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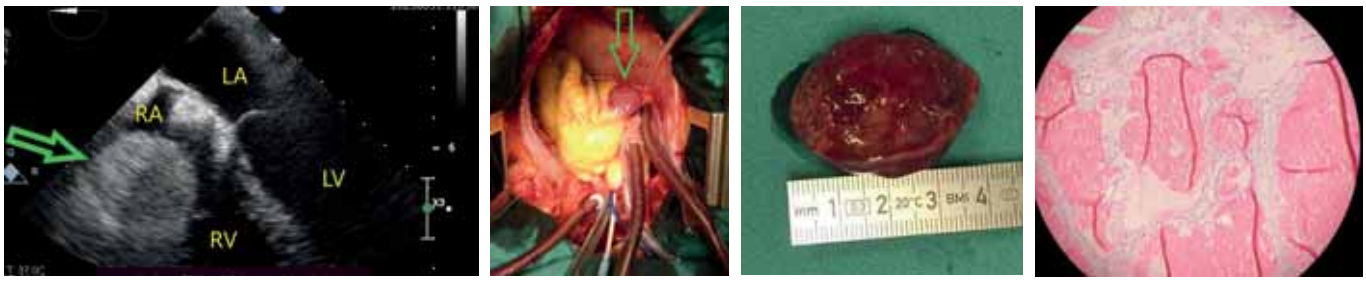

Capillary hemangioma removed from the right atrium of a 52-year-old man, see p. 106

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POLISH HEART JOURNAL
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87 WIOSENNA KONFERENCJA PTK

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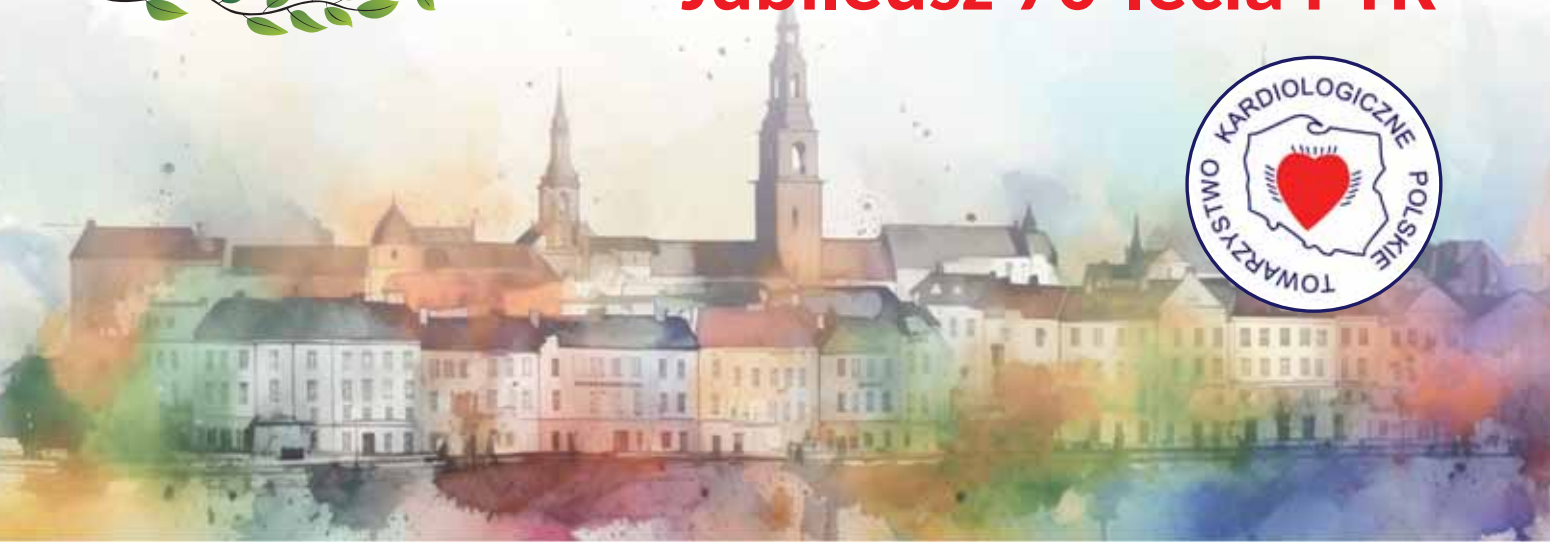
Jubileusz 70-lecia PTK



Zapraszamy do wzięcia udziału w **87 Wiosennej Konferencji PTK oraz XVI Konferencji „Kardiologii Polskiej”** w dniach **13-14 kwietnia 2024 roku**, które odbędą się w gmachu Opery i Filharmonii Podlaskiej w Białymstoku. Podczas Konferencji odbędzie się również **Jubileusz 70-lecia Polskiego Towarzystwa Kardiologicznego**.

Program naukowy został przygotowany przez najwybitniejszych specjalistów polskiej kardiologii i kardiochirurgii. Omówione zostaną wytyczne ESC z 2023 roku.

Pozostałe sesje zostały przygotowane przez przedstawicieli wszystkich grup tematycznych Komitetu Naukowego Kongresu i obejmują całe spektrum podspecjalizacji nowoczesnej kardiologii. Kilka ważnych i ciekawych zagadnień praktycznych zostanie zaprezentowanych w atrakcyjnej konwencji warsztatowej.

Jesteśmy przekonani, że taki program zachęci Państwa do udziału w Konferencji, przyniesie istotne korzyści praktyce klinicznej, a także przyczyni się do rozwoju Polskiego Towarzystwa Kardiologicznego.

Zapraszamy nie tylko kardiologów i kardiochirurgów, ale również rezydentów, lekarzy rodzinnych, internistów i studentów medycyny. Dla studentów udział w Konferencji jest bezpłatny.

Przewodnicząca Komitetu Organizacyjnego:
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Polish Heart Journal on the rising trajectory in 2024

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The current year 2024 brings new initiatives and hopes. We have modified the name of our journal from *Kardiologia Polska* to *Polish Heart Journal* (*Pol Heart J*), with a subsequently updated logo. We hope that our readers will like the new look of the journal's cover as much as we do. A small change, but its significance is second to none since after more than 60 years, just on the 70th anniversary of the Polish Cardiac Society's foundation, our journal has joined (as one of the latest) the large family of national cardiology journals affiliated with the European Society of Cardiology. Based on previous bibliometric reports, it is likely that the English name will enhance our visibility and boost the Impact Factor in a longer perspective. At the very beginning spreading the message on to properly cite articles from our journal and regularly monitoring the citation count at Clarivate is of paramount importance.

A major change in 2023 was the adoption a new format of our website on July 5, which we hope you all appreciate. We felt that the unaltered website of the journal no longer reflected our aspirations for being at the forefront of clinical research in heart diseases. We are all happy with the end result supported by the Polish Cardiac Society, which as we have noticed, has been implemented in other titles of our publisher within recent weeks.

In October 2023, we said farewell to Ms. Anna Młynarczyk, our dedicated managing editor, who showed her professionalism in the hardest time in mid-2021 at our return to the former publisher, Via Medica. This was a real loss for our editorial team. Since more than two months Ms. Aleksandra Markowska took over. We hope that the editorial process will go smoothly after the transition period. Another sad information at the end of 2023 was resignation of Mr. Mateusz Meisner from his position at Via Medica. He made efforts to enhance the standing of our journal for almost 2 years through strengthening support of our publisher and developing new strategies for Educational Issues that contain materials including guidelines, expert opinions and statements generated by working groups and associations of the Polish Cardiac Society, all valuable for everyday clinical practice beyond cardiologists. Since 2024 all Educational Issues will be available online, without issues in print. Hopefully in 2024, with no delay in access of the physicians to the latest guidelines.

Some numbers to summarize the year 2023 at the editorial office. After implementation of article processing charges in March 2022 (unaltered till the beginning of 2024) and the expected drop in submissions observed in the following months, the rate of manuscript submissions, including high-quality observational studies, has become rather stable at the level 607 by the end of December 2023 compared with 685 at the same time in 2022. This has been accompanied by a high rejection rate — now running at 72%.

Based on the recent estimation, our predicted 2024 two-year Impact Factor should be equal to our record value achieved in 2021, i.e., 3.7 or more. This will be a huge success given everyday difficulties and a highly competitive scholarly publishing market with a rising number of cardiology journals. It has not been feasible without the hard work of the Associate Editors who strive to help authors improve the quality of content and data presentation, in particular statistical analysis, *via* constructive reviewers' comments, suggestions for revision and robust adjudication. With more papers comes the need for more reviewers, especially those who can support our efforts to reduce

the time from submission to publication. I would like once more to encourage potential reviewers to accept invitations to review, and to provide comments in a timely fashion,as well as to express my gratitude to all who represent this team of key importance in the publication process.

We look forward to further growth and development for *Pol Heart J* in the months ahead, and we wish a successful and scientifically inspiring 2024 to all our authors, reviewers, and, of course, our readers.

Article information

Conflict of interest: None declared.

Funding: None.

SGLT2 inhibitors and the risk of contrast-induced acute kidney injury: Time for a PCI Trial?

Davide Capodanno, Simone Finocchiaro

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Related article
by Kültürsay et al.

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Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are effective in reducing major adverse cardiovascular events in patients with type 2 diabetes who have established atherosclerotic cardiovascular disease or are at high risk of this condition [1, 2]. Additionally, in SGLT2i users, a reduction in cardiovascular death and hospitalization for heart failure has been shown, irrespective of diabetes or left ventricular ejection fraction [3, 4]. In patients with chronic kidney disease, SGLT2i reduce the risk of disease progression or cardiovascular death [5]. Yet, the potential protective effect against contrast-induced acute kidney injury (CI-AKI) in patients who are on SGLT2i at the time of primary percutaneous coronary intervention (PCI) has not been assessed. ST-segment elevation myocardial infarction is associated with various complications, among which CI-AKI significantly impacts patient mortality [6].

In this issue of the Journal, Kültürsay et al. [7] shed some light on this topic with a report on their retrospective study of 295 diabetic patients with ST-segment elevation myocardial infarction undergoing primary PCI. The authors compared the risk of CI-AKI in patients with or without background therapy with SGLT2i (including empagliflozin and dapagliflozin). In the treatment group, the exposure time to the medication was at least 6 months before to PCI, ensuring sufficient time for the drug to exert its pleiotropic effects and impact the cardiorenal system. The authors employed a CI-AKI definition aligned with Kidney Disease: Improving Global Outcomes guidelines, characterized by a rise in creatinine level of ≥0.3 mg/dl above the baseline value within 48 hours of contrast media exposure or an increase of at least 1.5 times compared to the baseline value within 7 days. This definition is sensitive and commonly used in various studies, providing a comprehensive approach to identifying CI-AKI.

Interestingly, the incidence of CI-AKI after PCI was lower in the group using SGLT2i compared to the non-user group. This difference remained after statistical adjustment (adjusted odds ratio: 0.86 [0.76–0.98]; 95% confidence interval; $P = 0.028$). This effect size is consistent with previous research demonstrating the cardiovascular and renal benefits of SGLT2i in individuals with diabetes and cardiovascular disease [4]. However, some limitations of this study should be acknowledged. First and perhaps foremost, the study was nonrandomized. The effect of potential confounders was mitigated by the use of robust adjustment methods, but there is no statistical method that may account for unidentified confounders [8]. Second, the retrospective nature and single-center design may limit the generalizability of the findings. Third, the relatively small sample size and heterogeneity in the specific SGLT2i agents and dosages used by patients could also impact the results. Fourth, the average hospitalization time of four days in this study is considerably lower than the 7 days in the CI-AKI definition, which could have lead to the detection of only acute events and underdiagnosing late CI-AKI.

Despite these limitations, the finding of a potential renoprotective role of SGLT2i in patients undergoing PCI and exposed to contrast media is biologically plausible and

clinically intriguing. The glycosuric effect of SGLT2i, known for promoting active diuresis, may help maintain renal function during the critical period of contrast administration [9]. Additionally, the anti-inflammatory and anti-oxidative properties of SGLT2i could counteract hypoxic pathways involved in CI-AKI development [10]. This complements their metabolic role in reducing harmful uremic toxin buildup and enhancing renal protection with lower proximal tubule glucotoxicity [11].

Recently, the DAPA-MI study suggested that non-diabetic patients using SGLT2 inhibitors after a myocardial infarction experience metabolic improvements without impacting the composite of cardiovascular death or hospitalization for heart failure compared with placebo [12]. The study by Kultursay et al. [7] now suggests that diabetic patients already on SGLT2i before myocardial infarction might experience synergistic benefits due to the combined metabolic effect on diabetes and the renal system, potentially leading to better long-term cardiovascular outcomes after myocardial infarction.

The reported potential protective effect against CI-AKI in this investigation opens avenues for future research exploring the application of SGLT2i beyond current indications, possibly in PCI, to improve not only cardiac but also renal outcomes. As the field evolves, the potential of SGLT2i as a safeguard against renal complications in high-risk cardiac patients is promising. Future randomized studies with larger cohorts and comparative analyses of different SGLT2i may further validate and refine this hypothesis.

Article information

Conflict of interest: None declared.

Funding: None.

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SGLT2 inhibitors and contrast-associated acute kidney injury

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Related article
by Kültürsay et al.

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The association of increases in serum creatinine with the administration of iodinated contrast has been known for over 70 years. In that time, we have refined the definition of serum creatinine rises based upon the Kidney Disease: Improving Global Outcomes criteria, renamed the association from contrast-induced nephropathy to contrast-associated acute kidney injury (CA-AKI), learned much about the risk factors and predictors of CA-AKI, the pathogenesis of the condition, and increasingly appreciated the short and long-term consequences of CA-AKI. However, we have progressed little in the area of prevention despite a multiplicity of efforts involving devices, pharmaceuticals, and other physiologic maneuvers [1]. The search for a preventive measure is littered with unsuccessful attempts that had worked in animal models and early (Phase II) clinical trials. However, when applied to large prospective randomized multicenter phase III registration trials, the interventions fared no better than the control group. One might argue that over time, we got better at managing this adverse effect and thus the control groups did better, raising the bar for an effective intervention. This, however, does not seem to be the case as the incidence of CA-AKI has not changed that much in the past 2 decades. So we are left with the current American College of Cardiology/American Heart Association guidelines which simply recommend "adequate hydration" and limiting the amount of contrast administered, particularly in patients deemed to be at increased risk of CA-AKI due to underlying chronic kidney disease [2].

We are now beginning a new chapter in the prevention of CA-AKI. Sodium-glucose cotransporter 2 (SGLT2) inhibitors, originally developed for treating hyperglycemia, have been found to exert long-term benefits in the cardiovascular and renal systems. The mechanism(s) of these benefits is complex and not completely understood but does not seem to depend on any reduction in glycemia. Indeed, this class of medications is no longer considered a specialty-specific therapy but is increasingly being marketed to cardiologists and nephrologists for patients without diabetes.

In this issue of *Polish Heart Journal*, Kultursay and colleagues [3] used an existing database of patients with diabetes who were admitted with STEMI. Some patients had been taking SGLT2 inhibitors (SGLT2i) for at least 6 months while others had not. They first compared the incidence of CA-AKI (a 25% increase in serum creatinine over 48–72 hours) and found it was ~50% lower in the group that had been taking SGLT2i (9% vs. 18%). Recognizing that there were likely many differences between those taking and those not taking SGLT2i that might influence whether they suffered from CA-AKI, the authors used statistical techniques involving propensity matching to adjust for those variables that were different between the groups — age, sex, baseline creatinine, use of RAAS inhibitors, diabetic drugs, such as metformin. Although the benefit diminished somewhat (OR, 0.86), a significant benefit in the SGLT2 takers was still observed.

Similar observations have been made from the SGLT2-I AMI PROTECT registry which included 652 non-insulin-taking diabetes patients admitted with acute myocardial infarction, some (n = 111) taking an SGLT2i for longer than 3 months and others (n = 535) not taking. The overall incidence of CA-AKI

was 11.2%, 5.4% in SGLT2i takers vs. 13.1% in non-takers ($P = 0.022$) [4]. In a follow-up analysis, the reduction in CA-AKI was seen in both those with and without CKD (OR, 0.356; $P = 0.038$) [5]. Similar results from a single center in China support the protective effect of SGLT2 on CA-AKI when using propensity matching to address potential confounders [6].

Potential mechanisms of benefit are beyond this editorial. Suffice it to say that all pathologic mechanisms thought to account for CA-AKI, including mitochondrial injury causing direct nephrotoxicity, vasoconstriction causing ischemia, and generation of reactive oxygen intermediates reducing NO levels, are all favorably affected by SGLT2i treatment in *in vitro* and animal studies [7].

How enthusiastic should we be about these observations? While there is no question that we need an effective prevention for CA-AKI, we are a long way from establishing a role for SGLT2i.

First, no matter how exhaustive the adjustment for confounding variables, such as with propensity matching, residual confounding cannot be eliminated. This is why, "evidence-based medicine" relies on prospective, randomized trials where the number of events and number of patients are high enough that one expects (hopes) the randomization process to adjust for all confounders.

Second, we have no data on the pharmacodynamics of this potential benefit. The patients described in the study had been on SGLT2i for a minimum of 6 months. There were variable doses observed. The other observational studies, likewise, included only patients on SGLT2i for months. Would there still be a benefit if the SGLT2i was given 30 minutes or even 24 hours before exposure to contrast? Is the benefit better at high dose vs. low dose of SGLT2i?

These are questions that will hopefully be answered by future prospective randomized trials. At least one such trial is underway using a single low dose of SGTL2i administered for 5 days before elective percutaneous coronary intervention or coronary angiogram in high-risk patients (NCT04806633).

In conclusion, the observational data presented in this article is potentially another feather in the cap of SGLT2i. The risk of acute kidney injury may indeed be diminished in those taking this class of medications. However, I would not interpret the data to suggest that administering an SGLT2i immediately before to exposure to contrast is beneficial. That is a very slippery path that has not been navigated successfully by many other interventions despite the best of intentions.

Article information

Conflict of interest: None declared.

Funding: None.

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Oral anticoagulation for atrial fibrillation and high risk of bleeding in daily practice: What clinical considerations?

Giuseppe Boriani[1], Enrico Tartaglia[1], Jacopo F Imberti[1, 2]

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The benefits of oral anticoagulants in reducing the risk of stroke associated with atrial fibrillation (AF) have been demonstrated by randomized controlled trials (RCTs). Indeed, in patients with so-called "nonvalvular AF" the role of warfarin, with appropriate monitoring of the international normalized ratio vs. antiplatelets and, more recently the advantages of direct anticoagulants (DOACs) have been validated [1]. Taking into account all the RCTs comparing DOACs to warfarin, the use of DOACs was associated with statistically significant reductions in the risk of stroke/thromboembolism and intracranial hemorrhages, but not in major bleeding and gastrointestinal bleeding [1].

The risk of bleeding remains a major concern and an important barrier to full implementation of oral anticoagulants in patients at risk, particularly in elderly frail patients [2], in patients with advanced kidney disease [1], and in patients with severe co-morbidities such as cancer [3]. While RCTs are important for gathering high-level evidence for recommendations of consensus guidelines [4], assessment of management of AF patients in daily clinical practice through observational studies and "all-comer" registries is essential for defining what barriers may exist to full implementation of guidelines in daily practice.

In the present issue of the Journal, Maciorowska et al. [5] report on a group of 3598 patients enrolled in the POL-AF registry, a multicenter cross-sectional study enrolling consecutive patients with AF hospitalized for urgent or planned reasons (mainly AF and/or heart failure) in 10 Polish cardiology centers. The authors specifically focused on patients presenting a clinical profile with high risk of bleeding, as evaluated by a HAS-BLED score ≥ 3. The high HAS-BLED group accounted for around 29% of the entire patient population and was characterized by older age and more comorbidities, particularly coronary artery disease, peripheral artery disease, and chronic kidney disease. In the high HAS-BLED patient group, 14.5% of the patients did not receive anticoagulants. Among the patients treated with DOACs, the proportion of patients with inappropriate dose reduction was impressive, ranging from 8 to 47%, according to different used agents. The study highlights that even nowadays, despite around 10 years of experience in using DOACs in AF patients, the clinical profile: "at risk of bleeding" and/or a history of bleeding constitute important barriers to the provision of adequate antithrombotic prophylaxis for preventing stroke. The available data do not allow us to identify the number of patients who had true contraindications to anticoagulation (severe bleeding due to a non-correctable or non-reversible cause) as opposed to only an increased risk of bleeding, expressed by at high HAS-BLED score [6]. This has important implications since in the presence of absolute contraindications to long-term anticoagulation, use of left atrial appendage occluders is justified and appropriately applied [7, 8]. Notably, according to the ESC guidelines [9] a high bleeding risk score should not contraindicate anticoagulation in the long term; however, it, should prompt

Table 1. Scores for estimating bleeding risk and cut-offs for defining a high risk of bleeding

Risk scores proposed in the literature	Number of risk factors and associated scores	Cut-off for high risk of bleeding
HAS-BLED	**9 RF:** systolic BP >160 mm Hg (1) — severe renal/hepatic disease (1 each) — stroke (1) — bleeding (1) — labile INR (1) — age >65 (1) — APT/NSAIDs (1) — alcohol excess (1)	≥3
ORBIT	**5 RF:** age ≥75 (1) — reduced Hb/Hct/anemia (2) — bleeding history (2) — reduced renal function (1) — APT (1)	≥4
HEMORRHAGES	**12 RF:** hepatic/renal disease (1) — ethanol abuse (1) — malignancy — age >75 (1) — low Plt (1) — re-bleeding risk (2) — hypertension (1) — anemia (1) — genetic factors (1) — increased falls risk (1) — stroke (1)	≥4
ABC	**3 RF:** age — biomarkers (GDF-15 or cystatin C/CKD-EPI, cTnT-Hs, Hb) — previous bleeds	≥2
ATRIA	**5 RF:** anemia (3) — severe renal disease (3) — age ≥75 (2) — prior bleed (1) — hypertension (1)	≥5
Alfalfa-MB	**7 RF:** age >65 (10), history of bleeding (7.9) — anemia (4.8) — vascular disease (6.9) — no PPI (8.6) — antiplatelet therapy/NSAIDs (8.6) — rivaroxaban (4.2)	≥18.3

Abbreviations: APT: antiplatelet; BP: blood pressure; cTnT-hs: high-sensitivity cardiac troponin T; GDF-15: growth differentiation factor 15; HB: hemoglobin; Hct: hematocrit; INR: international normalized ratio; NSAIDs: nonsteroidal anti-inflammatory drugs; Plt: platelets; PPI: proton pump inhibitor; RF: risk factors

correction of modifiable risk factors for bleeding and increase patient monitoring and surveillance. However, this is often not applied to clinical practice where physicians are often particularly worried by the risk of bleeding, even more worried about bleeding than the risk of stroke [6], which is at odds with views and values of empowered patients, who usually prioritize the prevention of cardioembolism [1].

The HAS-BLED score has been commonly used since it was advised by 2020 ESC Guidelines [1, 9], but other risk scores have been also proposed [6], with some differences in terms of the number of risk factors considered and requirements for defining a condition of high-risk for bleeding (Table 1).

In daily practice, decision-making is frequently conditioned by the physician's perceptions rather than objective evidence. It was recently shown how frailty assessment in AF patients [10] may show an important disagreement between the physician's perceptions and objective definitions of frailty. Physician's perceptions may have important implications such as lack of prescription of anticoagulants in patients at risk but without clear contraindications or prescription of DOACs at low inappropriate dosing, as highlighted by Maciorowska et al. [5] and by Diemberger et al. [10]. Additionally, we can expect that physician's perceptions of bleeding risk may strongly affect, together with the occurrence of minor bleeding adherence and persistence to anticoagulants,, an issue that still requires substantial improvement, even if the situation is currently better with DOACs as compared to the past when only vitamin K antagonists were available [1].

Observational studies exploring the "real world" practice are important since they highlight that inappropriate provision of stroke prevention in AF patients at risk of stroke is still a problem [5, 11], and targeted educational programs should be planned. With this regard, it is important to recognize that prescription of aspirin or low molecular-weight heparin is not uncommon in real-world registries [11]. In these registries, low molecular heparin is frequently employed, despite the lack of evidence, in patients with AF and active cancer, which is a setting of difficult management considering the risk of bleeding and the lack of randomized studies [3, 12]. It is noteworthy that none of the scores proposed for estimating the risk of bleeding (Table 1) includes active cancer or a history of cancer, thus making any decision-making problematic. As a matter of fact, in the study by Maciorowska et al. [5], malignant neoplasms were strong predictors of non-use of anticoagulants. In the same study, the proportion of patients characterized as being at high risk of bleeding was important, accounting for around one-third of patients hospitalized for AF in cardiology wards [5], with even higher estimates expected in settings such as Internal Medicine, Geriatrics or Neurology wards [11].

Clinical management of patients at high risk of bleeding is challenging and requires a holistic integrated approach, also with involvement of different specialists, and it should follow all the pillars of the A-B-C pathway suggested by consensus guidelines [1, 9, 13]. It is well known that patients at high risk of bleeding may be concomitantly at high thromboembolic risk [1]. According to guidelines, pillars A (avoid stroke), B (better symptoms management) and C (cardiovascular and comorbidities management) should be followed, since adherence to A-B-C is associated with better outcomes in the long term [13], and this approach should be coupled with minimization of bleeding risk, by correcting modifiable risk factors (e.g.: hypertension) and by avoiding, if possible, concomitant treatment with aspirin [14] or other drugs that increase the hemorrhagic risk. Furthermore, it should be stressed that the bleeding risk may change over time, and HAS-BLED assessment should consider its dynamic changes [1, 6].

In conclusion, the availability of DOACs allowed for an increase in the effective prevention of stroke and, particularly, of disabling strokes in AF patients, but patients at high risk of bleeding still represent a clinical challenge that requires an evidence-based approach rather than relying on perceptions. There is an interesting perspective of uncoupling hemostasis and thrombosis by factor XI inhibitors [15], but their efficacy and safety in AF need to be confirmed by dedicated RCTs.

"Things should be made as simple as possible, but not simpler"

This famous line attributed to Albert Einstein can also be applied to decision-making in medicine, which is often problematic, as in the case of anticoagulation in patients at high risk of bleeding. Such cases be approached in a conscientious, responsible way, taking into account the risks and benefits of potential therapeutic decisions, and, discussed with appropriately informed and empowered patients.

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Understanding the impact of alcohol on blood pressure and hypertension: From moderate to excessive drinking

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ABSTRACT

Observational studies report a strong positive linear association between alcohol consumption and blood pressure but also suggested a lower cardiovascular risk with light drinking compared with abstainers. However, this potential cardioprotective effect of low-to-moderate alcohol intake seems attributable to a healthier life style in these individuals. Hence, more recent epidemiological and genetic Mendelian randomization studies indicated a continuous nonlinear positive relationship between alcohol intake and blood pressure (BP). The risk for hypertension increases in both men and women, if daily alcohol intake is at least one to two drinks (about 10–20 g alcohol) per day. Alcohol reduction close to abstinence is associated with a 3.3 and 2.0 mm Hg reduction in systolic BP and diastolic BP. A dose-dependent relationship between alcohol intake and BP was observed particularly in heavy drinkers consuming at least 6 drinks/day. In this group, more profound BP reductions can be expected by reducing alcohol intake. Additionally, both trial data and observational literature support the hypertensiogenic effect of binge drinking, which together with uncontrolled hypertension, is the most important risk factor for intracranial hemorrhage. Consequently, excessive (binge) drinking should be avoided, and patients with high risk for intracranial bleedings should be advised accordingly. Recommendations in different guidelines vary regarding the upper limits and definition of drinks, and recommendations for sex-specific upper limits for alcohol intake appear questionable. Moderation in alcohol intake and implementation of alcohol-free days during the week in both men and women who consume drinks that contain alcohol are recommended to improve BP control and overall health.

Key words: alcohol**,** blood pressure, cardiovascular risk, hypertension, stroke

INTRODUCTION

In 2019, global alcohol consumption averaged 5.5 liters of pure alcohol per person, with significant variations observed worldwide [1]. The range varies from region to region, with the lowest consumption, such as the Middle East at just 0.3 liters, to the highest consumption, notably in Europe at 9.2 liters [1]. Specifically in Europe, men consume an average of 14.9 liters *per capita*, while women consume 4.0 liters [1]. Alcohol attributable mortality is considerably higher among men, accounting for approximately 2.07 million fatalities, as opposed to 374 000 among women [2]. In both sexes, high systolic blood pressure (SBP) is a leading risk factor for deaths, responsible for 10.8 million fatalities in 2019 [2]. Alcohol consumption contributes to disability, measured in Disability-Adjusted Life Years, representing 6.3% of the global burden of disease. Following closely, high SBP accounts for 6% of Disability-Adjusted Life Years, particularly in the younger age group (25–49 years) [2].

What is the accepted definition and terminology for alcohol intake, particularly in the context of the "drink concept"?

A standard drink is a measurement of alcohol consumption, serving as a benchmark for the amount of pure alcohol in a beverage [3]. The term drink was introduced for pragmatic reasons, because this construct is used in epidemiological studies on alcohol consumption

Table 1. Recommendations of scientific societies about alcohol consumption in hypertension management guidelines

Guidelines	Recommendation(s)
ESC/ESH (2018) [8] ESH 2023 [4]	Less than 14 g for men and 8 g for women per week, alcohol free days, avoid binge drinking Below 3 drinks/day and close to abstinence in both men and women, avoid binge drinking
ACC/AHA (2017) [9]	Less than 2 standard drinks daily for men and 1 standard drink for women
ISH (2020) [10]	2 standard drinks for men and 1.5 for women, avoid binge drinking
Polish Society of Hypertension (2019) [11]	Up to 20–30 g of pure alcohol in men per day, but not more than 140 g per week and up to 10–20 g of pure alcohol per day in women but not more than 80 g per week, alcohol free days, avoid binge drinking
The Chinese Society of Hypertension (2018) [12]	Up to 25 g for men and 15 g for women per day and up to 140 g for men and 80 g for women per week
The Korean Society of Hypertension (2018) [13]	Less than 2 drinks per day for men, less than 1 for women. Appropriate moderate daily amount of alcohol is less than 20–30 g for men; 10–20 g for women. People with lower-than average body weight are permitted half of the recommended amount
The Japanese Society of Hypertension (2019) [14]	Up to 20–30 ml ethanol/day (man) or up to 10–20 ml ethanol/day (woman)

1 standard drink (US) =14 g pure alcohol; 1 standard drink (ISH) = 10 g alcohol; drink (Korean) not clear

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; ESC, European Society of Cardiology; ESH, European Society of Hypertension

based on self-reported alcohol intake as defined by drinks per day [4]. However, with no global consensus on the quantity of alcohol contained in a standard drink, definitions vary across countries and regions. In Europe, in general one drink contains between 10–12 g of alcohol [3]. In the United Kingdom, "units" of alcohol are used with one unit equating to about 8 g of alcohol [5]. The number of units in a drink depends on its size and alcohol strength by volume. In the United States, a standard drink contains roughly 14 g of pure alcohol. The World Health Organization (WHO) offers another standard, defining one unit as equivalent to 10 g of pure ethanol [6]. For example, one unit represents 125 ml of wine, 250 ml of beer, or 40 ml of vodka. This definition has been accepted by more countries than any other [5]. The inconsistency and variability in the definition of a standard drink create challenges in public health communication, research, guidelines, and accurate assessment of alcohol-related risks and effects.

Alcohol consumption is a common modifiable risk factor for a range of diseases, including cardiovascular (CV) conditions [4, 7]. National and international scientific societies issue guidelines and recommendations for acceptable alcohol consumption, typically classifying different levels of risk based on the amount of pure alcohol in grams or standard drinks, as seen in guidelines for hypertension management. Nevertheless, these recommendations frequently present divergent and incongruent definitions for acceptable alcohol intake (Table 1). The consensus on acceptable alcohol consumption for individuals with hypertension varies, but generally, moderation is the key. Moderate drinking is often defined by scientific societies as up to one drink per day for women and up to two drinks per day for men; therefore, placing a higher threshold for moderate drinking for men than women. This notion appears peculiar considering that the number of alcohol-related deaths in men is more than four times greater than in women [2]. Differences in blood pressure (BP) sensitivity to alcohol between sexes might explain these sex-specific recommendations. Women have a reduced ability to metabolize alcohol by first-pass metabolism and gastric mucosal alcohol dehydrogenases [15]. Furthermore, variations in body fat distribution, body size, and drinking habits contribute to these differences, as men tend to consume alcohol more frequently and in larger amounts compared to women [16].

How does drinking alcohol impact BP?

Numerous of both acute and chronic conditions, have proposed various mechanisms related to neural and hormonal reactions. These mechanisms involve sympathetic nervous system activation, increased renin and cortisol levels, modification of carotid baroreceptor response, and increased peripheral vascular muscle tone [17]. Additionally, experimental evidence indicates that alcohol consumption affects addversely endothelial function, reducing nitric oxide production and promoting generation of reactive oxygen species and oxidative stress [18] (Figure 1).

Acute effects of alcohol intake on BP

Acute alcohol consumption has a biphasic effect on BP with an initial dose-dependent reduction in both SBP and diastolic BP (DBP) and an increased heart rate (up to 17 hours after exposure). This is due to acute vasodilatory effects followed by a later rebound in BP [19]. A Cochrane meta-analysis [20] of 32 randomized controlled trials involving 767 participants found no effect of low-to-moderate alcohol intake (14 to 28 g) on BP when compared to placebo. However, high-dose alcohol (>30 g) resulted in an initial reduction in SBP (–3.5 mm Hg) and DBP (–1.9 mm Hg) within 6 hours followed by increased SBP (+3.7 mm Hg) and DBP (+2.4 mm Hg) after more than 13 hours.

While the relationship between the immediate effects of alcohol and the long-term elevation of BP remains unclear, there is substantial risk associated with heavy consumption, often referred to as binge drinking.

How hazardous is binge drinking?

Heavy episodic drinking, known as binge drinking, is a pattern of alcohol intake that may be defined as consuming 5 drinks or more in a row for men or ≥4 drinks for women

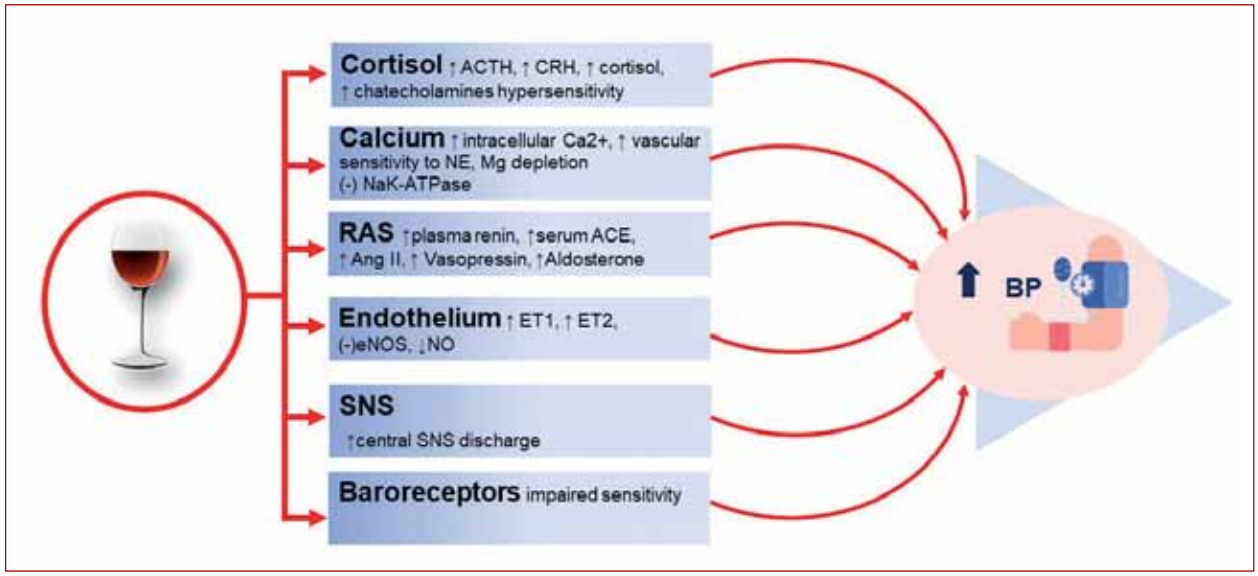

Figure 1. Mechanisms mediating the adverse effects of alcohol on blood pressure

Abbreviations: ACE, angiotensin-converting enzyme; ACTH, adrenocorticotropic hormone; Ang II, angiotensin II; CRH, corticotropin-releasing hormone; eNOS, endothelial nitric oxide synthase; ET, endothelin; NE, norepinephrine; NO, nitric oxide; SNS, sympathetic nervous system

per occasion within the past 30 days [21]. Frequent binge drinking over an extended period is associated with increased BP levels in adolescence and adulthood and may be implicated in the development of hypertension [22–24]. A large population-based study [25] reported a significant, positive association with both infrequent binge drinking (less than once a week) (OR, 1.23; 95% CI, 1.02–1.49) and frequent binge drinking (heavy consumption) (OR, 1.64; 95% CI, 1.22–2.22) with hypertension in adolescence. The highest risk was observed when frequent binge drinking was exercised in both adolescence and early adulthood (OR, 2.43; 95% CI, 1.13–5.20) [25].

In addition to its role in hypertension development, binge drinking is also linked to increased risk of stroke and is considered an independent risk factor for mortality from ischemic heart disease [26]. Heavy alcohol consumption increases the risk of both intracerebral hemorrhages (ICH) and subarachnoid hemorrhages mainly due to alcohol-induced hypertension and impaired hemostasis [27]. A vasoconstriction caused by episodic alcohol intoxication increases both SBP and DBP during intoxication and when blood alcohol levels are decreasing, usually at night, both pressure levels fall below the basic level [28]. This fluctuation in BP may contribute to the rupture of small cerebral arteries with blood entry into the brain parenchyma triggering hypertensive ICH [29]. Furthermore, vascular endothelium dysfunction promotes the occurrence of incident cerebral microbleeds [30]. ICH accounts for 20%–30% of all acute strokes, with notably high mortality rates exceeding 50% and a range of dismal functional and cognitive sequelae [31, 32]. Hypertension and excessive alcohol consumption are major risk factors for this condition [32]. Moreover, binge drinking further amplifies the mortality risk attributable to ICH for individuals with chronic drinking habits [33].

Chronic effects of alcohol on BP/incidence of hypertension: Threshold and sex-specific differences

The association between alcohol consumption and hypertension was first reported by Lian back in 1915 [34] and has been ever since documented by numerous studies [35]. A community study on atherosclerotic risks [35] examined the longitudinal association between patterns and amounts of alcohol consumption and the incidence of hypertension in a large multiethnic cohort. The study revealed a higher risk of hypertension in white men drinking ≥210 g of alcohol per week but no evident risk at low-to-moderate consumption levels (1–209 g per week) compared to non-drinkers [35].

A meta-analysis by Roerecke et al. [36] incorporated data from 20 cohort studies (125 907 men and 235 347 women, with 90 160 reported cases of incident hypertension) revealing sex-related differences in the association and a dose-response relationship. In men, a small (relative risk [RR] 1.19; 95% CI, 1.07–1.31) but significant risk of hypertension started already at a consumption level of 1–2 drinks (12–24 g of pure alcohol) per day. This risk increased significantly and consistently with higher alcohol intake: RR, 1.51 (0.95% CI, 1.30–1.76) for 3–4 drinks, and RR, 1.74 (0.95% CI, 1.35–2.24) for ≥5 standard drinks daily. In contrast, in women, an increased risk was observed for consumption of ≥3 drinks per day (RR, 1.42; 95% CI, 1.22–1.66) [36]. Hence, an increased risk could be observed with the lowest daily ingested amount in men but in women, the risk was only evident when the intake was beyond 2 drinks per day. Notwithstanding, women exhibited a steeper dose-response curve and higher effect size than men at the corresponding drinking levels [36].

The association between alcohol intake and incident hypertension at low levels of consumption was further scrutinized by another meta-analysis of 31 cohort studies (414 477 participants) by Liu et al. [37]. At 10 g/d, men showed a significantly higher risk (RR, 1.14; 95% CI, 1.07, 1.20) than women (RR, 0.98; 95% CI, 0.89, 1.06), with a comparable effect size as reported by Roerecke et al. [36]. In the dose-response analysis of both men and women, each 10 g/d increment of consumption increased the RR of hypertension by 6% (RR, 1.06; 95% CI, 1.05, 1.08) compared with non-drinkers while a consumption of 50 g/d, increased the risk by 35%. The study highlighted the sex-specific difference in the dose-response association evident also at low-level of alcohol consumption [37].

Recently, a dose-response meta-analysis of nonexperimental cohort studies indicated a linear relationship between alcohol intake and BP with no evidence of a threshold for the association [38]. The meta-analysis included 19 548 participants with a median follow-up of 5.3 years using a dose-response 1-stage meta-analytic approach; hence, the authors were able to assess a much broader range of exposure including low levels. Alcohol intake at 12 g of alcohol per day was associated with a small increase in SBP of 1.25 mm Hg (95% CI, 0.49–2.01) compared with nondrinkers [38]. Statistically significant differences in both SBP and DBP were more pronounced at higher levels such as 24 g/day where SBP increased by 2.48 mm Hg (95% CI, 1.40–3.56) and DBP by 2.03 mm Hg (95% CI, 1.19–2.86). Sex-specific analyses showed an almost linear association between baseline alcohol intake and SBP changes in both men and women, with no threshold for the association in either sex [38]. The association had a steeper slope for SBP in men than in women, whereas for DBP the relationship was linear for men only [38]. Notably, women constituted only 32% of the total sample.

Recommendations from the contemporary national and international guidelines advise to moderate alcohol intake to low-to-moderate alcohol consumption of up to 2 standard drinks per day for men and up to 1 drink per day for women in the context of managing hypertension. However, the safety and benefits of such low-to-moderate consumption are being called into question, as they may not be entirely risk-free.

Weighing the benefits of alcohol against the risks — is there somehow a right balance?

An important issue is addressing the total effect of alcohol and the controversies about the amount of alcohol associated with risk, which begs the question: is alcohol entirely bad?

While long-term heavy drinking is an established cause of hypertension, responsible for approximately 16% of cases of hypertension worldwide [39], findings from different studies on the effects of alcohol in CV disease (CVD) have been contradictory. Several epidemiological studies identified a protective association between low-to-moderate consumption of alcohol, BP, and CVD [40–42]. They reported a J-shaped or U-shaped association with benefits at low consumption and harmful effects at high consumption. The belief that alcohol could be beneficial for health is related to the "French paradox" based on findings from the WHO MONICA project [43]. This project, conducted primarily in Europe, aimed to explore the connection between saturated fat consumption and CVD mortality. A correlation between higher saturated fat intake and increased cardiovascular-related deaths was observed. However, this pattern did not hold true in all regions, with France presenting a striking anomaly. It exhibited notably high consumption of saturated fats but a lower than expected CV mortality rate. This intriguing phenomenon, labeled the "French paradox", was attributed to higher alcohol consumption in France, primarily in the form of red wine [43].

A meta-analysis of 10 studies [44] confirmed the J-shaped association between wine consumption and vascular events as well as CV mortality with a maximum protection observed at 21 g of wine per day [44]. Another comprehensive meta-analysis of one million participants found that low-to-moderate alcohol consumption is linked to significant reductions in total mortality [45]. In men, the maximum benefit was achieved at one to two drinks daily, leading to a 17% reduction in total mortality (95% CI, 15%–19%) and for women, half to one drink daily, resulting in an 18% decrease in total mortality (99% CI, 13%–22%). Intake levels exceeding 2.5 drinks per day for women and 4 drinks per day for men, were associated with progressively higher mortality rates in a dose-dependent manner [45].

In another study involving 245 000 individuals, both light (up to 3 drinks per week) and moderate drinkers (4–7 drinks per week for women, 4–14 drinks per week for men) drinking was linked to lower CV mortality when compared to heavy users (>7 drinks per week for women or >14 drinks per week for men) or those who abstained from alcohol [46].

Moreover, a pooled analysis of eight prospective studies encompassing 192 067 women and 74 919 men from North America and Europe found a negative association between alcohol intake and the risk of coronary artery disease [47].

A valid explanation to the "French paradox" and the seemingly protective behavior exhibited by wine as an alcoholic beverage at low consumption levels lies mainly in the presence of biological active compounds, namely, polyphenols, in its composition [48]. These include the flavonoids, e.g., quercetin, catechin, and the non-flavonoids, such as stilbenes (resveratrol and polydatin) [49]. The protective effect of the bioactive compounds in wine is attributed to their anti-oxidant, anti-thrombotic, and anti-inflammatory properties [50], which was confirmed by meta-analyses reporting on the beneficial effects of the polyphenols, from red wine or berries on the CV health [51, 52].

Furthermore, long term low-to-moderate wine consumption was reported to increased high-density lipoprotein levels, an effect mediated by ethanol, presumably by increasing hepatic lipoprotein production and transport rate [53]. However, certain factors challenge the robustness of the data substantiating this assertion [48]. The majority of these observational admit limitations in the study design allowing for residual confounding and bias. These include, for example, misclassification of former drinkers as nondrinkers. Former drinkers might have ceased alcohol consumption due to health-related factors such as serious illness thus overestimating the health benefits of alcohol in the other comparator group [54]. Many studies focus on cohorts with participants above 35 years of age, potentially biasing the assessment of lifetime drinking effects. Episodes of binge drinking are more common in one's 20s, and individuals who engaged in heavy or binge drinking during their 20s are more likely to become abstainers after the age of 35 [55]. As a result, their CV risk, even though they are categorized as nondrinkers in some studies, may be elevated due to the underestimation of heavy or binge drinking during their youth [56]. Inconsistency in participant self-reporting of the amount of alcohol consumed, and failure to estimate the actual consumption further add to the limitations. Moreover, individuals who consume modest amounts of alcohol tend to have higher socioeconomic status, adopt nutritious dietary habits, and engage in a more physically active way of life. These limitations highlight the complexity and challenges of studying the relationship between alcohol consumption and CV health due to many forms of bias introduced into the studies. Considering all these limitations, the CV benefits of low-to-moderate alcohol consumption remain questionable, or even overestimated.

How different levels of habitual alcohol consumption, from low to heavy, affect cardiovascular health?

The potential challenges associated with establishing causation through observational studies and the limited scope and duration of trials on moderate alcohol consumption have created a situation of uncertainty. While epidemiologic studies have advocated CV benefits with low alcohol intake, compared to either abstinence or heavy consumption, suggesting J- or U-shaped relationship, emerging evidence form Mendelian randomization (MR) studies suggests otherwise. MR studies use genetic information to mitigate confounding between exposure and outcome [57]. They can investigate causal connections by using naturally occurring genetic variations as impartial substitutes for an exposure [57], which is advantageous since genetic predisposition is unaffected by confounders. In this case, the residual confounding described earlier due to healthier lifestyle, socioeconomic, and behavioral factors that tend to coincide with modest alcohol drinking could be alleviated. A cohort study [58] using data from the UK Biobank (2006–2010, follow-up until 2016) involving 371 463 (54% women) individuals employed both linear and nonlinear MR in the analysis. The study demonstrated a consistent nonlinear, risk-increasing relationship between alcohol consumption and CV diseases (hypertension and coronary artery disease). The risk was modest at low consumption level but escalated at higher levels, indicating that even low alcohol intake was associated with a modest increase in risk. Therefore, it provided evidence that alcohol consumption, across all levels, is associated with increased CV risk including also the amounts considered harmless by current international guidelines. Moreover, the study reported attenuation in the apparent protective associations between modest alcohol intake and CV risk when confounding lifestyle factors were adjusted for [58]. Hence, the cardioprotective associations observed with the J- and U-shaped epidemiologic curves are largely unsubstantiated.

The idea of carrying out large multicenter randomized intervention trials to investigate the influence of moderate alcohol consumption on CV health appears promising but comes with significant challenges and complexities. In 2018, the National Institutes of Health in the United States initiated a randomized clinical trial (MACH 15) to examine the effects of daily moderate alcohol intake (11–15 g of ethanol or one standard drink) compared to abstention on the risk of major CV events [59]. However, this study was swiftly terminated due to ethical concerns and the potential for bias and conflict arising from industry influence [60].

Apart from the questionable CV benefits of low-to-moderate alcohol consumption, excessive drinking can lead to adverse health consequences. Heavy alcohol intake is dangerous and is a leading risk factor for death and disability. A study examining the impact of vodka consumption on premature death among 200 000 Russian adults found that heavy vodka consumption significantly increased the risk of death. Among male smokers who consumed ≥3 bottles of vodka per week, the 20-year risk of death was 35% and 64% at age range 35–54 and 55–74 years, respectively [61]. Another study [62] analyzed data from nearly 600 000 current drinkers in 19 high-income countries without prior CVD to determine the thresholds associated with the lowest risk of all-cause mortality and CVD. They found that, in both men and women, those who drink 100–≤200 g alcohol per week or higher have lower life expectancy at age 40 years compared to those who consume less. Moreover, alcohol consumption was linearly associated with higher CVD risk such as stroke, coronary disease, heart failure, of fatal hypertensive disease [62]. A threshold for the lowest risk of all-cause mortality of around 100 g of alcohol per week was suggested which is lower than the alcohol consumption limits recommended by most guidelines [62], highlighting the lack of a safe level.

Beyond hypertension: What other CV ramifications of alcohol consumptions should be considered?

There's a well-documented association between excessive alcohol consumption and an increased risk of numerous CV conditions, among which are arrhythmias, coronary artery disease, and cardiomyopathy [63]. These complications may arise due to prolonged hypertension or through various other pathophysiological mechanisms not directly related to hypertension. Excessive alcohol consumption significantly affects the heart, potentially triggering arrhythmias and, albeit infrequently, even leading to sudden cardiac death [64]. Hence, a term "holiday heart" was devised for acute arrhythmias, mostly atrial fibrillation (AF), in individuals who engage in heavy or binge drinking during festivities or celebrations [65]. Alcohol can induce arrhythmias through various mechanisms acting as a trigger for AF by disrupting the heart's electrical system, shortening the atrial effective refractory period and slowing atrial conduction [66]. It can disrupt electrolyte balance, impact the autonomic nervous system, directly affect cardiac cells, and increase the heart rate [66]. Habitual drinking contributes to a progressive remodeling of the atria and is a modifiable risk factor for AF and left atrial dilation [67]. A recent meta-analysis [68] analyzing data from 13 prospective studies encompassing over 10 million participants with 214 365 AF cases showed a 6% increase in AF risk per 1 drink per day (about 12 g) rise in alcohol intake across sexes (RR, 1.06; 95% CI, 1.03–1.08). The relationship was linear in men but J-shaped in women indicating that moderate alcohol consumption might have a different impact on AF risk in women [68]. Alcohol can also exacerbate the risk of developing AF by increasing BP while hypertension *per se* is a significant risk factor for developing AF [69]. Therefore, both hypertension and AF can be exacerbated or triggered by excessive alcohol consumption. Hence, alcohol consumption may potentially worsen the clinical presentation of hypertensive individuals and should be an integral part of comprehensive management of hypertension and arrhythmias to reduce the risk of complications.

While alcohol-induced BP elevation is a significant contributor to left ventricular dysfunction, the overall impact of alcohol on the heart is multifaceted. Alcohol exerts direct toxic effects on cardiac cells, propagates alcoholic cardiomyopathy and arrhythmias which are crucially involved in compromising the function of the left ventricle in individuals with alcohol abuse disorders [70]. Alcohol abuse exacerbates the complications of hypertension on the heart, particularly the left ventricle, significantly increasing the risk and severity of left ventricular dysfunction in individuals with both alcohol abuse and hypertension [71]. Chronic alcohol use can induce various echocardiographic alterations reflecting structural and functional damage caused by alcohol in the heart that vary based on the duration and extent of alcohol consumption. In a study, chronic alcohol intake over an average of 16 years in a dose of 4 alcohol units per day caused left ventricle hypertrophy, diastolic and systolic dysfunction with an increase in left atrial volume, decreased ejection fraction and impaired global and layer-specific longitudinal strain [72].

Finally, alcohol abuse can significantly contribute to the side effects observed in patients on antihypertensive medications by amplifying drug side effects including the risk of orthostatic hypotension and falls [73]. This is especially relevant for older adults who are more susceptible to these adverse effects. Antihypertensive drugs mostly implicated in this context are diuretics, vasodilators such alpha blockers, and centrally acting antihypertensives [74]. Alcohol exerts diuresis which, when combined with diuretics, might increase the risk of dehydration, exacerbating side effects such as dizziness or electrolyte imbalances. These interactions necessitate careful monitoring and clear guidance on alcohol use alongside medication to mitigate risks in older adults.

The prevalence of potentially serious alcohol-medication interactions in older adults was studied in the Irish Longitudinal Study on Ageing (TILDA) [75] cohort, which demonstrated an overall prevalence of potential interactions in 18% of participants with 8% at risk of one interaction and 10% at risk of at least two interactions. The most common interactions involved, indeed, CV agents with estimated 15% of older adults identified as being at risk of a serious alcohol-medication interaction.

A question to the physician: "Which lifestyle changes do you recommend to your patients with hypertension?"

Alcohol consumption should be assessed at the primary care level when dealing with elevated BP, which is advocated by the guidelines for hypertension management including the European guidelines. The latter specify that all patients should have their alcohol consumption assessed and encouraged to reduce their intake if they drink heavily [4]. However, it appears that addressing alcohol intake remains one of the least prioritized aspects of hypertension management [76].

A survey conducted among 1064 physicians assessed physician behavior regarding alcohol consumption screening and awareness of the European guidelines on moderate alcohol consumption [77]. The survey revealed that while 81.9% of physicians generally quantify alcohol consumption in hypertensive patients, only 28.6% screened alcohol consumption in patients with newly detected hypertension, and 14.5% in patients with treatment-resistant hypertension. The study highlighted a deficit in clinical practice and the need for improved screening and management of alcohol consumption in hypertensive patients [77].

How effective is alcohol reduction in lowering BP? Is there a threshold for the effect?

A systematic review and meta-analysis [78] analyzed 36 randomized controlled trials involving 2865 participants

(of whom 401 were women) and showed that moderating alcohol consumption has the potential to lower BP in a dose-dependent manner, suggesting a threshold effect of ≥3 drinks per day. The study found that the most substantial reduction in SBP (–5.5 mm Hg [95% CI, –6.7 to –4.3]) and DBP (–4.0 mm Hg [95% CI, –4.7 to –3.3]) was among individuals consuming ≥6 drinks per day when their alcohol intake was reduced by 50%. The results may be more applicable to men, as women constituted only a small fraction of the participants in the trials included.

CONCLUSION

Moderation in alcohol intake and implementation of alcohol-free days during the week in both men and women who consume drinks that contain alcohol represents an important lifestyle intervention in patients with hypertension and is recommended to improve BP control and overall health.

Article information

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How can we increase the efficacy of antihypertensive treatment?

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ABSTRACT

Hypertension is the leading risk factor for cardiovascular diseases; however, only one-fifth of the treated population is believed to attain sufficient blood pressure control levels. A common barrier to the effectiveness of antihypertensive treatment is suboptimal adherence to medications. Non-adherence often stems from low health literacy and unawareness, complex medication regimens and asymptomatic nature of the disease itself. Increased co-morbidities of the patient and side effects of the drugs also play significant role in drug adherence problems. Another common challenge in achieving blood pressure control is therapeutic inertia, marked by the reluctance to raise drug dosage or introduce additional medications. Employing single-pill combination therapy, as recommended by the guidelines, has the potential to overcome this problem and address issues related to drug non-adherence. Novel antihypertensive drugs, which are still under development, show promise for achieving long-term blood pressure control with just a single dose. Non-pharmacological interventions, such as weight loss, low sodium intake and increased physical activity play a crucial role in achieving target blood pressure levels. In this review, key factors for improving the effectiveness of antihypertensive treatment are summarized under the headings of implementing the guideline recommendations, increasing medication compliance, encouraging lifestyle changes and future perspectives for increased treatment efficacy. We aimed to outline the strategies to overcome the global problem of insufficient blood pressure control levels in the light of latest scientific data and recommendations.

Key words: adherence, antihypertensive treatment, efficacy, lifestyle modifications

INTRODUCTION

Hypertension is the strongest modifiable risk factor for cardiovascular diseases and the most common cardiovascular disorder in the world [1]. Globally, it affects nearly 1.28 billion adults aged 30–79 years and two thirds of them are living in low to middle income countries [2]. In a pooled analysis, the average prevalence of hypertension in adults of 30–79 years was documented as 34% in men and 32% in women in the year 2019 and the total number of adults with hypertension has doubled from 1990 to 2019 [3]. The well-established correlation between elevated blood pressure (BP) and the heightened risk of heart failure, stroke, and the progression of chronic kidney disease is widely recognized. This association begins with systolic BP exceeding 115 mm Hg and diastolic BP exceeding 75 mm Hg in office measurements. The target BP is aimed at <140/90 mm Hg and only around 20% of the hypertensive population has been reported to achieve the target levels worldwide [4].

European Society of Hypertension (ESH) presented the latest clinical practice guidelines on hypertension in June 2023 [2]. There was a noticeable shift towards placing greater importance on out-of-office BP measurements and encouraging patient empowerment to enhance adherence. This recognition stems from the acknowledgement that new strategies are necessary to attain improved global outcomes in BP control. Efforts to enhance the proper implementation of guidelines are essential, and considerable progress is required to achieve effective BP control at satisfactory levels. In this review main strategies for improving the efficacy of

antihypertensive treatment are summarized, aligning with the latest guidelines and highlighting the most recent pieces of evidence.

IMPLICATIONS TO ENHANCE THE EFFICACY OF ANTIHYPERTENSIVE TREATMENT

During the last decades, high BP prevalence has shifted from high-income to low- to middle-income countries. This is mostly due to the insufficient changes at the rates of control, awareness and treatment of hypertension in those regions [5]. Despite the extensive endeavors in education and screening as well as the availability of various effective antihypertensive drugs, controlled BP rates remain unsatisfactory, even in the developed regions of the world [6]. To effectively combat the insufficient control rates, a comprehensive strategy is essential. This should encompass a multifactorial approach, involving individualized strategies targeting both the patients and healthcare providers, as well as considering socioeconomic factors and improvements to the healthcare system. Proper implementation of the guidelines, drug adherence and lifestyle modifications are the key factors for positive clinical outcomes [6]. Other potential steps for the enhanced treatment efficacy, such as heightened awareness and education, personalized approach and utilization of telemonitoring, will be discussed under the heading of adherence.

Proper implementation of the guidelines

The universal guidelines clearly establish well-defined target levels for BP. Various strategies for initiating and combining antihypertensive drugs have been developed. Until 2018, the recommended approach was stepped care, where additional drugs were introduced when patient could not achieve target BP levels on the maximum dose of monotherapy. In 2018, the European Society of Cardiology (ESC)/ESH guidelines on hypertension recommended a simple and pragmatic treatment strategy, highly applicable for most of the patients [7]. Initial combination therapy, preferably with single-pill combination (SPC) was recommended as effective evidence-based strategy to improve BP control. This recommendation was strongly emphasized in the latest update of the ESH guidelines in 2023 [2]. Evidence indicates that with guideline-directed therapy BP control can be achieved in majority of the patients, with 90%–95% of them reaching target levels [8]. According to this evidence, the main problem in the era of insufficiently controlled BP is not the inefficiency of the drug therapies. Improper implementation of the guidelines might be one of the problems, as therapeutic inertia was shown to exert an important role in lack of BP control [9]. This means the hesitation or failure of the doctor to initiate or intensify the treatment and it exerts a major adverse role on the lack of BP control [10]. In randomized controlled trials, therapeutic inertia is minimal, for example at ACCOMPLISH, 80% of study participants were at target BP levels] [9, 11]. Among randomized controlled trials conducted in the western world, this trial achieved the highest rates of BP control [9]. However in real-world practice, high rates of inertia with low levels of adherence are one of the major problems contributing to ineffective BP control rates [10].

Initial combination therapy, as recommended, can easily bypass the problem of inertia of dose uptitration, and it was shown to decrease the incidence of adverse outcomes with better short- and long-term results [12]. There is an emphasis on achieving a BP target of <130/80 mm Hg in most of the patients and present guidelines imply the requirement of combination therapy, preferably as SPC. Research indicates that combination therapy at low doses is more effective than monotherapy at maximal doses, likely due to the targeting of multiple mechanisms [13]. Combined treatment leads to faster BP reduction with minimal side effects and more frequent BP control within the first year of treatment. This period is crucial, as it corresponds to the highest rates of discontinuation [12, 14]. It should be considered that the drug tolerability profile becomes more favorable when used in low-dose combinations, as opposed to their high-dose mono forms [15]. Reducing therapeutic inertia while improving persistence and adherence are essential pillars for an effective antihypertensive treatment. These goals can readily be accomplished by adopting the single-pill combination strategy, as outlined in the guidelines [2, 7]. The polypill strategy, which consists of antihypertensive drugs combined with statin, with or without low dose acetyl salicylic acid, is recommended by the guidelines for primary and secondary cardiovascular prevention [2]. The justification for this strategy is that hypertensive patients commonly exhibit dyslipidemia and elevated cardiovascular risk and streamlining treatment through a single pill, instead of multiple pills daily, enhances adherence and treatment persistence [6].

Proper office BP assessment is the fundamental step in diagnosis of hypertension; however, recent guidelines recommended the application of out-of-office BP measurements; home BP monitoring (HBPM) and ambulatory BP monitoring (ABPM) [2, 7]. Those are valid tools for diagnostic work-up and follow-up. HBPM is more acceptable by the patients and is an easily accessible tool. Latest trials have demonstrated the good correlation between ABPM and HBPM for diagnostic accuracy [16–18]. The evidence supports the clinically significant BP reductions by HBPM in hypertensive patients [19–21]. Self-monitoring of the patient enables the self-engagement and increases adherence to the therapy [19, 22]. Moreover, obtaining BP values outside the office setting reduces the therapeutic inertia exhibited by doctors. Much of the hesitation in dose escalation often stems from uncertainty related to high office BP values. A Dutch cohort study conducted in primary care settings in 2021 assessed that there was therapeutic inertia in 87% of the cases with uncontrolled hypertension. It was similar in men and women and was more likely to occur when BP was near target, compared

Table 1. Strategies for improvement of drug adherence

Levels	Strategies
Physician	• Patient counseling with providing enough time, improving health literacy and hypertension awareness • Positive feedback on behavioral and clinical improvement • Collaboration with other healthcare personnel (especially nurses and pharmacists) • Identify adherence related issues, avoid high doses of drugs with adverse effects • Reduce pill burden, prefer SPC • Simplify drug regimen, match therapy with daily routines • Empowerment and integration of the patient
Patient	• Self monitoring of BP • Telemonitoring, using applications and reminders • Motivation of the patient with health care provider, nurse, family members • Self management with simple patient guiding systems
Health system	• Increasing medication accessibility, reducing co-payments • Increased population awareness about hypertension • Supporting development of monitoring systems such as telemonitoring and e-health • Reimbursement of SPC • Availability of national database of prescription
Pharmacy companies	• Public educational activities • Monetary incentive in drug refills • Reminder packaging

Abbreviations: BP, blood pressure; SPC, single pill combination

with very high levels [23]. Reasons for ongoing therapeutic inertia was documented as skepticism regarding the high office measurements, waiting for out-of-office readings, near-target values of the patient and patient's choice of not having their medications intensified [23, 24]. Implementation of the out-of-office BP measurement recommendation can serve to persuade both the patient and the doctor to initiate or adjust the doses of antihypertensive drugs.

Adherence

Patient non-compliance or non-adherence to antihypertensive treatment is one of the best documented, but least understood health behaviors [25]. It is a multifactorial problem including the patient, doctor, patient's family and health myths passing around in many different regions. A statement of Dr. C. Everett Koop is relevant here: "Drugs don't work in those who don't take them".

In the management of hypertension, inadequate adherence to medication poses a specific challenge. The chronic and asymptomatic nature of the disease may lead individuals to perceive occasional or frequent omission of drug doses as inconsequential. As a result, adherence tends to vary significantly throughout the treatment process, typically decreasing with the rise in the number of medications and the complexity of the dosing regimen [26]. One year after initiation, medication adherence for hypertension management is reported to be less than 50% [27]. It has also been demonstrated that 20%–30% of the newly prescribed medications are not obtained or filled by the patients [28]. A trial from Italy revealed that around 36% of the newly treated patients did not renew their initial prescriptions a second time [29]. In general, non-adherence rates are higher in low- to middle-income countries, compared with westernized societies and more common in patients with suboptimal BP control compared with general hypertensive group [13, 30].

Screening for non-adherence should be a routine part of the follow-up of hypertensive patients. Adherence should be checked at every appointment, especially before escalation of the BP lowering treatment, before screening for secondary hypertension and on the suspicion of resistant hypertension. Objective methods for detecting non-adherence, either indirect or direct (such as reviewing pharmacy records, using electronic monitoring devices, directly witnessing medication intake, or detecting medicine in urine biochemically), are generally preferable over subjective approaches such as physician's impressions from patient interviews [31]. However, in settings with limited resources, obtaining confirmation of non-adherence from the patient can still provide valuable information. Medical history taking should provide precise details regarding the use of drugs or substances that could potentially interfere with BP control, such as non-steroidal anti-inflammatory drugs, glucocorticoids, decongestants, estrogens and progestins, substances of abuse and stimulants [2].

The ESC/ESH hypertension guideline has recommended multiple strategies for improvement of the drug adherence and they are summarized in Table 1 [32]. There is not a single strategy that can help to manage non-adherence in all patients, it should be tailored to the modifiable drivers of the problem in each patient individually. Discussion between the patient and the doctor in non-judgemental way will help to identify the barriers to adherence. It was shown that there is a positive association between patients' perceived risk of complications and adherence to the antihypertensive therapy [33]. Strong communication between patients and doctors is essential, as poor communication increases the risk of non-adherence by 19% [34]. Doctors should take time to educate the patient on risks of uncontrolled hypertension and benefits of therapy. The implementation of a healthcare model, led by non-physician health workers, but involving primary care physicians, has shown to improve BP control and cardiovascular risks [35].

Healthcare team organized education and screening programs will further rise the awareness of the disease.

A further step for increased medical adherence should be involving the patient in the medical decision process [36]. Shared decision making increases the patient's engagement to the therapy and self BP monitoring increases patient empowerment. Newly diagnosed hypertensive patients, younger age and accompanying depressive symptoms are other factors interfering with adherence [37]. By implementation of the HBPM with the use of validated and low cost automated BP measuring devices, patient can take role in treatment follow-up and tailoring the therapy. While practical cuffless devices for BP monitoring applied on smart electronic devices has been introduced, their applicability and accuracy in clinical practice needs to be proven [38]. E-health and telehealth technologies, which have gained increased importance lately, may play important role in patient integration to the therapy with increased awareness and adherence. The use of technology may range from simple text message reminders to more complex telemonitoring and wearable devices [39, 40]. Additionally, mobile health system relying on smartphone applications, has been found to improve certain clinical outcomes [41]. In a meta-analysis of 13 875 patients, home BP telemonitoring by self-measurement at home and transmitting data to their doctors resulted in significant BP reductions, with systolic and diastolic decrease by 3.99 mm Hg and 1.99 mm Hg, respectively, when compared to usual care [42].

Antihypertensive drugs have the potential to induce side effects, ranging from mild to, in certain cases, severe, prompting treatment discontinuation. Side effects play a significant role in treatment non-adherence and discontinuation, and can be either associated with BP reduction itself or arise due to class-specific effects [43]. The major recommended antihypertensive drugs generally exhibit good tolerability, although some medications like diuretics showed lower persistence than others [44]. One-size-fits-all strategy does not work in the precision medicine era and patients can significantly benefit from personalized treatment approaches. [45]. Tailoring treatment based on factors such as age, sex, comorbidities, ethnicity, metabolic profile, past experiences with different drugs, and personality traits allows for more appropriate selection of individual treatment plan [46]. Patients with hypertension and other comorbidities are typically elderly individuals on multiple medications and need to be paid particular attention. The guidelines recommend against considering age alone as a barrier to antihypertensive treatment and recent studies suggest support for an intensive approach to BP lowering, emphasizing the importance of targeting tight control [2, 47, 48]. However, the cardiovascular benefits of intensive therapy may be accompanied by significant drawbacks, especially in older patients who typically face a higher risk of complications related to hypotension [49]. Several observational studies involving older individuals indicate an elevated risk of serious adverse effects under intensive antihypertensive treatment, particularly when they are frail [50, 51].

Despite numerous clinical trials for hypertension, there is often underrepresentation of women, or no sex-specific analysis is conducted to assess the effects of treatment. Polaczyk et al. [52] conducted an analysis of the frequency of adverse drug reactions in women and men with hypertension and comorbidities, and aimed to assess the sex-specific predisposing factors. Women were found to be more prone to reporting adverse reactions such as hypotension, coughing and edema compared to men, risk increasing with age. Drug reactions can have a substantial impact on the quality of life for patients, influencing their acceptance of the disease and adherence to therapy, consequently leading to a less favorable prognosis [53].

The debate over whether it is preferable to take antihypertensive drugs in the morning or evening has persisted for years. TIME Study assigned 21 104 patients randomly to evening or morning dosing groups. After a median follow-up of 5.2 years they found no significant difference in the risk of cardiovascular events, with hazard ratio: 0.95 (95% CI, 0.83–1.10); $P = 0.53$. No safety concerns were identified and non-adherence was noted as 22.5% with morning dosing as opposed to 39% with evening dosing ($P < 0.001$) [54]. Also, in a meta-analysis of randomized clinical trials where patients were randomized to morning versus evening dosing, evening dosing was shown to have no clear impact on cardiovascular outcomes [55]. These data align with the guidelines, which suggest allowing individuals to choose the timing based on their convenience [2, 7].

Reducing the pill burden is probably the most effective approach to increase treatment adherence. Recent data suggests that with each additional antihypertensive medication, there may be an associated increase in non-adherence, around 80% [44]. As discussed before, SPC is the preferred treatment regimen to achieve better results of drug adherence and cardiovascular endpoints [2]. START-study analyzed propensity score matching data from 57 998 hypertensive patients using SPC or identical multiple pill forms. Results revealed that employing antihypertensive combination therapy by using up to three antihypertensive drugs in a SPC led to a reduction in both all-cause mortality and cardiovascular events, compared to the use of the same drugs administered separately in a multipill combination [56]. Patients who rapidly attain their target BP need fewer modifications in their treatment plans. Likewise, individuals who do not encounter adverse effects are less prone to frequent alterations in prescriptions, all increasing the likelihood of adhering to the prescribed treatment.

At the population level, national health agencies should organize nationwide screening calls and increase public health awareness about hypertension. A recent European

study revealed that increasing the antihypertensive therapy adherence to a level of 70% in 5 European countries (France, Germany, Italy, Spain and England) would lead to total savings of €332 million over a 10 year period and 82.235 fewer cardiovascular events [57]. Improving access to healthcare with reduced costs will undoubtedly increase adherence. Other health system strategies to support drug adherence are summarized in Table 1.

Achieving hypertension control extends beyond prescribing medications. It involves forming a medical alliance and taking actions to support adherence, not only to medication but also to lifestyle. It should be kept in mind that hypertension treatment is a multifactorial strategy with several functional pillars. Pharmacological treatment plan can work effectively only with functional non-pharmacological strategies, mainly implementing the proper lifestyle changes.

Lifestyle modifications

The adoption of a heart-healthy lifestyle is a crucial strategy for preventing onset of hypertension and increasing efficacy of antihypertensive treatment. Individuals maintaining a favorable lifestyle experience an approximately 4–5 mm Hg lower BP compared to those with an unfavorable lifestyle. Additionally, embracing a healthy lifestyle can enhance the BP lowering effects of pharmacological interventions, potentially reducing the need for multiple drugs to control BP [58]. The effectiveness of lifestyle interventions tends to be more pronounced when the start is with higher BP levels. Nevertheless, it is' crucial to emphasize that lifestyle changes should not impede the initiation of drug therapy in cases where antihypertensive drugs are proven to be protective and benefits necessitate BP reductions beyond what lifestyle changes alone can achieve [2].

While the available evidence primarily stems from observational studies and their meta-analyses, all lifestyle interventions appear to confer heart-healthy benefits that extend beyond their impact on BP. Among the most significant and well-established lifestyle interventions proven to help BP control and decrease morbidity and mortality are: weight loss, adherence to the DASH diet, reduction of salt intake, increased consumption of potassium, regular physical exercise and moderation of alcohol consumption [59–64]. Furthermore, quitting smoking and implementing additional lifestyle measures are crucial not only for BP management but also for overall well-being.

The vulnerability of treatment strategies based on non-pharmacological interventions lies in the limited sustainability of the prescribed measures. Following the prescription of lifestyle changes to hypertensive patients for achieving BP control, physicians should establish a follow-up program and aim to assess adherence, determine the attained therapeutic goals, and crucially motivate and integrate the patient to the therapy [65]. Implementing such a program is notably essential to increase the efficacy of antihypertensive treatment, especially in patients persisting with uncontrolled BP. Below, the proven lifestyle measures for BP control are summarized.

Weight reduction: Being obese or overweight is directly associated with hypertension and weight loss strategies are recommended to lower BP [66]. A meta-analysis concluded that for each loss of one kilogram body weight, systolic and diastolic BP reduced approximately by 1 mm Hg [59]. Encouraging modest weight loss is a crucial recommendation, ideally attained through a combination of a low-caloric diet and regular exercise [67]. Prehypertensive adults were shown to experience reductions of 6.5 mm Hg for systolic BP and 4.6 mm Hg for diastolic BP after adopting a low-caloric diet [67]. For individuals who do not achieve their targets through non-pharmacological interventions, the consideration of pharmacotherapy is an option. Recent advancements in the pharmacological treatment of obesity using glucagon-like peptide-1 receptor agonists revealed the potential to address excess body weight as a means to enhance BP control [68]. Alternatively, bariatric surgery proves to be an effective and enduring strategy for managing BP and cardiovascular risk factors in morbidly obese patients. It may be considered in cases where all measures have failed, particularly in patients with severe obesity [69].

Restriction of sodium intake: There is compelling evidence indicating a link between elevated sodium consumption and higher BP, in both general population and individuals with hypertension [70]. Additionally, randomized trials and meta-analyses have consistently affirmed the relationship between sodium-restricted diets and improved BP control [2, 71]. A meta-analysis investigating the reduction of sodium intake to levels as low as 800 mg/day (1000 mg sodium = 2500 mg salt) demonstrated a linear decrease in BP [61, 71]. Nevertheless, the optimal therapeutic approach regarding unlimited sodium restriction remains a subject of debate. Observational studies have indicated an increased mortality in both hypertensive patients and general population below the further reduction of sodium intake below 3.5 g/day [72]. However, the most significant limitation in those results is the lack of proper long-term randomized trials assessing the effects of various degrees of sodium restriction on outcomes. In studies revealing a J-shaped curve in the relationship between dietary sodium and cardiovascular outcomes, sodium intake was evaluated based on sodium excretion in spot urine and faced criticism for its inability to accurately reflect the 24-hour amount of urinary sodium excretion [73]. To provide more clarity on this issue, larger sized and more precisely controlled intervention studies with longer follow-ups are required.

Any reduction in sodium intake is advantageous, as the correlation between sodium and BP reduction follows almost a linear pattern. A decrease of 1000 mg in sodium intake is associated with a systolic BP reduction of approximately 3 mm Hg [61]. An ideal alternative would be

a salt substitute with low-sodium content and evidence is supporting the use of substitutes in adults with prehypertension and hypertension [74]. Recent 2023 ESH guidelines recommend daily salt intake to <5 g/day (<2 g sodium) as class I, level of evidence B indication to reduce BP in hypertensive adults [2].

Increasing dietary potassium intake: Dietary potassium is linked to BP and recent data suggested a U-shaped relationship. It indicates that an adequate intake of potassium is desirable for achieving a lower BP level, but excessive potassium intake should be avoided [75]. The Salt Substitution and Stroke Study, a recent large randomized controlled trial, found that increasing potassium intake by substituting 25% of sodium chloride with potassium chloride in salt reduced the risk of stroke, cardiovascular diseases and mortality in patients with elevated cardiovascular risk and with low potassium and high sodium intake at baseline [74]. Diets rich in potassium are favored over potassium supplementation through pills. Noteworthy sources of dietary potassium are fruits, vegetables, low-fat dairy products, certain fish and meats and nuts. Generally, four to five servings of fruits and vegetables can furnish 1500 to over 3000 mg of potassium. Adhering to a potassium-rich diet, such as the DASH diet, proves to be an effective way to achieve these recommended levels [2].

Physical activity: Physical activity is a key lifestyle modification for managing hypertension. Extensive epidemiological studies, accounting for age and other influencing factors, consistently provide evidence of an inverse relationship between hypertension and habitual physical activity levels. The acute rise in BP during dynamic and isometric exercise should not discourage the adoption of regular, long-term physical activity. Notably, 10 metabolic equivalent of task hours per week in leisure time physical activity, corresponding to the recommended minimum of 150 minutes per week, was associated with a 6% reduction in the risk of developing hypertension [76]. In adults with normal BP, aerobic exercises such as brisk walking, swimming, dancing or gym exercises typically result in an average reduction of 2–4 mm Hg in systolic BP. For individuals with hypertension, the average systolic BP reductions tend to be higher, ranging from approximately 5–8 mm Hg [77].

Moderation of alcohol intake: Observational studies reveal a positive linear correlation between alcohol consumption and BP [78]. It's noteworthy that, the global attributable impact of alcohol intake on mortality is more than four times higher in men than in women [79]. The risk for hypertension increases in both men and women when daily alcohol intake reaches at least one to two drinks, equivalent to at least 10–20 grams of alcohol per day [80]. Binge drinking should be avoided as its' hypertensiogenic effect is revealed by clinical data [81]. A meta-analysis involving 36 randomized controlled trials demonstrated that reducing alcohol consumption, close to abstinence, was associated with a reduction of 3.3/2.0 mm Hg in systolic/diastolic BP [64].

Other lifestyle interventions: Tobacco smoking stands as the single largest preventable cause of death and is notably linked to a significant increase in the risk of cardiovascular diseases. Smokers often exhibit masked hypertension, characterized by normal office and higher daytime ambulatory BP values. Smoking a cigarette leads to sympathetic nervous system activation and a prolonged increase in BP, approximately 30 minutes, contributing to increased daytime BP variability with fluctuations in BP levels [82]. Smoking cessation and supportive care programs should be recommended.

Stress and anxiety are linked to an elevated risk of hypertension and BP control. Individuals experiencing mental distress may encounter a sudden rise in BP, which could normalize when the distress is alleviated [83]. Meditation and breath control practices, such as yoga, are recognized as effective stress reduction interventions for reducing BP [67]. However, it is important to note that while these practices are beneficial, their effect sizes are relatively smaller compared to the primary lifestyle interventions.

Combined lifestyle modifications exert the maximal benefit among non-pharmacologic approaches. DASH diet combined with weight management strategy was compared with DASH diet alone and usual diet control groups in ENCORE trial. DASH diet combined with weight management revealed 16.1/9.9 mm Hg BP reduction, compared to 11.2/7.5 mm Hg reduction in DASH diet group and 3.4/3.8 mm Hg reduction in usual diet control group [84]. Another trial compared high sodium intake control group with low sodium content DASH diet in hypertensive individuals. Results showed a reduction of 11.5 mm Hg in systolic BP [85]. It is noteworthy to realize that these values are equal to the BP lowering effect of a single-drug regimen.

In the TRIUMPH trial, BP lowering effects of multiple lifestyle interventions were examined during a cardiac rehabilitation program. Supervised, center-based exercise training with low-salt DASH diet and behavioral weight loss strategies during a 4 month cardiac rehabilitation program resulted an ambulatory BP decrease of 7/3.9 mm Hg. Control group was the patients having educational sessions on BP control and applying low-salt DASH diet with exercise and weight loss recommendations [86]. Cardiac rehabilitation programs represent a significant opportunity to implement comprehensive programs addressing various health promoting behaviors. These may include smoking cessation, weight reduction, adopting a healthy diet, reducing salt intake, supervised exercise and providing behavioral change support. These are particularly important for individuals with complex clinical conditions such as resistant hypertension [65].

FUTURE PERSPECTIVES ON ENHANCING TREATMENT EFFICACY

Despite the strategies to overcome the problem of insufficient BP control, effectively treated hypertensive popula-

tion is still at significantly low levels. Main obstacle is poor adherence to medications. Furthermore, novel therapies aiming the target key regulatory mechanisms with minimal counter-regulatory escape and simplified therapeutic regimens which are better tolerated are needed [87].

In recent years, there has been notable interest in a novel therapeutic approach for hypertension involving small interfering RNAs (siRNAs) that target angiotensinogen. Zilebesiran is an innovative first-in-class siRNA therapeutic, which recently revealed successful results at the end of the phase II clinical evaluation, KARDIA-1 trial (unpublished data). Single-dose, long-lasting vaccine therapy for hypertension control may be a promising approach for long-term adherence and efficacy of antihypertensive treatment.

Other recent advancements in hypertension field include interventional strategies to control BP, such as renal sympathetic denervation, baroreflex activation therapy, carotid body ablation, and central iliac arteriovenous anastomosis [88]. However, with the exception of renal denervation, other interventional strategies are still far from routine clinical use. According to recent evidence from a meta-analysis, renal denervation has shown a significant but modest reduction in both ambulatory and office BP (by approx. 4/2 mm Hg) [89]. The ESH guidelines for hypertension reported that renal denervation therapy can be an additional treatment option for patients with true resistant hypertension, provided that the estimated glomerular filtration rate is greater than 40 ml/min/1.73 m^2. The recommendation level is class II, level of evidence B [2].

The growing recognition of the potential role of artificial intelligence (AI) in cardiovascular medicine and hypertension is evident. The rise of digital technologies, including social media, mobile applications and wearable devices capable of generating continuous and real-time health data, highlights the potential for utilizing AI and big data analytics. Furthermore, AI could assist in crafting accurate risk prediction models for individuals and it has the potential to contribute to the formulation of personalized treatment strategies for hypertensive patients [90]. Results from ongoing and upcoming clinical trials of AI-integrated healthcare will furnish additional insights into the advantages and practicality of incorporating AI into clinical practice and will hopefully help to increase the efficacy of antihypertensive therapy.

CONCLUSION

Hypertension stands as the most prevalent cardiovascular disease globally. While effective BP control is shown to be achievable in 90% of patients through the proper use of the drugs and combination therapies, the reality of insufficient global control rates is alarming. We need to intensify our efforts to combat this global threat. Limited awareness about hypertension, coupled with its often asymptomatic progression results in non-compliance with medication and lifestyle recommendations, all significantly diminishing the effectiveness of antihypertensive treatment. A comprehensive and multi-focused solution is essential, involving not only the physician and patient, but also national health services, pharmaceutical companies, and the media. Adhering to recommendations of guidelines, promoting medication compliance, and encouraging lifestyle changes are fundamental steps to enhance the effectiveness of antihypertensive interventions. Focusing on effective BP control rates should be a global public health strategy. It necessitates attention and additional efforts, encompassing not only increased number of high quality clinical researches, but also greater emphasis on heightened public awareness.

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Potential renoprotective effect of SGLT2 inhibitors against contrast-induced AKI in diabetic STEMI patients undergoing primary PCI

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ABSTRACT

Background: It has been demonstrated that there is a significant reduction in the incidence of cardiovascular events, mortality rates, and worsening kidney disease in patients using sodium-glucose cotransporter 2 inhibitors (SGLT2i). However, there is limited information about the effect of SGLT2i on the incidence of contrast-induced acute kidney injury (CI-AKI) in patients undergoing primary percutaneous intervention (pPCI).

Aims: Our research was focused on examining how SGLT2i exposure impacts CI-AKI occurrence in patients with ST-segment elevation myocardial infarction (STEMI) and undergoing pPCI.

Results: This retrospective, single-center, case-control study included diabetic patients diagnosed with STEMI who underwent pPCI in a tertiary healthcare center between 2021 and 2022. The study population included SGLT2i users (n = 130) and non-SGLT2i users (n = 165). Inverse probability propensity score weighting and doubly robust estimation were performed to decrease bias and to balance covariate distribution for estimating average treatment for those treated. In a doubly robust inverse probability weighted regression model, in which covariates were balanced, CI-AKI risk was also found to be lower in the SGLT2i-user group (OR: 0.86 [0.76–0.98]; 95% CI; $P = 0.028$). In addition, ejection fraction, admission creatinine, albumin, and volume of contrast media were found to be independent predictors of CI-AKI in patients presenting with STEMI and undergoing pPCI.

Conclusion: Our study provides evidence supporting the potential protective effect of SGLT2i against CI-AKI in diabetic patients presenting with STEMI and undergoing pPCI.

Key words: acute kidney injury, diabetes mellitus, primary percutaneous coronary intervention, renoprotection, SGLT2 inhibitor

INTRODUCTION

Primary percutaneous coronary intervention (pPCI) is a crucial treatment used in management of ST-segment elevation myocardial infarction (STEMI), a severe and life-threatening manifestation of coronary artery disease (CAD) [1]. The main objective of pPCI is to minimize infarct size and reduce STEMI-related mortality rates [1]. However, a proportion of STEMI patients undergoing percutaneous coronary intervention procedures involving the use of contrast medium may experience acute kidney injury (AKI), so-called contrast-induced acute kidney injury (CI-AKI) [2]. CI-AKI ranks as the third most common cause of hospital-acquired AKI [3]. The incidence of CI-AKI is closely related to the patient's baseline kidney function, amount of contrast medium administered, presence of diabetes, and pre-existing kidney disease. CI-AKI incidence can vary from

WHAT'S NEW?

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are a new generation of hypoglycemic drugs used in the treatment of patients with type 2 diabetes mellitus (T2DM). Several multicenter studies have demonstrated a significant reduction in the incidence of cardiovascular events, mortality rates, and worsening kidney disease in patients using SGLT2i. However, there is limited information available about the effect of SGLT2i on the incidence of contrast-induced acute kidney injury (CI-AKI) in patients undergoing primary percutaneous coronary intervention (pPCI). In our study, we investigated the potential protective effect of SGLT2i against CI-AKI in patients with ST-segment elevation myocardial infarction (STEMI) who underwent pPCI. Our findings suggest a potential renoprotective role of SGLT2i in patients who were exposed to contrast media due to pPCI. The observed reduction in CI-AKI incidence highlights the importance of further investigation of the role of SGLT2i in renoprotection during PCI procedures.

1.3% to 33.3% [2]. However, this ratio is higher in diabetic patients compared to the general population [4, 5].

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are a new generation of hypoglycemic drugs used in the treatment of patients with type 2 diabetes mellitus (T2DM). These inhibitors function by specifically blocking reabsorption of glucose in the renal tubules, leading to increased glucose excretion and lower blood glucose levels [6–8]. Several multicenter studies have demonstrated a significant reduction in the incidence of cardiovascular events, mortality rates, and worsening kidney disease in patients using SGLT2i [7–9]. However, there is limited information about the effect of SGLT2i on the incidence of CI-AKI in patients undergoing pPCI. Therefore, our research was focused on examining how SGLT2i impact CI-AKI occurrence in STEMI patients undergoing pPCI.

METHODS

Study design and population

This retrospective, single-center, case-control study included patients diagnosed with STEMI who underwent pPCI in Kartal Kosuyolu Heart and Research Hospital between 2021 and 2022. In total, 1382 patients were reviewed, and 295 patients met the inclusion criteria. Study inclusion criteria were determined as patients with diabetes mellitus, who presented in the hospital with chest pain in the first 12 hours from the onset of symptoms, and who were diagnosed with STEMI (flowchart is shown in Figure 1). The study group was further divided into two subgroups: one with patients who had been on SGLT2i, including empagliflozin and dapagliflozin, and the other with patients who had not been on SGLT2i. The exposure time to the medicine, determined by electronic health records, had to last at least 6 months before pPCI. Study exclusion criteria were severe renal failure (estimated glomerular filtration rate <30 ml/min/1.73 m^2) on admission, having been treated with hemodialysis, history of CAD, and history of treatment with insulin. We excluded patients receiving insulin treatment to mitigate potential bias, as this group often presents with more advanced disease and its related complications, including severe kidney disease and atherosclerosis. Patients' baseline demographic, clinical characteristics, and laboratory results were obtained from the hospital database. Their last laboratory results obtained from the national database before undergoing pPCI were used as baseline values. This study was conducted in accordance with the Declaration of Helsinki and approved by Kartal Kosuyolu High Training and Research Hospital's Institutional Review Board.

Definitions

According to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines, CI-AKI is defined as a rise in creatinine level of ≥0.3 mg/dl (26.5 µmol/l) above the baseline value within 48 hours of contrast media exposure or an increase of at least 1.5 times above the baseline value within 7 days [10].

Hypertension (HT) was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or the use of antihypertensive medications [11].

Hyperlipidemia was defined as total cholesterol levels >200 mg/dl, or low-density lipoprotein cholesterol (LDL-C) levels >116 mg/dl, or triglyceride levels >150 mg/dl, or the use of lipid-lowering drugs [12].

STEMI was defined as the presence of ST-segment elevation of at least 1 mm in two or more contiguous leads, except for leads V1–V3, where the criteria for ST-segment elevation were ≥2 mm. In leads V3R, V4R, and V7–V9, the ST-segment elevation was defined as at least 0.5 mm. Additionally, a new-onset left bundle branch block was included in the criteria for diagnosing STEMI. The manifestation of acute myocardial infarction was classified according to the Killip classification: Killip I, no evidence of heart failure; Killip II: heart failure; Killip III, severe heart failure or acute pulmonary edema; Killip IV, cardiogenic shock [1].

A diseased vessel was defined as the stenotic diameter exceeding 50% in major epicardial arteries. Coronary angiography was performed using a Siemens Artis floor angiography device. All patients underwent a pPCI procedure for culprit lesions. Thrombolysis in myocardial infarction (TIMI) was defined as having the number of cine-frames needed for contrast to reach the standardized distal landmarks of coronary arteries. All patients were given aspirin, a loading dose of ticagrelor or clopidogrel, and 70 U/kg unfractionated heparin before the procedure.

During hospitalization, all patients underwent post-procedural transthoracic echocardiography (Vivid 5 or

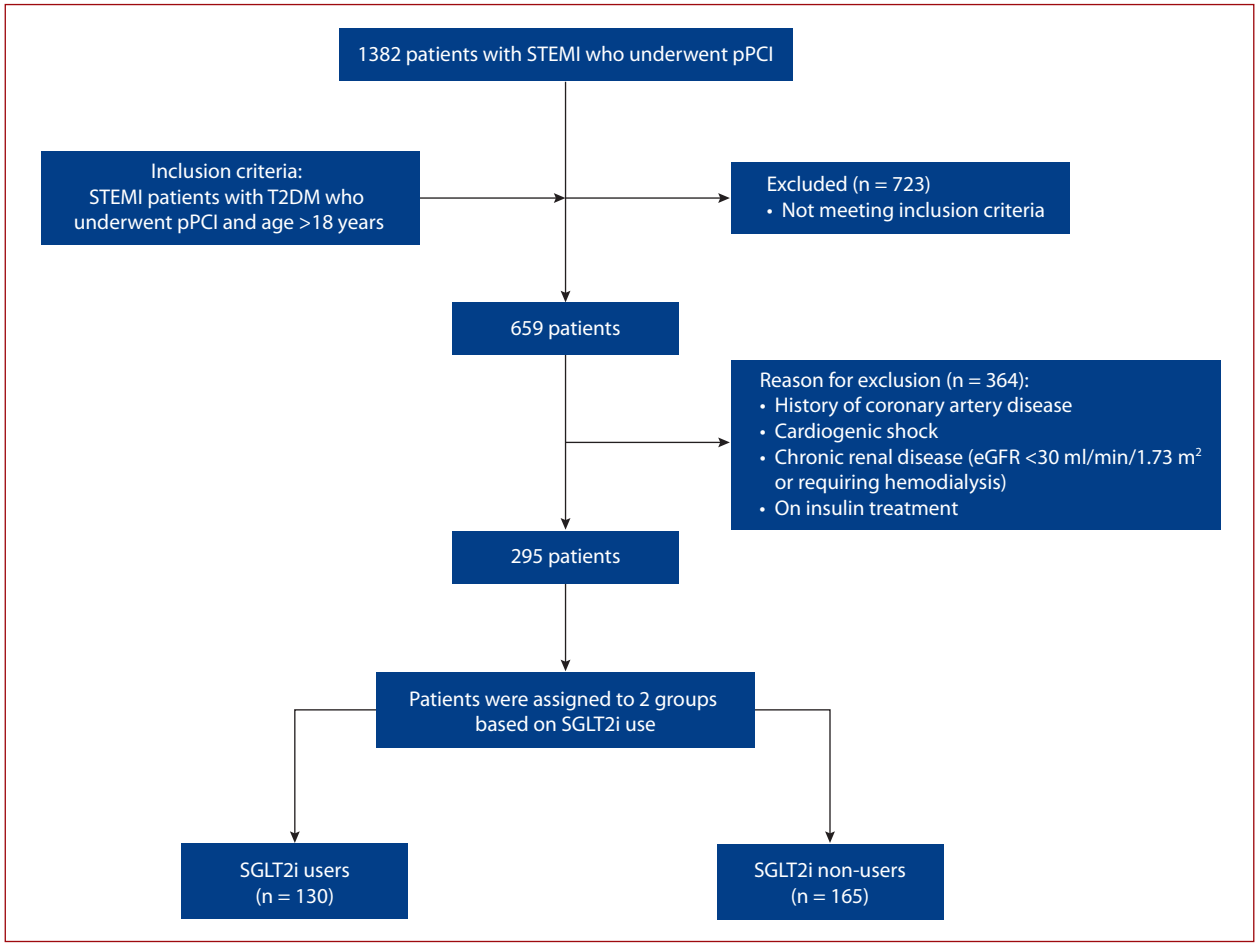

Figure 1. Consort flow diagram for inclusion in the study

Abbreviations: eGFR, estimated glomerular filtration rate; pPCI, primary percutaneous coronary intervention; SGLT2i, sodium-glucose cotransporter 2 inhibitors; STEMI, ST-segment elevation myocardial infarction; T2DM, type 2 diabetes mellitus

Vivid 7; GE Vingmed Ultrasound AS, Horten, Norway). Left ventricular ejection fraction (LVEF) was calculated using the biplane Simpson method.

Statistical analysis and modeling

Normally distributed continuous data were expressed as mean and standard deviation values, whereas non-normally distributed data were expressed as medians and interquartile ranges, and categorical data were described as absolute and percentage values. Independent samples t-test and Mann-Whitney U test were used for comparisons of independent continuous data groups, and Pearson χ^2 or Fisher's exact tests were used for comparisons of categorical data groups.

In this study, inverse probability weighted propensity score weighting and doubly robust estimation were performed to decrease bias and to balance covariate distribution for estimating average treatment for those treated. Based on prior research and expert knowledge [13, 14], the following variables were chosen as covariates for logistic regression analysis to assess the impact on the outcome: SGLT2i treatment, age, sex, hypertension, admission creatinine levels, prior use of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (ACEI/ARB), previous use of metformin, and the number of prescribed oral antidiabetic drugs (OAD) excluding metformin. The probabilities derived from the model were utilized to compute stabilized inverse probability weights. These weights were subsequently applied to assess the impact of each individual's contribution to both AKI and the logistic regression model. Balance diagnostics of baseline covariates between treated and untreated subjects before and after propensity scoring were presented in terms of absolute standardized mean differences. Then, another regression model, including confounders such as age, sex, hypertension, Killip class, ejection fraction, prior ACEI/ARB use, prior metformin use, SGLT2i, number of prescribed OADs, albumin, admission creatinine, hemoglobin A1c, and contrast media volume was applied for double robustness. The model's coefficient was represented using odds ratio (OR), and CI was determined as 95%.

For all statistical analyses, 2-tailed probability (*P*) values of less than 0.05 were deemed to indicate statistical significance. All statistical analyses were performed using Jamovi and R 4.01 software (Vienna, Austria) with "ipw", "ggplot", "cobalt", and "rms" packages.

Table 1. Comparison of baseline clinical, demographic, and peri-procedural characteristics of the study population according to sodium-glucose cotransporter 2 inhibitors (SGLT2i) use

	Non-SGLT2i users (n = 165)	SGLT2i users (n = 130)	*P*-value
Demographic variables			
Age, years	61.4 (9.0)	58.5 (9.6)	0.008
Sex, male, n (%)	103 (62.4)	99 (76.1)	0.012
Smoking, n (%)	97 (58.8)	73 (56.2)	0.649
HT, n (%)	99 (60)	110 (84.6)	<0.001
COPD, n (%)	21 (12.7)	9 (6.9)	0.102
PAD, n (%)	13 (7.9)	14 (10.8)	0.393
CVD, n (%)	7 (4.2)	6 (4.6)	0.877
Hyperlipidemia, n (%)	61 (37)	76 (58.5)	<0.001
Previous AF, n (%)	13 (7.9)	8 (6.2)	0.567
CHA_2DS_2-VASc score	3.0 (2.0–4.0)	3.0 (3.0-4.0)	0.021
Procedural characteristics			
Type of ADP_{P2Y12}, n (%)			0.228
Clopidogrel	8 (4.8)	11 (8.5)	
Ticagrelor	155 (93.9)	115 (88.5)	
Prasugrel	2 (1.2)	4 (3.1)	
STEMI type, n (%) (Anterior STEMI)	35 (21.2)	60 (46.2)	<0.001
Killip III vs. I–II, n (%)	3 (1.8)	14 (10.8)	0.001
Total ischemia duration, minutes	240 (120–600)	298.5 (174–556)	0.151
Diseased vessel number (>50% narrowing), n (%)			
1	67 (40.6)	55 (42.3)	0.668
2	65 (39.4)	54 (41.5)	
3	33 (20)	21 (16.2)	
Amount of contrast media, ml	265 (205–315)	290 (223.5–350)	0.122
No reflow, n (%)	16 (9.7)	23 (17.7)	0.044
Final TIMI flow, n (%)			
0	0	0	0.441
1	10 (6.1)	4 (3.1)	
2	16 (9.7)	11 (8.5)	
3	139 (84.2)	115 (88.5)	
Post-PCI characteristics			
Post PCI-EF	48 (42–57.5)	45 (37.5–55)	0.002
Need for re-CAG, n (%)	4 (2.4)	25 (19.2)	<0.001
Stent thrombosis, n (%)	2 (1.2)	4 (3.1)	0.411
CI-AKI, n (%)	41 (24.8)	22 (16.9)	0.099
CPR, n (%)	1 (0.6)	5 (3.8)	0.091
VT/VF, n (%)	7 (4.2)	5 (3.8)	0.864
Requirement for intravenous inotropic treatment, n (%)	6 (3.6)	13 (10)	0.027
In-hospital mortality, n (%)	4 (2.4)	4 (3.1)	0.735
Hemorrhagic events, n (%)	9 (5.5)	7 (5.4)	0.979
Need for transfusion, n (%)	1 (0.6)	3 (2.3)	0.324
ICU stay duration, hours	24 (18–34)	30 (24–36)	<0.001
In-hospital stay duration, days	4 (3–5)	4 (3–4)	0.746

Continuous variables are given as means and standard deviations or medians and interquartile ranges ($25–75^{th}$)

Abbreviations: ADP_{P2Y12}, adenosine diphosphate$_{P2Y12}$; AF, atrial fibrillation; CI-AKI, contrast-induced acute kidney injury; COPD, chronic obstructive pulmonary disease; CPR, cardiopulmonary resuscitation; CVD, cerebrovascular disease; HT, hypertension; ICU, intensive care unit; PAD, peripheral arterial disease; post-PCI EF, post-percutaneous coronary intervention ejection fraction; post-PCI TIMI flow, post-percutaneous coronary intervention thrombolysis in myocardial infarction flow; re-CAG, re-coronary angiography; STEMI, ST-segment elevation myocardial infarction; VT/VF, ventricular tachycardia/ventricular fibrillation; other — see Figure 1

RESULTS

The study population (n = 295) included SGLT2i users (n = 130) and non-users (n = 165). Baseline clinical, demographic, and peri-procedural characteristics in the whole population are shown in Table 1. The majority of users were on dapagliflozin (86, 66.15%). Dapagliflozin users all received a 10 mg dosage, while 7 (15.9%) of the empagliflozin users were prescribed 25 mg, and the remaining 37 (84.1%) were prescribed 10 mg. The mean age was higher in non-users than in the SGLT2i-user group (61.4 [9.0] years vs. 58.5 [9.6] years). Of 295 patients, 94 (31.7%) were female. While post PCI-LVEF was higher in the non-user group ($P = 0.002$); HT, hyperlipidemia, anterior STEMI, Killip III vs. I–II, no-reflow, and need for re-coronary angiography were significantly more frequent in the SGLT2i-user group. There were no differences in the history of smoking, chronic obstructive pulmonary disease, peripheral artery disease, cerebrovascular disease, previous atrial fibrillation, total ischemic duration, post-TIMI flow, diseased vessel number, amount of contrast media, type of ADP_{P2Y12} (type of antiplatelet agent), stent thrombosis,

Table 2. Comparison of baseline laboratory variables between sodium-glucose cotransporter 2 inhibitors (SGLT2i) users and non-users

Variables	Non-SGLT2i users (n = 165)	SGLT2i users (n = 130)	*P*-value
Glucose on admission, mg/dl	168 (136–249)	202 (146–290.5)	0.003
Glucose at 24 hours, mg/dl	176 (130–222)	200.5 (158–282)	<0.001
Urea, mg/dl	25.7 (16–36.4)	26.5 (18–35)	0.801
Admission creatinine, mg/dl	0.84 (0.73–1.09)	0.80 (0.67–0.94)	0.013
Peak creatinine, mg/dl	0.95 (0.80–1.26)	0.88 (0.77–1.03)	0.002
Total protein, g/dl	6.3 (5.8–6.9)	7.3 (6.7–7.7)	<0.001
Albumin, g/l	3.9 (3.6–4.1)	4.1 (3.8–4.3)	<0.001
CRP, mg/l	5.6 (2.5–13.8)	6 (2.7–21.3)	0.517
Uric acid, mg/dl	5.6 (4.4–6.7)	6.3 (5.1–7.0)	<0.001
HbA1c, %	7.2 (6.5–8.6)	8.6 (7.1–10.3)	<0.001
WBC count, 10^3/µl	9.9 (8.6–12)	10.5 (8.1–14.9)	0.100
Hb, g/dl	13.3 (12.4–14.7)	13.8 (12.5–14.9)	0.433
Platelet count, 10^3/µl	245 (211.5–280)	295 (228–404.5)	<0.001
Neutrophil count, 10^3/µl	6.9 (5.6–9.1)	7.4 (5.1–11)	0.261
Lymphocyte count, 10^3/µl	2 (1.3–2.7)	2 (1.5–2.2)	0.039
Total Cholesterol, mg/dl	164 (146–206)	195.2 (161.4–220.9)	<0.001
HDL-C, mg/dl	35 (32–43)	21 (15.5–29)	<0.001
LDL-C, mg/dl	119 (89–142)	126 (101–154.2)	0.024
Triglyceride, mg/dl	161 (111–244.5)	194.5 (131.7–227)	0.028
Total bilirubin, mg/dl	0.49 (0.35–0.80)	0.90 (0.60–1.0)	<0.001
TSH, µIU/l	1.52 (0.84–3.04)	1.1 (1.0–1.5)	0.077
Peak troponin, ng/ml	0.8 (0.3–3.1)	3.4 (1.2–7.0)	<0.001

Continuous variables are given as means and standard deviations or medians and interquartile ranges (25–75th)

Abbreviations: Hb, hemoglobin; CRP, C-reactive protein; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein; TSH, thyroid-stimulating hormone; WBC, white blood cell; other — see Figure 1

Table 3. Comparison of medications used in the study population

Variables	Non-SGLT2i users (n = 165)	SGLT2i users (n = 130)	*P*-value
ACEI/ARB, n (%)	124 (75.2)	103 (79.2)	0.409
Metformin, n (%)	116 (70.3)	95 (73.1)	0.600
DPP4i, n (%)	57 (34.5)	52 (40)	0.335
GLP-1RAs, n (%)	0 (0)	1 (0.8)	0.441
Sulfonylurea, n (%)	28 (17)	15 (11.5)	0.189
Number of drugs excluding metformin, n (%)			
0	91 (55.2)	74 (56.9)	
1	63 (38.2)	44 (33.8)	
2	11 (6.7)	12 (9.2)	0.597

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; DPP4-I, dipeptidyl peptidase 4 inhibitors; GLP-1Ras, glucagon like peptide-1 receptor agonists; other — see Figure 1

CI-AKI, cardiopulmonary resuscitation, ventricular tachycardia/fibrillation, requirement of intravenous inotropic treatment, intensive care unit duration, duration of hospital stay, and in-hospital mortality between groups.

A comparison of laboratory parameters according to SGLT2i exposure is shown in Table 2. In the group of non-SGLT2i users, admission creatinine, peak creatinine, and high-density lipoprotein cholesterol levels were significantly higher. Glucose level on admission, glucose level at 24th hour, total protein, albumin, uric acid, glycated hemoglobin (HbA1c), total cholesterol, LDL-C, triglyceride, total bilirubin, and peak troponin levels as well as platelet count were significantly lower than in SGLT2i users. Other intergroup comparisons of laboratory parameters are shown in Table 2.

Table 3 presents a comparison of the medications used in the study population. There were no significant differences between groups in terms of OAD use.

In the non-weighted and adjusted multivariable logistic regression model, CI-AKI risk was found to be lower in the SGLT2i-user group (OR, 0.23 [0.092–0.579; 95% CI; P = 0.001). Moreover, in the same model, the volume of contrast media used and albumin were found to be independent predictors of CI-AKI in patients presenting with STEMI and undergoing pPCI (OR, 2.05 [1.30–3.23], 95% CI; P = 0.001) and OR, 2.23 (1.00–4.95, 95% CI; P = 0.048). Correspondingly, in the doubly robust inverse probability weighted regression model, in which HT covariates, admission creatinine, sex, age, previous ACEI/ARB use, metformin use, and number of OADs were balanced (Figures 2 and 3), CI-AKI risk was also found to be lower in the SGLT2i-user group (OR, 0.86 [0.76–0.98], 95% CI; P = 0.028). In addition, LVEF and admission creatinine were found to be independent predictors of CI-AKI in patients presenting with STEMI and undergoing pPCI (OR, 0.99 [0.986–0.998],

Table 4. Inverse probability weighted model of multivariable logistic regression analysis

Variables	Inverse probability weighted model		
	Odds ratio	95% CI	*P*-value
Age	0.999	0.995–1.003	0.721
Sex	0.873	0.765–0.995	0.052
HT	0.922	0.812–1.047	0.223
Killip class	1.221	0.959–1.554	0.114
Post PCI-EF	0.992	0.986–0.998	0.021
Albumin	1.072	0.906–1.269	0.419
Admission creatinine	1.274	1.099–1.476	0.003
HbA1c	1.028	0.985–1.072	0.208
Contrast volume (per 100 ml)	1.059	0.998–1.123	0.065
ACEI/ARB	0.891	0.773–1.026	0.121
Metformin	1.125	1.028–1.231	0.015
SGLT2i	0.863	0.762–0.978	0.028
Number of OADs	0.943	0.885–1.006	0.088

Abbreviations: see Tables 1, 2, 3 and Figure 2

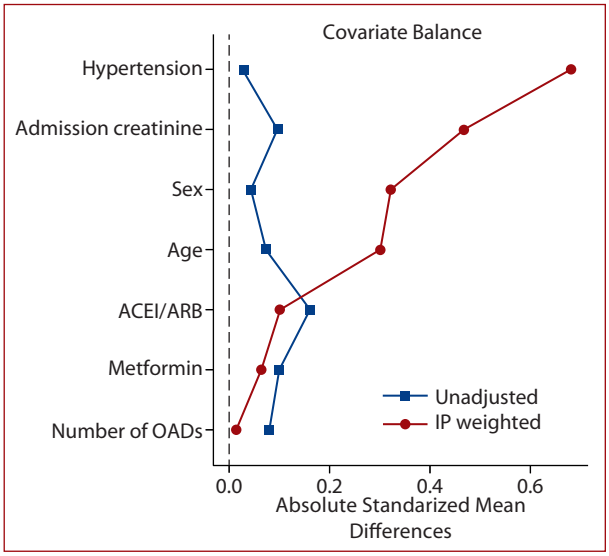

Figure 2. Covariate balancing after inverse probability (IP) weighting shown as absolute standardized mean differences

Abbreviations: OAD, oral antidiabetic drugs

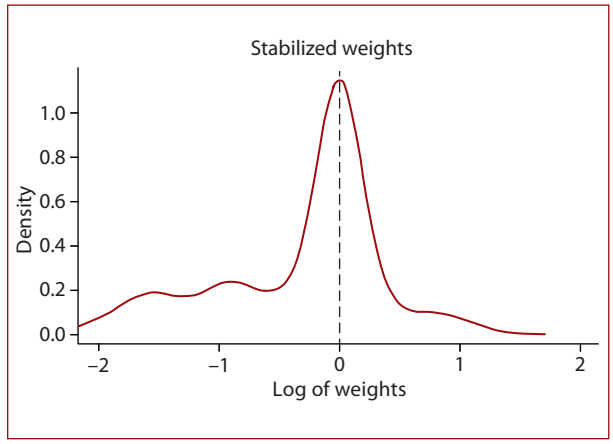

Figure 3. Stabilized weighting density plot between sodium-glucose cotransporter 2 inhibitor users and the non-user group

95% CI; *P* = 0.021 and OR, 1.27 [1.10–1.48], 95% CI; *P* = 0.003) (Table 4).

DISCUSSION

In contemporary cardiology practice, indications for using SGLT2i are growing after every single major clinical trial [15]. Treatment of T2DM, chronic renal disease (CKD), and chronic heart failure (HF) can be listed as the major indications for SGLTi [16]. Current guidelines support using SGLT2i after acute coronary syndrome, regardless of T2DM or LVEF level in HF to minimize the risk of worsening HF or cardiovascular mortality [1, 16, 17]. Beyond their glucose-lowering impact, these medications appear to have pleiotropic biological effects that cannot be solely attributed to the reduction in hyperglycemia. These effects include reduction in cardiovascular mortality, hospital admissions for HF, and adverse renal outcomes. The distinctive mechanism of action of SGLT2i, which involves enhanced renal glucose excretion resulting in a net energy loss, could also make SGLT2i good candidates for managing obesity, especially given its relationship with CAD and diabetes [18]. However, there are no sufficient data on the safety of using SGLT2i before and during pPCI in diabetic STEMI patients who have a high risk of CI-AKI. Our study represents an initial report of potential kidney-protective effects associated with SGLTi in this particular patient population.

In our study, we investigated the potential protective effect of SGLT2i against CI-AKI in STEMI patients who underwent pPCI. Our findings showed that in T2DM patients presenting with STEMI for the first time, the incidence of CI-AKI after pPCI was similar in the group using SGLT2i and the group not using SGLT2i. However, we observed trends toward decreased risk of CI-AKI with SGLT2i use after propensity weighting.

This observation suggests a potential renoprotective role of SGLT2i in patients who were exposed to contrast media due to pPCI. The mechanism behind this protective effect may be multifaceted. SGLT2i have been previously shown to improve renal outcomes in patients with diabetes

by promoting glycosuria, leading to reduced glucose and sodium reabsorption in the proximal tubules [15]. This diuretic effect may contribute to maintaining renal function during the critical period of contrast administration. Additionally, SGLT2i have been reported to have anti-inflammatory and anti-oxidative properties, which could counteract the pathways involved in CI-AKI development [19, 20]. The latest work by Huang et al. [21] showed that dapagliflozin, an SGLT2i, may ameliorate CI-AKI *in vitro* and *in vivo* by decreasing the hypoxia-inducible factor (HIF)-1a/human epididymis protein 4 (HE4)/NF-κB signaling pathway [21].

Our study also demonstrated that the use of SGLT2i was associated with an approximately 20% reduction in the odds of developing CI-AKI. This effect size is clinically relevant and consistent with prior research that has demonstrated that SGLT2i have cardiovascular and renal advantages in patients with diabetes and cardiovascular disease [7–9]. Furthermore, our study provides valuable insights into the specific subset of T2DM patients undergoing pPCI, where the risk of CI-AKI is particularly pronounced.

Lately, multiple studies have presented some evidence indicating that SGLT2i do not raise the risk of AKI in patients diagnosed with T2DM or heart failure [22–24]. Additionally, some studies have proposed that initiating an SGLT2i is associated with a reduction in AKI when compared to other glucose-lowering strategies [25, 26]. Moreover, SGLT2i have demonstrated a reduction in the odds of developing AKI in both randomized trials and real-world settings [27]. Nonetheless, there is a scarcity of studies investigating the impact of SGLT2i on the risk of CI-AKI in patients with CAD undergoing PCI. Our study, demonstrating a lower incidence of CI-AKI in individuals using SGLT2i, supports the evidence that SGLT2i may have a more significant potential protective effect on kidney function in patients undergoing PCI. Hua et al. [13] demonstrated that the use of SGLT2i for more than 6 months before PCI provides renal protection in T2DM patients. Our results support these findings as our patients used the medication for at least 6 months prior to pPCI. Furthermore, investigating SGLT2i use besides the conventional hydration therapies before coronary interventions in non-diabetic patients could be a subject of future research to assess whether the potential protective effects against contrast-induced damage persist.

The potential protective effect against CI-AKI reported in our study supports the safety of using SGLT2i before coronary interventions and shows that there is no need to withhold SGLT2i to decrease CI-AKI risk in diabetic STEMI patients. Not only in coronary interventions but also in structural interventions, such as transcatheter aortic valve implantation, AKI represents the most important predictor of post-procedural major adverse cardiovascular events and poor prognosis [28]. Therefore, investigating the use of SGLT2i in invasive cardiac procedures beyond coronary interventions should be the subject of future research to assess whether the potential protective effects against AKI will be sustained.

Limitations

Despite these promising results, some limitations of our study should be acknowledged. First, the sample size was relatively small, which might have influenced the statistical power of our analyses. Further studies with larger cohorts are warranted to confirm our findings and explore potential subgroups that could benefit most from SGLT2i. Second, the specific SGLT2i agents and dosages used in our study varied among patients, and this heterogeneity might have influenced the outcomes. A comparative analysis of different SGLT2i would be valuable to identify potential differences in their renoprotective effects. Third, we did not have data about obesity status. Considering the association between obesity, CAD, and T2DM, data on body weight could have improved our analysis and results.

CONCLUSION

Our study provides evidence supporting the potential protective effect of SGLT2i against CI-AKI in T2DM patients presenting with STEMI and undergoing pPCI. The observed reduction in CI-AKI incidence highlights the importance of investigating further the role of SGLT2i in renoprotection during pPCI procedures.

Article information

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Oral anticoagulation therapy in atrial fibrillation patients at high risk of bleeding: Clinical characteristics and treatment strategies based on data from the Polish multicenter register of atrial fibrillation (POL-AF)

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Editorial
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ABSTRACT

Background: Despite its benefits, oral anticoagulant (OAC) therapy in patients with atrial fibrillation (AF) is associated with hemorrhagic complications.

Aims: We aimed to evaluate clinical characteristics of AF patients at high risk of bleeding and the frequency of OAC use as well as identify factors that predict nonuse of OACs in these patients.

Methods: Consecutive AF patients hospitalized for urgent or planned reasons in cardiac centers were prospectively included in the registry in 2019. Patients with HAS-BLED ≥3 (high HAS-BLED group) were assumed to have a high risk of bleeding.

Results: Among 3598 patients enrolled in the study, 29.2% were at high risk of bleeding (44.7% female; median [Q1–Q3] age 72 [65–81], CHA_2DS_2-VASc score 5 [4–6], HAS-BLED 3 [3–4]). In this group, 14.5% of patients did not receive OACs, 68% received NOACs, and 17.5% VKAs. In multivariable analysis, the independent predictors of nonuse of oral OACs were as follows: creatinine level (odds ratio [OR], 1.441; 95% confidence interval [CI], 1.174–1.768; P <0.001), a history of gastrointestinal bleeding (OR, 2.918; 95% CI, 1.395–6.103; P = 0.004), malignant neoplasm (OR, 3.127; 95% CI, 1.332–7.343; P = 0.009), and a history of strokes or transient ischemic attacks (OR, 0.327; 95% CI, 0.166–0.642; P = 0.001).

Conclusions: OACs were used much less frequently in the group with a high HAS-BLED score than in the group with a low score. Independent predictors of nonuse of OACs were creatinine levels, a history of gastrointestinal bleeding, and malignant neoplasms. A history of stroke or transient ischemic attack increased the chances of receiving therapy.

Key words: antithrombotic treatment, atrial fibrillation, high bleeding risk

INTRODUCTION

Oral anticoagulants (OACs) significantly reduce the risk of strokes and systemic thromboembolism in patients with atrial fibrillation (AF) [1, 2]. Despite their high efficacy, OAC therapy is associated with an elevated risk of hemorrhagic complications [3]. Balancing the benefits of OACs against the risks they pose is crucial to ensuring their optimal use in clinical practice. The potential risk of bleeding should be assessed before initiating OAC therapy [4, 5]. Various bleeding risk scores, which include modifiable and non-modifiable risk factors, have been designed for this purpose [4]. According to a systematic review of 38 studies, the HAS-BLED score (hypertension, abnormal renal and/or liver function, history of stroke or thromboembolism, history of bleeding or bleeding diathesis [e.g., severe anemia], age >65 years, use of aspirin or nonsteroidal anti-inflammatory drugs, and alcohol abuse) is the best tool for predicting bleeding risk (moderate strength of evidence) [4, 6]. Following the European Society of Cardiology guidelines, a high bleeding risk score should not lead to discontinuation of OACs, as their clinical benefit in this patient population is even greater than that in patients with a low bleeding risk score [4]. Instead, given that bleeding risk is dynamic, after OAC therapy is initiated, modifiable risk factors should be reassessed and managed at each patient visit. High-risk patients with non-modifiable bleeding risk factors should be identified and monitored more frequently.

In a Taiwanese study, the mean HAS-BLED score of the study population increased from 1.54 to 3.33. After 12-month follow-up, 20.9% of patients had an increase of their HAS-BLED scores to ≥3, mainly due to newly diagnosed hypertension, stroke, bleeding, and concomitant drug therapies. In 4777 patients who consistently had a HAS-BLED score ≥3, 22.2% stopped their use of OACs, while patients who were kept on OACs (77.8%) even after their HAS-BLED scores increased to ≥3 had a lower risk of ischemic stroke, major bleeding, all-cause mortality, and any adverse events [7]. In the mAFA-II trial, in patients who had more frequent bleeding risk assessments according to the HAS-BLED score (together with holistic App-based management), incidental bleeding events decreased significantly (1.2% to 0.2%, respectively; P <0.001), while total OAC usage increased (from 63.4% to 70.2%) during 12-month follow-up. OAC use decreased significantly by 25% in AF patients receiving usual care when comparing baseline to 12 months (P <0.001) [8]. In the PREFER in AF study for each single point decrease on a modifiable bleeding risk scale, a 30% lower risk of major bleeding events was observed (OR, 0.70; 95% CI, 0.64 to 0.76; P <0.01) [9].

Although there are only a few absolute contraindications to OACs, such as serious active bleeding, associated comorbidities (e.g., severe thrombocytopenia: platelet levels between 51 000 and 21 000 microliters of blood, severe anemia under investigation), or a recent high-risk bleeding event (e.g., an intracranial hemorrhage) [4], underuse of anticoagulants remains a significant clinical problem [10, 11]. In this study, we aimed to evaluate the clinical characteristics of AF patients at high risk of bleeding, to assess the frequency of OAC use in these patients, and to identify factors that predict nonuse of OACs.

METHODS

Study design and patients

The Polish Registry of Patients with Atrial Fibrillation (POL-AF) is a multicenter, cross-sectional study, which includes AF patients hospitalized in 10 Polish cardiac centers. The registry aimed to assess clinical characteristics and pharmacotherapy of hospitalized Polish AF patients. The research methodology has been described in detail elsewhere [12, 13]. The present study was registered in ClinicalTrials.gov (NCT04419012). The study was approved by the ethics committee of the Swietokrzyska Medical Chamber, Kielce, Poland (104/2018). The ethics committee waived the requirement for obtaining informed consent from the patients.

Patients hospitalized for urgent and planned reasons were enrolled in the registry between January and December 2019, during two selected weeks each month. The inclusion criteria were age over 18 years and AF diagnosed

WHAT'S NEW?

To our knowledge, this is the largest study describing antithrombotic treatment strategies in patients with atrial fibrillation and high risk of bleeding in clinical practice in Poland. Patients at high risk of bleeding represented a significant proportion of the hospitalized patient population. Our results showed that oral anticoagulants were used less frequently in this group than in the low-risk group. Furthermore, we found that although the vast majority of our registry was based in academic centers, non-vitamin K antagonist oral anticoagulant doses were often inappropriately reduced contrary to existing recommendations.

on admission to the hospital or during hospitalization, except for patients who were scheduled for ablation (in centers with an electrotherapy team). To avoid a biased selection of patients and achieve a cohort close to reality, no explicit exclusion criteria were designed. In the present study, AF patients at high risk of bleeding were evaluated. To avoid the effect of antiplatelet drugs on oral anticoagulant dosing, patients who underwent percutaneous coronary angioplasty were excluded from the study. In our previous study, we presented the label adherence of a reduced non-vitamin K antagonist oral anticoagulant (NOACs) dose during combination therapy [13]. We also described everyday practice in antithrombotic therapy in 10 cardiology departments in a nationwide cohort of hospitalized AF patients undergoing elective or urgent PCI and its accordance or non-accordance with current guidelines [13]. In addition, patients who died during hospitalization were also excluded from the study.

Data were collected on demographics, medical histories, comorbidities, types of AF, laboratory and echocardiography results, and pharmacotherapies recommended at discharge, with particular emphasis on OAC use. Laboratory tests performed on admission to the hospital included evaluation of renal function (estimated glomerular filtration rate [eGFR] and creatinine level) and blood cell counts. eGFR was calculated from the Modification of Diet in Renal Disease or Chronic Kidney Disease Epidemiology Collaboration formula [14]. Chronic kidney disease was defined as diagnosed kidney damage or eGFR <60 ml/min/1.73 m^2 for 3 months or more, irrespective of cause. Previous bleeding was considered to be clinically relevant bleeding (including cerebrovascular bleeding) or a history of spontaneous bleeding. Echocardiography was performed during hospitalization. The following echocardiographic parameters were analyzed: left ventricular ejection fraction, left atrial diameter, intraventricular septum diameter, and left ventricular mass index. CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke, vascular disease, age 65–74 years, sex category [female]) and HAS-BLED scores were calculated for each patient according to the established guidelines [15, 16]. According to these guidelines, a HAS-BLED score ≥3 was assumed to represent a high risk of bleeding [4]. In the case of patients with malignant neoplasm history, the data concerning active disease or treatment completed <12 months were included in the registry. As an appropriate NOACs dosage reduction was considered: dabigatran 220 mg/day for patients aged ≥80 years; creatinine clearance (CrCl) 30–49 ml/min with high bleeding risk (defined as HASBLED ≥3); using antiplatelet drug/drugs with high bleeding risk (defined as HASBLED ≥3) or concomitant use of verapamil;

Rivaroxaban 15 mg/day for patients:

- with CrCl 15–49 ml/min;
- using antiplatelet drug/drugs with high bleeding risk (defined as HASBLED ≥3);

Apixaban 5 mg/day for patients:

- with CrCl 15–30 ml/min;
- with more than two of the following: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dl;

concomitant using of antiplatelet drug/drugs. Following the guidelines of the Working Group on Cardiovascular Pharmacotherapy of the Polish Cardiac Society, NOACs are considered to have been inappropriately reduced if the dosage is reduced despite not meeting the above criteria [17].

Ethical approval

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the Swietokrzyska Medical Chamber in Kielce (104/2018). Patient consent was waived due to the observational character of the registry.

Statistical analysis

All data analyses were performed using Statistica 13.0 (StatSoft Inc., Tulsa, OK, US). Continuous variables were presented as mean (standard deviation [SD]) or median (interquartile range), and categorical variables were presented as numbers and percentages. The distribution patterns of continuous variables were evaluated by the Kolmogorov–Smirnov test. Independent t-tests, Mann–Whitney *U,* and χ^2 tests were applied to compare two groups of continuous and categorical variables. To identify the predictors of OAC nonuse, uni- and multivariable logistic regression analyses were performed. While selecting variables for the univariable and multivariable model, we were guided by statistically significant variables, i.e. differentiating the groups of people being compared (OAC use vs. OAC nonuse). If highly correlated parameters were present, only one representative was chosen for the multivariable analysis, based on its *P*-value in the univariable analysis and its biological validity. A *P*-value of <0.05 was considered statistically significant.

RESULTS

Analysis of high HAS-BLED and low HAS-BLED risk groups

In total, 3999 patients were enrolled in the POL-AF study. Three hundred sixty-four patients who underwent percutaneous coronary angioplasty during hospitalization and 37 patients who died were excluded from the present study. The final analysis comprised 3598 patients. The main reasons for hospitalization were AF and heart failure symptoms (Supplementary material, *Table S1*).

In the study group, 29.2% (n = 1049) of patients had a high risk of bleeding (high HAS-BLED group). The patients at high bleeding risk, compared to those at low bleeding risk, were older and had more comorbidities. Hypertension, heart failure, vascular disease, coronary artery disease, in addition to a history of myocardial infarction, peripheral artery disease, stroke, previous bleeding, including gastrointestinal bleeding, chronic kidney disease, malignant

Table 1. Characteristics of the high and low HAS-BLED risk groups

Clinical characteristics	Whole group	High HAS-BLED group (n = 1049)	Low HAS-BLED group (n = 2549)	*P*-value
Demography				
Age, years; median (Q1– Q3)	72 (65–81)	76 (70–83)	70 (63–79)	<0.001
Age ≥75 years, n (%)	1561 (43.4)	594 (56.6)	967 (37.9)	<0.001
Female, n (%)	1563 (43.4)	469 (44.7)	1094 (42.9)	0.32
BMI, kg/m^2; mean (SD)	29.2 (5.4)	28.9 (5.5)	29.4 (6.5)	0.01
Medical history				
Hypertension, n (%)	2995 (83.2)	1003 (95.8)	1992 (78.2)	<0.001
Diabetes mellitus, n (%)	1181 (32.8)	446 (42.5)	735 (28.8)	<0.001
Heart failure, n (%)	2339 (65)	785 (74.8)	1554 (61)	<0.001
Coronary artery disease, n (%)	1625 (45.2)	663 (63.2)	962 (37.7)	<0.001
Myocardial infarction, n (%)	700 (19.5)	316 (30.1)	384 (15.1)	<0.001
Peripheral artery disease, n (%)	500 (13.9)	248 (23.6)	252 (9.9)	<0.001
Stroke/TIA, n (%)	428 (11.9)	354 (33.7)	74 (2.9)	0.001
Peripheral embolism, n (%)	38 (1)	15 (1.4)	23 (8.8)	0.16
Bleeding, n (%)	112 (3.1)	97 (9.2)	15 (0.6)	<0.001
Gastrointestinal bleeding, n (%)	141 (3.9)	85 (8.1)	56 (2.2)	<0.001
Chronic kidney disease, n (%)	906 (25.2)	403 (38.4)	503 (19.7)	<0.001
Creatinine level, mg/dl; median (Q1–Q3)	1.1 (0.91–1.37)	1.21 (1–1.6)	1.07 (0.9–1.3)	<0.001
eGFR, ml/min/1.73 m^2; median (Q1–Q3)	58 (45–71.5)	54 (37.9–71)	61.6 (50–82.3)	<0.001
Hemoglobin, g/dl; mean (SD)	13.2 (1.9)	12.19 (2.3)	13.6 (1.6)	<0.001
Malignant neoplasm, n (%) (active or treatment completed less than 1 year)	181 (5)	69 (6.6)	112 (4.4)	0.006
Excessive alcohol consumption (defined as 8 or more drinks per week), n (%)	136 (3.8)	81 (8.1)	55 (2.3)	<0.001
Smoking (active or in the past), n (%)	785 (21.8)	281 (28.2)	504 (21)	<0.001
COPD, n (%)	314 (8.7)	109 (10.4)	205 (8)	0.02
CHA_2DS_2-VASc score; median (Q1–Q3)	4 (3–5)	5 (4–6)	4 (3–5)	<0.001
Echocardiographic parameters; median (Q1–Q3)				
EF, %	55 (40–60)	50 (40–60)	55 (42–60)	<0.001
LAd, mm	47 (42–51)	47 (42–52)	47 (42–51)	0.07
IVSd, mm	11 (10–13)	11 (11–13)	11 (10–12)	<0.001
LVMI, g/m^2	122 (102–143.3)	128 (111–155)	118 (101–140)	<0.001
Anticoagulant treatment, n (%)				
OAC	3295 (91.6)	897 (85.5)	2398 (94.1)	<0.001
VKA	599 (16.6)	184 (17.5)	415 (16.3)	0.36
NOAC	2696 (74.9)	713 (68)	1983 (77.8)	<0.001
Rivaroxaban	1099 (30.5)	244 (23.3)	855 (33.6)	<0.001
Rivaroxaban dose (15 mg once a day)	339 (30.8)	135 (55.3)	204 (23.8)	<0.001
Inappropriately reduced dose of rivaroxaban	32 (9.4)	11 (8.1)	21 (10.3)	0.58
Dabigatran	742 (20.6)	183 (17.5)	559 (21.9)	0.002
Dabigatran (110 mg twice daily)	265 (35.7)	102 (55.7)	163 (29.2)	<0.001
Inappropriately reduced dose of dabigatran	66 (24.9)	22 (21.6)	44 (27)	0.48
Apixaban	855 (23.8)	286 (27.3)	569 (22.3)	0.002
Apixaban dose (2.5 mg twice-daily)	280 (32.7)	136 (47.5)	144 (25.3)	<0.001
Inappropriately reduced dose of apixaban	117 (41.2)	49 (36)	68 (47.2)	0.06

Abbreviations: BMI, body mass index; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke, vascular disease, age 65–74 years, sex category (female); COPD, chronic obstructive pulmonary disease; EF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; HAS-BLED, hypertension, abnormal renal and/or liver function, history of stroke or thromboembolism, history of bleeding or bleeding diathesis (e.g., severe anemia), age >65 years, use of aspirin or nonsteroidal anti-inflammatory drugs, and alcohol abuse; IVSd, intraventricular septum diameter; LAd, left atrial diameter; LVMI, left ventricular mass index; NOAC, non-vitamin K antagonists oral anticoagulant; OAC, oral anticoagulant; VKA, vitamin K antagonist

neoplasm, and chronic obstructive pulmonary disease were more frequent in the high HAS-BLED group. In addition, excessive alcohol consumption and smoking were more common in the high HAS-BLED group compared to the low HAS-BLED group. The patients in the high HAS-BLED group also had higher CHA_2DS_2-VASc scores than those in the low HAS-BLED group. Furthermore, as shown by the laboratory tests, they also had lower hemoglobin levels and worse kidney function (Table 1).

In the high HAS-BLED group, 14.5% of patients did not receive OAC treatment, compared to 5.9% in the low HAS-BLED group (P <0.001). There was no difference in the frequency of use of vitamin K antagonists (VKAs) in the two groups, whereas NOACs were more commonly prescribed

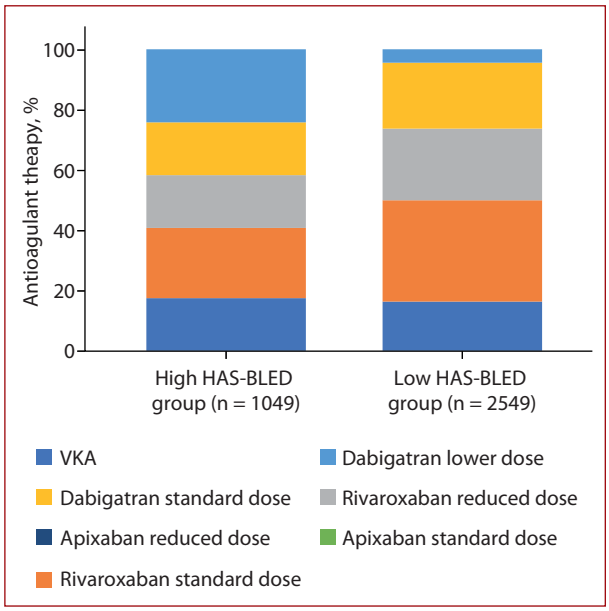

Figure 1. Anticoagulant treatment in the study cohort
Abbreviation: VKA, vitamin K antagonist

in the low HAS-BLED group. As shown in Figure 1, apart from rivaroxaban, reduced doses of the NOACs, apixaban and dabigatran, were more frequent in the high HAS-BLED group as compared to those in the low HAS-BLED group (55.7% vs. 29.2%; $P = 0.002$ and 47.5% vs. 25.3%; $P < 0.001$, respectively). The analysis demonstrated that the dose of apixaban was most often inappropriately reduced (Table 1) without a significant difference between the low and the high HAS-BLED group. Inappropriate dose reductions were the least common for rivaroxaban.

Comparison of clinical characteristics in the high HAS-BLED group according to use/non-use of OACs

When we compared the high HAS-BLED group that did not receive OACs with the high HAS-BLED group that received OACs, the former had a lower CHA_2DS_2-VASc score and fewer episodes of ischemic stroke or transient ischemic attack (TIA), in addition to a history of hemorrhagic stroke, bleeding, including gastrointestinal bleeding, chronic kidney disease, and cancer (active or with treatment completed less than 1 year earlier) (Table 2).

Predictors of OAC nonuse

In the multivariable analysis (Supplementary material, *Table S2*), creatinine level (OR, 1.441; 95% CI, 1.174–1.768; $P < 0.001$), a history of gastrointestinal bleeding (OR, 2.918; 95% CI, 1.395–6.103; $P = 0.004$), and malignant neoplasms (OR, 3.127; 95% CI, 1.332–7.343; $P = 0.009$) were independ-

Table 2. Characteristics of the high HAS-BLED group according to the use (+) or nonuse (–) of OACs

Clinical characteristics	OAC (+) group (n = 897)	OAC (–) group (n = 152)	*P*-value
AF pattern, n (%)			
Paroxysmal	419 (46.7)	66 (43.4)	0.54
Persistent	160 (17.8)	25 (16.4)	
Permanent	318 (35.4)	61 (40.1)	
Demography			
Age, years; median (Q1–Q3)	76 (70–83)	79 (71–85)	0.06
Female, n (%)	405 (45.1)	64 (42.1)	0.49
BMI, kg/m^2; mean (SD)	29.0 (5.5)	28.5 (4.7)	0.85
Medical history			
Hypertension, n (%)	861 (95.9)	142 (93.4)	0.15
Heart failure, n (%)	671 (74.8)	114 (75)	0.96
Vascular disease; n (%)	652 (72.7)	101 (66.4)	0.11
Coronary artery disease, n (%)	572 (63.8)	91 (59.9)	0.36
Myocardial infarction, n (%)	265 (29.5)	51 (33.5)	0.32
Peripheral artery disease, n (%)	212 (23.6)	36 (23.7)	0.99
Stroke/TIA, n (%)	328 (36.3)	26 (17.1)	<0.001
Peripheral embolism, n (%)	14 (1.6)	1 (0.6)	0.39
Any previous bleeding, n (%)	75 (8.4)	22 (14.5)	0.02
Gastrointestinal bleeding, n (%)	60 (6.7)	25 (16.4)	<0.001
Chronic kidney disease, n (%)	324 (36.1)	79 (51.9)	<0.001
Hemoglobin, g/dl; mean (SD)	12.3 (2.3)	11.5 (2.5)	<0.001
Creatinine level, mg/dl; median (Q1–Q3)	1.2 (0.99–1.53)	1.4 (1.05–2.06)	<0.001
eGFR, ml/min/1.73 m^2; median (Q1–Q3)	52.9 (38–66)	44.5 (29.3–60.1)	<0.001
Malignant neoplasm, n (%)	49 (5.5)	20 (13.1)	<0.001
Excessive alcohol consumption (defined as 8 or more drinks per week), n (%)	69 (8.1)	12 (8)	0.98
Smoking (active or in the past), n (%)	232 (27.3)	49 (32.9)	0.17
COPD, n (%)	90 (10)	19 (12.5)	0.36
CHA_2DS_2-VASc score; median (Q1–Q3)	5 (4–6)	5 (4–6)	0.03

Abbreviations: AF, atrial fibrillation; other — see Table 1

ent predictors of OAC nonuse. A history of stroke or TIA increased the chance of recieiving treatment (OR, 0.327; 95% CI, 0.166–0.642; *P* = 0.001).

DISCUSSION

There were four major findings of our study. First, nearly one-third of the study group had a high risk of bleeding; second, OACs were used much less frequently in the group with a high HAS-BLED score than in the group with a low HAS-BLED score (85.5% vs. 94.1%; *P* <0.001). The former results seem to represent a comparable proportion to those found in other studies. Third, we identified independent predictors of OAC use or nonuse, such as creatinine levels, a history of gastrointestinal bleeding, malignant neoplasms, and a history of strokes or TIAs, which are consistent with other data reported in the literature, as discussed below. Finally, although most of our registry was based in academic centers, we showed that NOACs were often inappropriately reduced contrary to the existing recommendations.

It is also worth emphasizing that our registry was conducted in 2019, so it presents relatively current trends in the use of NOACs in AF patients. Meanwhile, most of the data presented in the literature cover both the beginnings of NOAC use and their use in later years.

In clinical practice, anticoagulation therapy in AF patients is often challenging. In our study, almost one-third of the patients had a high risk of bleeding. This is a similar proportion to that found in other studies [15, 18]. In a Swedish registry study of AF patients or atrial flutter (conducted in 2010–2017), 34.4% of patients had a high HAS-BLED score [18]. The patients in that study were older (aged 75–104 years; n = 2943) than those in our cohort. In a retrospective observational study conducted in the Macau Special Administrative Region of China (from 2010–2018), which enrolled 3895 consecutive patients with nonvalvular AF, 35.47% of patients had a HAS-BLED score of 3 or more [19]. Polo Garcia et al. [20], in a cross-sectional multicentre study on a population with AF and moderate-high embolic risk (CHA_2DS_2-VASc ≥2; n = 1310) not treated with OACs, reported that 55.9% of patients have a HAS-BLED score ≥3. Unlike previous studies (data from 2016–2018), the ANAFIE registry (n = 32 726), a prospective, multicenter, observational Japanese study, reported a lower proportion (17%) of AF patients at high risk of bleeding [21]. However, this finding is most likely due to the study's inclusion of a healthier population and multiple exclusion criteria.

Even though over the years, the frequency of OAC use has increased significantly (35.63% in 2010–2012 vs. 61.18% in 2019–2021), there is still a proportion of patients who do not receive OAC therapy despite indications. In an Italian retrospective observational study [22], a higher predicted bleeding risk in clinical practice was associated with a lower OAC prescription rate, but the data analyzed in that study cover the years 2010–2014. In our study, 14.5% of patients in the high HAS-BLED group did not receive OAC treatment, compared to 5.9% in the low HAS-BLED group. The detailed characteristics of this group were discussed in a previous study based on an analysis of the POL-AF register [23]. In the GLORIA-AF study conducted quite long ago (2011–2014), 20% of patients did not receive OACs [24], with lower OAC use rates in patients with a high HAS-BLED score, compared to those with a low HAS-BLED score (75% vs. 83%, respectively).

In our study, a high proportion of NOAC dose reduction in the group with a high HAS-BLED score was observed. With regard to dabigatran and apixaban (but not rivaroxaban), reduced-dose NOACs were used much more frequently in the high HAS-BLED group in comparison with the low group (55.5 vs. 29.2% for dabigatran and 47.5 vs. 25.3% for apixaban). Prescribing NOACs in a reduced or full dose is important for providing AF patients with efficacious and safe treatment. In the group of patients treated with reduced doses of NOACs, a high proportion of people had inappropriate dose reduction on hospital discharge (apixaban 41.2%, dabigatran 24.9%, rivaroxaban 9.4%). This proportion of patients treated with an inappropriately reduced NOAC dose in our study was similar to other studies. In a large retrospective cohort study, which included 1020 patients from outpatient centers, inappropriate dosages of NOACs were found in 33% of cases [25]. Similar to our study, apixaban was dosed inappropriately most frequently. There was no difference in dosing appropriateness between primary and secondary care centers. That study was conducted on patients in America in 2010–2014 and consisted of both non-valvular AF patients and patients with thromboembolism. In another real-world retrospective cohort study by Gustafson et al. [26] including only patients with non-valvular AF, underdosing of NOACs was 47.5% and 42.5% for rivaroxaban and apixaban, respectively. In another large population of Asian AF patients, assessed retrospectively in 2013–2016 (a total of 53 649 patients with prevalent AF treated with NOACs), 31.2% of them were underdosed with NOACs [27]. Patients taking dabigatran and apixaban were prescribed too low doses more frequently. That study refers to both outpatient and hospitalized patients with prevalent AF. In the Polish literature, we did not find such extensive data on the evaluation of inappropriate NOAC dose reduction in AF patients. In an analysis including the entire population of the POL-AF trial [12], 36% of patients were treated with reduced NOAC doses, of whom 22.6% had inappropriate dose reductions.

Such frequent NOAC dose reductions in our analysis despite the lack of guideline-specific indications may be due to the presence of other less common factors that significantly increase the risk of bleeding, such as frailty syndrome or psycho-organic disorders, which were not evaluated in our registry. Another factor may be the high mean age of our patients (median 72 years [65–81]). It has been shown that in the elderly patient population, up to 51% of patients received a reduced dose despite not meet-

ing formal dose reduction criteria [28]. Finally, it is important to note one factor that may have contributed to such frequent inadequate dose reductions in our analysis. The first is the relatively large group of patients hospitalized for device implantation and the associated fear among physicians of local anticoagulation-related complications.

In conclusion of this part of the discussion, it should be strongly emphasized that a high risk of bleeding assessed by a high HAS-BLED score should not be a reason for inappropriate NOAC dose reduction, as this may increase the risk of thromboembolic complications in our patients. A recent large systematic review with meta-analysis showed again that inadequate dosing of NOACs beyond the indications does not reduce bleeding and may be associated with an increased risk of mortality [29].

Our results provide more evidence about factors favoring withdrawal of anticoagulant therapy. In our study, the predictors of OAC nonuse included a higher-than-average (median) creatinine level, history of gastrointestinal bleeding, and malignant neoplasms. A history of stroke or TIA increased the chance of receiving treatment. These results are consistent with most data in the literature but not equivalent. In a few previous registries, treatment with antiplatelet drugs was associated with a lower likelihood of OAC use [10, 20]. Analysis of antiplatelet therapy in the POL-AF study group, which was the subject of a previous publication, showed that triple antithrombotic therapy (dual antiplatelet therapy and OAC) was used more frequently than recommended by the guidelines [30]. On the other hand, patients received reduced doses of NOACs much more frequently than recommended in guidelines. In the GLORIA-AF study, a history of falls was another factor favoring OAC therapy withdrawal. According to guidelines, it is one of the potentially modifiable bleeding risk factors. Unfortunately, the data on the history of falls were not collected in the POL-AF study.

In an American ambulatory-based cardiology registry, in contrast to our observations, a history of bleeding or bleeding predisposition were associated with a greater likelihood of OAC use, although in individuals with a higher estimated bleeding risk, the proportion of individuals prescribed OAC was substantially lower [10].

All types of cancer show an increased risk of causing AF. Furthermore, AF can be a marker of the disease or may develop in patients undergoing surgery, chemotherapy, or radiotherapy [31]. The decision-making process for long-term therapy should include analysis of thromboembolic risk, bleeding risk assessment, drug-drug interactions, and patient preferences. In our study, malignancy was one of independent factors of nonuse of OAC therapy, which is consistent with previous publications [32]. What is interesting, the GLORIA-AF study reported an even higher proportion of cancer patients (17.1% in the whole study group), compared to the POL-AF population; however, cancer did not turn out to be a statistically significant factor in the decision to start OAC therapy. In a retrospective analysis of a post-stroke cohort of Danish patients, the predictors of OAC nonuse were consistent with our findings (cancer, chronic kidney disease, and prior bleeding events). Age older than 74 years, alcohol abuse, chronic obstructive pulmonary disease, dementia, and ischemic heart disease also proved to be significant [32]. It may be related to a much bigger study population (n = 33 308) and different baseline characteristics (patients were admitted to the hospital with ischemic stroke or TIA, older than in our study). In an Australian study on factors that influenced antithrombotic treatment initiation in general practice among patients newly diagnosed with AF (based on a general practice dataset), a low risk of bleeding, male sex, and no history of dementia were independently associated with OAC initiation [33]. In a Balkan-AF survey, age ≥80 years, prior myocardial infarction, and paroxysmal AF were independent predictors of OAC nonuse [34]. Unlike our study, almost one-third of that cohort was enrolled in outpatient health centers, the patients were younger, had lower HAS-BLED, and had fewer comorbidities. In the EURObservational Research Programme on AF, which analyzed consecutive AF patients presenting to cardiologists in 250 centers from 27 European countries, there were a few independent predictors of OAC use in multivariable analysis: age, previous ischemic stroke, but also symptomatic AF, planned cardioversion or ablation. On the other hand, previous hemorrhagic events, chronic kidney disease, and admission for acute coronary syndrome or non-cardiovascular causes independently predicted OAC nonuse [35].

Strengths and limitations

The present study provides insights into OAC treatment and prescribing practices in Poland in daily clinical practice. The main limitation of this study was its observational nature. Thus, some data are missing for some patients. The information concerning the history of falls was not included in the registry. Another limitation is the absence of long-term follow-up of the patients in the POL-AF registry. For this reason, the long-term prognosis for AF patients who were not treated with NOACs and a high bleeding risk cannot be assessed. In addition, as previous publications have shown, there may be differences in patient characteristics and applied treatment between academic and district hospitals [36]. However, we would like to point out that due to their relatively large size, the results of the carried-out analyses may be conclusive enough. Finally, we evaluated hospitalized AF patients. Among these, only a proportion had a first-time diagnosis of AF, and only these patients started NOACs. For this reason, although our registry refers to hospitalized patients, in most patients OAC treatment was started in the outpatient setting. It is difficult to say what impact this factor had on the decision to start NOAC treatment in previously untreated patients.

CONCLUSIONS

Oral anticoagulants were used much less frequently in the group with a high HAS-BLED score as compared to the group with a low score. Creatinine levels, a history of gastrointestinal bleeding, and malignant neoplasms were independent predictors of nonuse of OACs, and a history of strokes or TIAs increased the chances of getting OAC treatment. Furthermore, although the vast majority of our data was collected in academic centers, NOAC doses were often inappropriately reduced contrary to existing recommendations. The results of our registry indicate that we should strictly adhere to existing European and, especially, national expert recommendations when deciding on OAC dosing in AF patients.

Supplementary material

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

Article information

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Angiotensin-converting enzyme inhibitors and angiotensin-II-receptor antagonists modulate sodium handling based on endogenous lithium clearance

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ABSTRACT

Background: Numerous studies based on assessment of lithium clearance demonstrated higher sodium reabsorption in renal proximal tubules in individuals with hypertension, overweight, obesity, metabolic syndrome, or diabetes.

Aims: We aimed to assess the influence of angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin-II-receptor antagonists (ARB) treatment on sodium handling.

Methods: In a sample of 351Caucasian subjects without diuretic treatment with prevailing sodium consumption, we studied associations between renal sodium reabsorption in proximal (FPR_{Na}) and distal (FDR_{Na}) tubules assessed by endogenous lithium clearance and daily sodium intake measured by 24-hour excretion of sodium ($U_{Na}V$), in the context of obesity and long-term treatment with ACE-I or ARB.

Results: In the entire study population, we found a strong negative association between FPR_{Na} and ACE-I/ARB treatment (b = –19.5; SE = 4.9; P <0.001). Subjects with FPR_{Na} above the median value showed a significant adverse association between FPR_{Na} and age (b = –0.06; SE = 0.02; P = 0.003), with no association with ACE-I/ARB treatment (P = 0.68). In contrast, in subjects with FPR_{Na} below the median value, we found a strongly significant adverse relationship between FPR_{Na} and ACE-I/ARB treatment (b = –30.4; SE = 8.60; P <0.001), with no association with age (P = 0.32).

Conclusions: ACE-I/ARB long-term treatment modulates FPR_{Na} in the group with lower reabsorption, but not in that with higher than median value for the entire study population.

Key words: ACE-I/ARB treatment, endogenous lithium clearance, sodium handling

INTRODUCTION

Sodium handling is characterized by osmolite excretion with anti-parallel water reabsorption that is achieved through interactions of multiple factors and undergoes complex regulation. Lithium ions undergo filtration in renal glomeruli, while their reabsorption takes place almost exclusively in proximal tubules. Because transporting lithium through cellular membranes involves the same mechanisms as transporting sodium and water, lithium clearance is a very accurate marker of fractional sodium reabsorption in renal tubules. High lithium clearance indicates a better ability to excrete sodium from the corresponding tubule [1]. Numerous studies based on assessment of lithium clearance demonstrated higher sodium reabsorption in renal proximal tubules in individuals with hypertension, overweight, obesity, metabolic syndrome, or diabetes [2–4]. Among the factors influencing sodium handling, the impact of angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin-II-receptor antago-

WHAT'S NEW?

In a large group of Caucasian subjects without diuretic treatment, we demonstrated associations between long-term treatment with angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin-II-receptor antagonists (ARB) and renal sodium reabsorption in proximal tubules as assessed by endogenous lithium clearance. Treatment with ACE-I/ARB modulates proximal sodium reabsorption in the group with reabsorption that is lower than the median value for the entire study population, but not in the group with higher reabsorption. Therefore, we concluded that the effect of ACE-I/ARB treatment on sodium reabsorption in proximal tubules may be one of the antihypertensive effects of this class of drugs.

nists (ARB) has not yet been fully explained. The impact of short-term usage of ACE-I/ARB on renal sodium reabsorption has been analyzed in individual studies and has yielded variable results [5–9]. Notably, the effect of ACE-I/ARB on sodium handling was dependent on sodium intake, with a significantly stronger effect in people with lower sodium consumption; however, the intensity of the effect did not depend on the dosage of the medication [5, 6]. In previous research assessing the impact of sodium handling and concomitant left ventricular diastolic dysfunction and insulin resistance on blood pressure and arterial stiffness in individuals without diuretic treatment, the results were adjusted for antihypertensive treatment [10, 11]. In several population-based studies and observational studies including hypertensive patients, those from Central and Eastern European countries had moderate-to-high sodium intakes [12]. Currently, we set out to investigate whether long-term treatment with ACE-I or ARB and possibly other confounding factors influence sodium handling in a large group of subjects with prevailing sodium intake. To the best of our knowledge, no similar studies have been published thus far.

METHODS

Study population

In the years 2010–2015, as part of our research grants, we enrolled 490 subjects: 135 hypertensive patients followed up at a tertiary outpatient hypertension center [10], 52 obese patients awaiting bariatric surgery [13], and 303 subjects from the general population, participants of the family-based long-term observational study, with the last follow-up data collection between 2012 and 2014 [14]. The patients with a history of malignancy, decompensated long-term diseases, cardiomyopathy of unknown etiology, hemodynamically significant valvular heart disease, or secondary hypertension were excluded from the study. Based on a questionnaire, information about the type of currently used long-term antihypertensive treatment was gathered. Some of the questionnaire data, regarding patients undergoing ambulatory treatment, did not include information about the dosages of their medications; therefore, the analysis included only medication class without taking into account the dosage. To avoid interference between sodium excretion/reabsorption and the use of diuretic agents, only the participants not receiving diuretic treatment (357 subjects) were included in the study. In the morning, a fasting blood sample was obtained from each participant for biochemical serum measurements. Each participant recruited to the study completed a 24-hour urine collection to measure the 24-hour excretion of sodium ($U_{Na}V$), creatinine, and lithium. The methodology of renal sodium handling assessed by lithium clearance measurements has been previously described [10, 15].

Six patients were excluded from the statistical analysis: 2 because of failure to complete the urine collection and 4 because of high serum lithium levels (>2.0 μmol/l) and urinary lithium levels (>25.0 μmol/l) that may have indicated external contamination or high dietary lithium intake. Thus, 351 subjects were included in the statistical analysis.

Ethics

This study protocol was reviewed and approved by the Bioethical Committee of the Jagiellonian University (approval numbers: KBET/141/B/2009, KBET/155/B/2011, and KBET/57/B/2010). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all participants included in the study.

Statistical analysis

Database management and statistical analyses were performed using SAS System 9.3 software (SAS Institute Inc., Cary, NC, US). The distributions of the analyzed quantitative variables were compared with the normal distribution using the Shapiro-Wilk and Kolmogorov-Smirnov tests. In the descriptive statistics, the quantitative data were expressed as mean values and standard deviations (for the data with normal distribution) or as median values and interquartile ranges (for the data that did not fulfill the criteria of normal distribution). The qualitative data were expressed as proportions. To compare the mean values in the groups of patients, Student's t-test was used. Alternatively, the Wilcoxon test was used in the case of skewed distribution of quantitative variables in some subgroups. The χ^2 Pearson's test or Fisher's test were used for qualitative variables. The correlations of quantitative sodium parameters were analyzed using the standardized Spearman correlation analysis. General linear models were used to obtain the mean values of sodium parameters. Multiple linear regression analysis was performed to identify the factors associated with the analyzed sodium parameters (FPR_{Na}, FDR_{Na}, $U_{Na}V$) in the whole study group

and the subgroups with FPR_{Na}, $FDR_{Na,}$ and $U_{Na}V$ below and above the median values.

RESULTS

Characteristics of the study population

The study population involved 351 individuals, including 158 men (45.0%) and 193 women (55.0%). The mean (standard deviation) age for the whole group was 47.6 (15.6) years, body mass index (BMI) was 27.9 (7.0) kg/m^2, and the number of patients treated with ACE-I or ARB was 75 (21.4%). The estimated median value of 24-hour sodium intake, assessed on the basis of 24-hour urine collection ($U_{Na}V$) was 153.6 (113.9–200.2) mmol. The median values of fractional lithium excretion (FE_{Li}), renal sodium reabsorption in proximal (FPR_{Na}) and distal (FDR_{Na}) tubules, assessed by endogenous lithium clearance were 17.9% (12.7–25.1%,) 82.1% (74.9–87.3%), and 96.3% (94.3–97.6%), respectively.

Factors determining sodium parameters and their mutual relations

In the available literature, two markers of sodium reabsorption in proximal tubules, such as FE_{Li} and FPR_{Na} have been described, and both of them were analyzed separately to assess their mutual dependence and relationships with other parameters of lithium and sodium management. The correlation analyses were conducted in the whole group and in the subgroups identified on the basis of the median values of sodium handling parameters. As the correlation between FE_{Li} and FPR_{Na} in the whole group as well as in groups divided according to the medians reached the value of r = 1.0 (P <0.001), in subsequent analyses, the FPR_{Na} parameter was used to facilitate interpretation of results, reflecting the co-linearity between the value of FPR_{Na} and the magnitude of sodium reabsorption in the proximal tubules.

In the whole group, above and below the median value of FPR_{Na}, FPR_{Na} showed a significant negative relationship with lithium clearance (r = –0.64; P <0.001; r = –0.35; P <0.001 and r = –0.57; P <0.001), respectively. FDR_{Na} in the whole group and after division by the median showed a significant positive relation with lithium clearance (r = 0.39; P <0.001; r = 0.51; P <0.001 and r = 0.43; P <0.001), respectively. In the whole group and in the subgroups above and below the median value of FPR_{Na}, FPR_{Na} did not show a significant relation with $U_{Na}V$ (r = 0.08; P = 0.12; r = 0.12; P = 0.10 and r = 0.11; P = 0.14), respectively. FDR_{Na} showed a significant negative relation with $U_{Na}V$ in the whole group (r = –0.45; P <0.001), and the subgroups above (r = –0.31; P <0.001) and below (r = –0.32; P = 0.001) the median.

Determinants of renal sodium handling

Based on the obtained data, sodium handling parameters i.e. dietary sodium intake (reflected by $U_{Na}V$) and sodium reabsorption in renal tubules (reflected by endogenous lithium parameters, that is, FPR_{Na} and FDR_{Na}), were standardized for age, sex, BMI, hypoglycemic treatment, antihypertensive treatment with beta-blockers, calcium channel blockers, and ACE-Is/ARBs. The analyses were conducted in the whole group and the subgroups with $U_{Na}V$, $FPR_{Na,}$ and FDR_{Na} above and below the median value. Clinical, biochemical, and medication characteristics of the study group divided by FPR_{Na} are summarized in Table 1.

Table 1. Clinical characteristics of the study population, biochemical studies in serum, 24-hour urine collection, and the parameters obtained using endogenous lithium clearance, divided by FPR_{Na} median

	FPR_{Na} < median n = 176	FPR_{Na} ≥ median n = 175	*P*-value
Clinical characteristics			
Age, years	48.9 (15.5)	46.2 (15.5)	0.11
Male, n (%)	74 (42.1)	84 (48.0)	0.26
Height, cm	168.5 (9.6)	170.2 (9.0)	0.07
Weight, kg	80.5 (22.1)	79.9 (20.8)	0.80
BMI, kg/m^2	28.3 (7.2)	27.5 (6.8)	0.31
Waist, cm	94.2 (18.2)	93.7 (16.3)	0.79
Hip, cm	106.2 (13.0)	105.6 (12.9)	0.69
WHR	0.88 (0.10)	0.88 ± (0.09)	0.87
Serum and 24-hour urine parameters			
Sodium, mmol/l	139.8 (2.1)	139.9 (2.2)	0.65
Creatinine, µmol/l	72.2 (13.2)	71.9 (14.6)	0.82
Volume, ml	1615.9 (611.3)	1504.3 (579.9)	0.08
Sodium excretion, mmol	165.3 (79.1)	165.3 (64.1)	0.99
Creatinine excretion, mmol	11.5 (4.1)	15.2 (15.1)	0.002
Sodium clearance, ml/min/1.73 m^2	0.8 (0.4)	0.6 (0.3)	0.98
FE_{Na}, %	0.8 (0.3)	0.6 (0.3)	0.001
Creatinine clearance, ml//min/1.73 m^2	116.6 (32.1)	130.6 (35.9)	0.13
Endogenous lithium clearance			
Serum lithium, µmol/l	0.07 (0.2)	0.15 (0.4)	0.05
Urine lithium, µmol/l	2.1 (3.4)	1.9 (4.3)	0.66
Lithium excretion, µmol/24 h	9.1 (8.1)	7.9 (13.3)	0.30
Lithium clearance, ml/min/1.73 m^2	27.7 (20.6–40.6)	14.3 (11.2–19.3)	0.001
FE_{Li}, %	25.1 (20.7–36.9)	12.7 (9.7–15.7)	0.001
FDR_{Na}, %	97.4 (96.4–98.3)	94.7 (92.8–96.3)	0.001
FPR_{Na}, %	74.9 (63.1–79.2)	87.3 (84.3–90.3)	0.001
Antihypertensive treatment			
ACE-I, n (%)	41 (23.3)	22 (12.6)	0.008
ARB, n (%)	5 (2.8)	7 (4.0)	0.55
CCB, n (%)	27 (15.3)	15 (8.6)	0.05
BB, n (%)	41 (23.3)	30 (17.1)	0.15
Hypoglycemic treatment, n (%)	4 (2.3)	4 (2.3)	0.42

The data are presented as arithmetical means (standard deviations), percentages, or median values with interquartile ranges

Abbreviations: BB, beta-blockers; BMI, body mass index; CCB, calcium channel blockers; FDR_{Na}, fractional distal sodium reabsorption; FE_{Li}, fractional lithium excretion; FE_{Na}, fractional sodium excretion; FPR_{Na}, fractional proximal sodium reabsorption; WHR, waist-to-hip ratio

The multiple regression analyses performed in the entire population showed a strong negative association between FPR_{Na} and ACE-I/ARB treatment (b = –19.5; SE = 4.9; P <0.001), with no relationship to other parameters. When we subdivided the study group according to the median

Table 2. Determinants of renal sodium handling

Determinants	FPR_{Na}	FPR_{Na} < median	FPR_{Na} ≥ median	FDR_{Na}	$U_{Na}V$
R^2	0.007	0.1	0.1	0.05	0.02
Partial regression coefficient (SE)					
Age, years	0.05 (0.1)	0.2 (0.2)	–0.06 (0.02)[b]	0.007 (0.01)	0.2 (0.3)
Sex (male)	–4.3 (3.3)	–7.4 (6.1)	–0.1 (0.6)	1.0 (0.3)[c]	–57.0 (7.5)[c]
BMI, kg/m^2	–0.3 (0.3)	–0.8 (0.4)	0.002 (0.02)	27.7 (7.6)	1.0 (0.6)
Hypoglycemic treatment	7.4 (7.6)	7.9 (13.7)	1.3 (1.4)	–1.0 (0.7)	11.9 (17.3)
Treatment with BB	6.9 (4.7)	10.8 (7.9)	–0.9 (1.0)	0.03 (0.4)	–1.8 (10.8)
Treatment with CBB	1.1 (5.6)	7.0 (9.4)	1.4 (1.1)	–0.3 (0.5)	5.3 (12.8)
Treatment with ACE-I/ARB	–19.5 (4.9)[c]	–30.4 (8.6)[c]	0.1 (0.9)	0.4 (0.4)	1.4 (11.2)

Significance of the partial regression coefficients: [a]$P \leq 0.05$; [b]$P \leq 0.01$; [c]$P \leq 0.001$

Abbreviations: see Table 1

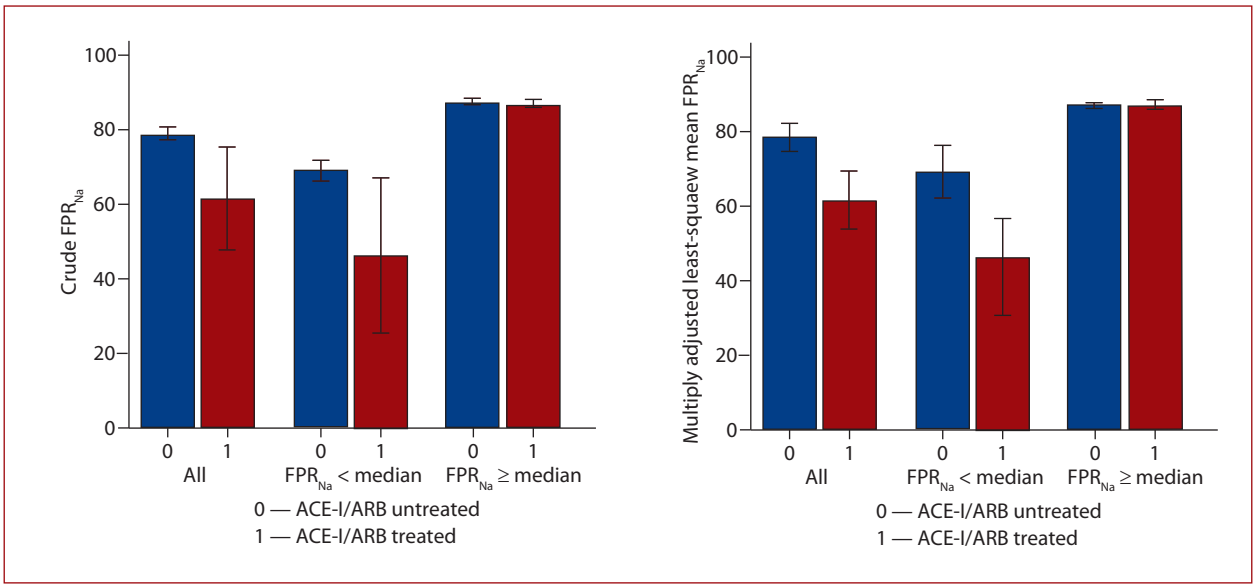

Figure 1. Associations between sodium reabsorption in proximal tubules and ACE-I/ARB treatment according to the median value of FPR_{Na}

The data are presented as arithmetic means (standard deviations)

Parameters of fractional sodium reabsorption in renal proximal tubules (FPR_{Na}) with reference to angiotensin-converting enzyme inhibitors (ACE-I)/angiotensin-II-receptor antagonists (ARB) treatment, in the whole group and in the subgroups divided by the median values of FPR_{Na}. The data in groups divided relative to ACE-I/ARB treatment were crude and standardized for age, sex, body mass index, hypoglycemic treatment, antihypertensive treatment with beta-blockers, calcium channel blockers, and ACE-Is/ARBs.

value of FPR_{Na}, individuals with higher sodium reabsorption in proximal tubules showed a significant adverse association between FPR_{Na} and age (b = –0.06; SE = 0.02; P = 0.003), with no association with ACE-I/ARB treatment (b = 0.1; SE = 0.9; P = 0.90). On the contrary, in subjects with FPR_{Na} below the median value, we found a strong significant negative relationship between FPR_{Na} and ACE-I/ARB treatment (b = –30.4; SE = 8.6; P <0.001), with no association with other parameters (Table 2). In these analyses, FPR_{Na} was significantly associated with long-term ACE-I/ARB treatment in individuals in whom sodium reabsorption in proximal tubules was lower than the median value for the entire study population. In contrast, only in these individuals whose proximal sodium reabsorption was higher than the median value, FPR_{Na} was significantly associated with age. However, that association was not apparent in the whole studied group. As statistically significant relationships were found, we conducted additional analyses using adjusted analysis of variances (ANOVA) for the whole group of subjects and in the subgroups according to median values of FPR_{Na}, with respect to ACE-I/ARB treatment (Figure 1).

Sensitivity analysis, conducted in the groups divided by sex (P <0.03 in sex groups above the median value of FPR_{Na}, and P <0.05 in sex groups below the median value of FPR_{Na}) and by the median of $U_{Na}V$, confirmed the relationship between FPR_{Na} and ACE-I/ARB treatment. In subjects with $U_{Na}V$ below the median value, a significant negative relationship between FPR_{Na} and ACE-I/ARB treatment was demonstrated (b = –31.2; SE = 9.04; P <0.001), with no association in the group with $U_{Na}V$ above the median value (b = –8.23; SE = 4.42; P = 0.08). Sensitivity analysis performed in individuals with $U_{Na}V$ above the median value did not confirm prior findings for age (b = –0.14; SE = 0.11; P = 0.23). Determinants of renal sodium handling in relation to FDR_{Na} and $U_{Na}V$ are presented in Table 2, with no relationship with ACE-I/ARB treatment.

DISCUSSION

In a large group of Caucasian subjects without diuretic treatment with prevailing sodium consumption, we demonstrated the associations between long-term treatment with ACE-I or ARB and renal sodium reabsorption in proximal tubules as assessed by endogenous lithium clearance. Treatment with ACE-I/ARB modulates FPR_{Na} in the group with lower reabsorption, but not in that with reabsorption higher than the median value for the entire study population. Sensitivity analysis, conducted in the groups divided by sex and median of daily sodium excretion confirmed the abovementioned relationships. The results of the study, therefore, allow us to assume that the effect of ACE-I/ARB treatment on sodium reabsorption in proximal tubules may be one of antihypertensive effects of this class of drugs.

The processes of sodium excretion and reabsorption undergo complex regulation. The method of a single measurement of sodium in a 24-hour urine sample was considered for many years a gold standard [16]; however, in light of the newest studies, it has been found to be susceptible to the possibility of significant measurement errors. It turned out that a single $U_{Na}V$ measurement does not reflect daily sodium intake, and the measurement error can be as high as 3.0 g NaCl/day [17], which indicates the necessity of taking multiple measurements [18] and using alternative measurement methods. One of the alternative methods of assessing sodium handling could be the technique of measuring daily endogenic lithium clearance. Studies in animal models showed that under steady-state conditions, evaluation of proximal renal sodium reabsorption can be free of measurement bias [19]. Expression of renal clearance of lithium as fractional excretion provides a measure that is factored for the glomerular filtration rate (GFR) and free of possible bias such as incomplete urine collection or difference in the urinary flow rate [20]. In clinical trials, most researchers prefer to use FE_{Li} [2–4], which represents clearance of lithium divided by the glomerular filtration rate assessed by creatinine clearance, rather than FPR_{Na} [21, 22], which is a surrogate taking into account the value of FE_{Na}.

Extensive research suggests that higher FPR_{Na} has been found in individuals with abdominal adiposity, metabolic syndrome, diabetes, or insulin resistance [2–4]. Schwotzer et al. [23] analyzed the influence of insulin resistance assessed by adipokines (leptin and adiponectin) on sodium handling parameters in a group of untreated people of African descent. They found that leptin was positively associated with $U_{Na}V$ and FPR_{Na}, and sex and obesity were the major confounders of that association. In a recently published study performed in a group of 1409 untreated participants in relation to environmental and genetic factors, both FE_{Li} and FDR_{Na} were significantly associated with season and humidity, but not with outdoor temperature or atmospheric pressure. After adjustment for host and environmental factors, among the 19 studied genetic variants, only one of them — rs12513375 was significantly associated with FE_{Li} and FDR_{Na} and accounted for 1.7 % of the variance [24].

Kidneys have many angiotensin II (Ang II) receptors, whose activation alters hemodynamics, glomerular permeability, and urinary electrolyte excretion. In animal and human models, infusion of Ang II results in a decrease of renal flow and subsequent reduction of GFR due to vasoconstriction. Moreover, Ang II directly affects the glomerulus, leading to a reduced ultrafiltration index and GFR [25, 26]. These mechanisms, together with the direct effects of Ang II on renal tubules, lead to decreased urinary sodium excretion and stimulation, first an increase in FPR_{Na} and later an increase in FDR_{Na} [26]. ACE-I have the opposite effect and tend to enhance both absolute and fractional sodium excretion [27]. Hollenberg et al. [5] demonstrated that a single dose of captopril (of 5 to 100 mg) increases renal blood flow, maintains GFR, and enhances sodium excretion. This effect was more pronounced in subjects with high activity of the renin–angiotensin–aldosterone system (which is physiological in people on a low-sodium diet), and the higher doses of ACE-I prolong the duration of the drug impact on renal function, but they do not enhance the magnitude of response to ACE-I. In the available literature, only limited studies use the lithium clearance technique to establish effects of short-term ACE-I treatment on sodium reabsorption in renal tubules. In a group of 32 patients with essential hypertension who received 2-week placebo and then 4-week open-label ACE-I treatments, GFR, renal plasma flow, and lithium clearance were measured after orally administrated lithium to establish the degree of sodium reabsorption in renal tubules. It transpired that short term ACE-I treatment significantly reduced sodium reabsorption in proximal tubules [9]. In the literature, however, no works have assessed the impact of long-term ACE-Is treatment on renal sodium reabsorption using endogenic lithium clearance. Regarding ARBs, Burnier et al. [6] performed a detailed review of the effects of single-dose of 100 mg of losartan vs. placebo on hemodynamics and renal reabsorption of sodium assessed using endogenous lithium clearance. They suggested a direct relationship between the renin–angiotensin–aldosterone activity caused by sodium consumption and the magnitude of the drug effect, mainly expressed in distal renal tubules. In a subsequent study of 10 hypertensive patients receiving 50 mg of losartan daily for 1 month, the results were different, suggesting that FPR_{Na} rather than FDR_{Na} is influenced by the treatment [8]. Similar to ACE-I, none of the studies assessed the impact of long-term treatment with ARBs on renal sodium absorption as measured by endogenic lithium clearance. In our study, performed in a group of 351 subjects with prevailing sodium consumption, we found that the long-term treatment with ACE-I/ARB strongly influences FPR_{Na} in the subgroup with lower sodium reabsorption and in the subgroup on a low sodium diet. A combined analysis of the impact of ACE-I and ARB on parameters of endogenic lithium clearance appears to be

a sensible approach. Only one study conducted on a group of 10 healthy volunteers, found that a one-time administration of 20 mg of enalapril and a subsequent administration of 50 mg of losartan did not significantly affect endogenic lithium clearance parameters [7]. Otherwise, it appears that in relation to synergistic effects of medications on pressure and hormonal parameters, their impact on lithium and sodium reabsorption is also synergistic and might only become apparent after a longer period of use.

Our results should be interpreted in the context of the strengths and limitations of this study. The presented group of 351 people is, as far as we are aware, the largest group in which analysis of factors influencing sodium management taking into account long-term ACE-I/ARB treatment as measured by endogenic lithium clearance was performed. However, this group, free from diuretic treatment, was not homogeneous — 19.9 % were recruited from patients with long-standing treated hypertension, 7.7% from patients with morbid obesity qualified for bariatric surgery, and 72.4% from the general population. The percentage of people undergoing ACE-I/ARB treatment in the study group was 21.4%. Additionally in the group recruited from the general population, comprising 42.7% of people undergoing ACE-I/ARB treatment, no information regarding the dosages of administered antihypertensive medication was gathered. The lack of this information made it impossible to assess the impact of ACE-I and ARB dosage on sodium handling parameters. Our previous studies using the endogenous lithium technique [10, 11] took into account antihypertensive treatment in the standardization. In light of the aforementioned results, it would appear, that standardization should be narrowed down to ACE-I and ARB medications, especially in populations with low or moderate sodium consumption.

Article information

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Impact of lead position on tricuspid regurgitation, ventricular function, and heart failure exacerbation and mortality after cardiac implantable electronic device implantation. Preliminary results from the PACE-RVTR Registry

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ABSTRACT

Background: The most frequent mechanism of lead-related tricuspid regurgitation (LRTR), which occurs in 7.2% to 44.7% of patients implanted with a cardiac implantable electronic device (CIED), is leaflet impingement or the restriction of its movement by a ventricular lead. It is unclear if the position of the lead tip — in the right ventricular apex (RVA) or other location (non-RVA) — has any influence on the development of LRTR.

Aims: The study aimed to determine the impact of the CIED lead tip position on the development or progression of tricuspid regurgitation (TR) and its potential impact on heart failure exacerbation and mortality.

Methods: One hundred and two consecutive patients who received CIEDs between March 2020 and October 2021 were included in the prospective registry (PACE-RVTR). Patients were assigned to two groups depending on the lead position — the RVA group and the non-RVA group. All patients underwent echocardiographic evaluation before implantation and one year later.

Results: In terms of baseline clinical characteristics, the two groups did not differ. Before CIED implantation, patients in the non-RVA group had better left ventricular systolic function ($P = 0.004$). Pacemakers were implanted more often in the non-RVA group ($P = 0.001$) while implantable cardioverter-defibrillators in the RVA group ($P = 0.008$). Progression to severe or massive TR was more common in the non-RVA group ($P = 0.005$).

Conclusion: Severe and massive TR occurred more often in patients with the non-RVA position of the lead. The right ventricular lead position did not impact heart failure progression or all-cause mortality at two-year follow-up.

Key words: cardiac implantable electronic device, heart failure, right ventricle, tricuspid regurgitation, valve disease

WHAT'S NEW?

Severe and massive tricuspid regurgitation occurred more often in patients with the non-right ventricular apex position of the lead. The position of the right ventricular lead did not affect the progression of heart failure and all-cause mortality at one-year follow-up. Tricuspid regurgitation progression by one grade was unaffected by the type of the implanted device.

INTRODUCTION

The development or progression of tricuspid regurgitation (TR) after implantation of cardiac implantable electronic devices (CIEDs) is a growing concern [1–4]. This complication occurs in 7.2% to 44.7% of patients who received CIEDs [1, 2, 5–24]. It may result from ventricular remodeling in the natural course of heart failure (HF) or from a direct interaction between the lead and the tricuspid leaflets. The most frequent mechanism is leaflet impingement or leaflet movement restriction by a ventricular lead [11, 15, 21, 25–28]. Many authors reported that the posterior and septal leaflets are most often affected [10, 11, 15, 17, 21, 23, 26]. The most favorable position of the lead is the center of the valve orifice or one of the commissures [15, 17, 21, 23, 26, 29, 30]. It seems that placement of the lead in the right ventricular apex (RVA) more often causes TR than other locations [27]. The reason for this may be the placement of the lead closer to the posterior leaflet and its impingement [27]. Targeting a non-RVA location for the lead usually results in a central position of the tricuspid orifice [5, 27, 31, 32]. On the other hand, Cheng et al. [26] reported that significant progression of TR after CIED implantation occurred more often when the lead tip was placed in the interventricular septum (IVS). Polewczyk et al. [28] reported that in patients with lead-related tricuspid regurgitation (LRTR), the non-apical location of the lead was more frequent. Some authors claim that the position of the lead is irrelevant to TR development [17, 33, 34]. Nevertheless, coexisting TR in patients with CIEDs is associated with increased mortality [2, 7, 8, 22, 28, 35] and right ventricular failure more often than in patients without TR [6, 8, 11, 12, 22, 23]. Thus, our study aimed to determine the impact of the CIED lead tip position on TR development and progression as well as on the function of the right and left ventricles and decompensated HF-free and survival.

METHODS

Design of the study

One hundred and two consecutive patients who received a CIED — pacemaker (PM), implantable cardioverter-defibrillator (ICD), cardiac resynchronization therapy defibrillator (CRT-D), or pacemaker (CRT-P) between March 2020 and October 2021 were involved in the single-center PACE-RVTR registry. Patients were assigned to two groups depending on the lead position — the RVA group and the non-RVA group, including the upper lower parts of the IVS, the right ventricular outflow tract (RVOT), and His bundle. The position of the lead was determined on the basis of the description of the implantation procedure and chest radiography in the posteroanterior view, performed routinely after surgery (Figure 1). All patients underwent echocardiographic evaluation directly before and one year after CIED implantation (15.2 [12.0–16.0] months). Clinical data, including mortality and hospital admissions, were retrieved from the electronic medical records. HF-free survival was defined as hospitalization for HF exacerbation

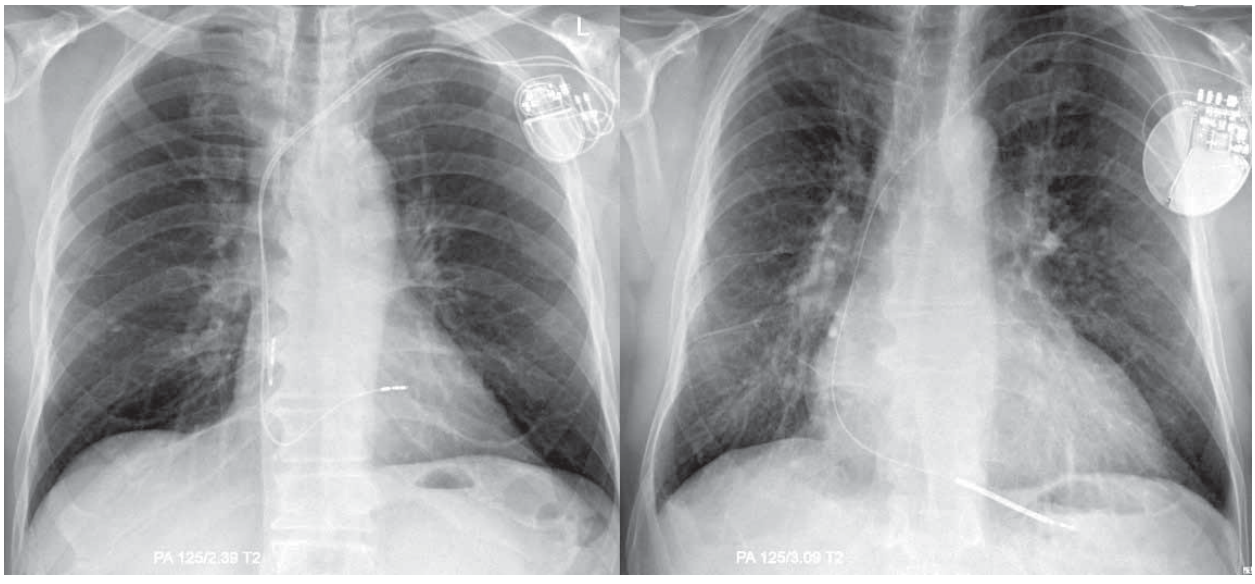

Figure 1. Position of the lead. **A.** Non-right ventricular apex. **B.** Right ventricular apex

or an increase in diuretic doses up to the last check-up of the medical records in July 2023 (25.5 [17.0–34.0] months). LRTR was defined as an increase in TR severity by at least one grade. The percentage of ventricular pacing was checked one year after implantation.

Echocardiographic examination

Two-dimensional transthoracic echocardiography was performed before CIED implantation-and one year later by Vivid 7 GE Healthcare (Chicago, IL, US). TR grade (trivial/none 0, mild 1, moderate 2, severe 3, massive 4), other valvular insufficiencies, dimensions, and function of the right ventricle (RV) and the left ventricle (LV) were evaluated in accordance with the guidelines of the European Association of Cardiovascular Imaging [36, 37]. In the case of the RV, the evaluated parameters included RV and tricuspid valve (TV) diameters in the four-chamber view, RV area, fractional area change, tricuspid annular plane systolic excursion (TAPSE), TAPSE/tricuspid regurgitation peak gradient, and right ventricular systolic pressure; in the case of the left ventricle, these were diastolic and systolic volume and ejection fraction (EF) measured by the Simpson method. The analysis of dyssynchrony was performed according to a review by Galderisi et al. [38], and the main focus was on interventricular dyssynchrony and measured interventricular mechanical delay. According to that article, interventricular mechanical delay >40 ms was considered dyssynchrony.

Data analysis

The Kolmogorov-Smirnov test was used for the evaluation of data distribution. The numerical variables were presented as mean value and standard deviation or median and percentile distribution, depending on the result of the Kolmogorov–Smirnov test. For normally distributed independent and dependent variables, Student's t-test and paired Student's test were used, respectively. The Mann–Whitney U test was used for comparing the non-parametric independent variables, and the Wilcoxon test for dependent variables. Differences in categorical parameters were checked using Yates's χ^2 and Fisher's exact tests or McNemar's test in the case of dependent variables. P <0.05 was adopted as statistically significant. HF-free survival and overall survival were analyzed using the log-rank test and the Kaplan-Meier estimator. Calculations were performed using Statistica 10 software (TIBCO Software Inc., Palo Alto, CA, US).

RESULTS

Baseline characteristics

The average period from CIED implantation to echocardiographic examination was 15 (6) months. The RVA group included 24 patients (17 men) and the non-RVA group — 78 patients (40 men). In the non-RVA group, 65.7% of patients had the lead in the upper part of the IVS, 5.9% in the lower part, 1.9% in the RVOT, and 2.9% in the His bundle. Median age was 67.9 (60.0–77.0) years old and was similar in both groups (P = 0.39). The groups did not differ in the prevalence of atrial fibrillation (P = 1.0), coronary heart disease (P = 0.24), diabetes mellitus (P = 0.61), or chronic obstructive pulmonary disease (P = 1.0) (Table 1).

Before CIED implantation, patients in the non-RVA group showed better LV systolic function — 52.5% (33.0–57.0%) vs. 32.5% (23.5–49.5%); P = 0.004; they also a lower New York Heart Association (NYHA) classification grade (P = 0.03). They exhibited lower LV end-diastolic volume (113.0 [81.5–157.0] ml vs. 175.5 [149.0–219.0] ml; P = 0.001) and systolic volume (45.5 [33.0–95.0] ml vs. 129.0 [92.0–154.0] ml; P = 0.001); the same relation persisted after CIED implantation. The groups did not differ in terms of the right ventricular dimension and function or TR and other valvular diseases (Table 2).

Pacemakers were implanted more often in the non-RVA group and ICDs in the RVA group (P = 0.003). CRT devices were implanted in both groups with the same frequency. The groups did not differ in terms of the pacing mode (P = 0.11) and ventricular pacing percentage (group 1: 37.5% [1.0–99.0%] vs. group 2: 19.1 [1.0–91.0%]; P = 0.81) (Table 3).

Tricuspid valve and right ventricle at one-year follow-up

Tricuspid regurgitation progression in both groups was similar (by one grade P = 0.33; by two or more grades P = 0.35) (Table 4). Comparison of particular TR degrees before and after CIED implantation, respectively, is as follows (Table 5):

- The non-RVA group: none/trivial TR (61.5% vs. 24.4%; P = 0.001), mild TR (28.3% vs. 44.9%; P = 0.04), moderate TR (8.9% vs. 14.1%; P = 0.45), severe and massive TR (1.3% vs. 14.1%; P = 0.005);
- The RVA group: none/trivial TR (45.8% vs. 37.5%; P = 0.77), mild TR (41.7% vs. 33.3%; P = 0.76), moderate TR (12.5% vs. 25.0%; P = 0.46), severe and massive TR (0.0% vs. 4.2%; P = 1.00).

In the non-RVA group, TR progression by at least one grade was related to the position of the lead in the upper part of the IVS. Moreover, interventricular dyssynchrony did not affect TR progression in all patients (P = 0.55) (Table 6).

Tricuspid regression progression by one grade was independent of the type of the implanted device (patients with PM: non-RVA — 34.6% vs. RVA — 66.7%; P = 0.19 and with ICD/CRT-D/CRT-P: non-RVA 23.1% vs. RVA 27.8%; P = 0.74). Moreover, in patients in the non-RVA group with ICDs and CRT-Ds, there was a tendency for TR progression by 2 or more grades in comparison to patients with PMs (P = 0.06) (Table 4).

Fractional area change was higher in the non-RVA group than in the RVA group (43.1% [mean SD 11.1%] vs. 37.4 [mean SD 10.6%]; P = 0.03); however, other parameters of the right ventricular function and dimensions were comparable in both groups (Table 5).

Table 1. Patient characteristics

	All (n = 102)	RVA (n = 24)	Non-RVA (n = 78)	*P*-value
Men, n (%)	57 (55.9)	17 (70.8)	40 (51.3)	0.10
Age, years, median (Q1–Q3)	67.9 (60.0–77.0)	66.5 (58.0–77.0)	68.4 (61.0–76.0)	0.39
Weigh, kg, median (Q1–Q3)	83.7 (73.0–91.5)	84.0 (71.5–92.0)	83.6 (74.0–91.5)	0.68
Height, m, median (Q1–Q3)	1.70 (1.64–1.76)	1.73 (1.67–1.78)	1.69 (1.64–1.76)	0.25
Coronary artery disease, n (%)	52 (50.9)	15 (62.5)	37 (47.4)	0.24
Diabetes mellitus, n (%)	29 (28.4)	8 (33.3)	21 (26.9)	0.61
Pulmonary disease, n (%)	7 (6.9)	1 (4.2)	5 (6.4)	1.00
Atrial fibrillation, n (%)	38 (3.2)	9 (37.5)	29 (37.2)	1.00
NYHA class, n (%)				
I	60 (58.8)	8 (33.3)	52 (66.7)	0.03
II	34 (33.3)	14 (58.3)	20 (25.6)	
III	5 (4.9)	1 (4.2)	4 (5.1)	
IV	3 (2.9)	1 (4.2)	2 (2.6)	
Bilirubin, µmol/l, median (Q1-Q3)	12.8 (7.2–14.6)	11.3 (7.1–12.4)	13.3 (7.2–17.5)	0.33
INR, median (Q1–Q3)	1.6 (0.9–1.2)	1.2 (0.9–1.1)	1.7 (0.9–1.2)	0.49
Creatinine, µmol/l, median (Q1–Q3)	89.9 (75.0–103.0)	100.9 (81.5–114.5)	86.5 (69.0–101.0)	0.008
Time since CIED implantation, months, median (Q1–Q3)	15.2 (12.0–16.0)	15.7 (12.0–15.0)	15.1 (12.0–16.0)	0.97

Abbreviations: CIED, cardiac implantable electronic device; INR, international normalized ratio; NYHA, New York Heart Association; RVA, right ventricular apex

Table 2. Results of echocardiographic examination before cardiac implantable electronic device implantation

	All (n = 102)	RVA (n = 24)	Non-RVA (n = 78)	*P*-value
RV dimension in four-chamber view, mm, median (Q1–Q3)	37.0 (35.0–40.0)	38.0 (35.0–40.0)	37.0 (35.0–41.0)	0.86
Area of RA in diastole, cm^2, median (Q1–Q3)	17.4 (15.0–21.7)	16.9 (14.3–21.0)	17.7 (15.4–21.9)	0.33
Area of RA in systole, cm^2, median (Q1–Q3)	12.0 (10.4–16.3)	12.0 (11.0–14.9)	12.2 (10.3–16.5)	0.87
TV diameter, mm, median (Q1–Q3)	32.0 (29.0–38.0)	31.0 (29.0–35.0)	33.0 (29.0–38.0)	0.67
FAC, %, mean (SD)	38.4 (10.6)	38.1 (11.0)	38.5 (10.5)	0.89
TAPSE, mm, median (Q1–Q3)	20.0 (17.0–23.0)	18.0 (16.0–21.0)	20.0 (17.0–25.0)	0.15
RVSP, mm Hg, mean (SD)	33.8 (15.8)	33.5 (19.3)	33.9 (14.9)	0.94
TAPSE/TRPG, mm/mm Hg, median (Q1–Q3)	0.5 (0.4–0.9)	0.5 (0.3–0.9)	0.5 (0.4–0.9)	0.84
LV EDV, ml, median (Q1–Q3)	127.5 (86.0–169.0)	175.5 (149.0–219.0)	113.0 (81.5–157.0)	0.001
LV ESV, ml, median (Q1–Q3)	58.0 (36.0–120.0)	129.0 (92.0–154.0)	45.5 (33.0–95.0)	0.001
LVEF, %, median (Q1–Q3)	50.0 (30.0–55.0)	32.5 (23.5–49.5)	52.5 (33.0–57.0)	0.004
TR, n (%)				
None/trace	59 (57.8)	11 (45.8)	48 (61.5)	0.50
Mild	32 (31.4)	10 (41.7)	22 (28.2)	
Medium	10 (9.8)	3 (12.5)	7 (8.9)	
Severe	1 (0.9)	0 (0.0)	1 (1.3)	
Massive	0 (0.0)	0 (0.0)	0 (0.0)	
Aortic stenosis, n (%)				
None	88 (86.3)	23 (96.0)	65 (83)	0.13
Mild	10 (9.8)	0 (0.0)	10 (12.8)	
Medium	3 (2.9)	0 (0.0)	3 (3.8)	
Severe	1 (0.9)	1 (4.2)	0 (0.0)	
Aortic regurgitation, n (%)				
None	88 (86.3)	18 (75.0)	70 (90.0)	0.1
Mild	11 (10.8)	4 (16.7)	7 (8.9)	
Medium	3 (2.9)	2 (8.3)	1 (1.3)	
Severe	0 (0.0)	0 (0.0)	0 (0.0)	
Mitral stenosis, n (%)				
Mild	0 (0.0)	0 (0.0)	0 (0.0)	1.0
Medium	0 (0.0)	0 (0.0)	0 (0.0)	
Severe	0 (0.0)	0 (0.0)	0 (0.0)	
Mitral regurgitation, n (%)				
None	58 (56.8)	11 (54.2)	47 (60.3)	0.43
Mild	30 (29.4)	7 (29.2)	23 (29.5)	
Medium	9 (8.8)	4 (16.7)	5 (6.4)	
Severe	5 (4.9)	2 (8.3)	3 (3.8)	

Abbreviations: EDV, end-diastolic volume; ESV, end-systolic volume; FAC, fractional area change; LVEF, left ventricular ejection fraction; RA, right atrium; RV, right ventricle; SD, standard deviation; TAPSE, tricuspid annular plane systolic excursion; TRPG, tricuspid regurgitation peak gradient; TV, tricuspid valve; other — see Table 1

Table 3. Results of cardiac implantable electronic device implantation (CIED) controls and echocardiographic examinations after one year of follow-up

	All (n = 102)	RVA (n = 24)	Non-RVA (n = 78)	*P*-value
CIED type and parameters				
Type of device, n (%)				
PM	58 (56.9)	6 (25.0)	52 (66.7)	0.003
ICD	28 (27.5)	12 (50.0)	16 (20.5)	
CRT-P/CRT-D	16 (15.6)	6 (25.0)	10 (12.8)	
Pacing mode, n (%)				
AAI	0 (0.0)	0 (0.0)	0 (0.0)	0.11
VVI	27 (26.5)	8 (33.3)	19 (24.4)	
DDD	60 (58.8)	10 (41.7)	50 (64.1)	
BiV	15 (14.7)	6 (25.0)	9 (11.5)	
Percentage of ventricular pacing, %, median (Q1–Q3)	20.0 (1.0–93.0)	37.5 (1.0–99.0)	19.1 (1.0–91.0)	0.81
Echocardiographic parameters				
TV diameter, mm, median (Q1–Q3)	33.0 (30.0–38.0)	33.5 (29.0–38.0)	33.0 (36.0–42.0)	0.98
FAC, %, mean (SD)	41.7 (11.2)	37.4 (10.6)	43.1 (.11.1)	0.03
TAPSE, mm, mean (SD)	19.5 (4.7)	17.9 (4.2)	20.0 (4.8)	0.06
RVSP, mm Hg, mean (SD)	30.2 (14.2)	29.3 (17.5)	30.4 (13.4)	0.79
TAPSE/TRPG, mm/mm Hg, median (Q1–Q3)	0.62 (0.46–0.94)	0.53 (0.45–1.2)	0.65 (0.47–0.93)	0.57
LV EDV, ml, median (Q1–Q3)	114.8 (86.0–166.0)	149.5 (119.0–236.0)	108.2 (85.3–194.0)	0.003
LV ESV, ml, median (Q1–Q3)	59.0 (38.0–103.0)	93.0 (49.5–146.0)	55.5 (32.5–80.5)	0.003
LVEF, %, median (Q1–Q3)	49.0 (31.0–58.0)	30.0 (26.5–51.5)	53.0 (38.0–59.0)	0.003
TR, n (%)				
None/trace	28 (27.4)	9 (37.5)	19 (24.4)	0.33
Mild	43 (42.2)	8 (33.3)	35 (44.9)	
Medium	17 (16.7)	6 (25.0)	11 (14.1)	
Severe	10 (9.8)	1 (4.2)	9 (11.5)	
Massive	2 (1.9)	0 (0.0)	2 (2.6)	
Aortic stenosis, n (%)				
None	92 (90.2)	23 (96.8)	69 (88.5)	0.051
Mild	7 (6.9)	1 (4.2)	6 (7.7)	
Medium	3 (2.9)	0 (0.0)	3 (3.8)	
Severe	0 (0.0)	0 (0.0)	0 (0.0)	
Aortic regurgitation, n (%)				
None	88 (86.2)	16 (66.7)	72 (92.3)	0.1
Mild	11 (10.8)	5 (20.8)	6 (7.7)	
Medium	3 (2.9)	3 (12.5)	0 (0.0)	
Severe	0 (0.0)	0 (0.0)	0 (0.0)	
Mitral stenosis, n (%)				
None	97 (95)	22 (91.7)	75 (96.2)	0.19
Mild	4 (3.9)	1 (4.2)	3 (3.8)	
Medium	1 (0.9)	1 (4.2)	0 (0.0)	
Severe	0 (0.0)	0 (0.0)	0 (0.0)	
Mitral regurgitation, n (%)				
None	54 (52. 9)	9 (37.5)	45 (57.7)	0.09
Mild	30 (29.4)	10 (41.7)	20 (25.6)	
Medium	16 (15.7)	5 (20.8)	11 (14.1)	
Severe	2 (1.9)	0 (0.0)	2 (2.6)	
Interventricular dyssynchrony, n (%) IVMD >40 ms	13 (12.7)	2 (8.3)	11 (14.1)	0.719

Abbreviations: AAI, single atrial stimulation; BiV, biventricular stimulation; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; DDD, dual chamber stimulation; ICD, implantable cardioverter defibrillator; IVMD, interventricular mechanical delay; LV, left ventricle; PM, pacemaker; RVSP, right ventricular systolic pressure; TR, tricuspid regurgitation; VVI, single ventricle stimulation; other — see Tables 1 and 2

Table 4. Level of progression of tricuspid regurgitation (TR) after cardiac implantable electric device (CIED) implantation and the position of the lead

	All (n = 102)	RVA (n = 24)	Non-RVA (n = 78)	*P*-value
TR progression				
No progression, n (%)	42 (41.2)	13 (54.2)	29 (37.2)	0.16
TR progression by 1 grade n (%)	35 (34.3)	6 (25.0)	29 (37.2)	0.33
None/trace to mild	25 (24.5)	3 (12.5)	22 (28.2)	
Mild to moderate	5 (4.9)	2 (8.3)	3 (3.8)	
Moderate to severe	4 (3.9)	1 (4.2)	3 (3.8)	
Severe to massive	1 (0.9)	0 (0.0)	1 (1.3)	
TR progression by ≥2 grade, n (%)	16 (15.7)	2 (8.3)	14 (17.9)	0.35
None/trace to medium	9 (8.8)	2 (8.3)	7 (8.9)	
None/trace to severe	2 (1.9)	0 (0.0)	2 (2.6)	
Mild to severe	5 (4.9)	0 (0.0)	5 (6.4)	
Moderate to massive	0 (0.0)	0 (0.0)	0 (0.0)	
Regression, n (%)	10 (9.8)	3 (125)	7 (8.9)	0.69

	All (n = 102)			RVA (n = 24)			Non-RVA (n = 78)			*P*-value (Group 1 vs. Group 2)	
	PM (n = 58)	ICD/ CRT-D/ CRT-P (n = 44)	*P*-value	PM (n = 6)	ICD/ CRT-D/ CRT-P (n = 18)	*P*-value	PM (n = 52)	ICD/ CRT-D/ CRT-P (n = 26)	*P*-value	PM	ICD/ CRT-D/ CRT-P
TR progression due to CIED type											
No progression, n (%)	22 (37.9)	19 (43.2)	0.68	4 (66.7)	9 (50.0)	0.65	18 (34.6)	10 (38.5)	0.80	0.187	0.54
Progression by 1 grade, n (%)	24 (41.4)	11 (25.0)	0.09	1 (16.7)	5 (27.8)	1.00	23 (44.2)	6 (23.1)	0.09	0.384	0.74
Progression by ≥2 grades, n (%)	6 (10.3)	10 (22.7)	0.10	0 (0.0)	2 (11.1)	1.00	6 (11.5)	8 (30.8)	0.06	1.000	0.16
Regression, n (%)	6 (10.3)	4 (9.1)	1.00	1 (16.7)	2 (11.1)	1.00	5 (9.6)	2 (7.7)	1.00	0.497	1.00

Abbreviations: see Table 3

Table 5. Comparison of changes in echocardiographic parameters before and after implantation of cardiac implantable electric devices

Parameter	All (n = 102)			RVA (n = 24)			Non-RVA (n = 78)		
	Before implantation	After implantation	*P*-value	Before implantation	After implantation	*P*-value	Before implantation	After implantation	*P*-value
TR grade, n (%)									
None	59 (57.8)	28 (27.4)	0.001	11 (45.8)	9 (37.5)	0.77	48 (61.5)	19 (24.4)	0.001
Mild	32 (31.4)	43 (42.2)	0.15	10 (41.7)	8 (33.3)	0.76	22 (28.2)	35 (44.9)	0.045
Medium	10 (9.8)	17 (16.7)	0.21	3 (12.5)	6 (25.0)	0.46	7 (8.9)	11 (14.1)	0.45
≥Severe	1 (0.9)	12 (11.7)	0.002	0 (0.0)	1 (4.2)	1.00	1 (1.3)	11 (14.1)	0.005
RA in diastole, cm^2, median (Q1–Q3)	17.4 (15.0–21.7)	19.4 (16.3–24.0)	0.12	16.9 (14.3–21.0)	18.5 (15.4–21.3)	0.74	17.7 (15.4–21.9)	19.8 (16.6–24.2)	0.11
RA in systole, cm^2, median (Q1–Q3)	12.0 (10.4–16.3)	13.0 (11.3–16.9)	0.33	12.0 (11.0–14.9)	12.2 (10.1–15.5)	0.79	12.2 (10.3–16.5)	13.2 (11.5–18.1)	0.37
TV diameter, mm, median (Q1–Q3)	32.0 (29.0–38.0)	33.0 (30.0–38.0)	0.39	31.0 (29.0-35.0)	33.5 (29.0–38.0)	0.11	33.0 (29.0–38.0)	33.0 (36.0–42.0)	0.82
RV in 4 chambers, mm, median (Q1–Q3)	37.0 (35.0–40.0)	38.0 (36.0–42.0)	0.15	38.0 (35.0–40.0)	37.0 (34.0–42.0)	0.79	37.0 (35.0–41.0)	38.0 (36.0–42.0)	0.07
RV in diastole, cm^2, mean (SD)	18.9 (5.4)	20.5 (5.9)	0.004	18.3 (4.3)	21.0 (6.1)	0.06	19.2 (5.8)	20.3 (5.8)	0.03
RVSP, mm Hg, mean (SD)	33.8 (15.8)	30.2 (14.2)	0.06	33.5 (19.3)	29.3 (17.5)	0.39	33.9 (14.9)	30.4 (13.4)	0.08
FAC RV, %, mean (SD)	38.4 (10.6)	41.7 (11.2)	0.28	38.1 (11.0)	37.4 (10.6)	0.88	38.5 (10.5)	43.1 (11.1)	0.17
TAPSE, mm, median (Q1–Q3)	20.0 (17.0–23.0)	19.5 (4.7)	0.32	18.0 (16.0–21.0)	17.9 (4.2)	0.29	20.0 (17.0–25.0)	20.0 (4.8)	0.57
TAPSE/TRPG, mm/mm Hg, median (Q1–Q3)	0.5 (0.4–0.9)	0.62 (0.46–0.94)	0.12	0.5 (0.3–0.9)	0.53 (0.45–1.2)	1.00	0.5 (0.4–0.9)	0.65 (047–0.93)	0.10
LV EDV, ml, median (Q1–Q3)	127.5 (86.0–169.0)	114.8 (86.0–166.0)	0.38	175.5 (149.0–219.0)	149.5 (119.0–236.0)	0.72	113.0 (81.5–157.0)	108.2 (85.3–194.0)	0.51
LV ESV, ml, median (Q1–Q3)	58.0 (36.0–120.0)	59.0 (38.0–103.0)	0.36	129.0 (92.0–154.0)	93.0 (49.5–146.0)	0.49	45.5 (33.0–95.0)	55.5 (32.5–80.5)	0.69
LVEF, %, median (Q1–Q3)	50.0 (30.0–55.0)	49.0 (31.0–58.0)	0.003	32.5 (23.5–49.5)	30.0 (26.5–51.5)	0.24	52.5 (33.0–57.0)	53.0 (38.0–59.0)	0.006

Abbreviations: see Table 2

Table 6. Progression of tricuspid regurgitation in relation to the position of the lead within the right ventricle and interventricular dyssynchrony

	All (n = 102)	No progression or decrease in TR (n = 51)	Progression of TR by at least 1 degree (n = 51)	*P*-value
Upper part of IVS, n (%)	67 (65.7)	28 (54.9)	39 (76.5)	0.04
Lower part of IVS, n (%)	6 (5.9)	5 (9.8)	1 (1.9)	0.20
RVOT, n (%)	2 (1.9)	1 (1.9)	1 (1.9)	1.00
His bundle, n (%)	3 (2.9)	1 (1.9)	2 (3.9)	1.00
Apex, n (%)	24 (23.5)	16 (31.4)	8 (15.7)	0.10
Dyssynchrony, n (%)	13 (12.7)	5 (9.8)	8 (15.7)	0.55

Abbreviations: IVS, interventricular septum; RVOT, right ventricular outflow tract; TR, tricuspid regurgitation

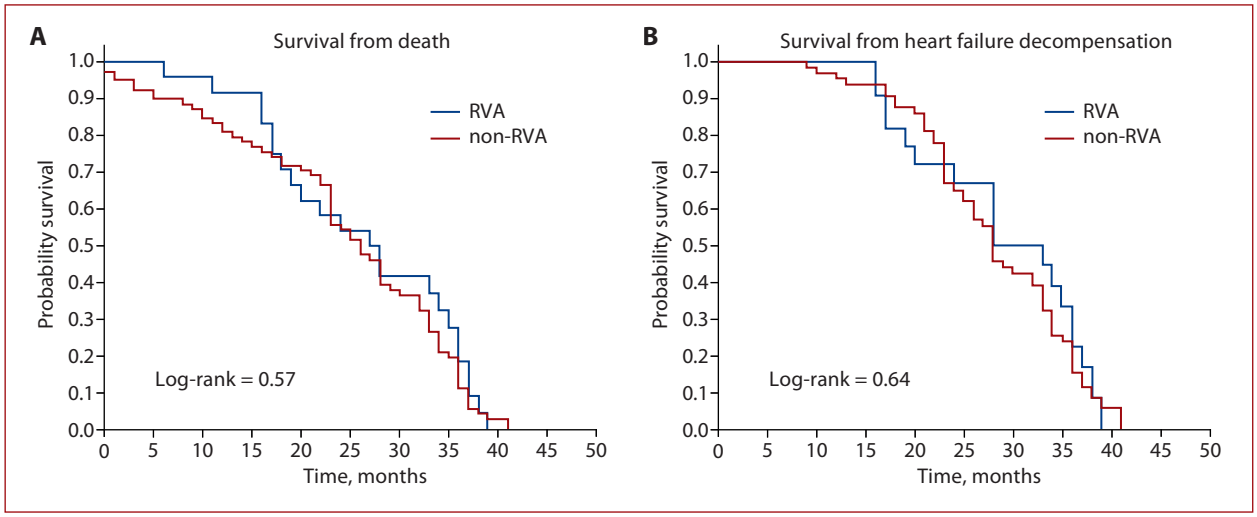

Figure 2. Overall survival and heart failure decompensation

Abbreviations: see Table 1

In the non-RVA group, the RV area was larger than before implantation (20.3 [mean SD 5.8] cm^2 vs. 19.2 [mean SD 5.8] cm^2 before implantation; $P = 0.03$), and EF increased to 53.0 (38.0–59.0)% from 52.5 (33.0–57.0)%; $P = 0.006$ (Table 5).

Mortality and heart failure exacerbation at two-year follow-up

The two groups did not differ in terms of the HF decompensation rate (RVA group 25.0% vs. non-RVA group 25.6%; $P = 0.64$) and deaths (RVA group 4.2% vs. non-RVA group 5.1%; $P = 0.58$) (Figure 2).

DISCUSSION

This study aimed to determine the impact of the CIED lead tip position on TR development and progression as well as on the RV and LV function and decompensated HF-free and overall survival.

The non-RVA group was more numerous, as it is believed that non-apical pacing is more physiological and ensures better function of the right and left ventricles; therefore, this position is preferable [39, 40]. At the beginning of the study, the group included healthier patients with higher EF and lower NYHA grades who could tolerate CIED implantation better and usually could bear longer attempts to place the lead in a position other than the RV apex. TR progression was more pronounced in the non-RVA group, with a significantly higher number of severe and massive TR. As TR progression was mainly related to the position of the lead in the upper part of the IVS, this may have resulted from damaging the TV apparatus when attempting to obtain the target position of the lead in the IVS, as the chordae tendineae of the TV are densely distributed in the RV and some of them are directly connected to the IVS [41]. This finding is consistent with the observations of Cheng et al. [26] and Polewczyk et al. [28]. On the other hand, in the study of Yu et al. [27], including only patients with pacemakers, targeting the lead to a non-RVA position resulted in placing it in the middle of the TV with the lowest chance of the leaflet impingement, while RVA placement was associated with TR progression. According to Saito et al. [33], the RV pacing site is not associated with TR worsening and did not directly affect RV function at a 2-year follow-up. Rothschild, Schleifer, and Poorzand drew a similar conclusion [17, 34, 42], and Anvardeen et al. [43] suggested that only tricuspid leaflet interference by the endocardial lead is a predictor of TR development or progression, which in turn, in studies by other authors, is more often found in the case of the RVA lead position [27].

The question arises which option is safer for the patient — the non-RVA position with more physiological pacing

and location in the middle of the TV (provided that the TV apparatus is not damaged during the attempts to achieve that position), or RVA placement with higher risk of the lead restricting movements of the posterior leaflet.

As non-RVA pacing prevents the RV and LV negative remodeling [40, 44], which is consistent with the results of our study, and, consequently, secondary TR, non-RVA lead placement seems to be a better solution if surgery is performed by an experienced electrophysiologist who can place the lead in the desired location without unnecessary manipulation and risk of entanglement and damage to the chordae tendinae. Three-D echocardiographic examination performed during the procedure and directly after lead implantation may help prevent severe TR development because it enables lead replacement if its position is not optimal for TV functioning.

The importance of pacing the heart as physiologically as possible led to the development of the idea of His bundle pacing. Zaidi et al. reported that patients with His bundle pacing had a lower risk of developing LRTR; they also had decreased severity of existing TR and improved LVEF [45].

According to Xin et al. [46], who conducted an almost 10-year follow-up of RVA pacing in patients with normal LV function, long-term RVA pacing significantly increased ventricular dyssynchrony and TR degree. In our study, which had a shorter follow-up period, we did not observe any difference in the occurrence of dyssynchrony between both groups or any impact on the progression of TR.

The impact of the lead position on heart function, decompensated HF, or mortality was not demonstrated in this study. The most significant limitation of our study is a relatively short follow-up period, while RV remodeling and TR development may occur after a longer period, as presented in a meta-analysis from 2022 [2]. In our study, none of the patients with severe or more advanced tricuspid regurgitation experienced deterioration of right ventricular function, which, in the light of the current ESC guidelines for the management of valvular heart disease [47], provided an argument for the Heart Team to forego both tricuspid valve correction and lead replacement. In fact, further observation is needed to determine whether early replacement of the right ventricular lead would be a better solution than waiting for the occurrence of the right ventricular enlargement or dysfunction, especially since it is safer to remove the lead soon after implantation before it adheres to the structures of the tricuspid valve apparatus and the right ventricle. The study participants are still followed up with periodical assessments of their symptoms and changes in parameters of the right ventricular function. If their condition worsens, they will be re-qualified for intervention. Rdzanek et al. suggested in their study [48] that the presence of PM leads, when they collide with the valve leaflets, decreases the chances of a successful percutaneous tricuspid edge-to-edge procedure. However, they did not consider the presence of CIED leads as an echocardiographic exclusion criterion and indicated that the commissural position is preferable for edge-to-edge repair [48]. An often-studied aspect is the impact of CIED type on TR progression. Some authors suggest that ICDs predispose to TR because defibrillator leads are thicker and more rigid than pacing leads, which makes it more difficult to maneuver them into the target position, and damaging the tricuspid valve apparatus is more likely [6, 18, 22, 26, 49, 50]. In our study, in patients in the non-RVA groups with ICD/CRT-D devices, there was a tendency for TR progression by two or more grades ($P = 0.06$) (Table 4).

Limitations of the study

The most significant limitations of the study are the small number of patients and the relatively short follow-up period. Moreover, the difference between both groups in terms of LVEF, LV end-diastolic volume, LV ESV, creatine level, and NYHA class is the major drawback of our study. We did not perform systematic imaging of the tricuspid valve using a three-dimensional probe, which precluded the determination of the RV lead position within the tricuspid orifice.

CONCLUSION

Severe and massive TR occurred in patients with the non-RVA position of the lead. The position of the lead did not impact HF exacerbation or mortality at two years of follow-up.

Article information

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Deep learning-based diagnosis of aortic dissection using an electrocardiogram: Development, validation, and clinical implications of the AADE score

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ABSTRACT

Background: Aortic dissection (AD) is frequently associated with abnormalities in electrocardiographic findings. Advancements in medical technology present an opportunity to leverage these observations to improve patient diagnosis and care.

Aims: This study aimed to develop a deep learning artificial intelligence (AI) model for AD detection using electrocardiograms (ECGs) and introduce the AI-Aortic-Dissection-ECG (AADE) score to provide clinicians with a measure to determine AD severity.

Methods: From a cohort of 1878 patients, including 313 with AD, and 313 with chest pain (control group), we created training and validation subsets (7:3 ratio). A convolutional neural networks (CNN) model was trained for AD detection, with performance metrics like accuracy and F1 score (the harmonic mean of precision and recall) monitored. The AI-derived AADE score (0–1) was investigated against clinical parameters and ECG features over a median follow-up of 21.2 months.

Results: The CNN model demonstrated robust performance with an accuracy of 0.93 and an F1 score of 0.93 for the AD group, and an accuracy of 0.871 with an F1 score of 0.867 for the chest pain group. The AADE score showed correlations with specific ECG patterns and demonstrated that higher scores aligned with increased mortality risk.

Conclusions: Our CNN-based AI model offers a promising approach for AD detection using ECG. The AADE score, based on AI, can serve as a pivotal tool in refining clinical assessments and management strategies.

Key words: aortic dissection, artificial intelligence, deep learning, electrocardiogram, mortality risk

INTRODUCTION

Aortic dissection (AD) is a serious cardiovascular disorder despite its relative rarity [1–3]. Emergency physicians frequently face the challenging task of diagnosing and managing AD, as this condition can rapidly deteriorate and pose a life-threatening risk to patients. Therefore, prompt and accurate diagnosis and intervention are crucial, particularly in the emergency department (ED) [1–3]. Initial misdiagnosis in 14%–39% of AD cases can have severe or fatal consequences due to incorrect treatment [4].

Accurate AD diagnosis can be achieved using non-invasive imaging techniques like computed tomography angiography (CTA) and magnetic resonance angiography (MRA), but they are a lengthy process, impractical for bedside use, and unsuitable for elderly frail patients or those with renal insufficiency, which restricts their utility [4–6]. X-ray and echocardiography, while valuable for bedside

WHAT'S NEW

This article delineates significant progress in the diagnosis of aortic dissection achieved by deploying an innovative Convolutional Neural Networks model adept at differentiating with high precision aortic dissection from non-aortic dissection electrocardiograms (ECGs). The AI-Aortic-Dissection-ECG score exhibits substantial correlations with pivotal clinical parameters and aortic dissection-associated mortality risk. Transcending traditional diagnostic modalities, the AI-Aortic-Dissection-ECG score has a stronger association with D-dimer distribution, augments diagnostic acuity, and can be considered a supreme tool for exhaustive aortic-dissection risk evaluation. This study further elucidates the model's interpretability, highlighting crucial ECG signals pertinent to aortic dissection and associated aortic risk levels. This pioneering approach can substantially enhance aortic dissection diagnostic protocols and facilitate clinical decision-making processes.

AD diagnosis, especially for hemodynamically unstable patients, are limited in diagnostic precision and technical applicability [5, 7]. Many blood biomarkers, such as D-dimer, a product of thrombus formation and fibrinolysis, have been suggested as AD diagnosis biomarkers, yet they also have diagnostic limitations [8].

AD patients often present with electrocardiogram (ECG) abnormalities during their disease course [2, 9]. ECG examination, as a non-invasive method, is one of the most readily available assessments that can provide immediate results, and, therefore, is extensively implemented across medical institutions at all levels to facilitate expedited and accessible disease evaluation. ECG is good for recording cardiac electrical activity and can reflect physiological and pathological changes, which is pivotal in the diagnosis of many cardiovascular diseases [10]. However, when diagnosing AD, the diagnostic value of ECG is relatively weak [11].

Over the past decade, deep learning (DL), a type of AI, has significantly advanced and brought innovation in disease diagnosis [12, 13]. Unlike traditional machine learning, DL models (DLM) automatically extract complex features, improving disease detection, including in atrial fibrillation [14, 15], hypertrophic cardiomyopathy [16], left ventricular systolic dysfunction [17, 18], and aortic stenosis [19]. Compared to internal medicine doctors' identification of arrhythmias, deep learning models exhibit higher accuracy [12]. This indicates that deep learning has a promising clinical future in interpreting ECG [20].

In our study, we aimed to accurately identify AD patients through a DLM trained with a convolutional neural network (CNN) based on 12-lead ECG and to generate an AADE score that would correlate with disease severity. By applying deep learning technology to ECG diagnosis, we aim to develop a new and simpler method to enhance the accuracy of AD diagnosis and reduce misdiagnosis rates, thereby providing patients with more precise treatment plans.

METHODS

The confirmation of AD was based on the following criteria: CTA showed the presence of an intimal flap separating true and false lumens in the aorta, or there was an intramural hematoma; it involved the ascending aorta (defined as type A), the aortic arch, or descending aorta (type B). In our study, penetrating atherosclerotic ulcers and intramural hematomas were defined as AD, as they are similar in treatment and prognosis to typical AD [21]. This study was approved by the Review Committee of Tongji Hospital, affiliated with Tongji Medical College of Huazhong University of Science and Technology (TJ-IRB20230647).

Study population

Our retrospective study at Tongji Hospital's Emergency Department, conducted from January 2018 to July 2022, included 1878 patients. This cohort consisted of 313 individuals diagnosed with AD, 1252 general emergency patients without AD, and a specific control group of 313 patients with chest pain. We included all patients hospitalized with a diagnosis of AD during the study period. Exclusion criteria included patients without adequate electrocardiographic data, and those diagnosed by CTA or angiography but without follow-up data.

Data collection and analysis

Data collection focused on ECG features, demographics, biochemical indices, and medical histories of the AD group (Supplementary material, *Appendix 1*). We also compiled data for a control group of 1252 non-AD patients, matched 1:4 with the AD group based on age and sex. An additional control group of 313 non-AD patients with chest pain was also included (Supplementary material, *Figure S1*), confirmed by emergency and ward physicians. We conducted a follow-up of AD patients *via* telephone, with the follow-up period for all participants calculated from the date of diagnosis to the date of death or the end of the study, with a median duration of 21.3 months; the interquartile range (IQR) was approximately 15.51 months (11.6 months, 27.1 months). To address the problem of missing data during the follow-up period, we utilized Multiple Imputation by Chained Equations (MICE) [22]. We defined death as the endpoint event.

ECG data

For our study, we analyzed each patient's first pre-treatment ECG, recorded at 500 Hz using a Philips PW TC10 and stored in XML format. ECG interpretations were performed manually by experienced cardiologists. Our dataset included 1878 ECGs, encompassing records from both AD and

Table 1. Comparison of the characteristics of aortic dissection (AD) patients and non-AD patients

Variables	AD (n = 313)	Non-AD (n = 1252)	*P*-value
Age, year, mean (SD)	59.1 (12.9)	59.1 (13.2)	0.9
Female, n (%)	58 (18.5)	233 (18.6)	0.87
BMI, mean (SD)	25.6 (3.9)	24.9 (4.2)	0.21
Body temperature, mean (SD)	37.2 (0.8)	37.1 (0.9)	0.82
SBP, mm Hg, mean (SD)	142.2 (25.9)	131.6 (27.5)	<0.001
DBP, mm Hg, mean (SD)	82.1 (17.2)	72 (16.3)	<0.001
Hypertension, n (%)	269 (85.9)	642 (51.3)	<0.001
Diabetes, n (%)	176 (56.4)	760 (60.7)	0.18
Hyperlipidemia, n (%)	266 (85.2)	806 (64.4)	<0.001
Renal insufficiency, n (%)	101 (32.2)	81 (6.5)	<0.001
Coronary artery disease, n (%)	83 (26.8)	60 (4.8)	<0.001
Cerebrovascular disease, n (%)	9 (2.8)	20 (1.6)	<0.001
Respiratory system diseases, n (%)	24 (7.6)	99 (7.9)	0.74
Digestive system diseases, n (%)	11 (3.5)	102 (8.2)	<0.001
Trauma or injury, n (%)	2 (0.6)	114 (9.1)	<0.001
Smoke, n (%)	220 (70.3)	895 (71.5)	0.36
Alcohol, n (%)	223 (71.2)	881 (70.4)	0.41
Hospital death, n (%)	17 (5.4)	18 (1.4)	<0.001

Values are mean (SD) or n (%)

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; SD, standard deviation

non-AD patients. The samples were divided into training and validation sets in a 7:3 ratio, with no overlap.

Model development and performance evaluation

We employed a CNN as the primary architecture for our deep learning model to extract features from the 12-lead ECGs (detail in Supplementary material, *Appendix 2* and *Figure S2*). The model's training process involved optimization and adjustments to improve AD diagnosis accuracy. A 10-fold cross-validation method was used to ensure the model's robustness. To further evaluate the effectiveness of our deep learning model in identifying AD, we compared the model's predictive results with the actual diagnostic outcomes. We also conducted model testing with 313 patients experiencing chest pain and 313 patients with AD to evaluate the model's performance in these two specific groups. The model's performance was evaluated using metrics like accuracy, sensitivity, specificity, and the area under the receiver operating characteristic (ROC) curve. In addition to the original 1:4 matched sample set, we also tested 1:1, 1:2, and 1:3 ratios to assess whether there were significant changes in the model's accuracy and stability with different sample sizes and patient proportions.

AADE score and patient characteristics

The model produced an AADE score, reflecting the likelihood of AD on each ECG. We explored correlations of AADE scores with patient characteristics, including demographics, biochemical indicators, and D-dimer levels. D-dimer concentrations were divided into four quartiles: low (<0.840 ug/ml), medium (0.840~1.450 ug/ml), medium-high (1.451~5.700 ug/ml), and high (>5.700 ug/ml), The relationship between these concentrations and AADE scores was visualized using box plots, and statistical comparisons were made using the Kruskal-Wallis test.

Statistical analysis

We displayed continuous variables with a normal distribution in the sample information as means (standard deviations). For continuous variables that are not normally distributed, the medians and IQRs from the first quartile (Q1) to the third quartile (Q3) were used for presentation. In addition, we used the Student's t-test to analyze comparisons between the two groups. Categorical data were presented as frequency and percentage and compared using the Chi-squared (χ^2) test and Spearman correlation coefficients for continuous variables, and point-biserial correlation coefficient for binary variables. We employed the Kruskal-Wallis test to compare the distributions of the medians. Additionally, Kaplan-Meier survival curve analysis was applied in our study. In all hypothesis tests, a two-sided significance level of 0.05 was adopted. Histograms were used to plot the classification of ECG features. We used accuracy, sensitivity, specificity, F1 score, and area under the receiver operating characteristic curve (ROC-AUC) to evaluate the generated models. R packages (ggplot2, pROC, survminer) were used for statistics and plotting. *P*-value <0.05 was considered statistically significant, all tests were two-sided.

RESULTS

Study population characteristics

In this study, we compared the clinical characteristics of 313 patients with AD with 1252 non-AD patients (Table 1). Our findings showed differences in average age (59.1 years)

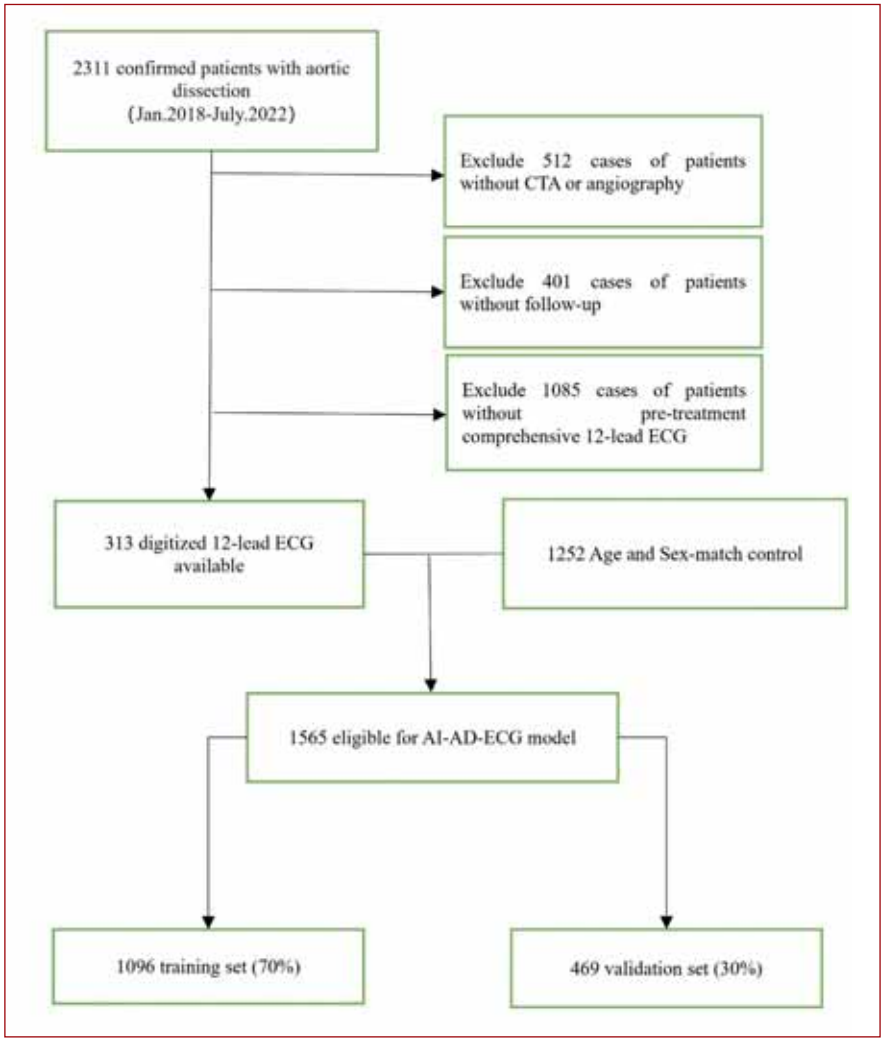


Figure 1. Study flowchart

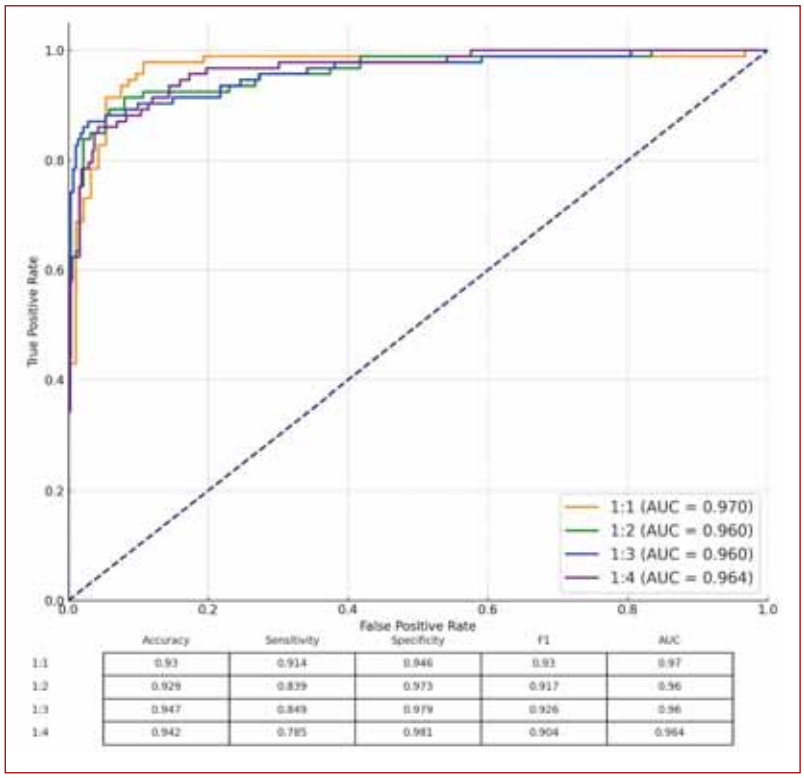
Abbreviations: AD, aortic dissection; CTA, computed tomography angiography; ECG, electrocardiogram

and sex distribution (approximately 18.5% female) between the groups (*P*-values of 0.9 and 0.87). However, disparities were noted in several key health indicators. Specifically, the AD group exhibited higher mean systolic blood pressure (142.2 mm Hg vs. 131.6 mm Hg), mean diastolic blood pressure (82.1 mm Hg vs. 72 mm Hg), prevalence of hypertension (85.9% vs. 51.3%), hyperlipidemia (64.4% vs. 85.2%), and renal insufficiency (32.2% vs. 6.5%), compared to the non-AD group (all P <0.001). Additionally, the incidence of coronary artery disease and cerebrovascular disease were higher in the AD group than in the non-AD group (P <0.001). In the non-AD group, there was a higher incidence of digestive system diseases, trauma, or injuries (P <0.001), which may be associated with diversity of emergency department patients. However, there were no differences between the groups in the prevalence of diabetes, incidence of respiratory system diseases, smoking and drinking habits (*P*-values of 0.18, 0.74, 0.36, and 0.41, respectively). We analyzed the ECG characteristics of the 313 AD patients (Supplementary material, *Figure S3*).

These findings indicate that, while patients with AD and the emergency department control group were similar in certain baseline characteristics, there were significant differences in blood pressure, prevalence of chronic conditions and specific diseases, as well as hospital mortality rates.

Model performance

The CNN demonstrated excellent performance as a model within the validation group. We selected a control group of patients (n = 1252) that matched the age and sex of the AD patients (n = 313) and used a standard 10-second 12-lead ECG full model. We tested the model with control group ratios of 1:4, 1:3, 1:2, and 1:1, using an AADE score of 0.5 as the optimal threshold for diagnosing AD. Performances of all four models were good. We compared the AUC by calculating the model's accuracy, sensitivity, specificity, and F1 value (Figure 2). The 1:1 model showed an accuracy of 0.93, sensitivity of 0.914, specificity of 0.946, F1 value of 0.93, and an AUC of 0.97, all superior to other models' ratios, demonstrating that the AADE score's diagnostic effect is best at a 1:1 match. The CNN generated an AADE score, a continuous value between 0 and 1, indicating the estimated likelihood of AD on each ECG. Furthermore, in the specially introduced control group (Supplementary material, *Figure S4*) designed to enhance the model's



	Accuracy	Sensitivity	Specificity	F1	AUC
1:1	0.93	0.914	0.946	0.93	0.97
1:2	0.929	0.839	0.973	0.917	0.96
1:3	0.947	0.849	0.979	0.926	0.96
1:4	0.942	0.785	0.981	0.904	0.964

Figure 2. Performance of artificial intelligence algorithms in detecting aortic dissection. The ROC curves represent four lines corresponding to random matching with different ratios (1:1, 1:2, 1:3, and 1:4) based on age and sex

Abbreviation: AUC, area under the curve

adaptability to clinical scenarios (the cohort with chest pain, n = 313), the model also demonstrated satisfactory performance, albeit slightly reduced. Within this group, the model achieved an accuracy of 0.871, a sensitivity of 0.837, a specificity of 0.903, an F1 score of 0.867, and an AUC of 0.92 (Supplementary material, *Figure S5*).

Comparison of accuracy indicators for AADE groups and distribution of D-dimer

We collected the demographic characteristics information (Supplementary material, *Table S1*) and ECG features (Supplementary material, *Figure S6*) of the validation group. Assessing the correlation coefficients (r) between the AADE score and several laboratory-test-based markers of AD severity, we found that the AADE score positively correlated with AD type (P = 0.02) (Table 2). This means that an increase in these factors may be associated with an increase in AADE. Other variables, including sex, age, smoking, alcohol, height, weight, blood pressure, etc. showed no statistical correlation with AADE. Among the laboratory tests, D-dimer showed a difference in the risk score (Table 2).

Figure 3A depicts AADE score distributions across D-dimer groups. The median score increased from the low (<0.840 ug/ml) to medium (0.840~1.450 ug/ml) D-dimer groups (P = 0.04), remained stable for medium and medium-high (1.451~5.700 ug/ml) groups, but rose in the high group (>5.700 ug/ml, 0.983) compared to both low (P = 0.005) and medium-high groups (P = 0.003). Furthermore, the type A dissection group exhibited a higher median AADE score (0.985) compared to the type B group (0.823), with a P-value of 0.002 (Figure 3B).

Significant ECG features in the CNN model

To improve the CNN model's interpretability (Figure 4), we found that abnormal ECG was the most strongly correlated feature with the model's predictions (r = 0.384; P <0.001), highlighting ECG significance in the model's decision-making. ST-segment abnormalities (r = 0.302; P = 0.003) and ST-segment depression (r = 0.302; P = 0.003) also demonstrated positive correlations, suggesting their importance in AD diagnosis. Other ECG features, such as anterior and anterolateral wall ST-segment depression, sinus tachycardia, sinus bradycardia, and left ventricular hypertrophy, showed moderate correlations (r ranging from 0.219 to 0.263; P <0.05), indicating their relevance in the model's analysis. A correlation heatmap was created to visually represent these relationships, offering an intuitive view of how the CNN model interprets ECG data.

AD risk prediction according to the AADE score

In the Kaplan-Meier survival analysis depicted in Figure 5, an association was observed between the AADE score and the survival time (P = 0.02), with the high-AADE-score group exhibiting a substantially lower survival rate throughout the follow-up compared to the low-score group. This indicates a more rapid decline in several surviving patients in the high-score group. During the one-year follow-up, the mortality rate in the high-AADE-score group was 31.25%, compared to 10.34% in the low-score group. When the

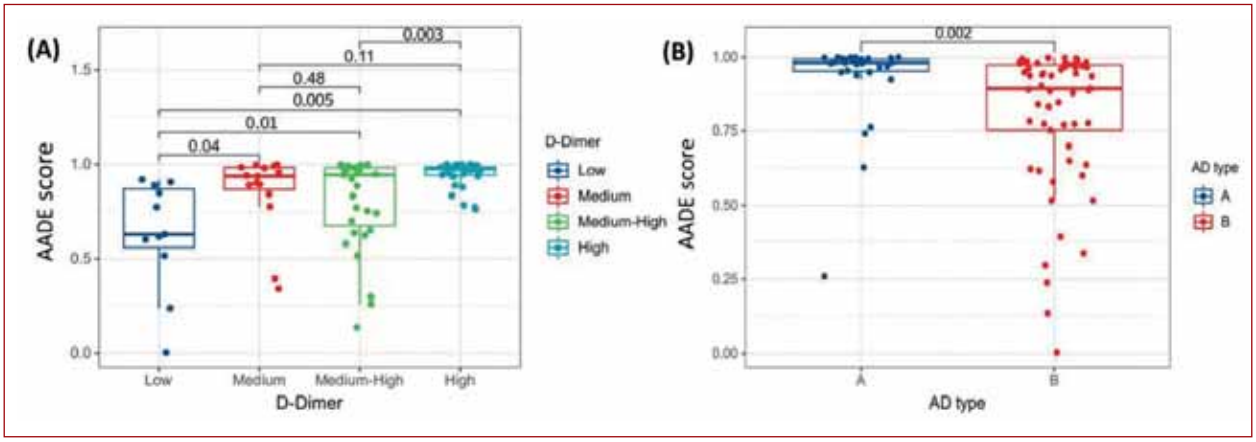


Figure 3. Distribution of AADE score values corresponding to D-dimer and type A and B dissection. **A.** D-dimers are categorized by quartiles on the x-axis. **B.** Types A and B dissection are categorized on the x-axis. The y-axis shows quartile values, with the top, middle, and bottom lines of the box indicating upper quartile, median, and lower quartile, respectively. Lines extending from the box represent the maximum and minimum values, with outliers marked as points outside the box. *P*-values between groups are indicated above the figur

Table 2. Correlations between AADE scores and clinical variables

Variable	Correlation coefficient	*P*-value
Sex	–0.076	0.47
Age	–0.003	0.97
Smoke	–0.14	0.18
Alcohol	–0.155	0.14
Height	–0.005	0.96
Weight	–0.087	0.41
SBP	–0.015	0.89
DBP	–0.073	0.48
Hospital death	0.084	0.42
Hypertension	0.059	0.57
Diabetes	–0.059	0.57
Renal insufficiency	0.074	0.48
Hyperlipidemia	–0.099	0.35
AD type	0.242	0.02
Creatinine	–0.082	0.44
eGFR	0.079	0.45
CRP	–0.078	0.46
CTn	0.095	0.37
PT	0.085	0.42
Fbg	0.057	0.59
APTT	0.094	0.37
TT	–0.048	0.65
D-dimer	0.322	0.002

Spearman Correlation Coefficients for continuous variables, Point-Biserial correlation coefficient for binary variables

Abbreviations: APTT, activated partial thromboplastin time; CRP, C-reactive protein; CTn, cardiac troponin; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; Fbg, fibrinogen; PT, prothrombin time; SBP, systolic blood pressure; TT, thrombin time

follow-up was extended to two years, the mortality rate in the high-score group rose slightly to 34.38% while in the low-score group, it remained stable. This means that the risk of death was higher in the high-score group.

DISCUSSION

In our study, we developed a CNN model based on ECG data (see the graphical abstract), which is capable of distinguishing between AD and non-AD ECGs with high accuracy. The results from the special control group further confirm the effectiveness of our model in differentiating between AD and non-AD patients, even among non-AD patients presenting in clinical settings with symptoms of chest pain. The model provides an AADE score that can effectively assess the likelihood of AD on each ECG. The AADE score is correlated with certain laboratory tests and types of dissection. Compared with existing DL research on AD, our study has several significant advantages [23]. Firstly, our model included more patients with AD. Secondly, we identified ECG features correlated with the model, improving the explanatory power of the AI model. More importantly, in our follow-up, we evaluated the mortality risk of patients through the AADE score, which could provide clinicians with a more accurate and comprehensive risk assessment tool.

D-dimer has turned out to be effective in distinguishing AD from other diseases, and its levels were positively correlated with AD mortality risk [24]. However, some AD patients may present negative D-dimer levels [25, 26], which underlines the necessity of utilizing a combination of diagnostic methods for accurate AD detection. Currently, combining the aortic dissection detection risk score and D-dimer offers higher diagnostic accuracy than using single indicators [27], but its sensitivity and specificity for acute aortic syndrome diagnosis fall short of our AADE score model [28]. Our study found a positive relationship between AADE scores and D-dimer distribution, suggesting that higher AADE scores correspond to an increased AD mortality risk. This adds another dimension to diagnostic precision, particularly, in identifying more severe cases of AD. In distinguishing between two AD types, A and B, which present different anatomical and clinical characteristics that affect treatment strategies [29, 30], the AADE score proves valuable. We observed that type-A AD generally scored higher on the AADE scale, indicating the potential use of this model in predicting AD type and thereby guiding treatment decisions.

ECG Features	Correlation Coefficient	P Value
Abnormal ECG	0.384	<0.001
ST abnormalities	0.302	0.003
ST depression	0.302	0.003
Anterior wall ST depression	0.263	0.01
Sinus bradycardia	0.255	0.01
Sinus tachycardia	0.234	0.02
Anterolateral wall ST depression	0.22	0.03
Left ventricular hypertrophy	0.219	0.03
Ventricular premature beats	0.194	0.06
Anterior wall T-wave inversion	0.155	0.14
ST-T abnormalities	0.153	0.14
Inferior wall ST depression	0.138	0.18
Inferior wall T-wave inversion	0.138	0.18
Left anterior fascicular block	0.132	0.21
Anterolateral wall T-wave inversion	0.13	0.21
ST elevation	0.085	0.42
T-wave inversion	0.083	0.43
Lateral wall ST depression	0.07	0.50
T-wave abnormalities	0.065	0.53
Left atrial overload	0.015	0.88
Atrial premature beats	0.014	0.89
Atrial fibrillation	-0.05	0.63
First-degree atrioventricular block	-0.066	0.53
Lateral wall T-wave inversion	-0.12	0.25
Right bundle branch block	-0.123	0.24

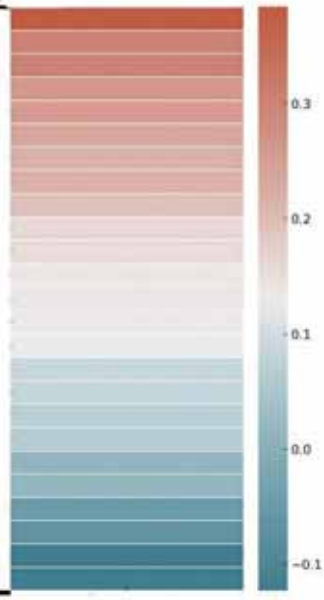


Figure 4. Correlations between AADE scores and ECG features. The figure includes a table and heatmap, illustrating Spearman correlations between AADE scores and ECG features. The table lists correlation coefficients, while the heatmap visually displays correlation strengths using color intensity.

Abbreviations: see Figure 1

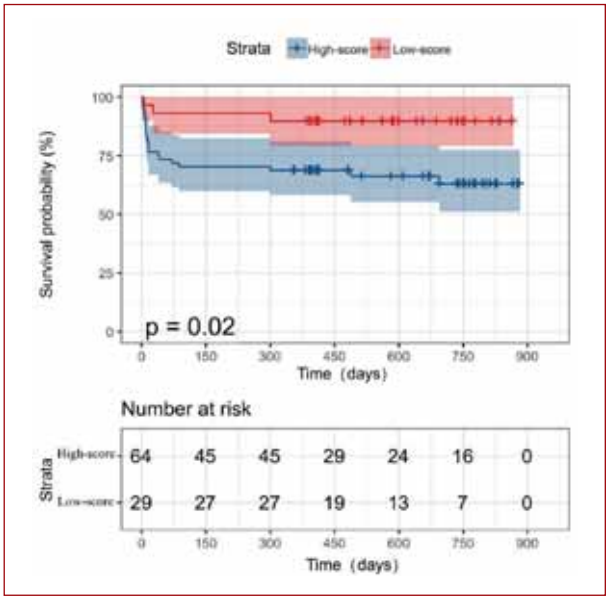
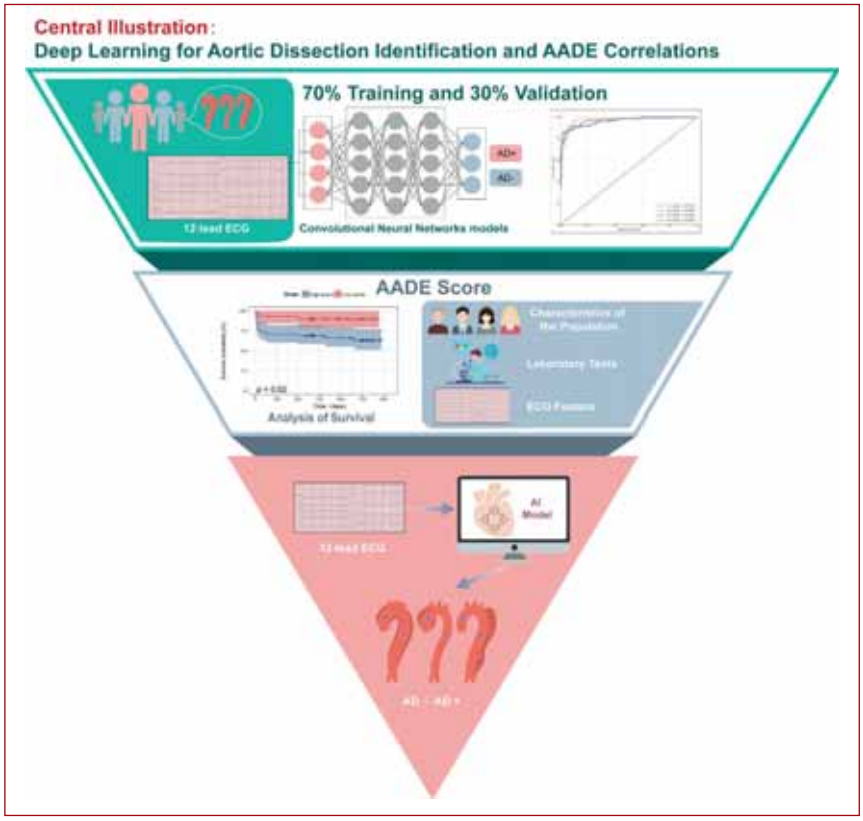


Figure 5. Aortic dissection Kaplan-Meier Survival Estimates. Kaplan-Meier survival estimates for high- and low-AADE-score groups, with survival probabilities from 0 to 100%. Participant numbers at risk are shown for 0, 150, to 900 days of follow-up. The optimal AADE score cutoff is set at 0.86 based on receiver operating characteristic analysis (Youden index, J =sensitivity + specificity – 1). Patients are classified into high and low-score groups.

Despite the lack of interpretability inherent to CNN models due to their "black-box" nature, our research utilizes advanced AI methods to discern strong AD signals on ECG and quantify these in relation to aortic risk levels. This not only boosts model interpretability but may also influence future clinical practices and studies. We discovered positive correlations between the AADE score and several ECG features including abnormal ECG, sinus tachycardia, sinus bradycardia, and ST-segment depression. Interestingly, while T-wave inversion was common, it showed no correlation with the AADE score, unlike ST-segment depression, which was the most closely linked. This suggests that, for ECG examinations of AD patients, ST-segment depression, particularly in anterior and anterolateral walls, could be a critical feature for the AI model to identify AD. However, the exact mechanism behind the link between ECG ST-segment changes and AD occurrence remains unclear [9], and further research is required to explain these potential connections.

In conclusion, our research shows that a CNN-based AI model can effectively distinguish between patients with and without AD based on 12-lead ECG data. In patients with chest pain, the model also demonstrated stable performance. After training at different ratios, the performance of the model was maintained, and the AI model indicated an AADE score related to the probability of assessing the risk of disease. Moreover, our study showed correlations between the AADE score and ECG features, D-dimer, and AD type. During the one and two-year follow-up periods, the mortality rate of the high-scoring group was significantly higher than the low-scoring group, indicating a significant association between the AADE score and the patient's survival period. This suggests that the AADE score is an important prognostic factor that may impact AD patients survival. These findings may provide valuable information for clinicians assessing the risk and severity of AD and help to diagnose and manage AD patients more accurately.



Graphical Abstract. Convolutional neural network models applied to electrocardiograms to diagnose aortic dissection (AD)

Early detection and timely treatment of AD are crucial for improving patient survival rates [31]. Our model can assist lower-level hospitals in rapid diagnosis of dissection without CTA. This can facilitate swift transfers to higher-level hospitals for further diagnosis and treatment and help avoid severe consequences of incorrect treatment. Additionally, in circumstances where patients have contraindications to CTA, including renal insufficiency, this algorithm can be useful in distinguishing a specific population that requires special attention. In the future, this model could be used to develop wearable devices to identify AD patients in non-hospital settings, aiding their swift triage.

Limitations

Our study has some limitations, including a small sample size that may affect reliability and generalizability of the results, and there is a necessity for larger studies. Its single-center nature and exclusion of certain patients limited its scope, highlighting the need for multi-center validation and more inclusive patient selection. Additionally, the study was retrospective, and future prospective studies could enhance the efficacy of this AI model.

Supplementary material

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

Article information

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Extra-anatomical bypass operation in patients with unilateral graft limb occlusion after endovascular aneurysm repair for abdominal aortic aneurysm

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INTRODUCTION

Femorofemoral crossover bypass is performed in high-risk patients who are not candidates for invasive open surgery due to comorbidities that exclude them from the procedure and in patients with critical limb ischemia or intermittent claudication where anatomic constraints exclude them from endovascular procedures to re-establish in-line flow [1].

An abdominal aortic aneurysm (AAA) is an abnormal dilatation of the abdominal aortic diameter by more than 50%, which is irreversible and permanent [2, 3]. Following endovascular aneurysm repair (EVAR) for AAA, graft limb occlusion is a serious and severe complication [4].

The management options for symptomatic patients with graft limb occlusion are endovascular or surgical. The endovascular options include thrombolytic therapy, angioplasty with or without stenting, and rheolytic therapy, whereas surgical treatment includes thrombectomy or extra-anatomical bypass in the form of femorofemoral crossover bypass. Each treatment option has its drawbacks and should be tailored to each patient.

Thrombolysis therapy can be complicated by hemorrhages, a new endoleak due to thrombus lysis in the aneurysm sack, and leg embolism. It is also time-consuming. On the other hand, surgical thrombectomy has disadvantages such as thrombus migration in the contralateral limb and hypogastric artery, component separation in modular devices, and stent-graft dislodgement [5].

The main objective of our study was to determine the durability of an extra-anatomical femorofemoral crossover bypass procedure in patients with unilateral graft limb occlusion after EVAR for AAA over a 20-year period.

METHODS

From January 2001 to March 2021, 1611 AAA patients were treated with EVAR using a bifurcated stent graft at the Department of General, Endocrine and Vascular Surgery at the Independent Public Central Clinical Hospital in Warsaw, Poland. A total of 33 high-risk patients (American Society of Anesthesiologists [ASA] class III and IV) required an extra-anatomical procedure in the form of femorofemoral crossover bypass due to occlusion of one of the limb branches of the bifurcated stent graft. Patients were included in the study continously and all primary procedures carried out were elective. Patients were re-examined at one month, 6 months, and one year, and then every year afterward, with clinical examination and a computed tomography scan. Four patients died during the follow-up period; all deaths were cardiac-related.

Commercially available devices that were used included Zenith (Cook Medical, Bloomington, Ind), Endurant (Medtronic, Minneapolis, MN, US), and Excluder (W. L. Gore & Associates, Newark, DE, US). Of the 33 patients that had a graft limb occlusion; one patient had an Endurant stent graft and the remaining patients had Zenith stent grafts. The choice of stent graft type was based on institutional practice and vascular surgeons' preference and depended on the technical aspects of the procedure.

The AAA diameter range was from 48 mm to 75 mm. The aortic bifurcation diameter range was from 21 mm to 40 mm. The right

and left iliac diameter range was from 10 mm to 46 mm and from 10 mm to 87 mm, respectively. Six mm, 7 mm, and 8 mm prostheses were used.

Computed tomography angiography was used to determine the occurrence of an occlusion. Patient operative details, immediate and long-term clinical outcomes, aneurysm characteristics, perioperative arteriograms, and computed tomography scans were stored prospectively in a dedicated database and analyzed retrospectively. An extra-anatomical procedure was performed when the patient was symptomatic. Patients were found to have an occluded graft limb when they presented with claudication or acute limb ischemia to the accident and emergency department or during their follow-up appointment.

Ethics

The study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the Bioethics Committee at the Medical University of Warsaw (AKBE/108/2022) in Warsaw, Poland. The need for informed consent was waived owing to the retrospective study design.

Statistical analysis

Statistical analysis was performed using STATISTICA for Windows software (StatSoft, Inc.). Patients were considered the unit of analysis for clinical data analysis. The Kaplan-Meier method was used to show the percentage of patients free from secondary intervention and the percentage of patients with patent grafts including secondary interventions.

RESULTS AND DISCUSSION

A total of 1611 AAA patients were treated with EVAR using a bifurcated stent graft. This study included 33 high-risk patients (2.05%), ASA class III and IV (30 men; mean [SD] age 70 [7.7] years, range 48–90) who required an extra-anatomical procedure in the form of a femorofemoral crossover bypass due to unilateral graft limb occlusion of the bifurcated stent- graft.

In seven patients, femorofemoral crossover bypass failed due to occlusion during the follow-up period. Five patients had thrombectomy, one patient required an above-the-knee amputation of the right leg due to critical limb ischemia after a failed femorofemoral crossover bypass due to unsuccessful attempts at restoring patency, and one patient was treated conservatively. However, four patients experienced femorofemoral crossover bypass re-occlusion. Two patients required another re-intervention, and the remaining two patients were treated conservatively. One patient had a re-intervention which consisted of an axillo-bifemoral bypass, and the other patient had a successful thrombectomy. In total, three patients were asymptomatic after the occluded femorofemoral crossover bypass was incidentally found on follow-up computed tomography angiography and were treated conservatively.

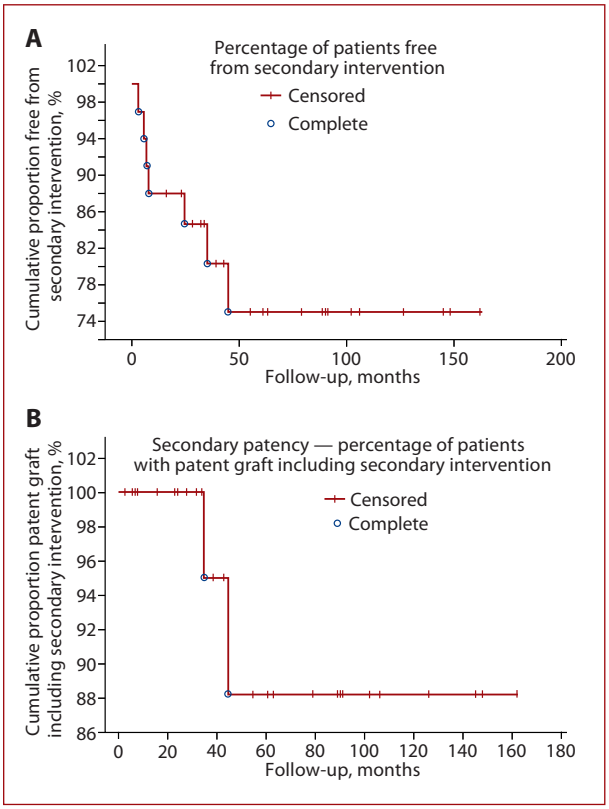

Figure 1. A. Percentage of patients free from secondary intervention. **B.** Percentage of patients with patent graft including secondary interventions

Four patients died during the follow-up period, all due to cardiac-related causes. There were no infections reported during the follow-up period.

Late occlusion (>1 month) occurred in seven patients, whereas early occlusion (<1 month) did not occur in any patient. Primary patency was 78.8% while secondary patency was 90.9%. Kaplan-Meier curves were used to show the percentage of patients free from secondary intervention (Figure 1A) and the percentage of patients with patent grafts including secondary interventions (Figure 1B).

Although EVAR is becoming the preferred treatment for AAA due to its clinical benefits and minimal invasiveness, there is an increase in the number of re-interventions and graft-related complications. Graft limb occlusion presents with severe acute rest pain in the lower extremity which is a significant complication following EVAR [6]. It is one of the top three reasons for readmission to the hospital [7, 8].

Our study shows good primary and secondary patency rates which is consistent with other femorofemoral crossover bypass studies [9, 10]. Our primary and secondary patency rates were 78.8% and 90.9%, respectively. Park et al. [9] showed similar primary and secondary patency rates at 5 years of 70% and 85%, respectively. In a study by Park et al., 32 patients (24%) showed graft occlusion due to thrombosis compared to our study, in which there were as few as 7 such patients (21%). However, our study involved

only 33 patients, whereas Park et al. reported a total of 133 patients, which could account for the difference.

In a study by Ricco et al. [10], primary and secondary patency rates were 71.8% and 89.8%, respectively. Thirty patients (40%) had crossover bypass graft failure; 14 had graft occlusion, 12 had stenosis of the donor iliac artery, and 4 had femoral anastomotic stenosis. However, if we are comparing graft occlusion, Ricco et al. reported 14 graft occlusions (18.9%), which is similar to our study (21%).

In our study, all 33 patients were high-risk patients (ASA class III and IV) with unilateral graft limb occlusion, who presented with either leg claudication or acute limb ischemia. It is our experience, similar to Parent et al. [11], that femorofemoral bypass grafting is frequently required when there is endograft limb occlusion. Femorofemoral crossover bypass is a minor procedure that can be performed under local anesthesia, making it particularly beneficial for patients who are high-risk, are not suitable for major surgery, or have contraindications. In addition, little or no preoperative preparation is required for this procedure to be carried out. All our patients were treated urgently right after unilateral graft limb occlusion, which resulted in continued patency of the limb vessels. However, larger prospective studies are required to validate this hypothesis.

Limitations

This study had several limitations. First, this was a retrospective study, limited by factors inherent in retrospective data analysis and interpretation. Second, the study was based on the experience of one institution with a moderate number of patients.

CONCLUSION

Femorofemoral crossover bypass as an extra-anatomical procedure following unilateral graft limb occlusion should be considered for high-risk patients who are not candidates for major surgery. It is a minor procedure, performed under local anesthesia, with good patency in the long-term and low operative mortality and morbidity.

Article information

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Results of atrial flow regulator implantation in pulmonary arterial hypertension patients with severe heart failure despite maximal medical therapy

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INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare severe progressive disease that leads to right heart failure and, ultimately, death [1]. Failure of medical therapy is an indication for referral for lung transplantation.

Balloon atrial septostomy has been proposed as a palliative measure or a bridge to transplant procedures in patients with PAH and severe heart failure, resistant ascites, and recurrent syncope despite maximal medical therapy.

The main disadvantages of this procedure are restenosis of the interatrial opening and unpredictable shunt size [2]. Recently, an atrial flow regulator (AFR) has been introduced to overcome these problems. The device allows for adjustment of fenestration diameter to interatrial pressure gradient, arterial oxygen saturation (SaO_2), and long-term maintenance of the interatrial shunt.

So far, 2 observational studies have presented the efficacy and safety of the AFR in patients with PAH treated with a combination of an endothelin receptor antagonist and a phosphodiesterase-5 inhibitor [3, 4]. The role of AFR in patients on maximal medical therapy has been reported only in single case descriptions.

In this study, we present the experience of 3 tertiary pulmonary hypertension centers with the use of the AFR in patients with PAH experiencing severe symptoms despite maximal medical therapy.

METHODS

We enrolled all consecutive adult PAH patients referred to 3 pulmonary hypertension tertiary centers in Poland (Krakow, n = 5; Gdansk, n = 2; Poznan, n = 2) for AFR implantation between May 21, 2018 and August 23, 2022 and followed them until September 26, 2022. Eight patients were enrolled in an international prospective clinical trial (THE AFR-PROPHET TRIAL; NCT03022851), and 1 patient received AFR as compassionate treatment outside the trial. We adopted the AFR-PROPHET's inclusion and exclusion criteria (https://clinicaltrials.gov/ct2/show/NCT03022851). In short, patients were eligible if they had recurrent decompensations of heart failure requiring hospital admissions, ascites resistant to treatment, or syncope due to heart failure despite use of conventional treatment.

The following measurements were analyzed: World Health Organization functional class (WHO-FC), N-terminal prohormone of brain natriuretic peptide level, results of 6-minute walk test, transthoracic echocardiography, and right heart catheterization (RHC).

The schedule of assessments (visits 0, 1, and 2) is presented in Figure 1.

AFR implantation was performed through the femoral vein. The procedure included RHC (before and after implantation of the device), atrial septal puncture, and implantation of the device. The AFR device was described by fenestration diameter (D1), diameters of the discs (D2), and waist (h) height. The protocol for AFR implantation followed the manufacturer's instructions.

The categorical variables were presented as n (%) and the continuous variables as medians (interquartile ranges). To assess differences of repeated measurements of continuous variables we used the Friedman test with a post-hoc Wilcoxon matched-pairs signed-rank test for variables measured 3 times and the Wilcoxon matched-pairs signed-rank test for variables measured twice. Exact McNemar's test was used to assess differences in repeated categorical variables. The significance level was set at $\alpha = 0.05$. The institutional ethics committee approved the study protocol (94/KBL/OIL/2018, NKBBN/247/2018) and written informed consent was obtained from each patient before the study.

RESULTS AND DISCUSSION

We enrolled 9 (6 men and 3 women) consecutive adult PAH patients from 5 PAH tertiary centers in Poland at a median (IQR) age of 48.6 (30.6–50.3) years. Idiopathic PAH was present in 6 patients, 2 patients had PAH associated with congenital heart disease after defect correction, and 1 patient had PAH associated with connective tissue disease. All patients were on the waiting list for lung transplantation. The median (IQR) time between PAH diagnosis and AFR implantation was 4.1 (1.9–7.5) years.

On enrollment, all patients presented advanced stages of PAH. Two (22%) patients were in the WHO-FC III and 7 (78%), in the WHO-FC IV.

All patients were treated with maximal medical therapy for PAH, including a combination of sildenafil (8 patients [89%]), an endothelin receptor antagonist (bosentan, 6 [67%]; macitentan, 3 [33%]), and prostacyclin analogs (epoprostenol 3, [33%]; treprostinil 6 [67%]). One patient did not receive sildenafil due to intolerance.

The indication for AFR implantation in all patients was severe heart failure with recurrent ascites resistant to diuretics. Patients did not report syncope.

Atrial septostomy was performed using balloons with diameters ranging from 8 to 12 mm. Then, the devices with the following characteristics were implanted: D1 of 6 mm and D2 of 18 mm in 7 (78%) patients; D1 of 8 mm and D2 of 21 mm in 2 (22%) patients.; h of 5 mm in 9 (100%) patients. The median (IQR) fluoroscopy time was 22 (18–30) minutes. The median (IQR) time of hospitalization after the procedure was 9 (4–12) days. Immediately after the procedure, a median (IQR) drop in SaO2 of 2 (0–4) percentage points was observed. We did not observe any other significant complications. All patients were prescribed 75 mg/d clopidogrel for 3 months starting from the day of AFR implantation.

On visit 2, echocardiography showed continuous right-to-left flow through AFR in all patients. Ascites reoccurred in 4 patients but only in those who had the smaller fenestration diameter (D1 = 6 mm). Despite significant hypoxia, exercise tolerance was maintained or improved probably due to increased cardiac output. Compared with baseline, the number of patients in WHO-FC IV decreased to 1, and apart from that person, all other patients remained in or improved their WHO-FC III ($P = 0.03$) while the median of 6-minute walk distance increased in the study group (Figure 1). The median (IQR) doses of diuretics tended to decrease as follows: furosemide by 60 (0–20) mg (38% [0%–51%]); ($P = 0.1$), torasemide by 10 (0–35) mg (17% [0%–35%]); ($P = 0.05$), and spironolactone by 50 (0–50) mg (50% [0%–50%]); ($P = 0.05$).

Changes in hemodynamic and clinical parameters from baseline (V0) to visit 2 (V2) in each study participant are presented in Figure 1. In Supplementary material, *Figure S1* presents changes in liver and kidney function parameters.

During the median (IQR) follow-up of 307 (111–413) days, 4 patients (44%) died due to progression of heart failure and 2 (22%) underwent lung transplantation.

To the best of our knowledge, this is the first study to show that implantation of an AFR in patients treated with maximal PAH therapy improves pulmonary hemodynamics and exercise capacity, reduces ascites, and tends to reduce the need for diuretics.

The positive hemodynamic and functional effects were reached at the cost of arterial blood oxygen desaturation, which was observed immediately after AFR implantation and continued at follow-up. To prevent severe hypoxia, fenestration diameter was selected based on the interatrial pressure and SaO_2. As our patients had low resting SaO_2 and high right arterial pressure before the procedure in most of them, only implantation of devices with a small fenestration diameter of 6 mm was possible. This is in contrast to 2 earlier case series studies, in which fenestrations of 10 mm or 8 mm were chosen in most patients [3, 4]. This difference could be explained by lower baseline right arterial pressure (9.4 [5.0] mm Hg and 10.16 [5.8] mm Hg) and higher resting SaO_2 (96.4% [85.5%] and 98.0% [0.18%]) in those 2 populations as compared with our population. Despite using smaller fenestration diameters in our patients, the increase of the cardiac index was similar in our study and the 2 abovementioned studies.

An unexpected result of our study was a drop in mean pulmonary pressure after AFR implantation. We hypothesize that it could be an effect of blood redistribution and a decrease in sympathetic activity due to hemodynamic improvement. In fact, we observed a decrease in the resting heart rate in the 3-month follow-up.

A recent meta-analysis of 16 studies showed that atrial septostomy is a safe procedure with an early mortality (48 hours) rate of 4.8% [5]. Safety of AFR implantation was

A

	Visit 0	Visit 1	Visit 2
WHO–FC			
6MWD			
NT-proBNP			
RHC			
HR			
SaO_2			

B

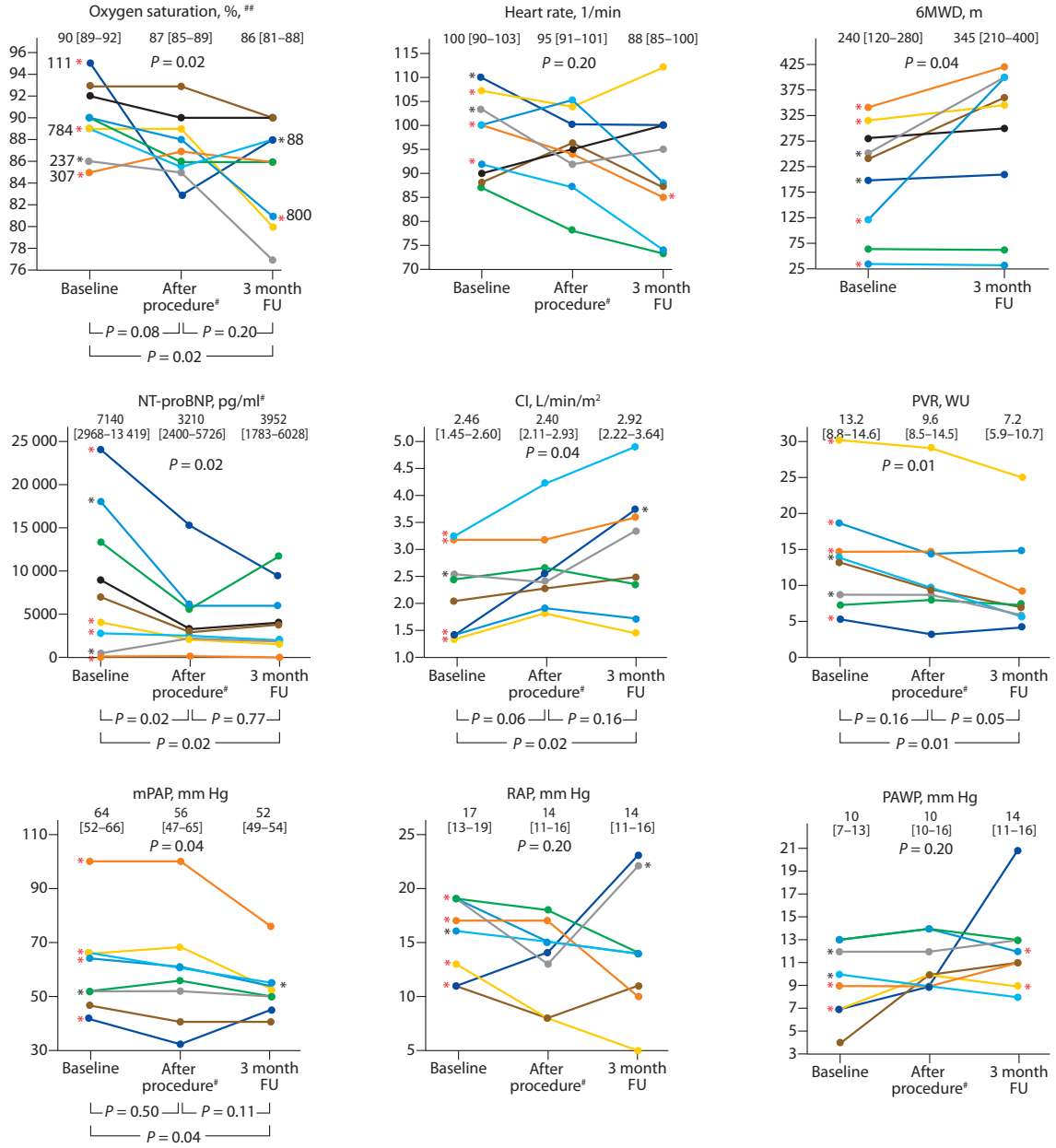

Figure 1. The sequence of measurements (**A**) and the results of atrial flow regulator implantation (**B**). The crossed cells in A denote the tests performed at different time points. The graphs show changes in parameters separately for each patient. Changes in median (interquartile ranges) values are shown above the graphs. Visit 0 denotes the day before AFR implantation; visit 1 is the period from the day of AFR implantation to hospital discharge; visit 2 indicates a follow-up of 3 months after AFR implantation. For variables measured at three time points, the *P* values are presented in red above each graph while the respective *P* values of post-hoc analyses are presented below each graph. Patients who died at follow-up are marked with red * and those who had lung transplantation with black *
Next to the lines denoting oxygen saturation, we added time to transplantation or death (days)
#Visit 1: NT-proBNP, heart rate, and pulse oximetry were measured on hospital discharge while hemodynamic parameters were measured immediately after AFR implantation; ##Pulse oximetry
Abbreviations: 6MWD, 6-minute walk distance; CI, cardiac index; HR, heart rate; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RAP, right arterial pressure; RHC, right heart catheterization; SaO_2, arterial blood oxygen saturation; WHO-FC, World Health Organization functional class

also shown in 2 case series studies [3, 4] and confirmed in our study (no periprocedural deaths). Importantly, all shunts were active during the follow-up period as assessed by echocardiography.

Despite AFR implantation, the long-term mortality rate was high. However, only patients with the most severe end-stage PAH were enrolled, and no further treatment options apart from lung transplantation could have been considered in those cases. Notably, 2 patients survived lung transplantation after AFR implantation.

In conclusion, AFR implantation in addition to maximal medical therapy improves symptoms and hemodynamics in patients with PAH and severe heart failure with resistant ascites. As it is also a safe procedure, it should be regarded as a bridge to transplantation, especially in regions with prolonged lung transplantation waiting times.

Supplementary material

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

Article information

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Decreasing numbers of valve-related infective endocarditis cases. An urgent call to action to improve diagnostic pathways: A retrospective tertiary center perspective (2015–2022)

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INTRODUCTION

Over the last few decades, the number of cases of infective endocarditis (IE) worldwide has been increasing [1] and has doubled over the last 20 years [2]. The widespread use of echocardiography should lead to early diagnosis and implementation of more effective antibiotic therapy. Additionally, improvements in cardiac surgery and intensive care may potentially lower the mortality rate. We carried out an analysis to verify these assumptions in a tertiary center dealing with patients with IE in a stable population of 2.5 million inhabitants. The study aimed to analyze mortality and clinical predictors of death in hospitalized patients with valve-related IE in the years 2015–2022.

METHODS

From all hospital admissions in our Department, we selected patients with acute valve-related IE hospitalized from January 2015 to the end of December 2022 and qualified for both surgical and conservative treatment. Transthoracic and transesophageal echocardiography were basic diagnostic tools for establishing IE diagnosis in all cases. We retrospectively analyzed the total number of cases, number of fatal cases, and in-hospital mortality. We defined preoperative death as death occurring before the surgical procedure (including patients qualified for both conservative and surgical treatment) and perioperative death as death occurring during or after surgical treatment. We analyzed the impact of multiple variables (including clinical features such as sex, IE localization, etiological factors, and the presence of the artificial valve) on in-hospital mortality to find predictors of deaths (also divided into overall, pre-, and perioperative deaths).

Statistical analysis

Statistical analysis was performed using Statistica 13.1 software (Tibco, Palo Alto, CA, US) and R version 4.2.1. Nominal values were presented as both absolute values and percentages. Variables that did not follow normal distributions (as verified with the Shapiro–Wilk test) were presented as medians with interquartile ranges (IQR). In-hospital mortality was presented as a percentage value. Trends in the number of deaths during the analyzed period were assessed using the Mann-Kendall test (to determine the trend) with Sen's slope evaluation (to determine if the trend is positive or negative). Univariate binomial logistic regression was used to assess the impact of specific factors on mortality, divided into overall, pre-, and perioperative mortality. A P-value <0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Overall, 194 patients were hospitalized for acute IE, and the majority of them were men (75.3%; n = 146). The results are presented in Supplementary material, *Table S1*. The median age of the studied group was 62 years, and patients between the ages of 58 and

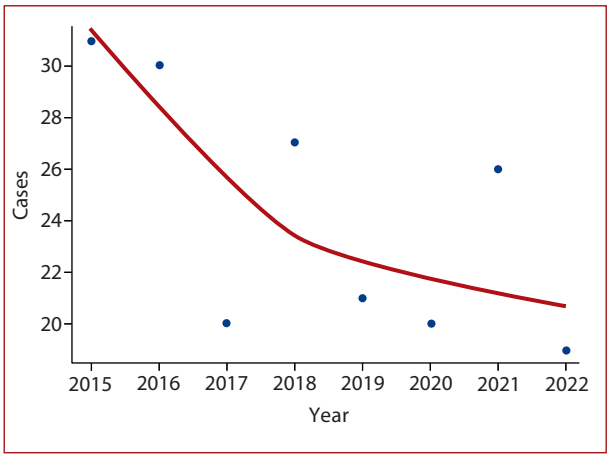

Figure 1. The incidence of infective endocarditis over the analyzed period ($P = 0.046$; Sen's slope: –1.17)

68 were the most numerous group (n = 66). In cases with a confirmed etiological factor (n = 117), the most common causes of IE were *Staphylococcus spp.* (51.3%), *Enterococcus spp*. (22.2%), and *Streptococcus spp*. (15.4%). Left-sided IE was observed in the vast majority of cases (92.3%). Native valve-related IE (NV-IE, 72%) also prevailed. Surgical treatment was performed in 64.9% of patients. Overall, 27.8% (n = 54) of patients died during hospitalization (the preoperative mortality was 14.4%, n = 28). The general trend in the overall number of IE cases significantly decreased over the analyzed period ($P = 0.046$; Sen's slope, –1.17; 95% confidence interval [CI], –3.0 to –0.001; Figure 1), but we observed no change in the number of fatal cases or the mortality rate ($P = 0.618$; Sen's slope, –0.33; 95% CI, –1.5 to –1.8). In 2021, during the COVID-19 pandemic, mortality peaked at 58% (n = 15), which probably interfered with our results. Fatal cases in 2021 were mostly preoperative (60%; n = 9; Supplementary material, *Table S1*).

We also analyzed predictors of in-hospital mortality and found that an unidentified etiological factor in IE significantly increased the risk of death in cases of both preoperative and perioperative deaths (odds ratio [OR], 4.66; 95% CI, 1.07–20.23; $P = 0.04$). Moreover, we found *Staphylococcus spp*. as a perioperative predictor of in-hospital death (OR, 0.16; 95% CI, 0.04–0.071; $P = 0.02$), along with the number of infected valves (OR, 2.27; 95% CI, 1.19–6.23; $P = 0.02$) and age as a preoperative predictor of death (OR, 1.04; 95% CI, 1.00–1.07; $P = 0.03$).

Our results show a declining number of IE cases over the analyzed period, while the overall global incidence of IE is increasing [1]. The population we studied is similar to those reported from different European countries in the EURO-ENDO Registry [1] and the LEIOT [3]. The ICE Prospective Cohort Study, which contains data on over 5000 patients with confirmed and suspected IE, also showed similar demographics results (men 69.4%; age 63.7 years; NV-IE 68.3%; *Staphylococcus spp*. as the most frequent etiological factor) [4]. Furthermore, the above-mentioned study highlights a decreasing mortality rate over the last decades despite an increasing complexity of IE cases.

The most worrying result of our analysis, in contrast to global observations, is the decreasing trend in the number of confirmed IE cases. A delay in establishing an IE diagnosis leads to a higher mortality rate, which in our study was, indeed, higher than the one reported in the EURO-ENDO Registry (17.1%) and ICE (19.3%). Healthcare authorities should conduct careful analysis of the management of patients suspected of having IE and the availability of diagnostic tools (such as echocardiography) in hospitals across the region.

The retrospective character of our study is its main limitation. Due to incomplete data, we were unable to analyze the impact of "time from diagnosis to cardiac surgery" on in-hospital mortality. Additionally, the exclusion of device-related IE patients may have impacted our results. However, it is worth noting that the staff of our Department and available equipment as well the number of local inhabitants remained relatively unaltered throughout the study period. Furthermore, the study period started just before the publication of the 2015 IE guidelines (September 2015). Although the diagnostic principles remained constant, we decided to initiate our analysis at the beginning of 2015.

The COVID-19 pandemic also had a significant impact on our study, as we had to pay special attention to patients with elevated body temperature or fever. This may have contributed to the higher number of confirmed IE cases in 2021. Furthermore, the time to diagnose IE was prolonged due to pandemic-related restrictions, which likely led to more complex cases and worse clinical conditions There are inconsistent worldwide data on reported IE cases during the COVID-19 pandemic. For example, Cabral et al. reported an increased number of IE patients during the first semester of 2020 [5], while a Danish study found no difference in IE incidence before and during lockdown. A study by XinPei et al. [6] from Beijing reported a lower number of IE patients admitted to their cardiac surgery department. The above-mentioned study from China also highlighted a higher surgical risk (EuroSCORE II) in admitted patients during the COVID-19 pandemic although this was not associated with higher postoperative mortality. Similar observations were reported from Spain, where fewer IE incidences and fewer cardiac surgeries performed did not impact in-hospital mortality in IE patients [7].

In conclusion, our study shows a decreasing trend in the number of confirmed IE cases in our region, which is at variance with the global trend of increasing IE incidence. Further analysis is necessary to understand the reasons behind this observation and to improve IE diagnostic pathways in the Lodz region. The impact of the COVID-19 pandemic on IE incidence and diagnosis should also be considered in future studies. These findings highlight

the need for continuous monitoring and improvement of IE diagnosis and management to reduce mortality and improve patient outcomes.

Supplementary material

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

Article information

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In patients with systemic lupus erythematosus and antiphospholipid syndrome renal function is associated with endothelial dysfunction and an NT-proBNP increase: Pilot study

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INTRODUCTION

Cardiovascular complications of systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS) are frequent and show specific clinical features, rare in the general population [1, 2]. Hypertension is common among SLE patients as it occurs in up to 56% of this population, almost twice as frequently as in healthy age-matched subjects [3]. The etiology of hypertension in SLE is multifactorial, yet not completely understood. According to the available data, it is not only driven by renal glomerular damage but also renal vascular endothelial dysfunction. However, it may occur in patients without renal dysfunction [4] and is attributed, by some authors, to generalized endothelial dysfunction [5]. Among factors contributing to the development of hypertension, there are also abnormalities in the immune system, and blood pressure (BP) may be influenced by the current state of the disease [6].

Abnormal 24-hour BP pattern in the form of non-dipping is observed in up to 62% of the SLE population already in childhood [7]. Non-dipping is associated with increased arterial stiffness expressed by pulse wave velocity (PWV) and constitutes an independent cardiovascular risk factor [8]. However, to date, no study has evaluated association between endothelial dysfunction and 24-hour BP pattern in adult SLE patients. We aimed to evaluate the association between endothelial dysfunction assessed by the reactive hyperemia index (RHI) and 24-hour ambulatory blood pressure monitoring (ABPM) in patients with SLE and APS.

METHODS

In this prospective observational study, we screened consecutive patients diagnosed with SLE, APS, or both at the Department of Connective Tissue Diseases, National Institute of Geriatrics, Rheumatology and Rehabilitation between 2017 and 2020. The 2012 SLE classification criteria according to SLICC (Systemic Lupus International Collaborating Clinics) were applied [9]. APS diagnosis was verified based on the 2006 APS classification criteria [10]. The exact inclusion and exclusion criteria are described in Supplementary material. Subsequently, all included patients were evaluated at the outpatient center of the First Department of Cardiology, Medical University of Warsaw. Data on medical history, physical examination, cardiovascular risk factors, laboratory results, and treatment were collected. Every patient underwent measurement of digital flow-mediated dilation during reactive hyperemia (EndoPAT®, Itamar Medical, Caesarea, Israel), 24-hour ABPM (Spacelabs Healthcare, US), and simultaneous labora-

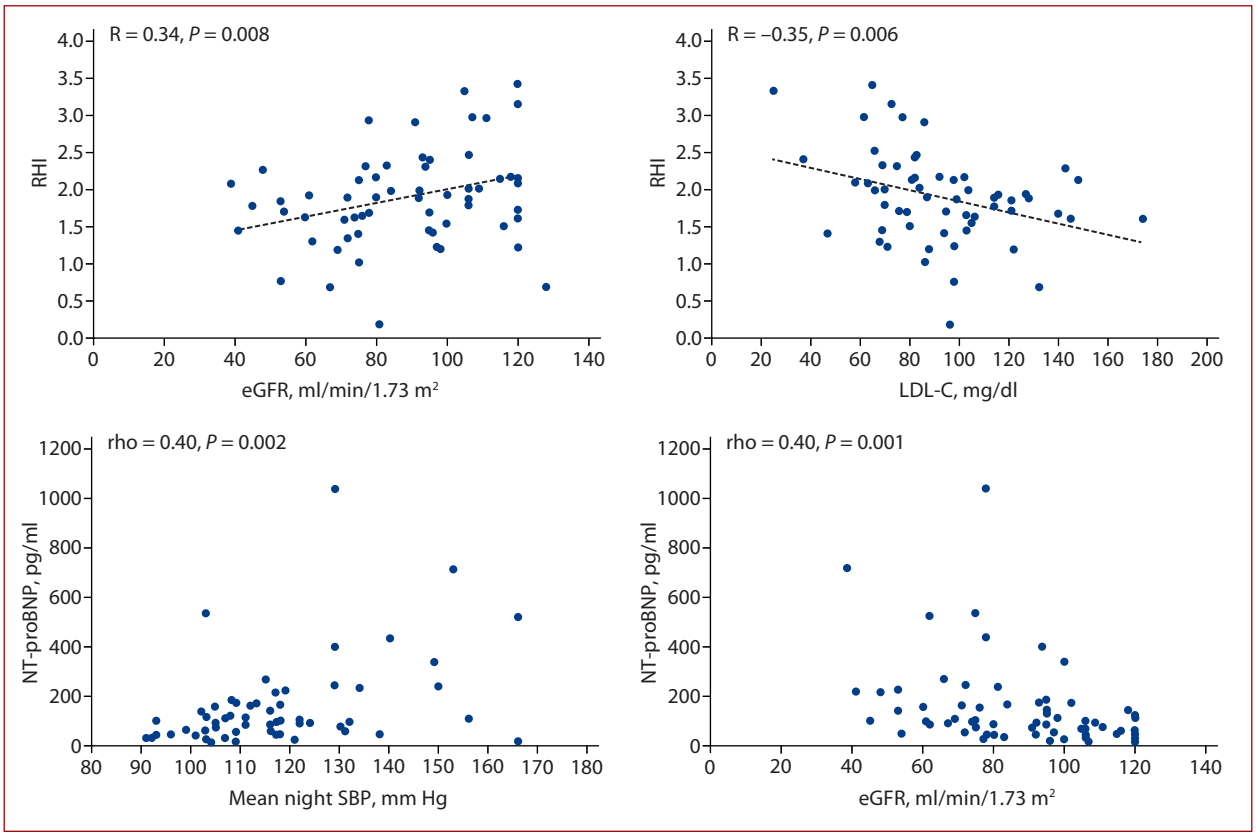

Figure 1. Correlations between investigated variables

Abbreviations: eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; RHI, relative hyperemia index

tory assessment. The study was approved by the ethics committee (no. KB/19/2017) and conducted in accordance with the Declaration of Helsinki. All the included patients signed informed consent.

Statistical analysis

Continuous variables with normal distribution were presented as mean (standard deviation, SD), whereas the median and interquartile range (IQR) were presented in the case of non-normality. Categorical variables were presented as counts and percentages. The Pearson or Spearman correlations were used to investigate the association between numerical variables. Pearson correlation coefficient R and Spearman rho were presented. For categorical variables, Fisher's exact test was used. *P*-values <0.05 were considered significant. All analyses were performed with SPSS (IBM Corp. Released 2022, Version 29.0. Armonk, NY, US).

RESULTS AND DISCUSSION

The study included 66 patients (60 [90%] females, mean age [SD] 42 [13] years). Of them, 50 were diagnosed with SLE (33 without APS, 17 with APS associated with SLE), and 16 with primary APS. Among APS patients (n = 33), 17 (51%) were triple positive and 23 (70%) had positive lupus anticoagulant. Twenty-three of 33 (70%) APS patients had thrombotic APS defined as APS diagnosed on the basis of venous and/or arterial thrombosis and persistent laboratory results for antiphospholipid antibodies (aPL). The mean estimated glomerular filtration rate (eGFR) was 88 (±22) ml/min/1.73 m^2, LDL-C was 93 (±29) mg/dl, and median NT-proBNP was 97 (120) pg/ml.

Overall, the mean RHI in the study population was 1.91 (±0.62). The RHI was abnormal (<1.67) in 21 (32%) patients. Mean daytime systolic blood pressure (mdSBP) was 128 (±15) mm Hg, mean daytime diastolic blood pressure (mdDBP) was 79 (±9) mm Hg, median nocturnal SBP (mnSBP) was 115 (24) mm Hg, and mean nocturnal DBP (mnDBP) was 69 (±11) mm Hg. Non-dipping was observed in 46% of patients. We found no significant correlation between RHI and ABPM values including mdSBP, mdDBP, mnSBP, mnDBP as well as night-day SBP (ND-SBP) ratio and night-day DBP (ND-DBP) ratio.

We evaluated other potential correlates of the RHI with laboratory and clinical variables, and we found a significant correlation between the RHI and eGFR (r = 0.34, *P* = 0.008) and LDL cholesterol (r = –0.35; *P* = 0.006), but no correlation between the RHI and albumin-to-creatinine ratios was observed (Figure 1A, B). Both eGFR and LDL-C correlated with each other significantly; however, the RHI correlated with eGFR also after adjustment for LDL-C (partial correlation R for eGFR = 0.30; *P* = 0.03), and LDL-C correlated with the RHI, also after adjustment for eGFR (partial correlation R for LDL-C = –0.28, *P* = 0.03). The RHI did not correlate with any indices of disease activity such as white blood

cells, C-reactive protein, or erythrocyte sedimentation rate, neither with vitamin D concentrations nor antihypertensive or statin treatment.

We also investigated other potential correlates of BP values. MnSBP (rho = 0.40; $P = 0.002$) and mnDBP (rho = 0.39; $P = 0.002$) as well as the ND-SBP ratio (rho = 0.33; $P = 0.009$), the ND-DBP ratio (rho = 0.37, $P = 0.004$) correlated with NT-proBNP, whereas no other significant correlations between nocturnal BP parameters and remaining variables were found. Other correlates of NT-proBNP included eGFR (rho = –0.40; $P = 0.001$) and age (rho = 0.45; $P = 0.001$).

There were no significant differences between LA-positive and LA-negative APS patient subgroups (Supplementary material, *Table S2*). Moreover, there was no difference between patients with antibodies against beta2-glycoprotein I in class IgG vs. IgM or anticardiolipin antibodies in class IgG vs. IgM with respect to sex, age, RHI, nighttime and daytime BP values, LDL-C, GFR, NT-proBNP, and the prevalence of thrombotic APS.

To the best of our knowledge, this is the first study to assess the relationship between the BP dipping pattern and the RHI in adult SLE patients. We observed that almost half of the study population presented a non-dipping BP pattern. We did not observe a significant association between the ND-SBP/ND-DBP ratio or the RHI in our study population. However, the relationship between the RHI and the BP dipping pattern has been so far evaluated in a small pediatric SLE cohort (n = 18), and the authors found a moderate correlation with the percentage of DBP dipping, as well as a moderate association between the percentage of SBP dipping and mean carotid intima-media thickness, which is a marker of subclinical atherosclerosis [11]. We observed that the nocturnal BP and night-day BP ratios were significantly associated with NT-proBNP, and may therefore indicate an unfavorable prognosis [12].

Importantly, we observed that one-third of our study population presented with an abnormal RHI, which is an independent predictor of coronary microcirculation impairment [13]. Similar to our results, the association between the RHI and the lipid profile was described previously in a population of patients with suspicion of coronary artery disease [14], which raises the question of when to start the treatment with statins in the SLE population as no specific recommendations in this population exist.

We found that renal function is significantly associated with the RHI. The relationship between eGFR and the RHI in a population of pre-dialysis chronic kidney disease patients (stages G1–5) was observed earlier [15]. For the first time, we have described this association in a cohort of SLE patients with relatively good renal function, mostly at stage G1 or G2. These data indicate the importance of considering renal impairment as a CVD risk factor in this population.

One limitation of our study is heterogeneity in terms of patients' sex, with the great majority of patients being female. We aim to increase the size of the male subgroup in the ongoing study.

In conclusion, among SLE and APS patients, nocturnal hypertension was frequently observed, and the RHI was found to correlate with renal function and lipid profile. While no association between nocturnal hypertension and endothelial dysfunction was observed in this investigation, nocturnal BP values and the night-day BP ratio, as well as a decline in renal function, were associated with higher NT-proBNP values.

Supplementary material

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

Article information

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Atrial fibrillation: An early marker of ventricular myocardial dysfunction

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INTRODUCTION

Whether patients with atrial fibrillation (AF) and structurally normal hearts carry a higher risk of life-threatening ventricular arrhythmias and sudden cardiac death (SCD) remains currently uncertain [1]. It is possible that factors causing atrial interstitial fibrosis underlying atrial myopathy also impact the ventricular myocardium, creating conditions for ventricular ectopia. In that case, AF could rather imply silent, generalized myocardial dysfunction than isolated atrial myopathy in patients with apparently normal hearts.

In this context, we sought to assess the risk of ventricular arrhythmogenesis in patients with AF in the absence of structural heart disease using ventricular late potentials (LPs) detected by signal-averaged electrocardiography (SAECG).

METHODS

We recruited patients aged 18 to 80 years with documented, permanent, or paroxysmal AF and no apparent organic heart disease, referred to the Electrophysiology Department at the Hippokration General Hospital in Athens from September 2018 until June 2022 for AF evaluation. The demographic and clinical patient data were collected. All subjects were submitted to SAECG according to a previously described protocol [2]. SAECG tests from healthy subjects, used as a control group, were also obtained. The test was considered positive for the presence of ventricular LPs if 2 of the following 3 criteria were met: 1) filtered QRS duration was ≥114 msec, 2) duration of low amplitude signal (LAS) was ≥38 msec and 3) root mean square amplitude of the last 40 ms of the QRS signal (RMS40) was ≤20 μV. The protocol of this prospective, single-center study was approved by the institutional ethics review board.

Statistical analysis

Data analysis was performed using SPSS Statistical Package (version 26.0, IBM Corp., Armonk, NY, US). Descriptive statistics were used for the presentation of baseline characteristics. Continuous variables were expressed as mean values with standard deviation. Categorical variables were expressed as frequencies and percentages. Student's t-test was used for the comparison between continuous variables. Potential correlations were evaluated with Pearson correlation or Spearman rank correlation tests, as appropriate. Categorical data were analyzed with the chi-square test or Fisher's exact test, as appropriate. Control for potential confounding factors was performed with multivariable regression analysis. A two-tailed $P<0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

In total, 158 patients and 45 healthy adults, matched for age, were studied. Their mean age was 65 (13.2) years while 85 (53.8%) patients were men. The majority of patients had paroxysmal AF (96.2%), and only 6 (3.8%) patients had permanent AF. Twelve (7.6%)

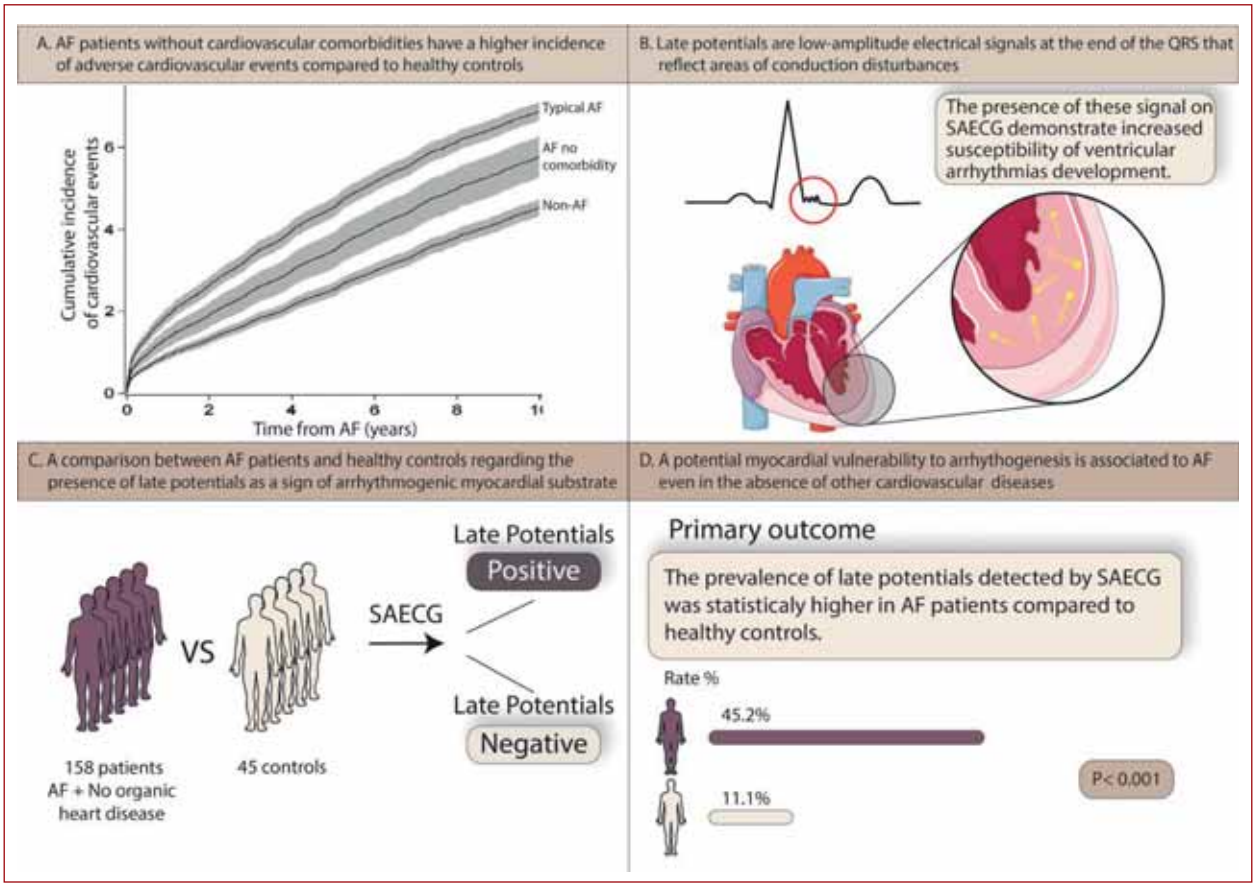

Figure 1. Graphical abstract. The chart presented in quartile (**A**) has been adapted from: Kim et al. Atrial fibrillation without comorbidities: Prevalence, incidence and prognosis (from the Framingham Heart Study). Am Heart J. 2016; 177: 138–144 [3]

Abbreviations: AF, atrial fibrillation, SAECG, signal-average electrocardiogram

patients had undergone one or more catheter ablation procedures for paroxysmal AF, whereas ablation for complex ventricular ectopic activity had been performed in 2 patients. Besides AF, frequent (>1000/24 hours) ventricular contraction or short episodes of non-sustained ventricular tachycardia were detected in 14 (8.8%) patients on 24-hour Holter monitoring. Baseline and demographic data are summarized in the Supplementary material, *Table S1*.

Most patients were on antiarrhythmic medication for sinus rhythm maintenance. Sixty-one (38.5%) patients were in treatment with flecainide, 24 (15.4%) on amiodarone, 18 (11.5%) on propafenone, and only 6 (3.8%) were treated with sotalol.

Concerning SAECG tests, a significantly higher proportion of AF patients met either 2 or 3 criteria for the diagnosis of ventricular LPs compared to the control group (72 [45.2%] vs. 5 [11.1%]; P <0.001). Most patients in flecainide treatment had at least 2 positive criteria for LPs (60.6%) (Figure 1). Nevertheless, no significant correlation between flecainide treatment and a positive SAECG test for LPs was observed (P = 0.379).

The principal findings of our study can be summarized in the following way: 1) Patients with a history of AF and normal heart structure had a higher prevalence of ventricular LPs compared to healthy controls, as detected by SAECG, and 2) treatment with antiarrhythmic drugs may induce the development of LPs but cannot completely explain their high prevalence in this population.

The association of AF with development of life-threatening ventricular arrhythmias is controversial, particularly in the absence of structural heart disease. A recent analysis of a Korean nationwide database including approximately 10 million patients, demonstrated an association of new-onset AF with 4.6-fold increased risk of ventricular tachyarrhythmia over a 10-year follow-up [3]. While evidence in this field is scarce, the precise pathogenetic mechanisms that could explain the link between AF and ventricular arrhythmias in the absence of organic heart disease are yet to be investigated. On the other hand, a link between AF and heart failure has been previously established. More specifically, in patients with heart failure, AF is considered a marker of a more advanced ventricular dysfunction as well as a predictor of worse clinical prognosis. In the presence of impaired left ventricular systolic function, AF and an elevated heart rate have also been identified as independent predictors of concomitant right ventricular dysfunction, which may also constitute another marker of advanced heart failure [4]. A holistic and multidisciplinary

approach, including regular assessment of left ventricular function as well as management of comorbidities, is, therefore, of crucial importance in AF patients [5].

There is a growing recognition that atrial myopathy characterized by atrial fibrosis is strongly related to the development of AF, especially in the absence of other prominent risk factors [6]. Multiple factors have been proposed as potential contributors to atrial remodeling, including intrinsic cardiac aging, oxidative stress, inflammation, and abnormal intracardiac pressures [7]. The same processes may account for pathologic changes in the ventricular myocardium, such as scar tissue formation, which gives rise to ventricular arrhythmogenesis. Another possible explanation is that genetic variations affect both the atria and ventricles and, hence, result in the development of both AF and ventricular arrhythmias. Specific genetic variations underlying the phenotypic expression of channelopathies or cardiomyopathies have been found to play a role in AF pathogenesis [8].

The increased prevalence of LPs in AF patients, compared to healthy controls, could indicate co-existing, clinically silent, dysfunction of the ventricular myocardium. LPs represent low-amplitude electrical signals at the end of the QRS complex that arise from areas of the slowly depolarizing myocardium and are considered to form a substrate for ventricular arrhythmogenesis. Obtained by signal-averaging techniques, LPs represent a recognized, non-invasive marker for the prediction of potential arrhythmic events [9]. Their prognostic value has been more thoroughly investigated in coronary artery disease and arrhythmogenic right ventricular cardiomyopathy, while their role in nonischemic cardiomyopathy is currently limited [10]. At the moment, though, the observed association between AF and the presence of LPs on SAECG does not necessarily establish a cause-effect sequela.

Class I antiarrhythmic drugs commonly used for rhythm control in AF, reversibly bind to and block fast sodium channels, thereby reducing cardiac conduction velocity. Sodium channel blockers have been found to selectively prolong QRS LPs due to preferential effects on the slowly conducting myocardium [11]. That means that they induce a more pronounced conduction delay in cardiac tissue with decreased baseline conduction velocity compared to cardiac tissue with normal baseline conduction. In fact, when studied in patients with symptomatic and repetitive ventricular arrhythmias, propafenone, mexiletine, and flecainide produced significant changes in SAECG parameters, unrelated to their antiarrhythmic efficacy. Moreover, in a study of 25 patients, flecainide induced significant changes to SAECG indices regardless of the underlying disease or a history of ventricular tachycardia [12] Whether such SAECG changes indicate a greater risk of ventricular arrhythmogenesis, reflecting a proarrhythmic activity of the specific drug, especially in patients with normal heart structure, remains an open question.

Limitations

This study is not without limitations. The relatively small sample size and lack of follow-up data do not allow for drawing valid conclusions about the study hypothesis that should be ideally assessed in a long-term randomized controlled clinical study. Due to missing data, we did not search for imaging or ECG factors that could potentially predict the presence of LPs in our cohort. We acknowledge that LP detection demonstrates a low positive predictive value for arrhythmic events. Yet, SAECG remains an inexpensive, reproducible, and non-invasive tool that provides valuable information regarding the risk of malignant arrhythmic events in various clinical settings.

CONCLUSIONS

Patients with AF and no structural heart disease present more often LPs on SAECG compared to healthy controls, which cannot be solely explained by the use of antiarrhythmic drugs.

Supplementary material

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

Article information

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Differences in early outcomes for left ventricular assist device recipients implanted before and during the COVID-19 pandemic

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INTRODUCTION

Advanced heart failure (HF) affects between 1% and 10% of all HF patients, and its prevalence is increasing. Prognosis is particularly poor, with mortality ranging from 25% to 75% of patients after one year [1]. As advanced HF is severe and progressive, it is of paramount importance that the appropriate timing is found for successful but, otherwise, highly-sophisticated therapies. These interventions are not without risk and entail high costs; they include heart transplantation (HTX) or implantation of left ventricular assist devices (LVADs). Over the years, LVADs have become a mature and effective option in selected patients with advanced HF [1]. Ever since the first cases of the coronavirus disease (COVID-19) were reported at the end of 2019, the pandemic has continued to spread globally, profoundly impacting healthcare systems worldwide. Presently, it is unknown to what extent LVAD programs and the qualification process for patients have been affected during the COVID-19 outbreak. Since the introduction of an LVAD program at our center, more than 100 patients have undergone LVAD implantation. As in other centers, our experience has substantially accumulated over the years, clearly indicating a "learning curve" [2]. Thus, for the first time, we present an analysis of the impact of COVID-19 on the LVAD program.

METHODS

This is a single-center observational study. The study population involved all of the 104 patients who were implanted with an LVAD in Krakow, Poland, including 73 patients implanted between 20th October 2015 (first LVAD implantation) and 31st December 2019 (i.e., the pre-COVID-19 period), and 31 patients implanted from 1st January 2020 to 31st December 2021 (i.e. during the COVID-19 period). Patient demographics, clinical characteristics, laboratory, echocardiographic, management, and outcomes were extracted from the electronic medical records. Follow-up data were collected through June 2022. The main outcomes of our study were survival rate, number, and reasons for urgent hospital admissions, including right heart failure, drive line infections, stroke, LVAD thrombosis, gastrointestinal bleeding, and serious ventricular arrhythmia (ventricular tachycardia/fibrillation). The study was approved by the relevant ethics committee (number 1072.6120.253.2021).

Statistical analysis

Continuous data were presented as means (standard deviations) or medians with interquartile ranges. The normality of distribution of variables was assessed with the Shapiro-Wilk test. Comparisons of laboratory, clinical, echocardiographic, and hemodynamic

Table 1. Six-month outcomes for LVAD recipients

Parameter	Pre-COVID-19 group (n = 73)	COVID-19 group (n = 31)	*P*-value
Survival rate, n (%)	60 (82.2)	23 (74.2)	0.23
Death during hospitalization for implantation, n (%)	10/13 (76.9)	6/8 (75)	0.32
Number of patients hospitalized for LVAD-related causes, n (%:)	21 (35)	15 (65.2)	**0.03**
RHF	**6 (28.6)**	**13 (86.7)**	**0.007**
Drive-line infection	9 (42.9)	1 (6.7)	0.15
Stroke	1 (4.8)	0	0.72
LVAD thrombosis	0	1 (6.7)	0.28
Gastrointestinal bleeding	3 (14.3)	0	0.37
VF/VT	2 (9.5)	0	0.52
NYHA, median (IQR)	1.5 (1–2)	2.5 (1.5–3.0)	0.007
NYHA, n (%)	I — 22 (36.7)	I — 3 (13.0)	<0.001
	II — 27 (45.0)	II — 2 (8.7)	
	III — 8 (13.3)	III — 13 (56.5)	
	IV — 3 (5.0)	IV — 5 (21.7)	
NYHA III–IV, n (%)	11 (18.3)	18 (78.3)	<0.001
NT-proBNP, pg/ml median (IQR)	1386 (745–2315)	**2721.5 (1274–37 975**)	0.05
Hb, g/dl, median (IQR)	12.6 (11.5–14.2)	12.8 (10.8–13.7)	0.35
PLT, × 10^3/µl, median (IQR)	221.5 (190–265)	256 (197–323)	0.16
INR, median (IQR)	2.3 (2.02–2.74)	1.91 (1.7–2.9)	0.23
LDH, U/L, median (IQR)	399 (318–472)	216 (212–228)	<0.001
eGFR, ml/min/m^2, median (IQR)	71.5 (57–87)	65 (45–105)	0.9
Creatinine, µmol/l, median (IQR)	99 (85–122)	121.5 (99–141)	0.09
Sodium, mmol/l, median (IQR)	140 (138–142)	138 (133–141)	0.06
Potassium, mmol/l, median (IQR)	4.4 (4.1–4.6)	4.9 (4.5–5.9)	<0.001
Aspat, U/l, median (IQR)	25 (20–30)	22.5 (19–28)	0.49
Alat, U/L, median (IQR)	21 (16–30)	17.5 (12–30)	0.36
Bilirubin, µmol/l, median (IQR)	10.9 (7.4–14.9)	8.4 (6.6–13.5)	0.24

Abbreviations: Alat, alanine aminotransferase; Aspat, aminotransferase aspartate; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; IQR, interquartile range; INR, international normalized ratio; LDH, lactate dehydrogenase; LVAD, left ventricular assist device; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; PTL, platelet; RHF, right heart failure; VE, ventricular extrasystole; VT/VF, ventricular tachycardia/fibrillation

parameters between the two groups were conducted with the Mann–Whitney U test or Student's t-test, depending on the normality of the distribution. Categorical data were presented as numbers (percentages), and χ^2 or Fisher's exact tests were used to compare them. Results were considered statistically significant when the *P*-value was <0.05. Statistical analyses were conducted with Statistica 13.1.

RESULTS AND DISCUSSION

The annual number of procedures was similar in both periods. The LVAD recipients during the COVID-19 period were older: mean (standard deviation) 60.6 (8.5) vs. 56.1 (10.2); *P* = 0.02. The etiology of HF differed between the groups: before the COVID-19 pandemic, the majority of patients had HF due to coronary artery disease (CAD; n = 60; 82.2%), with the remaining patients suffering from dilated cardiomyopathy (DCM). However, during the COVID-19 period, there were 18 (58.1%) patients with CAD, and 13 (41.9%) with DCM (*P* = 0.009). Another difference was that more than two-thirds (69.9%) of the patients from the pre-COVID-19 period were in New York Heart Association (NYHA) class IV in comparison to one-third (32.3%) from the COVID-19 period (*P* = 0.02) (Supplementary material, *Table S1*).

There were no differences in terms of the 6-month survival rate: 60 (82.2%) vs. 23 (74.2%) (*P* = 0.23) between patients operated on before and during the COVID-19 pandemic. In both groups, the substantial majority of deaths occurred during hospitalization for implantation (76.9% of all deaths in the pre-COVID-19 and 75% in the COVID-19 periods; *P* = 0.32). Nonetheless, it turned out that more patients from the COVID-19 period required hospitalization in the first 6 months. There were also significant differences among the causes of admissions between the groups, with right heart failure (RHF) as the main cause of hospitalization during the COVID-19 outbreak (13/15 [86.7%] vs. 6/21 [28.6%]; *P* = 0.007) (Table 1). Still, at the 6-month follow-up, patients from the COVID-19 period displayed inferior functional status compared to the pre-COVID-19 group (NYHA class: median [interquartile range] 1.5 [1–2] vs. 2.5 [1.5–3.0]; *P* = 0.007); in terms of the number of patients in NYHA class III–IV (18 [78.3%] vs. 11 [18.3%]; *P* <0.001).

At the beginning of the COVID-19 pandemic, all HTX programs were jeopardized. Bearing in mind the numerous advantages of HTX over LVAD, the fact remains that LVAD pumps are readily available and can be scheduled for implantation whenever needed, a set of circumstances that

will never be the case for HTX. Overall, according to the 12th INTERMACS report, there were 26 688 continuous-flow LVAD procedures in the years 2011–2020, with a precipitous decrease in 2020 due to the pandemic [1]. However, there are also centers, including our own (reporting 16 implants in 2020 and 15 in 2021, which closely parallels the 14–20 annual procedures in 2016–2019) which recorded similar rates of LVAD implantation during the pandemic years [1].

For at least the last 10 years, it has been a common trend worldwide that older patients burdened with more comorbidities have been implanted with LVADs [1]. At the same time, clinical status at the index procedure has gradually become less severe; approximately 10 years ago, the vast majority of patients were in NYHA class IV or INTERMACS 1–2 profile, whereas at present, the majority are in 3–4 INTERMACS [1, 2]. Although we did not observe significant differences in INTERMACS scores between patients from the pre-COVID-19 and COVID-19 periods, before COVID-19, 6 of 73 (8.2%) patients were in INTERMACS 1 while no such patient was implanted during the COVID-19 period. We report that patients implanted during the COVID-19 pandemic were at least four years older than before the pandemic, which reflects a global trend. Importantly, we also observed a significant shift in the HF etiology, which was predominantly CAD before the pandemic; however, during the COVID-19 outbreak itself, the ratio of CAD and DCM etiology was found to be similar.

In the first randomized REMATCH trial (LVAD vs. medical therapy), 1-year survival after LVAD implantation was 52% and only 25% in medically treated patients. In the most recent (pre-COVID-19 years), 1 and 2-year survival soared to 82.8% and 74.1%, respectively; still, this is somewhat inferior to the 1-year survival rate of more than 90% of patients after HTX [1]. Additional data have been provided by Gyoten et al. [3], who recently published 1-, 3-, and 5-year survival rates following LVAD implantation (2009–2020) of 66%, 49.4%, and 37.4%, respectively. To the best of our knowledge, no separate data on survival following LVAD implantation in patients during the COVID-19 pandemic has been published yet. Here, we report a 6-month survival rate of 82.2% and 74.2% in LVAD recipients from the pre-COVID-19 and COVID-19 periods, respectively. Although numerically the 6-month survival rate in patients implanted during the COVID-19 pandemic appears a little worse, it is statistically insignificant and seems to be within an acceptable range.

It is worth noting that the majority of deaths occurred during hospitalization for implantation, which is typical and was also reported previously [2–4]. Unfortunately, complications still occur following LVAD implantation, e.g. in one report from the UK, 5 years after the LVAD procedure, 26.1% of patients suffered a stroke, 23.6% acquired an LVAD-related infection, and 13.4% underwent LVAD re-implantation. Patients implanted during the COVID-19 outbreak were more often hospitalized for LVAD-related complications than those operated on previously. Interestingly, we noticed distinct causes for hospitalization during those two periods. In the pre-COVID-19 period, it was mainly drive-line infections, gastrointestinal bleeding, and strokes with RHF which were found to occur in approximately one-fourth of cases. This was different during the COVID-19 period when it was predominantly RHF which was encountered in more than half of the hospitalized patients. Perhaps, it is too early to draw any firm conclusions, but it may be that right ventricle in older patients is more susceptible to the increased flow created by the LVAD. We also saw that patients from the COVID-19 period more often had atrial fibrillation, a confirmed cause of progressive RHF. It is not surprising that both end-stage HF candidates for LVADs and LVAD recipients are particularly vulnerable to severe and complicated course of SARS-CoV-2 infection as this association has been already demonstrated. Lastly, latent SARS-CoV-2 infections, primarily affecting the lungs, may impose an additional burden on the right ventricle.

In conclusion, we found that LVAD recipients implanted during the COVID-19 pandemic differ significantly from those operated on earlier in terms of numerous variables, including age, HF etiology, and LV diameter. Although 6-month mortality was similar in both groups, patients implanted during the COVID-19 pandemic were more frequently re-admitted for RHF.

Supplementary material

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

Article information

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Serious consequences of enterococcal endocarditis in an active diving instructor

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A 58-year-old man, diving instructor, after two aortic coarctation surgeries at the age 14 and 37, with a history of mild mitral regurgitation (MR), urolithiasis, and urosepsis caused by *Enterococcus faecalis* 10 months earlier, was admitted with anemia, elevated C-reactive protein, D-dimer and N-terminal pro-B-type natriuretic peptide. He reported of recurring fever, sweats, back pain, and exercise intolerance over the last five months. Antibiotics, such as linezolid, vancomycin, and ampicillin with sulbactam were used for 10–14 days, however, the cause of symptoms was still unexplained.

During the same period, the patient suffered an ischemic stroke in the right posterior cerebral artery and a permanent local visual loss.

Currently, blood cultures have shown *Enterococcus faecalis* growth again. Transthoracic echocardiography performed due to a loud systolic murmur showed severe eccentric MR (Figure 1A; Supplementary material, *Video S1*) and transoesophageal echocardiography (TOE) confirmed mitral valve (MV) infective endocarditis (IE) (Figure 1B). Three-dimensional TOE visualized bacterial vegetations up to 8–9 mm long, at the posterior mitral leaflet, a smaller one (4.5 mm) at the anterior leaflet, and a large MR jet (Figure 1C [1, 2]; Supplementary material, *Video S2*). No vegetations were observed at the site of aortic coarctation surgery (Figure 1D).

Contrast-enhanced magnetic resonance of the spine revealed spondylodiscitis infection-related lesions at the levels of Th10/Th11 and Th11/Th12 and an inflammatory infiltrate in the paravertebral soft tissues (Figure 1E). Targeted ampicillin and ceftriaxone therapy, lasting 6 weeks resulted in clinical improvement and vegetation regression on TOE. On positron emission tomography/computed tomography (PET/CT) after 4 weeks, only post-inflammatory lesions in the spine were described (Figure 1F). The patient was discharged in good condition. He underwent MV repair with implantation of a semi-rigid ring and artificial cords to the posterior leaflet.

Enterococcus faecalis is responsible for over 90% of enterococcal IE, and it has been acknowledged in the 2023 recommendations as a typical IE bacterium [1]. Some new registries indicate an increased IE incidence caused by this pathogen [2].

An early IE diagnosis is essential because *E. faecalis* is highly resistant and requires prolonged therapy (up to 6 weeks) of synergistic bactericidal antibiotics [1].

In the described case, the time to establish the correct diagnosis was almost 6 months, so the previous antibiotic therapy time was too short, which resulted in further complications, such as an ischemic stroke, disc inflammation, severe MR, and the need for repeated cardiac surgery.

It is worth noting, that spondylodiscitis is the most frequent hematogenous osteoarticular septic complication in the IE population, with an enterococcal etiology being one of the most common [1, 3]. In patients with spondylodiscitis and positive blood cultures with typical bacteria, echocardiography is

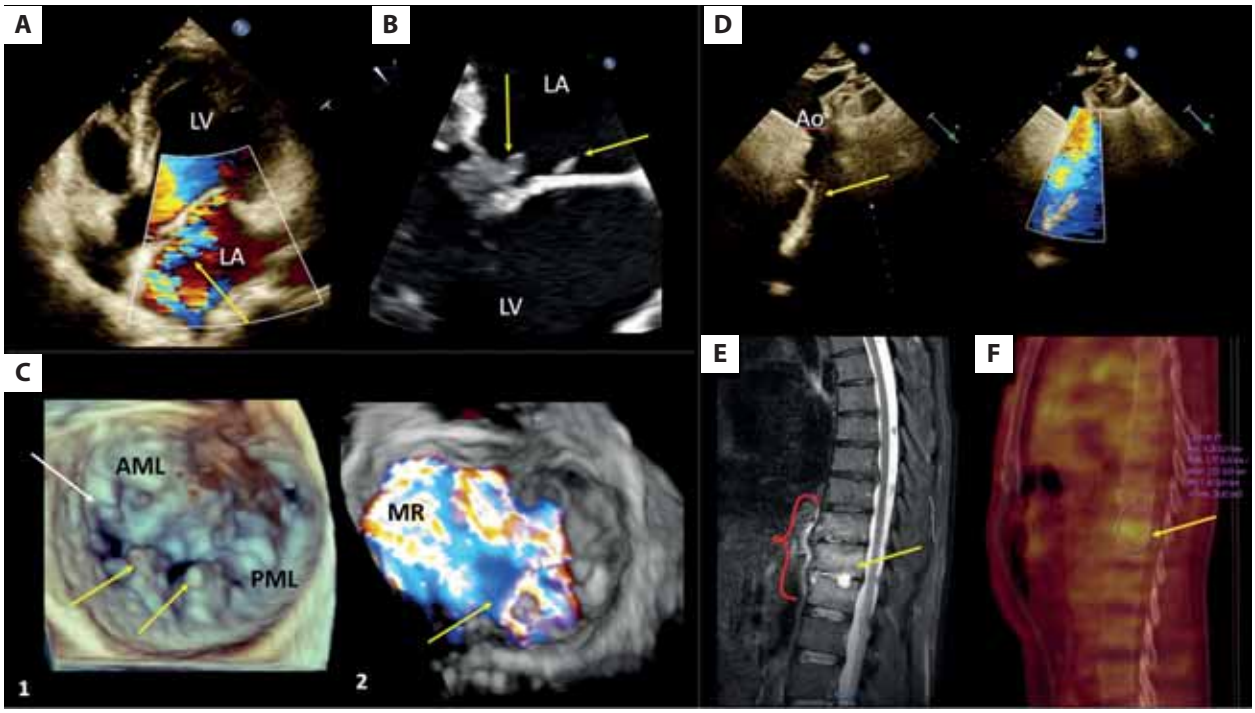

Figure 1. Echocardiography, magnetic resonance of the spine and PET/CT in a patient with mitral valve endocarditis. **A**. Eccentric jet of severe mitral regurgitation (arrow); two-dimensional transthoracic echocardiography, color Doppler (Supplementary material, *Video S 1*). **B**. Mitral valve infective endocarditis; bacterial vegetations attached to the mitral leaflets (arrows); 2-dimensional transoesophageal echocardiography; **C.** Bacterial vegetations attached to the posterior mitral leaflet (yellow arrows) and the anterior leaflet (white arrow) (**1**) and a wide jet of mitral regurgitation on color Doppler (arrow) (**2**); 3-dimensional transoesophageal echocardiography (Supplementary material, *Video S2*); **D.** Descending aorta at the level of the previous coarctation surgery (arrow); 2-dimensional transthoracic echocardiography (left panel), color Doppler (right panel). **E**. Spondylodiscitis: infectious lesions at the levels of Th10/Th11 and Th11/Th12 (arrow) and an inflammatory infiltrate in the paravertebral soft tissues (red brace); contrast-enhanced magnetic resonance. **F**. Post-inflammatory lesions in the spine (arrow); positron emission tomography/computed tomography

Abbreviations: AML, anterior mitral leaflet; Ao, aorta; LA, left atrium; LV, left ventricle; MR, mitral regurgitation; PML, posterior mitral leaflet

recommended to rule out IE [1]. The role of three-dimensional TOE in diagnosing IE is indispensable, especially in precise MV assessment [4]. PET/CT is recommended in symptomatic IE patients to detect peripheral lesions [1] and is useful in monitoring their response to therapy.

A significant delay in establishing the diagnosis leads to serious consequences and contributes to higher mortality [5], therefore, we should urgently perform an echocardiogram in patients with recurrent fever and a heart murmur, back pain, or patients after previous heart surgery.

Supplementary material

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

Article information

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An aberrant case of rapidly progressing lung adenocarcinoma in a Ukrainian refugee

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A 65-year-old Ukrainian female refugee with a low-differentiated adenocarcinoma of the right (R) lung (diagnosed 1.5 years earlier) reported to the Emergency Department with shortness of breath, fever, and a wet cough. A thoracotomy was performed during her previous hospitalization in Ukraine. Microscopic examination, performed at that time, confirmed low- low-differentiated G3 lung adenocarcinoma, and immunogenetic tests detected the ALK+ tyrosine kinase gene rearrangements. The patient had received several courses of treatment with ALK inhibitors — crizotinib and alectinib. Due to cancer progression, therapy with another ALK blocker, brigatinib, had been initiated in the third line. On admission to the Department of Pulmonology and Oncology, physical examination showed tachycardia, tachypnoea and a decrease in the alveolar murmur over the R lung and the upper parts of the left lung. Laboratory test results initially revealed significantly elevated markers of inflammation (leukocytosis with the left shift: leukocytes — 60750 cells/μl, neutrophils — 58660 cells/μl), elevated C-reactive protein (218 mg/l, upper limit of normal = 5 mg/l), and procalcitonin (4.72 ng/ml, upper limit of normal <5 ng/ml). Chest computed tomography angiography showed that the R lung was practically completely airless (Figure 1A) and there was a pathological nodular lesion in the R lung (adjacent to the bifurcation of the pulmonary trunk, surrounding the branches of the R pulmonary artery, infiltrating the R upper lobe artery, segmental arteries to the 3R segment and peripheral branches of the subsegmental arteries to the R middle lobe) obstructing the bronchi of the R lung (Figure 1B). We observed the impression of the nodular mass on the superior vena cava and the R atrium. A pathological soft-tissue mass was visualized in the lumen of the left atrium (LA) of approximately 63 × 32 mm (right-left × anterior-posterior), protruding through the mitral valve into the left ventricle (Figure 1B), compressing the left ventricular outflow tract (LVOT) and the aortic valve. Massive mediastinal, cervical, and supraclavicular lymphadenopathy and pathological effusion in both pleural cavities and in the pericardium were found. Right-sided pneumonia was diagnosed, secondary to the underlying disease, and broad-spectrum intravenous empirical antibiotic therapy (amoxicillin + clavulanate, ciprofloxacin) improved the patient's condition.

Transthoracic echocardiography revealed a tumor filling almost the entire LA (Figure 1C–E), originating from the R superior pulmonary vein. Four-chamber view (color Doppler) showed stenotic mitral flow (Figure 1F). The disease was identified as T4N3M1 stage IV. The patient was disqualified from cardiac surgery by the Heart Team due to the very advanced stage of cancer. Brigatinib treatment was continued. She was discharged for further outpatient care and died a month later.

Lung adenocarcinoma with *ALK* gene rearrangement is a specific molecular subtype of lung adenocarcinoma [1] characterized by a high ability to give rise to distant metastases, including heart cavities. Mechanisms by which LA involvement occurs may be direct invasion by the primary tumor, involvement of lymph nodes, or, the least common, pulmonary venous transfer of the original lesion [2]. The condition requires surgery, which, however, may involve the risk of neoplastic dissemination, hemorrhage, and a higher probability

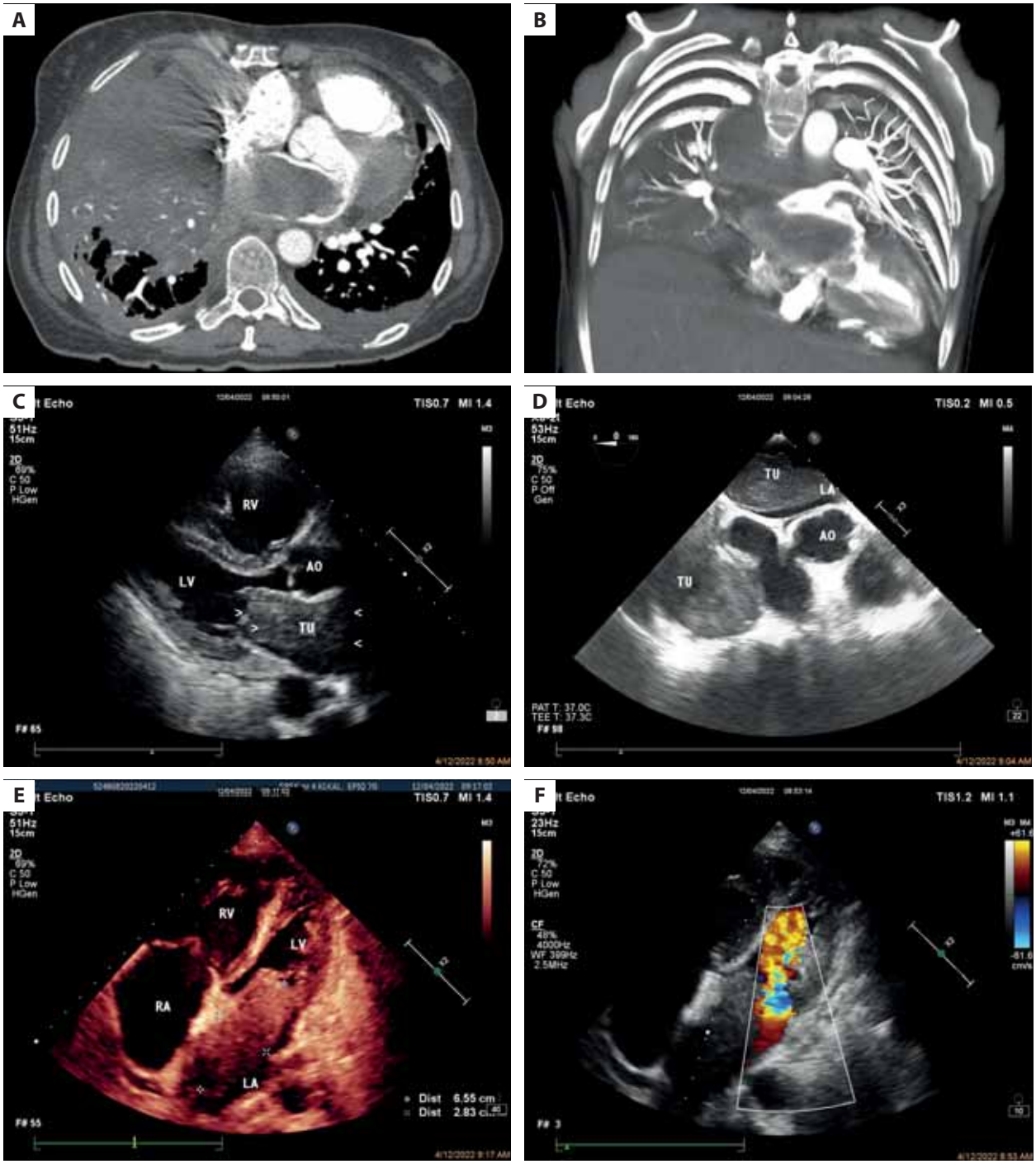

Figure 1. A. Axial projection of CT in the arterial phase. Extensive mass located in the right lung filling almost the entire left atrial cavity. A small amount of fluid in both pleural cavities. **B.** CT, 3D volume rendering presenting nodule masses in the mediastinum and the right lung, poor vascularization of the right lung, and a nodule mass passing from the LA to the LV. **C.** TTE, parasternal long axis view, tumor mass visible in the LA (arrows). **D**. TEE, aortic valve level, tumor visible in the right lung and the LA **E**. TTE, apical 4-chamber (A4C) view, pathological soft-tissue mass visualized in the LA (6.5 cm × 2.8 cm), protruding through the mitral valve into the LV. **F**. TTE, Apical 4-chamber view, color Doppler, stenotic mitral flow due to the mass protruding into the LV

Abbreviations: CT, computed tomography; LA, left atrium; LV, left ventricle; LVOT, left ventricular outflow tract; RA, right atrium; RV, right ventricle; TTE, transthoracic echocardiography; TEE, transesophageal echocardiography; TU, tumor

of infection [3, 4]. The decision on the best therapeutic approach should be made by a multidisciplinary team, regarding especially life expectancy. Lung cancer resection can be performed simultaneously with cardiac surgery, but in advanced cases, heart surgery takes precedence over that of the lung [5]. If cardiac surgery is not possible, conservative preparatory treatment with highly selective ALK inhibitors such as alectinib, crizotinib, and brigatinib is recommended.

Article information

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Horse riding as an atypical type of rehabilitation to improve physical capacity in a patient after cardiac surgeries and before liver transplantation

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End-stage liver failure, regardless of etiology, is a progressive and fatal disease characterized by the loss of liver function which affects other organs [1]. Cardiopulmonary Exercise Testing attracts great interest as a functional test used for assessing the risk before liver transplantation (LTx). It may be helpful to predict mortality, morbidity and length of hospitalization after a non-cardiac procedure [2]. Horse riding is a non-standard physical activity in patients before LTx and after cardiac surgeries. It aims to improve motor functions, body posture, and stamina [3].

A 58-year-old male patient with a history of liver cirrhosis and other co-morbidities was admitted for surgery for a brachycephalic trunk aneurysm. A graft was used to create an anastomosis between the ascending aorta and the right common carotid artery (CCA), and an anastomosis with the distal segment of the brachycephalic trunk was performed. Postoperative complications occurred: respiratory and renal failure, paroxysmal atrial fibrillation, and a worsening of the hepatic function.

Over time, the patient was admitted to the hospital due to moderately severe condition with symptoms of hepatic encephalopathy, jaundice, and ascites. LTx was considered due to end-stage liver disease. Computed tomography angiography showed an aneurysm-like bulge, adjacent to the origin of the left CCA (Figure 1A). It could have been a false aneurysm or the stump of the aneurysm resected earlier. A hybrid procedure based on the implantation of a stent graft into the aortic arch covering the brachycephalic trunk and the left CCA and a right to left carotid-carotid bypass graft (Figure 1B). Qualification for LTx was postponed. Four months later spirometry revealed pulmonary obturation. Cardiopulmonary Exercise Testing demonstrated exercise oscillation of ventilation and ventilatory obstruction (Figure 1C and 1E), reduced exercise capacity with peak oxygen uptake (VO_{2peak}) 18.9 ml/kg/min and oxygen uptake at anaerobic threshold (AT) 11.2 ml/kg/min (Figure 1G). The 6-minute walk test was aborted at 5.5 METS due to the patient's fatigue. Additionally, complex exertion-induced ventricular arrhythmia was diagnosed. Qualification for LTx was delayed for further 4 months, and pharmacological treatment was initiated: beta-adrenolytics and bronchodilators. At the next qualification attempt, persistent pulmonary obturation and decreased physical capacity were noted, and LTx was postponed for further 2 months. After that time, without any new pharmacotherapy, the patient demonstrated an improved physical capacity compared with previous exams: better profile of ventilation (Figure 1D and 1F), improved VO_{2peak} of 21.9 ml/kg/min, AT of 14.2 ml/kg/min (Figure 1H), and the 6-minute walk test with 6.3 METS. No significant heart rhythm disturbances were observed. It turned out that the patient had taken up horse riding as his new hobby and rehabilitation, which improved his physical performance and allowed for his qualification for LTx, which was performed without complications.

Physical capacity is an important parameter determining the success of an operation [4]. Unfortunately, there is a lack of data on the beneficial effects of horse riding as

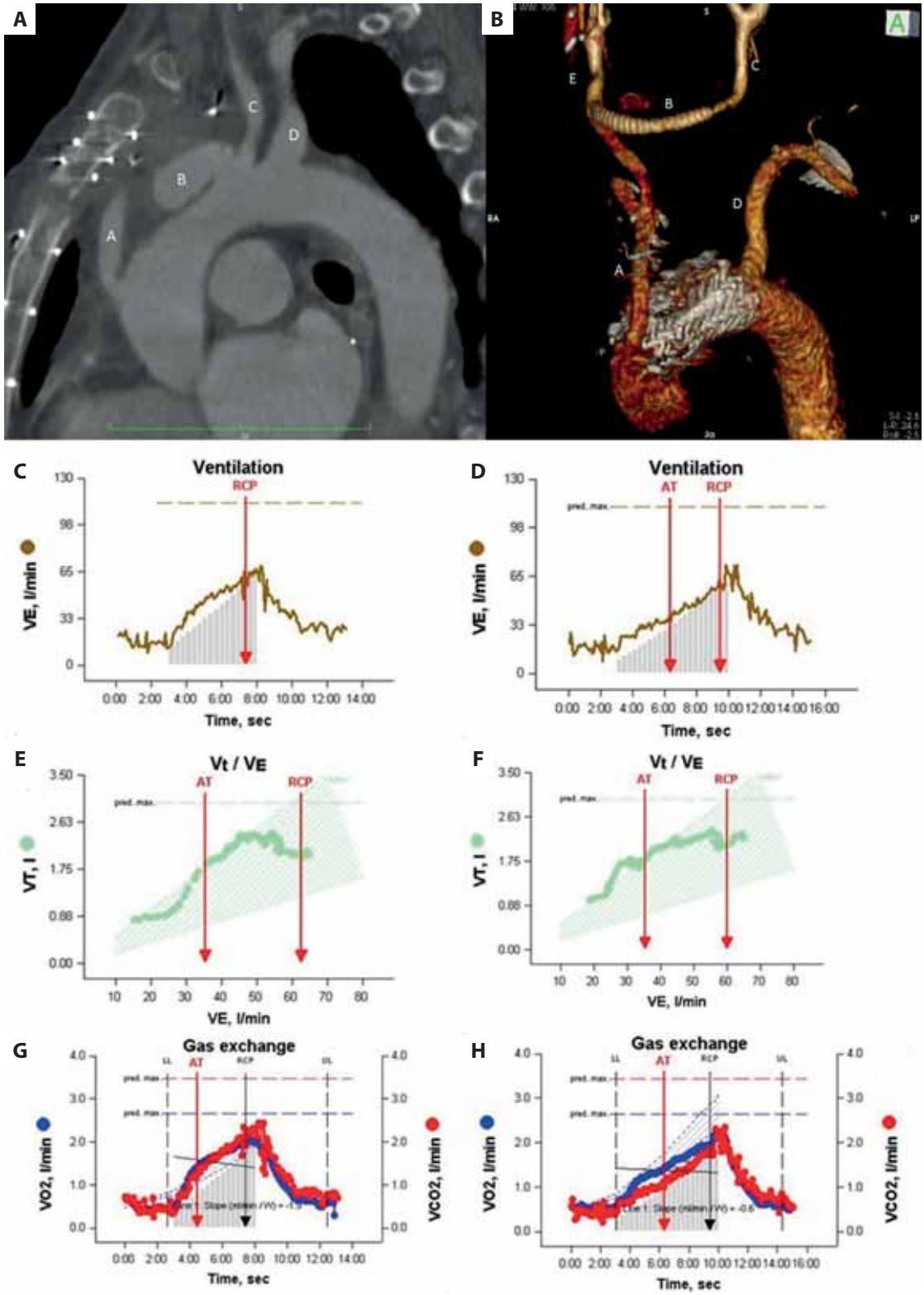

Figure 1. A–B. CT before and after hybrid angiosurgery: **A.** CT scan after cardiac surgery and before hybrid angiosurgery. Pseudoaneurysm of the aortic arch on the level of the origin of the LCCA: A — by-pass from the ascending aorta to the BCA; B — pseudoaneurysm; C — LCCA; D — LSA. **B.** Computed tomography angiography 3D reconstruction after hybrid angiosurgery: A — by-pass from the ascending aorta to the BCA; B — carotid-carotid by-pass; C — LCCA; D — LSA; E — RCCA; **C–H.** Cardiopulmonary Exercise Testing before (left panels — after angiosurgery, right panels — improvement after rehabilitation before liver transplantation): **C, D.** 1st Wasserman's panel: Changes in the profile of ventilation during exercise. **E, F** 7th Wasserman's panel: Changes in relationship between VT and VE during exercise. Left panel presenting a severe pattern of obturation; right panel – improvement). **G, H.** 3rd Wasserman's panel: Profiles of VO_2 and VCO_2 during exercise. Right panel — better cardiopulmonary capacity with higher AT

Abbreviations: AT, anaerobic threshold; BCA, brachiocephalic artery; CT, computed tomography; LCCA, left common carotid artery; LSA, left subclavian artery; RCCA, right common carotid artery; VCO_2, carbon dioxide production; VE, minute ventilation; VO_2, oxygen consumption; VT, tidal volume

rehabilitation in patients suffering from heart and liver diseases. It was analyzed as a therapy for many diseases, but never as a form of rehabilitation after surgery [5]. More research is needed to evaluate the benefits of horse riding on the circulatory system and before LTx.

Article information

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First Polish pediatric experience with percutaneous self-expandable pulmonary valve implantation

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Percutaneous pulmonary valve implantation is an alternative way of restoring valve function to the right ventricular outflow tract [1]. More recently, self-expandable valves have been providing additional options, especially for patients with large outflow tracts [2, 3]. We present the first Polish experience with the Venus P-valve (Venus MedTech) in two pediatric patients. Both were born with tetralogy of Fallot with unusual coronary artery anatomy; both underwent surgical repair with a monocusp pulmonary homograft and presented with progressive pulmonary regurgitation, which was confirmed with non-invasive imaging (Supplementary material, *Table S1*). Virtual Reality models (VMersive) were created to present the anatomy and simulate valve size and position [4].

PATIENT A

In a 10-year-old girl (37 kg), the virtual model showed a 30 × 25 mm Venus P-valve as the most suitable (Figure 1A). After initial angiography and measurements, a 40 mm PTS-X sizing balloon (NuMed) was inflated to check the size and distensibility of the outflow tract. Diameters of the outflow tract could also allow a large balloon-expandable valve but, due to the close proximity and the course of the anomalous coronary artery, discouraged this option. Through a 24 Fr Dryseal sheath (Gore), a 30 × 25 mm Venus P-valve was deployed from the right pulmonary artery (Figure 1B). Control angiography showed proper expansion of the valve, with tapering of the distal flare on lateral imaging (Figure 1C and D). Oversizing of the valve could lead to infolding of one of the walls and significant regurgitation [5]. Although the latter was not observed, the distal segment was adapted with the PTS-X balloon (Figure 1E) to gain further expansion. A control angiogram confirmed the proper position and function of the valve and excluded coronary artery compression (Figure 1F). Pre-discharge and 6-month follow-up echocardiograms showed good function of the valve with trivial central regurgitation. ECG-Holter monitoring showed no arrhythmia.

PATIENT B

In a 17-year-old boy (75 kg), the virtual model revealed a conical-shaped outflow measuring 35 mm proximally and 23 mm just before the bifurcation (Supplementary material, *Figure S1A*, *Video S1*). After an initial angiogram (Supplementary material, *Figure S1B*) and subsequent balloon (40 mm PTS-X) sizing with coronary compression exclusion (Supplementary material, *Figure S1C*), a 36 × 25 mm Venus P-valve was introduced through a 26 Fr Dryseal and positioned in the proximal left pulmonary artery (Supplementary material, *Figure S1D*). During the uncovering of the distal flare, the valve shifted below the bifurcation to the middle of the outflow tract. It was recaptured with the Dryseal sheath and once more deployed from the proximal left pulmonary artery with more push on the system. This enabled covering of the distal main pulmonary artery narrowing with the distal flare of the valve. The final angiogram confirmed the full expansion of the valve with unobstructed flow to the pulmonary arteries and a trace of regurgitation (Supplementary material, *Figure S1E*). Retrospectively, a deployment from the right pulmonary artery might have allowed positioning of the distal flare at the bifurcation, beyond the narrowing. Pre-dis-

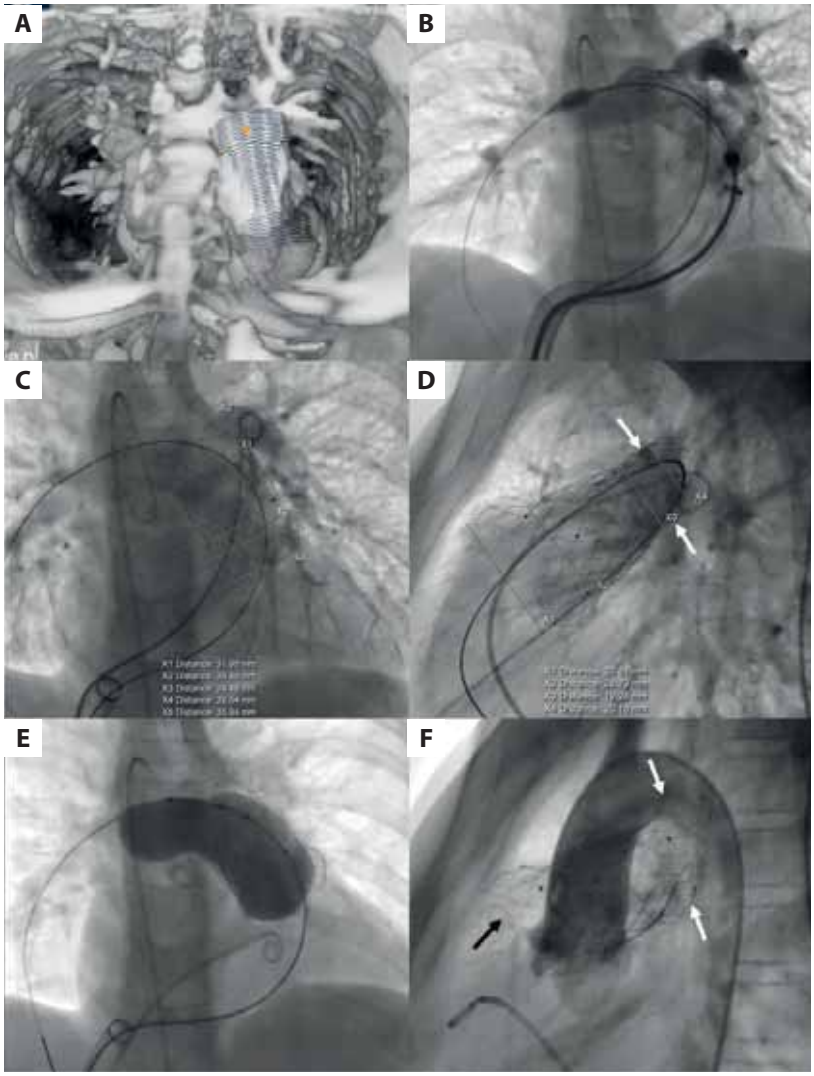

Figure 1. Percutaneous Venus P-valve (Venus MedTech) implantation in a 10-year-old tetralogy of Fallot patient with anomalous coronary artery (an additional left anterior descending artery from the right coronary artery) after patch repair in infancy and currently with significant pulmonary regurgitation. **A.** Virtual reality model processed from cardiac magnetic resonance scans with VMersive software (VR-Learning, Poland) to simulate a 30 mm diameter and 25 mm length of Venus P-valve. **B.** An angiogram during deployment of the distal flare in the proximal right pulmonary artery. **C.** Full expansion of the valve in cranial projection. **D.** The valve tapers towards the distal end (white arrows) in the lateral view. **E.** Adaptation of the distal flare of the valve with a 40 mm PTS-X (NuMed) balloon. **F.** The control aortography shows unobstructed coronary artery flow, including the additional left descending artery (black arrow) originating from the right coronary artery. The widened distal flare (white arrows) of the valve is seen as well

charge (Supplementary material, *Figure S1F*) and follow-up echocardiograms confirmed good valve function. ECG-Holter monitoring showed a slow irregular sinus rhythm.

Supplementary material

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

Article information

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Implantation of a coronary sinus reducer for refractory angina due to coronary microvascular dysfunction

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A 65-year-old male patient was referred to our Cardiology Department due to angina pectoris, classified as class III according to the Canadian Cardiovascular Society (CCS) which persisted despite 6 months of optimal anti-anginal medical therapy (isosorbide mononitrate, nebivolol, amlodipine, and trimetazidine).

The patient's medical history included hypertension, hyperlipidemia, and coronary artery disease with subsequent percutaneous coronary revascularization. In 2014, he experienced a non-ST-elevation myocardial infarction and underwent percutaneous coronary intervention (PCI) in the right coronary artery with a drug-eluting stent (DES). In 2015, he had PCI in the left anterior descending artery (LAD) with a DES, in 2019, PCI in the right coronary artery with a DES. In 2021 another non-ST-elevation myocardial infarction led to PCI in the circumflex artery with DES implantation.

Echocardiography revealed normal left ventricular function with ejection fraction of 60%. Due to significant clinical symptoms, the patient underwent coronary angiography, which showed no significant coronary artery stenosis (Figure 1A–C).

In addition, coronary microcirculation was assessed using a pressure wire (PressureWireX, Abbott, US) and adenosine to evaluate coronary microvascular reserve (CFR). Coronary microvascular resistance (IMR) was assessed using the thermodilution method with 0.9% saline. A CFR of 2.2 and an IMR of 46 were obtained, indicating significant coronary microvascular dysfunction (CMD) (Figure 1E).

Due to significant symptoms despite optimal medical therapy and the lack of conventional revascularization options, the patient was eligible for coronary sinus reducer (CSR) implantation (Figure 1 D).

At the 6-month follow-up, coronary microvascular function improved, with a CFR of 4.1 and an IMR of 11 (Figure 1F). The patient's angina symptoms resolved and were reclassified as CCS class I. Furthermore, improvements were observed in the 6-minute walk test (90 to 300 meters), Seattle Angina Question (SAQ-7), EQ-5D, and SF-36.

Despite complete revascularization and optimal pharmacotherapy, up to 10% of patients experience refractory angina pectoris [1]. The pathogenesis of this phenomenon is multifactorial, and CMD may be one of the contributing factors [2].

CSR represents a novel therapeutic approach for patients with refractory angina pectoris without obstructive CAD [3] A growing body of evidence suggests the effectiveness of CSR in alleviating angina symptoms. [4] The presented case suggests the effectiveness of this therapy in CMD.

Article information

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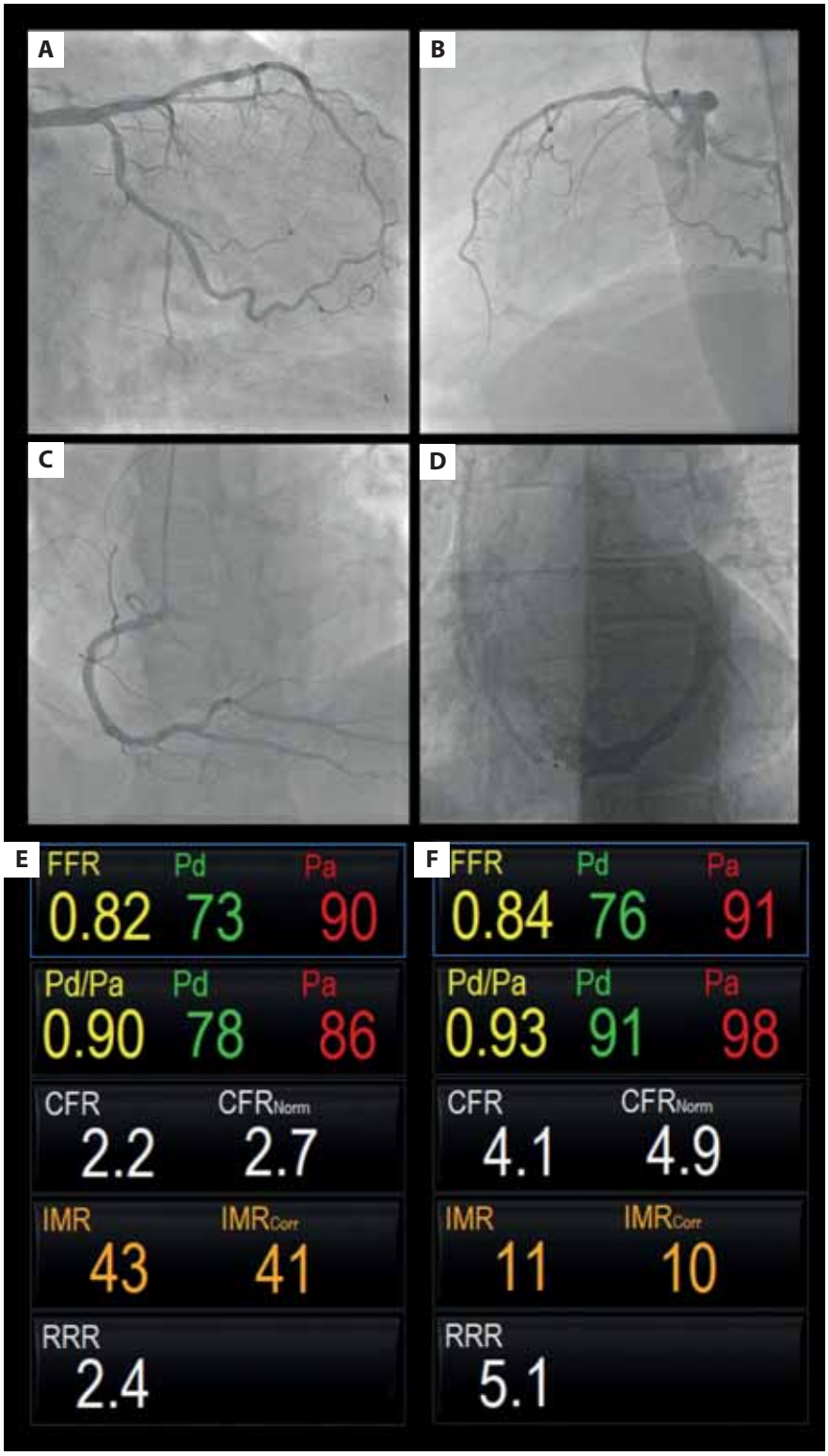

Figure 1. A–B. Coronary angiography of the left coronary artery. **C.** Coronary angiography of the right coronary artery. **D.** Implantation of the coronary sinus reducer. **E.** Baseline physiological indices. **F.** 6-month follow-up — physiological indices

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Pericardial hemangioma: An extremely rare cardiac tumor

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We present a case of a 52-year-old male patient referred to a cardiologist due to increased fatigue over the past few months. The patient mentioned only arterial hypertension as a comorbidity. We observed a tumoral mass in the right atrium on transthoracic echocardiography. Transesophageal echocardiography (TEE) confirmed a tumor, characteristic of myxoma, in the view of the right atrium, measuring 35 × 31 mm, attached to the free wall of the right atrium above the entrance of the inferior vena cava (Figure 1A). The complete valvular apparatus was without pathological changes. Coronary angiography was normal. The Heart Team recommended surgical intervention.

The operation was performed under general endotracheal anesthesia through a medial sternotomy. Pericardiotomy showed normocardia, a heart of regular size and systolic function, with a visible solid, oval, clearly circumscribed epicardial tumor mass on the free lateral wall of the right atrium and right ventricle (Figure 1B). A complete excision of the tumor was performed (Supplementary material, *Video S1*). The formation was dark red in color, oval, with a vermiform consistency (Figure 1C).

The postoperative course was uneventful. Control echocardiography showed preserved systolic and diastolic functions of the heart without pericardial effusion. Pathohistological analysis showed that it was a benign tumor, made up of many distended vascular spaces of the capillary type, whose inner walls were lined with thin, flattened endothelium, and the lumens are filled with blood. Some capillary blood vessels have very thickened walls, and the lumens were empty. Dense clusters of angioblasts without central lumens were focally visible. The described histological picture corresponded to a capillary hemangioma (Figure 1D). The patient was discharged on the sixth postoperative day in good general condition.

Primary cardiac tumors are rare, with an incidence rate of 0.0017%–0.019% in the autopsy series [1]. Most often, these are benign tumors, mainly myxomas, fibroelastomas, and lipomas. Cardiac hemangiomas are rare cardiac tumors, with an incidence of less than 2% [2]. Cardiac hemangioma can originate from any of the three cardiac layers, either the endocardium, myocardium, or epicardium [3]. The epicardium is the rarest site of origin for these tumors. So far, only 13 cases of pericardial hemangioma have been described in the world literature [4]. Although the first pericardial hemangioma was described in 1963, the remaining 12 cases were reported in the last 20 years, which leads to the conclusion that the diagnosis of these tumors has been improved by better diagnostic tools. In our case, TEE showed a tumoral mass in the right atrium, but it was actually in the pericardial space, which confirms that TEE cannot determine the exact location of the tumor with absolute certainty. Clinical presentation can be different depending on the size and localization of the tumor. Some of the cases described so far were asymptomatic, and most were accompanied by dyspnea, syncope, and chest pain [4]. It is recommended that surgical excision be performed as soon as possible.

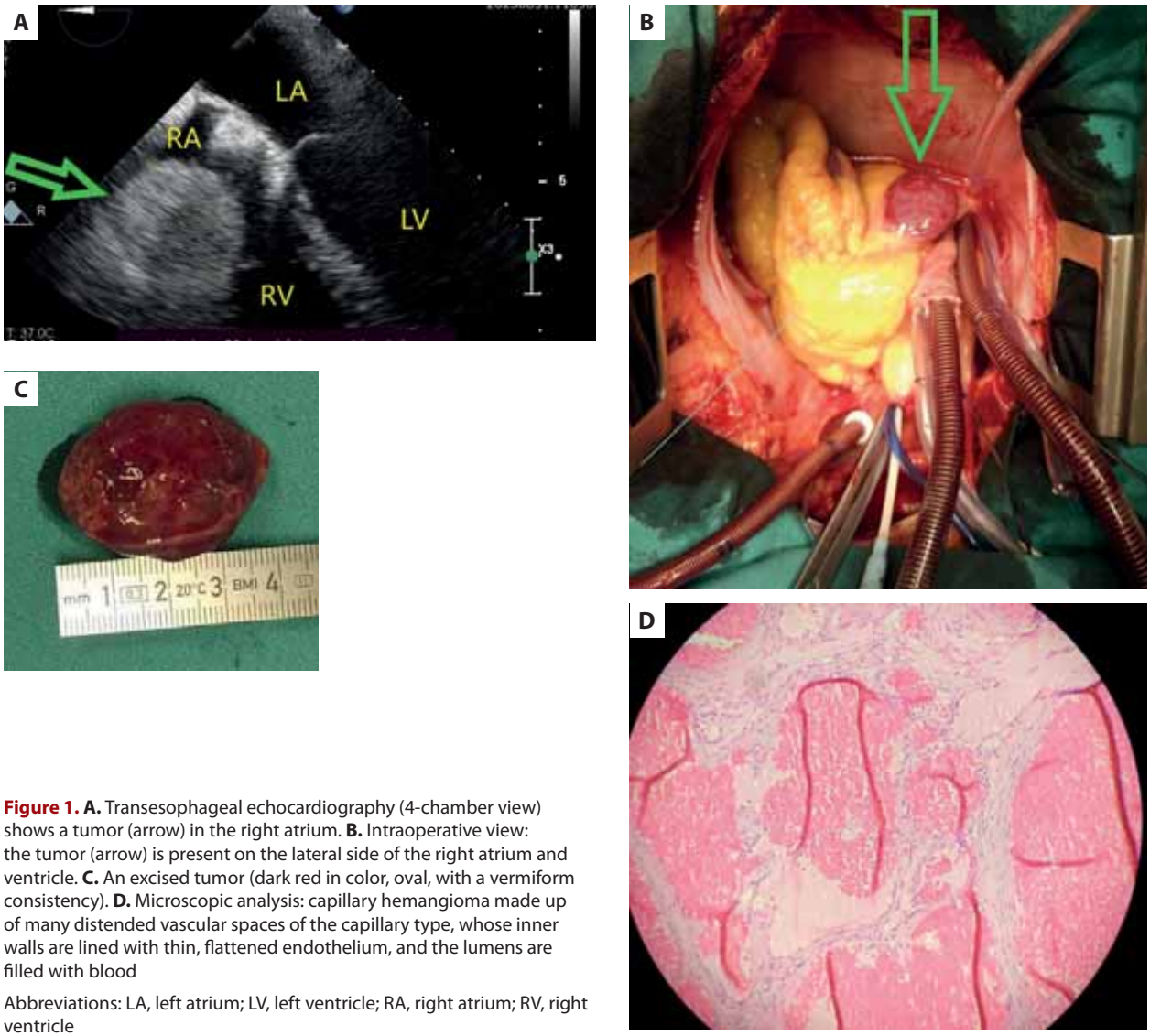

Figure 1. A. Transesophageal echocardiography (4-chamber view) shows a tumor (arrow) in the right atrium. **B.** Intraoperative view: the tumor (arrow) is present on the lateral side of the right atrium and ventricle. **C.** An excised tumor (dark red in color, oval, with a vermiform consistency). **D.** Microscopic analysis: capillary hemangioma made up of many distended vascular spaces of the capillary type, whose inner walls are lined with thin, flattened endothelium, and the lumens are filled with blood

Abbreviations: LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle

Supplementary material

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

Article information

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Vasospastic angina, plaque erosion, ischemia, and cardiac arrest: Four of a kind or a straight?

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A 56-year-old woman, a current smoker with a history of arterial hypertension and dyslipidemia was previously examined due to recurrent syncope with associated chest pain in recent months. Normal cardiac morphology and function were confirmed by echocardiography, and coronary computed tomography angiography showed a noncalcified plaque with 40% stenosis in the left anterior descending coronary artery (LAD) (Figure 1A). Single antiplatelet therapy and a statin were started.

One month later, she was admitted to the intensive care unit after resuscitation following out-of-hospital cardiac arrest. Post-return of spontaneous circulation electrocardiogram showed ST-segment elevation in the anterior leads, which led to emergent coronary angiography, but no obstructive coronary artery disease was found.

On admission, the patient presented satisfactory neurological and cardiac development with significantly increased troponin levels. Anterior myocardial edema (Figure 1B) was found on T2 mapping images without late gadolinium enhancement (Figure 1C) on cardiac magnetic resonance. Due to suspicion of vasospastic angina, an acetylcholine (Ach) invasive provocation test was performed. The first Ach bolus of 20 mcg in the LAD induced chest pain along transient ST-segment elevation in the anterior leads and severe spasm in the mid anterior descending coronary artery (Figure 1D–E) relieved by intracoronary nitroglycerin. In addition, optical coherence tomography assessment of the LAD revealed a small erosion in the mid segment (Figure 1F). Dual antiplatelet therapy, dihydropyridine calcium channel blocker, and long-acting nitrates were started, and a subcutaneous implantable cardioverter defibrillator was implanted in secondary prevention.

We have reported a case of an out-of-hospital cardiac arrest secondary to acute ischemia due to vasospastic angina and with the additional finding of plaque erosion. In this scenario, a causative role of spasm leading to plaque erosion has been proposed (a straight), and we believe that explanation is more feasible than the simultaneous coincidence of several factors (four of a kind).

Article information

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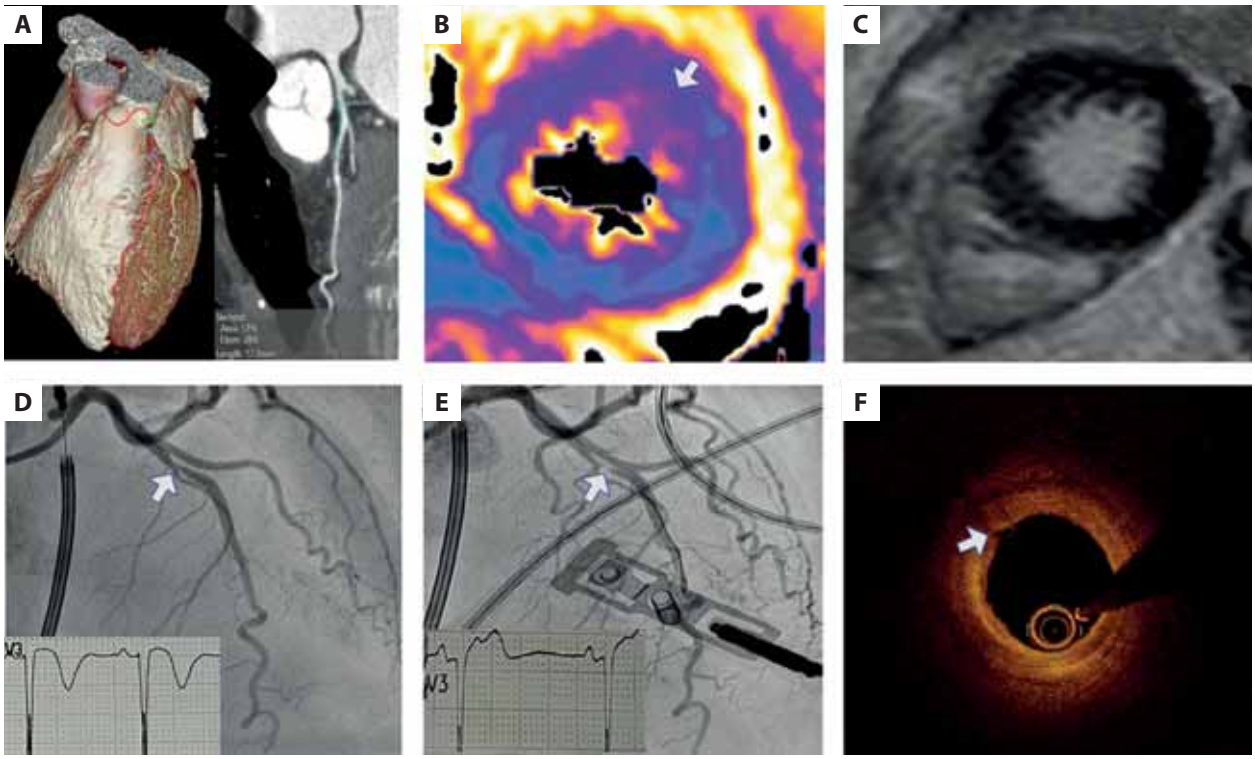

Figure 1. A. Computed tomography angiography; noncalcified plaque with 40% stenosis in the left anterior descending coronary artery. **B, C.** Cardiac magnetic resonance; anterior myocardial edema on T2 mapping (**B**) without late gadolinium enhancement (**C**). **D, E.** Severe spasm in the mid-anterior descending coronary artery. **F.** Optical coherence tomography, small erosion in the mid segment

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Hematoma of the interatrial septum after surgery for a giant aneurysm of the sinus of Valsalva

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A sinus of Valsalva aneurysm (SVA) is a rare but potentially life-threatening condition. The prevalence of SVAs in the general population is estimated at 0.09% to 0.1% [1, 2]. In most patients, SVA is a congenital rather than acquired cardiac abnormality. Interatrial septum dissection and hematoma is a very rare complication. It may occur after aortic root or mitral valve surgery and casuistically after percutaneous interventions (ablation) or cardiopulmonary resuscitation [3].

A 66-year-old woman was admitted to the hospital for an extended diagnostic workup after an incidental finding of a giant SVA during routine transthoracic echocardiography (TTE) before cardioversion for paroxysmal atrial fibrillation. The patient underwent TTE (Figure 1A), transesophageal echocardiography (TEE), and cardiac computed tomography (including coronary computed tomography angiography), which revealed a giant non-coronary sinus of Valsalva aneurysm (97 × 55 mm) (Figure 1B), without aortic dissection, no significant lesions in the coronary arteries were reported. In addition, a bicuspid aortic valve without significant dysfunction and pericardial effusion of up to 8 mm were shown.

Surgical treatment (Figure 1C) included resection of the aneurysm from the side of the pericardium and reconstruction with a dacron graft sutured at the left ventricular outflow tract below the aortic annulus (as in David procedure). Next, the graft was sutured to the aorta, using the continuous suturing technique. Aortic valve repair was performed. Intraoperative TEE revealed no regurgitation. After declamping the aorta, bleeding from the roof of the left atrium appeared (the dissection occurred after cutting through the aneurysm as an extension of the cut after applying traction to the aneurysm sac). The dissection was sutured. Follow-up TEE showed severe aortic valve regurgitation requiring bioprosthetic aortic valve implantation (Hancock II, 23 mm).

After the procedure, we observed a worsening of kidney function, increased levels of inflammatory markers, second-degree atrioventricular block requiring temporary cardiac pacing, and atrial fibrillation and flutter. TTE revealed an interatrial septal hematoma (Figure 1D). The hematoma was caused by damage to the mitro-aortic curtain while which happened placing sutures on the non-coronary leaflet. During hospitalization, the patient was treated with antiarrhythmic drugs and antibiotics. Conduction disorders resolved and kidney function improved. Partial resorption of hematoma was also noted (Figure 1E). Cardiac rehabilitation was uneventful. Complete resorption of the hematoma was noted at the 1-year follow-up (Figure 1F). The patient is currently in good clinical condition and remains under the care of the cardiac center.

Both the SVA and interatrial septal hematoma may cause considerable concern. If an unruptured SVA is present, surgical treatment of symptomatic or large aneurysms is acceptable (the cutoff varies depending on the presence of other abnormalities, such as bicuspid aortic valve or connective tissue disease) [4]. On the other hand, the management of patients with intramural hematoma is debatable [5]. It seems that the choice of treatment should be guided by the patient's clinical condition and pericardial bleeding [5]. Both invasive and noninvasive cardiologists should have sufficient knowledge about both conditions to be able to make adequate decisions on patient management.

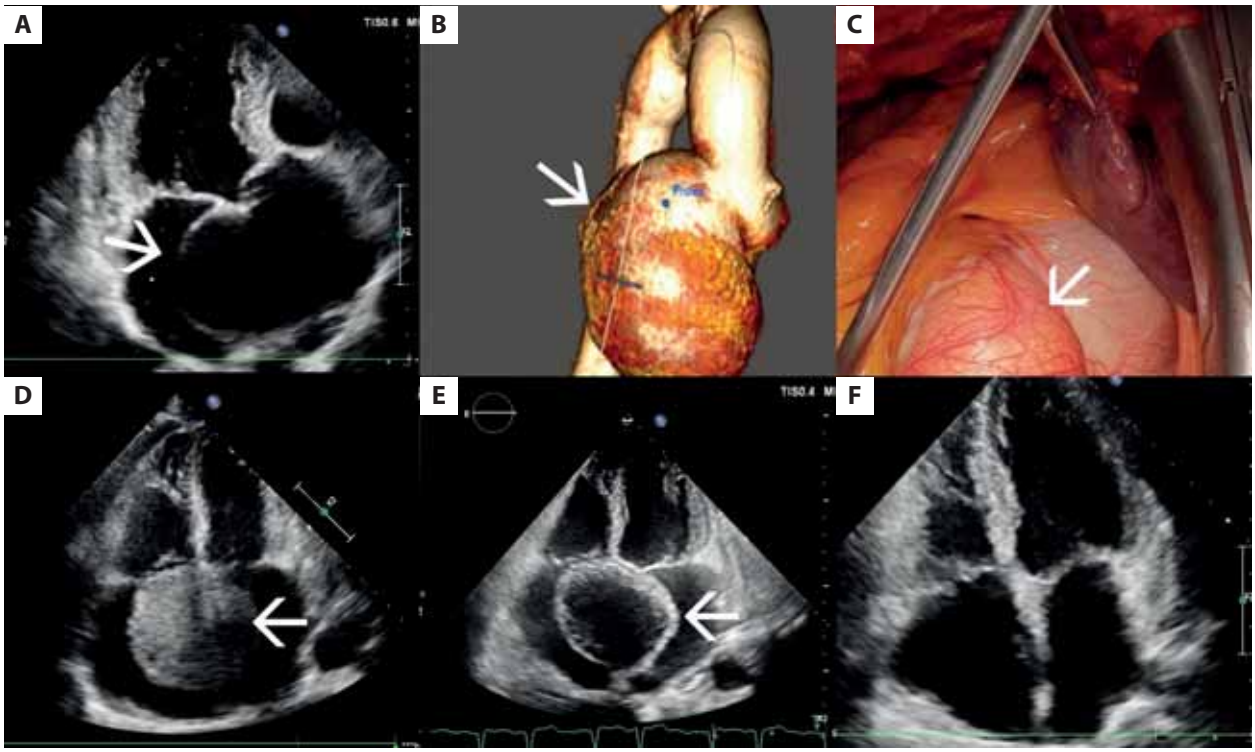

Figure 1. A. Transthoracic echocardiogram (TTE) before the procedure, modified 5-chamber view (arrow indicates the sinus of Valsalva aneurysm). **B.** Cardiac computed tomography angiography: 3-dimensional reconstruction (arrow indicates the sinus of Valsalva aneurysm). **C.** Periprocedural image. **D.** TTE; 4-chamber view (arrow indicates an intramural hematoma). **E.** TTE, 4-chamber view 7 days after the procedure, partial resolution of the hematoma (arrow indicates an intramural hematoma). **F.** TTE, 4-chamber view 1 year after the procedure, resolution of the hematoma

Article information

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Complex multistage endovascular repair of dissection of the arch, thoracic, and abdominal aorta in a pediatric patient

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Aortic dissection coexisting with a large pseudoaneurysm is a rare entity in pediatric patients [1]. Usually, such dissections are seen in Marfan syndrome, anatomical anomalies of the aortic arch, or accompanying blunt chest injuries [1, 2]. Here we present a case of such an aortic dissection in an 11-year-old girl. Fourteen months earlier, this patient had undergone surgical aortic valve replacement with St. Jude valve and Galweave aortic prosthesis due to aortic dissection of unknown non-Marfan origin. At that time, the aortic dissection extended from the ascending to abdominal aorta, and the false lumen diameter was 20–32 mm. Due to a coexisting dissection of the left subclavian artery, she underwent stent implantation at the level of this dissection. Still, this procedure solved the problem only partially and made future reconstructions even more challenging.

Considering progressing enlargement of the dissections and severe dysphagia resulting from compression of the esophagus, we decided to attempt endovascular repair of this complex vascular lesion. On admission, the patient presented with a large aortic dissection, beginning about 4 cm proximally from the brachiocephalic trunk and extending to the level of the celiac trunk. The dissection was the widest next to the left subclavian artery: 61 mm (Figure 1A); throughout the descending aorta, it had a diameter of 40–50 mm. Entry points to the false lumen were situated at the levels of the brachiocephalic trunk, left subclavian artery (LSA), in the upper part of the descending aorta, and above the celiac trunk. The LSA was also dissected, and this dissection extended to the distal part of the brachial artery. In addition, this patient presented with a dominant left vertebral artery while the right vertebral artery was occluded in the V3 segment.

Due to the unfavorable anatomy of the vertebral arteries, we decided to address the dissection of the LSA first and to close dissections and entry points to the false lumen thereafter (Figure 1B). In the first step, we implanted a covered stent in the proximal part of the LSA, closing the dissection of this artery. Then, using the kissing-stent technique, smaller covered stents were implanted in the distal part of the LSA and the left vertebral artery. In the second stage, we implanted covered stents in the brachiocephalic trunk, right subclavian and right common carotid arteries. Then, the aortic dissection was closed with two covered stents, which were fixed with two self-expanding stents. The entry point to the false lumen at the level of the LSA was closed with the Amplatzer Vascular Plug, and the false lumen was embolized with 5 coils. Since this endoleak was still present at follow-up (Figure 1C), during the next procedure it was closed with Onyx glue and several additional coils. The follow-up 12 months after the last procedure revealed complete closure of dissections and good inflow to the aortic branches (Figure 1D). The aortic true lumen had a diameter of 27 mm. This case demonstrates that even very complex aortic dissections in vulnerable pediatric patients can be successfully managed if the procedure is staged and different endovascular devices are used.

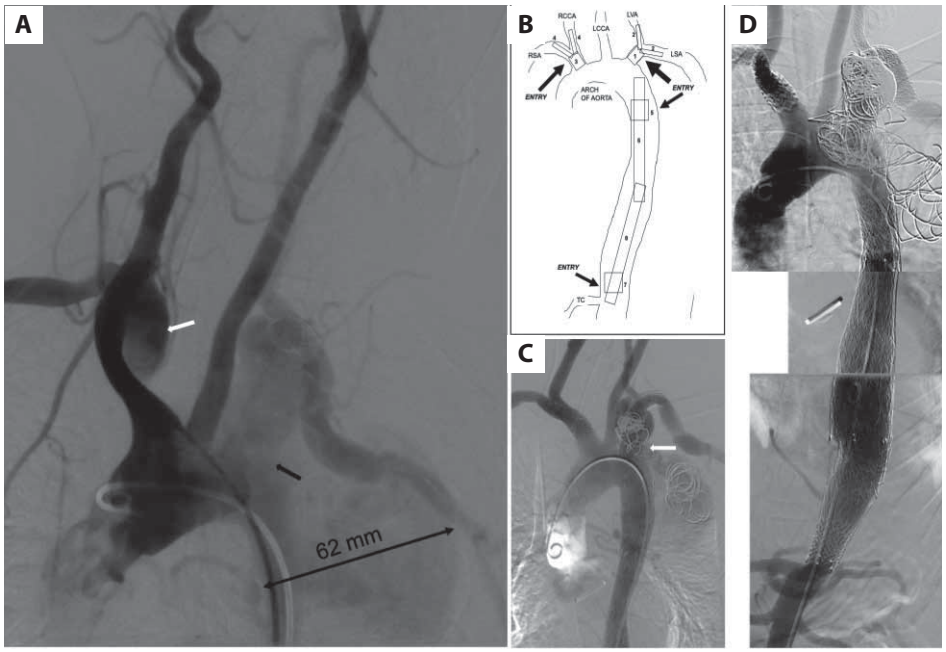

Figure 1. A. Procedural aortography: the white arrow points to the endoleak to the false lumen at the level of the left subclavian artery; the black arrow indicates the endoleak to the false lumen at the level of the brachiocephalic trunk. **B.** Scheme of endovascular repair: 1: covered stent in left subclavian artery, 2: covered stents in the left subclavian and left vertebral arteries, 3: covered stent in the brachiocephalic trunk, 4: covered stents in the right common carotid and right subclavian arteries, 6 and 8: covered stents in the aorta, 5 and 7: self-expanding stents in the aorta. **C.** Residual endoleak at the level of the left subclavian artery (arrow), coils in the false lumen. **F.** Final result of the repair

Abbreviations: LCCA, left common carotid artery; LSA, left subclavian artery; RCCA, right common carotid artery; RSA, right subclavian artery; TC, celiac trunk

Article information

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Congenital coronary aneurysm and cameral fistula embolization in a teenager

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Coronary interventions in children are rare and mostly caused by congenital acquired anomalies, including abnormal vessel origin from the pulmonary trunk, coronary and cameral fistulas, and vasculitis (e.g., Kawasaki and Takayasu diseases or systemic lupus erythematosus with aneurysm development) [1–3] or cardiac surgeries with coronary transplantation.

A 17-year-old girl was referred for cardiac evaluation due to a heart murmur found on auscultation in a pediatric office. In medical history, the patient was asymptomatic without symptoms of chest pain or easy fatigability. A diagnosis of right coronary artery (RCA) aneurysm with a cameral fistula was established in a cardiology department on transthoracic echocardiography (TTE), computed tomography, and coronary angiography, with a negative treadmill exercise stress test. The patient was referred for heart surgery. On admission to the cardiac surgery center, the vital signs were normal with a regular heart rate of 72 beats per minute and blood pressure of 100/60 mm Hg. Myocardial biomarkers (NT-proBNP and troponin) were within the normal range. An electrocardiogram (ECG) showed normal sinus rhythm without features of ventricular hypertrophy or myocardial ischemia. TTE revealed normal myocardial contractility, dilated proximal RCA (6 mm) with turbulent flow over the right ventricular (RV) wall. The child was qualified for initial interventional RCA aneurysm embolization and in case of failure, surgery was an option.

Aortic root angiography showed proximal RCA dilation, critical pre-aneurysmal stenosis (1 mm), large right coronary aneurysm (10 × 7 mm) with a cameral fistula stealing the blood into the RV (Figure 1A–C, Supplementary materials, *Videos S1–S3*). The aneurysm continued into the distal RCA supplied abundantly from the circumflex artery (Cx) collateral circulation. A balloon occlusion test of the RCA aneurysm with a 4 mm Tyshak balloon catheter was performed with simultaneous ECG evaluation. It showed normal ECG tracings indicating sufficient Cx collateral circulation.

An arterio-venous wire loop was established with a multipurpose catheter over a 0.014-inch guidewire and an Amplatz 6 mm Goose Neck™ snare system (ev3, Plymouth, MN, US) by crossing the aorta, right coronary aneurysm, cameral fistula, RV and inferior vena cava (Supplementary materials, *Videos S4–S7*). Unfortunately, access to the aneurysm with a 4 F multipurpose catheter *via* cameral fistula was inapplicable due to the small size of the fistula (less than 2 mm).

Finally, the approach through the aortic root and, critically, RCA stenosis was established with a 2.9 F catheter. The aneurysm was successfully embolized with neurological detachable Penumbra Coil 400 system and PAC coils (Penumbra, Alameda, CA, US) (Figure 1D–F; Supplementary materials, *Videos S8–S11*). The clinical course was uneventful with normal ECG and myocardial contractility on TTE. The troponin level was transiently elevated up to 90 ng/l (normal range <26.2 ng/l) with normalization within 3 days.

In 1 year follow up the girl was in good condition with normal TTE and magnetic resonance imaging (LVEF 60%, RVEF 59%) without features of myocardial ischemia.

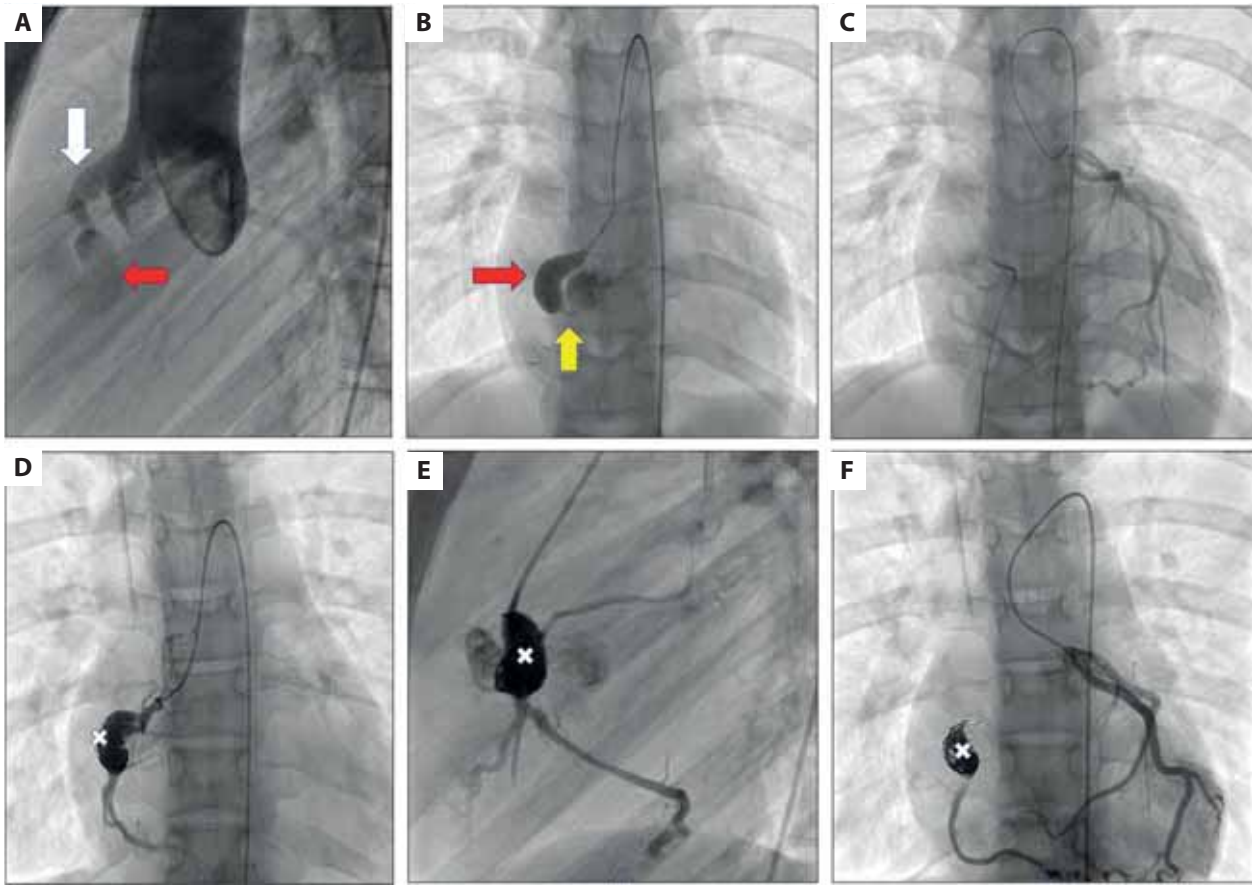

Figure 1. A. Aortography in the lateral view showing right coronary proximal dilation (white arrow), pre-aneurysmal stenosis, and a large coronary aneurysm (red arrow). **B.** Selective right coronary angiography (anteroposterior view) showing a large aneurysm (red arrow) and a cameral fistula (yellow arrow) draining the blood into the right ventricle. **C.** Selective left coronary angiography (antero-posterior view) showing collateral circulation with the right coronary artery. **D** and **E.** Selective right coronary aneurysm embolized with Penumbra coils (white cross). **F.** Selective left coronary angiography (anteroposterior view) showing collateral circulation without steal phenomenon *via* the embolized cameral fistula

In conclusion, we would like to underline that percutaneous or hybrid coronary interventions have become alternative options in children with coronary abnormalities [4]. The dilemma of whether to embolize an RCA in the case of a life-threatening aneurysm may be resolved with a balloon occlusion test and left coronary angiography showing sufficient collateral circulation [5].

Supplementary material

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

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Additional factors underlying pacing-induced cardiomyopathy in patients who underwent right ventricular pacing and His bundle pacing

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I have read with great interest the article comparing the impact of right ventricular pacing (RVP) and His bundle pacing (HBP) on cardiac fibrosis and systolic function. Mizner et al. [1] reported that HBP is related to better systolic function, compared to RVP, and to increases in fibrosis markers in patients whose ejection fraction was reduced by more than 5% during follow-up.

Although the most common cause of advanced atrioventricular (AV) blocks is idiopathic fibrosis of the conduction system caused by aging; cardiomyopathies and drug toxicities also may result in advanced AV blocks [2]. Sarcoidosis and amyloidosis are well-known diseases related to cardiac involvement and advanced conduction system disorders. Both sarcoidosis and amyloidosis tend to progress despite the current optimal treatment [3]. Therefore, it would be valuable if the study population had been screened for such cardiomyopathies because the reduction in ejection fraction and increased fibrosis markers might have indicated the progression of the underlying disease rather than pacing-related cardiomyopathy.

Current evidence from heart failure treatment points out that some medications including renin- angiotensin-aldosterone system inhibitors and SGLT2 inhibitors have beneficial effects on cardiac remodeling [4]. A significant proportion of the study population had comorbidities such as hypertension, diabetes, and coronary artery disease, so most of these patients might have been under treatment with the abovementioned drugs. The use of these drugs might have affected the results including changes in ejection fraction and fibrosis markers.

Programming the cardiac implantable electronic device is crucial because it may affect the pacing rates. Heart rate decreases during the night [5] and if the heart rate reduces below the limit, the pacemaker intercedes, resulting in increased pacing rates. Beta-blockers also decrease heart rates and may cause increased ventricular pacing burden. Therefore, I think it is important to take into account the baseline-set lower heart rate limit and the use of beta blockers in assessing the burden of ventricular pacing.

To conclude, of course, pacing-induced cardiomyopathy may develop in patients with high ventricular pacing burden, however, the impact of used medications and possible underlying cardiomyopathies should not be overlooked.

Article information

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Additional factors underlying pacing-induced cardiomyopathy in patients who underwent right ventricular pacing and His bundle pacing. Author's reply

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Thanks to Dr. Şener for their comments. We agree that concomitant diseases such as cardiac sarcoidosis (CS) and amyloidosis (CA) might influence the clinical course in patients with bradycardia. The clinical spectrum of transthyretin cardiac amyloidosis (ATTR-CA) symptoms includes advanced conduction disorders requiring pacemaker implantation. It had been documented that 3%–13% of ATTR-CA patients had pacemakers implanted before they were diagnosed with CA [1]. However, in the European population, the prevalence of ATTR-CA in pacemaker patients was very low (only 2%) [2]. Cardiac sarcoidosis (CS) also leads to advanced symptomatic atrioventricular blocks, and according to Kandolin et al. [3], it was the first symptom in up to 44% of patients with diagnosed CS. However, the prevalence of CS remains very low in the European population, where it is a rare condition. We initiate further diagnostic steps only if other risk factors are present [3]. Therefore, we believe that the low prevalence of these diseases and the randomized study design should not affect the differences in the left ventricular ejection fraction between studied groups. On the other hand, we agree that due to the pathophysiology of the diseases, scanning for CS and CA could be helpful while measuring the markers of collagen metabolism.

Pharmacological treatments, such as SGLT2 inhibitors and others, may influence left ventricular ejection fraction and myocardial fibrosis. We have not provided their numbers, but SGLT2 inhibitors were not as available during the study period as they are now. Again, the randomized nature of the project should minimize their effect on the results.

We also agree that it is possible to adjust the pacemaker programming to avoid ventricular pacing. On the other hand, it is known that sacrificing atrioventricular synchrony at the cost of AV delay prolongation promotes atrial fibrillation and may worsen patients' clinical course. In light of this information and our experience, we are convinced that right ventricular pacing is fundamentally inappropriate treatment for bradycardia. It increases ventricular dyssynchrony, while His bundle pacing and left bundle branch pacing do not [4].The pacemaker's primary purpose should be to keep an adequate heart rate and preserve the atrioventricular and ventricular synchrony as close to the physiological state as possible. Moreover, it should also follow other physiological needs of the human organism: not only a decline in the basal heart rate during rest or sleep but also a change in the heart rate in concordance with breathing [5].

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The first septal perforating artery in the setting of percutaneous coronary interventions: More than just a side branch

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In patients undergoing percutaneous coronary interventions (PCIs), occlusion of small side branches, including the first septal perforating artery (SPA), has been generally ignored by performing operators [1]. However, the first SPA might have a pivotal role in the perfusion of critical areas of the cardiac conduction system with important implications [1–3]. The recent article by Pavlov et al. [1] has reported a case of heart failure complicated by the occlusion of the first SPA and consequent atrioventricular (AV) block during PCI and has also described the management strategy of this challenging case [1]. Accordingly, we would like to comment on clinical and practical implications regarding the acute occlusion of the first SPA during PCI.

First, perfusion of the major conduction structures, including the His bundle, right bundle branch, anterior and posterior fascicles of the left bundle branch, was previously demonstrated to have a significant variation in the population [2]. Accordingly, each of these structures may be perfused exclusively by the first SPA or AV node artery or both (dual perfusion) [2]. Therefore, occlusion of the first SPA may result in any of the following scenarios during PCI [2, 3]:

- No impact on the conduction system due to dual or AV node artery perfusion in these structures;
- Right bundle branch block (RBBB);
- Bifascicular block (RBBB mostly with anterior fascicular block);
- Isolated fascicular block;
- Rarely, left bundle branch block (LBBB);
- Even more rarely, intra-Hisian block (since the perfusion of the His bundle is mostly dual or from the AV node artery) [2, 3].

The patient had a transient AV block possibly due to acute intra-Hisian or infra-Hisian ischemia (possibly due to a co-existing new-onset RBBB and LBBB) [1]. Patients with this kind of AV block are well known to present with wide QRS morphology, along with severe bradycardia and hemodynamic compromise due to the ventricular origin of the escape rhythm [2]. Therefore, we wonder about the clinical features of the AV block in the patient (morphology, rate, and associated symptoms) [1].

Second, the size of the occluded first SPA might also matter in terms of clinical outcomes including infarct size and emerging conduction blocks. An earlier study suggested that RBBB might be strongly associated with SPA occlusion accompanied by a substantial anteroseptal scar in patients with severe systolic dysfunction [3]. This may also suggest that the magnitude of septal ischemia, and consequent scar formation in the setting of the first SPA occlusion may be correlated with the size of the occluded artery. Moreover, occlusion of large first SPAs (as in the patient [1]) during PCI is more likely to be associated with any of the aforementioned conduction blocks (mostly RBBB with or without fascicular block [1, 3]). Therefore, an existing large first SPA during PCI of the proximal left anterior descending (LAD) artery should prompt the operator to take necessary measures (wiring the SPA before LAD stenting, venous access for possible temporary pacemaker implantation, etc.). Moreover, new-onset conduction blocks following uneventful PCI may denote late SPA occlusion and warrant a repeat coronary angiogram, and where necessary, PCI for SPA before considering radical therapeutic modalities such as permanent pacemaker or re-synchronization therapy.

Finally, wiring of the first SPA, particularly with ostial stenosis, may be extremely challenging due to its perpendicular take-off from the LAD in most cases. This may be even more challenging following stent implantation in the proximal LAD (as in the patient [1]). Therefore, safeguarding a large first SPA with a stiff guidewire (mostly with the assistance of a microcatheter for guidewire exchange to avoid SPA dissection) might significantly reduce its take-off angle, and might significantly facilitate re-wiring of the SPA following LAD stenting (re-wiring with another soft guidewire while the stiff guidewire in SPA is left jailed under the stent). Thereafter, the procedure may be completed with kissing balloon inflation. This might have been a reasonable strategy for the patient as well [1]. Notably, stenting of the SPA should be avoided due to its intramural course [4]. Stent misplacement in the SPA was previously reported to be associated with a variety of complications including septal hematoma and coronary-cameral fistula [4].

In conclusion, the article by Pavlov et al. [1] should be highly commended due to its didactic features. The first SPA should not be regarded as just a side branch; it is an artery that might have important clinical and practical implications in patients undergoing PCI [1–4].

Article information

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Septal branch in percutaneous coronary intervention: A strange and rare brew. Author's reply

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We wish to express our gratitude to Yalta et al. [1] for showing interest in our case report depicting important consequences of septal branch (SB) occlusion during percutaneous coronary intervention (PCI) on the left anterior descending (LAD) coronary artery [2]. As Yalta et al. remarked, several conduction abnormalities can ensue following SB occlusion. We observed a newly developed complete right-bundle branch block progressing within minutes into a complete atrioventricular (AV) block with wide QRS ventricular rhythm (38/min). In such circumstances, hemodynamic support provided by iVAC 2L is diminished. Indeed, blood pressure dropped to the level of 80/30 mm Hg. In addition, the system provides no support in the event of malignant ventricular arrhythmia, a complication potentially triggered by acute ischemia, bradycardia, and ventricular premature beats. To overcome this, urgent temporary electrostimulation was established via right femoral venous access. As described, restoring SB flow resulted in the resolution of conduction abnormalities and recurrence of narrow QRS with regular AV conduction.

The size of potential myocardial infarction (MI) following SB occlusion is not negligible; however, it was not the main indication for pursuing SB reperfusion. As shown in the accompanying video material, the extensive transseptal collateral network supplying chronic total occlusion (CTO) of the right coronary artery, and considerable remaining SBs would possibly render newly developed MI less substantial. During SB occlusion, the patient reported only slight chest discomfort while consistent ST-segment disturbances could not be observed due to conduction abnormalities and electrostimulation. Although MI of any size may have diminished the potential for recovery in this patient, PCI was continued to avoid deleterious hemodynamic effects of complete bundle branch block and the need for permanent electrostimulation (resynchronization therapy in this case).

Yalta et al. imply that safeguarding SB with a stiff wire may have facilitated further SB intervention in the event of occlusion. We argue against routine SB wiring during LAD PCI. As mentioned in the case report, a favorable take-off angle (approaching 90°), collateral network, and small calibers render SB protection unnecessary. The scarcity of similar cases and the high rate of clinically silent SB occlusion also advocate a more conservative approach. Avoiding double-layer stenting over the SB ostia may be also a prudent strategy (as applied in our case). SBs are usually spared from profuse chronic calcific atherosclerosis [3]. Soft atherosclerotic plaque or thrombus shift was the source of the SB occlusion in our case. In such circumstances, accessing SB should not be challenging with contemporary armamentarium. The main focus of the PCI should be long-term results on the main branch, a goal easily disrupted by a stiff wire in the steeply angled side branch. If side branch balloon dilatation is sufficient to restore the SB flow, we advise against routine balloon kissing dilatation. In any case, and, in particular, if kissing balloon dilatation is inevitable, we strongly suggest employing abundant balloon postdilatation to optimize the main branch stent, as performed in our case. One should also bear in mind the possibility of endothelial damage by a "cheese cutting" effect of the wires placed in septal branches (for example, while retrieving a jailed wire), a phenomenon well described in CTO procedures [4].

Although a strange brew, relevant consequences of SB occlusion during LAD PCI are primarily a rare brew. Every interventional cardiologist should, however, be aware of the potential implications of such an event, reaching much further than the occlusion of any other similarly sized side branch. As for protective strategies, we suggest the "less-is-more" principle with a focus on perfecting the main branch stent scaffolding.

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The use of andexanet alpha in the Polish setting: An interdisciplinary protocol. Expert consensus statement of the Polish Cardiac Society

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ABSTRACT

Andexanet alfa (AA) is a recombinant inactive analog of human activated factor X (FXa), effectively reversing the effects of its inhibitors — rivaroxaban and apixaban, which are available in Poland. The drug was approved for clinical use registration after the publication of the results of the ANNEXA-4 trial (Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of FXa Inhibitors 4), in which its efficacy in restoring hemostasis in life-threatening hemorrhages in patients receiving using the aforementioned anticoagulants was demonstrated. Hence, AA is now recommended for patients on apixaban or rivaroxaban therapy with massive and uncontrollable hemorrhages, including hemorrhagic strokes (HS) and gastrointestinal bleeding.

Drug-specific chromogenic anti-Xa assays are generally best suited for estimating rivaroxaban and apixaban plasma levels, aside from direct assessment of their concentrations. The absence of anti-Xa activity, determined using these assays, allows us to rule out the presence of clinically relevant plasma concentrations of any FXa inhibitor. On the other hand, the dose of AA should not be modified based on the results of coagulation tests, as it depends solely on the time that elapsed since the last dose of FXa inhibitor and oon the dose and type of FXa inhibitor.

AA is administered as an intravenous (*i.v.*) bolus, followed by an *i.v.* infusion of the drug. The maximum reversal of anti-Xa activity occurs within two minutes of the end of the bolus treatment, with the continuation of the continuous *i.v.* infusion allowing the effect to be maintained for up to two hours afterwards. Because anticoagulant activity can reappear after the infusion is completed, it is currently unclear at what point after AA administration FXa inhibitors or heparin should be re-administered. In Poland AA is starting to become available and its urgent need to administer it to patients with severe bleeding on apixaban or rivaroxaban.

Key words: andexanet alfa, antidote, apixaban, bleeding, non-vitamin K antagonist oral anticoagulants, rivaroxaban

INTRODUCTION

In recent years, non-vitamin K antagonist oral anticoagulants (NOACs) or direct oral anticoagulant inhibitors (DOACs) have mostly replaced vitamin K antagonists (VKAs) due to their efficacy, safety, and predictable therapeutic effects. The use of NOACs, compared to VKAs, is associated with a lower risk of minor, clinically significant hemorrhages, as well as major hemorrhages, including those resulting in death. However, there is a greater risk of gastrointestinal bleeding in patients taking NOACs, probably due to the presence of the active NOAC in the gastrointestinal tract.

Due to the increasing number of users of NOAC, we encounter them more frequently among trauma patients and those referred to surgical wards. The presence of overt acute bleeding, or the need for immediate surgical intervention, necessitate reversing the anticoagulant effects of previously taken medications. Up until recently, for in-hospital use, the only available drug of this type was idarucizumab that reverses the activity of dabigatran. In recent years, a product that reverses the action of activated factor X (FXa) inhibitors, such as rivaroxaban and apixaban, has just started to become available in clinical practice. in Poland after successful randomized clinical trials. That product is a recombinant, modified, and inactive analog of FXa — andexanet alfa (AA) [1, 2].

FXA INHIBITOR ACTION MECHANISMS

The use of NOACs is effective, safe, and recommended in:

- prevention of stroke and peripheral embolism in patients with established permanent or paroxysmal atrial fibrillation;
- treatment and prevention of venous thromboembolism (VTE).

The NOACs available in Poland include dabigatran, a thrombin inhibitor, and FXa inhibitors, namely rivaroxaban and apixaban. FXa inhibitors are selective direct inhibitors of FXa, which catalyzes the conversion of prothrombin to thrombin, with the effect of the drugs directly proportional to their concentration. The bioavailability of rivaroxaban is 80%–100%, with a half-life of 7–11 hours, while that of apixaban is 50% and 12 hours, respectively. Both drugs are excreted in one-third by the kidneys in an unchanged form, while two-thirds are metabolized by CYP3A4. Unlike dabigatran, FXa inhibitors show a higher percentage of plasma protein binding, hence dialysis does not significantly reduce the concentration of these drugs [3, 4].

One of many significant advantages of NOACs is the lack of need for routine monitoring of blood clotting parameters, as is the case with VKA therapy. However, it is important to remember that these drugs significantly affect the results of most coagulation tests (Table 1). Routine monitoring of plasma NOAC concentrations for dosage

Table 1. The influence of NOACs on hemostasis results

Test	Dabigatran	Rivaroxaban	Apixaban	Comments
A. Routine testing (screening for NOAC)				**Interference vs. measurement**
PT	–/↑	↑/↑↑	–/↑	Different reagents show different sensitivity; order of sensitivity: rivaroxaban > dabigatran > apixaban; only a few reagents are sensitive to apixaban
APTT	↑/↑↑	–/↑	–/↑	Different reagents show different sensitivity; order of sensitivity: dabigatran > rivaroxaban > apixaban
B. Quantitative tests (measurement of NOAC concentration)				
dTT/DTI	↑↑	–	–	Tests sensitive to dabigatran; insensitive to anti-Xa inhibitors
ECT/ECA	↑↑	–	–	Tests sensitive to dabigatran; insensitive to anti-Xa inhibitors
Anti-Xa	–	↑↑	↑↑	Insensitive to dabigatran. Sensitive to anti-Xa inhibitors

Based on: Favaloro E, Lippi G. Blood Transfus. 2017; 15(6): 491–494

Abbreviations: APTT, activated partial thromboplastin test; dTT, diluted thrombin time; ECT, ecarin clotting time; ECA, ecarin chromogenic assay; PT, prothrombin time; TGA, thrombin generation assay; TT, thrombin time

Table 2. Non-vitamin K antagonist oral anticoagulant dosage for stroke prevention in patients with atrial fibrillation

	Rivaroxaban	Apixaban	Dabigatran
Standard dose	20 mg 1 × per day	5 mg 2 × per day	150/110 mg 2 × 1
Reduced dose	15 mg 1 × per day *Dose reduction at CrCl ≤15–49 ml/min	2.5 mg 2 × per day *Dose reduction when 2 of these criteria are met: 1. body weight ≤60 kg, 2. age ≥80 years, 3. serum creatinine level ≥133 µmol/L (1.5 mg/dl), or based on a single criterion: when CrCl 15–29 ml/min	110 mg 2 × 1, if: age ≥80 years, a patient treated with concurrent verapamil, increased risk of gastrointestinal bleeding

Based on: [1]

Abbreviation: CrCl, creatinine clearance

Table 3. Treatment of deep vein thrombosis and pulmonary embolism

	Rivaroxaban	Apixaban	Dabigatran
Initial treatment	15 mg 2 × per day for 21 days	10 mg 2 × per day for 7 days	UFH or LMWH
Continued treatment	20 mg 1 × per day (without dose reduction, unless the risk of bleeding outweighs the risk of recurrent thromboembolism)	5 mg 2 x per day (without dose reduction)	150 mg 2 × 1 (without dose reduction)
Prolonged anticoagulant treatment after pulmonary embolism in patients without malignancies (after 6 months of anticoagulant treatment at therapeutic doses) — recommendation class IIa	10 mg 1 × per day	2.5 mg 2 × per day	150 mg 2 x 1 (dose reduction criteria as in AF)

Based on: [1]

Abbreviations: AF, atrial fibrillation; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin

adjustment is not recommended, as it has not yet been investigated if such an approach has any positive effects on outcomes of long-term treatment. The dosage of most FXa inhibitors is currently determined solely by the indication for their use and renal function while dosing apixaban is additionally determined by the patient's age and weight. The recommended dosages for each clinical indication are shown in Tables 2 and 3 [1, 5].

ROLE OF BIOCHEMICAL EXAMINATIONS IN ASSESSING INDICATIONS FOR TIMING OF ANDEXANET ALFA ADMINISTRATION

At 2–3 hours (±1) after NOAC administration, both the plasma drug concentration and the effects on coagulation parameters are at their highest. Unfortunately, routine determination of baseline coagulation parameters does not accurately assess anticoagulant effect and adherence to drug intake recommendations, let alone the time elapsed since the last drug dose.

In the event of bleeding in patients treated with FXa inhibitors, in addition to routine laboratory tests (blood count, activated partial thromboplastin time [APTT], prothrombin time [PT], fibrinogen, aminotransferases, and creatinine clearance), evaluation of plasma drug levels is advised, and immediate action should be taken as dictated by clinical evaluation, without waiting for laboratory test results.

Based on the results of observational studies, the International Commission for Standardization in Hematology, in its 2021 recommendations, has expanded the indications in which NOAC measurements may be useful to determine appropriate strategies to reverse the anticoagulant effects of the drugs and/or required dosing and to guide further treatment. Urgent indications for laboratory evaluation of NOAC levels generally include severe bleeding, urgent surgery, and acute ischemic stroke, with consideration of thrombolysis. Planned indications for such evaluations are helpful in the long-term care of patients with extreme weight, renal/liver disease, suspected malabsorption syndrome, or drug interactions. Tests evaluating NOACs (over a wide range of concentrations) are covered by most international external quality control programs. Despite lack of standardization, good correlations between different testing systems were demonstrated, with rivaroxaban and apixaban assays showing low coefficients of variation.

The minimum NOAC concentration that can contribute to bleeding is not known. Expert-based guidelines from the International Society on Thrombosis and Haemostasis (ISTH) suggest considering NOAC reversal in patients with severe bleeding and NOAC concentrations >50 ng/ml, and in preoperative patients at high risk of bleeding and NOAC concentrations >30 ng/ml [1, 6–8].

Methods for evaluating the anticoagulant activity of FXa inhibitors

While routine clotting times (PT and APTT) cannot be used to accurately assess the effect of rivaroxaban and apixaban, both clotting times are prolonged in the presence of anti-Xa inhibitors in a drug type- and dose-dependent manner. However, these test results do not demonstrate sufficient linearity, are not very accurate, and depend on the sensitivity of the reagents and the type of coagulometer. PT is considered only as a screening test for the use of rivaroxaban, which, with adequate sensitivity, will result in PT prolongation at the time of therapeutic drug concentration. On the other hand, this parameter should not be used to assess the concentration of apixaban, since in this case, PT prolongation can only occur at the maximum

concentration. It is also worth mentioning that the result of the assay depends on the reagent used. Thus, a normal PT does not necessarily exclude a therapeutic concentration of rivaroxaban, let alone apixaban. Hence, we should not rely on the PT result in the course of clinical management.

The usefulness of POCTs (point-of-care tests) for assessing NOAC activity (including thromboelastography/thromboelastometry, surface acoustic wave, dry blood spot and microsampling techniques, and urine strip tests) has not been confirmed. The tests show low sensitivity at low NOAC concentrations, while urine determinations do not correlate with plasma drug concentrations. Currently, none of the POCT methods meet the parameters of *in vitro* device clinical trials, as they use an animal model or data from a small sample of patients, including a limited number of patients on NOACs, or are based on NOAC-enriched blood *in vitro*. Portable analyzers designed to monitor VKA treatment also do not accurately reflect the coagulation parameters in patients treated with NOACs. Research to implement rapid NOAC testing is still ongoing.

According to the literature, the most clinically useful method to determine the concentration of rivaroxaban and apixaban is the chromogenic "anti-Xa" method, adjusted using drug-specific calibrators. The method is simple to perform, has adequate sensitivity, a wide range of linearity, and a good correlation with NOAC reference mass spectrophotometry methods. Until recently, the anti-Xa method was considered highly specialized and relatively expensive. Today, due to the availability of commercial reagent kits, it can be performed around the clock using virtually any coagulation analyzer, with the result available in 30–60 minutes. The method relies on adding a reagent with a high concentration of FXa to citrated plasma. Factor Xa binds to the FXa inhibitor present in the patient's plasma, and the "free" FXa remaining in the reaction mixture is measured using the amidolytic chromogenic method. The reaction with the chromogenic substrate produces a yellow product (p-nitroaniline), and the measured increase in optical density is inversely proportional to the NOAC concentration. The results are read from a calibration curve plotted using a reagent of known concentration. The test shows a strong correlation with serum concentrations of rivaroxaban and apixaban, hence, it can be used as a clinically reliable monitoring tool. The absence of anti-Xa activity determined using these assays excludes clinically relevant plasma concentrations of the drug. Based on the available literature, it has been determined that anti-Xa activity <0.50 IU/ml corresponds to a plasma concentration of rivaroxaban or apixaban <30 ng/ml, which is the cutoff value for safe undertaking rescue procedures. At the same time, dose adjustment and the use of anticoagulant reversal therapies based on anti-Xa level results are still an area of interest. Firstly, therapeutic ranges have still not been established, and long-term data on the efficacy and safety of interventions targeting the anti-Xa levels are still lacking. Moreover, the value of the anti-Xa index, based on which we could select a higher or lower AA dose is also unknown. Moreover, in clinical practice, measuring the change of anti-Xa activity is also not useful for predicting clinical response following AA administration. In fact, the results of the ANNEXA-4 study showed no significant relationship between hemostatic efficacy and reduction in anti-Xa activity [1, 2, 6, 8, 9].

Conclusions

Quantitative NOAC measurements may be useful in detecting overexposure to these drugs with a risk of bleeding (also in terms of drug reversal strategies), under-exposure to NOACs with a risk of thrombosis, and identification of drug interactions, which should be confirmed by studies in larger cohorts. The fact that personalized NOAC dosing can improve the benefit-risk ratio in some patients has been confirmed by high inter-individual variability observed in phase III clinical trials, and numerous factors affecting pharmacokinetics and the dose-response relationship.

At present, it is believed that drug-specific chromogenic anti-Xa assays are the most suitable tools for measuring NOAC plasma concentrations. The cost of performing an anti-Xa test (about 100 PLN) is higher than PT/APTT, but comparable to many specialized coagulation tests. Given that their use is limited to specific situations, the burden on healthcare systems should be lower than that currently incurred when treating patients using VKAs.

In Poland, only a handful of laboratories undertake measurement of anti-Xa activity, to the disadvantage of patients in whom NOAC measurement is indicated, especially considering the limitations of the analytical and clinical value of screening tests. With assay automation and the availability of stable, liquid reagents, as well as the increasing use of NOACs, laboratories should enable clinicians to measure concentrations of these drugs. They should also define the sensitivity of measurement systems and participate in international quality control programs that include assessing the impact of NOACs on quantitative and qualitative hemostasis diagnostic tests.

There is a need to establish target therapeutic ranges and standardize NOAC assays, which will improve the safety of these drugs and ensure inter-laboratory reproducibility of results.

Increasing the availability and performance of NOAC concentration assays is essential for the development and implementation of guidelines for the optimal management of patients treated with NOACs as well as for determining strategies for administration and monitoring of the effects of reversal agents for these drugs.

To date, neither the NOAC concentration nor the anti-Xa index value, based on which we could select a higher or lower AA dose, is known. Therefore, in most cases of unknown timing of the last NOAC dose, such as in unconscious patients, it is recommended to administer a higher dose (if the patient is continuously taking 20 mg of rivaroxaban and 5 mg of apixaban) or a lower dose of the drug (patients

continuously treated with a reduced dose of rivaroxaban and apixaban).

ANDEXANET ALFA

Registered and unregistered indications

Andexanet alfa is a recombinant inactive human FXa analog that, through non-specific binding, prevents the action of all known FXa inhibitors, including low-molecular-weight heparin (LMWH) and unfractionated heparin (UFH).

AA is registered for use in patients with serious or life-threatening bleeding, treated with apixaban or rivaroxaban. The efficacy and safety of AA have been confirmed in numerous studies. Initially, the effect was evaluated in animal models [10, 11], followed by a phase II study using different doses of the drug in healthy volunteers receiving FXa inhibitors, to establish a dosing regimen [12, 13]. The effects of bolus administration and i.v. infusion of AA on apixaban and rivaroxaban concentrations, anti-Xa activity, and thrombin generation were documented in two phase III studies, ANNEXA-A for apixaban and ANNEXA-R for rivaroxaban [14]. In the end, AA was approved after the publication of the results of the ANNEXA-4 trial, a multicenter prospective open-label study that recruited 352 patients who experienced acute major bleeding, mainly intracranial and gastrointestinal, treated with FXa inhibitors. Primary endpoints included the percentage change in anti-FXa activity and the percentage of participants who achieved a good or excellent hemostatic effect within 12 hours after the infusion [2].

Based on the available literature, it is also known that AA administration can be considered off-label in life-threatening clinical situations requiring urgent surgical intervention [1, 15, 16].

Dosage regimen and pharmacokinetics

Low dose: Initial i.v. bolus of 400 mg (at 30 mg/min, about 15 min), then continuous i.v. infusion of 4 mg/min over 120 min (480 mg)

High dose: initial intravenous bolus of 800 mg (at 30 mg/min, approx. 30 min), then continuous i.v. infusion of 8 mg/min over 120 min (960 mg).

The choice of AA dose depends on the dose of FXa inhibitor administered and the time that elapsed since the last dose (Figures 1 and 2). Maximum reversal of anti-Xa activity occurs within two minutes of the end of the bolus. In contrast, the follow-up continuous i.v. infusion allows the reduction in anti-Xa activity to be maintained for two hours after it ends. Then, the anti-Xa level returns to or exceeds the activity recorded in the placebo group [1, 2, 17].

Treatment monitoring, contraindications, possible side effects

As mentioned, the determination of anti-Xa activity is not applicable for monitoring the reversal of the anticoagulant effect of FXa inhibitors. In fact, commonly available assays are inadequate for determining anti-Xa activity after AA administration. The high dilution of the sample and the reversibility of AA binding to the Xa inhibitor, leading to dissociation of the inhibitor and AA, result in overestimation of anti-Xa activity, which can cause significant underestimation of the drug effect.

Treatment monitoring should be based primarily on clinical parameters, namely assessment of hemostasis or side effects.

Interactions

Given the lack of clinical data on the safety of the combined use of AA and prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (aPCC), recombinant factor VIIa, fresh frozen plasma (FFP) or whole blood, such use should be avoided unless absolutely necessary. Several case series have been published on this topic, with the results highlighting the potentially increased thrombotic risk associated with the use of the AA and PCC combination [18, 19].

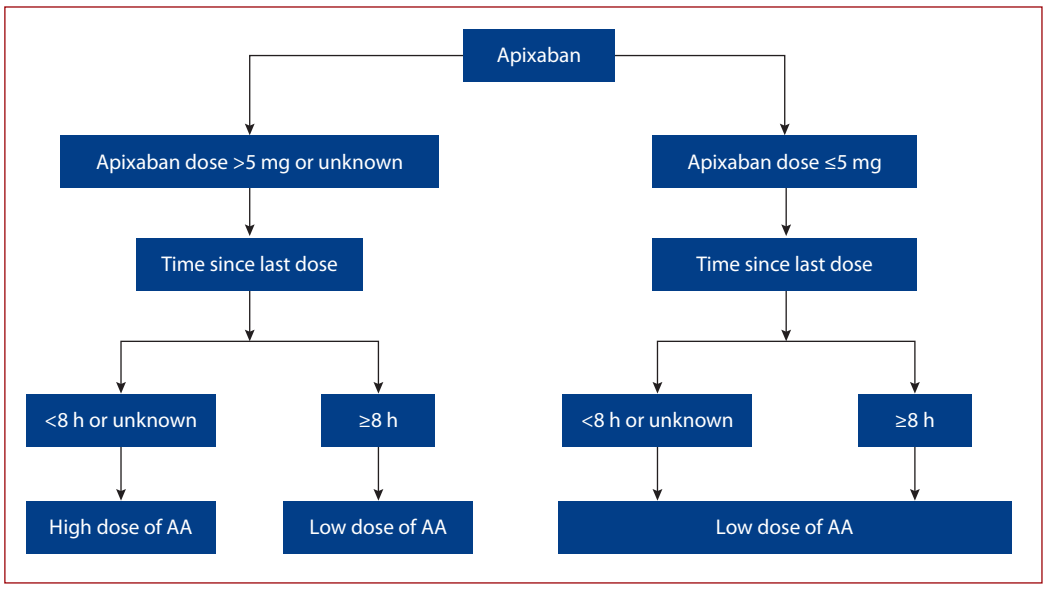

Figure 1. Dosage of andexanet alfa (AA) when using apixaban (based on: [17])

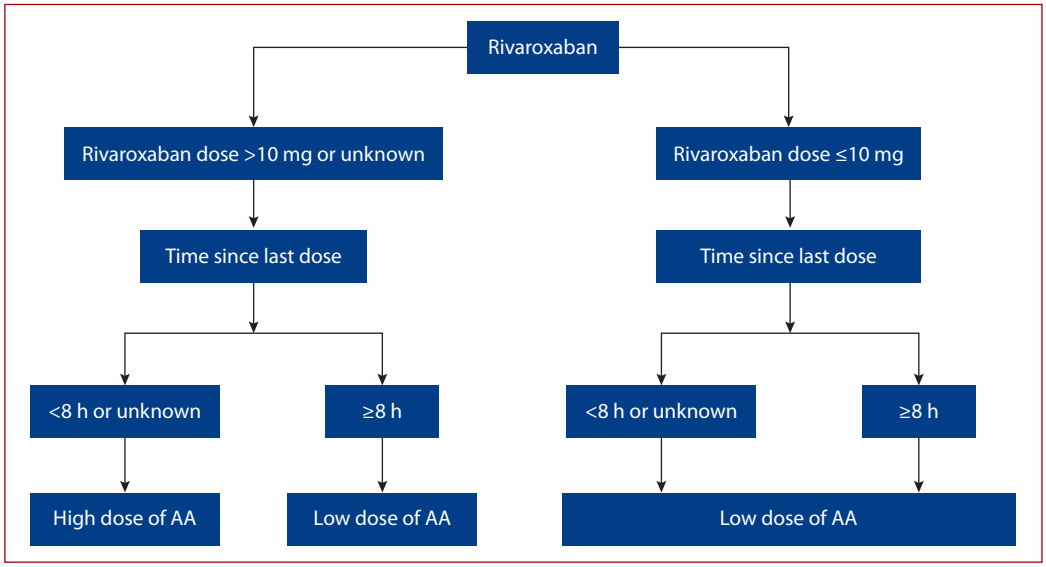

Figure 2. Dosage of andexanet alfa (AA) when using rivaroxaban (based on: [17])

The use of AA should also be avoided in the case of planned heparinization during surgery, as it may result in unresponsiveness to heparin. AA, however, has not yet been registered as an antidote to reverse the effects of heparins [20, 21].

In about 10% of patients, non-neutralizing antibodies to AA appear in low concentrations during treatment. However, the clinical consequences of their presence have not been demonstrated.

Contraindications to the use of the drug include hypersensitivity to the active compound or any other components of the formulation and a known allergic reaction to hamster proteins [17].

Side effects

The most common mild side effects are infusion-related reactions such as hot flashes, facial flushing, chest discomfort, or increased sweating.

If such mild side effects are observed, careful monitoring of the patient may suffice. In the case of symptoms of moderate severity, short-term interruption or slowing of the infusion with resumption after discomfort has subsided may be considered. Antihistamine administration may also be considered [17].

The use of AA is associated with significant risk of thrombosis. This complication usually results from the underlying disease that is the basis for NOAC therapy (mainly venous thromboembolism, atrial fibrillation), anticoagulant withdrawal, activation of coagulation in the course of bleeding, frequent bed immobilization during hospitalization, as well as the use of drugs reversing the anticoagulant effect of the FXa inhibitor. AA has an independent procoagulant effect, related to tissue factor pathway inhibitor (TFPI) inhibition. The period of increased risk in AA-treated patients remains unknown, but the described thromboembolic events can occur up to 30 days after infusion. In the ANNEXA-4 study, thromboembolic complications affected 10.4% of patients with a median time of occurrence of 9 days. These included cerebrovascular incidents, deep vein thrombosis, pulmonary embolism, and even acute myocardial infarction. Importantly, these did not occur in any patient after NOAC was restarted. Of the 50 patients who developed thromboembolic complications, 34 either did not resume anticoagulant treatment or suffered from thrombosis before it was resumed.

Hence, it is extremely important to monitor patients for signs or symptoms of thrombosis and to consider resuming anticoagulant treatment as early as possible after a bleeding event. To date, however, there is lack of results from randomized trials regarding the optimal time to re-initiate anticoagulant treatment. The clinical decision should, therefore, be made on an individual basis, considering the benefit-risk ratio [2, 17].

As for laboratory tests, increases in D-dimer and prothrombin fragments 1 + 2 above 2 times the upper normal limit were often observed after AA infusion in healthy subjects. These changes lasted from a few hours to a few days but were not related to the occurrence of thromboembolic complications.

AA exhibits modest renal clearance, and there is no need to adjust the drug dose according to renal and hepatic function. It is rapidly degraded in plasma by endogenous proteases, which results in its relatively short half-life (one hour) [17].

PATIENT POPULATIONS WITH SEVERE BLEEDING AND INDICATIONS FOR ANDEXANET ALFA

Patients with hemorrhagic stroke/hemorrhage to the central nervous system

Stroke is caused by restriction of blood supply to the brain or extravasation of blood and, accordingly, is classified as ischemic stroke (80%), hemorrhagic stroke (HS) (15%), or

subarachnoid stroke (5%). The incidence of HS increases sharply with age and is, therefore, expected to remain high due to population aging, even with improvements in blood pressure treatment [22, 23]. Another growing source of HS is the increasing use of oral anticoagulants for treatment [22, 24]. The incidence of intracranial bleeding associated with oral anticoagulants in phase III trials (comparing NOACs with warfarin and aspirin therapy) ranged from 0.2 to 0.5 per 100 person-years. It is worth noting, however, that the risk of such a complication during NOAC treatment is still about twice as low as with chronic warfarin therapy [25]. In two multicenter randomized trials comparing warfarin with rivaroxaban 20 mg daily (ROCKET-AF) or apixaban 2 × 5 mg daily (ARISTOTLE), intracranial hemorrhage incidence was estimated at 0.8% over a median of 707 days of follow-up (0.5/100 person-years) in the ROCKET-AF trial, and 0.33% per year in the ARISTOTLE trial. In comparison, the rates for warfarin treatment were, respectively: 1.2% (0.7/100 person-years) (hazard ratio [HR], 0.67) and 0.8%/year (HR, 0.42) [26, 27].

Known risk factors for intracerebral hemorrhage, despite adequate NOAC therapy, include advanced age, concomitant use of antiplatelet drugs, history of stroke or transient ischemic stroke, history of bleeding, decreased serum albumin levels, thrombocytopenia, race (Asian, Latin American, or black) and, especially, hypertension [25–28].

Hemorrhagic stroke, which occurs more often in patients taking oral anticoagulants, is associated with increased hematoma volume and expansion, as well as increased morbidity and mortality [22, 29]. The mortality rate in HS associated with taking oral anticoagulants is about 60% [30]. The use of NOACs is associated with lower, but still significant, risk of stroke compared with VKAs [31].

There is no doubt that reversal of NOACs should reduce the risk of emergence of hemorrhagic foci. Therefore, therapy should consider the possibility of using fast-acting specific inhibitors of these compounds [22].

The ANNEXA-4 trial showed that 79% of patients with an indication for reversal of factor Xa inhibitors related to HS achieved excellent or good hemostatic efficacy, defined as <35% increase in hematoma volume after 12 hours [2, 32]. Other retrospective studies have shown comparable results of AA hemostatic efficacy, ranging from 64.7 to 88.9% [33–35].

Current retrospective studies or case series have directly compared the risks and benefits of AA and prothrombin complex clotting factor concentrate (PCC) in patients with traumatic and spontaneous intracerebral hematomas (sICH). However, these studies have yielded conflicting results regarding the superiority of any of these medications in achieving hemostasis and decreasing the risk of death or thromboembolic events. Thus, the currently available evidence does not unequivocally support the clinical efficacy of AA or PCC in reversing FXa inhibitor-related acute major bleeding, nor does it allow for a conventional meta-analysis of potential superiority [36–42]. Further clinical trials are underway that will hopefully clarify the role of each agent in the treatment of sICHs [43].

Hemorrhagic stroke is a complex clinical event requiring multidisciplinary care. A patient with HS taking oral anticoagulants should be provided with medical care including clotting compensation, anticoagulation reversal, intensive blood pressure lowering, and the possibility of neurosurgical intervention, and should be treated in a stroke unit or intensive care unit. Brain imaging is essential to distinguish HS from ischemic stroke and to determine hematoma volume. Computed tomography of the head is the most widely used imaging method for confirming HS due to its widespread availability, speed and ease of performance, and high diagnostic accuracy. Imaging of the brain during the acute phase of HS can provide prognostic information and help monitor the evolution of the focus, development of hydrocephalus, and cerebral edema, especially, in patients whose neurological condition has deteriorated as well as those with impaired consciousness. The therapeutic goal in HS is to minimize the risk of hematoma expansion that results in rapid neurological deterioration. Hematoma expansion tends to occur early (usually within the first 24 hours) and is associated with poor prognosis and mortality. The risk of hematoma expansion is increased in patients taking oral anticoagulants.

In addition, most patients with acute HS have elevated blood pressure, which is also associated with higher risk of hematoma expansion and requires close monitoring.

Therefore, if HS is found to be associated with FXa inhibitor therapy, the use of such drugs should be halted, and efforts should be made to restore clotting function as soon as possible. In these patients, immediate administration of a specific antidote or, possibly PCC, should be considered. Treatment should be administered when clinically significant anticoagulant levels are suspected, based on the type and timing of FXa inhibitor administration. The decision to administer AA is made by the neurologist in conjunction with the neurosurgeon after deciding on conservative or surgical treatment. When considering the use of drugs to restore clotting function, it is important to consider the patient's performance status before HS, the extent of the hemorrhagic focus, the patient's general and neurological condition, and chances of survival. Cost, hospital formulary status, and drug availability may limit the choice of reversal agents, especially in small local hospitals.

The consensus of the European Stroke Organisation recommends immediate reversal of dabigatran anticoagulation with idarucizumab in the case of HS, and immediate administration of AA (grade C) in the case of HS related to factor Xa inhibitors. If AA is not available, high-dose 4-factor PCC (50 IU/kg) is recommended (grade C) [1]. Due to the lack of high-level recommendations for reversal strategies for NOAC-related sICH treatment, further clinical trials are needed. The choice of anticoagulation reversal agents in HS will continue to evolve, as will our understanding of their efficacy, safety, and risk of thromboembolism.

Patients with gastrointestinal bleeding

The management of patients with gastrointestinal bleeding resulting from overdose/abuse of factor Xa inhibitors is regulated by guidelines of research societies. Since FXa inhibitors, similar to other NOACs, are characterized by a relatively short half-life (12–24 hours), in most cases of gastrointestinal bleeding resulting from their use, temporary withholding of the supply of the preparations in question constitutes sufficient management. The joint 2021 recommendations of the British Society of Gastroenterology (BSG) and the European Society of Gastrointestinal Endoscopy (ESGE) [44] recommend the use of AA (considering its prothrombotic risk) as a reversal agent for factor Xa inhibitors only in hemodynamically unstable gastrointestinal bleeding patients (weak recommendation, low data quality).

Regarding specific sources and etiologies of gastrointestinal bleeding, the ESGE guidelines for upper gastrointestinal (UG) bleeding of non-variceal etiology [45] recommend temporarily withholding anticoagulants, including FXa inhibitors. This management should not delay UG endoscopy. In cases of severe, persistent bleeding, reversal agents should be considered (strong recommendation, low data quality). However, the guidelines refer to agents that reverse the effects of FXa inhibitors, including AA, as compounds of limited availability [46].

The ESGE guidelines for UG bleeding of variceal etiology [47] recommend the use of FXa inhibitor reversal agents exclusively in the absence of hemodynamic stabilization of the patient. The decision to use AA should be made in conjunction with a hematologist, taking into account the risk of thromboembolic complications that may occur as a result of the drug in question (strong recommendation, low-quality data). In other cases, it is recommended that FXa inhibitor therapy be temporarily withheld until its effect ceases on its own.

The ESGE guidelines for lower gastrointestinal bleeding [48] suggest the use of AA for bleeding that persists despite the implementation of endoscopic treatment and for persistent hemodynamic instability of the patient (weak recommendation, low data quality). In such a situation, hemodynamic evaluation of the patient is once more suggested. In addition, the guidelines note the limited availability of the agent, its high cost, and possible complications due to prothrombotic activity [2].

The joint 2022 guidelines of the American College of Gastroenterology (ACG) and the Canadian Association of Gastroenterology (CAG) do not recommend the use of AA in patients with suspected gastrointestinal bleeding resulting from FXa inhibitors (conditional recommendation, very low-quality data) [49]. The above position is based on the very low quality of available literature data (including lack of a control group and methodological inconsistency in terms of the endoscopic treatment implemented), high costs, and possible side effects of the compound in question. Nevertheless, the ACG and CAG guidelines allow the use of AA in cases of life-threatening gastrointestinal bleeding, in patients who have taken rivaroxaban or apixaban in the prior 24 hours.

Summarizing the recommendations of the scientific societies presented above, in the case of gastrointestinal bleeding resulting from FXa inhibitors, the use of AA is reserved for hemodynamically unstable patients and those with persistent bleeding despite implemented endoscopic treatment. Regardless of the etiology and source of gastrointestinal bleeding, measures to reverse the effects of FXa inhibitors, i.e., administration of AA, should not delay gastrointestinal endoscopy and should be preceded by a hematological consultation.

Patients hospitalized in the Emergency Department

The statutory tasks of the Emergency Department are specified as the delivery of healthcare services, consisting of preliminary diagnosis, and undertaking treatment to the extent necessary to stabilize the vital functions of persons in a state of sudden danger to life or health, from internal or external causes, and in particular in the event of an accident, trauma, and poisoning in adults and children [50]. Among the victims of traffic accidents and patients who have suffered injuries in other circumstances, patients with head injuries are the biggest concern in the Emergency Department. NOAC-associated intracranial hemorrhages are characterized by rapid deterioration of the patient's condition within 24–48 hours, as the hematoma volume increases, while the poor prognosis is related to the extent of the hematoma and intraventricular bleeding. In these cases, rapid reversal of NOAC effects prevents hematoma enlargement and facilitates appropriate surgical intervention. In general, the NOAC should be discontinued, the time of the last dose should be established, and the time of elimination of the drug from the body should be determined. Other measures include evaluation of the morphology, clotting tests, and measurement of creatinine/estimated glomerular filtration rate. A normal hemodynamic compromise should be reached, and if possible, surgery should be postponed, and bleeding should be controlled.

AA should be used in patients taking FXa inhibitors who are victims of traffic accidents, or trauma victims in other circumstances with life-threatening post-traumatic bleeding.

Detailed management of hemorrhagic side effects of FXa inhibitors

Breakdown of bleeding severity and management approaches

The management of bleeding in patients treated with NOACs should be dictated by the severity of bleeding; it should also be based on the patient's clinical condition and risk factors. To date, numerous scales for assessing the severity of bleeding have been developed, with the most

Table 4. Definition of major bleeding in non-surgical patients according to the International Society on Thrombosis and Haemostasis

1	Fatal bleeding and/or
2	Symptomatic bleeding in a critical area or organ (e.g., intraspinal, intracranial, intraocular, articular, pericardial, retroperitoneal, or intramuscular bleeding with fascial compartment syndrome) and/or
3	Bleeding accompanied by a decrease in hemoglobin concentration of ≥2 g/dl (or to an absolute concentration of ≤8 g/dl with no previous result) or requiring transfusion of ≥2 units of whole blood or red blood cell concentrate

Based on: Schulman S, Kearon C. Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. Thromb Haemost. 2005; 3: 692–694.

Table 5. BARC — Bleeding Academic Research Consortium scale

0		No bleeding
1		Inactive bleeding, not requiring specialized assistance, which may only contribute to discontinuation of antiplatelet or anticoagulant therapy
2		Overt, active bleeding that does not meet the criteria for types 3–5, but meets one of the three following criteria: 1) requires medical non-surgical intervention; 2) leads to hospitalization; 3) requires immediate evaluation
3	a	Overt bleeding associated with a decrease in Hb concentration of 3–5 g/dl or requiring blood transfusion
	b	Overt bleeding associated with a decrease in Hg of ≥5 g/dl or cardiac tamponade or bleeding requiring surgical intervention
	c	Intracranial or intraocular bleeding
4		CABG-related bleeding
5	a	Probably fatal bleeding (clinical suspicion without confirmation by autopsy or imaging)
	b	Fatal bleeding (overt or confirmed by imaging/autopsy)

Abbreviation: CABG, coronary artery bypass grafting; Hb, hemoglobin

common being the TIMI, ACUITY, and GUSTO scales or the ISTH, frequently used in studies of anticoagulant reversal agents (Table 4). The BARC scale (Bleeding Academic Research Consortium), which is recommended for use in cardiac intensive care units, is a standardized version of these various classifications [51, 52] (Table 5).

Patient-related risk factors include:

- anticoagulant treatment used, including the time that elapsed from the last dose of the drug;
- age;
- renal and hepatic function;
- comorbidities (e.g., coexisting cancer that increases the risk of bleeding or thrombosis);
- drugs that affect NOAC metabolism (this mainly refers to P-gp inhibitors and CYP3A4 inhibitors), concomitant use of antiplatelet drugs and non-steroidal anti-inflammatory drugs (NSAIDs);
- thromboembolic risk, which is important in the context of returning to anticoagulant treatment [1].

The European Society of Cardiology (ESC) guidelines differentiate bleeding into:

- mild (usually BARC 2);
- severe, non-life-threatening (BARC 3a);
- life-threatening or critical organ bleeding (BARC 3b).

General recommendations for bleeding during NOAC treatment include assessment of baseline hemostatic parameters (hemoglobin, hematocrit, platelet count, PT, TT, APTT) and renal function. As mentioned earlier, the effect of FXa inhibitors should not be assessed and the time of the last dose should not be estimated on the basis of coagulation parameter results. It should be kept in mind that such parameters can be abnormal for several other reasons, especially in cases of massive bleeding or intravascular coagulation syndrome. Only normal anti-Xa activity, evaluated using methods with adequate sensitivity, excludes therapeutic levels of Xa inhibitors.

The following are the recommendations for bleeding management according to its severity:

- Mild bleeding:
  - delay or skip the next NOAC dose;
  - the dose and type of NOAC used should be carefully reviewed before restarting treatment, and the need for other medications that increase the risk of bleeding should be verified.
- Severe, non-life-threatening bleeding:
  - it is important to stop bleeding and maintain adequate vascular volume: mechanical surgical or endoscopic compression to achieve hemostasis, fluid therapy, transfusion of red blood cell concentrate when Hb is reduced to under <7–8 g/dl, transfusion of platelet cell concentrate if the platelet count is ≤50 G/l or patient has been taking antiplatelet drugs, administration of tranexamic acid, causal treatment of bleeding;
  - the timing of the last NOAC dose should be determined;
  - activated charcoal may be considered within 3–4 hours of taking the NOAC;
  - in patients treated with dabigatran, consider idarucizumab or hemodialysis.

Life-threatening bleeding or bleeding into a critical organ

In patients treated with NOACs who experience such bleeding, in addition to implementing standard bleeding management (as above), it is advisable to reverse the anticoagulant effect. According to the recommendations of the European and American clinical societies, the first-line

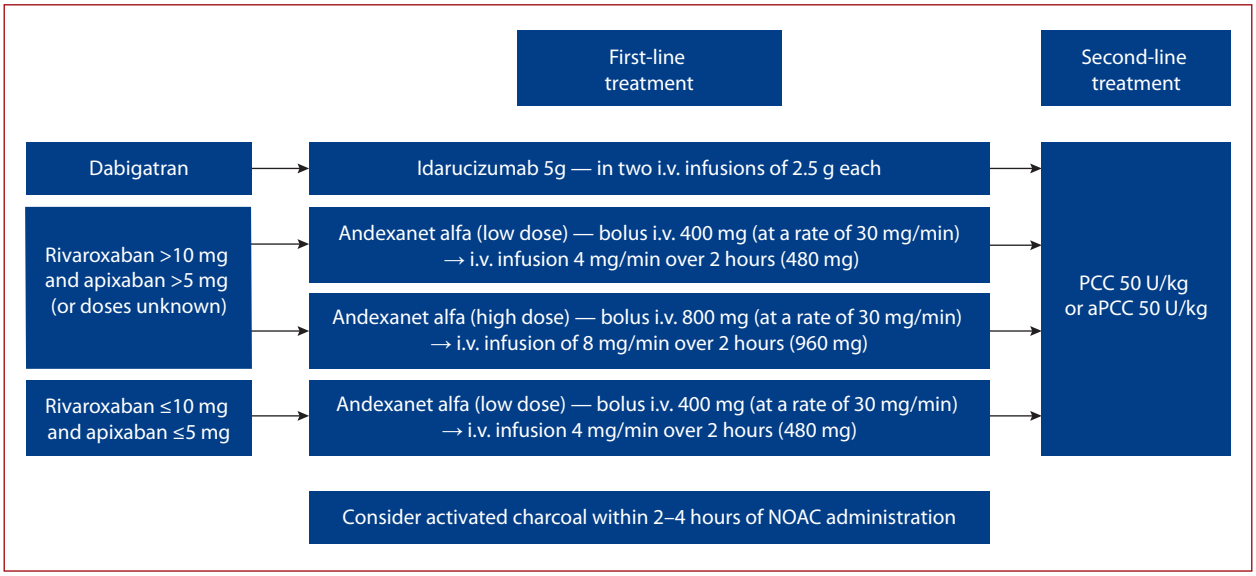

Figure 3. Reversal of non-vitamin K antagonist oral anticoagulant action. Based on: Tomaselli GF, Mahaffey KW, Cuker A, et al. 2017 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants: A report of the American College of Cardiology Task Force on expert consensus decision pathways. J Am Coll Cardiol. 2017; 70: 3042–3067

Abbreviations: aPCC, activated prothrombin complex concentrates; i.v., intravenous; PCC, prothrombin complex concentrates

management should be idarucizumab 5 g i.v. for patients treated with dabigatran, or AA for patients treated with apixaban and rivaroxaban (dosage above).

PCC or aPCC, on the other hand, are recommended as NOAC reversal drugs in the absence of an available antidote. PCC is used at a dose of 25 IU/kg body weight, and the dose can be repeated 1–2 times, if necessary, up to a dose of 50–75 IU/kg body weight. aPCC is used at a dose of 50 IU/kg body weight, up to a maximum of 200 IU/kg body weight.

Although the reversal of NOAC anticoagulant effect is sometimes insufficient by itself to stop bleeding, it may allow for other needed invasive interventions.

Neither vitamin K nor protamine sulfate is effective in treating bleeding in NOAC-treated patients. Similarly, FFP is not applicable to control bleeding in such patients. This is mainly due to the NOACs present in the plasma, which inhibit the activity of clotting factors after FFP administration. Hence, a transfusion of a large volume of FFP would be needed to achieve a clinically relevant effect [1, 51].

Figure 3 presents the American College of Cardiology recommendations for the management of bleeding in patients treated with NOACs [53].

Andexanet alfa vs. PCC (current therapeutic standard)

Based on the ESC guidelines, PCC or aPCC are recommended as NOAC reversal drugs for life-threatening bleeding in the absence of an available antidote, and the choice between the two agents should depend on the availability and experience of individual centers [1].

For major bleeding, AA has more evidence of effective and safe anticoagulant reversal than PCC. Several cohort studies on bleeding patients treated with anti-Xa agents who received PCC have been published, with somewhat conflicting results [54–57]. While Schulman and Majeed reported similar efficacy of PCC and AA, the study group sizes were quite small (66 and 84 patients, respectively). AA, on the other hand, underwent an extensive preclinical program on animal models followed by cohorts of non-bleeding patients treated with various anti-FXa agents [58, 59]. Its effectiveness was finally confirmed in the ANNEXA-4 trial, which recruited patients with severe bleeding (intracranial or gastrointestinal) treated with various anti-Xa agents [2].

Studies comparing the Food and Drug Administration approved AA and off-label PCC. A study by Costa et al. [36], argues in favor of AA due to its greater potential to achieve hemostasis. Schmidt et al. [59], on the other hand, documented similar efficacy of both agents, with a higher incidence of thrombotic events after AA. Evaluation of both products head-to-head is attempted in the ongoing ANNEXA-I trial (NCT03661528), comparing the use of AA with "usual care" in patients with intracranial hemorrhage taking FXa antagonists, with usual care in many situations consisting of PCC. However, the trial began in early 2019 and is still ongoing.

Resumption of anticoagulant treatment

It is unclear at what time after AA administration factor Xa inhibitors or heparin can be re-administered. The effect of AA ceases about 2 hours after drug infusion is stopped, at which time the reappearance of low concentrations of rivaroxaban and apixaban in the bloodstream can be observed.

Returning to anticoagulant therapy after a history of severe bleeding is associated with a better prognosis, a reduction in the risk of death and thromboembolic complications, but also with increased risk of bleeding [60]. In

contrast, the risk of bleeding, especially hematoma expansion in the HS, is highest within the first 72 hours. Hence, the timing of NOAC reintroduction is a crucial but currently unclear issue. Current retrospective studies, expert opinions, and clinical practice regarding the timing of resumption of anticoagulant treatment vary widely. The ESC guidelines recommend resuming NOAC treatment after 4–8 weeks following intracranial bleeding, after considering the benefits and risks and taking imaging results into account. For gastrointestinal bleeding, NOACs should be started as soon as clinically feasible [1, 2, 60].

Factors associated with increased risk of recurrent gastrointestinal bleeding:

- no identified source of bleeding and no reversible cause;
- bleeding during a break in NOAC use/while on non-therapeutic doses of NOACs;
- multiple angiodysplasia-like lesions in the gastrointestinal tract;
- chronic alcohol abuse;
- old age.

Factors associated with increased risk of recurrent CNS bleeding:

- lack of reversible cause;
- bleeding during interruption of NOAC use/during use of non-therapeutic doses of NOACs;
- concomitant antiplatelet treatment;
- modifiable risk factors:
  - uncontrolled hypertension,
  - alcohol/nicotine/sympathomimetic drug dependence,
  - low low-density lipoprotein/triglycerides,
  - concomitant antiplatelet treatment;
- non-modifiable:
  - older age,
  - Asian race,
  - male sex,
  - renal failure,
  - small vessel disease,
  - cerebral amyloid angiopathy,
  - microbleed presence in brain imaging.

Currently, there are no randomized trials on the timing of NOAC resumption after bleeding. Four phase III trials on resumption of anticoagulant treatment after intracranial bleeding are ongoing (ENRICH AF, ASPIRE, PRESTIGE-AF, and Restart TICrH) [2].

At present, the decision to resume anticoagulant treatment should be based on the patient's clinical condition, his/her thromboembolic risk, and whether the bleeding site has been identified and treatment to stop the bleeding has been successfully implemented.

In the case of bleeding resulting from reversible causes or post-traumatic bleeding, anticoagulant treatment can usually be initiated after the cause has been identified and eliminated. There are aspects of both gastrointestinal bleeding and intracranial hemorrhages that support the reintroduction of anticoagulant treatment or its discontinuation.

For major bleeding without an identified, reversible cause, the decision on anticoagulant treatment should depend on the possible net benefit of treatment and assessment of the risk of recurrent bleeding. Another option, in the case of contraindications to anticoagulant therapy in atrial fibrillation, is percutaneous closure of the left atrial appendage (recommendation grade IIb). However, even in this case, the patient requires continuation of antiplatelet therapy [1].

PATIENTS BEFORE SURGICAL PROCEDURES

Only non-cardiac surgical procedures performed on an elective and expedited basis require that discontinuation of anticoagulants at an appropriate time. NOACs, with normal creatinine clearance, should be discontinued more than 24 hours before low-risk surgery and 48 hours before high-risk surgery (e.g., procedures on the aorta, visceral and iliac arteries). The longest withdrawal, over 72 and 96 hours, is required for dabigatran in patients with impaired renal function (Table 6).

The exact timing of discontinuation should depend primarily on the type of treatment and the patient's renal function. In contrast, there is no evidence that the timing of withdrawal of NOACs before surgery depends on their

Table 6. The amount of time that should pass from the last dose of non-vitamin K antagonist oral anticoagulants (NOACs) before planned surgical procedures

	Apixaban/rivaroxaban		Dabigatran	
Bleeding risk	**Low**	**High**	**Low**	**High**
CrCl ≥80 ml/min	≥24 h	≥48 h	≥24 h	≥48 h
CrCl 50–79 ml/min			≥36 h	≥72 h
CrCl 30–49 ml/min			≥48 h	≥96 h
CrCl 15–29 ml/min	≥36 h		Contradicted in the MPI	
CrCl < 15 ml/min	Contradicted in the MPI			

For procedures with a very low risk of bleeding, the procedure should be performed during the period of minimum plasma concentrations of NOACs (12 or 24 hours after the last dose for twice-daily or once-daily administration, respectively)

Based on [1].

Abbreviations: CrCl, creatinine clearance; MPI, Medication Package Insert

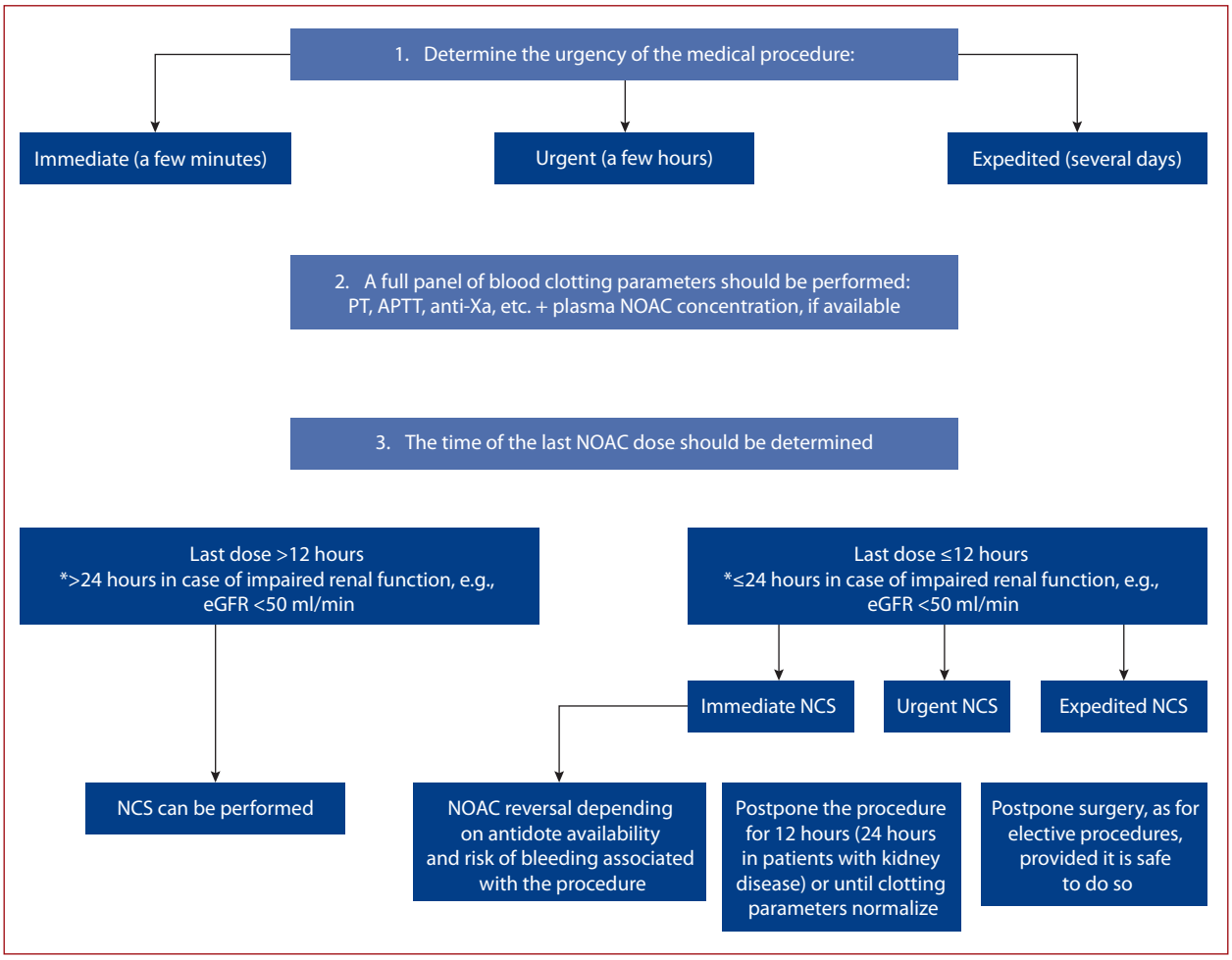

Figure 4. Proposed regimen for patients treated with NOACs before NCS (based on: [61])

Abbreviations: eGFR, estimated glomerular filtration rate; NCS, non-cardiac surgery' NOAC, non-vitamin K antagonist oral anticoagulants; other — see Table 1

residual plasma concentrations. In addition, the concentrations of NOACs that allow safe performance of particular surgical procedures are not known [61].

The situation is different for procedures with immediate and urgent indications. In these cases, according to the ESC recommendations, it is recommended that NOACs be discontinued immediately, and a full blood clotting panel (PT, aPTT, anti-Xa, etc.) and plasma NOAC determination, if available, should be performed. Surgery or intervention, if possible, should be delayed for at least 12 hours, and optimally for 24 hours after the last NOAC dose. If the patient requires immediate life-saving surgery associated with intermediate or high risk of bleeding, and the last dose of anticoagulant was taken earlier, it is advisable to use reversal agents (Figure 4) [1, 61].

Studies on NOAC reversal in urgent surgery situations, part of the process to register AA and idarucizumab, are difficult to compare.

A phase IIIb to IV study (ANNEXA-4) evaluated the efficacy and safety of AA in patients with acute major bleeding treated with FXa inhibitors but did not include patients receiving anticoagulant therapy, requiring surgery, or emergency invasive procedures [2]. In addition, the exclusion criteria for ANNEXA-4 included planned surgery within 12 hours. Nevertheless, off-label administration of AA is allowed in exceptional situations when there is a need for immediate life-saving surgical intervention in patients treated with a FXa inhibitor. The effectiveness of such a post-treatment strategy has been confirmed repeatedly in clinical cases and retrospective studies [15, 16, 62]. Unfortunately, because of AA's ability to non-specifically bind all factor Xa inhibitors, the treatment is problematic for interventions requiring the administration of UFH or LMWH [20]. The AA treatment should not be monitored based on anti-Xa activity. Commercially available anti-Xa activity assays are inadequate for its measurement after AA administration, as the resulting anti-Xa activity assay results are overestimated, leading to a significant underestimation of the change in AA activity [63]. If NOAC reversal agents are unavailable, PCC or aPCC should be considered despite lack of clear evidence of their safety and efficacy in this indication

(Table 5). An additional option is the use of recombinant activated factor VII [1].

The composition of PCC includes clotting factors: II, VII, IX, and X, with less protein C and protein S, and a small amount of heparin. In aPCC, on the other hand, there are both activated and non-activated factors II, VII, IX, and X. PCC preparations supplied by different manufacturers vary slightly in the amount of clotting factors and their inhibitors.

To minimize the risk of supratentorial hematoma, it is also advised to preferentially choose general anesthesia, not spinal anesthesia, in cases requiring urgent or immediate surgery.

In vascular surgery departments, immediate and urgent procedures are primarily performed to treat:

- ruptured aneurysms of the abdominal aorta, thoracoabdominal aorta, iliac arteries, or visceral arteries;
- traumas in which large vessels were damaged, including those responsible for limb vitality;
- acute ischemia of the upper or lower extremities.

Ruptured aneurysm surgery carries a very high risk of hemorrhagic complications. This is influenced by the condition of the patient admitted with such a diagnosis — most often with symptoms of hemorrhagic shock and coagulation disorders already present. Classic surgery with opening of the peritoneal cavity and retroperitoneal space, with active anticoagulants, is fraught with a major risk of uncontrollable bleeding and, thus, a substantial risk of death. Nowadays, it is possible to perform surgery for ruptured aortic aneurysms using an endovascular approach, which can potentially reduce the risk of hemorrhagic complications. However, this should not change the surgical approach in this group of patients, as conversion from endovascular to conventional surgery may be necessary during the procedure. Large vessel injuries in the abdominal or thoracic cavity, absolutely require the use of FXa inhibitor reversal drugs. This is primarily related to the extent of the surgery and the need to supply the injured vessels.

Surgeries for acute ischemia of the upper and lower extremities are very common procedures within the remit of the vascular Emergency Department. Even though these procedures are much less burdensome for the patient, usually with little vascular access and skin incision, NOAC inhibition should also be considered in such cases. Some of these procedures can be performed percutaneously, in the form of mechanical thrombectomy. In cases of both open and endovascular procedures, there is a risk of iatrogenic perforation of the vessel, and, consequently, uncontrolled bleeding. In cases of acute, long-lasting ischemia of the limb, compartment syndrome may occur. This symptom should absolutely be treated surgically by performing a fasciotomy, usually in a three-compartment open approach. This procedure involves decompressing the swollen and, with high probability, necrotic muscle groups of the ischemic limb by cutting through the fascia and skin, which involves the risk of major bleeding.

Although there have been no publications on fibrinolytic treatment in patients treated with NOACs, it seems that thrombolytic treatment of acute limb ischemia should be contraindicated in this group of patients.

The current position on open and endovascular procedures with vascular access is that preventing complete control of bleeding (e.g., femoral access) for immediate and urgent vascular surgery requires the use of NOAC reversal in all cases.

Unfortunately, the effect of AA persists only for about 2 hours after the end of the infusion, which is a significant problem for patients undergoing surgical procedures that last several hours. In such cases, inhibition of anti-Xa activity by AA may not be sufficient to maintain hemostasis [17].

Given the above, in the absence of life-threatening bleeding, AA administration should be delayed until immediately before surgery to ensure maximum anticoagulant reversal and avoid repeated doses. However, there are examples in the literature of double administration of a standard dose of AA [64] or a single standard dose of AA with prolonged infusion of the drug at a half-reduced rate during prolonged surgery [65].

Hence, it remains necessary to create multidisciplinary guidelines for determining the risk of perioperative bleeding, as well as the timing of AA administration for specific procedures. As new data emerge, we expect that the use of AA in the perioperative setting will evolve.

THE IMPORTANCE OF COORDINATING INTERDISCIPLINARY COLLABORATION IN DECISIONS TO USE ANDEXANET ALFA

The decision to reverse the action of a NOAC and administer an antidote in the form of an AA is difficult and requires assessment of the possible benefits and risks. Such a decision can only be made through interdisciplinary cooperation of specialists from different fields. Depending on the type of side effects of NOAC use, the decision-making process will include neurologists, surgeons, or emergency medicine physicians. However, cardiologists definitely have the most experience in the use of NOACs because these drugs are mostly administered for cardiac indications. It would, therefore, be advisable for cardiologists to coordinate these multispecialty teams and for AA to be located in cardiology departments.

DETERMINATION OF ANDEXANET ALFA FINANCING CONDITIONS

Currently, the only substance registered in Europe and the United States for the specific reversal of the anticoagulant effect of apixaban and rivaroxaban is AA (ATC code: V03AB38 — all other drugs, antidotes). The US Food and Drug Administration registered the drug as a breakthrough designation in November 2013. In May 2018, the drug received accelerated approval [66, 67]. In Europe, including Poland, the European Medicine Agency, in April 2019, granted AA conditional approval, which is used for drugs

Table 7. Recommendations for the use of andexanet alfa in patients with life-threatening or unmanageable hemorrhages

Anticoagulation Forum 2018	Suggested	[68]
American Society of Hematology 2018	Suggested	[69]
European Stroke Organisation 2019	Recommended in the first-line treatment	[70]
American College of Cardiology 2020	Recommended in the first-line treatment	[71]
Japanese Circulation Society/Japanese Heart Rhythm Society 2022	For consideration	[72]
American College of Emergency Physicians 2020	Recommended	[73]
American Heart Association/American College of Cardiology/Heart Rhythm Society 2019	Potentially useful	[74]
Asia Pacific Heart Rhythm Society 2021	Potentially useful	[75]
European Heart Rhythm Association 2021	Recommended	[76]
Deutsche Gesellschaft für Neurologie 2022	For consideration	[77]
American College of Chest Physicians 2018	Recommended	[78]
Spanish Society of Digestive Pathology/Spanish Society of Thrombosis and Haemostasis 2022	Recommended, if available	[79]

of particular public health importance and to address population health needs when the clinical benefits outweigh the risks of their use [17].

Thus, AA is currently recommended for reversal of rivaroxaban and apixaban in patients with life-threatening or unmanageable hemorrhages, i.e. for use in emergency and life-threatening conditions in the hospital setting, and in Poland, there is currently no dedicated public funding for this drug in the hospital lump sum system (Table 7). Thus, there is an urgent need to create a billing product for this drug, e.g. by including it in the aggregated product catalog allowing it to be included with other procedures performed within the existing diagnosis-related groups dedicated to the treatment of hemorrhage, or the catalog of separate products: 5.52.01.0001384 — hospitalization for reasons not covered elsewhere. Before this can happen, however, there is an urgent need for hospitals to seek alternative methods of financing for individual patients.

CONCLUSIONS

Andexanet alfa is recommended for patients with life-threatening and unmanageable hemorrhages (major bleeding according to the ISTH or BARC 3b), including HS and post-traumatic bleeding, in patients using FXa inhibitors. Prothrombin complex factor concentrate or aPCC, on the other hand, are recommended as reversal agents for all NOACs in the absence of an available antidote.

Management of patients with severe bleeding includes determining the type and dose of NOAC used and the time that elapsed from its last administration. A full panel of clotting parameters should be performed, including plasma NOAC concentrations, if the test is available. The ISTH suggests considering NOAC reversal in patients with severe bleeding and NOAC levels >50 ng/ml. Currently, it is believed that drug-specific chromogenic anti-Xa assays are most appropriate for estimating rivaroxaban and apixaban plasma levels. The absence of anti-Xa activity determined using these assays excludes clinically relevant plasma NOAC levels.

In contrast, the AA dose should not be modified based on the results of hemostasis tests. Rather, it should depend solely on the time that elapsed from the last dose of the FXa inhibitor and the long-term dosage of the anticoagulant. When using rivaroxaban >10 mg, apixaban >5 mg, or when the dose is unknown, it is recommended to administer a high dose of AA when the drugs were taken within 7 hours, or a low dose when a minimum of 8 hours has passed. When using rivaroxaban ≤10 mg and apixaban ≤5 mg, a low dose of AA is recommended. When the time of the last NOAC dose is unknown, a high dose should be administered to long-term users of higher doses of NOACs, and a low dose for long-term users of lower doses.

AA is administered as an i.v. bolus of 400 mg (low dose) or 800 mg (high dose) at a rate of 30 mg/min. An i.v. infusion of the drug is then introduced, at a rate of 4 mg/min (low dose) or 8 mg/min (high dose) for 120 minutes. Maximum reversal of anti-Xa activity occurs within two minutes of the end of the bolus, and continued continuous i.v. infusion allows the effect to be maintained for 2 hours afterward.

Measuring anti-Xa has no use in monitoring FXa anticoagulant effect reversal. Treatment monitoring should be based mainly on clinical parameters — evaluation of hemostasis or side effects, including thromboembolic events.

Due to the high and multifactorial thromboembolic risk in patients requiring AA administration, resumption of anticoagulant treatment should be considered as early as possible after bleeding is contained.

Based on the available literature, it is also known that the use of AA can be considered off-label in life-threatening clinical situations requiring urgent surgical intervention. Surgery or intervention, if possible, should be delayed for at least 12 hours, and optimally for 24 hours, after the last NOAC dose. When a patient requires immediate life-saving surgery associated with intermediate or high risk of bleeding, and the last dose of anticoagulant has already been taken, antidote administration is indicated. Unfortunately, the short duration of AA action after the end of the infusion poses a significant problem for patients undergoing surgical procedures lasting many hours. Formulating definitive recommendations on the use of AA for this indication requires further research. The ISTH suggests the need to reverse FXa inhibitors before surgery in patients with high risk of bleeding and NOAC levels >30 ng/ml.

Unfortunately, in Poland, there is no dedicated public funding for AA in the hospital lump sum funding system.

Thus, there is an urgent need to create a billing product for this drug and to seek alternative methods for financing for individual patients within hospital procedures.

Article information

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IX Konferencja czasopisma FOLIA CARDIOLOGICA

Warszawa, 20 kwietnia 2024 roku

Przewodnicząca Komitetów Naukowego i Organizacyjnego
prof. dr hab. n. med. Beata Wożakowska–Kapłon
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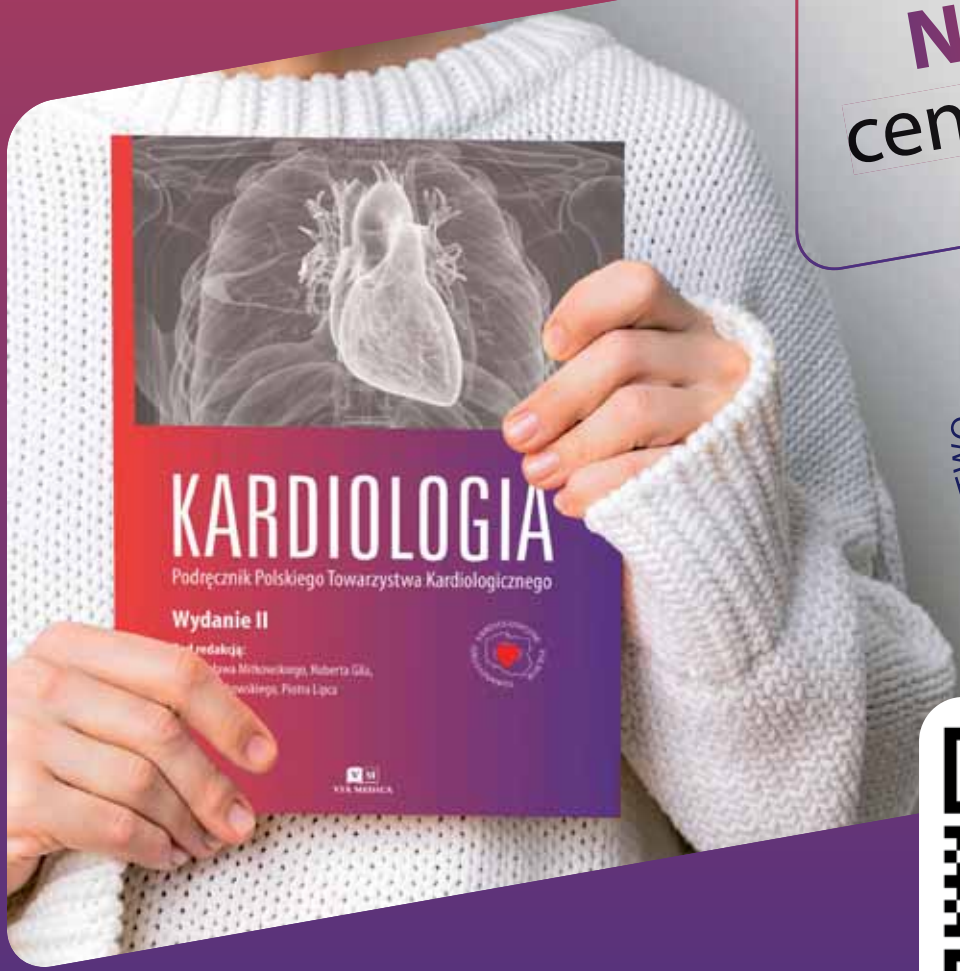

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