedure had the following results at final PVS: negative PVS ($n = 12$; 35.3%), partial success ($n = 13$; 38.2%), or failure ($n = 8$; 23.5%), and PVS was not performed in only one patient (2.9%). The median interval of time from the previous ablation was 3.5 (1–24) months. Seven of the eight patients with previous procedural failure underwent the repeated ablation during the same hospitalization. The median interval of time from the previous ablation was different ($P = 0.001$) in relation to the result of the previous procedure: negative PVS — 24 (7.5–51) months vs. partial success — 3 (1–4.5) months vs. failure — 0.75 (0.5–1) months. Only four out (11.8%) of the 34 repeat-RFA patients underwent epicardial ablation during the previous procedure.

There were 9 (27.2%) (single-RFA 5 [7.5%] vs. repeat-RFA 4 [11.8%]; $P = 0.48$) patients diagnosed with arrhythmogenic cardiomyopathy, 4 (12.1%) patients with non-compaction cardiomyopathy (single-RFA 1 [1.5%] vs. repeat-RFA 3 [8.8%]; $P = 0.11$), 4 (12.1%) patients with valvular cardiomyopathies (single-RFA 3 [4.5%] vs. repeat-RFA 1 [2.9%]; $P = 0.54$), 6 (5.9%) post-myocarditis cardiomyopathy (single-RFA 3 [4.5%] vs. repeat-RFA 3 [8.8%]; $P = 0.4$), 11 (10.9%) patients with idiopathic DCM (single-RFA 6 [8.9%] vs. repeat-RFA 5 [14.7%]; $P = 0.11$).

In the repeat-RFA group, epicardial ablation was more frequent in NICM vs. ICM (8 patients [53.3%] vs. 3 patients [15.8%]; $P = 0.03$). There was no difference in the rate of positive PVS in RMN procedures vs. manual procedures ($n = 24$ [30.4%] vs. $n = 8$ [36.4%]; $P = 0.61$).

Nine patients (11.5%) developed ablation-related non-vascular complications, predominantly in the repeat-RFA group ($n = 6$ [24%]; $P = 0.027$) vs. single-RFA group ($n = 3$ [5.7%]). These were mostly attributed to post-ablation

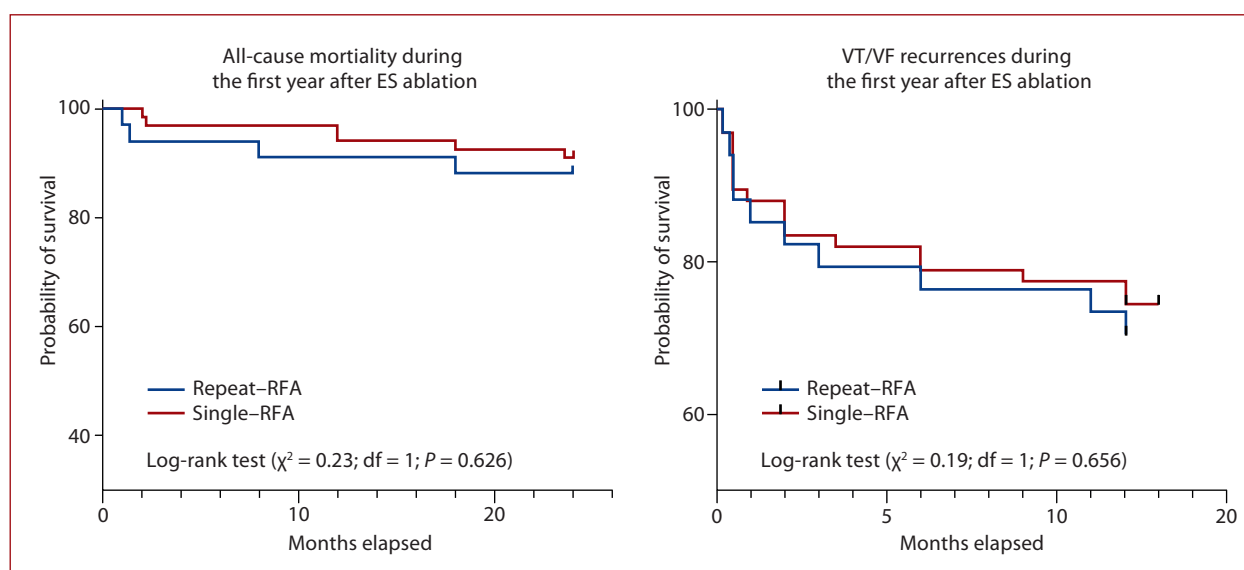


Figure 3. Kaplan–Meier survival curves showing all-cause mortality (top) and VT/VF recurrences (bottom) during the first year after ablation dichotomized by the type of RFA (single- vs. repeat-RFA subgroups)

Abbreviations: LVEF, left ventricular ejection fraction; other — see Figure 1

pericardial effusions in the repeat-RFA group ($n = 4$ [14.8%]) vs. the single-RFA group ($n = 1$ [1.6%]; $P = 0.02$). None required pericardiocentesis, and they were treated conservatively. In the repeat-RFA group, one patient (3.3%) developed transient coronary spasm that responded to intravenous nitroglycerine and one patient (3.3%) developed periprocedural thromboembolic stroke. There were no such complications in the single-RFA group. One patient in the single-RFA group (1.9%) developed brachial artery thromboembolism during the ablation procedure and required mechanical thrombectomy. One patient in the repeat-RFA group developed a subcutaneous hemorrhage (3.3%) during epicardial puncture attempt, which was treated conservatively, but mandated the deferral of the procedure. There were three local vascular complications represented by self-limited hematomas (two [6.3%] in the repeat-RFA group and one [1.5%] in the single-RFA group; $P = 0.24$), which were treated conservatively.

During a median interval of 32.8 (10–68) months there were 31 (30.7%) deaths overall. There were 10 deaths (29.4%) in the repeat-RFA group vs. 21 (31.3%) in the single-RFA group ($P = 0.99$). Overall, there were 36 (35.6%) recurrences. There were 13 recurrences (38.2%) in the repeat-RFA group vs. 23 (34.3%) in the single-RFA group; $P = 0.82$. Only 3 patients (14.3%) died from the repeat-RFA subgroup out of the 21 that did not experience recurrences during follow-up, compared to seven (53.8%) out of 13 that experienced recurrences. There were no differences regarding death during follow-up in the single-RFA group that did not experience recurrences (8 [18.2%] out of 44; $P = 0.69$) or those who experienced recurrences (13 [56.5%] out of 23; $P = 0.87$).

During the first year after ablation, there were 37 events (death or VT/VF recurrences) observed during follow-up,

as follows: 10 (9.9%) patients died during follow-up; there were 6 (9%) deaths in the single-RFA group vs. 4 (11.8%) deaths in the repeat-RFA group ($P = 0.729$). There were 27 (26.7%) patients with VT/VF recurrence; there were 10 (29.4%) patients in the repeat-RFA group vs. 17 (25.4%) in the single-RFA group ($P = 0.66$). Kaplan–Meier survival log-rank analysis (Figure 3) did not demonstrate differences in all-cause mortality ($P = 0.62$) or recurrences ($P = 0.65$) between repeat-RFA vs. single-RFA subgroups during the first year after ablation (Figure 3). Positive PVS (Table 2) was the only independent factor to predict death or VT/VF recurrences during the first year after ablation (hazard ratio [HR], 8.8; 95% confidence interval [CI], 3.6–21.2; $P = 0.001$).

Figure 4 shows that Kaplan–Meier survival curve analysis did not demonstrate differences regarding all-cause mortality and VT/VF recurrences during follow-up stratified by PVS result (log rank pairwise comparison for all-cause mortality between single-RFA vs. repeat-RFA for negative PVS $P = 0.49$, positive PVS $P = 0.53$; log rank pairwise comparison for VT/VF recurrences between single-RFA vs. repeat-RFA for negative PVS; $P = 0.84$, positive PVS $P = 0.75$) and type of disease (log rank pairwise comparison for all-cause mortality between single-RFA vs. repeat-RFA for ICM $P = 0.21$; log rank pairwise comparison for VT/VF recurrences between single-RFA vs. repeat-RFA for NICM $P = 0.55$, ICM $P = 0.49$). Additionally, repeat-RFA did not influence first-year all-cause mortality (HR, 1.36; 95% CI, 0.38–4.84; $P = 0.628$) or first-year VT/VF recurrences (HR, 1.19; 95% CI, 0.54–2.601; $P = 0.66$) in Cox regression analysis. This was evident even after adjusting for positive PVS for both all-cause mortality (HR, 0.127; 95% CI, 0.36–4.52; $P = 0.706$) and recurrences (HR, 0.106; 95% CI, 0.48–2.33; $P = 0.86$).

Table 2. Univariate and multivariate Cox proportional hazards analysis for predictors of death or VT/VF recurrences during the first year of follow-up after ablation

Parameter	Univariate model		Multivariate model	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age	1.03 (0.9–1.06)	0.071		
Repeat-RFA	1.1 (0.5–2.4)	0.768		
NYHA III/IV at admission	2.4 (1.1–5.1)	0.018	1.6 (0.7–3.4)	0.218
Moderate or severe FMR at admission	1.7 (0.8–3.6)	0.156		
AF at admission	1.4 (0.9–2.2)	0.110		
LVEF	0.97 (0.94–1.006)	0.108		
NICM	1.9 (0.9–4.1)	0.075		
BZ/total scar area percentage	1.02 (0.9–1.05)	0.177		
Positive PVS	9.7 (4.1–22.9)	<0.001	8.8 (3.6–21.2)	< 0.001
Ablation-related non-vascular access- related complication	2.4 (0.8–7.4)	0.115		

Abbreviations: BZ, border zone; FMR, functional mitral regurgitation; HR, hazard ratio; NICM, non-ischemic cardiomyopathy; RFA, radiofrequency catheter ablation; other — see Table 1

We observed that during the first year after ablation no patients died after obtaining negative PVS, whereas 3 out of 12 (33.3%) with positive PVS died ($P = 0.011$). Recurrences were observed more frequently during the first year in repeat-RFA patients with positive PVS ($n = 8$; 66.7%) compared to negative PVS ($n = 2$; 9.1%; $P = 0.001$).

DISCUSSION

Patient and procedural characteristics

Current evidence regarding repeat-RFA VT procedures stems from five previously published sources [3–7]. Notably, our paper exclusively analyzed ES patients requiring repeat-RFA (which only represented up to 60% of previous cohorts [3]). The rationale of a dedicated analysis was based on the previous observation that patients who require redo procedures are more likely to present in electrical storm conditions [3, 4]. Repeat-RFA patients are more frequently affected by NICM and require more epicardial access and ablation, which has been demonstrated [3]. The incremental value of epicardial substrate identification and ablation has also been shown in patients with previously failed endocardial ablations (even in the setting of ischemic cardiomyopathies with endo-epicardially extending scars) [5, 7]. Although both compared subgroups had similar LVEF and heart failure severity at admission, repeat-RFA subjects had a higher severity of functional mitral regurgitation and significantly longer hospitalizations. This is a consequence of more frequent pericardial effusions that required specific management, considering the higher need for epicardial ablation (one in three repeat-RFA patients). Interestingly, although we expected repeat-RFA procedures to encounter greater extensive total scar and BZ area due to previous ablations, there was no significant difference compared to single-RFA cases.

Importantly, the rate of SMVT elimination by ablation was comparable in the single-RFA and the repeat-RFA subgroups (in approximately two-thirds of cases), which is similar to reported results stemming from post-infarction repeat-RFA cases [5]. In contrast, Tzou et al. [3] showed

that repeat-RFA is less effective than index ablations, as almost 40% of patients are still inducible after ablation. Notably, even though pre-ablation amiodarone treatment was comparable between subgroups, it was more prevalent than in the work by Tzou et al. [3], which may impact the observed rate of residual VT inducibility. Both subgroups had a significantly comparable high rate (>75%) of RMN use during ablations, which is particular to our center compared to others in the vicinity. However, Akca et al. [6] emphasized that RMN-based VT ablations appear not to improve procedural results or outcomes compared to manual ablations and only reduce fluoroscopy exposure.

In conclusion, it seems that despite higher procedural complexity in terms of epicardial ablation and more frequent non-ischemic substrate, repeat-RFA procedures may achieve similar rates of SMVT non-inducibility as single ablations.

All-cause mortality and VT/VF recurrences during follow-up

In our cohort, both single-RFA and repeat-RFA subgroups demonstrated high but comparable all-cause mortality (approximately one-third) over 2 years of monitoring. Furthermore, survival analysis during the first year showed comparable rates of death in single- vs. repeat-RFA patients, both in LVEF $\leq 40\%$ and LVEF $> 40\%$ subgroups, in ICM cases, and in both positive and negative results to PVS. Similarly, one-year all-cause mortality was also in line with previously reported data by Tzou et al. [3]. One of the key factors influencing survival after VT ablation is arrhythmic recurrence [2]. Although based on a limited number of cases, this is also evident in our data, as more than one in two patients that suffered recurrences died during follow-up, irrespective of undergoing one or multiple ablations. In contrast, mortality rates for both single- and repeat-RFA patients that did not develop recurrences were approximately 15% over two years of follow-up. Notably, our data suggest that the need for a redo VT ablation procedure did not influence mortality by itself, which differs from current evidence. Data published by the International VT Ablation Center

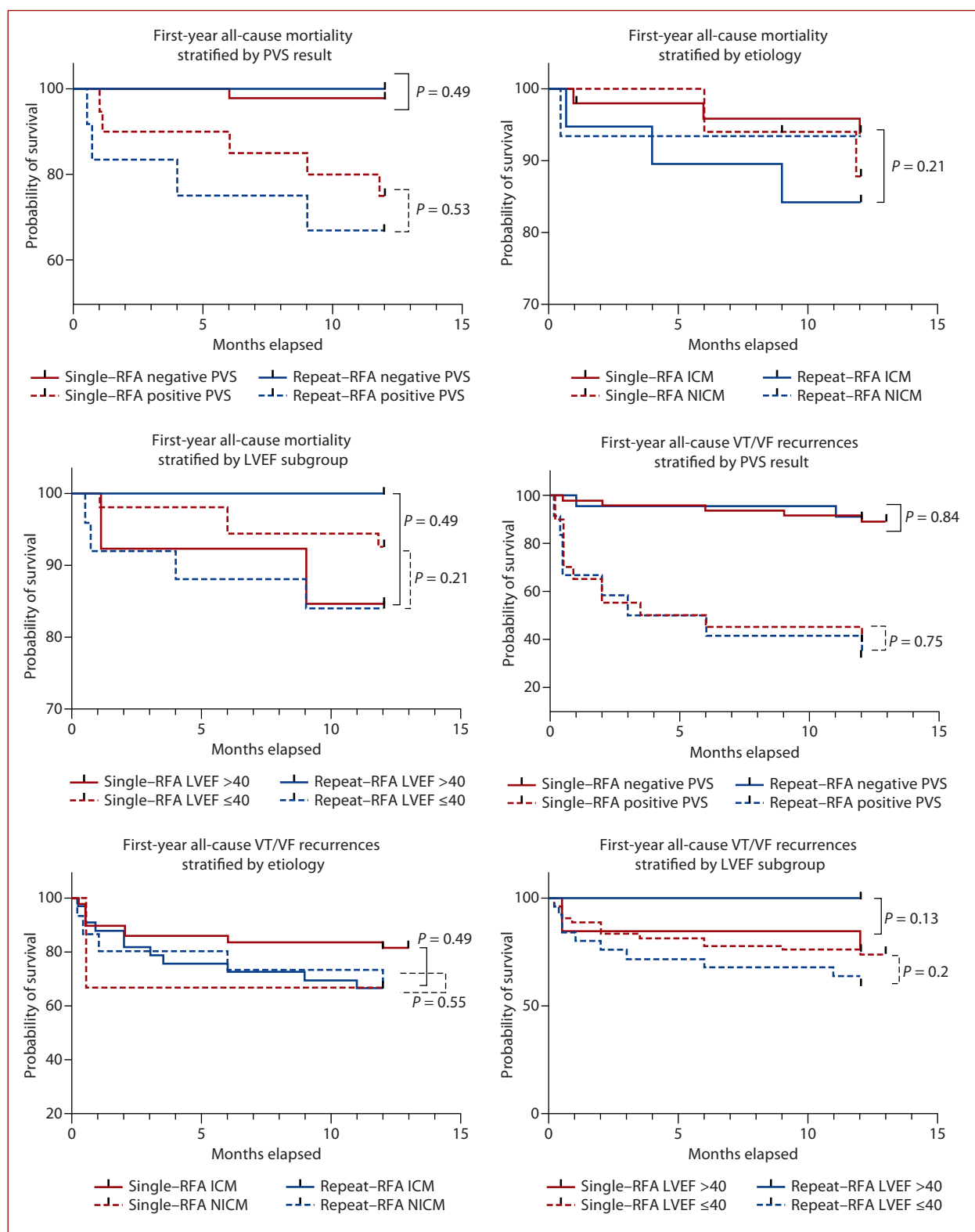


Figure 4. Kaplan–Meier survival curves showing all-cause mortality and VT/VF recurrences during follow-up dichotomized by the type of RFA (single vs. repeat-RFA subgroups) and stratified by PVS result (left column) and type of etiology (ICM vs. NICM) (central column) and LVEF subgroup (right column)

Abbreviations: ICM, ischemic cardiomyopathy; NICM, non-ischemic cardiomyopathy; PVS, programmed ventricular stimulation; other — see Figures 1 and 3

Collaborative Group [3] clarify that repeat-RFA procedures have worse outcomes compared to single-RFA. However, the authors emphasize that if post-ablation VT recurrence is efficiently precluded (by adequate arrhythmogenic substrate elimination), survival is comparable to that of single-RFA cases [3]. Notably, during the first year after ablation in the repeat-RFA subgroup, achieving end-procedural negative PVS was not followed by any deaths, whereas a positive PVS was associated with a rate of mortality of 33.3%, which emphasizes the importance of obtaining VT non-inducibility for redo procedures.

Recurrences were similar in repeat-RFA compared to single-RFA cases, affecting 38.2% and 34.3% of patients, respectively, over the monitored interval. Residually inducible SMVTs at end-procedural PVS independently induced an eight-fold higher risk of events during the first year after ablation in our prediction model. In this sense, elimination of all arrhythmogenic substrate is paramount to reduce the risk of future arrhythmic episodes. However, as shown by Yokokawa et al. [19], new VTs after an index ablation may rely on either new circuits formed at the vicinity of the radiofrequency sites or on a distinct substrate that was not considered to be potentially arrhythmogenic and was not the focus of ablation or end-procedural testing, or on newly-formed substrate [20]. Evidently, incomplete index ablation is also commonly encountered and should mandate adequate end-procedural testing [20]. Our data showed that persistent VT inducibility at the end of the previous ablation significantly shortened the time to requiring a redo procedure. This was particularly evident for patients with previous ablation failure (i.e., persistent inducibility of clinical SMVT), which demonstrated a median interval of three weeks separating the procedures (which were performed during the same hospitalization in seven out of eight cases). This is why more aggressive PVS protocols (which have already been discussed in previous papers) or the utilization of prior-to-discharge noninvasive PVS may enhance detection of residual VT circuits [12, 21–23].

One other observation is that chronic amiodarone treatment was more frequently present compared to previous reports (70.1% compared to 55% in the repeat-RFA subgroup) [3]. Di Biase et al. [24] demonstrated that “on” amiodarone ablations had a higher rate of long-term recurrences possibly due to the effect of hiding relevant substrate during PVS.

Hence, our data suggest that repeat-RFA procedures can offer a similar clinical course in terms of all-cause mortality and recurrences as single-RFA procedures. This, however, requires further validation in larger-scale samples dedicated to ES patients.

Limitations

This study included a limited number of consecutive patients (101) who developed a limited number of events during follow-up (10 deaths and 27 VT/VF recurrences during the first year after ablation and 31 deaths and 36 VT/VF

recurrences overall) that were retrospectively evaluated, which may create statistical bias; furthermore, repeat-RFA subjects had previous ablation procedures performed in other centers before referral to the study hospital, which may impact the uniformity of procedural strategies previously applied; however, it seems there were no significant differences between outcomes in patients who had been previously treated by ablation in other hospitals; moreover, previous three-dimensional mapping information was not available to establish dynamic scar changes responsible for VT recurrences. Due to limited consistency in the collection of data regarding causes of death, we only reported all-cause mortality, irrespective of cardiovascular (arrhythmic or non-arrhythmic) or non-cardiovascular causes.

CONCLUSION

Despite a higher need for epicardial ablation and more frequent non-ischemic myocardial substrate, repeat-RFA for individuals with electrical storm appears to be associated with similar long-term all-cause mortality and recurrences compared to single-RFA patients during the first year after ablation.

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The impact of sacubitril/valsartan on catheter ablation for atrial fibrillation complicated with hypertension: A comprehensive retrospective analysis

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INTRODUCTION

Atrial fibrillation (AF) is one of the most common types of arrhythmia, and it is a significant cause of ischemic stroke and heart failure. Catheter ablation (CA) is considered as a first-line treatment for symptomatic AF, but there is still some recurrence due to atrial structural and/or electrical remodeling and autonomic nervous system dysfunction [1]. This implies that the reverse of atrial structural remodeling may be a promising therapeutic strategy in reducing AF recurrence after CA [2].

Sacubitril/valsartan (Sac/Val) is a combined inhibitor of angiotensin receptor and enkephalin receptor, commonly used for patients with heart failure. In addition to the function of valsartan, Sac/Val inhibits the degradation of biologically active natriuretic peptides, which in turn stimulate natriuresis, diuresis, and vasodilation. It has been shown that Sac/Val can reverse ventricular remodeling and reduce readmission rates and mortality [3]. Up to now, most research of Sac/Val has focused on patients with heart failure (HF) and hypertension. Our study aims to examine the impact of Sac/Val on AF patients with hypertension who have undergone CA, to provide a new idea for the comprehensive treatment of AF.

METHODS

A total of 202 patients (≥ 18 years) with AF and hypertension, who had undergone CA between January 2021 and April 2023, were enrolled in this study. All eligible patients were divided into a Sac/Val group ($n = 124$) and an angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker (ACEI/ARB) group ($n = 98$). The anteroposterior diameter of left

atrium measured by echocardiography was no more than 50 mm. All enrolled individuals had left ventricular ejection fraction (LVEF) $\geq 35\%$. The detailed descriptions of inclusion/exclusion criteria and the follow-up schedule can be found in Supplementary material.

This study was reviewed and approved by the Ethics Committee at Changhai Hospital, Naval Medical University, and it was conducted in accordance with the Declaration of Helsinki and its amendments. The patients/families gave their written informed consent to participate in this study prior to the procedures.

Mapping and ablation were performed under the guidance of CARTO (Biosense Webster, Diamond Bar, CA, US) or EnSite (St. Jude Medical, St Paul, MN, US) mapping systems in addition to standard fluoroscopy. For patients with paroxysmal AF (Par-AF), standard pulmonary vein isolation was performed, while for those with persistent AF (Per-AF), additional linear and/or complex fragmented atrial electrogram ablations were carried out according to the physician's discretion. Sinus rhythm was restored by either ablation or electric cardioversion. Class III drugs (amiodarone) were recommended for Per-AF patients with structural cardiomyopathy, and class I C (propafenone) otherwise. Antiarrhythmic drugs were only used during the 3-month blanking period. No pharmacotherapy was taken after CA for Par-AF.

Statistical analysis

Statistical analysis was performed using SPSS 26 software. The quantitative data are represented as mean (standard deviation) or median

(interquartile range), whereas the categorical data are displayed as frequencies and percentages. The study utilized independent sample t-tests or Wilcoxon rank-sum tests to compare quantitative data, while χ^2 analysis was applied to compare categorical data. A $P < 0.05$ was considered statistically significant. The Kaplan–Meier estimator was used to analyze the freedom of atrial arrhythmia, with the P -value obtained by the log-rank test. Multivariable logistics regression analysis was applied to determine the risk factors of the recurrence of atrial arrhythmias; the items for which $P < 0.2$ values were chosen to build the multivariable model. We have seen that the AF recurrence after CA may be gender related. Other variables such as the left atrium dimension (LAD) and stroke history are strongly related to the treatment effect of atrial fibrillation, so they were built into the multivariable model.

RESULTS AND DISCUSSION

A total of 202 patients were enrolled in the study; 124 received Sac/Val and 98 received ACEI/ARB treatment (Supplementary material, Figure S1). Clinical baseline characteristics between the two groups are shown in Supplementary material, Table S1.

In patients with Per-AF, LVEF increased and N-terminal pro-B-type natriuretic peptide and LAD decreased 1 year after CA compared to the ACEI/ARB group, which were not found in Par-AF (Supplementary material, Table S2). The Sac/Val group showed a reduction of AF recurrence 1 year after CA in Per-AF (47.22% vs. 17.65%; $P = 0.005$) (Supplementary material, Table S3).

Univariate logistic regression analysis showed LAD and Sac/Val were related to the recurrence of AF (Supplementary material, Table S4). The Kaplan–Meier curve analysis (Figure 1) showed that taking Sac/Val after CA in Per-AF can improve the AF-free survival (persistent: log-rank $P = 0.011$).

This study has shown that, compared with ACEI/ARB, Sac-Val can reduce the AF recurrence rate, improve cardiac remodeling, reduce the LAD and N-terminal pro-B-type natriuretic peptide, and increase LVEF after CA for Per-AF, which demonstrates the additional clinical efficacy of dual-acting ARB and neprilysin inhibitor in AF treatment. However, the above findings were not observed in Par-AF.

Atrial remodeling is characterized by atrial enlargement and interstitial fibrosis, which is thought to be the main cause and an independent risk factor of AF [4]. The purpose of upstream therapy of AF is to reverse or stop the negative pathophysiological process leading to atrial remodeling, to reduce the occurrence and recurrence of AF [5].

The left atrial function of patients with AF who received Sac/Val treatment was better than that of valsartan, reflected by the LA peak systolic strain increase, left atrial appendage emptying speed, and ejection fraction [6]. In our study, based on maintaining sinus rhythm after CA, the changes of cardiac structure and LAD in Per-AF have been

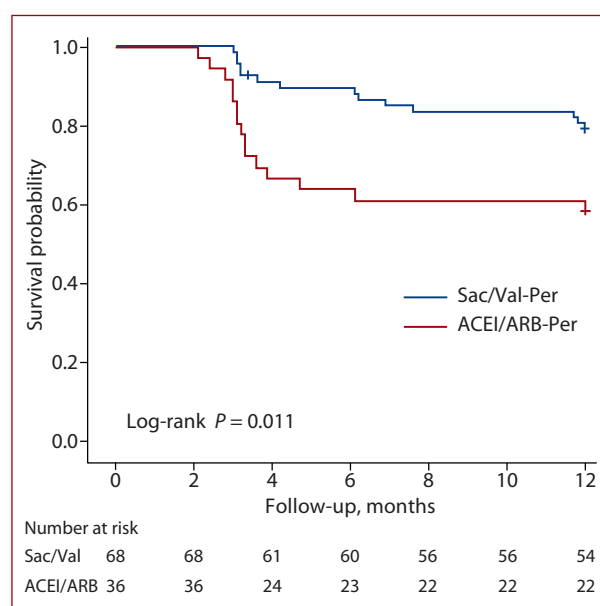


Figure 1. The Kaplan–Meier curve analysis of AF-free survival probability for persistent AF

Abbreviation: ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; Sac, sacubitril; Val, valsartan

observed. Growing evidence indicates that anti-fibrosis may be a potential therapeutic target for AF. The PARABLE trial showed that Sac/Val can increase the LA volume index in the setting of reduced markers of filling pressure in patients with HF. Natriuretic peptide-modulating therapy delivered improved vascular compliance and reduced cardiac chamber stiffness [7], which may indicate that atrial remodeling improvements are the main benefit in Per-AF, with subsequent function improvements. It has also been reported that Sac/Val can improve atrial matrix and electrical remodeling and reduce the susceptibility to AF by inhibiting atrial fibrosis [8]. An experiment on the susceptibility to atrial arrhythmias in rats showed that Sac/Val can reverse LA remodeling, reduce collagen deposition, inhibit the progression of atrial fibrosis, and reduce the susceptibility to atrial arrhythmias by inhibiting p-Smad2/3, p-p38 MAPK, and p-JNK pathways [9]. No difference in AF recurrence was found in Par-AF, which may be due to healthy atrial substrate.

Our study demonstrated that, compared with ACEI/ARB, Sac/Val treatment after ablation of Per-AF can enhance AF-free survival time and improve cardiac remodeling. However, it was a retrospective study, and patients enrolled in our study had both AF and hypertension, so whether Sac/Val can achieve the same effect in patients with normal blood pressure remains to be further studied.

Supplementary material

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

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Cancer patients' knowledge about their therapy and the associated cardiac risk

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INTRODUCTION

Due to progress in medicine, we are now often able to cure cancer patients or manage cancer as a chronic illness. In 2019, the number of cancer survivors reached 16.9 million people, and it is estimated to reach 22 million by 2030 [1].

Advances in cancer treatment have contributed to the growing number of people who have been cured of cancer but may have potential cardiac complications from cancer therapy. The awareness of such complications is therefore becoming important, as it is cardiac complications that primarily affect the prognosis after cancer. Estimates show that cardiac disease is the second cause of death in oncology patients [2]. The European Cardio-oncology Guidelines emphasize that after the completion of cardiotoxic oncologic treatment, reassessment of cardiovascular risk is recommended to determine the course of long-term control. The risk of the above complications depends on the type of chemotherapy. However, in the case of radiation therapy directed at the chest, there is no safe dose for the heart, and the number of complications increases with time [3].

The aim of the study was to find out patients' knowledge and opinions on the cardiac risks associated with cancer therapy and the need for cardiac surveillance during and after treatment.

MATERIAL AND METHODS

Based on a literature review and recommendations, a self-developed questionnaire was prepared with 40 questions (37 single choice and 3 multiple choice) and with 8 additional socio-demographic questions. The tool was consulted with 4 experts in cardiology, public health, patient education, and health care.

The resulting instrument aimed to gather information on respondents' knowledge about their treatment, awareness of the cardiac risk of cancer treatment, and positive and negative health behaviors. A total of 243 patients of the outpatient cardio-oncology clinic located in Poznań filled in the anonymous survey between October 2023 and April 2024. The Bioethics Committee of Poznań University of Medical Sciences, in its statement KB — 919/22, confirmed that the study did not constitute a scientific experiment.

Categorical data were analyzed with the χ^2 test, Fisher–Freeman–Halton test, and/or as the difference between two proportions. Comparison of two groups was performed using the Mann–Whitney U-test. All results were considered significant at $P < 0.05$. Statistical analyses were performed with Statistica 13.0 (StatSoft Inc.) or StatXact 11.0 (Cytel Inc.).

RESULTS

Characteristics of the surveyed group

A total of 243 patients with active cancer agreed to participate in the study. Of these, 24.3% were men and 75.7% were women. The predominant cancers among the respondents were breast cancer (135 [55.6%]) and lymphoma (41 [16.9%]). There were also 16 patients with uterine cancer (6.6%), 7 with lung cancer (2.9%), 13 with leukemia (5.3%), 7 with kidney cancer (2.9%), and 23 with ovarian cancer (9.4%).

Among the respondents, as many as 171 people (70.4%) were afraid of possible cardiac complications after oncological treatment. The following survey questions aimed to determine the actual state of pa-

tients' knowledge of cardiac complications of oncological therapy. When asked about the need for periodic follow-up cardiology examinations, 76 people (31.3%) said they were necessary for up to one year after the end of chemotherapy, 24 people (9.9%) said for up to 5 years, 6 people (2.5%) said for 10 years, and 75 people (30.9%) said for the rest of their lives. More than 20% did not know whether they should have cardiac monitoring after completing chemotherapy treatment. The patients were also asked if cardiac monitoring was necessary 10 years after radiotherapy; as many as 74.1% did not know the answer. Only 20.7% of the respondents answered that cardiac monitoring after chest radiotherapy was necessary for the rest of their lives, and 48.1% of the patients believed such checks were unnecessary.

The same group of respondents was asked about cardiac monitoring during cancer treatment; 68.3% of the patients remembered being consulted by a cardiologist, 81.5% remembered had an electrocardiogram, and 53.5% responded that they had an echocardiogram. Next, the respondents were asked if their doctor had informed them about possible cardiac complications of chemotherapy, and 55.1% said no, while another 20.6% did not remember. A similar question about chest radiotherapy was answered as follows: 57.2% reported that they were not informed by the doctor about possible cardiac complications, and 30.5% did not remember.

Notably, female patients' answers to most of the questions in [Table 1](#) significantly differed from those of male patients.

When asked if they were concerned about possible cardiac complications of cancer treatment (question 1), more women than men answered "Yes". In questions 5 and 6 regarding cardiac monitoring during cancer treatment, fewer men ($P < 0.001$) than women answered "Yes", while more answered "I do not remember". As many as 13.04% of female (F) respondents and 32.20% of male (M) respondents answered "I do not remember" to question 5 and 4.89% (F) and 18.64% (M) to question 6, respectively.

DISCUSSION

Depending on the risk of cardiovascular toxicity, long-term cardiac monitoring should include cardiac follow-up, patient education, and mitigation of cardiovascular risk factors. Our survey shows the state of patients' knowledge during and after oncology treatment. It also shows the extent to which patients feel educated by their physicians about the need to perform cardiovascular checks [4].

In our survey, as many as 70.4% of the patients were concerned about cardiac complications after cancer treatment. On the other hand, only 66.3% of the respondents believed that cardiac checks after chemotherapy are

necessary. The data are even more alarming for chest radiation therapy: just 32.1% of the patients thought that it is harmful to the heart. What is more, only 20.2% of the patients believed that these complications can occur even 10 years after radiation therapy. While not every patient is actively interested in their treatment, it is surprising that in this group of respondents, 46.9% considered their health knowledge to be very good or good.

The presented results may cause considerable concern about the lack of follow-up for many cardio-oncology patients after cancer treatment. This concern is even more significant if we consider the recommendations for cardiac follow-up in this group of patients. Adult asymptomatic cancer survivors in the very high-risk and early high-risk groups should undergo transthoracic cardiac echocardiography at 1, 3, and 5 years after the completion of cardiotoxic cancer treatment and every 5 years after that [5]. Patients after thoracic radiotherapy should also have non-invasive screening for coronary artery disease and carotid artery disease [6]. Even in patients at moderate risk of complications, cardiovascular evaluation after oncology treatment should be considered every 5 years, including clinical examination, electrocardiography, echocardiography, and natriuretic peptide determination.

General population surveys show that more men than women perceive their health as excellent or very good. In addition, it is well known that women are more aware of health warnings related to various health risks and use health services more often than men. For example, it is normative for men in many cultures to avoid health care [7]. Risky health behaviors are an expression of masculinity for men, but for women, gender norms can limit women's power and restrict their ability to take control of their health. In this area, our findings suggest that female patients are more aware of cardiac risks and feel the need for cardiological surveillance than male cancer patients.

The available research demonstrates the critical role of oncology healthcare professionals in promoting healthy lifestyle changes in cancer survivors and informing researchers and healthcare professionals about the methods and strategies they can use to do that effectively [8].

Cancer and cardiovascular disease are significant causes of morbidity and mortality in developed countries. Our study shows that there is a need to educate cancer patients about the impact of cancer therapy on cardiovascular health. Also, special attention should be paid to men because their health literacy might be lower than that of women. Unfortunately, patients are often not informed by practitioners at all or are not informed in an efficient way, which might result from insufficient time for conversations with patients or a lack of training to inform and communicate effectively.

Table 1. Patients' opinions (n = 243) and knowledge about cardiac risk and cardiologic treatment during cancer therapy and sex differences

Results from 243 patients (184 women, 59 men)	Yes		No		P-value of female– male comparisons ^a	
1. Are you concerned about possible cardiac complications of cancer treatment?	171 (70.4%) ♀ 137 (74.46%), ♂ 34 (57.63%)		72 (29.6%) ♀ 47 (25.54%), ♂ 25 (42.37%)		0.014	
	Yes	No	I don't remember		P-value of female– male comparisons ^a	
2. Did your doctor inform you about possible cardiac complications caused by cancer drugs?	59 (24.3%) ♀ 55 (29.89%), ♂ 4 (6.78%)	134 (55.1%) ♀ 94 (51.09%), ♂ 40 (67.80%)	50 (20.6%) ♀ 35 (19.02%), ♂ 15 (25.42%)		0.001	
3. Did your doctor inform you about possible cardiac complications caused by radiation therapy to the chest?	30 (12.3%) ♀ 29 (15.76%), ♂ 1 (1.70%)	139 (57.2%) ♀ 104 (56.52%), ♂ 35 (59.32%)	74 (30.5%) ♀ 51 (27.72%), ♂ 23 (38.98%)		0.010	
4. Did a cardiologist examine you during cancer treatment?	166 (68.3%) ♀ 121 (65.76%), ♂ 45 (76.27%)	61 (25.1%) ♀ 52 (28.26%), ♂ 9 (15.25%)	16 (6.6%) ♀ 11 (5.98%), ♂ 5 (8.48%)		0.115	
5. Did you have an echocardiogram, known as a cardiac echo, during your cancer treatment?	130 (53.5%) ♀ 103 (55.98%), ♂ 27 (45.76%)	70 (28.8%) ♀ 57 (30.98%), ♂ 13 (22.03%)	43 (17.7%) ♀ 24 (13.04%), ♂ 19 (32.20%)		0.003	
6. Did you have an electrocardiogram during your cancer treatment?	198 (81.5%) ♀ 155 (84.24%), ♂ 43 (72.88%)	25 (10.3%) ♀ 20 (10.87%), ♂ 5 (8.47%)	20 (8.2%) ♀ 9 (4.89%), ♂ 11 (18.64%)		0.007	
	Yes	No	I don't know		P-value of female– male comparisons ^a	
7. In your opinion, can chemotherapy “damage” the heart?	182 (74.9%) ♀ 146 (79.35%), ♂ 36 (61.02%)	18 (7.4%) ♀ 13 (7.07%), ♂ 5 (8.47%)	43 (17.7%) ♀ 25 (13.59%), ♂ 18 (30.51%)		0.011	
8. In your opinion, should the heart be monitored during chemotherapy?	196 (80.7%) ♀ 160 (86.96%), ♂ 36 (61.02%)	8 (3.3%) ♀ 4 (2.17%), ♂ 4 (6.78%)	39 (16%) ♀ 20 (10.87%), ♂ 19 (32.20%)		<0.001	
9. In your opinion, should one go to a cardiologist for follow-up after cancer treatment?	161 (66.3%) ♀ 128 (69.57%), ♂ 33 (55.93%)	11 (4.5%) ♀ 9 (4.89%), ♂ 2 (3.39%)	71 (29.2%) ♀ 47 (25.54%), ♂ 24 (40.68%)		0.092	
10. In your opinion, should the heart be monitored after radiation therapy to the chest?	80 (32.9%) ♀ 76 (41.30%), ♂ 4 (6.78%)	79 (32.5%) ♀ 50 (27.17%), ♂ 29 (49.15%)	84 (34.6%) ♀ 58 (31.52%), ♂ 26 (44.07%)		<0.001	
11. In your opinion, can radiation therapy to the chest “damage” the heart?	78 (32.1%) ♀ 70 (38.04%), ♂ 8 (13.56%)	16 (6.6%) ♀ 15 (8.15%), ♂ 1 (1.69%)	149 (61.3%) ♀ 99 (53.80%), ♂ 50 (84.75%)		<0.001	
12. In your opinion, can cardiac complications occur 10 years after radiation therapy to the chest?	49 (20.2%) ♀ 42 (22.83%), ♂ 7 (11.86%)	14 (5.8%) ♀ 12 (6.52%), ♂ 2 (3.39%)	180 (74.1%) ♀ 130 (70.65%), ♂ 50 (84.75%)		0.093	
13. Do you think that every patient undergoing cancer treatment should have a cardiology consultation?	232 (95.5%) ♀ 177 (96.20%), ♂ 55 (93.22%)	3 (1.2%) ♀ 2 (1.09%), ♂ 1 (1.69%)	8 (3.3%) ♀ 5 (2.72%), ♂ 3 (5.08%)		<0.001	
	Very good	Good	Average	Bad	Very bad	P-value of female– male comparisons ^a
14. How would you rate your health knowledge?	30 (12.3%) ♀ 30 (16.30%), ♂ 0 (0%)	84 (34.6%) ♀ 73 (39.67%), ♂ 11 (18.64%)	108 (44.4%) ♀ 72 (39.13%), ♂ 36 (61.02%)	17 (7%) ♀ 6 (3.26%), ♂ 11 (18.64%)	4 (1.6%) ♀ 3 (1.63%), ♂ 1 (1.69%)	<0.001

^aThe last column presents differences ($P < 0.05$) between the answers of male and female respondents. Data were analyzed with the Fisher–Freeman–Halton test or the Mann–Whitney U-test

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Mid- and long-term outcomes of balloon aortic valvuloplasty in pediatric patients. A single-center experience

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INTRODUCTION

Since its introduction, balloon aortic valvuloplasty (BAV) has shown good short- and long-term outcomes in isolated congenital aortic stenosis (AS), comparable to surgery [1], making it the preferred treatment in many centers. However, patients undergoing BAV often require reinterventions, and risk factors for suboptimal outcomes remain unclear. We analyzed our single-center experience to assess the mid- and long-term outcomes of BAV and to identify risk factors for suboptimal results.

MATERIALS AND METHODS

Between 1998 and 2023, a total of 170 patients with AS underwent primary BAV at our center. Of these, 117 patients were included in the study; exclusion criteria were neonatal age at the time of the procedure, previous BAV, or complex heart defect. Follow-up data were available for 90 patients (77%) with median follow-up time of 7 years (interquartile range [IQR] 1.0–13 years). Follow-up was collected up to May 31, 2024. Data were obtained from inpatient and outpatient records. The primary long-term endpoint was the need for reintervention. The study protocol was approved by the Local Ethics Committee (approval no. BNW/NWN/0052/KB/152/24).

At our institution, BAV is the preferred treatment for patients with AS who meet widely accepted criteria [2].

The balloon was selected to achieve a balloon-to-annulus ratio between 0.8 and 1.0. If the initial valvuloplasty did not yield satisfactory results (gradient exceeding 35 mm Hg or a gradient reduction <50%), a subsequent valvuloplasty was performed using the same or a 1–2 mm larger balloon. The degree of

aortic regurgitation (AR) was assessed using both echocardiography and aortography.

Early procedural success was defined according to previously established criteria [3]. A suboptimal outcome was defined for patients meeting at least one of the following conditions: a residual gradient <35 mm Hg, <50% gradient reduction, and more than minor (≥ 1 grade) change in AR.

Echocardiographic Z-scores were derived from the study by Lopez et al. [4].

Statistical analysis

Statistical analyses were performed using MedCalc software (MedCalc Software, Ostend, Belgium). Normality of data distribution was assessed using the Shapiro–Wilk test. Data are presented as median with IQR to account for the non-normal distribution of variables in the study group. Quantitative data were compared using the Mann–Whitney U test for independent samples or the Wilcoxon test for paired samples. Categorical variables were compared using the Pearson χ^2 test or the Fisher’s exact test. Kaplan–Meier survival curves were used to assess survival and freedom from reintervention, with the log-rank test comparing curves between subgroups. Potential predictors of reintervention after BAV were assessed using Cox proportional hazards regression analysis. A two-tailed $P < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

Of the 117 patients included in the study (83% male, $n = 97$), 61 (52.14%) were infants. The median age was 1 year (IQR 0.17–9 years), and the median weight was 10.9 kg (IQR 5.8–39 kg). The median aortic valve (AV) di-

ameter measured 13 mm (IQR 9.5–19 mm), corresponding to a median Z-score of +1.3 (range +0.4 to +2.5). The AV morphology was predominantly bicuspid in 56 patients (47.9%), tricuspid in 38 patients (32.5%), and undefined in 23 patients (19.7%).

Prior to the procedure, mild AR was observed in 19 patients (16.2%), and moderate AR was identified in one individual.

Vascular access was obtained *via* the femoral artery in 114 patients and the carotid artery in 3 patients. To ensure balloon stability during the procedure, rapid ventricular pacing was used in 37 patients (31.6%), while adenosine injection was administered to 7 patients (6%), particularly in smaller children. After BAV the median peak-to-peak gradient decreased from 69 mm Hg (IQR 55–82.5) to 30 mm Hg (IQR 18–38; $P < 0.001$).

Comprehensive baseline characteristics and early effects of BAV are shown in Supplementary material, *Table S1*. After BAV, non-trivial (more than mild) AR was observed in 14 patients (12%), out of which in 8 (6.8%) patients AR was moderate and in 6 patients (5.1%) it was moderate/severe; none of those patients required immediate surgery.

Significant complications occurred in 4 patients (3.4%) — persistent femoral artery occlusion ($n = 2$), balloon catheter rupture ($n = 1$), and acute pulmonary edema after induction of anesthesia in a hemodynamically unstable patient ($n = 1$).

An optimal BAV outcome was achieved in 60 patients (51.3%). Among the 57 patients (48.7%) with suboptimal outcomes, non-trivial AR (more than mild) was identified in 14 patients (12%), less than 50% gradient reduction in 34 patients (29%), and a residual gradient exceeding 35 mmHg in 36 patients (30.7%). Some patients exhibited multiple contributing factors associated with suboptimal outcomes. No risk factors for suboptimal early outcome were found. Univariate analysis of variables affecting early outcomes is available in Supplementary material, *Table S2*.

No mortality was observed among patients following BAV.

Thirty-four of 90 patients with long-term follow-up (38.2%) required reintervention. The median time from BAV to reintervention was 13.4 years (95% CI, 9.2–17.3). Reinterventions included the following: surgical aortic valve replacement in 27 patients (30%), repeated BAV in 5 patients (5.5%), Ross surgery in one patient, and Ozaki surgery in one patient; indications and timing of reintervention are available in Supplementary material, *Table S3*. At 5 and 10 years after BAV, the proportion of patients without reintervention was 80.3% and 61%, respectively (**Figure 1A**). The cumulative incidence of freedom from reintervention at 20 years post-BAV was 31%. In the subgroup of patients with an optimal early result, 18 (52.2%) required reintervention compared to 16 (47.8%) patients with suboptimal early effect ($P = 0.92$).

Patients who underwent BAV during infancy had higher reintervention-free survival vs. older children, with 10-year

freedom from reintervention rates of 84.2% vs. 41.7%, respectively ($P < 0.001$) (**Figure 1B**). Patients with tricuspid aortic valve fared better than those with bicuspid valve, showing 10-year freedom from reintervention rates of 73.5% versus 54.8%, respectively ($P = 0.046$) (**Figure 1C**). Additionally, patients achieving a residual peak-to-peak gradient reduction of $\geq 50\%$ after BAV had better outcomes than those with less than 50% reduction, with 10-year freedom from reintervention rates of 67.7% vs. 41%, respectively ($P = 0.04$) (**Figure 1D**). Long-term outcomes of BAV are presented in **Figure 1**. The univariate analysis of variables associated with the need for reintervention is detailed in Supplementary material, *Table S4*. Bicuspid AV emerged as the only predictor of reintervention in the Cox regression model, with an HR of 3.2 (95% CI, 1.0–9.9; $P = 0.049$). The results of the Cox proportional regression analysis are provided in Supplementary material, *Table S5*.

BAV remains a safe and effective treatment for pediatric AS, offering outcomes comparable to surgical interventions [1]. Advantages of BAV include faster patient recovery and the absence of surgical scarring and adhesions, which is crucial given that many patients require future cardiac surgeries such as the Ross procedure or surgical aortic valve replacement.

Despite its benefits, long-term outcomes of BAV are variable, with 10-year freedom from reintervention rates ranging from 46% [1] to 89% [5]. Despite advancements, long-term results of BAV in pediatric patients have remained relatively consistent over the years [6]. This unpredictability in long-term results is also observed in adult BAV procedures [7], where early improvements do not consistently correlate with sustained benefits, emphasizing the need for close and precise follow-up in both pediatric and adult patients. Our study reinforces that patients with bicuspid aortic valves have worse long-term outcomes compared to those with tricuspid valves. This finding supports that valve morphology plays a significant role in long-term prognosis.

The most novel finding of our study is that we found that infants had a higher probability of freedom from reintervention, which has only been hinted at in previous studies [8, 9]. While this contrasts with some studies reporting poorer outcomes in very young children, those studies often included neonates with critical valve stenosis and hypoplastic valves [6]. In infants, the valve tissue may be more responsive to dilation before significant fibrosis of fused commissures occurs, potentially explaining the better outcomes observed [10].

Attempts to improve BAV outcomes, such as the use of right ventricular pacing (RVP), have yielded inconsistent results. Our study did not demonstrate a significant benefit of RVP, aligning with other research that questions its efficacy in this context [6].

The following limitations of our study should be borne in mind: retrospective design, limited follow-up retention, small sample size (especially affecting the results of

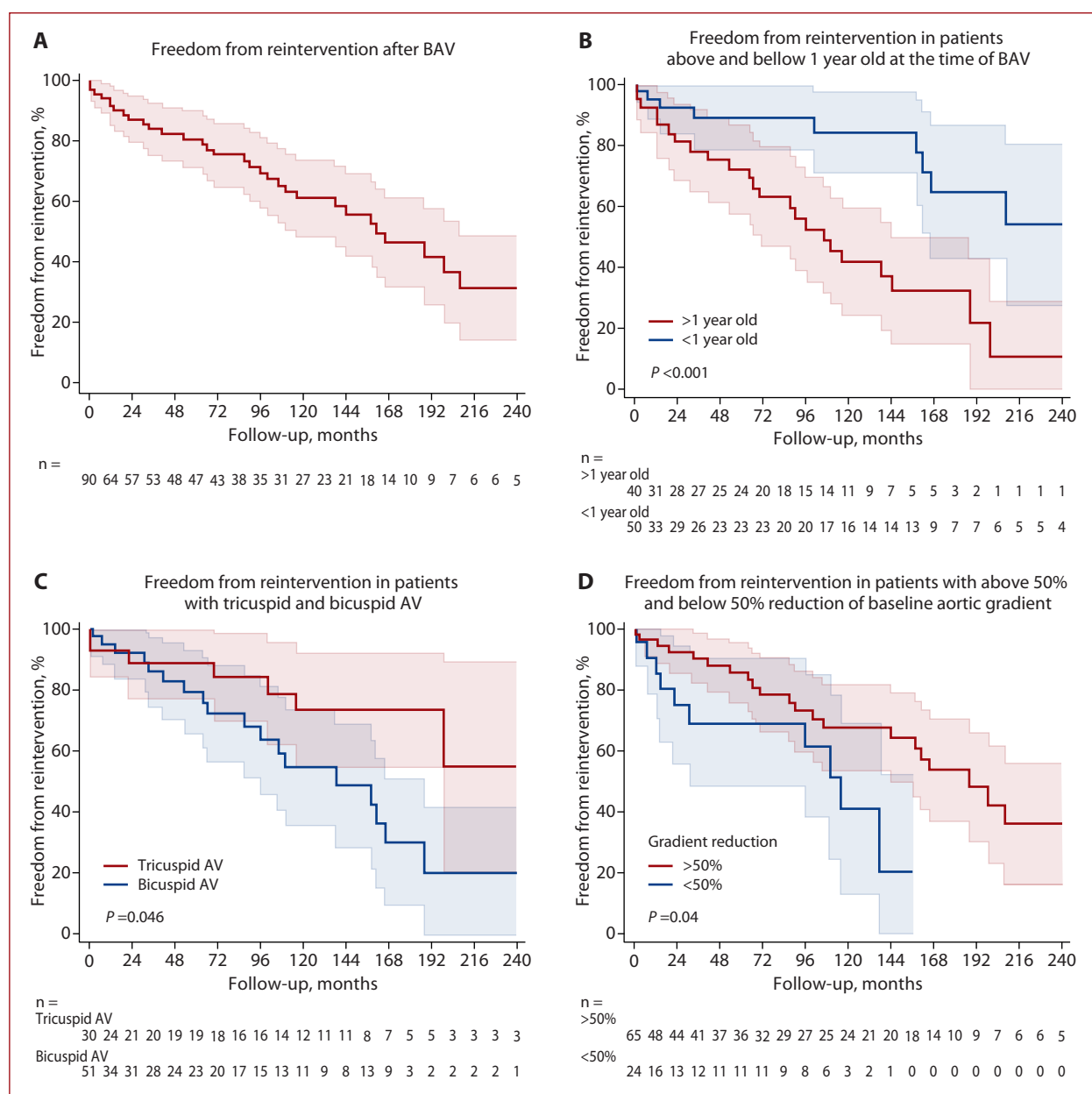


Figure 1. Long-term outcomes of BAV

Abbreviations: AV, aortic valve; BAV, balloon aortic valvuloplasty

multivariable regression analysis), basic characterization of aortic valve morphology, and the long duration of patient enrollment.

Overall, BAV continues to be an effective palliative procedure with satisfactory mid- to long-term results. Future improvements may come from enhanced patient selection based on aortic valve morphology, the timing of the procedure, and further research into techniques like RVP to optimize long-term outcomes.

Supplementary material

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

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Impaired occluders endothelialization after transcatheter paravalvular leak closure

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INTRODUCTION

Transcatheter closure of intracardiac defects has a history spanning several decades. The occluders used in this method are designed to become covered by endothelium over time, which isolates their surface from contact with blood. The duration of this process is estimated to take 3 to 6 months for occluders used in the closure of atrial septal defects [1–3]. Data on endothelialization of other intracardiac occluders are rather casuistic [4]. According to the European Society of Cardiology guidelines, antiplatelet therapy is recommended for at least this duration [5]. However, it is noteworthy that the American College of Cardiology/American Heart Association guidelines do not specify the duration of such therapy [6]. Various therapeutic strategies are proposed for other intracardiac implants, such as occluders used for left atrial appendage closure [7] or transcatheter valve implantation [8], which typically involve at least several months of antiplatelet therapy.

Transcatheter closure of paravalvular leaks (PVLs) is an established therapeutic method, recommended in class IIa under specific circumstances [8, 9]. However, there is lack of data describing the healing process of the occluders used in this method. Recommendations regarding antiplatelet therapy following the procedure.

The aim of the present study was to collect data describing the process of endotheli-

alization on explanted occluders used for transcatheter closure of PVLs.

MATERIAL AND METHODS

The study material was collected retrospectively from centers performing transcatheter closures of PVLs on surgically implanted valves. The inclusion criterion was a minimum of 30 days between occluder implantation and explantation, along with the presence of photographic documentation of the explanted occluder. The process of endothelialization was assessed visually based solely on the provided images.

RESULTS AND DISCUSSION

Data were obtained from 10 patients who had their occluders explanted in 5 referral centers. In 6 cases, the patients required reoperation, during which the previously implanted devices were removed. In 3 cases, the occluders were removed percutaneously, and one device was evaluated during autopsy. The shortest duration of device retention at the implantation site was 30 days, while the longest was 2332 days. The explanted occluders represented the most commonly used types during transcatheter closure of PVLs: Occlutech Paravalvular Leak Device Occluder (PLD) and Amplatzer Valvular Plug III (AVP III). Occluders removed from paravalvular leaks around the mitral valve predominated.

Table 1. Explanted paravalvular leak (PVL) occluders — summary of clinical and procedural data

No	Sex; age	Position	Valve type	Plug	Removal reason	Approach	Time to removal, days	ATT
1	M; 57	Mitral	Mech.	PLD	MHA	S	40	VKA
1'	M; 64	Aortic	Biol.	PLD	MHA, HF	S	2332	VKA
2	W; 61	Mitral	Mech.	PLD	Leaflet entrapment	S	173	VKA
3	M; 58	Mitral	Biol.	PLD	MHA	S	78	ASA
4	W; 63	Mitral	Mech.	PLD	MHA	S	61	VKA
5	M; 73	Mitral	Biol.	AVPIII	MHA	S	50	VKA +ASA
6	W; 67	Mitral	Mech.	AVPIII	Embolization	P	180	VKA
7	M; 70	Mitral	Mech.	AVPIII	HF	S	450	VKA
8	M; 70	Mitral	Mech.	PFOO	HF	S	30	VKA
9	W; 66	Mitral	Mech.	AVPIII	Leaflet entrapment	P	90	VKA
10	W; 57	Aortic	Biol.	AVPIV	MHA, HF	P	1095	ASA

Abbreviations: ASA, acetylsalicylic acid; ATT, antithrombotic therapy; AVP III, Amplatzer Vascular Plug III; AVP IV, Amplatzer Vascular Plug IV; HF, heart failure; M, man; MHA, mechanical hemolytic anemia; P, percutaneous; PLD, Occlutech Paravalvular Leak Device; S, surgical; VKA, vitamin K antagonist; W, woman

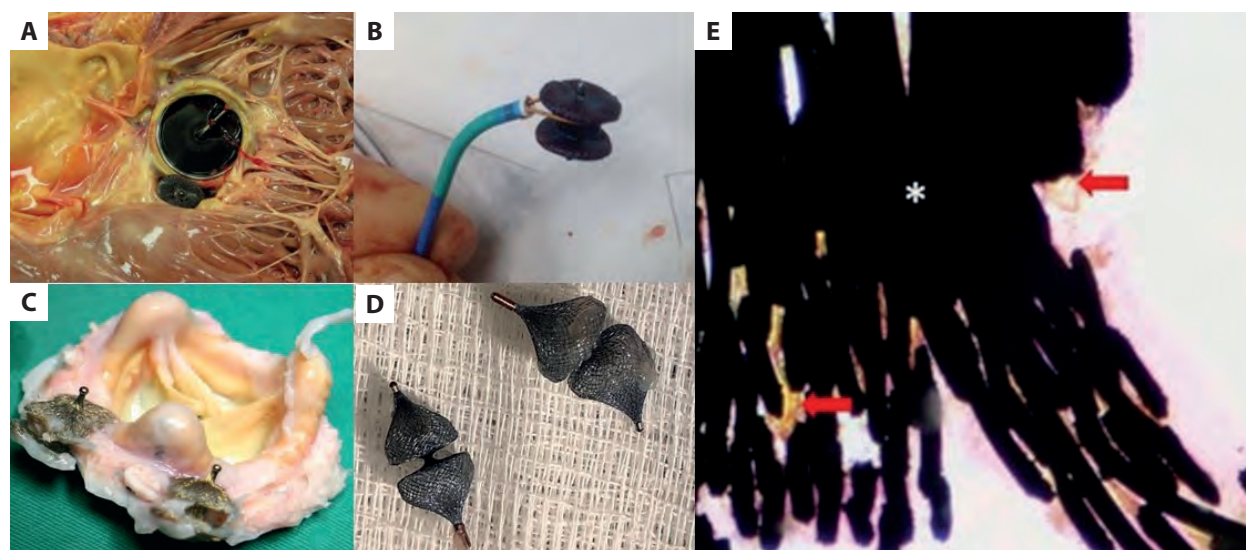


Figure 1. A series of explanted paravalvular leak occluders. Visual assessment revealed incomplete endothelialization of the devices. **A.** Case of a patient with a history of mitral mechanical valve replacement and paravalvular leak closure with the Amplatzer Vascular Plug III device explanted 15 months post-implantation. **B.** The AVP III occluder removed percutaneously 180 days after the procedure due to device embolization. **C.** Aortic bioprosthesis and Paravalvular Leak Device Occlutech occluders removed due to recurrent hemolytic anemia and heart failure symptoms almost 6 years after the index procedure. **D.** Percutaneously explanted Amplatzer Vascular Plug IV device in a patient with a history of aortic valve replacement 3 years after the procedure. **E.** Histological examination of paravalvular leak occluder removed after 6 months due to embolization. Occluder elements (black) (*), small thrombi (arrows), hematoxylin and eosin (HE) staining, magnification 40×

A complete summary of clinical and procedural data is provided in Table 1. Visual assessment showed that none of the occluders was fully covered by endothelium; only small islets of tissue covering a minor portion of the device were visible (Figure 1A–D). In one case, in addition to visual evaluation, histological examination was obtained, which pertained to an AVP III occluder that embolized 6 months post-implantation (Figure 1E).

The collected material documents cases of incomplete endothelialization of devices implanted percutaneously for paravalvular leaks around surgically implanted heart valve prostheses, even in long-term observations. This pertains to the main types of occluders used for PVL closure; however, it may be presumed that impaired healing could affect all devices used in these procedures. The process of device neoendothelialization in humans is not well understood,

and data regarding possible differences between particular intracardiac locations are lacking. Currently, there is no reliable method to assess the endothelialization of intracardiac occluders *in vivo*. One proposed solution is angiographic evaluation [10], which allows for the detection of areas of the occluders not covered by tissue, but it is unlikely to confirm complete endothelialization. A method with greater resolution is optical coherence tomography, which has been successfully used to evaluate intracardiac devices [11]. Computed tomography permits assessment of the entirety of intracardiac devices, as demonstrated in studies evaluating the healing process of left atrial appendage occluders [3], although this method has significantly lower spatial resolution compared to optical coherence tomography.

It is worth noting that a significant portion (50%) of the explanted occluders was due to persistent severe hemol-

ysis. This underscores the necessity for meticulous closure of the leak during the procedure, particularly given the low likelihood of residual leaks diminishing in long-term follow-up [12].

The presented data cannot serve as a basis for recommending a specific anticoagulant/antiplatelet strategy following transcatheter closure of PVLs. In most cases, these patients either require chronic oral anticoagulation or antiplatelet therapy for other indications. It seems challenging to recommend escalating these therapies in this group for several months post-implantation due to the lack of a defined timeline for the healing of occluders.

CONCLUSION

Occluders implanted for paravalvular leaks around surgically implanted heart valves, especially in more complex clinical scenarios, may not undergo endothelialization in long-term follow-up. Drawing conclusions regarding recommended anticoagulant/antiplatelet therapy in this patient group requires further clinical research.

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Impact of intravascular imaging on five-year mortality in patients undergoing unprotected left main coronary artery PCI: A propensity score-matching analysis from the BIA-LM registry

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INTRODUCTION

Intravascular imaging-guided percutaneous coronary intervention (PCI) was recently shown to reduce risk of cardiac death, target vessel-related myocardial infarction (MI), and recurrent revascularization as compared to angiography-guided complex coronary angioplasties [1, 2]. Favorable results of the RENOVATE-COMPLEX-PCI and OCTOBER randomized clinical trials (RCT) found reflection in the upgrade to class I recommendation in the latest 2024 European Society of Cardiology guidelines for the management of chronic coronary syndromes [3]. Although both studies permitted patients with unprotected left main coronary artery (LMCA) disease, this population is widely underrepresented in most of conducted RCTs, leaving a significant gap in evidence, especially in terms of all-cause mortality reduction.

Thus, the aim of the study was to assess the impact of intravascular imaging-guided PCI on survival in patients undergoing LMCA angioplasty [4].

MATERIAL AND METHODS

Study population, design, and procedures

The design and study population of the BIA-LM Registry (Białystok Left Main Registry) was described previously [4]. In brief, the registry included 998 patients undergoing LMCA PCI in years 2008–2022. For the needs of the

current analysis, the population included 815 patients with unprotected LMCA, who were divided into two groups based on the use of intravascular imaging. In the registry, the decision on the type, timing, and modality of used tools was left to the operator's discretion. Images were obtained using commercially available intravascular ultrasound (IVUS) or optical coherence tomography (OCT) devices. The decision on stent sizing, technique of angioplasty, and eventual peri-procedural complication management was made by the operator, based on the experience and local protocols. Post-PCI antiplatelet regimen was prescribed in accordance with the pertinent European Society of Cardiology recommendations.

The analyzed endpoint was mortality at five-year observation, which was obtained for all the patients from the Center for Information Technology, Minister of Digital Affairs, Poland (valid as for 13.06.2022).

Ethical considerations

The study was approved by the Bioethics Committee of the Medical University of Białystok, Białystok, Poland (approval no. APK.002.78.2022 obtained on 10.02.2022) and adheres to Helsinki Declaration as revised in 2013.

Statistical analysis

Summary statistics are presented as number (n) of occurrences and frequencies (%) for cat-

Preliminary results were presented at ESC Congress, August 30–September 2, 2024, London, United Kingdom and International Congress of the Polish Cardiac Society, September 19–21, 2024, Katowice, Poland

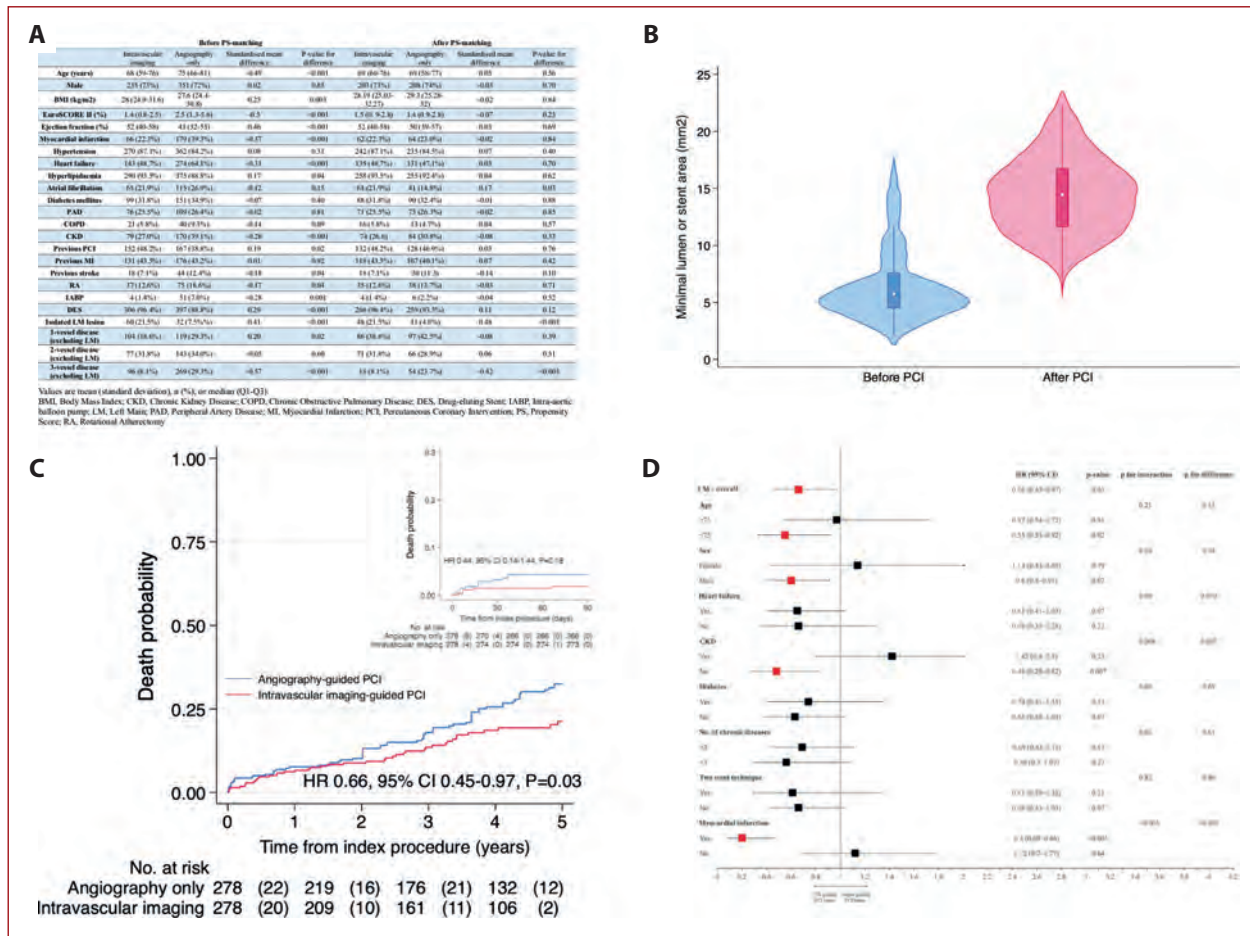


Figure 1. Study population baseline characteristics and outcomes. **A.** Baseline characteristics of the studied population before and after propensity score matching. **B.** Violin plot showing baseline minimal lumen area and minimal stent area in the left main coronary artery after PCI. **C.** Kaplan–Meier curves showing differences in 5-year survival after propensity score matching. Inner graph shows 90-day mortality. **D.** Forest plot showing subgroup analysis after propensity score matching

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; LM, left main coronary artery; PCI, percutaneous coronary intervention

egorical variables and mean with standard deviation (SD) for continuous variables if normally distributed. Non-normal distributions of continuous variables are summarized as median and interquartile range (IQR). Differences between subgroups were assessed using Student's t-test or the Wilcoxon rank-sum test for continuous variables and using the χ^2 test or Fisher exact test (in cases when the expected count of variable was <5) for categorical variables.

Multivariable Cox proportional hazard regressions with variables identified with LASSO cross validation were used to determine mortality predictors. Then, a model including variables identified in multivariable analysis for propensity score matching (PSM) was built (a one-to-one nearest neighbor matching was performed with replacement [caliper 0.2]) [5]. Finally, we assessed differences between subgroups and moderation effects in predefined groups.

Differences in survival were assessed using Cox proportional hazard regression models in the unmatched and matched cohorts. Results are presented as hazard ratio (HR) with 95% confidence interval (CI). For all analyses, the level of statistical significance was set at $P < 0.05$.

All statistical analysis was performed using Stata Statistical Software (StataCorp, 2023, version 18, TX, US).

RESULTS AND DISCUSSION

Detailed information regarding baseline characteristics and outcomes before and after PSM are presented in **Figure 1**. Unadjusted analysis included 815 patients undergoing LMCA PCI ($n = 322$ with intravascular imaging). Propensity score matching resulted in final cohort of 278 balanced for clinical and procedural characteristics pairs. Median age was 69 years (IQR 59–77), and the majority of patients were male (74%). Out of the cohort of 278 patients, 262 patients underwent an IVUS-guided procedure, 16 patients had OCT-only guidance, and 2 patients had OCT- and IVUS-guided PCI. The median pre-procedural minimal lumen area was 5.8 (4.5–7.6) mm² and post-PCI minimal stent area 14.5 (11.6–16.8) mm². Total time at risk was 654,723 days, and the median follow-up was 3.6 years during which there were 114 (20.5%) deaths.

Intravascular imaging was associated with 68% (HR, 0.32; 95% CI, 0.24–0.44; $P < 0.001$) mortality reduction in

the unmatched population. After PSM, use of intravascular imaging was still associated with significant 34% (HR, 0.66; 95% CI, 0.45–0.97; $P = 0.03$) mortality reduction as compared to angiography-guided procedures. The subgroup analyses estimates were directionally consistent toward benefit of intravascular imaging, with significant differences and interaction in patients with chronic kidney disease ($P_{\text{difference}} = 0.007$, $P_{\text{interaction}} = 0.008$) and MI ($P_{\text{interaction}} = 0.001$).

Our findings align with trends reported in studies investigating the impact of intravascular imaging among patients undergoing complex PCI, and they give further insight into benefits in term of all-cause mortality reduction after LMCA angioplasty [1, 2, 4, 6]. In subgroup analysis there was a mostly homogenous trend across subgroups for better survival with use of intravascular imaging. Significant interactions suggest that the impact of additional tools may be different, especially in patients with sustained renal function and those with MI.

When it comes to the overall impact of intravascular imaging, the results from RCTs differ from those of observational studies [7]. While OCTOBER and RENOVATE-COMPLEX-PCI showed reduction in major adverse cardiovascular event (MACE) rates in the population undergoing complex PCI, Bruno et al. [8] in their recent analysis of the BIFURCAT-ULTRA registry found that IVUS-guided PCI was associated with a reduction in MACE rates only in patients with LMCA lesions (HR, 0.62; 95% CI, 0.46–0.83), while such an approach was not superior to angiography alone in non-LMCA bifurcations (HR, 1.12; 95% CI, 0.83–1.51; $P_{\text{interaction}} = 0.006$) [1, 2, 8]. Our investigation contributes to real-world evidence, showing that intravascular imaging may not only be related to a reduction in terms of MACE, but also in the hard endpoint — all-cause mortality [7].

Moreover, we tried to investigate subgroups that may benefit from intracoronary imaging. This is especially important when considering the increasing burden of multimorbidity with the concurrent trend towards worse prognosis 30 days after the procedure [6]. Better outcomes of intravascular imaging-guided PCI in the population of patients with acute coronary syndrome (ACS) and complex coronary artery true bifurcation lesions were reported by Chen et al. [9]. In our analysis, MI patients benefited more from intravascular imaging, which might be related to less frequent geographical miss and better stent expansion — both factors known to have a negative impact on patients with ACS [9, 10]. We also found that intravascular imaging could be more suitable for patients without chronic kidney disease — whether this is related to prolonged procedural times and a greater amount of used contrast dye is yet to be elucidated.

The current study has several limitations, apart from those described previously [4]. Firstly, the BIA-LM Registry was conducted at an experienced invasive cardiology referral center within a large tertiary hospital. Consequently, one inherent limitation of single-center registries is the restrict-

ed generalizability of their outcomes. Secondly, subgroup analysis was conducted in relatively small populations and should be considered hypothesis-generating only. Despite the use of PSM and well-balanced baseline characteristics, significant differences were observed, particularly a higher rate of patients with isolated LMCA lesions in the intravascular imaging arm. Although a larger number of patients with additional lesions might have influenced survival, we stress the fact that the information provided regarding the moment of index procedure and the analyzed data did not include stepwise revascularization during follow-up, which is a standard procedure in our department.

In conclusion, use of intravascular imaging was related with lower rates of five-year mortality in the overall and propensity score-matched population. Subgroup analysis demonstrated potential benefits, especially in patients with MI and with sustained renal function. To elucidate the optimal treatment strategy, future studies investigating differences in outcomes of intravascular imaging-guided PCI and coronary artery bypass grafting should be considered.

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Women in interventional cardiology: Analysis of procedural volumes, academic achievements, and scientific contributions in Poland

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INTRODUCTION

Gender-related disparities persist across multiple domains of medicine, affecting not only access to medical care, clinical presentation, and therapeutic approaches, but also scientific research participation [1, 2]. While numerous global initiatives, including networking opportunities, mentoring programs, and Women in Cardiology working groups, strive to address these disparities, significant challenges remain. For instance, recent studies have examined gender gaps in leading author positions within Polish cardiology publications [3, 4]. Although opportunities for women's medical education are increasingly promoted, the path to becoming a successful specialist remains challenging. Female physicians face unique obstacles in balancing personal and professional responsibilities, while societal expectations and gender biases impede career advancement. Still, women in medicine continue to be underrepresented in managerial positions, receive lower compensation, and face higher rates of workplace discrimination, including mobbing and nepotism [5, 6].

Given the ongoing relevance of these gender-based disparities in cardiology, our study aims to examine two specific aspects within the Polish medical community: women's participation in interventional cardiology and their scientific achievements.

METHODS

Data from the Polish National Registry of PCI (ORPKI) were analyzed for all operators who performed at least one coronary angiography or percutaneous coronary intervention (PCI) between 2014 and 2023. After reviewing for completeness and duplicates, operator gender was determined by given name. The database was enriched with information on work experience and scientific achievements. Professional experience was calculated from medical license obtainment to 2024 or date of death, using the central register of medical doctors (<https://rejestr.nil.org.pl/>). For missing data, dates were estimated based on specialty certification. Scientific degree information was collected from the central register of medical doctors and <https://ludzie.nauka.gov.pl/>. Publication metrics were gathered manually from two sources: PubMed (<https://pubmed.ncbi.nlm.nih.gov/>) for total publications and first/last author positions, and Web of Science Core Collection (Clarivate Analytics) for publication count, citations, and H-index. Papers outside cardiology and multicenter trials without direct authorship were excluded.

Categorical variables are presented as frequencies (percentages), with group differences assessed by χ^2 test or Fisher's exact test. Continuous variables, all non-normally distributed, are shown as medians with inter-

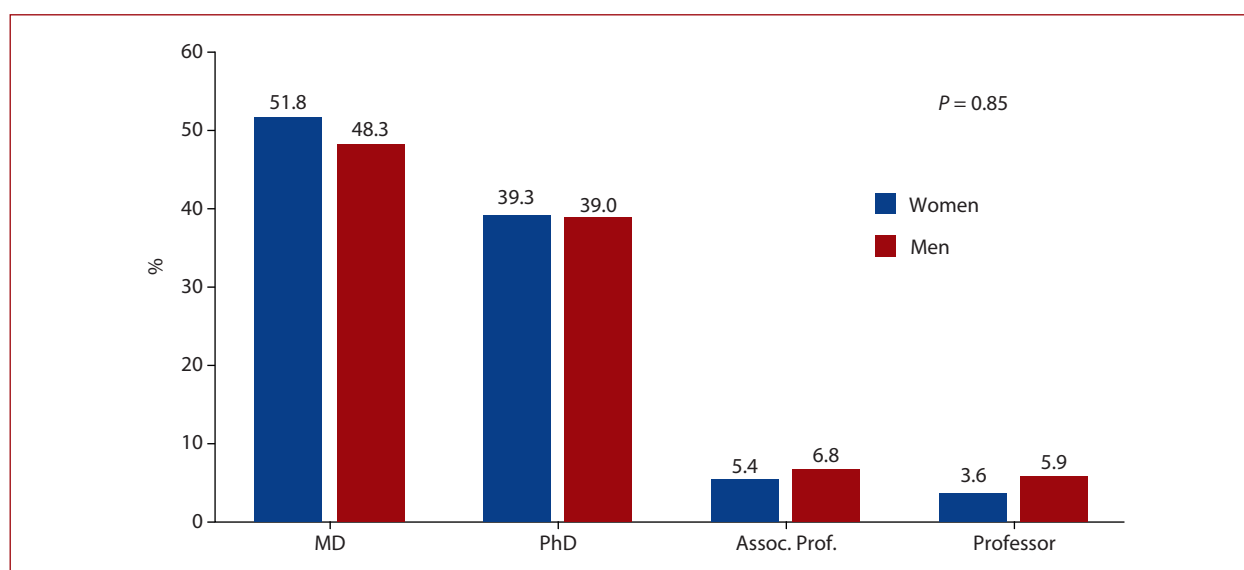


Figure 1. Distribution of academic degrees among female and male interventional cardiologists
Abbreviations: MD, Medical Doctor; PhD, Doctor of Philosophy; Assoc. Prof., Associate Professor

quartile ranges and compared using the Mann–Whitney U test. Independent predictors of procedure volumes and publication counts (Web of Science data) were identified using nonparametric kernel density multivariable regression models. Bootstrap resampling was employed to calculate standard errors and confidence intervals. Variables showing significant correlation were excluded from the final multivariable model. Statistical significance was set at $P < 0.05$. Analyses were performed using IBM SPSS version 29.0.0 and Stata version 18.5.

RESULTS

Among 1005 invasive cardiology operators in the ORPKI database (2014–2023), 56 (5.6%) were women. The proportion of female PCI operators showed a non-significant increase from 3.3% (2014) to 5.2% (2023) ($P = 0.10$; Supplementary material, *Figure S1*). Women had shorter median work experience (20.0 years [13.5–28.5] vs. 23.0 years [17.0–30.0]; $P = 0.006$).

Of 2 777 511 total procedures (1 762 295 coronary angiographies, 1 015 216 PCIs), women performed fewer median procedures across all categories: total procedures (1909.0 [581.0–2946.5] vs. 2628.5 [1095.0–4314.5]; $P < 0.001$), coronary angiographies (1256.0 [352.0–2073.5] vs. 1634.5 [730.5–2792.0]; $P < 0.001$), and PCIs (497.0 [210.0–1077.5] vs. 923.0 [363.0–1668.5]; $P = 0.006$). Female operators conducted 3.4% of all procedures, with increases observed over time ($P < 0.001$; Supplementary material, *Figure S2*). The multivariable regression model (Supplementary material, *Table S1*) indicated that work experience positively and significantly affects the number of all procedures performed, with an estimated increase of 66.9 procedures per additional year of experience. Gender differences were also significant, with women showing 955.45 fewer procedures than men, even after controlling for other factors. Other

variables, such as academic title and number of publications, did not significantly influence the outcome. Across all levels of work experience, male operators consistently perform more procedures than their female counterparts (Supplementary material, *Figure S3*).

Scientific grade distribution was similar in both (*Figure 1*). Based on the PubMed data, the median number of papers published by a given operator (3.0 [0.0–11.5] vs. 4.0 [0.0–17.5]; $P = 0.30$) as well as those published as the first (0.0 [0.0–2.0] vs. 0.0 [0.0–2.0]; $P = 0.86$) and the last author (0.0 [0.0–1.0] vs. 0.0 [0.0–1.0]; $P = 0.76$) was comparable between women and men. Similarly, the median number of papers listed for a given operator in the Web of Science database did not differ between genders (2.5 [0.0–15.5] vs. 4.0 [0.0–20.0]; $P = 0.51$). Papers from women and men gained a similar number of citations (9.0 [0.0–124.5] vs. 13.0 [0.0–137.0]; $P = 0.51$) and citations after exclusion of self-citations (8.5 [0.0–122.0] vs. 12.0 [0.0–132.0]; $P = 0.52$), resulting in a comparable H-index of 1.0 (0.0–4.5) vs. 2.0 (0.0–6.0); $P = 0.52$. The multivariable regression model (Supplementary material, *Table S2*) confirmed that first- and last-author publications significantly positively impacted the total number of publications, contributing 4.07 and 3.87 additional publications, respectively. Work experience was also a marginally significant predictor, with an increase of 0.24 publications per year. Gender differences and academic titles did not show a statistically significant effect on publication count.

DISCUSSION

Our findings align with global trends regarding women's underrepresentation in cardiology, particularly in interventional cardiology [7, 8]. The data demonstrate that female operators perform significantly fewer interventional procedures compared to their male counterparts and tend to

handle more cases involving single-vessel disease [8]. This gender disparity extends beyond Poland's borders. Wang et al. [9] reported that in the United States, women constitute only 4% of interventional cardiologists and perform merely 3% of all PCI procedures, figures that closely parallel our observations. However, encouragingly, our data show an annual increase in PCI procedures performed by female interventionalists. Importantly, studies have found no difference in periprocedural complications between patient-operator gender concordant and discordant pairs [10].

The underrepresentation of women extends beyond clinical practice into academic leadership and research. Despite increasing numbers of women entering medical school, they remain underrepresented in leadership positions within organized medicine and academia, and as principal investigators in major research initiatives [5, 6, 11, 12]. Most female leaders specialize in non-interventional cardiology and have fewer scientific publications compared to their male colleagues [12], although the proportion of women authors has shown an upward trend over time [3, 4].

The barriers facing women in medicine stem from deep-rooted structural and systemic inequalities. These challenges include gender bias, disproportionate domestic and parental responsibilities, work-life integration difficulties, and career interruptions related to pregnancy and child-rearing [5]. Nevertheless, our data show comparable scientific achievements between genders in terms of academic degrees. The median number of total publications, first-author and last-author positions, citation counts, and H-indices showed no significant gender differences among Polish interventional cardiologists. However, it is noteworthy that most scientific output among women was concentrated among a few highly productive female PCI operators and authors (Supplementary material, Figure S4), suggesting the need for initiatives to encourage broader scientific engagement across both genders.

Study limitations include potential underestimation of procedures due to incomplete ORPKI registry reporting and possible discrepancies in public data sources regarding academic achievements. These limitations affect both gender groups equally. While surveys might provide more detail, low response rates (exemplified by the 15.1% rate in a Polish Cardiac Society survey [5]) present alternative challenges.

In conclusion, the narrowing gender gap in interventional cardiology shows promising progress. By highlighting existing disparities and increasing female participation, we aim to encourage more women to pursue this subspecialty and advance cardiovascular medicine.

Supplementary material

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

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Emergency transcatheter aortic valve-in-valve procedure with a novel intra-annular system in a patient with cardiogenic shock due to severe stenosis of a failed bioprosthetic heart valve

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Transcatheter aortic valve implantation (TAVI) has emerged as a standard of therapy for patients who are not suitable for classic aortic valve replacement [1]. However, data regarding TAVI procedures in cardiogenic shock and urgent patients in general remain limited. Accessible evidence shows that emergency TAVI (eTAVI) can result in lower overall mortality than balloon aortic valvuloplasty therapy and can be a reasonable option of treatment [2–4].

A 41-year-old male was referred to the hospital due severe deterioration of left ventricle systolic function caused by rapid degeneration of an aortic bioprosthesis. His medical history included surgical aortic valve replacement in 2015 (Carpentier Edwards Perimount Magna Ease 27A) due to severe aortic regurgitation, class III obesity (body mass index of 43 kg/m²), heavy tobacco smoking, dyslipidemia, hypertension, atrial flutter, and linea alba hernia. The choice of biological aortic valve was made due to the patient's preference.

On admission, the patient presented massive peripheral and lung oedema with ascites and required non-invasive ventilation.

Baseline echocardiography showed a severely reduced left ventricle ejection fraction (LVEF) (15%) with bioprosthetic valve failure (max/mean gradient of 55/35 mm Hg) with calcification and valve leaflet stiffness. His N-terminal pro-B-type natriuretic peptide

levels exceeded 50 000 pg/ml. On coronary angiography no significant lesions were observed. Despite intensive intravenous diuretic treatment and levosimendan infusion, there was no improvement in the clinical state of the patient. The atrial flutter ablation attempt resulted in paroxysmal atrial fibrillation.

Five days after coronary angiography, two episodes of sudden cardiac arrest occurred in pulseless ventricular tachycardia and ventricular fibrillation mechanisms, with successful return of spontaneous circulation. However, the patient remained in cardiogenic shock requiring inotropes infusion.

Repeated bedside echocardiography showed an aortic valve area (AVA) of 0.5 cm², with a transprosthetic gradient of 72.5/42.9 mm Hg and a trace of aortic regurgitation (Supplementary material, *Figure S1A–B*).

Performed computed tomography angiography showed favorable conditions for urgent valve-in-valve TAVI (ViV TAVI) in terms of vascular access and valve-in-valve anatomy. (Supplementary material, *Figure S2*).

The procedure was performed using a novel Navitor Vision 27 (Abbott, Chicago, IL, US) with two-time repositioning. Due to relatively high gradients, postdilation was performed with a 22 mm balloon (Osypka, Germany), with an optimal outcome, without coronary obstruction or perivalvular leak (mean gradient 18 mm Hg; *Figure 1*). High-pressure balloon stretching was used to enable potential

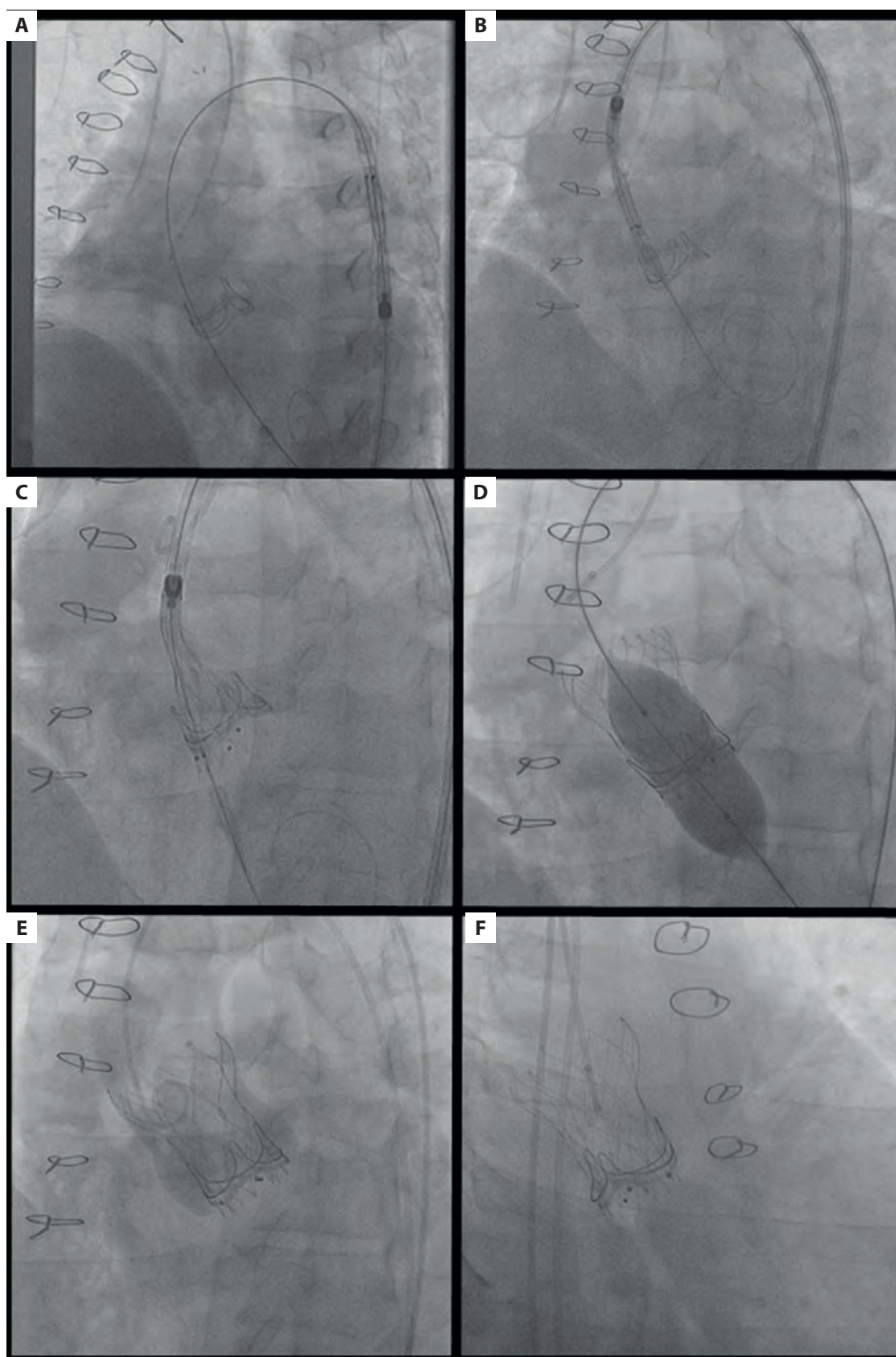


Figure 1. Valve-in-valve (ViV) transcatheter aortic valve implantation procedure. **A.** Rotation of Navitor Vision system for commissural alignment in descending aorta in left anterior oblique projection. Two markers should overlap. **B.** Delivery of transcatheter heart valve with confirmation of commissural alignment. **C.** Positioning and opening of Navitor Vision. **D.** Postdilatation of Navitor Vision. **E.** Final result of ViV procedure in 3 cusp view. **F.** Result of ViV procedure in cusp overlap view

future re-TAVI [5]. Immediately after eTAVI, the inotropes were discontinued because the patient's blood pressure recovered up to 140 mm Hg and LVEF increased to 25%.

Three days after the procedure, the LVEF improved to 25%–30% with mean gradient of 19 mm Hg (Supplementary material, *Figure S1C–D*).

Further hospital stay was uneventful. The patient was discharged from the unit in good overall condition. At the 6-month follow-up visit at our outpatient unit, according to our best knowledge, he was in overall good condition.

Treatment for cardiac shock patients is challenging. The following case emphasizes the value of urgent ViV-TAVI as a viable treatment option and provides great learning material for all interventional cardiologists.

Supplementary material

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

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Percutaneous pulmonary valve implantation with a Myval Octacor device in an adolescent patient: First Polish experience

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Percutaneous pulmonary valve implantation is a widely accepted alternative to surgery for selected patients with right ventricular outflow tract or pulmonary valve dysfunction [1]. Regarding the anatomical and etiological factors contributing to right ventricular outflow tract dysfunction, self-expandable and balloon-expandable (BE) valves are available. Two BE valves, the Melody® (Medtronic) [2] and the Edwards SAPIEN XT (Edwards Lifesciences), have been CE-marked for use in humans. Recently, several platforms have emerged in the pulmonary position. Notably, the self-expandable Pulsta® valve [3] and the BE Myval Octacor (Meril Life Sciences) [4, 5] are particularly noteworthy.

We report the first Polish experience with percutaneous implantation of a BE Myval Octacor valve in the pulmonary position.

A 16-year-old girl with DiGeorge syndrome and severe scoliosis was admitted for a comprehensive medical evaluation. The patient's medical history involved a series of surgical interventions during her early life, including truncus type I and ventricular septal defect correction at two months of age and a series of subsequent cardiac procedures, including pulmonary arteries angioplasty. On admission, the patient exhibited symptoms of exercise-induced dyspnea of class III severity according to the New York Heart Association functional classification. Cardiac catheterization showed a markedly elevated right ventricle (RV) pressure, equal to 90% of the systemic value, while transthoracic echocardiography (TTE) showed a peak Doppler gradient across the pulmonary valve of 66 mm Hg with mod-

erate regurgitation (Figure 1A). Both angiography and computed tomography indicated severely hypertrophied RV with a massively calcified proximal part of the main pulmonary artery (MPA) (Figure 1B).

After a thorough discussion, the decision was made to proceed with percutaneous treatment. Following evaluation of the individual characteristics of CE-marked devices, including the availability of intermediate sizes, the Myval Octacor system emerged as the most suitable choice (Figure 1C). The procedure was performed under general anesthesia. After vascular access was obtained, the pulmonary arteries were dilated with an Atlas Gold balloon 14/20 mm (Bard Medical) at 10–12 atm. The MPA was then pre-stented using a BeGraft (Bentley InnoMed) aortic stent graft 22/37 mm (Figure 1D), which was post-dilated with an Atlas Gold balloon 24/30 mm up to 12 atm. Complete coverage and full dilatation of the MPA was achieved (Figure 1E). To facilitate the procedure and avoid potential damage to the tricuspid valve, the vascular sheath was exchanged for a Dry-Seal 24F (Gore). Thereafter, the Myval Octacor 24.5 mm valve was delivered on a Lunderquist wire (Cook Medical) and implanted into the pulmonary position (Figure 1F). Both angiography and TTE indicated no paravalvular leakage. Peak Doppler gradient across the pulmonary valve dropped to 13 mm Hg, whereas the hemodynamic evaluation showed a notable reduction in RV pressure to 49% of the systemic pressure. The patient was discharged on the third day after the procedure with no procedure-related complications. After two

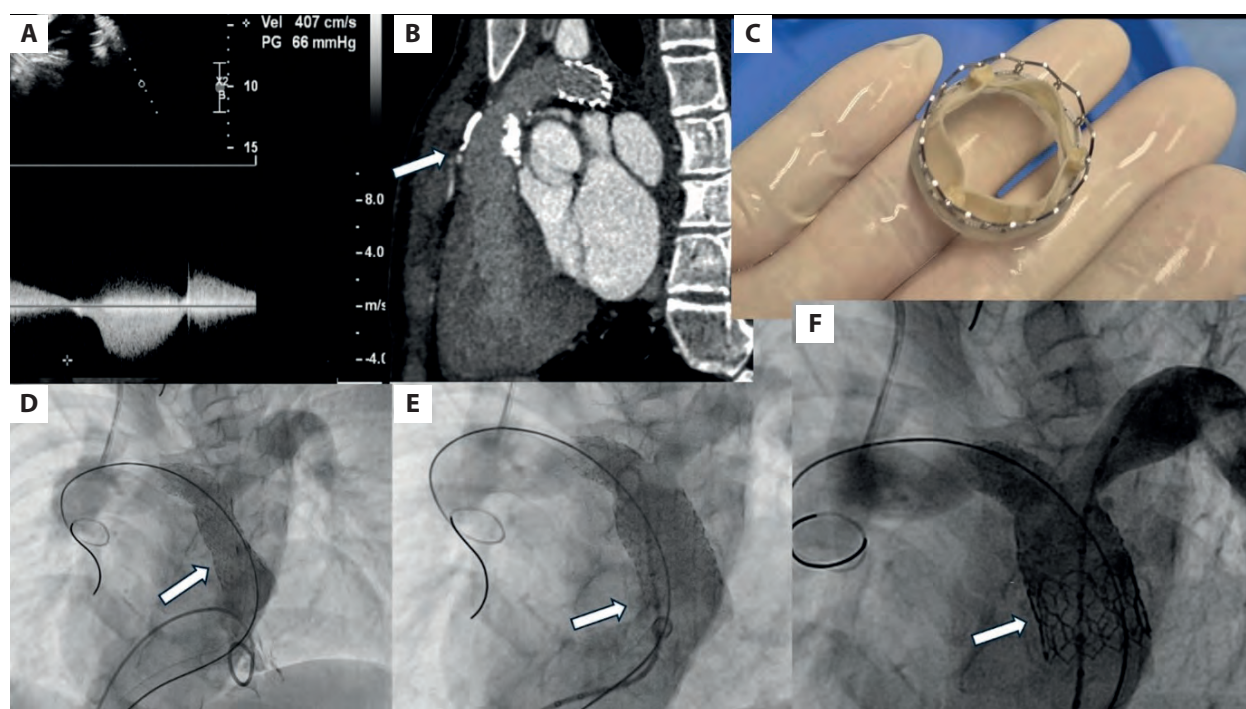


Figure 1. TTE indicates a significantly elevated peak Doppler gradient across the pulmonary valve of 66 mm Hg (A). Cardiac angio-CT shows extensive proximal MPA calcification (white arrow) (B). Myval Octacor valve (C). Angiography shows pre-stented MPA with aortic stent graft before (D) and after (E) post-dilation. White arrows indicate the position of the stent graft. The final angiography shows the Myval Octacor valve (white arrow) implanted in the pulmonary position (F)

Abbreviations: CT, computed tomography; MPA, main pulmonary artery; RV, right ventricle; TEE, transthoracic echocardiography

weeks, the girl reported a significant improvement in exercise capacity. The TTE evaluation showed optimal function of the implanted prosthesis.

Given the growing global evidence supporting the use of the Myval Octacor platform in the pulmonary position, we conclude that the valve is both efficient and predictable, and due to the versatility of its size matrix, can serve as a valuable alternative to the established platforms.

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Integration of advanced imaging and interventional techniques for percutaneous closure of a giant fistula between the left pulmonary artery and the left atrium

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The rapid advancement of imaging methods has significantly improved pre-procedural diagnostics and planning, as well as enhancing safety in complex interventional procedures [1–5]. We report utilization of multimodal imaging and advanced interventional techniques to treat a male teenager with a large arteriovenous fistula between the left pulmonary artery (LPA) and left atrium (LA).

Diagnosed at birth due to mild desaturation (93%), the patient remained asymptomatic under echocardiographic follow-up by their cardiologist. At the age of 17 years, the patient was referred to our center due to LPA dilation and a large LPA-LA fistula that was noted on echocardiography (Supplementary material, *Figure S1A, B*) and consistent with a computed tomography (CT) scan performed one year prior to admission (Supplementary material, *Figure S1C–D*).

Based on the CT, virtual reality (VR; Vmersive, Poland) and 3D-printed models (Supplementary material, *Figure 1E–F, Video S1*) were created for precise anatomical evaluation. A tortuous fistula was observed, measuring 45 × 60 × 27 mm with an 8 mm narrowing near the pulmonary end and draining to the LA near the left upper pulmonary vein (Supplementary material, *Figure S1C–D, F*).

The patient underwent heart catheterization (Supplementary material, *Video S2*) via femoral vein access, catheter placement in the LPA, and 3D rotational angiography (3DRA). Although pre-procedural CT (performed one year earlier) could have been used for image fusion, 3DRA enabled dynamic analysis supported by 3D multi-plane computational

modelling and real-time fusion of current fistula dimensions and anatomical relationships.

Closure at the LA end (12 × 20 mm) raised concerns about the need for a large device, risk of left upper pulmonary vein obstruction, and continued inflow from the LPA, potentially causing fistula dilation or device migration. An approach from the LPA appeared more viable but posed challenges with catheter angle and stability. We decided to anchor the device at the pulmonary end of the fistula but deliver it via transseptal puncture from the LA end.

Through an additional venous access, transseptal puncture (BRK Transseptal Needle, Abbott, Chicago, IL, US) was performed under fluoroscopy and transesophageal echocardiographic guidance (*Figure 1A–B*). By advancing an 0.014" guidewire from the LPA and a snare from the LA, a veno-venous loop was created (*Figure 1C–D*). An 8 Fr long sheath was then advanced from the LA to the LPA, with notable resistance at the pulmonary end of the fistula, suggesting the potential for stable implant anchoring. With measurements from CT, VR, and 3DRA, balloon sizing was omitted and an Amplatzer Duct Occluder I (10–8 mm; Abbott) was deployed. Its proper position was verified with 3DRA (*Figure 1E*), confirming successful fistula occlusion before release from the delivery system. The 3DRA-based VR model was compared to traditional two-dimensional angiography (*Figure 1E, F*). While the former added valuable spatial information regarding implant position, stability, and relationship with nearby structures, the latter showed the residual leak and the LA side of the fistula better (distal to the occluder) [5].

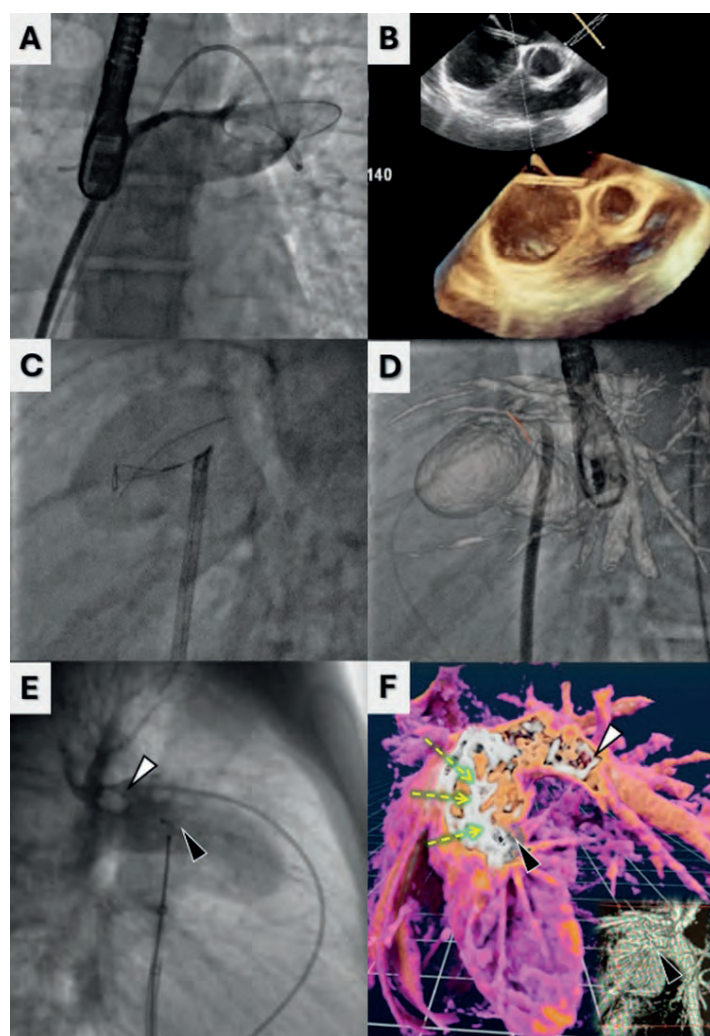


Figure 1. Transcatheter intra-procedural use of multimodal imaging. **A.** Fluoroscopy showing transseptal puncture of the interatrial septum (IAS) with guidewire insertion into the left atrium (LA) and contrast filling of the LA. **B.** Transseptal puncture guided by X-plane and 3D transesophageal echocardiography. **C.** Fluoroscopy image showing the left pulmonary artery (LPA)-LA fistula during capture of a guidewire introduced from the LPA side by a snare introduced from the LA side. **D.** Computed 3D reconstruction from rotational angiography (3DRA) overlaid onto the fluoroscopic image. **E.** Rotational angiography (3DRA) showing the implant anchored at the narrowest point of the fistula. **F.** Multimodal reconstructions (VR model and 3D computed model) based on 3DRA data. The white arrowhead points to the pigtail catheter in the LPA, indicating the contrast injection site. The yellow dashed arrows show contrast-filled sections of the LPA. Black arrowheads mark the narrowed area where the implant is positioned, with slight residual contrast in the remaining portion of the fistula, indicating the implant's secure position.

The patient was discharged on the third day on aspirin and acenocoumarol. Follow-up magnetic resonance imaging is/was scheduled.

CONCLUSION

Pre-procedural imaging for detailed planning and intra-operative imaging for precise navigation were crucial to the successful outcome. This case demonstrates the importance of integrating interventional techniques with advanced imaging modalities in managing rare and complex cardiovascular anomalies.

Supplementary material

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

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Infected perivalvular and circumaortic hematoma in a patient with severe endocarditis of bicuspid aortic valve: A disastrous beginning and a happy end

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A 46-year-old man with a history of a bicuspid aortic valve stenosis was admitted due to *Enterococcus faecalis* sepsis. On admission, transthoracic echocardiography showed severe stenosis and moderate aortic regurgitation, dilated ascending aorta, and a moderate amount of pericardial fluid (Figure 1A). Transesophageal echocardiography (TOE) revealed severe aortic infective endocarditis (IE) and a fissure at the annulus, suggesting its partial dehiscence (Supplementary material, Video S1). After 2 days of targeted antibiotic therapy (ampicillin, ceftriaxone), the patient underwent urgent Bentall de Bono surgery, and an SJM conduit with Valsalva sinus was implanted. Intraoperatively, massive vegetations, a pericardial abscess entering the muscle, and aortic detachment of 2/3 of the circumference were found (Figure 1B).

After 3 weeks of a relative clinical improvement, high fever returned and inflammatory markers increased. Follow-up TOE showed a thick tissue (up to 20 mm) with abscess cavities around the prosthesis, and a thickened cuff along the graft, suggestive of an inflammatory infiltration. It bulged into the right atrium, and a large, bifurcated vegetation (24 mm) was attached at its lower edge (Figure 1C–D; Supplementary material, Video S2). Antibiotic therapy was expanded to include vancomycin and gentamycin.

Computed tomography (CT) showed an active periprosthetic leak with a channel approximately 5 mm wide with several areas

of blood extravasations and an extensive cuff (up to 25 mm) indicating the periaortic hematoma within the mediastinum (Figure 1E). The decision about reoperation was difficult, and heart transplantation was considered.

Due to the worsening of the patient's clinical status after numerous consultations, 69 days after the first surgery, an aortic homograft (23 mm) extended with a vascular prosthesis was implanted (Figure 1F; Supplementary material, Video S3). Additionally, the first epicardial pacing and finally a DDDR-type pacemaker was implanted because of permanent third-degree atrioventricular block.

The patient was discharged in good condition after 147 days and remains so to this day.

In cases of native valve IE, the incidence of perivalvular process ranges from 10% to 30%, and it is higher in prosthetic valve IE [1]. Perivalvular extension occurs more frequently in aortic valve than mitral valve IE, and it is relatively often observed in patients with bicuspid aortic valve [1]. In complicated and life-threatening cases, more than one surgery may be required, and homografts are usually not available urgently.

Differential diagnosis of periaortic mass is challenging; it may include aortic abscess and pseudoaneurysm, as reported by Łoboz-Rudnicka et al. [2], and a conglomeration of unresorbed hemostatic fabrics described by Kezeviciute et al. [3].

TOE is obviously the primary diagnostic tool in perivalvular complications; however,

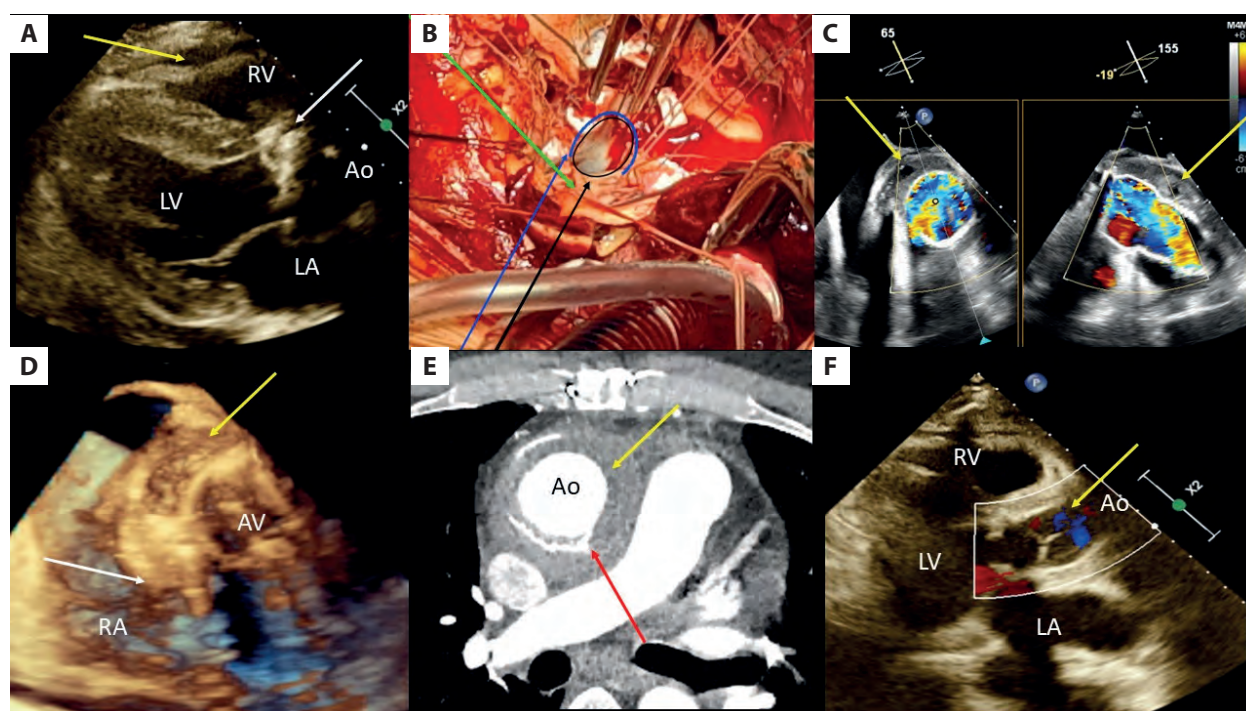


Figure 1. **A.** An abnormal image of the aortic valve and enlarged aortic bulb (white arrow); pericardial fluid (yellow arrow); 2D transthoracic echocardiography; a long-axis view. **B.** Intraoperative view: left ventricle outflow tract (LVOT) — black line and arrow, 2/3 of the detached circumference of the aorta — blue line and arrow, ostium of the left coronary artery — green arrow. **C.** Perivalvular and periaortic infiltration with abscess cavities (yellow arrows); 2-dimensional transesophageal echocardiography, X-plane view, color Doppler. **D.** Perivalvular infiltration with abscess cavities (yellow arrow) and a large, bifurcated vegetation attached at its lower edge (white arrow); 3D transesophageal echocardiography. **E.** An active periprosthetic leak (red arrow) and an extensive cuff indicating a periaortic hematoma (yellow arrow); contrast-enhanced computed tomography. **F.** Follow-up echocardiogram after aortic homograft implantation (arrow); 2D transthoracic echocardiography, color Doppler, long-axis view

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

it should be supplemented with another imaging modality, such as CT, cardiac magnetic resonance, or nuclear techniques [1]. The important role of cardiac magnetic resonance in the evaluation of para-aortic conduit abscess after Bentall procedure was described by Rudiene et al. [4]. Gupta et al. [5] emphasized the utility of contrast-enhanced CT and ^{18}F -fluorodeoxyglucose positron emission tomography/CT in the assessment of periaortic hematoma in a patient with staphylococcal IE of a bioprosthesis and an aortic graft.

Our case and all the above reports indicate that multimodal diagnostics and the enormous “endocarditis team” effort saved patients’ lives.

Supplementary material

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Rapid resolution of severe rheumatic mitral regurgitation following dapagliflozin and torasemide treatment

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A 77-year-old woman with arterial hypertension, treated with ramipril, lercanidipine, and bisoprolol, and a history of gastroesophageal reflux disease presented to the hospital with a severe chest pain and elevated blood pressure (150/74 mm Hg). Electrocardiogram showed ST-segment depression in leads aVF and V5–V6. Laboratory tests revealed elevated high-sensitive troponin, peaking at 70.8 ng/l (reference: <14.0). Due to suspected acute coronary syndrome, emergency coronary angiography was performed, which showed normal coronary anatomy. Transthoracic echocardiography performed prior to invasive coronary artery angiography demonstrated preserved left ventricular ejection fraction without wall motion abnormalities. However, severe mitral regurgitation (MR) was noted (vena contracta 9 mm, central large jet >50% of left atrium area, MR volume 48 ml) (Figure 1A–C; Supplementary material, Video S1). The left ventricle was normal in size, and no mitral valve prolapse was evident (Supplementary material, Video S2). Additional findings included mildly elevated N-terminal pro-B-type natriuretic peptide at 849 pg/ml (reference: <125) and no signs of pulmonary congestion on chest X-ray. Treatment was augmented simultaneously with torasemide (10 mg daily 2x) and dapagliflozin (10 mg/day). Within 2 days of hospitalization the patient's symptoms resolved and blood pressure normalized. Follow-up transthoracic and transesophageal echocardiography after 5 days showed improvement to mild/moderate MR (Figure 1C–D). The studies revealed thickened mitral valve leaflets with rheumatic changes (Figure 1E). She was discharged in stable condition with scheduled follow-up in the hospital's cardiology clinic.

Organic (primary) MR results from structural abnormalities of the mitral valve apparatus. Common causes include mitral valve prolapse, flail leaflet, rheumatic heart disease, coronary artery disease, infective endocarditis, and collagen vascular disorders. The etiology determines the management strategy [1]. Rheumatic heart disease, a severe sequela of rheumatic fever, can cause MR at any age [2]. It affects the mitral valve in up to 50% of cases, leading to insufficiency, mitral stenosis, or both. Rheumatic valves exhibit fibrous thickening, oedema, minimal calcification, non-fused commissures, annular dilatation, and anterior chordal elongation. In patients with overt heart failure (HF), pharmacotherapy should follow standard HF guidelines because no specific adjustments are recommended for primary MR. While sodium-glucose co-transporter 2 inhibitors are cornerstone HF treatments, evidence for their efficacy in organic rheumatic MR remains limited, although studies demonstrate benefits with dapagliflozin in functional MR [3]. The EFFORT study [3] examined functional MR over a 12-month follow-up period and used ertugliflozin rather than dapagliflozin. Although a drug class effect might be expected, potential differences in outcomes between specific medications cannot be ruled out. The rapid improvement in MR severity following hemodynamic optimization in our case suggests a potentially mixed mechanism, with an acute functional component superimposed on underlying rheumatic valve disease. Given the swift resolution of the valvular defect, we hypothesize there may be a synergistic effect of dapagliflozin and torasemide. However, further studies are needed to elucidate the role of sodium-glucose co-transporter 2 inhibitors in managing primary MR [4].

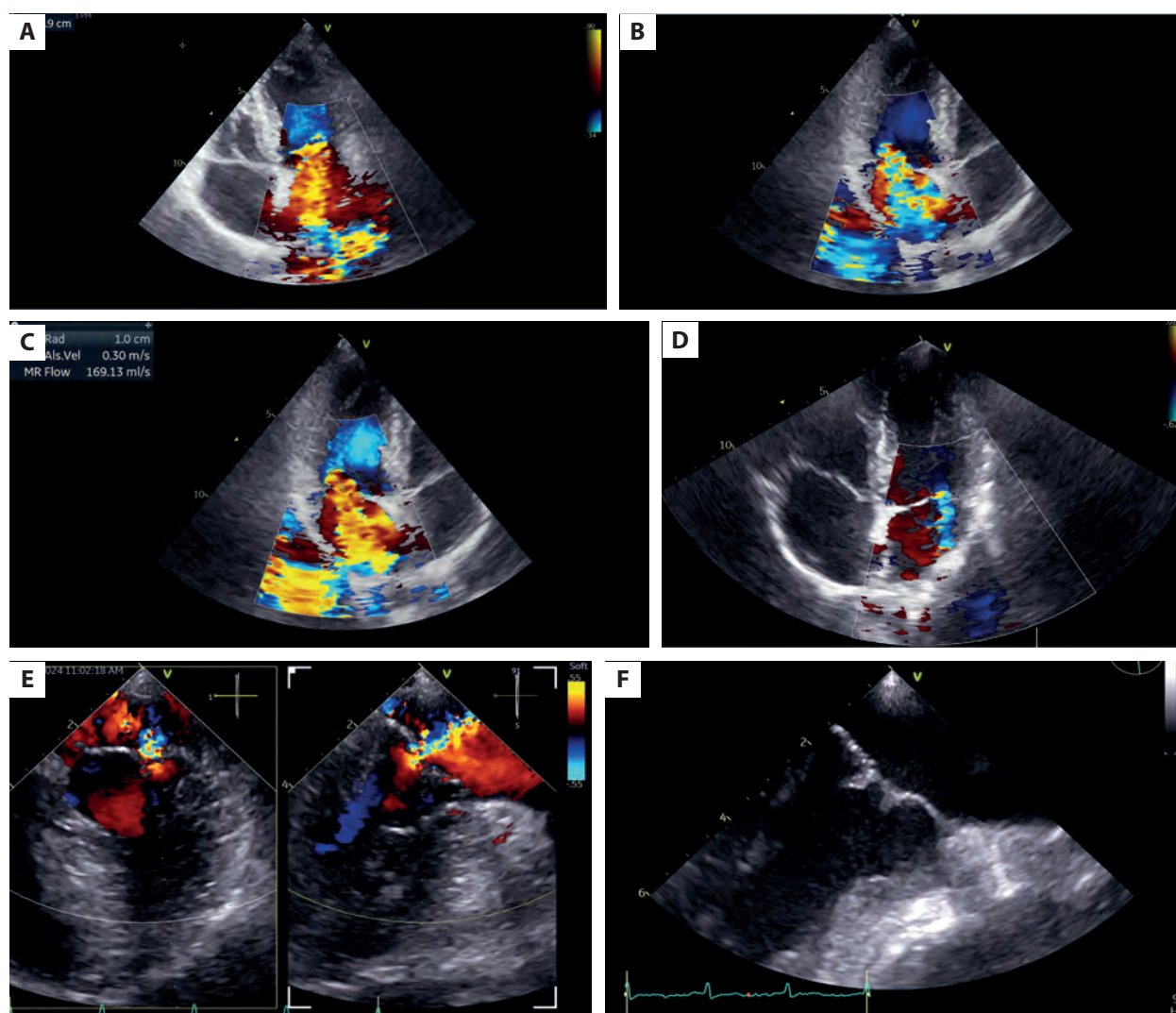


Figure 1. **A.** Severe mitral regurgitation (MR) in the 4-chamber view on transthoracic echocardiography (TTE); vena contracta measures 9 mm. **B.** Central large jet >50% of the left atrium area. **C.** Severe MR in the 3-chamber view on TTE; proximal isovelocity surface area measures 10 mm. **D.** Mild to moderate MR in the 4-chamber view on TTE after 5 days of treatment. **E.** Mild to moderate MR on transesophageal echocardiography (TOE) after 5 days of treatment. **F.** Rheumatic changes of the mitral valve observed on TOE

Supplementary material

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Primary leiomyosarcoma of the right ventricle with metastases in a young female

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Primary heart tumors (PHT) are an infrequent phenomenon affecting 0.02% of the population; among them, 25% are malignant tumors [1]. The most common PHT is angiosarcoma, while leiomyosarcoma accounts for less than 1% [2].

A 48-year-old female patient with a history of lower limb venous thrombosis and hysterectomy due to benign smooth muscle tumors was transferred to our department due to a tumor in the right ventricle found on transthoracic echocardiography (Figure 1A) and suspicion of metastases to the lungs, spine, and kidneys (Figure 1B). Nine days earlier, the patient was admitted to the emergency room with progressively worsening dyspnea, significantly increased fatigue, and exertional intolerance. On admission, she was classified as New York Heart Association class III/IV without angina. Physical examination showed lower limb edema, a heart murmur, and basilar lung rales. The patient underwent additional cardiac magnetic resonance (CMR) assessment, showing a tumor in the right ventricle (Figure 1C), and was consulted with oncologists.

Finally, after a Heart Team discussion, she was qualified for tumor resection with the collection of material for histopathological examination as a palliative life-saving procedure.

The patient was successfully operated on under general anesthesia. The tumor was removed in two fragments (Figure 1D–F). A biological valve implant (C-E Perimount 31 mm) was also needed in the tricuspid position. Postoperatively, a dual-chamber

pacemaker was implanted due to a complete atrioventricular block.

Histopathological examination showed leiomyosarcoma without signs of necrosis, classified by French *Fédération Nationale des Centres de Lutte Contre le Cancer* (FNCLCC) as Grade 2, without evidence of angioinvasion (LV10) and neuroinvasion (Pn0).

After hospital discharge and rehabilitation, the patient received systemic chemotherapy according to ADIS protocol (dacarbazine + doxorubicin).

Leiomyosarcoma can remain asymptomatic while consistently growing. At the time of diagnosis, it is often infiltrating the heart wall and is linked with metastases [4]. While malignant tumors present 14.1 months of estimated median survival time in the case of localization in the right heart or stage 4, leiomyosarcoma decreases it to only two months in patients with other organs involved [3, 5].

Interestingly, according to previous reports, there were patients who, before symptoms of leiomyosarcoma of the heart, had been diagnosed with uterine leiomyoma or had uterine fibroids removed, like our patient [5].

There is, therefore, a possibility that the tumor in our patient's heart was not a primary lesion.

This assumption is consistent with the involvement of the inferior vena cava, which is often the first place this generator produces output but most often metastasizes through continuity to the right atrium.

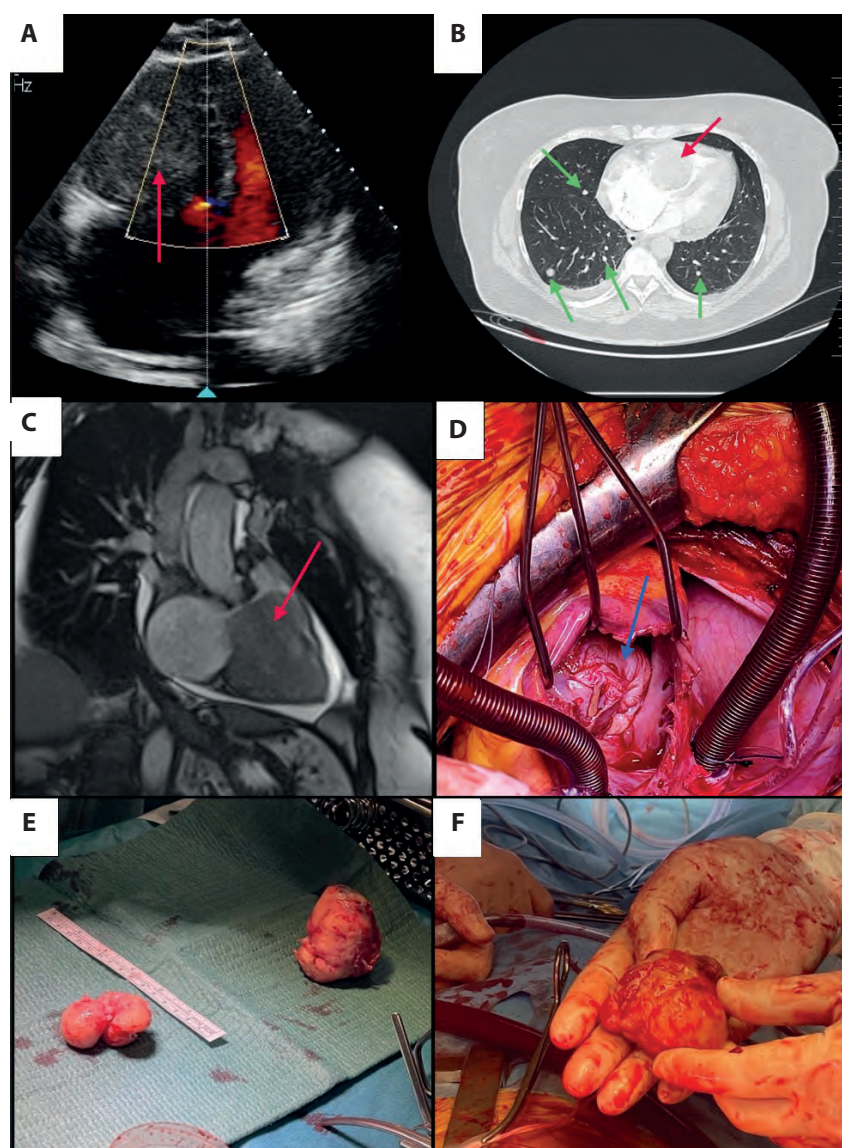


Figure 1. **A.** Echocardiography showing enlarged right ventricle with flow obturation due to enormous tumor (red arrow). **B.** Computed tomography scan of the tumor (red arrow) also showing multiple metastases (green arrows) and fluid retention in the lungs. **C.** Magnetic resonance imaging shows tumor mass (red arrow). **D.** Intraoperative photo of the tumor placed in the right ventricle (blue arrow). **E.** Photo of two pieces of the tumor. **F.** Intraoperative photo of the first part of the tumor

Another possibility is the existence of a rare genetic predisposition connecting these dots. Further research might shed more light on this topic.

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Left-sided accessory pathway ablation in a patient with mitral valve blood cyst. An example of the usefulness of intracardiac echocardiography in monitoring pediatric ablation procedures

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Accessory pathway ablation is the most common procedure performed in pediatric electrophysiology (EP) laboratories. Recently, intracardiac echocardiography (ICE) has been recommended as a valuable tool to address technical challenges in EP procedures, enhance safety, and reduce radiation exposure specifically in patients with congenital heart defects [1, 2]. Mitral valve blood cysts are rare congenital heart defects that, while typically benign, may complicate intracardiac catheterization procedures [3, 4].

We present the case of a 17-year-old female with recurrent, documented supraventricular tachycardias. Echocardiography

showed a blood cyst on the anterior mitral valve leaflet, located in the ventricular portion of the leaflet. The cyst measured 17 × 18 mm and did not cause any disturbances in mitral valve or left ventricular outflow tract blood flow. The resting 12-lead electrocardiogram showed no signs of preexcitation. The patient and her family chose to proceed with an ablation procedure. Given the potential thromboembolic risk associated with catheter-induced injury to the cyst, the procedure was planned with the use of ICE to enhance safety.

The procedure was conducted under general anesthesia. An EP study with a 3D mapping system was performed, and ICE

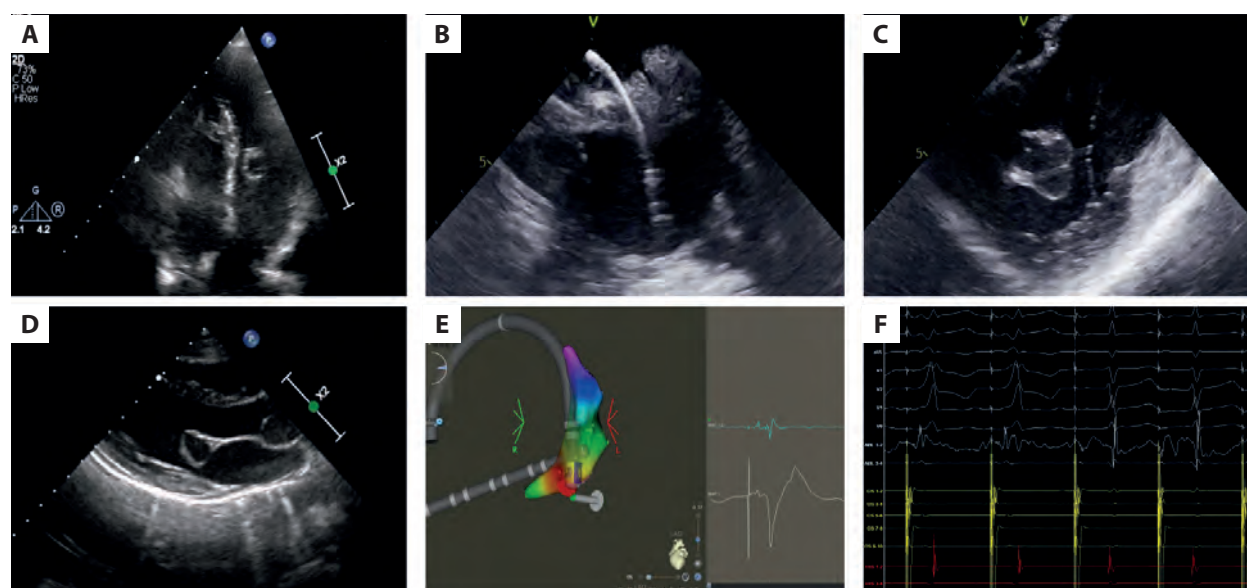


Figure 1. A and D. Transthoracic echocardiography images depicting a mitral valve blood cyst. B and C. Intracardiac echocardiography images showing the ablation catheter and mitral blood cyst. E. 3D mapping system image showing the lateral aspect of the mitral annulus and the site of successful ablation. F. Intracardiac tracings illustrating the radiofrequency application and the resolution of preexcitation features

monitoring was employed throughout. Atrial stimulation showed signs of preexcitation typical of a left-sided accessory pathway, and AVRT with eccentric atrial activation was reproducibly induced. A transseptal approach was then utilized, and careful mapping of the mitral annulus showed the earliest ventricular activation in the posterolateral region. Radiofrequency ablation at this site immediately eliminated the preexcitation. The effect remained stable during the observation period, and subsequent stimulation confirmed successful ablation of the accessory pathway.

Throughout the procedure, catheter positioning was closely monitored to avoid any injury to the cyst. Post-procedural echocardiography showed no changes in the cyst's appearance, no pericardial effusion, and normal left ventricular size and function. The electrocardiogram post-ablation showed sinus rhythm without preexcitation.

This case underscores the utility of ICE in pediatric ablation procedures, particularly in patients with structural heart abnormalities. Careful echocardiographic monitoring during ablation in a patient with a mitral valve blood cyst is crucial for preventing complications.

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Delayed aortic perforation following the implantation of a 3830 lead in the interatrial septum

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A 54-year-old female with recurrent dizziness and complete atrioventricular block documented on electrocardiogram was referred for pacemaker implantation. Coronary angiography showed approximately 90% stenosis in the left anterior descending artery. Pacemaker implantation was performed through the right subclavian vein because the left approach was not feasible. Also, due to fibrosis and remodeling of the right atrial appendage (RAA), interatrial septum (IAS) pacing using a SelectSecure C315 guiding catheter, along

with a 3830 lead, was performed (Figure 1A–C).

The pacing parameters were stable two months later, and computed tomography showed no catheter displacement (Figure 1D–E). Percutaneous coronary intervention was then performed for the left anterior descending artery, and the patient was administered dual antiplatelet therapy. Three days after the percutaneous coronary intervention, the patient developed pericardial tamponade requiring pericardiocentesis. An emergency

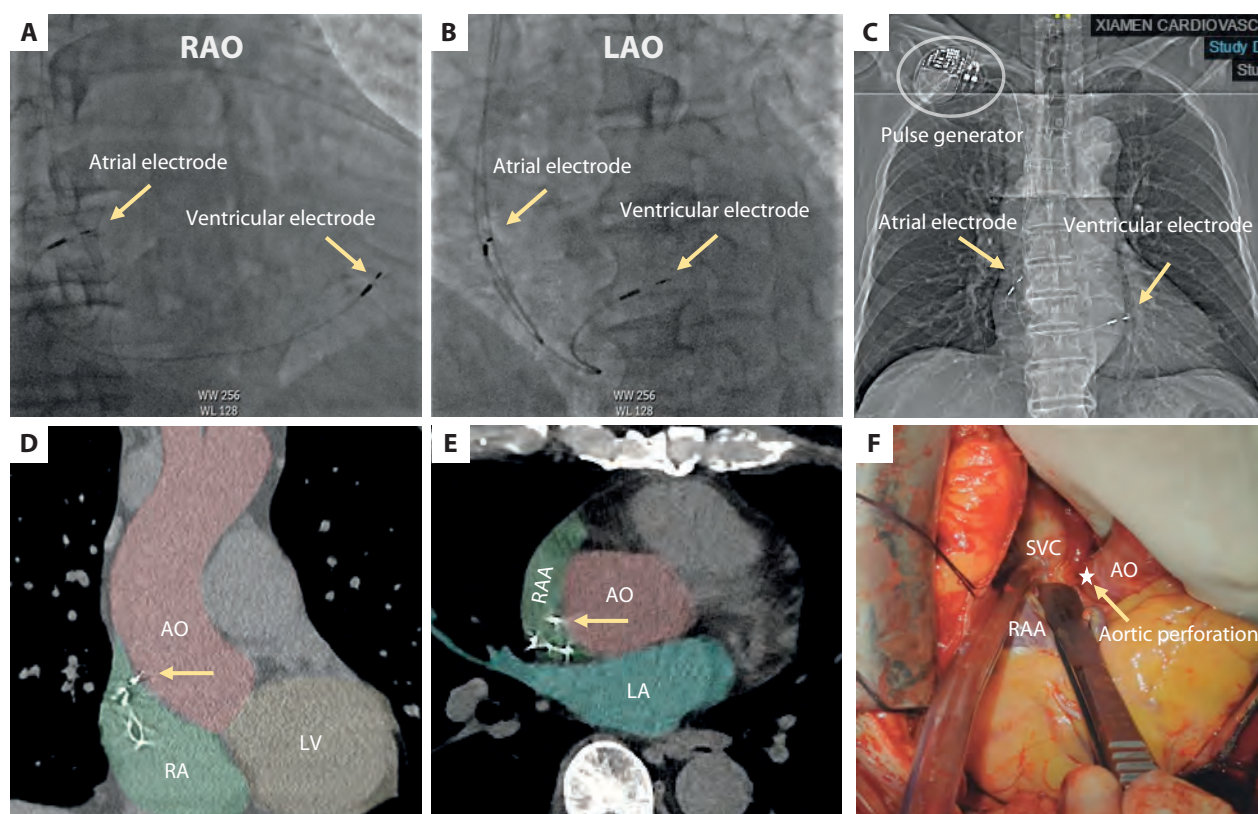


Figure 1. A. RAO fluoroscopic image illustrating the positioning of the atrial 3830 pacing lead. B. LAO fluoroscopic image showing the positioning of the atrial 3830 pacing lead. C. Post-procedural chest X-ray showing a dual-chamber pacemaker implanted via the right subclavian vein, along with the sites of the pacing leads. D. Chest CT in the coronal plane demonstrating the anatomical proximity of the atrial electrode to the aortic root. E. Chest CT in the horizontal plane demonstrating the anatomical proximity of the atrial electrode to the aortic root. F. Intraoperative view identifying the site of aortic perforation (white star)

Abbreviations: AO, aorta; CT, computed tomography; LA, left atrium; LAO, left anterior oblique; LV, left ventricle; RA, right atrium; RAA, right atrial appendage; RAO, right anterior oblique; SVC, superior vena cava

exploratory thoracotomy was performed after a coronary angiogram, ruling out coronary perforation. Active hemorrhage from the aortic root was observed intraoperatively, and the tip of 3830 lead was palpated in the adjacent antero-superior part of the IAS (Figure 1F and Supplementary material, Video S1). The patient recovered well after patch repair on both sides.

Currently, the 3830 lead is widely used for physiological ventricular pacing [1]. IAS pacing using 3830 leads has emerging applications as an alternative approach when RAA pacing is difficult, and it is safe and effective [2, 3]. However, the anterior edge of the septum and the proximal antral RAA are potentially dangerous regions primarily due to their proximity to the aortic root [4, 5], which should be avoided during the procedure.

Supplementary material

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

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Aortic dissection with inguinal hernia and organ cysts

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A 68-year-old man with a history of hypertension, dyslipidemia, and hyperuricemia complained of severe back pain. Contrast-enhanced computed tomography scans showed type-B aortic dissection (AD) (intramural hematoma) (Figure 1A–B, arrows and red shadow), huge right external inguinal hernia (Figure 1C–D, arrows), multiple hepatic cysts (Figure 1E, arrows), and an isolated left renal cyst (Figure 1F, arrow). Blood examinations indicated elevated white blood cell counts (11 300/ μ l) and D-dimer (5.6 μ g/ml). Because no physical characteristics of Marfan, Ehlers–Danlos or Loeys–Dietz syndrome were recognized, there were no earlier imaging studies or indications of systemic connective tissue disorders before the onset of the AD. The patient underwent optimal medical (antihypertensive and analgesic) treatment without surgical or endovascular intervention, uneventfully recovered, and is now doing well with the intramural hematoma shrinking 2 months after the onset of the AD.

It has been suggested that inguinal hernia and hepatic/renal cysts are associated with AD. In the multivariate analysis by Koechlin et al. [1], inguinal hernia was significantly ($P = 0.001$) associated with AD of the <55 mm ascending aorta. The prevalence of hepatic (28.8% vs. 11.0%; $P < 0.001$) and renal (39.3% vs. 19.9%; $P < 0.001$) cysts was significantly greater in patients with type-A AD than in those with coronary artery disease in the propensity-score-matched cohort by Dun et al. [2]. Furthermore, in the meta-analysis of 4 studies including 16 397 patients, Chewcharat et al. [3] demonstrated significantly greater than two-fold increased risk (pooled odds ratio, 2.44; $P = 0.003$) of AD in patients with renal cysts compared to the control. An imbalance between type I and type III collagen

and that between matrix metalloproteinases and their tissue inhibitors are proposed as common features of hernia and AD [1]. Moreover, it is hypothesized that matrix metalloproteinases may share a link between organ cysts and AD [2]. Transforming growth factor beta 1 (TGF- β 1) augmenting matrix degradation is enhanced by matrix metalloproteinase (MMP)-2 and accelerated regarding bioavailability by the constitutional changes in fibrillin-1 detected in Marfan syndrome, and elevated levels of both MMP-2 and active TGF- β 1 are also observed in the fascia transversalis of patients with hernia [1]. Furthermore, 8202A/G mutation in the MMP-9 gene is usually recognized in patients with simple renal cysts and AD [2]. Although the current guideline [4] does not refer to either hernia or cyst as risk factors of AD, connective tissue diseases are included in high-risk conditions of the AD detection risk score items as well as, e.g., the artificial intelligence aortic-dissection-electrocardiogram score [5]. On the basis of the above-mentioned high prevalence of hernia and cysts in patients with AD [1, 2], however, it might be suggested that at least the history and physical examination should be taken in patients with these conditions and suspected AD.

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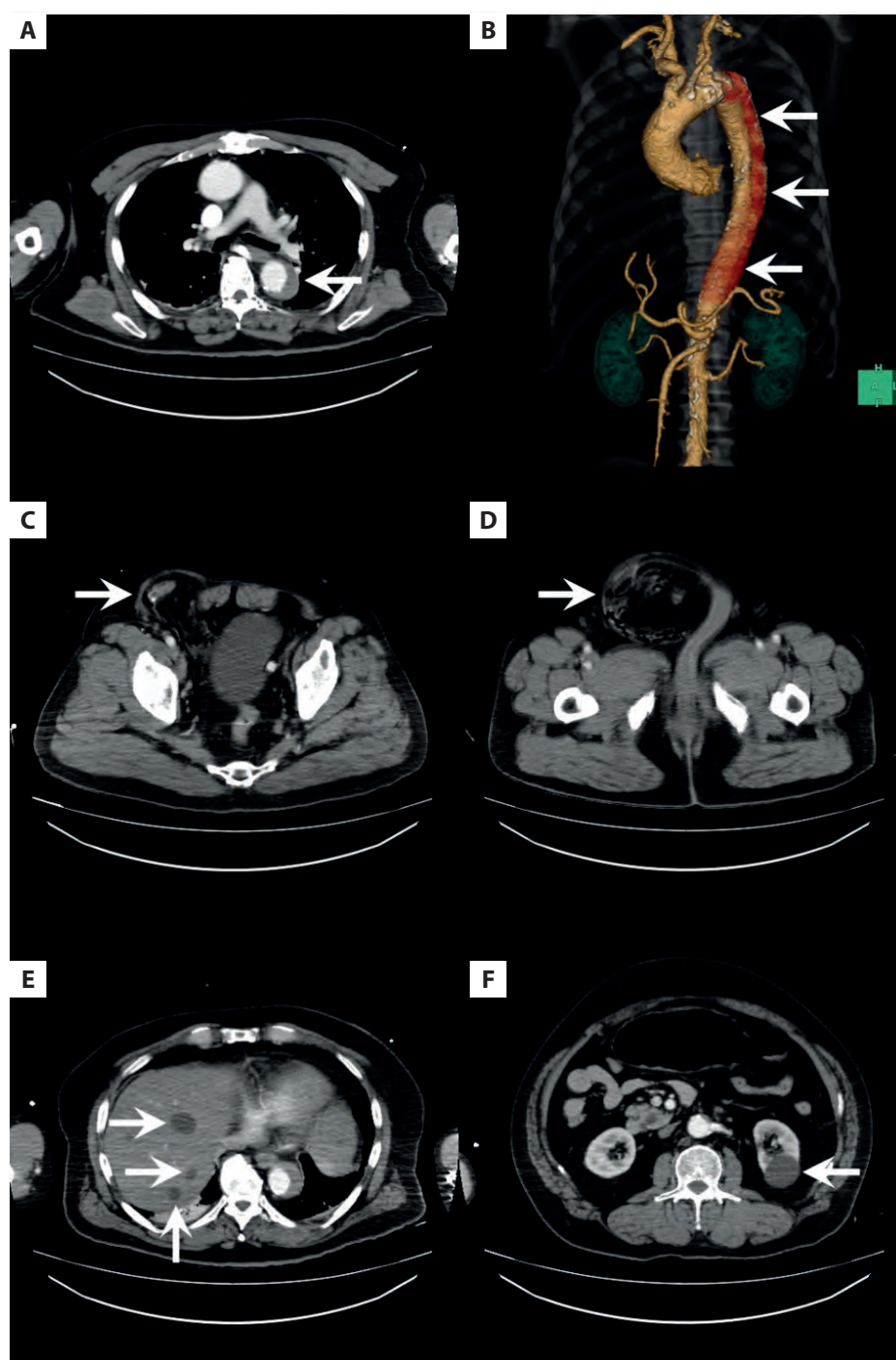


Figure 1. A–B. Type-B aortic dissection (arrows and red shadow, intramural hematoma). C. and D. Huge right external inguinal hernia (arrows). E. Multiple hepatic cysts (arrows). F. An isolated left renal cyst (arrow)

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Pulmonary vein isolation with pulsed field ablation in a patient with mechanical mitral and aortic valve prostheses

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Atrial fibrillation (AF) is a common arrhythmia in patients after mitral valve replacement (MVR). Management of AF in patients with a mechanical prosthesis poses unique challenges due to limited pharmacological efficacy and complexities associated with catheter ablation, including the possibility of catheter entrapment in valve discs and significant atrial enlargement [1]. Despite these concerns, evidence supports the efficacy of ablation in this patient population [2, 3]. In patients following the Bentall procedure, access to the left atrium (LA) can be further complicated by atypical aortic positioning and increased risk during transseptal puncture.

We report a case of successful AF ablation in a 53-year-old male after mechanical MVR and aortic valve replacement following a Bentall procedure, stent grafting of the descending aorta, and conservatively managed aortic arch dissection. The patient experienced paroxysmal atrial flutter (AFL) and AF significantly impairing his quality of life (European Heart Rhythm Association III). Comorbidities included hypertension, heart failure with moderately reduced ejection fraction (45%), and stage G3b/4 renal failure. Echocardiography showed significant LA enlargement (50 mm). Despite prior right atrial ablation of the cavotricuspid and intercaval lines, episodes of AF and AFL were recurring.

To minimize the risk of damaging the mechanical valve discs, we selected the FAR-AWAVE™ over-the-wire pentaspline pulsed field ablation (PFA) catheter (Boston Scientific, Marlborough, MA, US) [4, 5]. Continuous transesophageal echocardiography (TEE)

monitoring was employed to enhance safety and confirm catheter positioning.

The procedure was conducted under general anesthesia with endotracheal intubation. Two femoral vein punctures were performed under ultrasound guidance. Significant resistance during sheath insertion was encountered due to prior vascular access. Although the surgical approach for MVR did not involve the IAS, significant IAS fibrosis was observed during transseptal puncture under TEE guidance, requiring considerable force to advance the dilator and 8.5F sheath (Swartz™, Abbott, Chicago, IL, US) into the LA (Figure 1A, B, E). Placement of the 13F FARADRIVE™ (Boston Scientific) sheath was achieved using a double-wire technique over a Hi-Torque Supra Core™ wire (Abbott) directed toward the right superior pulmonary vein (RSPV) after prior IAS dilation.

In the LA, ablation was performed with 40 PFA applications: four in a flower shape and four in a basket shape per vein, with additional applications to specific regions (Figure 1C, D). Durable pulmonary vein isolation was confirmed by entry and exit block testing. During catheter positioning in the RSPV, AFL with a cycle length of 320 ms was induced. This AFL terminated spontaneously following pulmonary vein isolation and was non-inducible during the final electrophysiological study. Post-procedure, TEE confirmed proper valve function (Figure 1F).

Reports regarding PFA ablation in patients after MVR and aortic valve replacement with mechanical valves are scarce. In our opinion, the main difficulty during this procedure was

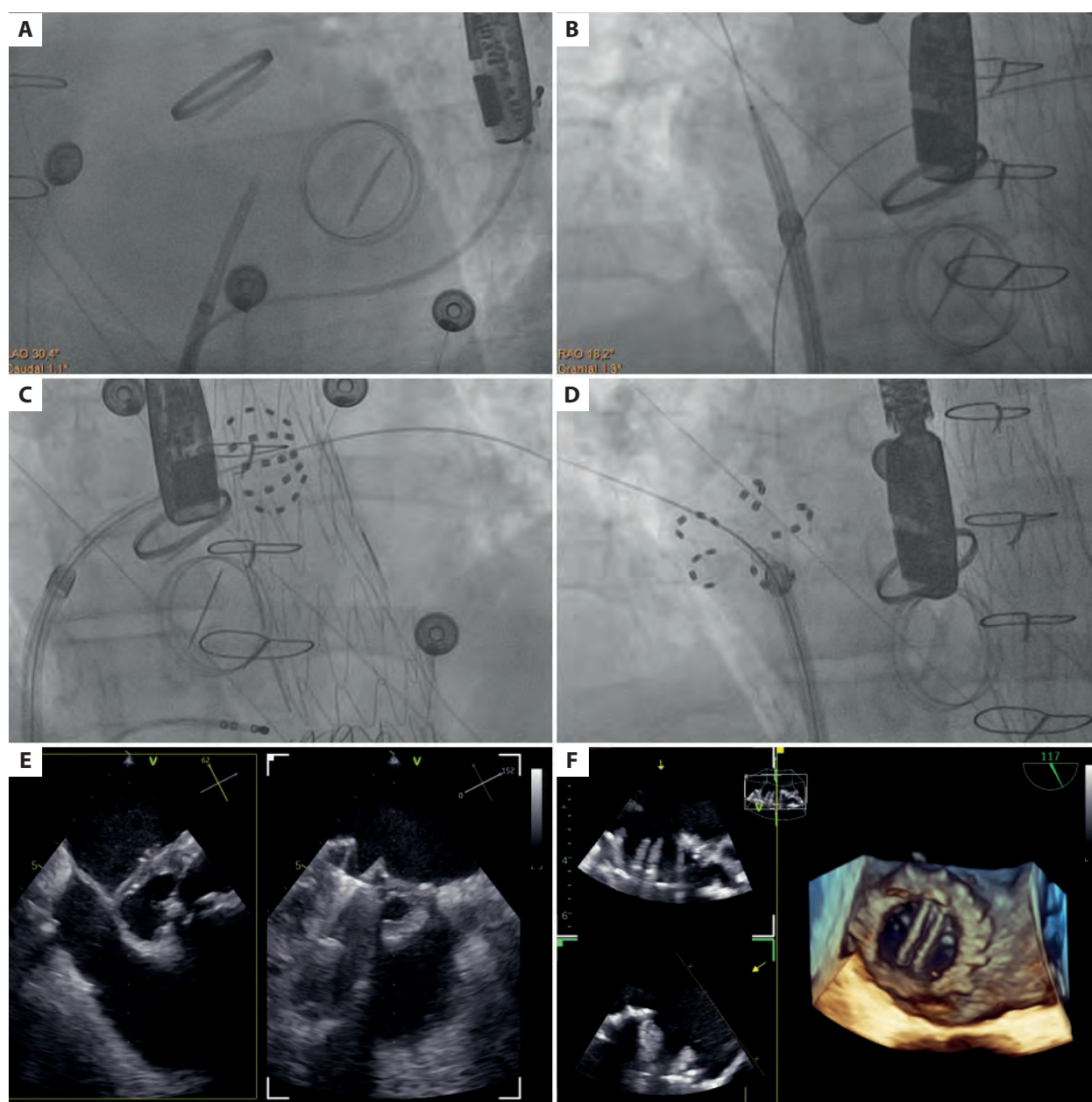


Figure 1. **A.** Fluoroscopy LAO view of transseptal puncture position. **B.** Fluoroscopy RAO view of 13F sheath advancement through the interatrial septum using the double-wire technique, directed towards the right superior pulmonary vein. **C.** Fluoroscopy RAO view of basket-shaped application in the left superior pulmonary vein. **D.** Fluoroscopy RAO view of flower-shaped application in the right superior pulmonary vein. **E.** Transesophageal echocardiography biplane view during transseptal puncture. **F.** Transesophageal echocardiography 3D view of the mechanical mitral valve

Abbreviations: LAO, left anterior oblique; RAO, right anterior oblique

passing the 13F FARADRIVE™ sheath through the groin area and IAS. This process required significant time and fluoroscopy, resulting in a 75-minute procedure with 28 minutes of fluoroscopy and a radiation dose of 741 mGy. Maneuvering the pentaspline PFA catheter in the LA with the mechanical valve, owing to its over-the-wire nature, did not cause significant difficulties. TEE guidance was instrumental in ensuring safety and confirming proper catheter positioning.

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The Naples Prognostic Score in TAVR patients: A promising tool requiring further validation

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We read with great interest the recent paper by Gitmez et al. [1] published in the *Polish Heart Journal*, which evaluated the Naples prognostic score (NPS) in predicting one-year mortality and major adverse cardiovascular events after transcatheter aortic valve replacement (TAVR) for severe aortic stenosis. The authors deserve recognition for investigating this novel, readily calculable score that integrates both nutritional (albumin, cholesterol) and inflammatory markers (neutrophil/lymphocyte ratio [NLR], lymphocyte/monocyte ratio [LMR]), addressing the recognized need for improved risk stratification in the complex TAVR population. Their finding that a high NPS (≥ 3) independently associates with significantly increased one-year mortality and major adverse cardiovascular events is potentially clinically relevant. However, while the study provides valuable preliminary data, several aspects warrant further consideration, highlighting the need for cautious interpretation and additional research.

First, the study's retrospective, single-center design inherently has limitations regarding selection bias and generalizability. Although the authors achieved statistically significant results in their cohort of 222 patients from Turkey, these findings require validation in larger, prospective, multicenter cohorts encompassing diverse patient populations and healthcare settings to confirm the robustness and external validity of the NPS in TAVR risk prediction.

Second, the definition and cut-off values used for the NPS components (albumin < 40 g/l, total cholesterol ≤ 180 mg/dl, LMR

≤ 4.44 , NLR > 2.96) were adopted from the original publication by Galizia et al. [2], which derived the score primarily in patients undergoing surgery for colorectal cancer. While inflammation and nutritional status are broadly relevant, the optimal thresholds for these markers might differ substantially between oncological surgery patients and elderly patients with severe aortic stenosis undergoing TAVR. Further studies should investigate whether these specific cut-offs are optimal for the TAVR population or if TAVR-specific thresholds might improve the score's predictive accuracy.

Third, the article highlights the limitations of traditional surgical risk scores like the STS score and EuroSCORE II in fully capturing TAVR patient complexity [1]. While NPS is presented as a potential complementary tool, the study does not formally assess its incremental predictive value when added to established risk models or other known predictors such as frailty indices, N-terminal pro-B-type natriuretic peptide, or detailed echocardiographic parameters. Demonstrating that NPS significantly improves risk reclassification or discrimination beyond existing tools would strengthen its case for clinical adoption. The wider context for this research is the ongoing search for better tools to predict outcomes after TAVR, particularly beyond the initial 30 days. Traditional scores often fail to adequately account for factors like frailty, malnutrition, and chronic inflammation, which are prevalent in the TAVR population and strongly influence intermediate and long-term survival and quality of life [3]. Composite scores like

the NPS, which attempt to objectively quantify aspects of patient vulnerability using routine laboratory tests, represent a promising approach. They potentially offer a more standardized assessment compared to subjective frailty scales, although they likely capture only part of the complex frailty syndrome. The link between poor nutritional status, heightened inflammation, and adverse cardiovascular outcomes is well-established [4, 5], and leveraging these markers for TAVR risk stratification is logical. Numerous other predictive tools have been proposed in post-TAVR risk stratification, including biomarkers such as nitric-oxide metabolites or alternative risk scores such as the TAVI-NHR model. However, none of these tools has hitherto reached widespread clinical application due to the lack of sufficient validation, similarly to the NAPLES prognostic score. Such validation is a prerequisite to truly replacing the standard risk stratification models, which remain the gold standard currently proposed in the guidelines.

In conclusion, the study by Gitmez et al. [1] provides important evidence suggesting the NPS could serve as a useful prognostic marker in TAVR patients. It effectively combines readily available biomarkers reflecting crucial pathophysiological domains often overlooked by conventional risk scores. However, before widespread clinical application, concerns regarding its derivation, optimal cut-offs for TAVR, generalizability, and proven incremental predictive value need addressing through rigorous, large-scale, prospective validation studies. Future research should also explore dynamic changes in NPS post-TAVR and its potential role in guiding post-procedural management.

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The Naples prognostic score in TAVI patients: A promising tool requiring further validation. Authors' reply

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We are grateful to Prof. Dziewierz and colleagues for their interest in our study "The performance of the NAPLES prognostic score in predicting one-year mortality and major adverse cardiovascular events after transcatheter aortic valve implantation in patients with severe aortic stenosis", and for their thoughtful and constructive comments [1, 2].

Firstly, we completely agree with the authors that our retrospective, single-center design constitutes a limitation, as indeed we acknowledged in our manuscript. Nevertheless, we are confident that our study provides a valuable contribution towards generating real world clinical evidence regarding the prognostic value of the Naples Prognostic Score (NPS) in transcatheter aortic valve implantation (TAVI) patients. Our findings, derived from a well-characterized risk, support the potential utility of integrating inflammatory and nutritional parameters into risk stratification, a need that, as the letter rightly notes, is not adequately addressed by conventional surgical risk scores.

We appreciate the concern regarding the adoption of cut-off values from the original oncology-based NPS study by Galizia et al. [3]. Indeed, while inflammation and malnutrition are relevant in both cancer and cardiovascular populations, optimal thresholds may vary. In our study, we used the original cut-offs to maintain consistency with studies in the literature and to facilitate comparisons

across studies [4, 5]. Determining whether alternative, TAVI-specific, cut-offs would improve discrimination indeed warrants further investigation, ideally through large, prospective multicenter cohorts. We are currently designing such efforts, and encourage others in the field to do the same.

Thirdly, we concur that the incremental predictive value of NPS over established models and frailty indices is of great interest. Although our study did not formally compare NPS to EuroSCORE II or STS scores in reclassification or net benefit analyses, the independent association of high NPS with both mortality and major adverse cardiovascular events in multivariate models, despite adjusting for key clinical predictors, is noteworthy.

These results highlight NPS as a readily available and inexpensive adjunct to existing tools. Compared to subjective frailty assessments, NPS offers a more objective, reproducible approach based on routine laboratory parameters, which could facilitate broader clinical implementation. We believe this highlights a valuable direction for future research, particularly given the multifactorial nature of long-term outcomes in TAVI patients, wherein traditional scores may not fully capture the impact of factors such as inflammation and malnutrition.

Finally, we appreciate the authors' emphasis on the evolving landscape of risk assessment post TAVI, and their call for the

integration of pathophysiological domains such as inflammation and malnutrition into standardized evaluation. We share this vision, and believe that our work adds meaningful preliminary evidence towards the adoption of a more holistic, patient-centered approach in TAVI candidates.

In summary, we are encouraged by the letter writers' recognition of our study's relevance and the call for validation. We welcome continued academic dialogue and multicenter collaboration to refine and validate NPS, or similar biomarker-driven indices, in this growing patient population.

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Patients with frailty syndrome and cardiac invasive procedures. An expert opinion statement from the Prevention and Epidemiology Section of the Polish Cardiac Society

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INTRODUCTION

The prevalence of cardiovascular diseases increases with age [1–4]. In early old age, 75% of patients are diagnosed with cardiovascular diseases, while in the oldest olds (patients over the age of 80 years), 9 out of 10 patients receive such a diagnosis. The incidence of hypertension in people over 80 years old reaches 90%, and the number of so-called long-lived individuals, meaning seniors aged 90 years and above, hospitalized each year due to myocardial infarction exceeds one per cent [3, 4]. The treatment of patients with cardiovascular diseases is particularly difficult. In the elderly individuals, additional factors such as multimorbidity, remaining lifespan, the risk of disease complications, and the potential side effects of the treatment itself make clinical decisions even more challenging. The optimal qualification and preparation for interventional treatment is especially demanding. Available evidence suggests a high

heterogeneity within the geriatric population, with one of the key differentiating factors being pre-frailty syndrome or clinically evident frailty syndrome (FS).

Despite increasing interest in the clinical relevance of FS, there still exist areas with significant uncertainty:

- screening tools for FS;
- the impact of FS on prognosis depending on age, sex, comorbidities, type of medical procedure, and FS severity;
- the benefits and the long-term effectiveness of interventional procedures in individuals with FS and those at risk of FS;
- management following cardiac procedures in patients with FS;
- the awareness of screening, diagnosis, and intervention options for FS among medical staff.

Despite advances in cardiac procedure treatment, FS at least doubles the risk of perioperative mortality. Therefore, incorporating

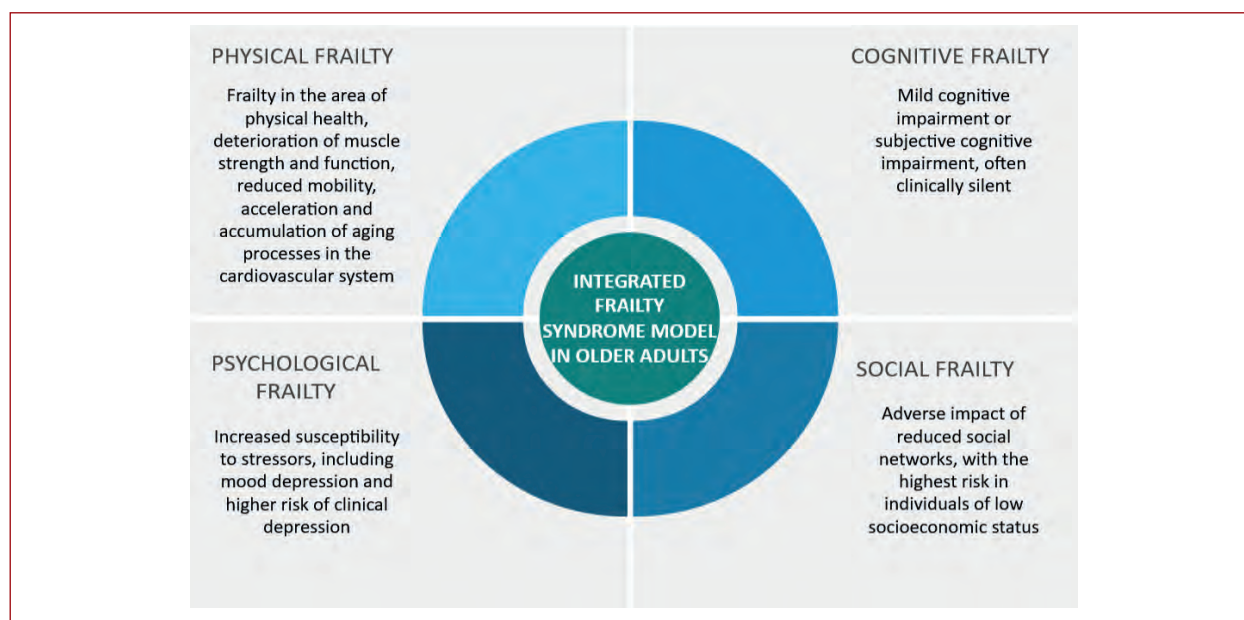


Figure 1. Integrated frailty syndrome model

FS into the decision-making algorithm is crucial when selecting the type and extent of interventional treatment and considering whether to forgo the procedure. Furthermore, delaying the intervention to implement prehabilitation, including physical activity, nutrition, cognitive stimulation, or addressing potentially reversible factors, should also be considered. Implementing such measures can reduce or even reverse the clinical features of FS, which experts emphasize is a potentially reversible condition. Despite emphasis of the role of FS by researchers and clinicians, there has been no consensus so far in respect of an optimal algorithm for assessing patients qualified for cardiac procedures [5]. This statement presents issues regarding the assessment and preparation process for cardiovascular invasive procedures in patients with FS.

DEFINITION, EPIDEMIOLOGY, AND CLINICAL CONSEQUENCES OF FRAILTY SYNDROME

Frailty identifies a group of patients who are more vulnerable to adverse effects, so-called stressors, across various areas, including physical and mental health. FS is now considered in a multidimensional context, as it involves physical and functional limitations or nutritional status and changes in cognitive function and social aspects. FS is related to the decrease in the physiological reserve and overlaps with the aging processes. Intensive treatment of patients with FS may contribute to an increase in adverse effects, loss of independence, worsening of coexisting diseases, and sometimes even worsening of the primary disease itself [6–8].

Although the prevalence of FS increases with age, it is not synonymous with the aging process or multimorbidity. However, in clinical assessment, individual aspects of FS should often be considered (Figure 1) [9]. Furthermore, in 2013, the International Academy on Nutrition and Aging

and the International Association of Gerontology and Geriatrics defined the coexistence of mild cognitive impairment or subjective cognitive impairment with FS or pre-frail as cognitive frailty syndrome. This diagnosis should be distinguished from previously diagnosed neurocognitive disorders, such as Alzheimer's disease [10–13].

The prevalence of FS in the elderly population ranges from around a dozen per cent when assessed in the home setting to over 60% among hospitalized patients. However, the estimation depends largely on the diagnostic tool used [14, 15]. It is worth mentioning that the highest prevalence of FS is observed among patients with cardiovascular diseases, and the relationship between them is characterized by a positive feedback loop.

There is a significant increase in the risk of perioperative complications, including stroke, other cardiovascular events, prolonged hospitalization, and more frequent institutionalization, among patients with FS. The presence of FS is also a well-documented independent predictor of both short- and long-term mortality following acute coronary syndrome or invasive cardiac procedures [16, 17].

SCALES USED FOR FRAILTY SYNDROME ASSESSMENT

When the predicted life expectancy is lower than one-year, intensive diagnostic and therapeutic interventions become futile and should be replaced with palliative care. If the expected survival significantly exceeds 4–5 years, regardless of the patient's age, the recommended treatment should be considered, taking into account the associated risks [18]. Unfortunately, the currently used risk assessment instruments, such as the European System for Cardiac Operative Risk Evaluation (EuroSCORE), PoSCORE-2015, SCORE2, the Society of Thoracic Surgeons risk score, or online mortality

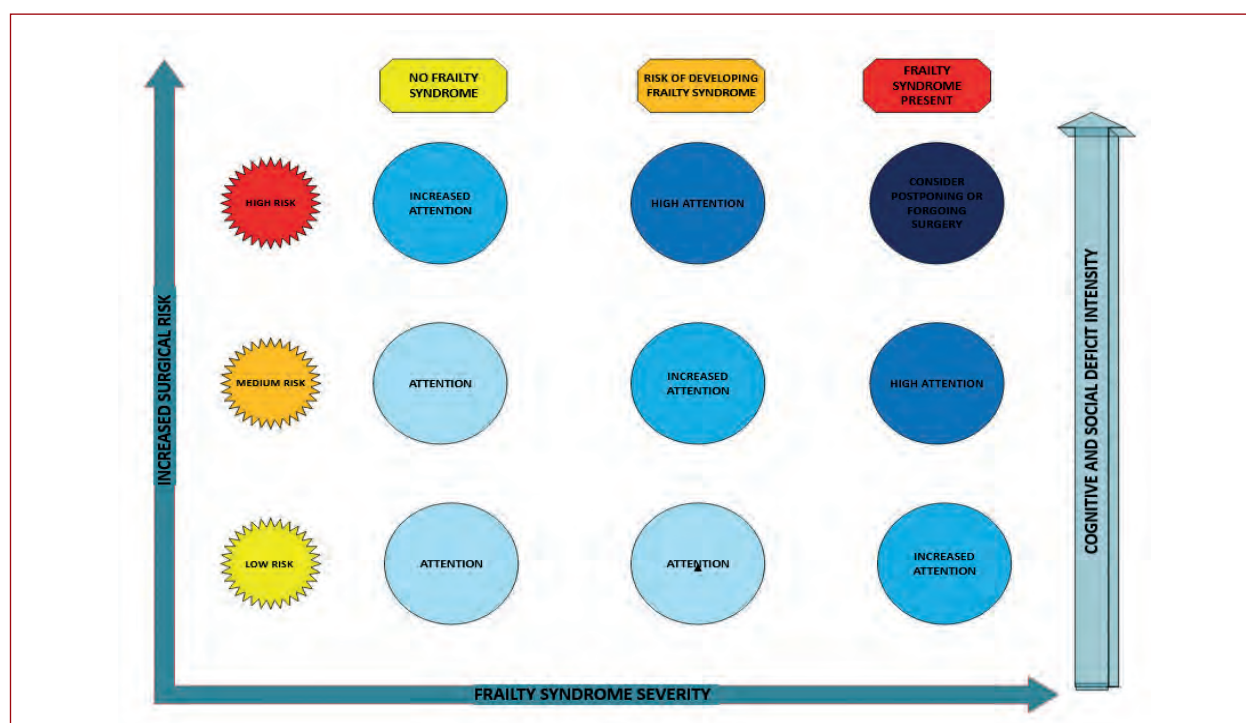


Figure 2. Perioperative risk in a patient with frailty syndrome

risk calculators (<https://eprognosis.ucsf.edu/drame.php>), do not take the FS phenotype into account [19–22].

One of the methods for identifying patients with suspected cognitive impairment is using the Mini-Cog scale [23] (Supplementary material, *Appendix 1*). However, given the high prevalence of multimorbidity in this population, which often complicates diagnosis, functional assessment remains crucial for differentiating the geriatric population, for example using tools such as the Activities of Daily Living (ADL) scale or the Vulnerable Elders Survey 13 (VES-13) [24–27].

Many questionnaires are used for FS diagnosis, which allow for comprehensive assessment in population studies. These include the Frailty Index, Clinical Frailty Scale, Groningen Frailty Indicator, Edmonton Frail Scale, PRISMA-7 Questionnaire, Tilburg Frailty Indicator, Osteoporotic Fracture Frailty Index, FRAIL scale, Short Physical Performance Battery, Multidimensional Prognostic Index, Kihon Checklist, Frailty Risk Score, Hospital Frailty Risk Score, and Linda Fried's phenotypic criteria — particularly useful for FS diagnosis in everyday clinical practice [28–36]. The Supplementary material (*Appendix 2*) presents proposed scales for use in hospital and/or outpatient care and the predictive significance of the main scales [37–40].

Although guidelines and expert documents recommend frailty syndrome assessment, it is often not reflected in everyday clinical practice [41, 42]. This is partly due to the variety of scales and the challenges in adapting them. The key issue is selecting tools that are quick to perform, easy to use, and explicit in evaluation, as well as those that allow the use of data available in medical history and scales that cover related areas [43].

The European Society of Cardiology recommendations (including guidelines on cardiovascular risk assessment and management in patients undergoing non-cardiac surgery) do not clearly indicate a specific tool or algorithm for FS management, with the exception of the most recent guidelines for the management of elevated blood pressure and hypertension, which recommend the use of the Clinical Frailty Scale (CFS) [44, 45]. Indeed, this scale is not time-consuming and can be used as a screening tool, especially in time-dependent procedures. When considering the key role of physical frailty in vulnerable patients, taking into account the time required to perform the assessment, its ease of use, sensitivity, and specificity, Fried's quantitative criteria might be used as a diagnostic tool. Additionally, tools such as the SARC-F questionnaire (strength, assistance walking, rising from a chair, climbing stairs, falls) and the timed up and go test (TUGT) or qualitative tests like CFS can be helpful in the quick identification of patients who require individualized therapy. Although FS assessment can be time-consuming, it is essential for the risk stratification of elderly patients undergoing surgical treatment of cardiac diseases [46]. Incorporating FS into predictive models may contribute to using less invasive surgical techniques [47, 48].

ROLE OF THE HEART TEAM AND PREHABILITATION

In patients with FS, the cumulative clinical risk of a procedure depends on the following factors: perioperative risk, the severity of frailty, and the coexistence of neurocognitive dysfunction and socio-environmental deficits (*Figure 2*).

Adequate assessment and treatment plans for patients with FS should become essential for the heart team. The composition of such a team typically includes a clinical cardiologist, an interventional cardiologist, and, in special cases, a geriatric specialist, physiotherapist, psychologist, imaging specialist, cardiac anesthesiologist, and cardiac surgeon. In particular, a geriatrician should take part in the evaluation of patients and the decision-making process in cases of patients with advanced FS. Early diagnosis of FS enables the initiation of prehabilitation, a multidimensional intervention aimed at preparing the patient for invasive procedures. Prehabilitation focuses on four key areas: physical optimization, nutritional optimization, cessation of harmful habits, and psychological support.

Data from the literature suggest potential benefits of prehabilitation, including shortened hospitalization time, reduced respiratory complications, fewer episodes of post-operative atrial fibrillation, and improved physical function [49, 50]. However, it is important to note the significant heterogeneity of the studies in the tests used to assess FS and the duration and scope of the interventions (including resistance exercises, nutritional intervention, pharmacological treatment, and cardiovascular disease prevention). Intervention in the elderly should be multidimensional, interdisciplinary and include elements of a comprehensive geriatric assessment, with adjusted physical exercises, cognitive activities, nutritional interventions, and reduction of polypharmacy. Based on currently available data, it seems that the minimum duration of prehabilitation should not be less than four weeks, allowing for the rebuilding of some physiological reserves.

Collaboration with a geriatric team within the heart team would be beneficial, especially for patients in late old age [51]. Such collaboration could help reduce the loss of self-sufficiency and other perioperative complications, as well as incorporate patient preferences, an acceptable quality of life following cardiac procedures and their impact on functional ability, and allow for individualized treatment [52–57]. Nursing staff also play a vital role within the team [58]. Following invasive treatment (including invasive treatment for acute coronary syndrome), coordinated multidisciplinary care is recommended, with kinesiotherapy being a crucial element.

QUALIFICATION FOR CARDIAC PROCEDURES

Qualification for a procedure requires consideration of lifestyle, clinical characteristics, biomarkers, and socio-environmental factors (Figure 3). The overlap of these factors not only contributes to the development of FS but may also intensify its progression.

The most commonly used interventional procedures include coronary angiography, coronary angioplasty, heart valve repair, implantation of a pacemaker, cardioverter-defibrillator, cardiac resynchronization system, or loop recorder, and ablation of ventricular or supraventricular arrhythmias.

In the case of **emergency** procedures, the intervention should be performed immediately, and qualification for the procedure is based on a general assessment of the patient's clinical condition, taking into account the known risk factors.

Urgent procedures should be performed without unnecessary delay, with qualification based on a general assessment of the patient's clinical condition, considering risk factors. In such cases, a shortened FS assessment protocol may be considered. The CFS may also be especially helpful in these circumstances, and if CFS ≥ 4 (vulnerable), the FS assessment protocol should be considered.

Expedited procedures should be performed as quickly as possible, with qualification based on a general assessment of the patient's clinical condition, considering risk factors. A shortened FS assessment protocol is recommended, and a full FS assessment should be considered if feasible.

Elective procedures should be performed within a timeframe that allows for a comprehensive patient assessment, including planning a prehabilitation period. Qualification for the procedure is based on a general assessment of the patient's clinical condition and risk factors, and on implementing a FS assessment algorithm.

Before an elective cardiac procedure, an initial screening assessment is recommended for elderly patients using quick-to-perform tools with high sensitivity and specificity. In cases where patients have normal results from such tests (e.g., TUGT and SARC-F) and only isolated risk factors for the development and progression of FS, the qualification for interventional treatment can proceed similarly to that for younger age groups (Figure 4).

Given the multitude of factors influencing FS, qualifying patients for cardiac procedures should focus not only on the immediate qualification process but also on perioperative care, reduction of potential complications, and coordinated care planning (Figure 5) [60]. The recommended algorithm proposed by the authors considers the potential reversibility of FS, particularly during the pre-frail stage (Figure 6).

POSTOPERATIVE MANAGEMENT IN PATIENTS WITH FS

All patients should undergo tertiary prevention, which focuses on preventing the progression of chronic diseases and maintaining functional ability. The interventions implemented during the preoperative and perioperative periods should be continued postoperatively. Furthermore, this group of patients should receive outpatient follow-up more frequently than those without FS, and coordinated care should be initiated in this group of patients.

Studies such as SPRINTT (Sarcopenia and Physical frailty IN older people: multi-component Treatment strategies) and FINGER (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability) have emphasized the effectiveness of multidimensional interventions [61, 62]. Therefore, the role of the multi-specialized team

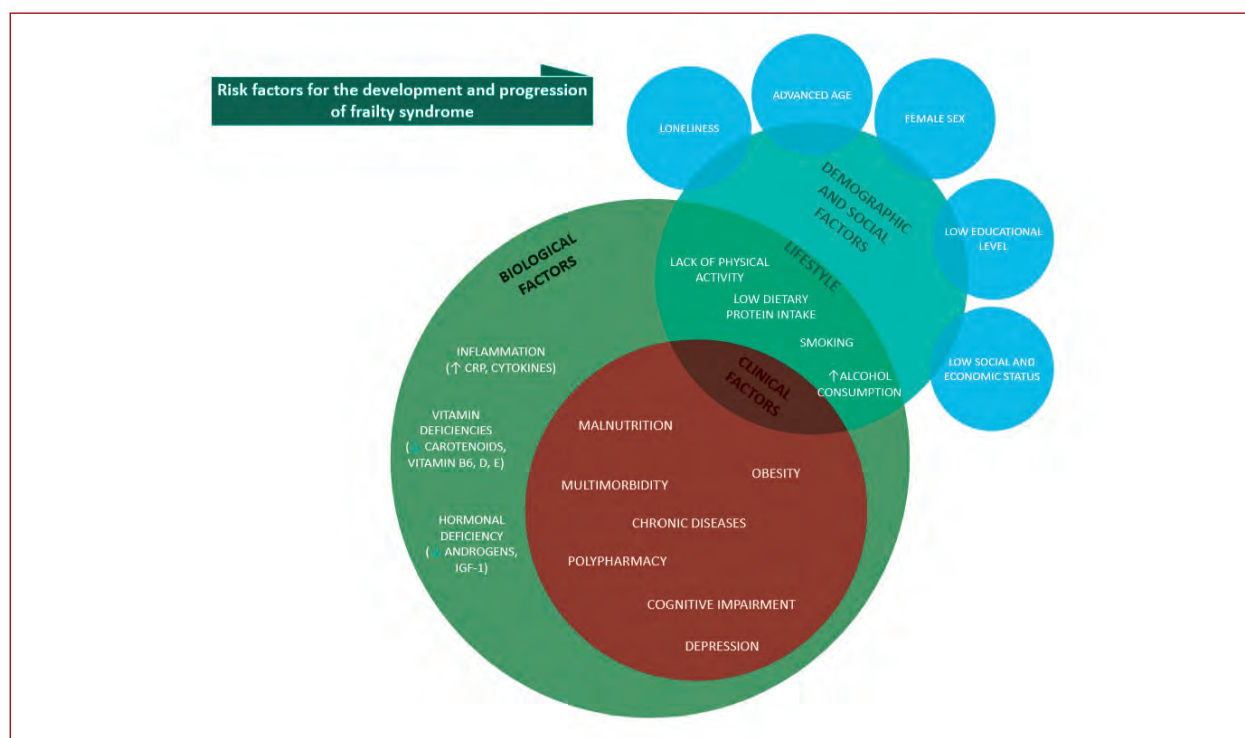


Figure 3. Risk factors for the development and progression of frailty syndrome, own elaboration based on Hoogendijk et al. [59]

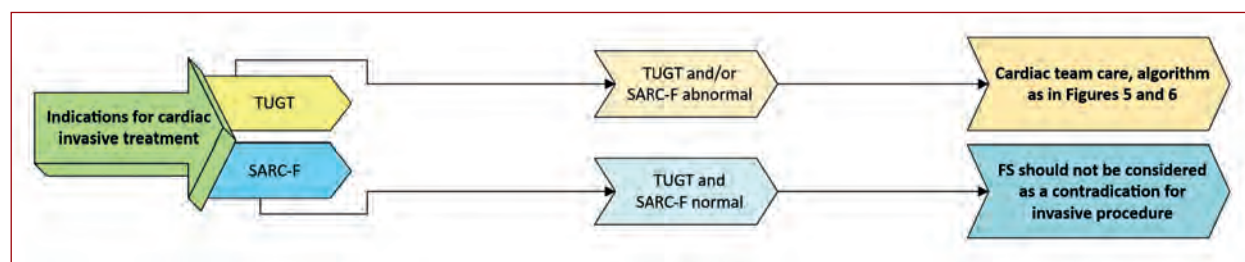


Figure 4. Shortened frailty syndrome assessment scheme in elderly patients before cardiac procedures

Abbreviations: SARC-F, strength, assistance walking, rise from chair, climb stairs, falls; TUGT, timed up and go test

managing patients with FS is to plan and implement at least the minimum initial recommendations for multidimensional intervention. For some patients, a referral for comprehensive geriatric assessment will be necessary to evaluate other typical geriatric syndromes. This is important considering that patients with frailty have not only higher in-hospital but also post-discharge risk of major adverse cardiac events, functional decline, and death as well as rehospitalization, cognitive impairment, delirium, and depression [63, 64].

SUMMARY

The cardiovascular invasive procedures of patients with FS present a significant challenge for researchers, clinicians, and healthcare systems. This is particularly true given that many patients with FS are in late old age and often suffer

from multiple comorbidities. FS itself is a dynamically evolving condition, and the effective implementation of interventions can prevent patient disability. Moreover, FS is a more significant prognostic factor than age alone, allowing the identification of high-risk patients. Using the proposed tools in daily practice may contribute to more effective assessment and significant clinical impact in patients with FS. Considering current medical knowledge, the assessment of FS should become an integral part of the preoperative qualification for cardiac procedures, and planning and organization of care for this patient group, particularly in the oldest olds.

Supplementary material

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

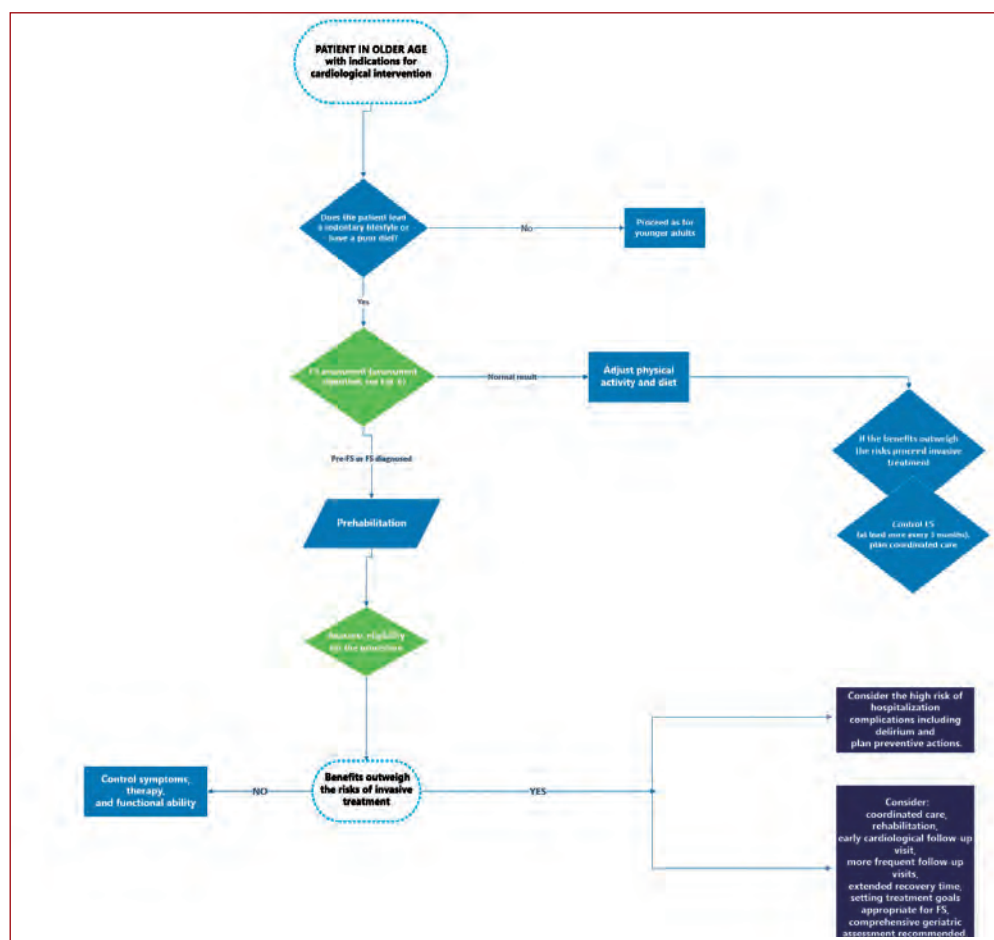


Figure 5. Preparation and qualification for cardiac invasive treatment in patients with suspected frailty syndrome

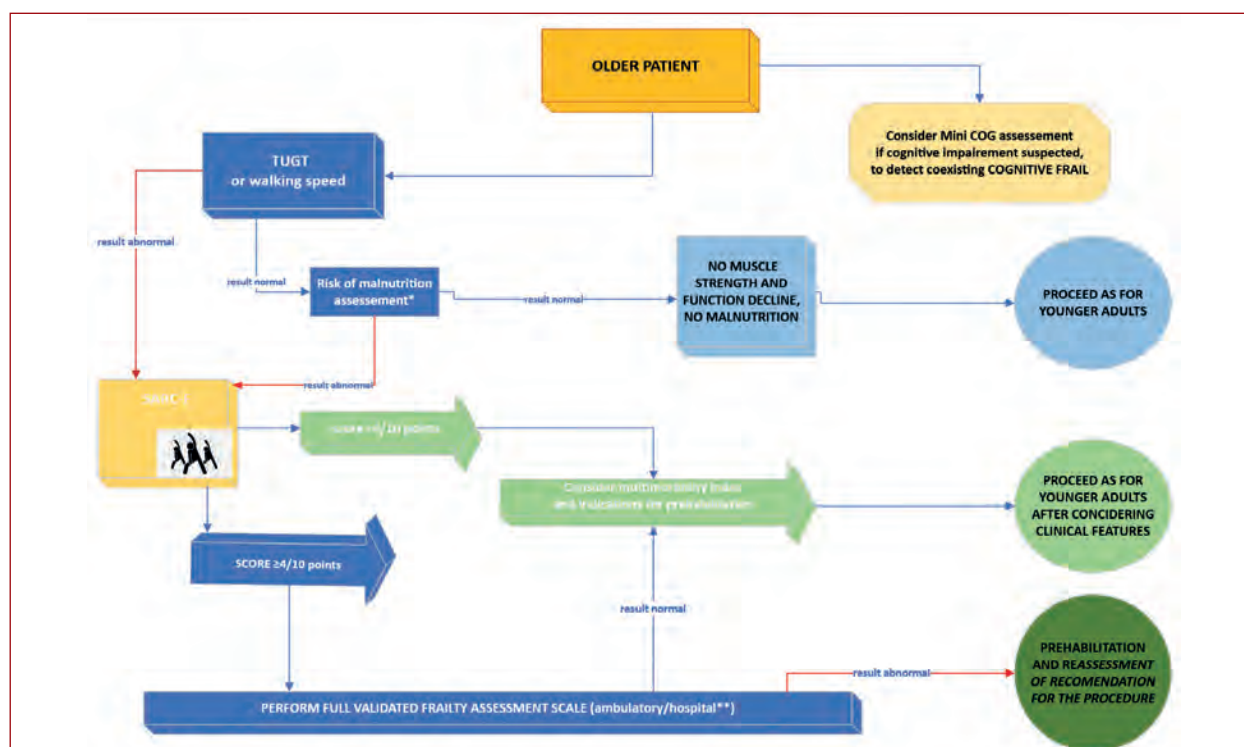


Figure 6. Perioperative management algorithm for a patient qualified for an elective cardiovascular invasive procedure

*Risk assessment scale for malnutrition such as Mini Nutritional Assessment (MNA)

** Validated frailty assessment scales, presented in Appendix 2

Abbreviations: Mini-Cog, Mini-Cognitive Assessment Test; SARC-F, Strength, Assistance walking, Rise from chair, Climb stairs, Falls; TUGT, Timed Up and Go Test; VES 13, Vulnerable Elders Survey

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