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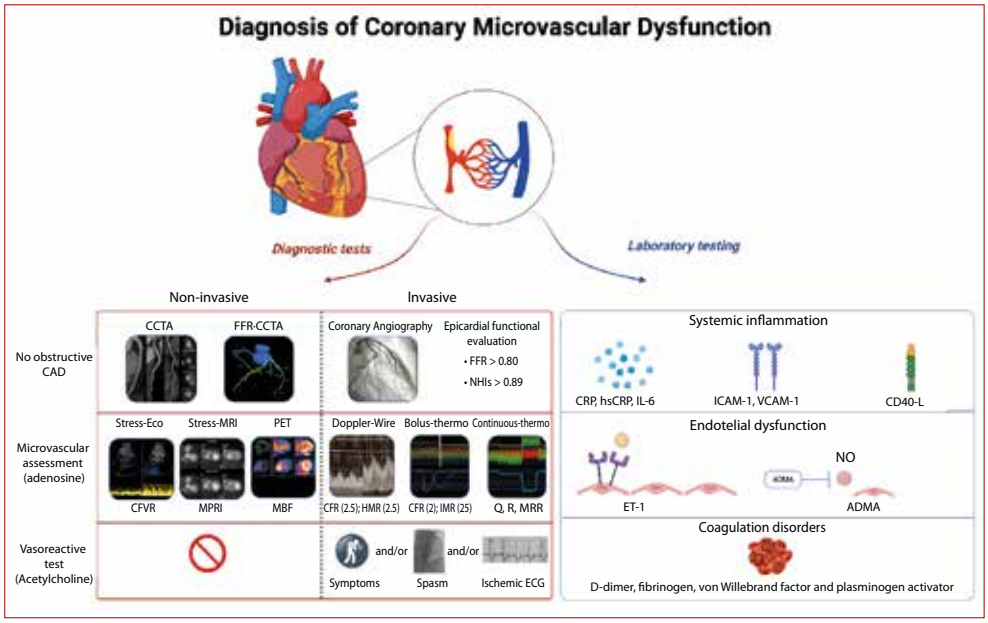
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Diagnosis of coronary microvascular dysfunction, see p. 271

REVIEWS

A brief history and clinical utilization of robotic procedures in the cardiovascular system

Coronary microvascular dysfunction in angina and no-obstructive coronary arteries

ORIGINAL ARTICLES

Carotid plaque characteristics and risk of stroke

Impact of Naples score on one-year outcomes in transcatheter aortic valve implantation patients

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Table of contents

EDITORIAL

Carotid plaque characteristics and stroke risk: More questions — or more answers? 257
Piotr Musiałek, Łukasz Tekieli, Anna Podlasek

Nutritional state, inflammation and TAVI outcomes. Just prognostic factors or a call to action? 260
Manuel Martínez-Sellés

REVIEW

A brief history and clinical use of robotic procedures in the cardiovascular system 262
Robert J Gil, Rafael Beyar, Michael Haude

Coronary microvascular dysfunction in angina and non-obstructive coronary arteries: Pathophysiology, diagnosis, novel markers, and therapy 269
Domenico Galante, Giulia La Vecchia, Antonio Maria Leone, Filippo Crea

ORIGINAL ARTICLE

MRI- and CT-derived carotid plaque characteristics and stroke: Insights from the ANTIQUE study 277
David Pakizer, David Netuka, Tomáš Hrbáč, Jiří Vrána, František Charvát, Tomáš Jonszta, Petra Kešnerová, Roman Herzig, Tomáš Heryán, Kateřina Langová, David Školoudík

The performance of the NAPLES prognostic score in predicting one-year mortality and major adverse cardiovascular events after transcatheter aortic valve implantation in patients with severe aortic stenosis 287
Mesut Gitmez, Tuncay Güzel, Mehmet Kis, Ferhat Coskun, Mehmet Ali İsik, Adem Aktan, Raif Kilic, Muhammed Demir, Faruk Ertas

Application of machine learning in predicting postoperative arrhythmia following transcatheter closure of perimembranous ventricular septal defects 295
Lintao Yan, Yuan Meng, Hongjie Sun, Xinlei Liu, Bo Han

Percutaneous coronary intervention and coronary artery bypass grafting in myocardial infarction complicated by cardiogenic shock 305
Mariusz Gąsior, Mateusz Tajstra, Marek Deja, Robert Gil, Jerzy Pacholewicz, Stanisław Bartuś, Marek Jasiński, Marek Gierlotka, Romuald Cichoń, Adam Witkowski, Jan Rogowski, Dariusz Dudek, Zdzisław Tobota, Wojciech Wojakowski, Kazimierz Widenka, Krzysztof Milewski, Bohdan Maruszewski, Janina Stępińska, Grzegorz Hirnle, Jacek Legutko, Piotr Suwalski, Przemysław Trzeciak, Piotr Przybyłowski, Tomasz Hrapkowicz

Allergic reactions during coronary angiography or PCI in Poland: Occurrence, trends, and long-term perspective based on the Polish ORPKI registry 313
Karol Kaziród-Wolski, Michał Zabojszcz, Paulina Jaskulska, Natalia Dardzińska, Ewa Strzelczyk, Krzysztof P Malinowski, Janusz Sielski, Zbigniew Siudak

SHORT COMMUNICATION

Rationale, objectives, and design of the HEart failuRe ObsErvational Study of the Polish Cardiac Society (HEROES) 321
Jarosław Drożdż, Robert Morawiec, Marcin Drozd, Paweł Krzesiński, Beata Wożakowska-Kapłon, Marcin Grabowski, Przemysław Leszek, Marek Kuch, Jarosław D Kasprzak, Marianna Janion, Marcin Gruchała, Agnieszka Pawlak, Jadwiga Nessler, Piotr Pruszczyk, Ewa Straburzyńska-Migaj, Przemysław Mitkowski, Marek Gierlotka, Mariusz Gąsior, Tomasz Hryniewiecki, Jarosław Kaźmierczak, Adam Witkowski, Tomasz Zdrojewski, Maciej Niewada, Grzegorz Opolski, Lech Poloński, Ewa A Jankowska, Aldo Maggioni, John McMurray, Andrew Coats, Marco Metra, Giuseppe Rosano, Petar Seferovic, Piotr Ponikowski

Transesophageal echocardiography in corroborating aortic stenosis severity in patients with low-gradient aortic stenosis with preserved ejection fraction 325
Patrycjusz Stokłosa, Anna Stec-Gola, Dariusz Zakrzewski, Anna Jasińska, Małgorzata Nieznańska, Ilona Kowalik, Ilona Michałowska, Tomasz Hryniewiecki

Heart failure epidemiology and outcomes in Poland from 2010 to 2021: A marked decline in HF hospitalization rate during the COVID-19 pandemic 329
Marta Załęska-Kocięcka, Krzysztof Podwojcic, Zuzanna Wojdyńska,Michał Zakrzewski, Małgorzata Celińska-Spodar, Tomasz Hryniewiecki, Przemysław Leszek

Single Perclose ProGlide vs. figure-of-eight suture technique for closure of large-bore sheaths in venous transcatheter procedures 333
Yassin Belahnech, Bruno García del Blanco, Gerard Martí-Aguasca, Rosa Vila-Olives, Vicenç Serra, Eduard Ródenas-Alesina, Andrea Monastyrski, Ignacio Ferreira-González

Is etiology the dominant modifier of prognosis in all heart failure phenotypes? 336
Tomasz M Rywik, Roman Topór-Mądry, Anna Drohomirecka, Hubert Łazarczyk, Agnieszka Doryńska

Initial experience with transvenous lead extraction in patients with left ventricular assist devices 339
Andrzej Ząbek, Krzysztof Boczar, Katarzyna Holcman, Magdalena Kostkiewicz, Mateusz Ulman, Anna Rydlewska, Karolina Golińska-Grzybała, Maciej Dębski, Jacek Lelakowski, Karol Wierzbicki

CLINICAL VIGNETTE

EP-Heart Team approach with sinus node sparing ablation for complex inappropriate sinus tachycardia and postural orthostatic tachycardia syndrome: A first experience in Central Europe 342
Sebastian Stec, Piotr Suwalski, Carlo de Asmundis, Mark La Meir, Agnieszka Reichert, Aleksandra Wilczek-Banc, Bartosz Szkaradek, Mariusz Kowalewski

Atrial tachycardia during pregnancy: Postnatal treatment 345
Julia Woźniak, Agnieszka Wojdyła-Hordyńska, Anastazja Murawska, Grzegorz Hordyński, Marek Gierlotka

Swan–Ganz catheter-induced pulmonary artery rupture with massive bronchial hemorrhage treated by implantation of cover stents 348
Sylwia Sławek-Szmyt, Aleksander Araszkiewicz, Marek Grygier, Paweł Sobczyński, Zbigniew Krasiński, Maciej Lesiak

Long road to success. Endocardial radiofrequency ablation of septal hypertrophy using three-dimensional electroanatomic mapping guided by echocardiography in a patient with hypertrophic obstructive cardiomyopathy and severe aortic stenosis 350
Dorota Żmudzińska, Krzysztof Ściborski, Paweł Szymkiewicz, Marek Mak, Artur Telichowski, Dorota Kustrzycka-Kratochwil, Adrian Doroszko, Waldemar Banasiak, Krystian Josiak

A persistent cough after cryoballoon ablation as an initial symptom of *Bordetella pertussis* respiratory tract infection 353
Irena Jodkowska, Paulina Trębińska,Radosław Ł Gortych, Michał M Farkowski

Orthotopic liver transplantation due to primary biliary cholangitis in a patient with ventricular septal defect: A cardiological perspective 355
Tomasz Cader, Edyta Karpeta, Krzysztof Jankowski, Wojciech Lisik, Piotr Pruszczyk, Katarzyna Kurnicka

Cor medusae trinity: Unraveling congenital coronary artery fistula complications through multimodality imaging 357
Bruno Bragança, Rafaela G Lopes, Inês Oliveira, Isabel Cruz, Glória Abreu, Adriana Pereira, Jorge Casanova, João Azevedo, Aurora Andrade

Severe bicuspid aortic valve regurgitation with ascending aortic aneurysm in a 53-year-old female patient with Turner syndrome 359
Kamil Banasik, Dominika Kowalczyk, Rafał Celiński, Marcin Łubiarz, Ewa Kurys-Denis

Right atrial anomalous muscle bundle. Clinical implications 361
Maciej K Michałowski, Maria Sudomir, Tomasz Oleksiuk, Paweł Tyczyński, Ilona Michałowska

Leadless pacing combined with extraction of an infected epicardial single chamber pacemaker in an 11-year-old girl 363
Maciej Kempa, Przemysław Mitkowski, Rafał Pawlaczyk, Radosław Jaworski, Szymon Budrejko, Ludmiła Daniłowicz-Szymanowicz, Grzegorz Romanowicz, Joanna Kwiatkowska

LETTER TO THE EDITOR

Vulnerable atherosclerotic plaque and iron homeostasis: the role of intraplaque erythrophagocytosis, ferroptosis, and heme oxygenase-1 overexpression 366
Paweł Rostoff, Anna Patrycja Majda, Grzegorz Gajos

IN MEMORIAM

A hope to save Esperanza. Robert Bartlett and the 50th anniversary of the first neonatal ECMO patient 368
Magdalena Mazurak

GUIDELINES

Guidelines for the management of hypertension in Poland 2024 — the position paper of the Polish Society of Hypertension and Polish Cardiac Society experts 370
Aleksander Prejbisz, Piotr Dobrowolski, Adrian Doroszko, Agnieszka Olszanecka, Agnieszka Tycińska, Andrzej Tykarski, Marcin Adamczak, Beata Begier-Krasińska, Marzena Chrostowska, Grzegorz Dzida, Krzysztof J Filipiak, Zbigniew Gaciong, Dariusz Gąsecki, Marek Gierlotka, Marcin Grabowski, Tomasz Grodzicki, Piotr Jankowski, Karol Kamiński, Agnieszka Kapłon-Cieślicka, Aneta Klotzka, Dariusz Kozłowski, Przemysław Leszek, Jacek Lewandowski, Mieczysław Litwin, Łukasz Obrycki, Artur Mamcarz, Przemysław Mitkowski, Beata Naumnik, Marek Rajzer, Janina Stępińska, Katarzyna Stolarz-Skrzypek, Anna Szyndler, Anna Tomaszuk-Kazberuk, Izabella Uchmanowicz, Marcin Wełnicki, Barbara Wizner, Beata Wożakowska-Kapłon, Tomasz Zdrojewski, Waldemar Banasiak, Andrzej Januszewicz, Agnieszka Mastalerz-Migas, Krzysztof Narkiewicz, Andrzej Więcek, Adam Witkowski, Robert Gil, Jacek Wolf

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Carotid plaque characteristics and stroke risk: More questions — or more answers?

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Despite the progress in pharmacologic therapies, atherosclerotic carotid artery stenosis remains an important mechanistic factor of ischemic stroke[1, 2]. Today, 20%–25% of strokes are caused by atherosclerotic carotid disease, and these continue to occur in people on optimized medical therapy [1–5]. Because of the large cerebral territory that can be affected, carotid-related strokes are often large and disabling [2, 3]. As the stroke burden is increasing worldwide [1, 3], it should be noted that numerous patients with stroke-related disability would prefer death to their life after stroke [1, 3]. Importantly, carotid atherosclerotic stenosis is a modifiable stroke risk factor; thus carotid-related strokes can be, in principle, prevented [1, 3].

The degree of carotid artery stenosis has been the conventional determinant of stroke risk assessment and — consequently — treatment decisions, including revascularization [1, 3, 4]. Landmark trials established the benefit of carotid endarterectomy and carotid artery stenting for patients with significant stenosis, leading to a widespread reliance on this single metric [1, 3]. However, a growing body of evidence indicates that focusing solely on the luminal "% stenosis" is an oversimplification of a complex dynamic process that occurs in the diseased artery wall [1, 3, 4, 6]. Moreover the "stenosis severity" concept, although theoretically attractive, faces significant ambiguities in every-day clinical decision-making [7]. Not all patients with asymptomatic carotid artery stenosis have the same stroke risk, and thus not all should receive the same treatment [1, 8]. Consistent with this notion, the risk scores based on stenosis luminal severity and traditional cardiovascular risk factors are not specific enough to drive evidence-based decision-making in asymptomatic patients [1, 8, 9]. Clearly, each symptomatic carotid stenosis starts is biologic "career" as an asymptomatic lesion [6]. The concept to concentrate attention on symptomatic stenoses has one fundamental limitation: frequently the treatment would arrive too late to save the functional brain and, in many instances, life [1, 2].

There is a growing body of evidence that plaque characteristics play a pathobiologic role that is far more important than the degree of luminal stenosis severity [1, 4, 10]. Plaque vulnerability is determined by a complex interplay of multiple lesion-level and patient-level factors (Table 1). Plaque morphology (the size of lipid-rich necrotic core and fibrous cap thickness, luminal surface irregularity/ulceration, plaque inflammation, neovascularization and intraplaque hemorrhage) are typical indicators of instability and increased risk of thromboembolic events [3]. For plaque characterization, the different imaging techniques have different resolution. Intravascular ultrasound with its axial resolution of 100–120 μm and tissue penetration of ~10 mm for 20 MHz transducers offers a direct live assessment of the atherosclerotic plaque with a field of view of ~15 × 15 mm but being invasive it is reserved as a primarily research tool [10]. In contrast to intravascular ultrasound, transcutaneous duplex ultrasound visualization resolution is significantly poorer (~400–800 μm for typical transcutaneous ultrasound transducers) [10]. Other commonly promoted

noninvasive techniques such as computed tomography or magnetic resonance imaging also have the fundamental limitation of image resolution (computed tomography: in-plane resolution of 400–500 μm and slice thickness of 1000 μm; magnetic resonance: in-plane resolution of 300–600 μm and slice thickness of 2000–3000 μm) [10].

A meta-analysis of 64 prospective studies in 20 751 participants with asymptomatic carotid stenosis demonstrated a pooled prevalence of high-risk plaques of 26.5% [11]. The most prevalent high-risk plaque features were neovascularization (43.4%) echolucency (42.3%), and lipid-rich necrotic core (36.3%) [11]. The incidence of ipsilateral ischemic cerebrovascular events in severe stenoses was 3.7 events per 100 person-years [11]. Plaque morphology appeared to play a greater role than stenosis severity, with the incidence of ipsilateral ischemic cerebrovascular events higher in patients with high-risk plaques (4.3 events per 100 person-years) than in those without (1.2 events per 100 person-years); odds ratio of 3.0 (95% CI, 2.1–4.3) [11].

Recent subanalysis from the ANTIQUE study, published in the current issue of *Polish Heart Journal* [12], investigated the association between plaque features by computed tomography and magnetic resonance imaging with stroke in 216 stenoses in 132 patients. Interestingly, rather than plaque morphology, the degree of stenosis (that was expressed properly, i.e., as diameter stenosis rather than area stenosis [7]) and alcohol consumption emerged as only independent predictors of recent stroke [12]. At a first glance, these results might seem to question the pathobiologic role of plaque morphology evidenced in prior, much larger and prospective studies [11]. However, it is crucial to interpret the present findings [12] within the context of the fundamental study limitations including not only its moderate size but also (and foremost) its retrospective nature. Not only part of the thromboembolic plaque material may detach and embolize when causing stroke but also carotid plaques have been shown to stabilize after stroke [13]; thus the lesion characteristics detected 3 months after the cerebrovascular event (i.e., as studied by of Pakizer et al. [12]) may not reflect the ones at the point of stroke. Furthermore, clinically asymptomatic cerebral infarcts (Table 1) were not taken into consideration in the ANTIQUE analysis[12]. The ANTIQUE study's finding that alcohol consumption was an independent predictor of stroke risk [12] is intriguing and it is likely valid clinically. While moderate alcohol consumption may be associated with some cardiovascular benefit, excessive alcohol intake is a well-established risk factor for stroke [14]. There is an ongoing controversy whether red wine consumption may be more positive than other types of alcohol [14]. Alcohol consumption may contribute to plaque instability through several mechanisms, including increasing blood pressure, promotion of inflammation, and impaired lipid metabolism. Excessive alcohol consumption correlates with poor compliance with health advice, and it may be a marker of other unhealthy lifestyle factors that contribute to stroke risk, such as poor diet, lack of exercise,

Table 1. Atherosclerotic carotid stenosis: Increased stroke risk characteristics

Feature	Imaging modality	Increase in risk[a]
Lesion level		
Intraluminal floating thrombus	DUS, Angio, IVUS	Brain/life-threatening
Thin/ruptured fibrous cap[b]	CT, IVUS	5.93 (2.65–13.20)
Intraplaque hemorrhage[b]	MRI	4.59 (2.91–7.24)
Lipid-rich necrotic core	CT, VH-IVUS, NIRS	3.00 (1.51–5.95)
Echolucent plaque	DUS	2.61 (1.47–4.63)
Stenosis severity progression	DUS, CT, MRI	1.92 (1.26–2.92)
Ulceration/Surface irregularity	CT, Angio, MRI, IVUS, DUS	1.80 (1.14–2.83)
Plaque inflammation	PET, MRI	Magnitude-dependent
Neovascularisation	MRI, DUS*	Magnitude-dependent
Intraluminal calcific nodules	IVUS, CT	Clinically significant
Intraplaque micro/nanoplastics	EM	4.53 (2.00–10.27)
Brain level		
Microembolic signals	TCD	7.46 (2.24–24.89)
Impaired cerebrovascular reserve	TCD	6.14 (1.27–29.5)
Clinically silent ipsilateral cerebral infarct	CT, MRI	3.0 (1.46–6.29)
Contralateral stroke/TIA	CT, MRI	3.0 (1.9–4.73)
Patient level		
Diabetes	N/A	2.0 (1.6–2.6)
Insulin		7.2 (3.2–16.2)
Contralateral carotid occlusion	DUS, CT, MRI, Angio	23% increase over 5 years
Family history positive for stroke	N/A	Major

[a]Fold-increase (95% confidence interval) according to the largest study(-ies) available (unless specified otherwise); for details see [3]. [b]Mechanisms of plaque growth; in mild/moderate plaque burden often clinically silent [6]
*Contrast-enhanced DUS

Abbreviations: Angio, catheter angiography; CT, computed tomography; DUS, duplex ultrasound; EM, electron microscopy; IVUS, intravascular ultrasound; MRI, magnetic resonance imaging; N/A, not applicable; NIRS, near-infrared spectroscopy; PET, positron emission tomography; VH, virtual histology

smoking, and poor compliance with cholesterol-lowering and anti-hypertensive therapy [14].

While standardized reporting systems are being developed for carotid plaque composition and morphology evaluation using different modalities (transcutaneous ultrasound, computed tomography, magnetic resonance imaging) [15], it must not be ignored that evolution of plaque morphology is a dynamic and heterogenic process [6]. Plaque progression beyond 40%–50% luminal diameter narrowing typically occurs secondary to repeated episodes of intraplaque hemorrhage and/or plaque rupture [6]. These events represent an important mechanism of plaque growth and they are often clinically silent [6]. Remarkably, the plaque rupture events are more likely to be silent in less severe lesions [6].

Overall, the present body of evidence indicates a clear need to use imaging to identify high-risk plaque composition and thus plaques (and patients!) that may benefit from more aggressive management. One fundamental question today is how to practically implement plaque-level and characteristics (Table 1) in a clinical decision-making model. Until carotid-related stroke risk prediction scores become validated (such as classic CHA_2DS_2-VASC scale or a more recent calculator of absolute stroke risk in atrial fibrillation, CARS/mCARS), the "roulette wheel" of applying (or not applying) the particular increased stroke risk characteristics in managing carotid stenosis will continue to turn over the necks of underestimated-risk patients [1].

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Nutritional state, inflammation and TAVI outcomes. Just prognostic factors or a call to action?

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Related article
by Gitmez et al.

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Calcific aortic stenosis (AS) affects approximately 12% of adults older than 75 years and symptoms due to severe AS are associated with a 1-year mortality rate of up to 50% without aortic valve intervention [1]. Transcatheter aortic valve implantation (TAVI) reduces mortality to that of age-matched control patients and already is the standard treatment for most symptomatic patients. Despite advances in procedural safety and efficacy, accurate risk stratification remains a cornerstone of clinical decision-making. Traditional risk scores, derive from risk assessment tools, originally designed for open-heart procedures, as the Society of Thoracic Surgeons and the European System for Cardiac Operative Risk Evaluation (EuroSCORE) II, do not include geriatric conditions [2], comorbidity and factors as systemic inflammation and nutritional status.

Nutritional and inflammatory markers have emerged as pivotal determinants of cardiovascular outcomes, influencing immune response, endothelial function, and overall resilience to procedural stress. Gitmez et al. [3] replicate the previous larger study by Hakgor et al. [4] and confirm the impact of the Naples Prognostic Score (NPS) on the prognosis of patients undergoing TAVI. The NPS is easy to calculate (only needs serum albumin, cholesterol, lymphocyte/monocyte ratio, and neutrophil/lymphocyte ratio) and provides information about nutritional status and inflammation. Both studies, in spite of their small sample sizes, strongly suggest that the NPS allows for a more nuanced evaluation of TAVI-related risk.

Nutritional status before TAVI is frequently poor and does not seem to improve after the procedure [5], emphasizing the need of a global assessment before TAVI that should include clinical, blood multimarkers, and electrocardiographic variables [6–8]. Regarding inflammation, it plays a significant role in AS [1]. Inflammation contributes to endothelial dysfunction, exacerbates atherosclerosis, and impairs tissue repair mechanisms, all of which can compromise recovery following TAVI. Moreover, TAVI is known to increase inflammation [9] and inflammatory biomarkers have been shown effective in predicting mortality following TAVI [10, 11]. In fact, some TAVI valves seem to be associated with a reduced inflammatory response and the incidence of new left bundle branch block could be related with inflammation [12]. Previous data suggest that minimizing peri-procedural inflammatory insults may improve outcomes [13].

The integration of nutritional and inflammatory markers into a risk score aligns with the growing recognition of their role in cardiovascular health. The NPS effectively encapsulates these interrelated factors, making it a compelling candidate for inclusion in risk assessment protocols. However, although the incorporation of the NPS into routine clinical practice could significantly enhance risk stratification for TAVI patients, its benefit from the clinical point of view is unclear. Moreover, while the NPS integrates crucial biomarkers, it remains one component of a multifaceted risk assessment landscape. Incorporating additional parameters — such as frailty and comorbidity scores, imaging and electrocardiographic parameters — could further refine predictive accuracy. Moreover, the dynamic nature of inflammatory and nu-

tritional markers suggests that serial assessments rather than single-time point measurements may provide deeper prognostic insights.

In any case, if no interventions are incorporated to improve nutrition and inflammation, the only potential benefit could be a closer post-procedural monitoring. Nutritional optimization is useful before surgical interventions [14] and anti-inflammatory drugs like colchicine have been shown to decrease inflammation in different cardiovascular conditions like heart failure [15] and could improve outcomes after TAVI. Prospective randomize studies to study the benefits of these targeted interventions type of approach would be welcome.

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A brief history and clinical use of robotic procedures in the cardiovascular system

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ABSTRACT

Robotic-assisted percutaneous coronary intervention (r-PCI) exemplifies the advancement of interventional cardiology by integrating robotics to improve procedural control, operator safety, and potentially patient outcomes. This is a brief history of the development of r-PCI and robotics in cardiac surgery. r-PCI is currently more common in elective PCI cases, where time and precision are prioritized, however, the progress that has been made in surgical robotics allows us to believe in rapid progress of robots dedicated to complex coronary lesions treatment. The successful remote PCI in China highlights the potential of robotic systems to revolutionize interventional cardiology by offering both precision and remote accessibility, particularly in regions with limited access to specialized cardiovascular care.

Key words: surgical robotics, robotic-PCI, remote-PCI

Very soon we will celebrate the fortieth anniversary of the first percutaneous coronary angioplasty performed by Andreas Gruentzig [1]. Since this time, enormous progress has been made in terms of procedural effectiveness and patient safety; however practically nothing has changed from the operators' perspective. After obtaining vascular access, operators are condemned to manual manipulation of the wires and catheters at the operating table. Operators have to use X-ray applications and, therefore, are forced to wear heavy protective aprons. This is one of the reasons why ailments related to the musculoskeletal system are reported for the staff of catheterization laboratories [2]. Despite decreasing radiation dose [3], much remains to be done regarding the operator's risk resulting from radiation exposure. For these issues, remotely performed percutaneous coronary intervention (PCI) seems to be an appropriate alternative solution. However, this idea was not very popular in the interventional cardiology community for years. The success of surgical robotics promoted the possibilities of their usefulness in the area of percutaneous revascularization procedures.

The story of surgical robotics started in the early 1970s when concept ceased to be a pipe dream and it was only a matter of time before a version was created that met the surgeon's expectations [4] (Figure 1).

The 1990s were a time of enormous progress in surgical robotics, which resulted in the first robotic-assisted heart surgery in 1997 performed by Dr. Friedrich Mohr and his team at the Leipzig Heart Center in Germany, using a prototype called the "Aesop 3000". This early system allowed for more precise movements in thoracoscopic procedures, showing potential for more complex cardiac surgeries in the future. The first robotic assisted coronary artery bypass grafting was accomplished in 1998 by Dr. Randall Wolf and his team at the Ohio State University Medical Center in Columbus, Ohio. One year later, in 1999, Dr. Randas Batista performed the first robotic mitral valve repair surgery using the da Vinci system [5].

In 2000, the da Vinci system received Food and Drug Administration approval for general laparoscopic surgery, and by 2001, it was approved for cardiac surgery, marking the beginning of its widespread clinical use.

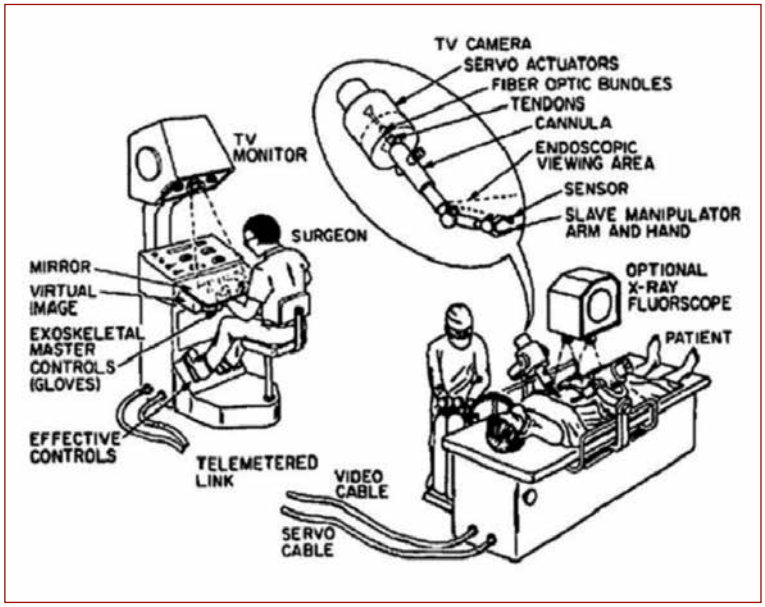


Figure 1. The first telesurgical robotic system from a US project proposal (picture from the internet). A. D. Alexander, "Impacts of telemation on modern society" January 1973

Around the same time, the merger of Intuitive Surgical with Computer Motion allowed for the creation of a tool appreciated by cardiac surgeons, and the increased number of robotic procedures forced further development of robotics in heart procedures. Indeed, in 2003, Dr. Jacques Marescaux and Dr. Alain Carpentier in Strasbourg, France, performed the first totally endoscopic coronary artery bypass (TECAB) procedure using the da Vinci robot [6]. This milestone showed that robotic-assisted surgery could potentially replace conventional open-heart surgery for selected patients.

By the 2010s, robotic-assisted surgery became more commonplace for mitral valve repair, coronary artery bypass grafting, and even complex arrhythmia surgeries. Advances in imaging, miniaturization of tools, and improvements in robotic systems allowed for better outcomes and shorter recovery times. As a consequence, throughout the mid-2000s, robotic-assisted cardiac surgeries gained popularity in specialized centers. The da Vinci system was improved in design with smaller instruments and better ergonomics. The 2020s have seen AI integration into robotic systems, improving navigation, precision, and personalized surgical planning. As technology advances, robotic-assisted cardiac surgery may expand to more complex heart procedures, possibly in conjunction with AI-driven decision-making and machine learning for real-time analysis. The field continues to evolve with the hope that robotic-assisted platforms will make cardiac surgeries and interventional procedures safer, less invasive, and more accessible for patients worldwide [6].

In this context, it is worth mentioning Polish achievements in this field, which are noticeable. Kowalewski et al. [7] showed that robotic cardiac surgery is not rare in Poland as a minimally invasive procedure and had a positive impact on the prognosis of patients with tricuspid regurgitation and atrial fibrillation. Suwalski et al. [8] used the da Vinci

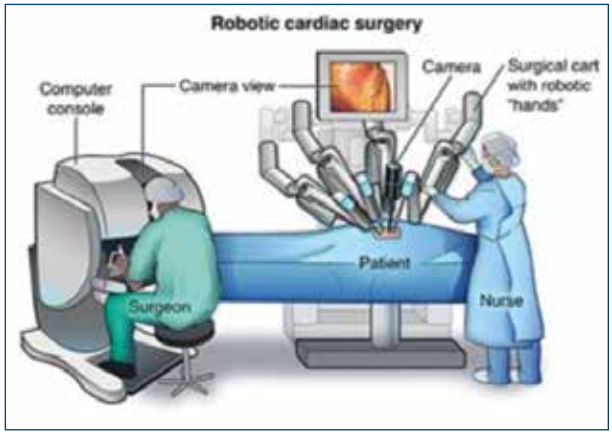


Figure 2. Illustration of the robotic surgical operation (from the Internet)

system to perform sympathetic denervation in a patient with ventricular tachycardia, and this procedure is performed quite frequently in Poland (Figure 2).

The history of robotics in percutaneous revascularization is much shorter. Undoubtedly, the success of robotics in surgery has promoted work in this area. The idea of robotic-assisted PCI stemmed from the need to increase precision and reduce occupational hazards (especially radiation exposure) for interventional cardiologists.

NaviCath, a company incubated by Company of Technion and Rambam, was founded in 2002 as the first company focused on developing robotic solutions for vascular interventions. It built a prototype robot with a game joystick and two parallel motors for wire and device manipulation. The degrees of freedom for the wire controller were advance, retract and rotate and the device parallel motor was designed to advance and retract, as well as provide discrete 1 mm steps. After gathering safety data on animals, a clinical trial with 18 patients was conducted. The first procedures meeting the criteria for PCI with robotic

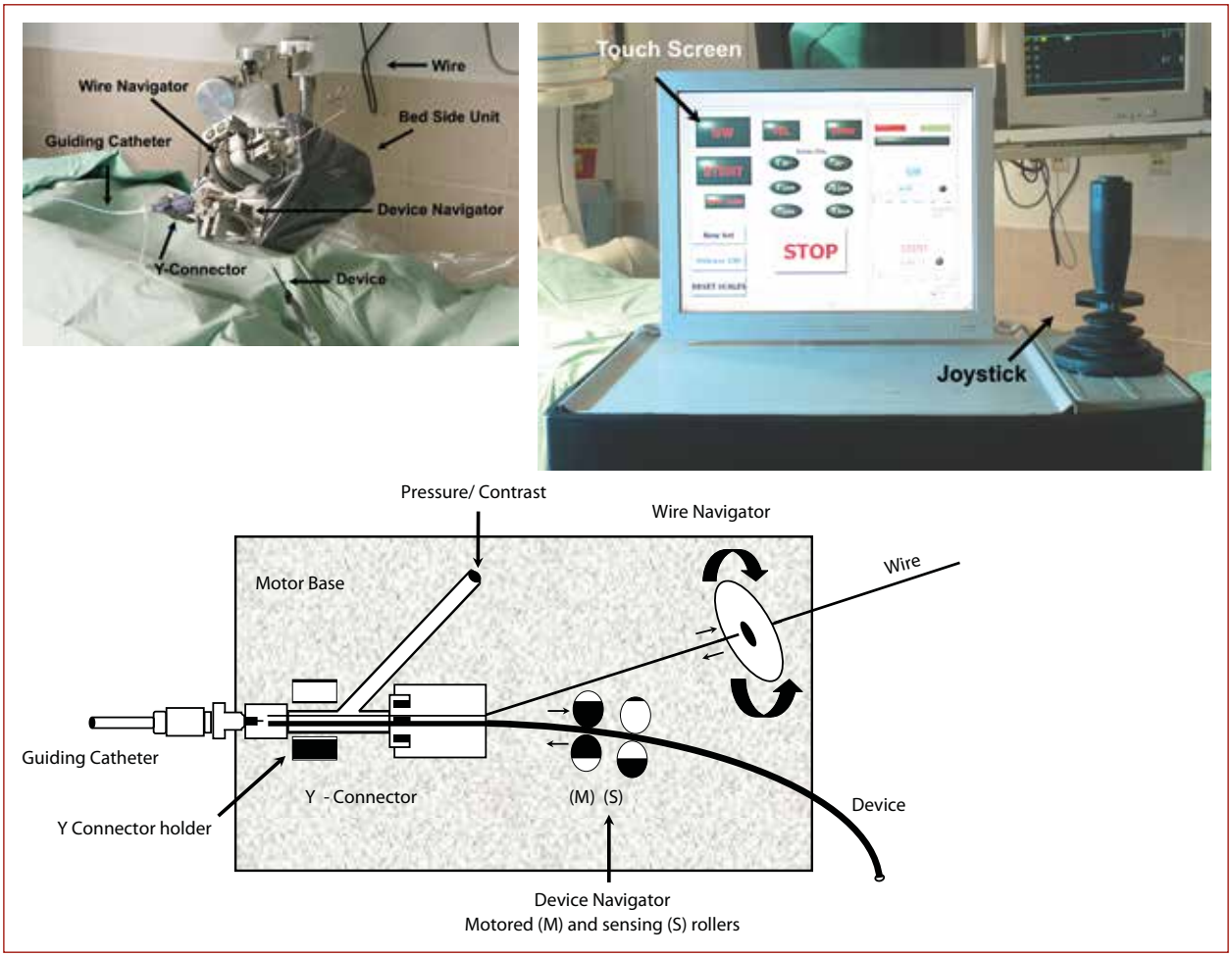


Figure 3. Bedside unit of the NaviCath remote controller. The wire navigator can move in, out and rotate. The device navigator advances and retracts the device and can do that in small 1 mm steps. The system is operated with a single joystick which can switch between wire and device control. Reproduced from Beyar et al. [9] with permission

support were performed by Rafael Beyar and his team at Rambam Medical Center (Haifa, Israel) and in Fundeni Hospital, (Bucharest, Romania) in 2004. This system is presented in Figure 3.

Positive results of that trial [9] allowed for raising more funds, the company moved from Haifa to Boston and the name changed to Corindus Vascular Robotics (personal communication — R. Beyar).

In the following years Corindus developed early prototypes of robotic systems for coronary procedures. The first robotic-assisted PCI using the CorPath 200 robotic system was performed in 2010 by Dr. Joseph P. Carrozza Jr., at St. Elizabeth's Medical Center in Boston (MA, US) [10]. These systems aimed to enhance the precision and control of catheter-based interventions, enabling cardiologists to perform PCI procedures with more accurate stent placements and potentially reducing operator`s radiations exposure. This system allowed for precise manipulation of guidewires and stents, with millimeter-level accuracy, showing that robotic assistance could bring greater control to PCI procedures. In 2012, the CorPath 200 system by Corindus became the first FDA-approved robotic system specifically designed for PCI 11]. In 2016, Corindus launched the CorPath GRX, a second-generation system with enhanced features, including improved precision and control of additional devices such as guide catheters [12] (Figure 4).

The CorPath GRX facilitated more complex procedures, including multivessel PCI, and supported more flexible stent and guidewire manipulation. The first remote (distance was over 20 miles) robotic-assisted PCI was performed in 2017 by Dr. Tejas Patel with the use of the CorPath GRX system [13]. This breakthrough demonstrated the potential of robotic PCI for remote interventions, which could expand access to PCI for patients in underserved or remote areas.

Siemens Healthineers acquired Corindus Vascular Robotics in 2019, investing heavily in the future of robotic-assisted vascular and coronary interventions. This acquisition accelerated innovation and research. In the early 2020s, the CorPath GRX system continued to evolve with AI and advanced imaging support, enabling enhanced real-time guidance and potentially allowing less experienced operators to perform complex procedures. AI-driven imaging integration helps operators to navigate more precisely in



Figure 4. Illustration of the CorPath GRX robotic system (from the Internet)

complex anatomy and optimize stent placement. Studies in recent years have further validated the efficacy and safety of robotic-assisted PCI, particularly for patients with complex lesions and multivessel disease. This system became widely adopted in specialized centers, marking the beginning of robotic-assisted PCI as a practical option for routine clinical use [14].

Unfortunately, recently, though Siemens Healthineers (Corindus Vascular Robotics) is evolving the CorPath platform, the company stopped its coronary applications and shifted its focus toward broader applications within vascular and neurovascular spaces, along with a push toward fully remote interventions.

As a consequence, there are only two companies specializing in robotic assisted vascular interventions: Hansen Medical (now part of Philips) with The Magellan Robotic System and Robocath with the R-One system. Hansen Medical developed a robotic platform designed to enhance precision and control in catheter-based procedures, particularly in vascular interventions. It is primarily used for peripheral vascular and endovascular procedures, such as treatment for peripheral arterial disease (PAD) and complex vascular anatomy navigation [15]. Robocath, a French company, developed the R-One system for coronary and peripheral interventions. R-One allows for robotic control of guidewires and catheters, providing a remote-controlled environment to protect physicians from radiation exposure [16]. The system received a CE-mark in 2019 and is used mainly in Europe. This robot allows push, pull, and torque of wires and push and pull of catheters *via* two separate joysticks (Figure 5).

It can handle one wire and one catheter at the same time. The control station can be located in the operating room behind a glass protection wall or in the control room with visual contact with the operating room. It has been shown that the R-One system can handle monorail balloon and stent delivery systems as well as intravascular ultrasound catheters and advanced balloon systems such as scoring and cutting balloons or even intravascular lithotripsy catheters. Recently, a single-center prototype installation of the remote station outside of the cath lab has been introduced using a large multi-modality screen for controlling hemodynamic, X-ray, intracoronary imaging and pressure wire signals together with mechanical contrast injection.

This installation permits the performance of complete robotic intraventricular ultrasound and/or pressure wire-supported PCIs from the control room (Figure 6).

Lately, the first case of using the R-One system for precise implantation of a left ventricular lead in a patient requiring resynchronization pacing was presented, showing other options for clinical utilization of this system [17].

Robocath's R-One robotic platform has been used to successfully perform a remote PCI in China, marking a significant milestone in the advancement of telemedicine and robotic-assisted interventions. Remote PCI using Robocath's R-One system in China was conducted with an impressive distance of approximately 2800 kilometers (about 1700 miles) between the interventional cardiologist operating the robotic console and the patient using 5G connections [18]. This achievement showcases R-One's potential for bridging geographical gaps in healthcare by



Figure 5. Illustration of the R-One robotic system (from the Internet). The system comprises a radio-protected control unit to shield healthcare practitioners from harmful X-rays (right) and a telemanipulated robotic unit (left)



Figure 6. Command unit of the R-One system, which contains a catheter joystick, a guidewire joystick, a fluoroscopy command and C-arm command. In addition angio, hemodynamic and intraventricular ultrasound screens are visible

enabling specialists to perform complex interventions from a distance, offering new possibilities for access to care in remote or underserved areas. The R-One system lets the remote operator perform precise catheter and guidewire maneuvers, highlighting its reliability and stability in long-distance procedures.

Recently, yet another system enabling robotic revascularization procedures has appeared on the market. The ROSES robotic system (Robotically Operated Sensing and Enhancing Surgery) is a robotic-assisted platform developed for minimally invasive PCI procedures [19]. Designed to improve the precision and control in PCI, it allows interventional cardiologists to perform procedures with enhanced accuracy, particularly in complex or challenging cases.

The ROSES system uses robotic-assisted control to guide catheters, guidewires, and stents through the coronary arteries with fine-tuned precision. Its interface provides real-time, high-definition imaging and haptic feedback, which gives physicians a better sense of the forces they are applying. This approach minimizes the potential for errors and reduces physical demands on cardiologists, who traditionally perform these procedures manually.

CURRENT CLINICAL USE

Analysis of literature data confirms the high effectiveness, both clinical and technical, of percutaneous robotic procedures. Durand et al. [20] reported 100% clinical and 95.2% technical success rates in the R-EVOLUTION study. First Polish experience with the R-One system has also shown a high clinical and technical success rate (97.92% and 95.83%, respectively) of r-PCI [21]. A systematic review by Wagener et al. [22] found that, in selected patients, r-PCI provides high clinical and technical success rates, ranging from 93.3 to 100% and from 81 to 98.8%, respectively. It seems that the mean fluoroscopy time for r-PCI tends to be longer compared to classic PCI [21], which was reported by Bay et al.; however, without increased use of contrast medium and most importantly one-year follow-up showed no differences in all-cause mortality or major adverse cardiovascular event, supporting the safety of a robotic-assisted approach [23].

Currently, there are no clear contraindications to robotic assisted PCI. The literature contains descriptions of not only simple but also complex PCI performed with robotic support. Undoubtedly, the possibility of using intracoronary imaging as well as intravascular lithotripsy [24] and a laser catheter [25] during r-PCI increases the chance of success also in complex cases of percutaneous revascularization. Of course, the operator's experience plays a huge role, not

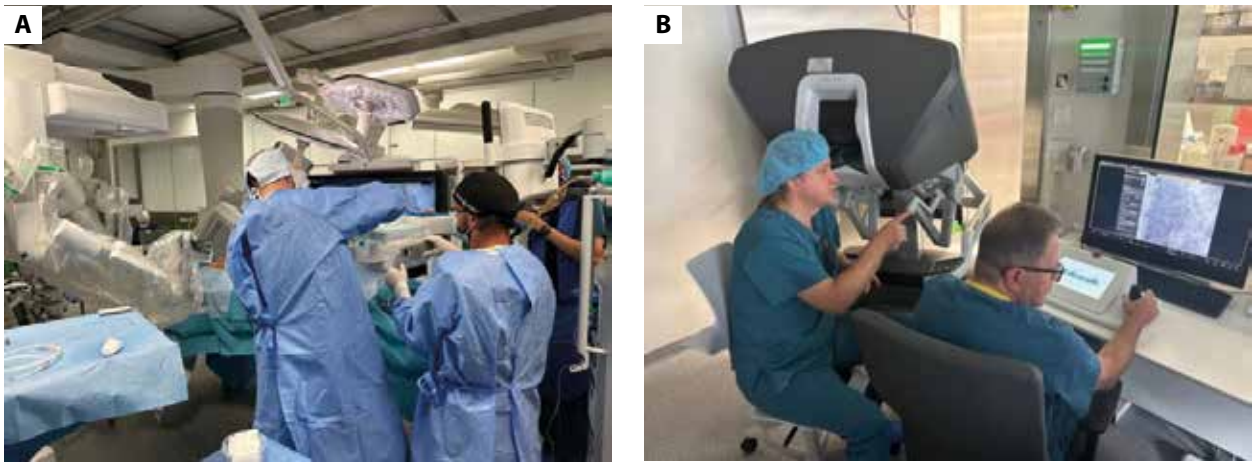


Figure 7. A. Preparation of the R-One for percutaneous intervention. The patient-side cart, with four articulated mechanical arms, which support the endoscopic instrument arms and camera arm during surgical procedures, is visible behind the X-ray angiography system. **B.** Cardiac surgeon assisting an interventionalist. The surgeon console is on the left; the command unit of the R-One system is on the right

only in relation to operating the robot but also to his/her overall experience in the field of classic interventional cardiology. Recent work of Bay et al. [26] provides interesting information on this matter. In this very elegant article the authors argue that nearly one of five (49/231 coronary lesions) in patients undergoing r-PCI required manual support, which was linked to longer procedural times, greater total contrast media volumes, longer fluoroscopy times, and higher dose-area products. Predictors of manual support reflected characteristics of more complex coronary lesions (e.g. aorto-ostial and bifurcation lesions, chronic total occlusions, true bifurcations and severe calcifications).

These results clearly indicate the weaknesses of the current generation of robotic systems used for r-PCI and the need for their further development, including the possibility of introducing system in which operators can handle two wires and two devices simultaneously (e.g. balloons, stents, etc.).

SUMMARY

Robotic-assisted PCI is a modern approach to performing PCI, a procedure used to restore the lumen of the stenosed coronary arteries. Robotic-assisted PCI exemplifies the advancement of interventional cardiology by integrating robotics to improve procedural control, operator safety, and potentially patient outcomes. Robotic-assisted PCI is currently more common in elective PCI cases, where time and precision are prioritized, however, the progress that has been made in surgical robotics allows us to believe in rapid progress of robots dedicated for complex coronary cases treatment. The successful remote PCI procedures in China highlight the role of robotic systems in revolutionizing interventional cardiology by offering both precision and remote accessibility, particularly in regions with limited access to specialized cardiovascular care.

It is also worth noting that robotic revascularization treatment seems to have quite good perspectives. Staged revascularization procedures are already being performed, where the cardiac surgery part is followed by a percutaneous stage in a robotic manner [27.

This form of coronary heart disease treatment is not only attractive to the patient, but also ensures complete revascularization with shortened hospitalization and cost optimization for treatment center (Figure 7).

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REVIEW

Coronary microvascular dysfunction in angina and non-obstructive coronary arteries: Pathophysiology, diagnosis, novel markers, and therapy

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ABSTRACT

Coronary microvascular dysfunction encompasses a wide variety of structural and/or functional abnormalities of the coronary microcirculation which are key determinants of myocardial ischemia in patients with angina and non-obstructive coronary artery disease, as well as in several other cardiovascular conditions. Diagnosis is based on demonstration of an impaired vasodilator capacity and/or evidence of microvascular spasm from invasive coronary angiography. Despite its relevant clinical and prognostic implications, there are no specific treatments to date specifically addressing coronary microvascular dysfunction. In this review article, we aimed to provide an overview of the pathophysiology, diagnostic work-up, and therapeutic management of patients with angina and non-obstructive coronary artery disease, focusing on emerging biomarkers, novel therapeutic targets, and remaining knowledge gaps and unmet needs.

Key words: angina, coronary microvascular dysfunction, non-obstructive coronary arteries

INTRODUCTION

Coronary microvascular dysfunction (CMD) refers to a wide spectrum of structural and functional abnormalities of coronary microcirculation, ultimately leading to impaired coronary blood flow (CBF) and myocardial ischemia [1, 2].

CMD has been increasingly recognized as the pathogenetic determinant of myocardial ischemia in different cardiovascular diseases, including angina with non-obstructive coronary artery (ANOCA), obstructive coronary artery disease, heart failure with preserved ejection fraction, takotsubo syndrome and cardiomyopathies [2–6].

Despite the emerging pathophysiological and prognostic role of CMD, randomized clinical trials addressing specific treatments for this condition are lacking. Moreover, CMD diagnosis is still challenging and mainly based on invasive coronary angiography.

This narrative review aims to provide a comprehensive overview of the pathophysiology, diagnosis, and therapeutic management of CMD in ANOCA focusing on emerging biomarkers, novel therapeutic targets, and remaining knowledge gaps and unmet needs.

PATHOPHYSIOLOGY

The coronary circulation comprises different compartments with distinct functions. The epicardial vessels offer a predominant capacitance function and little resistance to CBF [1, 3]. They exhibit endothelium-dependent dilation to maintain shear stress constant. Going distally, the pre-arteriolar vessels (500 to 100 μm diameter) are more sensitive to pressure changes. Their function is to maintain perfusion at the proximal level of the arterioles constant when perfusion pressure changes. Arterioles have diameters of less than 100 μm and are more responsive to changes in the intramyocardial concentration of metabolites with direct vasoactive properties, in particular adenosine [1].

CMD is due to structural and/or functional abnormalities of microcirculation, including pre-arterioles and arterioles [2, 3, 7].

FUNCTIONAL ABNORMALITIES

Functional abnormalities of the coronary microcirculation include reduced vasodilatation due to endothelial-dependent and/or independent alterations, and increased vasoconstriction (microvascular spasm).

Endothelial-dependent mechanisms involve a decreased production and/or increased degradation of vasodilating molecules released by the endothelium, such as prostaglandins, nitric oxide (NO), and endothelium-derived hyperpolarizing factors, or an enhanced bioavailability of vasoconstrictor molecules, such as endothelin-1 (ET-1) [2, 3, 8]. Chronic inflammation and oxidative stress were identified as the final common pathways leading to reduced availability of coronary vasodilators consequent to aging and exposure to cardiovascular (CV) risk factors. Indeed, inflammatory cytokines such as interleukin-6 and tumor necrosis factor-α enhance NAD(P)H oxidase (Nox) activity responsible for production of reactive oxygen species (ROS) [8–10]. Arginase II is an enzyme that metabolizes the NO synthase (eNOS) substrate L-arginine to urea and L-ornithine, and another important link between CV risk factors (e.g. diabetes) and vascular aging through ROS production [11]. In these conditions, elevated levels of intracellular ROS facilitate the conversion of NO into free radicals by promoting the formation of peroxynitrite radicals. As a result, NO-mediated vasodilation in large vessels is compromised, while vasoconstriction is enhanced through the activation of ET-1 [8, 12, 13]. Inflammation influences the release of other endothelial vasodilators, such as H2O2, which is involved in the tone regulation of small resistance vessels in response to shear stress [14, 15]. When the Nox system is hyperactivated, superoxide synthesis by endothelial cells and its subsequent rapid dismutation to H2O2 is impaired, thus contributing to the loss of a physiological arteriolar flow-induced vasodilation [16].

Endothelial-independent mechanisms are less understood and likely involve reduced vasodilation properties of vascular smooth muscle cells (VSMCs) or increased susceptibility to vasoconstrictor stimuli [3]. The RhoA/Rho-kinase pathway was shown to play a significant role in the increased constriction of VSMCs. This occurs through the regulation of calcium sensitivity and the phosphorylation of contractile myofilaments, which control the strength of smooth muscle contraction. This pathway is thought to contribute to the increased vulnerability of coronary vessels to spasms. Moreover, it further amplifies inflammation by promoting the release of ROS in both VSMCs and endothelial cells [13].

STRUCTURAL ABNORMALITIES

Beyond functional alterations, CMD may be caused by structural abnormalities of the coronary microcirculation, especially in patients with CV risk factors or underlying cardiomyopathies [17]. Hence, hypertrophic inward remodelling with medial wall thickening (mainly due to smooth muscle hypertrophy and increased collagen deposition), luminal narrowing of the arterioles and capillaries lead to perivascular fibrosis, microvascular rarefaction, and myocardial stiffness, all contributing to altered coronary physiology [3]. These phenomena are documented in clinical conditions characterized by an increased myocardial mass, such as in hypertensive heart disease and hypertrophic cardiomyopathy, where these pathological abnormalities extend beyond the vascular level toward the left ventricle and contribute to heart failure (HF) progression [18–20].

DIAGNOSTIC WORK-UP OF CMD

In patients with ANOCA the CMD diagnosis begins with the exclusion of obstructive epicardial stenoses [21]. A definitive diagnosis requires demonstrating an impaired vasodilator capacity and/or evidence of microvascular spasms [22].

The impairment of vasodilatory capacity can be assessed by measuring coronary flow reserve (CFR) and coronary microvascular resistance during maximal dilation obtained with adenosine administration. Microvascular spasm can be identified by assessing the response to Acetylcholine [23]. Acetylcholine provokes spasm through direct stimulation of muscarinic receptors on the surface of hyperreactive smooth muscle cells. Microvascular spasms are enhanced by endothelial dysfunction.

Over the recent years, numerous invasive and non-invasive diagnostic techniques have been developed to assess CMD, each with distinct advantages and limitations (Figure 1).

NON-INVASIVE DIAGNOSTIC TESTS

Non-invasive techniques primarily focus on investigating microvascular dysfunction, caused by reduced CFR, through a multimodality imaging approach. Computed tomography angiography (CCTA) or fractional flow reserve derived from CCTA (FFR-CCTA) are recommended to exclude obstructive CAD and dynamic CT perfusion imaging enables quantitative myocardial blood flow (MBF) estimation with diagnostic accuracy comparable to that of stress cardiac magnetic resonance (CMR) and positron emission tomography (PET) [24–26].

Stress transthoracic Doppler echocardiography allows the evaluation of the coronary flow velocity ratio, defined as the ratio of maximal diastolic coronary flow during adenosine or dipyridamole infusion to flow at rest. A cut-off between 2.0 and 2.5 demonstrates a good agreement with invasive coronary angiography to define normal CFR values [27]. Stress perfusion CMR using vasodilator agents (e.g., adenosine) allows a semi-quantitative evaluation of CFR by calculating the myocardial perfusion reserve index [28–30]. Among non-invasive techniques, PET with positron-emitting flow tracers remains the gold standard

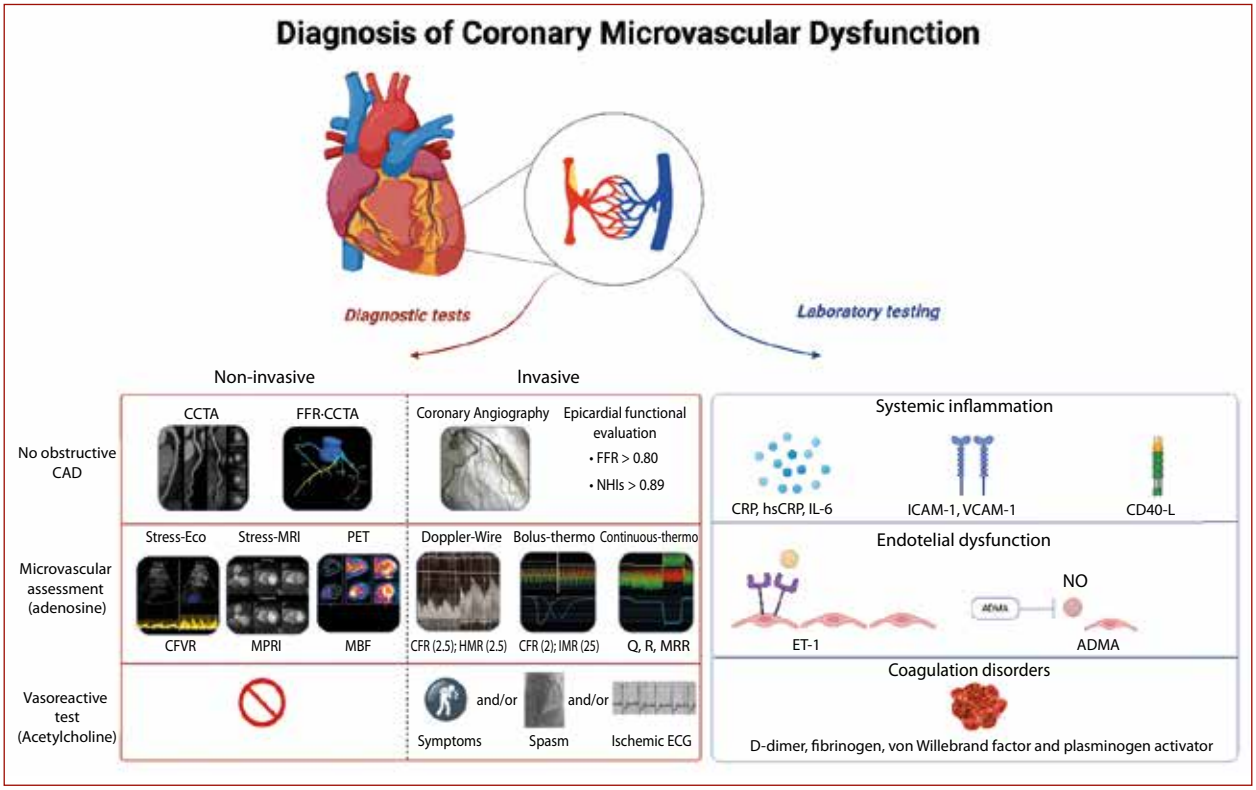


Figure 1. Diagnosis of coronary microvascular dysfunction. The figure illustrates invasive and non-invasive (both laboratory and diagnostic) tests to assess CMD

Abbreviations: ADMA, asymmetric dimethylarginine; CCTA, coronary computed tomography angiography; CD40-L, CD40 ligand; CFVR, coronary flow velocity reserve; CRP, C-reactive protein; ECG, electrocardiogram; ET-1, endothelin-1; FFR, fractional flow reserve; HMR, hyperemic microvascular resistance; hs-CRP, high-sensitivity C-reactive protein; ICAM-1, intercellular adhesion molecule-1; IMR, index of microcirculatory resistance; MBF, myocardial blood flow; MPRI, myocardial perfusion reserve index; MRI, magnetic resonance imaging; MRR, microvascular resistance reserve; NHIs, non-hyperemic indices; NO, nitric oxide; PET, positron emission tomography; Q, absolute quantification of coronary flow; R, absolute quantification of coronary resistance; VCAM-1, vascular adhesion molecule-1

for quantifying MBF and deriving CFR (expressed as the ratio of stress to rest MBF). In clinical practice, ^{13}N-labelled ammonia is the tracer most commonly employed due to its optimal balance between a suitable half-life and a high first-pass extraction fraction, thereby providing high-quality images and accurate MBF quantification. Conversely, ^{82}Rubidium showed promising results thanks to its generator-based availability and ultra-short half-life. Despite its high diagnostic accuracy, the widespread adoption of PET is hindered by limited availability, high operational costs, lengthy procedure times, and significant radiation exposure [31].

INVASIVE DIAGNOSTIC TESTS

The 2024 European Society of Cardiology Guidelines for the management of chronic coronary syndromes provide class I B recommendation to perform invasive coronary functional testing in patients with persistent symptoms and non-obstructive CAD (Figure 1) [32]. This approach enables comprehensive characterization of the full spectrum of CMD endotypes by combining flow and resistance parameters with vasoreactivity testing. Typically, this assessment complements coronary angiography, most often performed in the left anterior descending artery (due to its extensive perfusion territory) after ruling out obstructive functional CAD by non-hyperemic (NHIs >0.89) and hyperemic indices (FFR >0.80) [21].

CMD assessment involves pharmacological provocation tests using endothelial-independent vasodilators (e.g., adenosine) to induce hyperemia, whereas endothelial-dependent vasodilators (e.g., acetylcholine) are employed to evaluate endothelial dysfunction and vasospasm (microvascular and epicardial) [21]. One of the most widely utilized protocols to assess CMD is the #FullPhysiology approach. This stepwise approach begins with endothelium-independent hyperemia, typically induced *via* intravenous adenosine infusion, followed by vasomotor testing with escalating doses of intracoronary acetylcholine [33].

CFR and the index of microvascular resistance (IMR) are the primary parameters for diagnosing endothelium-independent microvascular dysfunction. Indirect assessments of CBF can be obtained using diagnostic guidewires equipped with Doppler sensors or employing the thermodilution technique. The Doppler method utilizes intracoronary diagnostic guidewires with either a single Doppler sensor (e.g., Flowire, Philips Volcano Corporation)

or a combined Doppler-pressure sensor (e.g., ComboWire XT, Philips Volcano Corporation). These devices measure average peak velocity (APV), with Doppler-derived CFR calculated as the ratio of hyperemic to resting APV [34].

Conversely, the thermodilution technique employs a guidewire with integrated pressure and temperature sensors (e.g., PressureWire X, Abbott Vascular). Blood flow velocity is estimated as the inverse of the mean transit time (Tmn) following intracoronary injection of a room-temperature saline bolus. CFR is determined by the ratio of the inverse of Tmn during hyperemia to that at rest [35]. Pathological CFR is defined as <2.0 for both Doppler and thermodilution methods, while a CFR <2.5 is prognostically unfavorable for Doppler but borderline for thermodilution (36).

Microvascular resistance is quantified by integrating flow and pressure data. For thermodilution, IMR is calculated as the product of hyperemic Tmn and distal coronary pressure (Pd). For Doppler assessment, hyperemic microvascular resistance (HMR) is computed as distal coronary pressure divided by APV during hyperemia. Diagnostic thresholds for CMD are IMR >25 units or HMR >2.5 mmHg/cm/s [37, 38].

A combined analysis of CFR and IMR/HMR allows the identification of 3 main CMD endotypes [33, 39]:

- low CFR, high IMR/HMR: elevated microvascular resistance indicates impaired vasodilation possibly due to functional alterations or adverse microvascular remodelling (e.g., fibrosis or hypertrophy);
- low CFR, normal IMR/HMR: the reduction in CFR is in this case caused by an increase in resting CFR probably due to impaired oxygen utilization;
- normal CFR, high IMR/HMR: this less well-characterized condition may reflect early microvascular structural damage that is partially compensated, as indicated by normal CFR values.

To improve diagnostic precision, continuous thermodilution has been introduced for absolute quantification of coronary flow (Q) and resistance (R) under baseline and hyperemic conditions. This technique employs a dedicated monorail catheter (RayFlow, Hexacath) delivering continuous saline infusion at 10 ml/min for baseline and 20 ml/min for hyperemia (induced by erythrocyte hemolysis) [40]. This method facilitates the calculation of the microvascular resistance reserve (MRR), a new microcirculation-specific index independent of epicardial stenosis with prognostic significance [41].

Smooth muscle cell hyperreactivity enhanced by endothelial dysfunction and responsible for microvascular spasm is assessed in the catheterization laboratory through the intracoronary administration of escalating doses (20–50–100 mcg) of acetylcholine (ACh). This procedure involves continuous 12-lead electrocardiogram (ECG) monitoring and angiographic imaging performed after each ACh injection or upon the onset of anginal symptoms or ischemic ECG changes [22]. Interpretation of the test is guided by the diagnostic criteria established by the International Study Group on Coronary Artery Vasomotor Disorders (COVADIS) [42]. Epicardial spasm is defined as a >90% vasoconstriction observed on coronary angiography, accompanied by the reproduction of anginal symptoms and ischemic ECG changes. In contrast, microvascular spasm is characterized by the presence of anginal symptoms and ischemic ECG changes without significant angiographic abnormalities. Despite initial concerns regarding its safety, recent evidence has demonstrated that adverse events associated with this provocative testing are rare, predominantly transient arrhythmias, thus supporting its increasing clinical use [43].

CIRCULATING BIOMARKERS OF CMD

In past decades, circulating biomarkers have gained increasing attention for CMD diagnosis and prognostication.

Several studies have explored the role of pro-inflammatory biomarkers, such as C-reactive protein (CRP) and high-sensitivity CRP (hs-CRP). Mechanistic studies have shown that levels of CRP and hs-CRP are elevated in CMD compared to healthy controls and that elevated values of these biomarkers are associated with myocardial ischemia and abnormal coronary reactivity testing [44–49]. Moreover, raised CRP and hs-CRP values independently predict microvascular angina [50]. The strength of hs-CRP (or CRP) is its high availability, although it is not specific to CMD. Other inflammatory biomarkers, including adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), have also been implicated in CMD. These molecules, upregulated during inflammation, promote leukocyte adhesion to the endothelium. Elevated levels of ICAM-1 and VCAM-1 have been demonstrated in CMD patients and correlate with CFR on invasive coronary angiography and myocardial perfusion reserve index on CMR [51–54]. Evidence supporting the role of other pro-inflammatory biomarkers (e.g. interleukin 6, cluster of differentiation 40 ligands) is less robust [55, 56].

Endothelial dysfunction plays a central role in CMD and is reflected by such biomarkers as asymmetric dimethylarginine (ADMA) and endothelin-1 (ET-1). Several studies demonstrated that ADMA, an inhibitor of NO synthesis, has higher levels in patients with diabetes, autoimmune diseases and CMD [57–59]. Moreover, Lu and co-authors documented that raised ADMA values in patients with CMD are associated with major adverse events (all-cause mortality, stroke and non-fatal myocardial infarction) at follow-up (HR, 0.19; $P = 0.013$) [59]. In addition, beyond lowering NO bioavailability, ADMA worsens endothelial dysfunction by upregulating angiotensin-converting enzyme (ACE) and enhancing oxidative stress *via* AT1 receptor activation, thereby advancing CMD progression [60]. Endothelin-1 is one of the most potent vasoconstrictor agents and is released by endothelial cells. It acts *via* the endothelin A and endothelin B receptors, the former mediating constriction

Table 1. Pathological mechanisms and target therapy of coronary microvascular dysfunction

	Pathological mechanisms	Therapy
CV risk factors	Microvascular inflammation and damage	1.Exercise activity, weight reduction 2. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, statins 3. SGLT-2 for the association with HF
High IMR/HMR, low CFR (high microvascular resistance)	Microvascular remodeling and inability to increase myocardial flow during exercise (fibrosis, capillary rarefaction, vascular remodeling)	1. Beta-blockers (nebivolol, carvedilol) 2. Ranolazine, 2nd generation DHP Ca-antagonists 3. SGLT-2 for the association with HF 4. Coronary sinus reducer
Low CFR, normal IMR/HMR (high flow at rest)	Increased resting flow probably caused by impaired oxygen utilization. Preserved microvascular resistance	1. Beta-blockers, ivabradine 2. Verapamil/diltiazem 3. Ranolazine, SGLT-2 for the association with HF 4. Coronary sinus reducer
Epicardial/microvascular spasm	Endothelial dysfunction and/or hypercontractility of smooth muscle cells	1. Verapamil/diltiazem 2. 2nd generation DHP Ca-antagonists 3. Nicorandil, fasudil
Persistent angina despite of optimal medical therapy	Enhanced nociception	1. Xanthines (theophylline) 2. Tricyclic antidepressants (Imipramine) 3. Non-pharmacological interventions

Abbreviations: CFR, coronary flow reserve; CV, cardiovascular; DHP, dihydropyridine; HF, heart failure; HMR, hyperemic microvascular resistance; IMR, index of microvascular resistance; SGLT-2, sodium-glucose cotransporter 2

and the latter vasodilatation. A pivotal study by Hoffman et al. [61] found that in 13 patients with INOCA, ET-1 levels were significantly higher compared to a control group (2.89 ± 1.24 pmol/l vs. 1.99 ± 0.81 pmol/l; P <0.02). Further studies strengthened these findings, also documenting a correlation between high ET-1 levels and IMR on invasive coronary angiography (r = 0.57; P <0.01) [62, 63].

Finally, markers of the coagulation cascade, such as von Willebrand factor, plasminogen activator, D-dimer, and fibrinogen are elevated in CMD and may contribute to a prothrombotic environment [64–67].

Despite the potential role of these biomarkers in diagnosing, stratifying the prognosis, and targeting therapy of CMD, their clinical use is still limited due to the small sample size, lack of specificity, and heterogeneous definition of CMD in most studies, necessitating further research.

TREATMENT OF CMD IN ANOCA AND FUTURE PERSPECTIVES

CMD is associated with adverse cardiovascular outcomes. Numerous studies and meta-analyses have demonstrated that reduced CFR, regardless of clinical context, correlates with a three- to four-fold increase in all-cause mortality and CV events [68]. Similar associations have been observed in patients with coronary vasospasm [69]. Despite its clinical relevance, large-scale clinical trials are still needed, and no specific therapy for CMD currently exists.

The efficacy of personalized treatments of ANOCA targeting the underlying pathophysiological mechanisms of ischemia has been supported by the CORMICA trial [70]. Additionally, the real-world application of the #FullPhysiology approach has been associated with a reduction in CV events when therapeutic decisions are guided by comprehensive assessments of coronary physiology and vasomotor responses [71]. Considering the role of traditional CV risk factors in both microvascular dysfunction and coronary vasospasm, current treatment strategies must prioritize risk factor management and tailored interventions based on individual phenotypic presentations (Table 1).

Pharmacological therapy targeting CV risk factors includes ACE inhibitors (ACE-Is), angiotensin receptor blockers and statins. The TREND study demonstrated that quinapril, an ACE-I, can reverse endothelial dysfunction [72]. Statins, primarily HMG-CoA reductase inhibitors, not only reduce plaque formation and macrophage infiltration but also exert beneficial anti-inflammatory effects in CMD patients. Synergically, these agents enhance myocardial perfusion and coronary endothelial function through anti-inflammatory and antioxidant mechanisms [73].

Anti-anginal therapy is guided by CMD endotype identification. In high-resistance CMD, where ischemia results from impaired microvascular dilation, pharmacological therapy includes third-generation beta-blockers (e.g., nebivolol, carvedilol) aimed at reducing myocardial oxygen demand and promoting nitric oxide-mediated vasodilation and vasodilators such as calcium channel blockers [74]. For poor responders, additional therapy with dihydropyridine calcium channel blockers may be considered. Ranolazine, a piperazine derivative, inhibits the late sodium current, reducing intracellular calcium accumulation and improving ventricular relaxation [75]. The CHAMP-CMD trial demonstrated that invasive CFR measurements could help identify patients who benefit from ranolazine [76].

In CMD characterized by elevated resting coronary flow associated with reduced CFR but with preserved microvascular resistance, beta-blockers or ivabradine are recommended as first-line therapy, followed by non-dihydropyridine calcium channel blockers. The approach is similar to that in patients in whom CFR is reduced by epicardial stenoses: to reduce myocardial oxygen consumption. In this patient group more information is needed regarding the mechanisms for a possible impaired oxygen consumption which can lead to new forms of therapy.

For coronary spasms, calcium channel blockers (e.g., verapamil, diltiazem, amlodipine) are preferred, often at higher-than-standard doses, while non-selective beta-blockers should be avoided as they increase coronary tone [77]. In cases of persistent symptoms, nicorandil, which promotes smooth muscle cell relaxation and increases NO bioavailability, may be considered.

Approximately 25% of CMD patients experience refractory symptoms despite optimal medical therapy, highlighting knowledge gaps in CMD pathophysiology and diagnosis. Tricyclic antidepressants (e.g., imipramine, amitriptyline) have been investigated for symptom relief due to their analgesic effects (78). These agents may alleviate symptoms in patients with altered cardiac nociception. Xanthine derivatives may benefit this subset of patients as they are antagonists of A1 adenosine receptors and adenosine is the main mediator of anginal pain [79].

Emerging therapies include sodium-glucose cotransporter-2 inhibitors. Empagliflozin has been shown to restore cardiac microvascular endothelial function and improve coronary flow velocity ratio in prediabetic models [80]. Positive outcomes from the EMPEROR-Preserved and DELIVER trials underscore the need for further research in CMD-specific populations [81, 82]. Fasudil, a selective Rho-kinase inhibitor, effectively prevents acetylcholine-induced coronary spasms by mitigating endothelial dysfunction and inflammation [83]. Conversely, zibotentan, an endothelin-A receptor antagonist, failed to show clinical benefits in CMD patients [84]. The ongoing WARRIOR trial evaluates intensive therapy with ACE-I/ angiotensin receptor blockers, high-dose statins, and aspirin in women with INOCA, though diagnoses are based on non-invasive imaging rather than functional testing [85].

Device-based therapies, such as the coronary sinus reducer, offer innovative solutions for refractory angina. The coronary sinus reducer increases venous backpressure, redistributing CBF to under-perfused myocardial regions. This mechanism promotes favourable microvascular remodelling, as evidenced by improved CFR and reduced IMR assessed *via* bolus thermodilution, ultimately resulting in symptom reduction [86]. However, the latest studies have failed to show benefits in terms of myocardial perfusion on CMR [87].

CONCLUSIONS

CMD is a key determinant of myocardial ischemia across different cardiovascular diseases and can significantly worsen clinical outcomes. Despite the potential clinical implications, there are no specific therapies addressing CMD, and its diagnosis is still based on invasive coronary angiography. A precision medicine approach to treat these patients remains a major challenge in cardiovascular medicine. Moreover, further studies are needed to define the role of non-invasive diagnostic markers (e.g., circulating biomarkers) in diagnosing and prognosticating CMD.

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MRI- and CT-derived carotid plaque characteristics and stroke: Insights from the ANTIQUE study

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Editorial
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ABSTRACT

Background: Carotid plaque composition plays a key role in plaque stability and patient risk stratification. Of unstable plaque features, intraplaque hemorrhage (IPH) is considered the main risk factor for stroke development.

Aims: We aimed to assess an association between the presence of IPH and other plaque characteristics detectable by computed tomography (CT) or magnetic resonance imaging (MRI) and stroke.

Material and methods: Of all consecutive patients from the ANTIQUE study, 132 (91 males; aged 70.0 [8.6] years) with 59 symptomatic and 157 asymptomatic stable carotid plaques were included in the retrospective analysis of prospectively collected data. Plaques in the vascular territory of ischemic stroke within 90 days were classified as symptomatic and were diagnosed by CT and MRI after symptoms occurred. Plaques without progression and clinical infarction were classified as asymptomatic stable. Univariate and multivariate logistic regression analyses were performed to identify risk factors.

Results: The presence, age, location, and volume of IPH were not related to stroke risk (P >0.05). Patients with symptomatic plaque were more likely to consume alcohol (P = 0.005), had more severe stenosis (CT median: 80% vs. 72%; P = 0.005; MRI median: 79% vs. 72%; P = 0.01), lower American Heart Association grade (P = 0.03), and more frequent lipid plaque (89.8% vs. 76.4%; P = 0.04) compared to patients with asymptomatic stable plaques. Stenosis severity (odds ratio [OR], 1.037; 95% CI, 1.015–1.059) and additionally alcohol consumption (OR, 3.571; 95% CI, 1.694–7.527) were found to be the only significant predictors of a recent stroke.

Conclusions: In this cohort, no IPH or other plaque characteristics were associated with stroke risk. The degree of stenosis and alcohol consumption were the only factors associated with ipsilateral stroke. Larger prospective studies considering plaque characteristics are needed.

Key words: carotid atherosclerosis, computed tomography, intraplaque hemorrhage, magnetic resonance imaging, stroke

WHAT'S NEW?

Intraplaque hemorrhage (IPH) is considered one of the strongest predictors of stroke of all carotid plaque characteristics. However, the presence of IPH varies in individual groups of patients. Of the 132 patients (59 symptomatic/157 asymptomatic stable carotid plaques) included, the presence, age, location, and volume of IPH were not related to the risk of cerebrovascular events. Only stenosis degree and additionally alcohol consumption were independent stroke risk factors. Our findings suggest that a complex evaluation of carotid plaque characteristics and common stroke/atherosclerosis risk factors should be considered rather than focusing only on IPH in high-risk patients needing prospective follow-up, risk stratification, and further treatment, but larger prospective studies are needed.

INTRODUCTION

Atherosclerosis-induced stenosis occurs most frequently at the site of the carotid bifurcation and the origin of the internal carotid artery (ICA) among all blood vessels that supply the brain, and its most common serious complication is ischemic stroke [1]. Growing atherosclerotic plaques cause stenosis in carotid arteries in up to 75% of men and 62% of women over the age of 65 years, and carotid artery stenosis causes approximately 18%–25% of all strokes [2, 3].

Carotid plaques can be split from the clinical point of view as stable, i.e., asymptomatic with a low chance of rupture and stroke development, and unstable, i.e., potentially symptomatic with a high risk of stroke, or symptomatic which caused acute brain ischemic events [4, 5]. Generally, unstable plaques are characterized by the presence of a thin fibrous cap overlying a large lipid core, show intraplaque hemorrhage (IPH), stenosis >90%, ulceration/fissure, active inflammation, and neovascularization, and they tend to be a source of silent microemboli [5–7]. Stable plaques are composed mainly of solid fibrous tissue, and they show calcification, with lipids either absent or present only in small amounts [4, 8].

IPH in carotid stenosis is considered one of the strongest predictors of stroke of all plaque characteristics in symptomatic and asymptomatic patients, and in patients with low stenosis [9–12]. However, the presence of IPH varied in frequency between symptomatic progressive plaques, symptomatic stable plaques, asymptomatic progressive plaque, and stable asymptomatic plaques [13, 14]. Therefore, there are problems related to the classification of IPH and stroke risk in individual groups of patients.

For the noninvasive diagnostic imaging of atherosclerotic plaques, carotid artery ultrasound, magnetic resonance imaging (MRI), and computed tomography (CT) are commonly used because they are widely available in developed countries and have high sensitivity and specificity [15].

The aims of this retrospective data analysis from a prospective multicenter observational study were 1) to assess an association between IPH detected by MRI and ipsilateral transient ischemic attack (TIA) and/or stroke, and 2) to compare other atherosclerotic plaque characteristics detectable by CT and MRI between symptomatic and asymptomatic stable plaques in the carotid bifurcation.

MATERIAL AND METHODS

All consecutive patients from the Atherosclerotic Plaque Characteristics Associated With Progression Rate of the Plaque in Carotids and Risk of Stroke study (the ANTIQUE study; ClinicalTrials.gov Identifier: NCT02360137) who underwent clinical and diagnostic examinations between October 2016 and March 2019 were included. The patients were recruited into the comprehensive stroke center's sonographic laboratory from those indicated for neurosonology examination in primary or secondary stroke prevention or acute stroke diagnostics [16]. Conservative and/or interventional treatment (carotid endarterectomy or stenting) was indicated according to valid guidelines for all patients [17]. Inclusion and exclusion criteria are shown in Figure 1.

Subsequently, only carotid plaque (the most stenotic lesion when multiple plaques were present) that caused at least 30% stenosis on ultrasound (transition from laminar to turbulent blood flow stated in Reynolds numbers as a critical value: 2000–2400) [18, 19] was analyzed.

Clinical characterization

Extracranial carotid atherosclerotic plaques were divided into two groups: symptomatic and asymptomatic stable plaques. Symptomatic plaques were defined as only carotid

Figure 1. Study inclusion and exclusion criteria

Inclusion criteria
• Age 30–90 years
• Location of the atherosclerotic plaque in the carotid bifurcation or the proximal part of the internal carotid artery (ICA)
• Carotid plaque thickness of ≥2 mm in the transverse plane of the ultrasound B-mode measurement
• Sufficient image quality of the atherosclerotic plaque in the carotid bifurcation and ICA with computed tomography (CT)/magnetic resonance imaging (MRI)
• Patient self-sufficiency (modified Rankin scale score 0–2)
• Provision of signed informed consent by the patient
Exclusion criteria
• CT or MRI of the neck not performed
• Insufficient CT and MRI quality
• Patient non-cooperation
• Detected carotid artery occlusion
• Stent implementation in the carotid bifurcation
• Invasive treatment (carotid endarterectomy or angioplasty and stenting) of the ipsilateral carotid artery

plaques in patients with clinical signs of ipsilateral cerebrovascular events (TIA, stroke, amaurosis fugax, and/or retinal infarction) in the carotid artery region in the prior 90 days, excluding patients with other potential stroke etiology (cardioembolic, lacunar, arterial dissection, vasculitis, other rare causes of stroke). Plaques in patients without clinical signs of TIA/stroke in the relevant arterial territory and without progression (changes <20% of plaque width) within the last 3 years were classified as asymptomatic stable plaques.

In case a patient experienced a clinical cerebrovascular event (TIA, stroke, amaurosis fugax, and/or retinal infarction), only ipsilateral carotid plaque to the affected territory was evaluated. In asymptomatic patients with bilateral stable plaques, both plaques of the right and left ICA were analyzed. All other plaques (asymptomatic progressive, with detected silent infarction, etc.) were excluded from the analysis to reach homogeneous groups of plaques.

When a patient had a cerebrovascular event, brain CT and ultrasound examination were performed as soon as possible. The patient was immediately scheduled for CT angiography (CTA) and MRI of the carotid arteries (performed within 30 days) in the case of detected carotid stenosis (at least 30%) and enrollment in the study.

Computed tomography

All patients underwent standard multi-detector helical CTA of the cerebral and carotid arteries on different machines with 50–100 ml of intravenous iodine contrast agent (CA). Detailed information is provided in the Supplementary material.

The degree of carotid artery stenosis was evaluated according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria [20]. The plaque structure was evaluated according to the representation of individual components in the plaque by measured density (expressed in HU). A distinction was made among lipid (<60 HU), fibrous (60–130 HU), and calcified components (>130 HU) by measurement on the voxel level using a drawn region of interest (2–10 pixels per region) in several sections covering the entire plaque (minimum of three sections) [21]. The plaques were further divided according to their surface morphology: smooth (plaque surface without signs of irregularity), irregular (small changes on plaque surface) or ulcerated (excavation >1 mm depth on plaque surface, visible in at least two planes) [22].

Magnetic resonance imaging

MRI examinations of carotid arteries were performed on different machines. The MRI carotid bifurcation examination protocol consisted of four basic sequences: T1w, 3D MPRAGE, T2w, and 3D TOF. In selected patients, 7.5–10 ml CA was administered (postcontrast T1w). Detailed information is provided in Supplementary material.

The signal intensities of the individual characteristics of the carotid plaques were visually compared with those of the sternocleidomastoid muscle. Intraplaque hyperintensity on MPRAGE sequences signaled the presence of IPH, further divided into acute (fresh, less than 1 week old: hyperintense on TOF and T1w images, and isointense to hypointense on T2w images) and subacute (recent, 1–6 weeks old: hyperintense on TOF, T1w, and T2w images; Supplementary material, *Figure S1*). The location of IPH, as superficial (juxtaluminal) or deep (saturated plaque), and the volume of IPH compared to the volume of the whole plaque (0%, 20%, 40%, 60%, and 80%) were evaluated only visually [23]. Evaluation of other plaque characteristics is available in Supplementary material.

One experienced rater (DP) evaluated all plaque characteristics on CT and MRI based on the described methods used in previously published studies. The rater was unaware of to the patient's status, medical history, and CT results during MRI evaluation.

Demographic data and clinical examinations

Age and sex were recorded from the patient demographic data. Information on the CT and MRI examinations performed and the side of ICA stenosis were recorded from the imaging data of patients. From the patients' anamnestic data, selected past and present diseases associated with atherosclerosis and stroke (arterial hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, myocardial infarction, atrial fibrillation, chronic kidney disease, and autoimmune disease) were recorded, and their definitions are listed in Supplementary material. Data on smoking (number of cigarettes per day) and daily alcohol consumption (1 unit/20 g of alcohol = 0.5 l of beer/2 dl of wine/0.5 dl of spirits) in the last year, together with the use of antithrombotic and statin medication were also recorded.

In addition to ischemic stroke, possible TIA, amaurosis fugax, and retinal infarction were recorded among the monitored ischemic disorders. Ischemic stroke was defined as an episode of neurological dysfunction caused by focal cerebral infarction persisting ≥24 hours confirmed by CT and TIA as focal arterial ischemia with transient symptoms lasting <24 hours without evidence of infarction on CT. Retinal infarction was defined as acute painless visual loss (retinal ischemic stroke) and amaurosis fugax as retinal TIA. Updated definitions by expert consensus were used to define cerebrovascular events [24].

Ethics

The study was approved by the Ethics Committee of the University Hospital of Ostrava (no. 605/2014) and performed according to the Declaration of Helsinki and its later amendments. All patients provided signed informed consent.

Statistical analysis

A pre-study statistical calculation determined that the minimum sample size of 198 carotid stenoses is required to demonstrate a 10% difference in IPH presence between symptomatic/asymptomatic stable carotid plaques with an

Table 1. Demographic data of patients enrolled in the study

	Asymptomatic stable carotid plaque	Symptomatic carotid plaque	*P*-value
Subjects, n	157	59	NA
Age of patients, years, mean (SD)	70.1 (8.2)	69.7 (9.6)	0.75
Male sex, n (%)	108 (68.8)	43 (72.9)	0.62
Right side of stenosis, n (%)	82 (52.2)	25 (42.4)	0.22
Ischemic stroke, n (%)	0 (0)	37 (62.7)	NA
Transient ischemic attack, n (%)	0 (0)	15 (25.4)	NA
Retinal infarction, n (%)	0 (0)	2 (3.4)	NA
Amaurosis fugax, n (%)	0 (0)	4 (6.8)	NA
Hemorrhagic stroke, n (%)	1 (0.6)	1 (1.7)	NA
Arterial hypertension, n (%)	147 (93.6)	52 (88.1)	0.25
Diabetes mellitus, n (%)	68 (43.3)	24 (40.7)	0.76
Dyslipidemia, n (%)	116 (73.9)	46 (78.0)	0.60
Coronary arterial disease, n (%)	50 (31.8)	13 (22.0)	0.18
Myocardial infarction, n (%)	30 (19.1)	7 (11.9)	0.23
Atrial fibrillation, n (%)	22 (14)	8 (13.6)	1.00
Chronic kidney disease, n (%)	9 (5.7)	5 (8.5)	0.54
Autoimmune disease, n (%)	0 (0)	0 (0)	1.00
Smoking, n (%)	49 (31.2)	24 (40.7)	0.20
Number of cigarettes per day, median (IQR)	0 (0–5)	0 (0–10)	0.23
Alcohol consumption, n (%)	54 (34.4)	33 (55.9)	0.005
Number of alcohol units per day, median (IQR)	0 (0–1)	1 (0–1)	0.003
Antithrombotic therapy, n (%)	140 (89.2)	51 (86.4)	0.63
Statin therapy, n (%)	122 (77.7)	43 (72.9)	0.48

Abbreviations: IQR, interquartile range; NA, not applicable; SD, standard deviations

alpha error of 5% and power of 80%. Shapiro–Wilk normality tests verified that only age had a normal distribution. A comparison of age samples was performed with a two-sample t-test. For other quantitative and ordinal variables, the Mann–Whitney U-test was used. Qualitative variables with absolute and relative frequencies were described, and group comparisons were performed with Fisher's exact test.

Multivariate analysis was performed with logistic regression using the backward stepwise (likelihood ratio) method with symptomatic stenosis (ischemic stroke, TIA, amaurosis fugax, and retinal infarction) as a dependent variable, and with selected demographic factors (age, sex, and side of stenosis), risk factors (arterial hypertension, diabetes mellitus, dyslipidemia, ischemic heart disease, myocardial infarction, atrial fibrillation, chronic kidney disease, smoking, alcohol consumption, antithrombotic therapy, and statin therapy), CT plaque characteristics (percentage of stenosis, lipid plaque, fibrous plaque, calcification, and plaque surface), and MRI plaque characteristics (IPH, age of IPH, location of IPH, volume of IPH, percentage of stenosis, AHA plaque type, lipid-rich necrotic core [LRNC], fibrous cap, and enhancement) as independent factors.

A *P*-value <0.05 was considered as statistically significant. SPSS Statistics 23 (International Business Machines Corporation, Armonk, NY, US) and STATA 17 (Stata Corp., TX, US) were used for statistical data processing.

RESULTS

Of 1863 patients enrolled in the ANTIQUE study, a total of 132 patients (91 males; mean age 70.0 [8.6] years) passed all inclusion and exclusion criteria and were included in the analysis. Of the 264 total imaged carotid bifurcations, 216 arteries were analyzed (excluded arteries due to carotid occlusion in 17 cases, carotid stenosis <30% in 10 cases, silent but not recent clinically manifested brain ischemia in 21 cases). Finally, a smaller number of carotid plaques was evaluated with MRI than with CT (199 vs. 216, respectively). In 17 carotid plaques evaluated by CT, the MRI image quality was not sufficient to perform an MRI analysis of plaque morphology. The study flow chart is presented in Supplementary material, *Figure S2*.

A total of 59 atherosclerotic plaques were classified as symptomatic (43 males; mean age 69.7 [9.6] years), and asymptomatic stable plaques were detected in 157 carotid arteries (108 males; mean age 70.1 [8.2] years). Comparing demographic stroke risk factors, patients with symptomatic plaques were significantly more likely to drink alcohol in greater quantities (demographic data in Table 1).

On MRI, we found no significant difference between symptomatic and asymptomatic stable plaque groups in the presence, age, location, or volume of IPH (Table 2). Patients with symptomatic carotid plaques were statistically significantly more often categorized by lower AHA plaque type (IV–V/VI) and exhibited a higher degree of stenosis (median: 79% vs. 72%) compared to asymptomatic stable plaques. The evaluation of carotid plaque characteristics on CT showed a significant difference between the symptomatic and asymptomatic stable plaque groups in stenosis severity (median: 80% vs. 72%) and lipid plaque (89.8% vs. 76.4%). Other characteristics assessed on CT or MRI did not differ significantly between the groups (Table 3 for MRI, Table 4 for CT).

Table 2. MRI-detected IPH

	Asymptomatic stable carotid plaque	Symptomatic carotid plaque	*P*-value
Subjects, n	145	54	NA
IPH, n (%)			
None	116 (80.0)	43 (79.6)	0.73
Acute	17 (11.7)	8 (14.8)	
Subacute	12 (8.3)	3 (5.6)	
IPH location, n (%)			
None	116 (80.0)	43 (79.6)	0.47
Superficial	11 (7.6)	2 (3.7)	
Deep	18 (12.4)	9 (16.7)	
IPH volume, n (%)			
0%	116 (80.0)	43 (79.6)	0.83
20%	8 (5.5)	1 (1.9)	
40%	9 (6.2)	3 (5.6)	
60%	6 (4.1)	4 (7.4)	
80%	6 (4.1)	3 (5.6)	

Abbreviations: IPH, intraplaque hemorrhage; MRI, magnetic resonance imaging

Table 3. Characteristics of carotid plaque evaluated on magnetic resonance imaging

	Asymptomatic stable carotid plaque	Symptomatic carotid plaque	*P*-value
Subjects, n	145	54	NA
Severity of stenosis in %, mean (SD)	66.5 (19.6)	74.8 (18.6)	0.005
Lipid part, n (%)	112 (77.2)	45 (83.3)	0.27
Type according to the AHA, n (%)			
IV–V	43 (34.7)	23 (46.9)	0.03
VI	35 (28.2)	17 (34.7)	
VII	22 (17.7)	5 (10.2)	
VIII	24 (19.4)	4 (8.2)	
Fibrous cap, n (%)			
None	46 (40.7)	14 (30.4)	0.22
Thick	37 (32.7)	14 (30.4)	
Thin	19 (16.8)	8 (17.4)	
Rupture	11 (9.7)	10 (21.7)	
Examination with CA, n (%)	56 (38.6)	51.9)	NA
Enhancement, n (%)	14 (25.0)	12 (42.9)	0.13

Abbreviations: AHA, American Heart Association; CA, contrast agent; other — see Table 1

Table 4. Characteristics of carotid plaque evaluated on computed tomography

	Asymptomatic stable carotid plaque	Symptomatic carotid plaque	*P*-value
Subject, n	157	59	NA
Severity of stenosis in %, mean (SD)	67.6 (18.9)	74.4 (18.5)	0.01
Lipid part, n (%)	120 (76.4)	53 (89.8)	0.04
Fibrous part, n (%)	89 (56.7)	34 (57.6)	1.00
Calcification, n (%)	136 (86.6)	48 (81.4)	0.39
Plaque surface, n (%)			
Smooth	9 (5.7)	4 (6.8)	0.88
Irregular	75 (47.8)	27 (45.8)	
Ulcerated	73 (46.5)	28 (47.5)	

Abbreviations: see Table 1

Age, sex, and the following variables with $P < 0.20$ were included in the logistic regression analysis: coronary arterial disease, smoking, alcohol consumption, lipid part, AHA plaque type, and stenosis measured on CT and MRI (enhancement was not included due to the small number of measured values). Multinomial logistic regression indicated that only alcohol consumption (odds ratio [OR], 3.571; 95% CI, 1.694–7.527) and stenosis severity on MRI (OR, 1.037; 95% CI, 1.015–1.059) were significant predictors of recent TIA/stroke. Detailed logistic regression results including all steps are presented in Supplementary material, *Table S1*. The distribution of carotid stenosis severity in both groups is presented in Supplementary material, *Figure S3*, and probability models of plaque being symptomatic for alcohol abuse and LRNC related to stenosis severity are shown in Figures 2 and 3, respectively. Finally, an associ-

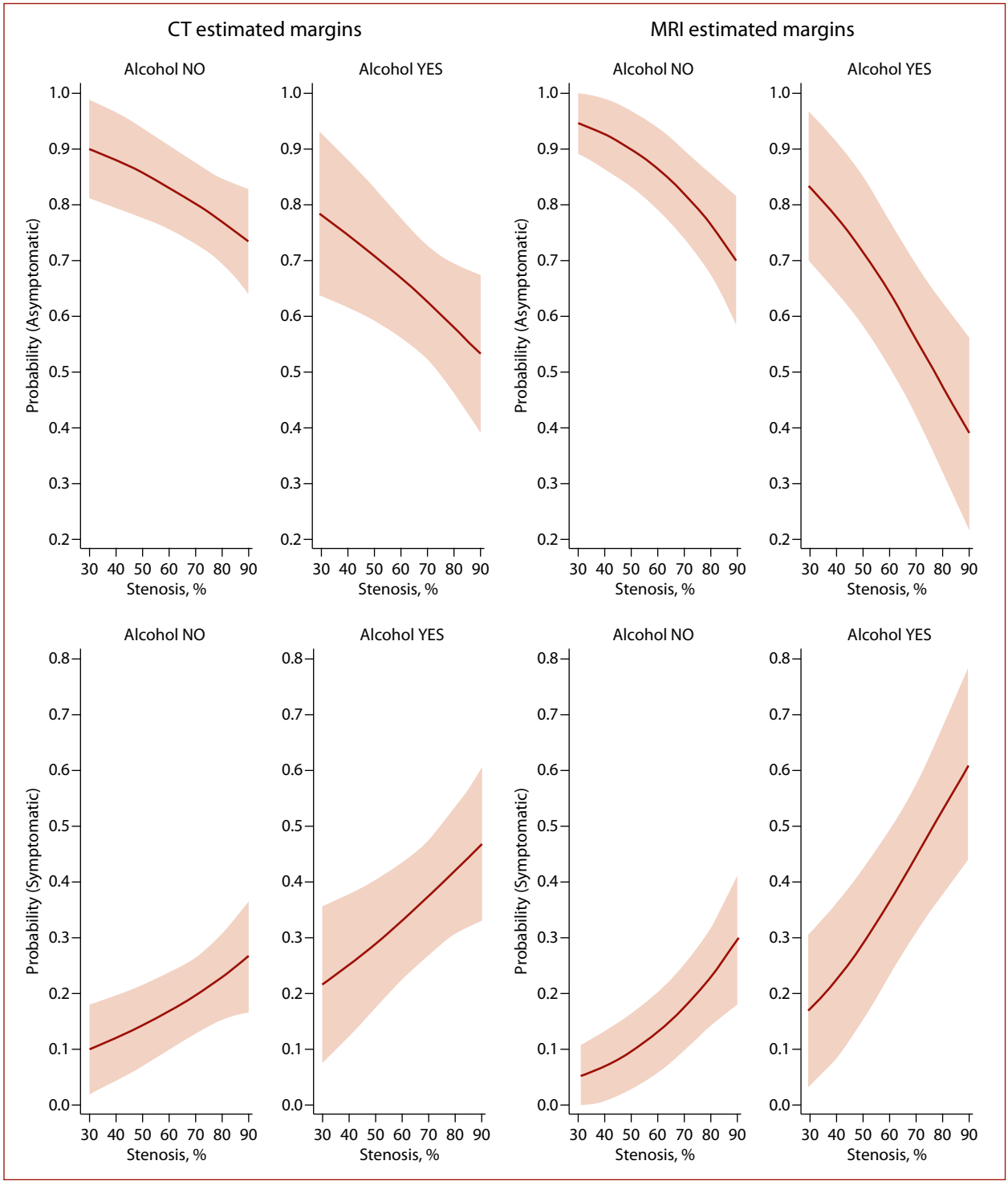


Figure 2. Probability model of carotid plaque to be symptomatic according to alcohol abuse and stenosis severity assessed by CT/MRI
Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging

ation between daily alcohol consumption and stenosis severity is shown in Figure 4.

DISCUSSION

The results of our study did not confirm that the presence, age, location, or volume of IPH are risk factors for ipsilateral TIA or stroke. In contrast, the significant predictors of stroke were found to be a lower AHA plaque type (IV–V and VI), a higher stenosis degree, lipid plaque on CT, and additionally alcohol consumption.

In some studies, IPH remained the strongest predictor of future stroke [9, 10, 25], and it is currently considered one of the at-risk characteristics for which intervention is recommended by guidelines [17]. Carotid IPH is considered the strongest predictor of stroke over any known clinical risk factor, as reported in a recent meta-analysis [9]. Moreover,

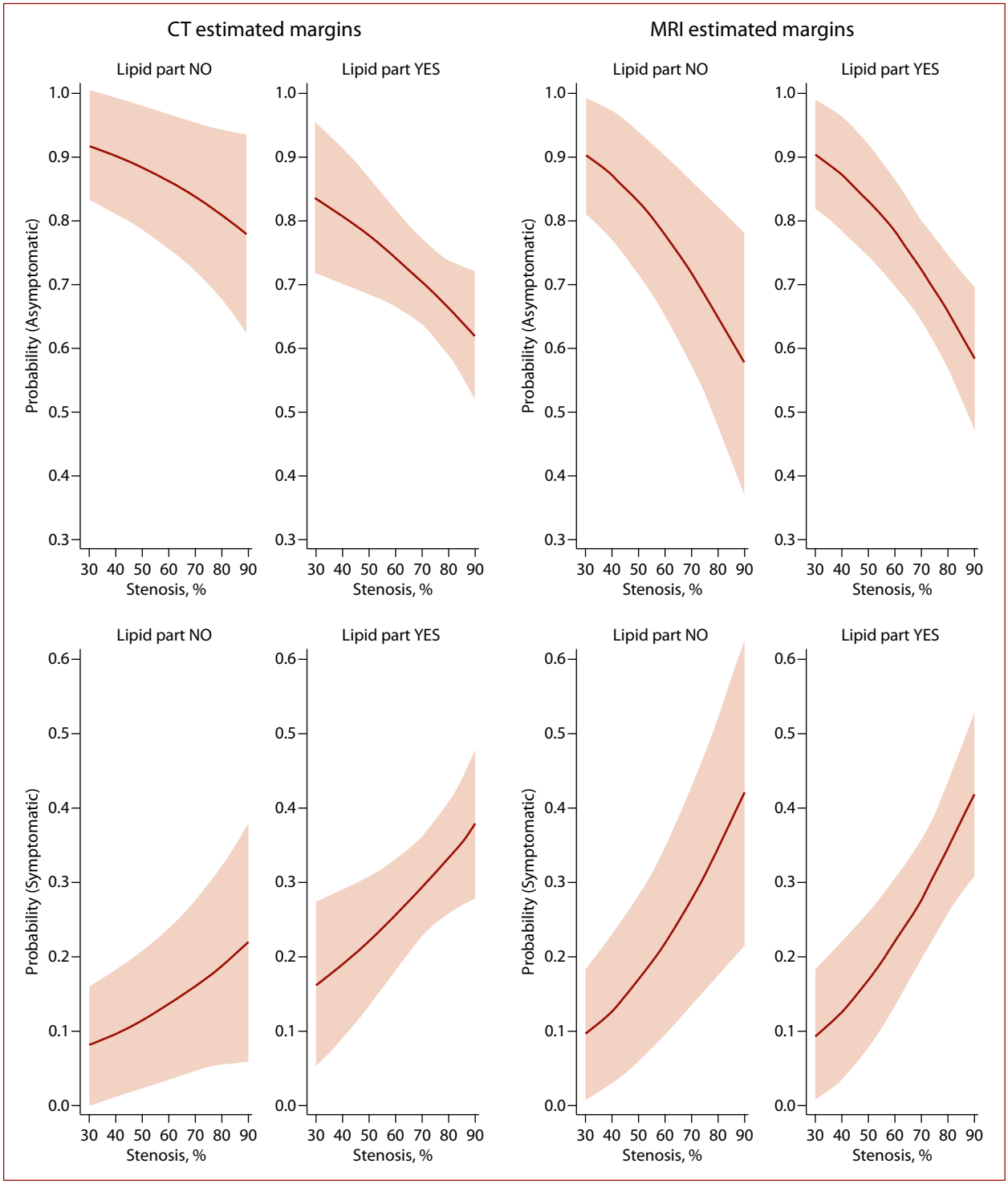


Figure 3. Probability model of carotid plaque to be symptomatic according to present lipid plaque and stenosis severity assessed by CT/MRI
Abbreviations: see Figure 2

juxtaluminal, fresh, and larger IPH volume were presented significantly more in symptomatic patients compared to asymptomatic, but no differences were found for the presence of IPH and recent IPH [26]. Our study did not show any significant difference between the presence, age, location, or volume of IPH in symptomatic and asymptomatic stable plaques. However, the result of our study shows a trend fora more frequent presence of IPH in symptomatic patients, but it did not reach statistical significance because, in the sample size calculation, we assumed a difference of at least 10%, but the result was 3.1%. Nevertheless, we found that large IPH volume (>50% of the plaque) was more often present in symptomatic patients compared to asymptomatic stable (58.6% vs. 36.4%). Several blinded studies achieved the same results, although no clinicopathological correlation between various types of IPH was found in symptomatic

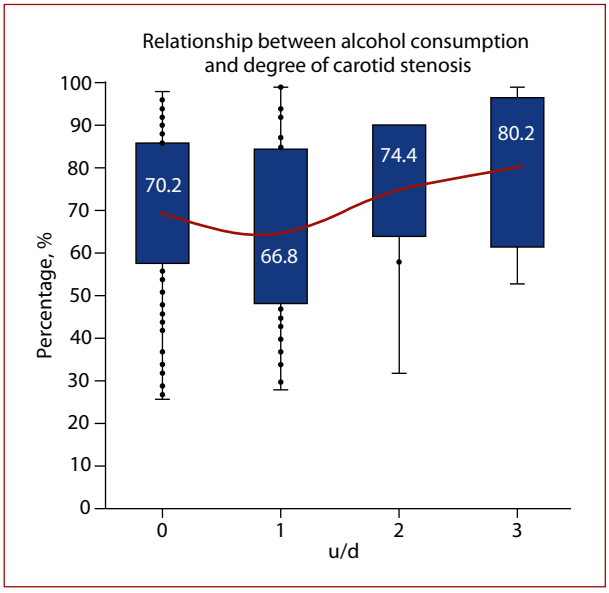


Figure 4. An association between daily alcohol consumption and the degree of stenosis measured on CT

Abbreviations: see Figure 2

versus asymptomatic patients [27, 28]. The persistent popularity of publishing only positive results of studies may bias the number of studies with positive and negative results. A systematic review concluded that the reliable interpretation of IPH in the production of cerebral ischemia was severely undermined by poor methodological quality, substantial heterogeneity, and probable publication bias [29]. Similarly to our study, more than half of the included studies in the mentioned systematic review showed no significant increase in symptoms based on IPH. Their findings indicate that studies with minor heterogeneity and high quality tended to yield negative results. Only more recent meta-analyses and recalculations of results show a strong association between IPH and stroke. According to the AHA classification, complicated type VI plaque was associated primarily with developing symptoms in the carotid arteries [30]. This result was confirmed in our study, where not only AHA plaque type VI but also plaque type IV–V were significantly more common than type VII and VIII in symptomatic plaques. However, plaque type IV–V appeared less often (type VI more often) in symptomatic plaques than in asymptomatic stable plaques in another study [26].

The finding that a higher degree of carotid stenosis poses a higher risk of stroke than a lower degree was demonstrated by the NASCET study [20]. Several studies [13, 31] showed that even mild stenosis can lead to cerebrovascular events, suggesting that plaque composition likely plays a key role in stroke risk. In addition, recently published studies [32, 33] revealed that patients with a higher stenosis degree had a higher stroke risk than those with a lower degree, in agreement with our study results (for both CT and MRI). However, according to recent valid guidelines, stroke risk associated with carotid plaques is attributable not only to stenosis degree but also to plaque composition [17].

Our results demonstrated a marginally significant association of lipid plaque on CT with symptomatic plaques. In a different study, a significant difference was found between the presence of lipid plaques detected by CT and brain ischemic lesions, which confirms our results [9]. LRNC and fibrous cap are considered the most important components of vulnerable plaques, characterized by the presence of a thin fibrous cap that covers a large LRNC containing macrophages and inflammatory cells [15]. Previous studies confirmed an association of both characteristics with the risk of cerebrovascular events [10, 30]. Statins represent the first-choice treatment in patients with atherosclerosis, aiming for low-density lipoprotein cholesterol reduction recommended by guidelines [17]. The stabilizing anti-inflammatory effects of statins on carotid plaque composition, including LRNC, have already been proven [34]. In our study, 76% of all patients used statins, with no significant difference between both groups.

Other carotid plaque characteristics evaluated in this study did not show significant differences between symptomatic and asymptomatic stable plaques. However, the presence of plaque surface irregularities and ulceration [20, 22], enhancement [35], and fibrous cap rupture [10, 26] have been associated with plaque vulnerability. The main reasons for the difference in our study results are the definition of vulnerable/symptomatic plaques, which differs between studies, and changes in plaques over time after stroke occurrence.

Finally, in terms of clinical and demographic factors, alcohol consumption was found to be closely related to stroke risk. Unlike heavy drinking (>4 units per day), the consumption of <1 unit of alcohol per day is associated with a lower risk of ischemic stroke [36]. We showed that even light to moderate regular alcohol consumption (1 unit per day/140 g of alcohol per week) was a significant predictor of recent TIA/stroke, which stands towards the mentioned meta-analysis, and another study claimed that 1–2 drinks per day could be associated with protection against stroke [37]. This result is very alarming for our population due to very high alcohol consumption in the Czech Republic, one of the highest globally [38]. When we compared daily alcohol consumption with stenosis degree on CT (Figure 4), we found that mild alcohol consumption was associated with a lower stenosis degree (no effect on atherogenesis) compared to either heavy drinkers or abstainers; these results follow those of large prospective studies (J-shaped curve) [39, 40].

The limitations of the study should also be described. First, due to the multicenter design of the study, multiple diagnostic devices were used, potentially leading to small differences in the evaluation of individual characteristics. Diagnostic devices were calibrated on five atherosclerotic plaques *in vitro* to minimize this error. Second, most of

the patients in the ANTIQUE study (approx. 90%) were not included in our study because of stenosis <30%, missing CT/MRI scans, and particularly because they could not be assigned to one of our groups (symptomatic/asymptomatic stable) so that there would be no overlap between them. Third, not all MRI examinations were performed with CA, so enhancement evaluation was not possible in a larger sample size. Therefore, other characteristics recommended for evaluation on postcontrast MRI sequences needed to be evaluated in other sequences in which the characteristics were more difficult to distinguish, thus potentially leading to errors in the evaluation. Moreover, not the same number of plaques were evaluated by MRI and CT. Fourth, ultrasound and histology evaluation of plaque characteristics would have been advantageous in addition to CT and MRI to obtain a comprehensive presentation of unstable characteristics. Fifth, the carotid plaque composition of symptomatic patients was detected by imaging modalities after the cerebrovascular event occurrence. Thus, plaque composition may have changed in the time between event occurrence and plaque imaging. Sixth, the evaluation of CT- and MRI-derived plaque characteristics was based on a single rater and rating, so intra-rater and inter-rater reliability are not available. Seventh, the exclusion of patients with clinically silent cerebral infarction(s) [24] led to homogenous study groups but reduced the study power in testing an association between carotid plaque morphology and stroke risk. Finally, laboratory markers were not measured in all patients because we were focused purely on the imaging-based carotid plaque composition and its association with stroke risk.

Our study results suggest that a complex evaluation of carotid plaque characteristics and common stroke/atherosclerosis risk factors should be considered rather than focusing only on IPH in high-risk patients in need of follow-up, risk stratification, and further treatment. A harmonized multi-specialty approach to multi-morbidity prevention in carotid stenosis patients was recently stressed in an evidence-based expert consensus [41]. However, large follow-up imaging studies using basic noninvasive diagnostic modalities and considering all plaque characteristics with their uniform evaluation are needed.

CONCLUSIONS

We did not find any relationship between IPH (presence, age, location, volume) and the risk of cerebrovascular events in our study; only stenosis severity and additionally alcohol consumption were found to be independent risk factors for recent TIA/stroke in carotid stenosis territory. We showed that multiparametric and multimodal plaque assessment should be considered in stroke risk assessment. Larger follow-up studies assessing all plaque characteristics are needed.

Supplementary material

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

Article information

Conflict of interest: None declared.

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The performance of the NAPLES prognostic score in predicting one-year mortality and major adverse cardiovascular events after transcatheter aortic valve implantation in patients with severe aortic stenosis

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Editorial
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ABSTRACT

Background: Existing risk scores for transcatheter aortic valve implantation (TAVI) may not fully capture patient complexity. Combining nutritional and inflammatory markers, the NPS (the NAPLES prognostic score) might improve outcome prediction.

Aims: This study investigated the associations of the NPS with one-year mortality and major adverse cardiovascular events (MACEs) in TAVI patients.

Material and methods: This retrospective analysis included 222 patients with severe aortic stenosis who underwent TAVI. The NPS was calculated based on the serum albümin concentration, cholesterol concentration, lymphocyte/monocyte ratio, and neutrophil/lymphocyte ratio. The patients were subsequently categorized into two groups: the low-NPS group (NPS 0–2) and the high-NPS group (NPS 3–4).

Results: A high NPS was significantly associated with increased one-year mortality (4.8% vs. 23.7%; P <0.001) and MACE rates (7.2% vs. 35.9%; P <0.001). Cox regression analysis demonstrated that a high NPS was an independent predictor of both mortality (HR, 5.94; 95% CI, 2.03–17.37; P = 0.001) and MACEs (HR, 5.09; 95% CI, 2.15–12.02; P <0.001).

Conclusions: The NPS emerged as a potential predictor of long-term mortality and MACEs in TAVI patients. Further validation through larger, multicenter, studies is warranted. This research contributes valuable data on the role of the NPS in TAVI risk stratification.

Key words: aortic valve stenosis, major adverse cardiac events, mortality, prognostic factors, transcatheter aortic valve ımplantation

WHAT'S NEW?

This study has introduced a pioneering approach in assessment of transcatheter aortic valve implantation risk by incorporating the Naples Prognostic Score (NPS), a composite marker of nutritional and inflammatory status. Unlike traditional risk scores, the NPS has shown a strong correlation with one-year mortality and major adverse cardiovascular events in our analysis of 222 patients. Its ability to act as an independent predictor of mortality and major adverse cardiovascular events positions it as a potentially transformative tool for enhancing patient selection, guiding clinical decisions, and improving communication regarding procedural risks. The integration of NPS into risk stratification models represents a significant advancement in personalized interventional cardiology.

INTRODUCTION

Aortic stenosis (AS) is a prevalent valvular heart disease in older adults and is associated with high morbidity and mortality if untreated. Transcatheter aortic valve implantation (TAVI) is currently considered the standard treatment for patients older than 75 years of age with native severe AS. TAVI has emerged as a valid alternative method offering a less invasive approach for this group of patients. Additionally, TAVI is a safe and effective option for patients with failed surgical and transcatheter prostheses, reducing the need for re-do surgery in high-risk patients. However, surgical aortic valve replacement (SAVR) remains the standard treatment method, especially for low-risk and younger populations [1]. Many studies have shown that TAVI is non-inferior or superior to SAVR in reducing mortality, stroke, and heart failure and improving quality of life in different surgical risk categories. Therefore, TAVI has become the preferred treatment modality for AS patients [2, 3].

Numerous prognostic scoring models, including the Society of Thoracic Surgeons score and the EuroSCORE II, have been established to predict clinical outcomes after TAVI [4, 5]. These instruments are routinely employed to categorize patients, evaluate their eligibility for surgical or percutaneous interventions, and appraise the risk of mortality both in intrahospital and within 30 days post-discharge, with a particular emphasis on the risk of surgical mortality. However, these scores have limitations in capturing the complexity and heterogeneity of the patient population, which has a high burden of comorbidities and may not benefit from valve replacement alone. Additional determinants, such as the overall cardiovascular profile, noncardiac comorbidities, and degree of frailty can exert a significant impact on the enduring TAVI outcomes that extend beyond the scope of valvular pathology [6–8]. Therefore, additional indicators that complement surgical risk scores are needed to improve the prediction of outcomes and optimize patient care after TAVI.

AS is a disease that shares a pathophysiology similar to that of atherosclerosis, including calcification, lipoprotein accumulation, and chronic inflammation. This is not only a consequence of aging, but also a dynamic inflammatory process. Therefore, using inflammatory biomarkers may be useful in predicting outcomes for patients undergoing TAVI. Furthermore, malnutrition is a frailty marker in elderly patients and a predictor of adverse outcomes in patients with severe AS. Low serum albumin levels, which could indicate malnutrition, inflammation, or cachexia, have been associated with the development of coronary artery disease and increased cardiovascular mortality risk in TAVI patients [9, 10].

The NPS is a novel scoring system that assesses the nutritional and inflammatory status of patients. The NPS is derived from biochemical markers such as the serum albumin level, total cholesterol level, lymphocyte/monocyte ratio (LMR), and neutrophil/lymphocyte ratio (NLR) [11, 12]. The NPS has been used as a prognostic score for various cancers in recent years [13–15]. The NPS has also been found to predict follow-up mortality in heart failure and myocardial infarction patients [16–18]. The role of the NPS in predicting mortality and major adverse cardiac event (MACE) risk after TAVI is unclear. This study aimed to examine the performance of the NPS in predicting one-year mortality and MACE risk after TAVI in patients with severe AS.

MATERIAL AND METHODS

Study design

This study is a retrospective analysis of patients who were diagnosed with severe AS and who underwent transfemoral TAVI, and self-expandable CoreValve Evolut valve implantation during the procedure, at the Dicle University Medicine Faculty, Department of Cardiology, Diyarbakir, Turkey between January 2015 and March 2022.

Before undergoing either elective or emergency TAVI procedures, the patients were evaluated by a multidisciplinary Heart Team. Experienced interventional cardiologists performed the valve implantations and follow-up with the patients.

We screened a total of 268 patients. We excluded 6 patients who died during the TAVI procedure, 14 patients who were lost to clinical follow-up before one year, 3 patients with severe anemia, 10 patients with chronic renal failure, 5 patients with valve-in-valve TAVI, and 8 patients with missing hospital medical records. Thus, 222 patients were included in the study.

Patients who had undergone previous pacemaker implantations, surgical aortic valve replacements, TAVI

procedures, balloon-expandable TAVI procedures, valve-in-valve procedures, or bicuspid aortic valves were excluded.

After the procedure, all patients were retrospectively evaluated on discharge and at 1-month and 1-year follow-up intervals. Demographic, physical, echocardiographic, and laboratory data were obtained from the hospital's database. The vital status of all patients was confirmed through the Turkish National Death Indices.

This study was conducted according to the principles of the Helsinki Declaration and was approved by the Institutional Ethics Committee of the Batman Training and Research Hospital (23/01/2024-373). Additionally, institutional permission was obtained from the chief physician of the Dicle University Faculty of Medicine and the head of the Department of Cardiology for accessing the archived records of the patients included in our study.

Periprocedural imaging and the TAVI procedure

Transthoracic echocardiographic images were taken before the TAVI procedure to assess AS severity. Twelve-lead standard electrocardiography was also performed for each patient. Computed tomography scans were performed to evaluate the anatomy of the aorta and the aortic valve. Analyses followed the Valve Academic Research Consortium 3-criterium Guidelines (VARC-3) [19]. The procedures were carried out with conscious sedation transfemoral access and anticoagulation with unfractionated heparin. Rapid pacing was utilized during the procedure, and vascular closure devices were employed for hemostasis at the access site.

Clinical endpoints

The effectiveness of the aortic valve replacement procedure was measured by evaluating the technical success of the procedure as the clinical endpoint. Any complications that occurred were classified according to the VARC-3 consensus report [19], which included issues such as left bundle branch block, periprocedural myocardial injury, arrhythmia, renal failure, hemorrhage, paravalvular regurgitation, duration of hospitalization, pericardial tamponade, and MACE (CV death, vascular complications, coronary obstruction, and periprocedural MI). Additionally, the study evaluated MACE and all-cause death during hospitalization, and at one month and one year.

Assessment of the NPS

The NPS score was calculated as follows: the NPS was based on the NLR, LMR, serum albumin concentration, and total cholesterol concentration. According to the method proposed by Galizia et al. [11] (the cutoff values of the NLR and LMR defined by MaxStat analysis), a serum total cholesterol level ≤180 mg/dl, an albumin level <40 g/l, an LMR ≤44 or an NLR >2.96 were each assigned 1 point; otherwise, they were assigned 0 points. The patients were subsequently categorized into two groups: the low-NPS group (NPS 0–2) and the high-NPS group (NPS 3–4).

Statistical analysis

We used SPSS 21.0 (IBM Corporation) for the analyses. To assess the normality of continuous variables, we utilized the Kolmogorov–Smirnov test. Continuous variables were presented as means (standard deviations) or medians (interquartile ranges), depending on the variable distribution, and were compared using either Student's t-test or the Mann–Whitney U test, as needed. Categorical variables were expressed as numbers and percentages (%) and were compared using either the χ^2 test or Fisher's exact test, as appropriate. We plotted survival curves using the Kaplan–Meier method and compared them with the log-rank test. To estimate the HR and 95% CI for mortality and MACE predictors, we used both univariable and multivariable Cox proportional hazards models. Parameters associated with mortality and MACE were included in the univariable regression analysis. Variables with significant *P*-values in the univariable analysis were further analyzed in the multivariable regression. The analysis results were also displayed with a forest plot graph. A P <0.05 value indicated statistical significance.

RESULTS

A total of 222 patients with severe AS who underwent TAVI were included in the study. The mean age of the patients was 79.2 (6.4) years, and 124 (55.8%) were female. Overall, 83 (37.4%) patients were in the low NPS group, and 139 (62.6%) patients were in the high NPS group. There was no difference between the two groups in terms of age, sex, or disease history. However, neutrophil (4.85 [1.54] vs. 5.77 [1.98]; P <0.001) and NLR (2.57 [1.15] vs. 3.91 [1.89]; P <0.001) levels were greater in the high NPS group. The baseline demographic and clinical characteristics of the two groups are shown in Table 1. Both one-year total mortality (4.8% vs. 23.7%; P <0.001) and one-year total MACE (7.2% vs. 35.9%; P <0.001) were greater in the high NPS group than in the low NPS group (Table 2).

We performed a comprehensive analysis using univariable and multivariable Cox regression analysis to determine the factors predicting one-year mortality and MACEs. Following a multivariable Cox regression analysis, it was found that high NPS, heart failure, and post-TAVI major bleeding independently predicted one-year mortality (HR, 5.94; 95% CI, 2.03–17.37; P = 0.001; HR, 0.386; 95% CI, 0.17–0.88; P = 0.024; HR, 5.147; 95% CI, 2.14–12.37; P <0.001, respectively) (Table 3 and Figure 1). Additionally, a high NPS and heart failure were identified as independent predictors of one-year MACE (HR, 5.09; 95% CI, 2.15–12.02; P <0.001 and HR, 0.511; 95% CI, 0.27–0.98; P = 0.04, respectively) (Table 4 and Figure 1).

In this study, we performed a Kaplan–Meier survival analysis to investigate the potential association between high NPS and mortality. Survival at the one-year follow-up was greater in the low NPS group than in the high NPS group (log-rank P <0.001) (Figure 2).

Table 1. Baseline demographic and clinical characteristics of the patients

Variables	Total (n = 222)	Low NPS (n = 83)	High NPS (n = 139)	*P*-value
Age, years	79.2 (6.4)	78.5 (6.7)	79.6 (6.2)	0.24
Gender (male), n (%)	98 (44.1)	30 (36.1)	68 (48.9)	0.06
BMI, kg/cm^2	21.8 (1.7)	21.4 (1.4)	22.0 (1.8)	0.01
Hypertention, n (%)	122 (54.9)	47 (56.6)	75 (53.9)	0.69
Diabetes mellitus, n (%)	54 (24.3)	24 (28.9)	30 (21.6)	0.22
Hyperlipidemia, n (%)	60 (27.0)	28 (33.7)	32 (23.0)	0.08
Prior PCI, n (%)	72 (32.4)	33 (39.7)	39 (28.1)	0.07
Prior CABG, n (%)	28 (12.6)	12 (14.5)	16 (11.5)	0.52
Heart failure, n (%)	82 (36.9)	36 (43.4)	46 (33.1)	0.15
Peripheral artery disease, n (%)	5 (2.3)	1 (1.2)	4 (2.9)	0.65
Cerebrovascular disease, n (%)	4 (1.8)	2 (2.4)	2 (1.4)	0.63
COPD, n (%)	22 (9.9)	9 (10.8)	13 (9.3)	0.82
CKD, n (%)	59 (26.6)	17 (20.5)	42 (30.2)	0.12
Anemia, n (%)	116 (52.3)	35 (42.2)	81 (58.3)	0.03
Atrial fibrillation, n (%)	49 (22.1)	16 (19.3)	33 (23.7)	0.51
Smoking, n (%)	51 (22.9)	17 (20.5)	34 (24.4)	0.52
LVEF, %	50.9 (40.0-60.0)	49.7 (40.0-60.0)	51.6 (45.0-60.0)	0.25
Aortic valve area, cm^2	0.67 (0.18)	0.68 (0.20)	0.67 (0.18)	0.85
STS risk score	9.40 (7.0-11.0)	8.86 (7.0-10.0)	9.72 (7.0-11.0)	0.25
Angular angle	48.10 (8.83)	48.90 (9.56)	47.63 (8.41)	0.43
Valve size, mm	28.73 (3.39)	28.29 (3.45)	28.99 (3.35)	0.14
GFR, ml/min/1.73 m^2	73.15 (25.12)	80.87 (30.07)	72.61 (27.82)	0.005
WBC, ×1000/µl	7.85 (2.21)	7.55 (1.89)	8.03 (2.37)	0.12
Hemoglobin, g/l	12.18 (1.89)	12.41 (2.01)	12.04 (1.79)	0.16
Lymphocyte, 10^9/l	1.77 (0.59)	2.05 (0.66)	1.61 (0.49)	<0.001
Neutrophil, 10^9/l	5.42 (1.87)	4.85 (1.54)	5.77 (1.98)	<0.001
Monocyte, 10^9/l	0.62 (0.19)	0.58 (0.17)	0.64 (0.21)	0.05
Platelet, 10^9/l	242.3 (79.7)	258.1 (87.5)	232.9 (73.5)	0.02
Creatinine, mg/dl	1.03 (0.70-1.10)	0.92 (0.64-0.99)	1.09 (0.73-1.24)	0.11
Total cholesterol, mg/dl	182.44 (39.16)	207.23 (34.46)	167.64 (34.07)	<0.001
LDL cholesterol, mg/dl	109.98 (36.89)	123.62 (41.58)	102.68 (31.96)	<0.001
HDL cholesterol, mg/dl	44.08 (12.57)	45.76 (10.19)	43.02 (13.81)	0.12
Albumin, g/dl	35.95 (4.33)	38.26 (3.56)	34.58 (4.18)	<0.001
NLR	3.41 (1.77)	2.57 (1.15)	3.91 (1.89)	<0.001
LMR	3.07 (1.16)	3.69 (1.23)	2.70 (0.94)	<0.001
AST, IU/ml	28.30 (17.0-32.0)	27.02 (17.0-31.0)	29.06 (17.0-33.8)	0.54
ALT, IU/ml	18.99 (10.95-20.0)	19.00 (11.0-21.0)	18.99 (10.8-20.0)	0.99

P <0.05 was considered statistical significant. Values are presented as n (%) or mean (standard deviation), or median (interquartile range), depending on the variable distribution

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LVEF, left ventricular ejection fraction; LDL, low-density lipoprotein; LMR, lymphocyte monocyte ratio; NLR, neutrophil lymphocyte ratio; NPS, Naples prognostic score; PCI, percutaneous coronary intervention; STS, the society of thoracic surgery risk score; WBC, white blood cell count

Table 2. Procedural complications and clinical endpoints of the patients

Variables	Total (n = 222)	Low NPS (n = 83)	High NPS (n = 139)	*P*-value
Major vascular complication, n (%)	14 (6.3)	6 (7.2)	8 (5.7)	0.78
Major bleeding, n (%)	14 (6.3)	3 (3.6)	11 (7.9)	0.26
Pacemaker implantation, n (%)	20 (9.0)	5 (6.0)	15 (10.8)	0.33
Cerebrovascular event, n (%)	8 (3.6)	1 (1.2)	7 (5.0)	0.26
Acute kidney injury, n (%)	11 (4.9)	2 (2.4)	9 (6.5)	0.22
Post-TAVI MACEs, n (%)	25 (11.3)	5 (6.0)	20 (14.4)	0.08
One-month MACEs, n (%)	32 (14.4)	5 (6.0)	27 (19.4)	0.006
One-year MACEs, n (%)	56 (25.2)	6 (7.2)	50 (35.9)	<0.001
İn-hospital death, n (%)	16(7.2)	3 (3.6)	13 (9.3)	0.18
One-Month death, n (%)	24 (10.8)	4 (4.8)	20 (14.4)	0.03
One-year death, n (%)	37 (16.6)	4 (4.8)	33 (23.7)	<0.001

P <0.05 was considered statistical significant. Values are presented as n (%)

Abbreviations: MACEs, major adverse cardiovascular events; NPS, Naples prognostic score; TAVI, transcatheter aortic valve implantation

Table 3. Independent predictors of one-year mortality in univariable and multivariable Cox regression analysis

Parameters	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age	1.029 (0.980–1.081)	0.25		
Gender (male)	0.857 (0.457–1.606)	0.63		
Diabetes mellitus	1.015 (0.497–2.070)	0.97		
Hypertension	0.933 (0.505–1.725)	0.83		
Heart failure	0.325 (0.144–0.733)	0.007	0.386 (0.169–0.883)	0.024
Body mass index	1.089 (0.916–1.293)	0.33		
Prior PCI	1.591 (0.854–2.962)	0.14		
Anemia	1.948 (1.021–3.717)	0.04	1.079 (0.526–2.211)	0.84
Platelets count	1.003 (0.999–1.006)	0.11		
Glomerular filtration rate	0.983 (0.971–0.994)	0.004	0.993 (0.981–1.006)	0.15
NAPLES prognostic score	7.052 (2.507–19.837)	<0.001	5.936 (2.028–17.372)	0.001
Post-TAVI major vascular complications	3.161 (1.328–7.522)	0.009	2.055 (0.768–5.494)	0.15
Post-TAVI major bleeding	7.343 (3.571–15.099)	<0.001	5.142 (2.138–12.370)	<0.001
Post-TAVI pacemaker implantation	0.769 (0.237–2.492)	0.66		
Post-TAVI cerebrovascular event	2.456 (0.756–7.982)	0.35		
Post-TAVI acute kidney injury	3.349 (1.311–8.556)	0.012	0.691 (0.210–2.271)	0.54

P <0.05 was considered statistical significant

Abbreviations: CI, confidence interval; HR, hazard ratio; PCI, percutaneous coronary intervention; TAVI, transcatheter aortic valve implantation

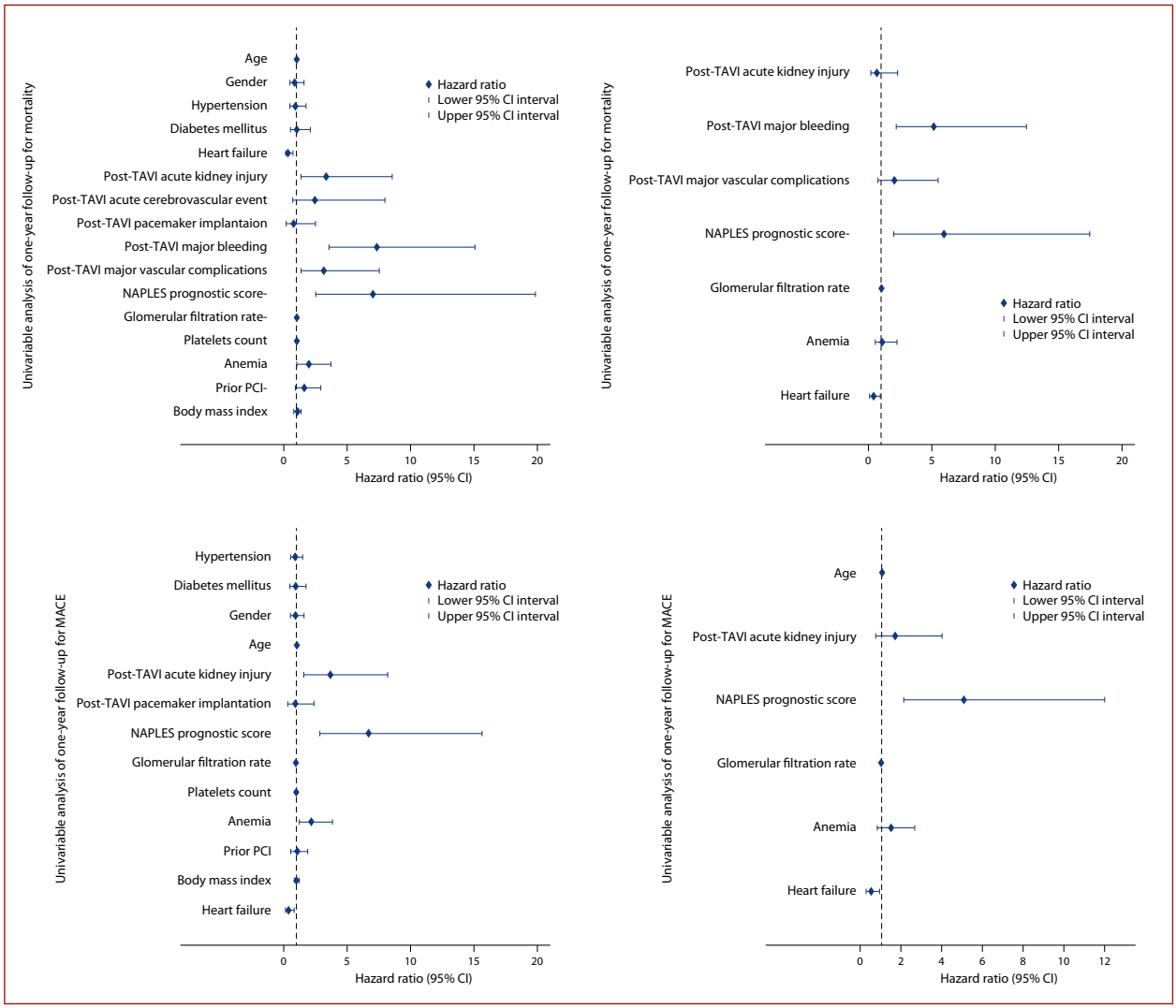


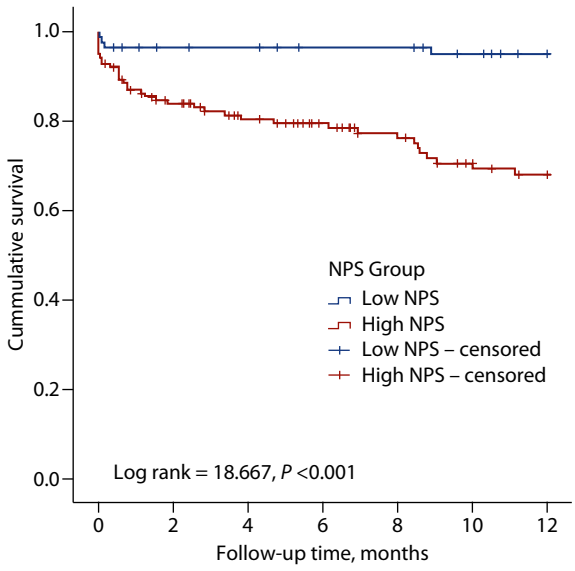
Figure 1. Forest plot showing the univariate and multivariate Cox regression analysis results for mortality and major adverse cardiovascular event at one-year follow-up

Table 4. Independent predictors of one-year MACE in univariable and multivariable Cox regression analysis

Parameters	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age	1.047 (1.003–1.093)	0.03	1.040 (0.993–1.090)	0.09
Gender (male)	0.954 (0.560–1.626)	0.86		
Diabetes mellitus	0.948 (0.510–1.763)	0.86		
Hypertension	0.927 (0.548–1.567)	0.77		
Heart failure	0.424 (0.224–0.802)	0.008	0.511 (0.267–0.979)	0.04
Body mass index	1.054 (0.903–1.230)	0.51		
Prior PCI	1.080 (0.616–1.893)	0.79		
Anemia	2.186 (1.247–3.832)	0.006	1.472 (0.812–2.669)	0.20
Platelets count	1.002 (0.999–1.005)	0.29		
Glomerular filtration rate	0.983 (0.973–0.993)	0.001	0.990 (0.980–1.001)	0.06
NAPLES prognostic score	6.679 (2.858–15.610)	<0.001	5.085 (2.151–12.017)	<0.001
Post-TAVI pacemaker implantation	0.950 (0.379–2.380)	0.91		
Post-TAVI acute kidney injury	3.695 (1.669–8.180)	0.001	1.702 (0.720–4.022)	0.22

P <0.05 was considered statistical significant

Abbreviations: CI, confidence interval; HR, hazard ratio; PCI, percutaneous coronary intervention; TAVI, transcatheter aortic valve implantation



	0. day	In hospital	1. month	6. month	12. month
Low NPS	83	80	79	79	79
High NPS	139	126	119	111	106

Figure 2. Kaplan–Meier survival curve for one-year mortality stratified by the Naples Prognostic Score (NPS)

DISCUSSION

Our study underscores the potential of the Naples Prognostic Score as a significant predictor of long-term outcomes in patients undergoing TAVI for severe AS. By exploring the association between NPS and one-year clinical outcomes, we provide new insights into its role in risk stratification, which could enhance decision-making processes and ultimately improve patient management in this high-risk population. These findings contribute to the growing body of evidence supporting the integration of nutritional and inflammatory markers into cardiovascular risk assessment models.

The prevalence of malnutrition is greater in TAVI patients than in those with other cardiovascular diseases, and malnutrition is correlated with increased mortality [20]. Various nutritional indices, such as the Mini Nutritional Assessment Short Form (MNA-SF), Controlling Nutritional Status (CONUT), Prognostic Nutritional Index (PNI), Nutritional Risk Index (NRI), and Geriatric Nutritional Risk Index (GNRI), have been investigated in TAVI patients and have demonstrated prognostic value in predicting outcomes [21, 22]. In a study by Kazemian et al. [23], a high incidence of malnutrition, as indicated by objective nutritional indices (CONUT, GNRI, NRI, PNI), was observed among TAVI patients, with malnutrition being linked to an increased risk of one-year all-cause mortality. In a study by Sudo et al. [24], it was found that a low total cholesterol-to-brachial index, indicative of right heart overload symptoms, increased the risk of three-year mortality, and the addition of the total cholesterol-to-brachial index to the EuroSCORE II improved the predictive value for all-cause mortality. In a study by Kucukosmanoglu et al. [25], other nutritional indices, such as the GNRI, PNI, and CONUT, were evaluated in TAVI patients and were associated with one-year all-cause mortality. In a study by Mas-Peiro et al. [26], the PNI was identified as a useful and practical nutritional marker strongly predictive of one-year survival in TAVI patients, showing superior predictive value compared to the GNRI and body mass index. Furthermore, according to a study by He et al. [27], the PNI was associated with short-term survival and fewer post-TAVI complications. These findings suggest that nutritional indices can offer valuable insights for risk stratification and outcome prediction in patients undergoing TAVI.

Albumin has been studied in various medical conditions to assess its association with mortality. In patients with acute heart failure, the use of albumin was found to be associated with lower 30-day mortality, especially in males, those with heart failure with reduced ejection fraction, and those without sepsis [28]. In patients with severe COVID-19,

low serum albumin levels were associated with severe disease and poor prognosis, with the neutrophil/albumin ratio, C-reactive protein/albumin ratio, and blood urea nitrogen/albumin ratio being more valuable predictors of prognosis [29]. Serum albumin is a multifunctional protein that may have direct or indirect effects on mortality in TAVI patients [30].

The NPS is a contemporary method for assessing malnutrition, which considers the serum albumin concentration, total cholesterol level, LMR, and NLR. The NPS is unique in that it takes account of both inflammation and nutritional status concurrently. The results of our study are consistent with the results of many previous studies investigating the relationships of the NPS with mortality and long-term outcomes in different patient groups. Researchers have noted the correlation between the NPS and long-term prognostic outcomes, as well as mortality rates, in patients who have undergone surgery for colorectal cancer [11]. Moreover, the NPS has been shown to be a reliable indicator of postoperative complications in patients who have undergone colectomy for diverticulitis [31]. The NPS has been confirmed to be a valuable tool for predicting outcomes in patients with heart failure. Studies have shown that it is linked to both short- and medium-term mortality as well as hospital readmissions [32]. Furthermore, it has been found to be significantly associated with long-term mortality in patients experiencing STEMI [33].

In a study conducted by Çetin et al. [34], one-year total mortality in TAVI patients was found to be 8.6% (5% in the low NPS group vs. 13% in the high NPS group; $P = 0.006$). In another study conducted by Demirci et al. [35], total mortality was 62% in TAVI patients in their 40-month long-term follow-up (42% in the low NPS group vs 87.9% in the high NPS group; $P < 0.001$). These two studies support our findings regarding NPS as a predictor of mortality. However, our study is important since it shows the additional predictive effect of NPS in terms of MACEs in addition to mortality.

However, there are currently insufficient data in the literature regarding the association of the NPS with mortality and morbidity in patients with severe AS undergoing TAVI. We believe that our study adds new data to clarify this uncertainty. Patients with higher NPS may benefit from closer monitoring, and correcting inadequate nutrition/malnutrition and limiting inflammation may help improve survival in patients undergoing TAVI.

There are several limitations to our study. First, it was primarily retrospective and involved a restricted patient sample size. Furthermore, we cannot determine the extent to which the exclusion of patients with incomplete data may have affected the study results. Another limitation is our inability to establish a correlation between the NPS and other inflammatory markers and nutritional indices. The study investigated the impact of the NAPLES risk score upon patients' admission. However, it is essential to acknowledge potential uncertainties related to dynamic changes in albumin levels and other blood parameters over time, the possibility of dehydration on admission, and variations in nutritional status.

CONCLUSIONS

In conclusion, the NPS is a key predictor of long-term mortality and MACEs in patients with severe aortic stenosis undergoing TAVI. As a measure of inflammation and malnutrition, the NPS enhances risk stratification and guides clinical decisions. Furthermore, multicenter and randomized controlled trials are needed to confirm these findings and explore their broader applicability.

Article information

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Application of machine learning in predicting postoperative arrhythmia following transcatheter closure of perimembranous ventricular septal defects

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ABSTRACT

Background: Arrhythmia is a frequent complication following transcatheter device closure of perimembranous ventricular septal defects (pmVSD). However, there is currently a lack of a convenient tool for predicting postoperative arrhythmia.

Aims: This research aimed to use machine learning algorithms to predict the risk of postoperative arrhythmia in pmVSD patients.

Material and methods: A retrospective study was conducted on 1384 children with pmVSD who underwent successful transcatheter device closure at a single-center hospital from March 2002 to March 2024. Subjects were assigned to a training set (n = 970) and a validation set (n = 414) in a 7:3 ratio. Four machine learning methods — SVM, LR, RF, and XGBoost — were used to develop models for predicting postoperative arrhythmia based on preoperative and intraoperative baseline information with clinical significance, as well as relevant content mentioned in previously published journals. The models' performance was evaluated using the area under the receiver operating characteristic curve (AUC), sensitivity, specificity, accuracy, negative predictive value, and positive predictive value. The optimal model was used to create a nomogram and further calibrated with calibration curves.

Results: In the prediction of postoperative arrhythmias, the LR model outperformed the XGBoost, SVM, and RF models, achieving an AUC of 0.863 (95% CI, 0.827–0.900). Consequently, we utilized the LR model to construct a nomogram based on 5 variables: weight, procedure time, defect diameter, pre-interventional arrhythmia, and the difference in the diameter between the occluder and defect exceeding 2 mm. The calibration curves illustrated a strong agreement between the actual and predicted outcomes.

Conclusions: The machine learning model accurately predicts postoperative arrhythmias, aiding in risk stratification of pmVSD patients and guiding clinical decisions.

Key words: arrhythmia, machine learning, perimembranous ventricular septal defect, prediction model, transcatheter closure,

INTRODUCTION

Ventricular septal defect (VSD) is a congenital cardiac condition where tissue abnormalities in the ventricular septum result in abnormal interventricular blood flow. About 40% of all congenital heart illnesses are related to this condition, which is one of the most prevalent. The most prevalent subtype is the perimembranous ventricular septal defects (pmVSD), accounting for 70% of cases [1, 2]. Transcatheter interventional occlusion for pmVSD has become a preferred option over traditional surgical procedures, thanks to advancements in occlusion devices and interventional techniques. This method is less invasive, has a quicker recovery time, and is more cost-effective compared to open-heart surgery [3, 4]. However, patients undergoing surgery are still at risk of postoperative complications, with an incidence ranging from 20% to 30%. Among these complications, arrhythmia is a common abnormality, with conduction blocks such

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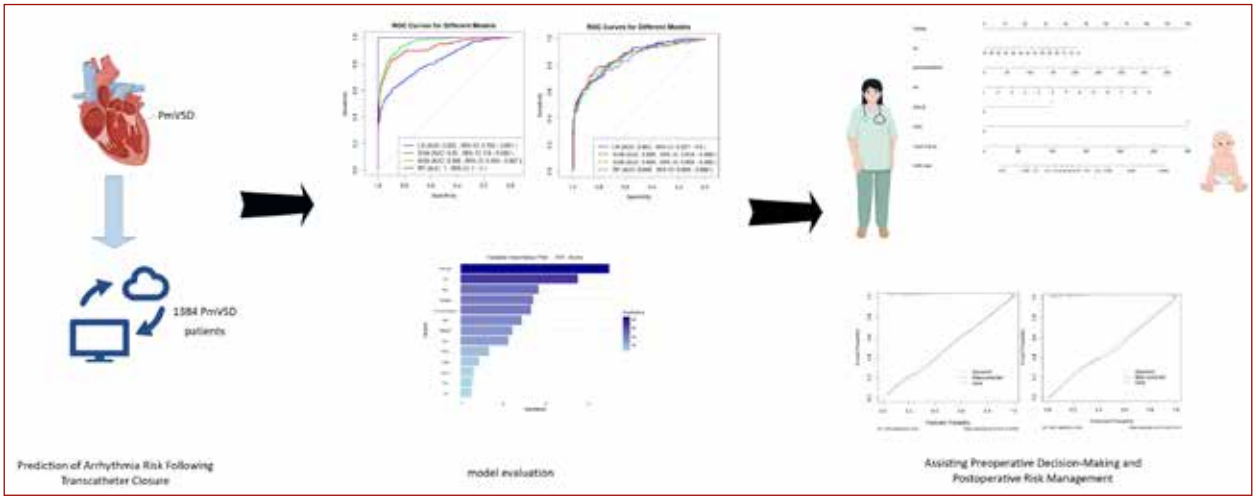
This study integrated multi-dimensional data, including physical examinations, medical history, electrocardiograms, echocardiograms, etc., for comprehensive analysis. Using advanced machine learning algorithms, such as logistic regression, extreme gradient boosting, support vector machines, and random forest, we constructed a predictive model. The developed risk assessment tool accurately predicts arrhythmias, facilitating precise forecasting. This data-driven tool helps clinicians make informed pre- and post-operative decisions, thereby improving patient outcomes. Interdisciplinary collaboration ensures the model's broad applicability and generalizability.

as bundle branch block and atrioventricular block being the primary types. Severe blocks can be life-threatening, necessitating the removal of the blocker, repair of the VSD, and installation of a pacemaker [2, 3]. Therefore, accurately predicting the occurrence of postoperative arrhythmias is crucial to assist healthcare providers in assessing the risk of developing arrhythmias in different scenarios and guiding clinical decision-making toward precision medicine. Unfortunately, existing studies lack predictive models for assessing the risk of early postoperative arrhythmias following transcatheter occlusion in pmVSD patients. With recent advancements in artificial intelligence and increased use of machine learning (ML) in the medical field, this study aimed to develop and validate an interpretable clinical predictive model using multiple machine learning methods and visualize its outcomes [5–7]. A graphical abstract by Figdraw (ID: STSYPfff41) summarizing the key findings of this study is provided.

MATERIAL AND METHODS

Study population and design

This retrospective study analyzed data from 1384 pmVSD patients who underwent successful transcatheter device closure at the Department of Pediatric Cardiology, Provincial Hospital of Shandong First Medical University, between March 2002 and March 2024. The inclusion criteria were age ≥2 years or weight ≥10 kg, confirmed diagnosis of hemodynamically significant pmVSD (e.g., cardiomegaly, left atrial enlargement, left ventricular volume overload on chest radiographs), defect detected by transthoracic echocardiography at the 9–12 o'clock position in the short-axis parasternal view, and pulmonary artery systolic blood pressure <70 mm Hg on transthoracic echocardiography. The exclusion criteria comprised non-membranous VSD, concomitant interventional closure procedures, and patients with crucial clinical data missing. Patient data, including vital signs and preoperative, intraoperative, and postoperative details, were sourced from the Platform for Epidemiological Investigation and Precision Treatment of Childhood Heart Disease, established by the Department of Pediatric Cardiology at the Provincial Hospital of the First Medical University of Shandong, China (http://www.pedhd.cn/). The study received approval from the local institutional ethics committee (Ethics Committee of Shandong First Medical University Hospital), and written informed consent was obtained from all patients' guardians. Data anonymization and confidentiality were ensured, and the study adhered to the principles of the Declaration of Helsinki.



Graphical abstract by Figdraw (ID: STSYPfff41). Schematic overview of application of ML in predicting postoperative arrhythmia following transcatheter closure of pmVSD

Abbreviations: AUC, area under the curve; CI, confidence interval; ML, machine learning; pmVSD, perimembranous ventricular septal defect; ROC, receiver operating characteristic

The study assessed the potential factors for the model's construction based on clinical significance, scientific understanding, and predictors found in previously published publications [8]. The variables evaluated in this study included preoperative clinical assessment data such as height, weight, body surface area, and age, along with risk factors identified from previous studies and selected based on clinical significance. These risk factors encompassed Pre-interventional arrhythmia (cardiac rhythm abnormalities present before the intervention), ventricular septal defect diameter (measured *via* ultrasound during intraoperative angiography), presence of membranous aneurysm (an abnormal bulging or aneurysmal structure formed due to structural abnormality or weakness in the membranous portion of the ventricular septum), and distance from the aortic valve to the defect (measured between the defect margin and the aortic valve, with a threshold of 3 mm). Additional procedural parameters included the type and diameter of occluder devices (comprising Amplatzer Duct Occluder II, eccentric occluder, symmetric occluder, and thin-waist occluder), the diameter difference between the occluder and ventricular septal defect (Ddov, with a threshold of 2 mm), procedure time, and first-attempt success (defined as successful device placement not requiring replacement with an occluder of a different type or diameter) [9–18].

Preoperative information, including sex, age, height, weight, and body surface area, was measured and calculated by the preoperative nurse. Preoperative arrhythmia was determined by multiple cardiologists through electrocardiogram examinations. Intraoperative information, such as defect diameter, tumor of the membranous part of the interventricular septum, and the distance of the aortic valve to the defect, was observed during intraoperative imaging. The procedure time, diameter and type of the occluder, diameter difference between the occluder and the ventricular septal defect, and success of the first attempt at occlusion were recorded by the operating surgeon.

Machine learning algorithms

XGBoost is an integrated learning algorithm based on decision trees, implemented through a gradient boosting framework, which can efficiently deal with non-linear relationships and high-dimensional data and is particularly suitable for large-scale datasets. Its ability to handle missing values and unbalanced data makes it excellent for complex clinical data. Logistic regression is a classical statistical method for estimating the probability of an event occurring and is suitable for binary classification problems. Because of its computational efficiency and ease of interpretation, logistic regression is widely used in clinical settings where explicit interpretation of model outputs is required. SVM performs classification by finding the optimal segmentation hyperplane in a high-dimensional feature space, which is suitable for handling small samples and high-dimensional data. It performs well in classification tasks with high-dimensional features, such as gene expression data, and can provide highly accurate classification results with small samples. Random forest improves model accuracy and stability by constructing multiple decision trees and combining their predictions. Its feature importance scoring function helps to identify key variables, which is particularly useful for classification and feature selection for complex conditions [7, 19–22].

Ethical approval

Written informed consent was obtained from the individuals and minors' legal guardians/next of kin for the publication of any potentially identifiable images or data included in this article.

Statistical analysis

To evaluate the normality of continuous variables, the Shapiro–Wilk test was employed. The test results indicated that the continuous variables in this study deviated from a normal distribution. Thus, we provided the median and interquartile ranges (IQR) for continuous variables, and we used the Mann–Whitney U test for comparisons between groups. Frequencies and percentages were used to summarize categorical variables. The χ^2 test or Fisher's exact test, if applicable, was used to compare categorical variables between groups. A two-tailed *P*-value of less than 0.05 was deemed statistically significant.

To prevent multicollinearity, stepwise regression was carried out by root Akaike information criterion and evaluated by the Variance Inflation Factor. All samples were randomly selected, with 70% serving as the training set and the remaining 30% as the validation set. Logistic regression was performed using the glm function to fit the data. Family parameters were set as binomial. Since the tune.svm function in the e1071 package allows for cross-validation optimization of tuning parameters and kernel functions, we utilized it to construct linear SVM models. This builds a linear SVM model using the e1071 package and operates using cross-validation. The random forest model was constructed using the random forest function found in the random forest package. There were 292 trees built, and the least mean of the squared residuals is used to identify the particular ideal tree. The XGboost package was used to build the model, and cross-validation was used to fine-tune the parameters, making use of 10-fold cross-validation optimization to validate every model. The pROC and caret packages were employed to calculate the area under the receiver operating characteristic (ROC) curve (AUC), as well as accuracy, sensitivity, specificity, negative predictive value, and positive predictive value to evaluate predictive performance. The effectiveness of a classification model can be determined by comparing its AUC, which indicates how near the model is to 1. Using the rms software, a nomogram was created for the best model based on the findings of the multivariable analysis. Each regression coefficient in the multivariable logistic regres-

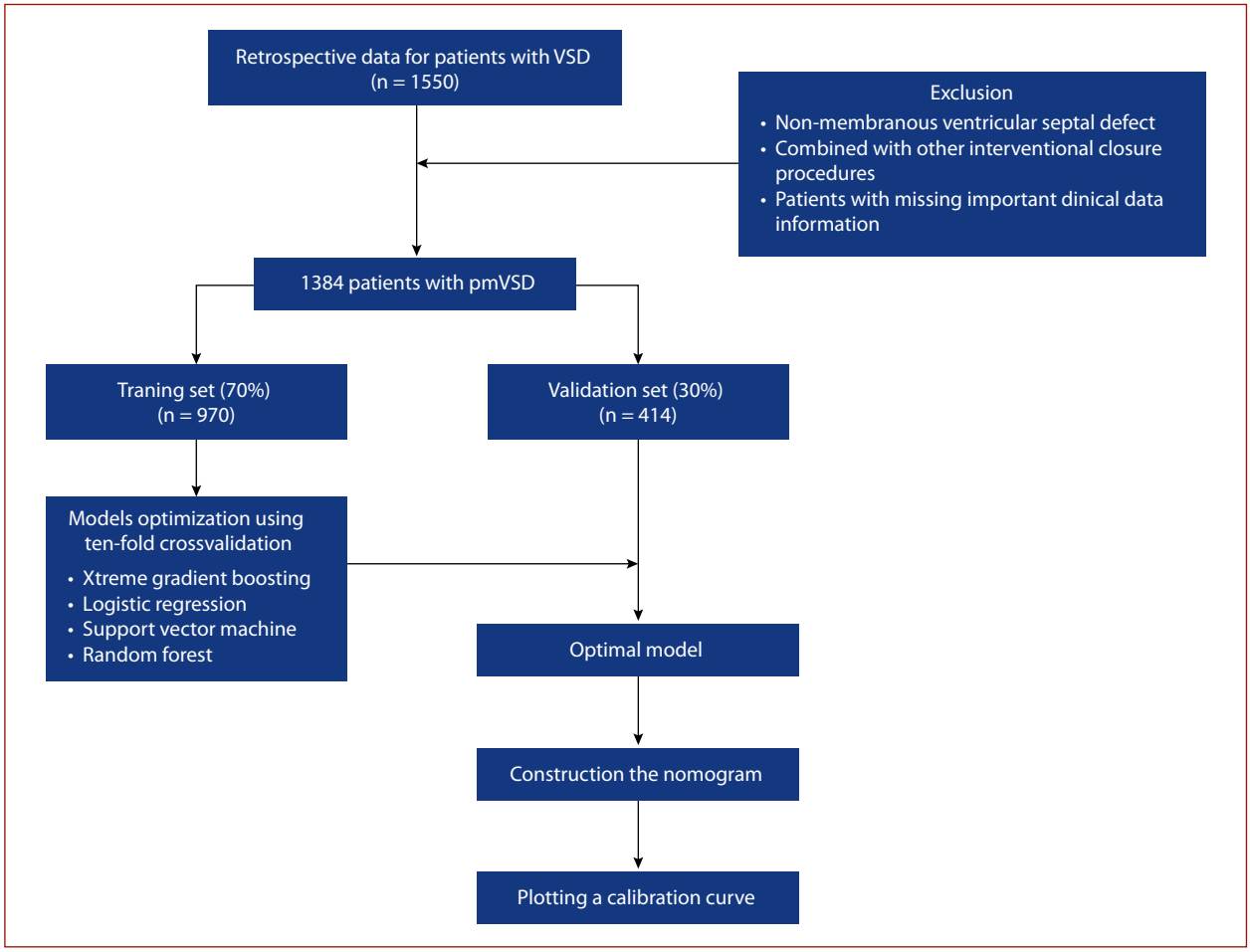


Figure 1. The flowchart of the study

Abbreviations: pmVSD, perimembranous ventricular septal defects; VSD, ventricular septal defects

sion was scaled and converted into a scale ranging from 0 to 100 to create the nomogram. A score of 100 is given to the variable whose effect has the highest beta coefficient (in absolute value). A total score is obtained by adding the scores of the independent variables, and this value is subsequently translated into a projected probability. The calibration curve was used to evaluate the relationship between the probability of actual observations and the predicted probability, which in a well-calibrated model should fall on a 45-degree diagonal. The consistency index was used to evaluate the nomograms' ability to discriminate. Internal validation was carried out utilizing bootstrapping (1000 resamplings) to prevent possible overfitting [23]. The flowchart is shown in Figure 1. In all analyses, P <0.05 was considered statistically significant. All data analyses were performed with R version 4.33.

RESULTS

Patient characteristics

In this study, 1550 patients underwent transcatheter closure of VSD, with 111 patients having non-pmVSD. Additionally, 39 patients had other transcatheter device closures, and 16 patients had incomplete clinical data. Ultimately, 1384 patients met the inclusion criteria, with 475 experiencing postoperative arrhythmias. The median age of the patients was 3.75 years, and 50.3% were female. The data were divided into a training set (n = 970) and a validation set (n = 414) in a 7:3 ratio for the modeling process. There were no significant baseline characteristic differences between the training and validation sets. Table 1 presents the univariate analysis of the total patient dataset and the baseline characteristics of the training and validation sets.

Machine learning algorithms and comparison prediction model performance

Four machine learning algorithms were used to construct our prediction models: XGBoost, LR, SVM, and RF. We then plotted the ROC curves and assessed each model's predictive performance in terms of AUC, sensitivity, specificity, precision, positive predictive value, and negative predictive value (Table 2 and Figure 2A–B). Five variables were ultimately chosen to be included in the logistic regression model. On multivariable analysis, weight, procedure time, defect diameter, pre-interventional arrhythmia (pre-ARR), and the diameter difference between the occluder and defect exceeding 2 mm were independently associated with postoperative arrhythmia (Table 3). Figure 3 displays

Table 1. Perioperative statistical data of participants

Characteristic	Total (n = 1384)		Training (n = 970)		Validation (n = 414)		*P*-value
	NO-ARR n = 909	ARR n = 475	NO-ARR n = 637	ARR n = 333	NO-ARR n = 272	ARR n = 142	
Sex, n (%)							0.130
F	471 (51.8%)	225 (47.4%)	329 (51.6%)	161 (48.3%)	142 (52.2%)	64 (45.1%)	
M	438 (48.2%)	250 (52.6%)	308 (48.4%)	172 (51.7%)	130 (47.8%)	78 (54.9%)	
Weight, kg, median (IQR)	16.0 (14.0–21.0)	15.0 (13.0–19.0)	16.0 (14.0–20.5)	15.0 (13.5–19.0)	16.5 (14.0–22.0)	15.0 (13.0–18.0)	<0.001
Height, cm, median (IQR)	103 (96.5–114)	100 (95.0–110)	102 (96.3–113)	100 (95.3–110)	104 (96.9–115)	99.0 (95.0–106)	<0.001
Bsa, m^2, median (IQR)	0.68 (0.60–0.81)	0.63 (0.59–0.76)	0.67 (0.60–0.80)	0.64 (0.59–0.77)	0.69 (0.60–0.83)	0.63 (0.58–0.72)	<0.001
Age, years, median (IQR)	3.83 (2.92–5.50)	3.50 (2.75–5.00)	3.83 (2.92–5.42)	3.50 (2.75–5.25)	3.96 (3.00–5.71)	3.42 (2.75–4.42)	0.001
Tom, n (%)							0.051
NO	240 (26.4%)	102 (21.5%)	179 (28.1%)	72 (21.6%)	61 (22.4%)	30 (21.1%)	
YES	669(73.6%)	373 (78.5%)	458 (71.9%)	261 (78.4%)	211 (77.6%)	112 (78.9%)	
Procedure time, min, median (IQR)	60.0 (55.0–80.0)	70.0 (60.0–110)	60.0 (55.0–80.0)	70.0 (60.0–110)	60.0 (55.0–85.0)	77.5 (60.0–110)	<0.001
Type, n (%)							0.023
Ado2	135 (14.9%)	63 (13.3%)	99 (15.5%)	47 (14.1%)	36 (13.2%)	16 (11.3%)	
Ecc	83 (9.13%)	52 (10.9%)	58 (9.11%)	38 (11.4%)	25 (9.19%)	14 (9.86%)	
Sym	641 (70.5%)	315 (66.3%)	447 (70.2%)	218 (65.5%)	194 (71.3%)	97 (68.3%)	
Tw	50 (5.50%)	45 (9.47%)	33 (5.18%)	30 (9.01%)	17 (6.25%)	15 (10.6%)	
Dev, mm, median (IQR)	6.00 (5.00–7.00)	6.00 (5.00–8.00)	6.00 (5.00–7.00)	6.00 (5.00–8.00)	6.00 (5.00–7.00)	7.00 (6.00–8.00)	<0.001
Fs, n (%)							<0.001
NO	97 (10.7%)	100 (21.1%)	71 (11.1%)	69 (20.7%)	26 (9.56%)	31 (21.8%)	
YES	812 (89.3%)	375 (78.9%)	566 (88.9%)	264 (79.3%)	246 (90.4%)	111 (78.2%)	
Dd, mm, median (IQR)	3.10 (2.30–4.23)	4.00 (2.90–5.90)	3.10 (2.30–4.25)	4.00 (2.80–5.80)	3.05 (2.46–4.14)	4.45 (3.00–6.00)	<0.001
Davd, n (%)							1.000
>3 mm	432 (47.5%)	226 (47.6%)	296 (46.5%)	156 (46.8%)	136 (50.0%)	70 (49.3%)	
≤3 mm	477 (52.5%)	249 (52.4%)	341 (53.5%)	177 (53.2%)	136 (50.0%)	72 (50.7%)	
Ddov, n (%)							<0.001
≤2 mm	366 (40.3%)	102 (21.5%)	263 (41.3%)	74 (22.2%)	103 (37.9%)	28 (19.7%)	
>2 mm	543 (59.7%)	373 (78.5%)	374 (58.7%)	259 (77.8%)	169 (62.1%)	114 (80.3%)	
Pre-Arr, n (%)							<0.001
NO	903 (99.3%)	305 (64.2%)	635 (99.7%)	220 (66.1%)	268 (98.5%)	85 (59.9%)	
YES	6 (0.66%)	170 (35.8%)	2 (0.31%)	113 (33.9%)	4 (1.47%)	57 (40.1%)	

Abbreviations: ado2, Amplatzer Duct Occluder II; Davd, the distance of the aortic valve to defect; Dd, defect diameter; Ddov, the diameter difference between the occluder and ventricular septal defect; Ecc, eccentric occlude; Fs, success of the first attempt; NO-ARR, no postoperative arrhythmia; Pre-Arr, pre-interventional arrhythmia; Sym, symmetric occlude; Tom, Tumor of membranous part of interventricular septum;Tw, thin-waist occlude

Table 2. Predictive performance of four machine learning models in the training and validation cohorts

TRAINING SET						
Model	AUC	Sen	Spe	Acc	PPV	NPV
XGB	0.955	0.925	0.834	0.865	0.743	0.955
LR	0.822	0.619	0.885	0.794	0.738	0.816
SVM	0.92	0.822	0.903	0.875	0.815	0.907
RF	1	1	1	1	1	1
VALIDATION SET						
Model	AUC	Sen	Spe	Acc	PPV	NPV
XGB	0.849	0.734	0.816	0.788	0.677	0.854
LR	0.863	0.683	0.868	0.804	0.729	0.84
SVM	0.859	0.776	0.827	0.81	0.703	0.875
RF	0.848	0.685	0.857	0.798	0.715	0.838

Abbreviations: NPV, negative predictive value; PPV, positive predictive value

the relevance ratings of the variables obtained from the random forest regressor. Weight, procedure time, defect diameter, the diameter difference between the occluder and ventricular septal defect >2 mm (Ddov2), and pre-ARR were the factors included in the model. The training set's AUC values for XGBoost, LR, SVM, and RF were 0.955, 0.822, 0.920, and 1, respectively; the validation set's AUC values for the same variables were 0.849, 0.863, 0.859, and 0.848. In the end, the order of AUC values indicated that the LR model was the best.

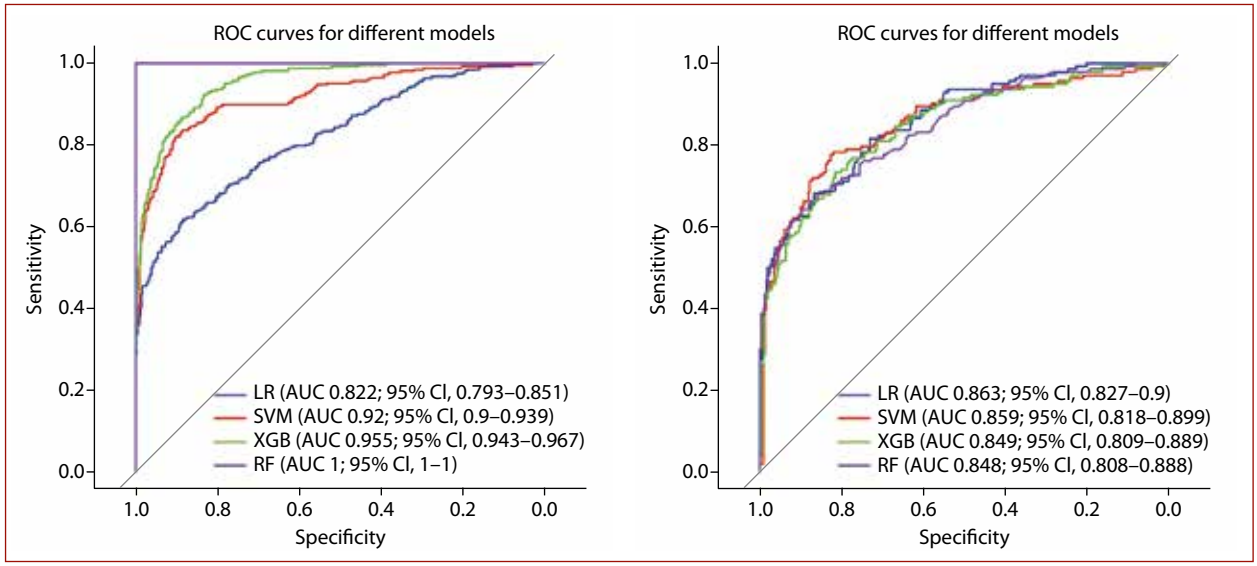


Figure 2. The ROC curves and AUC values with 95% CI for the four machine learning prediction models on the training and validation sets
Abbreviations: AUC, area under the curve; CI, confidence interval; ROC, receiver operating characteristic

Table 3. Multivariable logistic regression analysis on the training set

	ALL n = 970	NO-ARR n = 637	ARR n = 333	*P*-value
Weight, kg	16.0 (14.0–20.0)	16.0 (14.0–20.5)	15.0 (13.5–19.0)	0.009
Procedure time, min	70.0 (60.0–90.0)	60.0 (55.0–80.0)	70.0 (60.0–110)	<0.001
Dd, mm	3.50 (2.50–4.90)	3.10 (2.30–4.25)	4.00 (2.80–5.80)	<0.001
Ddov:				<0.001
≤2mm	337 (34.7%)	263 (41.3%)	74 (22.2%)	
>2mm	633 (65.3%)	374 (58.7%)	259 (77.8%)	
Pre-Arr:				<0.001
NO	855 (88.1%)	635 (99.7%)	220 (66.1%)	
YES	115 (11.9%)	2 (0.31%)	113 (33.9%)	

Abbreviations: NO-ARR, no postoperative arrhythmia; Dd, defect diameter; Ddov, the diameter difference between the occluder and ventricular septal defect; Pre-Arr, pre-interventional arrhythmia

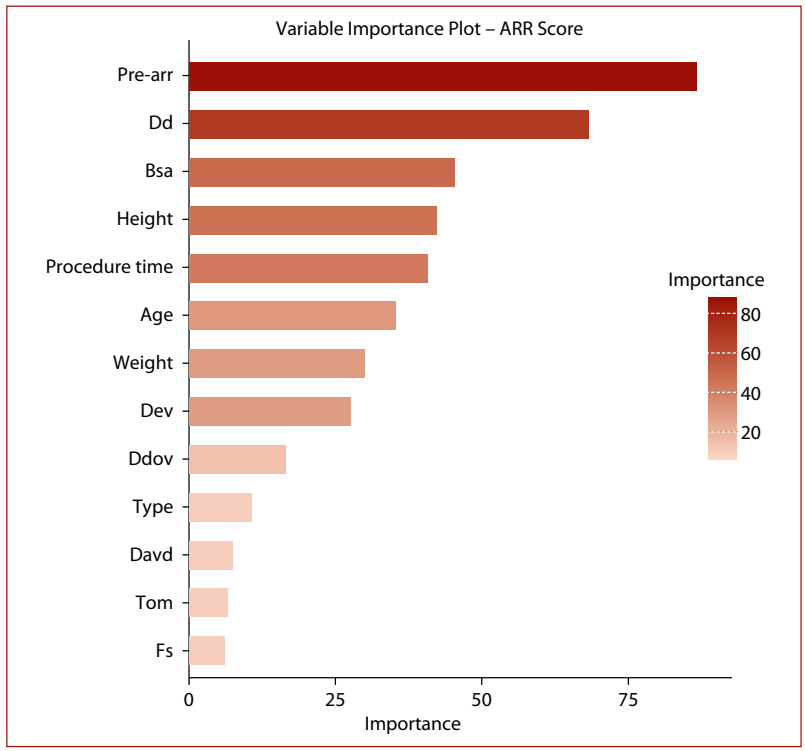


Figure 3. The important features derived from the random forest regressor

Abbreviations: Pre-Arr, pre-interventional arrhythmia; Dd, defect diameter; Dev, device diameter; Ddov, the diameter difference between the occluder and ventricular septal defect; Davd, the distance of the aortic valve to defect; Tom, tumor of membranous part of interventricular septum; Fs, success of the first attempt

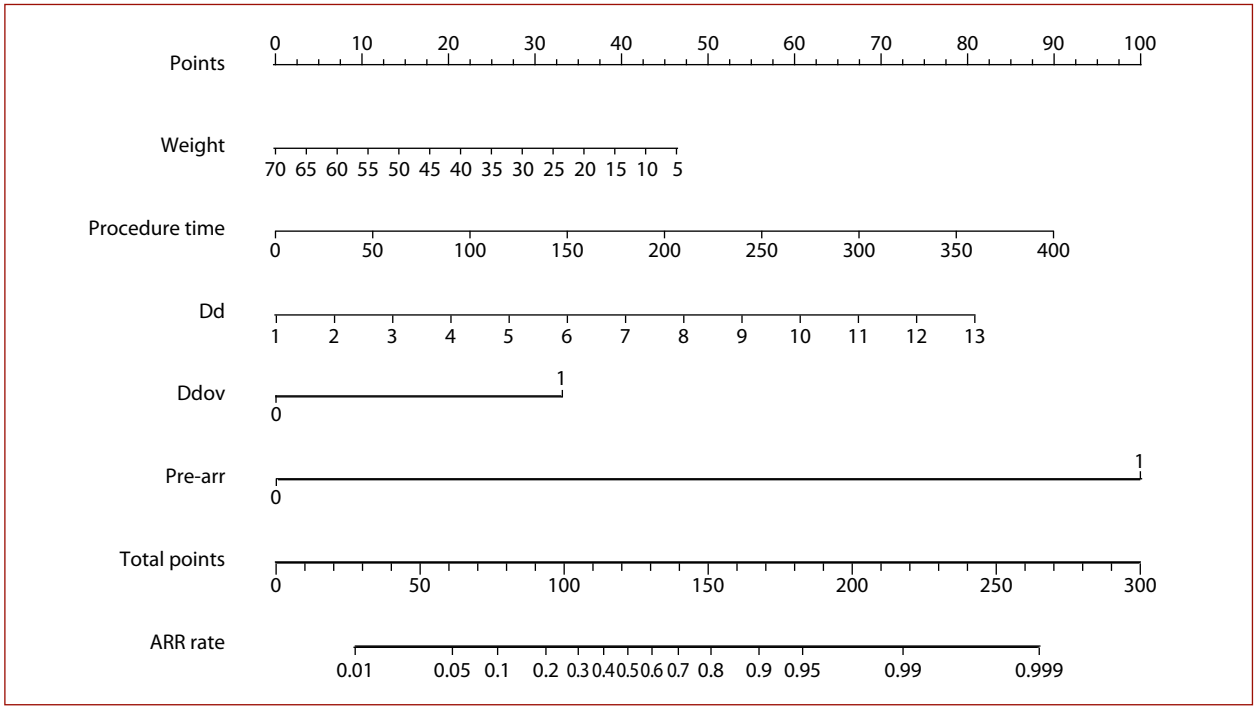


Figure 4. Nomogram used for predicting ARR after interventional occlusion in pmVSD patients. Logistic regression algorithm was used to establish nomogram. The total points is calculated as the sum of the individual scores of each of the five variables included in the nomogram

Development and validation of an ARR-predicting nomogram

The following variables were identified as independent risk factors for the development of arrhythmia (ARR) in pmVSD patients following interventional occlusion: body weight, procedure time, defect diameter, diameter difference between the occluder and ventricular septal defect >2 mm, and pre-ARR. The aforementioned five variables were incorporated into the predictive model and utilized to construct the nomogram (Figure 4). In comparison to complex logistic regression formulas, nomograms are relatively straightforward to comprehend and offer greater clinical utility. Based on the score of each independent variable, a score can be derived by projecting vertically to the top score axis. The corresponding total score is then located below, and the sum of the scores of each variable is projected onto the risk axis of postoperative ARR to predict the incidence of ARR in patients after pmVSD. The higher the total score, the higher the ARR risk. The nomogram was calibrated using calibration curves. The calibration curve's findings demonstrated that there was little deviation between the ideal and real curves. The prediction model had good accuracy because the actual prediction curves (B = 1000 resamples, mean absolute error of training set [A] = 0.012, mean absolute error of validation set [B] = 0.02) were consistent with the ideal curves. The prediction model had some predictive value following internal validation (Figure 5A–B). The nomogram's C-statistic was 0.822, indicating a high predictive value.

DISCUSSION

Technological advancements have made transcatheter device closure the more popular treatment option for pmVSD patients, but postoperative arrhythmias remain the most common and serious side effect. Atrioventricular block and complete left bundle branch block, in particular, can be extremely dangerous and even life-threatening, necessitating pacemaker implantation. According to past research, recovery from transcatheter blocker arrhythmias is more challenging the earlier they occur [24]. Consequently, a straightforward and intelligible instrument for gauging the probability of postoperative arrhythmia occurrences is of paramount importance for clinicians' surgical decision-making and early prompt intervention in postoperative high-risk children. By providing a more accurate assessment of the patient's overall condition before operation helps guide the selection of appropriate surgical techniques and optimal occluder size and type, thereby reducing the risk of postoperative arrhythmias. It also facilitates tailored post-operative monitoring plans, lifestyle adjustments, and psychological interventions for high-risk patients. Early detection and management of arrhythmias based on predictive models can prevent disease progression and improve patient recovery and long-term outcomes. Therefore, emphasizing the importance of postoperative arrhythmia prediction in clinical practice is critical in optimizing treatment strategies and improving patient care and overall prognosis.

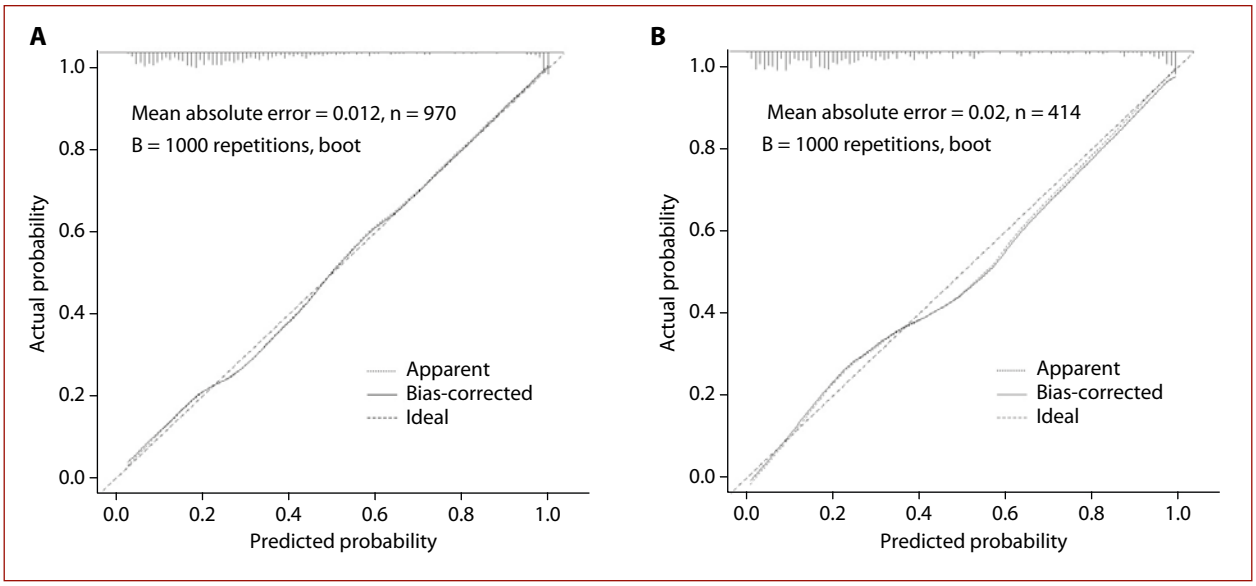


Figure 5. Calibration curve of the nomogram for the training set (**A**) and the validation set (**B**). The logistic regression algorithm was used to establish a nomogram. The X-axis represents the overall predicted probability of ARR after transcatheter device closure in pmVSD patients. and the Y-axis represents the actual probability. Model calibration is indicated by the degree of fitting of the curve and the diagonal

In this study, four machine learning algorithms were employed and validated to construct a prediction model to predict the probability of postoperative arrhythmia in pmVSD patients who underwent transcatheter device closure. The performance of the ML algorithms was evaluated, and the prediction model built by logistic regression was determined to be the optimal model. This model can assist clinicians in their decision-making.

The model we developed incorporated several preoperative intraoperative risk factors as the most important predictors of postoperative ARR, including pre-ARR, body weight, defect diameter, diameter difference between the occluder and ventricular septal defect, and procedure time. Our study found that pre-ARR plays a crucial predictive role. It has been shown that pre-ARR accounts for over 70% of postoperative arrhythmia cases in children after VSD transcatheter device closure. Pre-ARR is associated with hemodynamic abnormalities that lead to cardiac conduction block. If these hemodynamic abnormalities are not corrected after the procedure, the combination of surgical stimulation and increased conduction bundle compression can easily trigger arrhythmias [18]. The cardiovascular system of children with lower body weight is immature, making them more sensitive to surgical stress and increasing the probability of postoperative arrhythmia [25, 26]. The size of the defect is also a crucial factor. A larger VSD significantly impacts heart anatomy and electrical activity. Studies show that larger defect sealing may lead to a more significant local inflammatory response and scar tissue formation, affecting the stability of the heart's electrical activity [27, 28]. In pmVSD, the anatomic alignment of the atrioventricular (AV) conduction system varies. Typically, the His bundle travels along the posterior-inferior border of the defect, with its perforating branches only 2–4 mm from the edge. The left and right bundle branches, along with other branches, are sometimes wrapped in residual fibrous tissue at the edge of the defect [29]. Therefore, when the diameter difference between the occluder and the ventricular septal defect is greater than 2 mm, which means that the occluder is too large relative to the defect, it compresses the AV junction area. This leads to edema of the surrounding myocardial tissue, causing arrhythmias. This phenomenon is understandable from both clinical practice and anatomical perspectives. The longer the procedure, the more manipulation of the cardiac tissue is involved, which may increase local inflammation and affect the heart's electrical conduction system. Prolonged exposure to catheters and occlusion devices can mechanically irritate cardiac tissues, especially conduction pathways, thereby increasing the likelihood of arrhythmic events. This is consistent with the findings of many studies [2, 30].

More than 3 decades have passed since the introduction of transcatheter ventricular septal defect sealing, and many studies on postoperative arrhythmias have been conducted. However, various biases have arisen, likely due to inconsistent or overly detailed classifications of arrhythmias, small sample sizes, incomplete data, and confounding non-independent risk factors. Consequently, many mixed results have been obtained. Moreover, the literature on applying ML algorithms to predict arrhythmias after pmVSD is sparse. To our knowledge, this is the first study to develop a predictive model using ML algorithms to guide postoperative arrhythmia risk assessment from general clinical information.

Utilizing advances in computer science to incorporate clinical parameters may be more beneficial for risk prediction than relying on a single clinical parameter. The prediction model in this study establishes a visual

nomogram that can intuitively predict the risk of developing postoperative arrhythmias. Clinical staff can use the nomogram to calculate postoperative risk probabilities, aiding in intervention and clinical decision-making. Calibration curves showed that the model has good accuracy. Therefore, developing a clinical predictive modeling tool would facilitate timely interventions to prevent or mitigate postoperative arrhythmias.

However, there are limitations to this study. First, the nature of retrospective studies may lead to selection bias. Second, our ML algorithmic model is limited to specific mechanisms, which may restrict its generalization. This aspect needs further validation in real scenarios. Additionally, our current clinical database is a single-center database only for Chinese patients, limiting its predictive value. Finally, since our database includes only pediatric patients, the predictive validity for adult patients with post-pmVSD arrhythmias is unknown. Therefore, our next step is to establish a large, heterogeneous, multicenter, multinational, multi-age cohort to improve, homogenize, and validate the current clinical risk prediction models.

CONCLUSION

By analyzing clinical data from our database, we developed and evaluated machine learning algorithms to predict postoperative ARR risk in pmVSD patients using available preoperative and intraoperative variables. The logistic regression model performed the best. We also constructed an easy-to-use and internally validated nomogram. Clinicians can use this nomogram to predict the risk of postoperative ARR in pmVSD patients, enabling accurate surgical decisions and effective risk communication for better prognoses. The nomogram requires testing on a larger sample size for further external validation.

Article information

Conflict of interest: None declared.

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Percutaneous coronary intervention and coronary artery bypass grafting in myocardial infarction complicated by cardiogenic shock

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ABSTRACT

Background: Cardiogenic shock (CS) remains the leading cause of poor prognosis in patients with acute myocardial infarction (AMI), sustaining a high mortality rate of 40 to 50% within 30 days.

Aims: In this unique analysis of two national all-comers, real-life registries including patients with AMI complicated by CS, for whom early revascularization was planned, we aimed to compare the effect of percutaneous coronary revascularization (PCI) and coronary artery bypass grafting (CABG) on 30-day and 1-year all-cause mortality.

Material and methods: The study included consecutive patients with AMI complicated by CS included in the Polish Registry of Acute Coronary Syndromes (PL-ACS) and the Polish National Registry of Cardiac Surgical Procedures (KROK), treated with PCI and CABG, respectively. A layered analysis and Kaplan–Meier curves were used in the propensity score matched (PSM) groups.

Results: Between 2006 and 2022, a total of 1970 patients with AMI complicated by CS, with known coronary anatomy were included in PL-ACS and KROK registries. 1376 (69.8%) had PCI and 594 (30.2%) had CABG. Following a 1:1 PSM, a total of 822 patients were finally included in the analysis. The mortality rates were 48.2% in the PCI group compared with 38.6% in the CABG group at 30 days (P <0.001) and 53.5% compared with 41.1%, respectively, at 1 year (P <0.001).

Conclusions: Among patients with AMI affected by CS, those qualified to be treated with CABG had a higher survival rate at 30 days and one year as compared to those treated with PCI.

Key words: acute myocardial infarction, CABG, cardiogenic shock, PCI, prognosis

INTRODUCTION

Acute myocardial infarction (AMI) is the most common cause of cardiogenic shock (CS) [1]. AMI-related CS (AMICS) results in a deficiency of end-organ perfusion that is often characterized by a vicious circle of pathophysiological interactions in the course of a sudden loss of cardiac systolic function as a cause of acute coronary ischemia [2, 3]. The incidence of AMICS is 7%–10% and despite ongoing intensified efforts, including broad implementation of coronary revascularization and technological and logistic progress, the prognosis associated with AMICS remains poor, with 30-day mortality approximating unacceptable 40% to 50% [4–7].

In a subanalysis of the SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) trial and in a recently published study, coronary artery bypass grafting (CABG) had comparable mortality rates to PCI, even though more complex coronary artery disease (CAD) was revascularized surgically [8, 9]. Therefore, according to current practice guidelines, CABG in AMICS should be still considered as a valuable treatment option, especially in the presence of the complexity of CAD not amenable for or after failed PCI [10, 11]. However, the broader referral of AMICS patients to CABG is not observed [12], mainly due to a lack of robust clinical data coming from randomized clinical trials (RCT) and/or real-life, all-comer registries.

Taking the above into consideration, this study aimed to assess which strategy, PCI or CABG, is superior in the context of the reduction of all-cause mortality in patients with AMICS, based on the data from two national all-comer, real-world registries: the Polish Registry of Acute Coronary Syndromes (PL-ACS Registry) and the Polish National Registry of Cardiac Surgical Procedures (KROK Registry).

METHODS

Ethical review and approval were waived for this study because of retrospective analysis of the prospective PL-ACS and KROK registry.

Design of the registries

The PL-ACS is a national, multicenter, ongoing, prospective observational registry that includes data on patients hospitalized with acute coronary syndromes in Poland. It is a joint project of the Silesian Center of Heart Diseases in Zabrze and the Polish Ministry of Health, in cooperation with the National Health Fund [13]. The registry was founded in October 2003, and in May 2004, it was harmonized with the European Cardiology Audit and Registration Data Standards [13]. Participation in the registry is mandatory for every hospital treating patients with ACS in Poland. Full details on the rationale and methods of the PL-ACS have been previously described [13].

The KROK Registry, is a national, multicenter, ongoing, prospective observational registry of patients undergoing cardiac surgery, a joint initiative of the Polish Society of Cardiothoracic Surgeons and the Polish Ministry of Health. Details regarding the KROK Registry and the collection of follow-up data have been previously described [14].

Before enrollment, informed writing consent was given by all participants. Institutional review board approval was obtained for all participants. The authors declare that all supporting data are available within the article. No other cardiovascular endpoints (e.g. cardiovascular mortality and nonfatal myocardial infarction and stroke) are available in the registry. The primary outcome was death from any cause at 30 days.

Data on long-term all-cause mortality, including the exact date of death, were obtained from the National

WHAT'S NEW?

In this analysis of patients with acute myocardial infarction complicated by cardiogenic shock, we included consecutive patients enrolled in the Polish Registry of Acute Coronary Syndromes and the Polish National Registry of Cardiac Surgical Procedures, treated with percutaneous coronary revascularization (PCI) and coronary artery bypass grafting (CABG). The mortality rates as a primary endpoint were 48.2% in the PCI group compared with 38.6% in the CABG group at 30 days (P <0.001) and 53.5% compared with 41.1%, respectively, at 1 year (P <0.001).Among patients with acute myocardial infarction affected by cardiogenic shock, those treated with CABG had a higher survival rate at 30 days and one year as compared to treated with PCI.

Health Fund by December 2022. Follow-up time was censored at one year or the end of follow-up time (whichever came first).

Study patient population and definitions

Consecutive patients with AMICS included in the PL-ACS Registry and KROK Registry were included in the analysis. Patients with AMI were stratified by the presence of CS before revascularization. The selection of revascularization procedures was individualized for each patient at the discretion of site physicians.

The AMI was defined according to the Fourth Universal Definition of Myocardial Infarction [15]. CS was defined as 1) systolic blood pressure <90 mm Hg (in the absence of hypovolemia and after proper fluid resuscitation) for at least 30 min or the need for pharmacological support to maintain systolic blood pressure above 90 mm Hg; and 2) signs and symptoms of end-organ hypoperfusion. Patients with mechanical complications and/or who required surgical procedures other than CABG, were excluded from the analysis.

Statistical analysis

The normality of the distribution of quantitative variables was assessed using the Shapiro–Wilk test. Depending on the results, variables were presented as means with standard deviations or medians with interquartile ranges. Groups were compared using Student's t-test for variables with normal distributions or the Mann–Whitney U test for those that did not meet the normality assumption. Categorical variables were shown as percentages and groups were compared using the $\chi 2$ test. The study patients were matched to achieve similar age, sex, history of hypertension, diabetes, myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, peripheral arterial disease, current smoking habits, atrial fibrillation, left main disease, and multivessel coronary disease.

Data were matched using the Mahalanobis distance within propensity score calipers. The caliper radius was set to 0.2*sigma [16, 17]. Finally, the propensity score–matched groups included 411 individuals each. The standardized mean differences for groups after PSM were calculated. The matched cohorts were considered well-balanced for a given variable if the absolute standardized mean difference between the cohorts was ≤0.1.

A layered analysis was performed to further investigate the impact of the intervention on specific subgroups. Relative risks (RRs) were determined for the total sample and within each stratum. Moderation analyses were conducted using logistic regression models with interaction terms to determine whether sex, age over 65, diabetes, renal failure, PVD, and left main (LM) moderated the effect of procedure type on 30-day mortality.

Kaplan–Meier curves after PSM were drawn to show the cumulative survival in a 30-day and one-year observation period. Survival between the groups before and after PSM was compared using the log-rank test. Observation time was median: 0.2 years (IQR 0.005–3.7), 0.04 years (IQR 0.001–1.7), and 1.6 years (IQR 0.01–1.7) for the entire group, PCI and CABG respectively.

Statistical significance was defined as a 2-sided $P<0.05$. All statistical analyses were performed using TIBCO Statistica software (TIBCO Statistica, v. 13.3; TIBCO Software Inc, Palo Alto, CA, US).

RESULTS

Between 2006 and 2022, a total of 1970 patients with AMI complicated by CS, with known coronary anatomy were included in the PL-ACS and KROK registries. A total of 1376 individuals (69.8%) underwent PCI and 594 (30.2%) underwent CABG. After 1:1 PSM, a total of 822 patients were finally included in the analysis (Figure 1). The baseline clinical and angiographic characteristics before and after PSM are presented in Table 1. Before propensity score matching the higher prevalence of many comorbidities and much more complex CAD with left main disease were observed. After PSM, the groups were well-balanced in terms of baseline characteristics. The in-hospital outcomes are presented in Table 2. The mortality rate was 48.2% in the PCI group compared with 38.6% in the CABG group at 30 days ($P<0.001$) and 53.5% compared with 41.1%, respectively, at one year ($P<0.001$) (Table 2, Figures 2 and 3). Prespecified analyses showed results across all subgroups that were consistent with those in the primary analysis with significant interactions for diabetes and LM subgroups of patients (Figure 4), suggesting a relative benefit of CABG in these conditions, notwithstanding the in-hospital rate of stroke being significantly higher in the CABG group than in the PCI group (6.6% vs. 0.24%; $P<0.001$).

DISCUSSION

Approximately one in ten patients develops CS in the setting of AMI, resulting from acute, sudden, and severe coronary ischemia/thrombosis. This leads to a cascade of deleterious effects, including end-organ hypoperfusion, compensatory vasoconstriction, raised ventricular diastolic pressures with refractory coronary ischemia, pulmonary congestion, increased biventricular afterload, lactic acidosis, systemic inflammatory response, and ultimately, death [18].

To date, coronary reperfusion limited to the culprit infarct artery is the only therapy proven effective for prognosis in AMICS patients. Therefore, early intervention and restoration of perfusion to the infarct-related artery (IRA) is of paramount importance for patients with AMICS. However, since the landmark Should We Revascularize Occluded Arteries in Cardiogenic Shock (SHOCK) trial was published in 1999, despite significant efforts, AMICS continues to be linked with unacceptably high rates of morbidity and mortality risks reaching up to 40%–50% in the current RCT, and has not changed much over the last decade [5–7, 19, 20]. One of the valuable explanations for these suboptimal

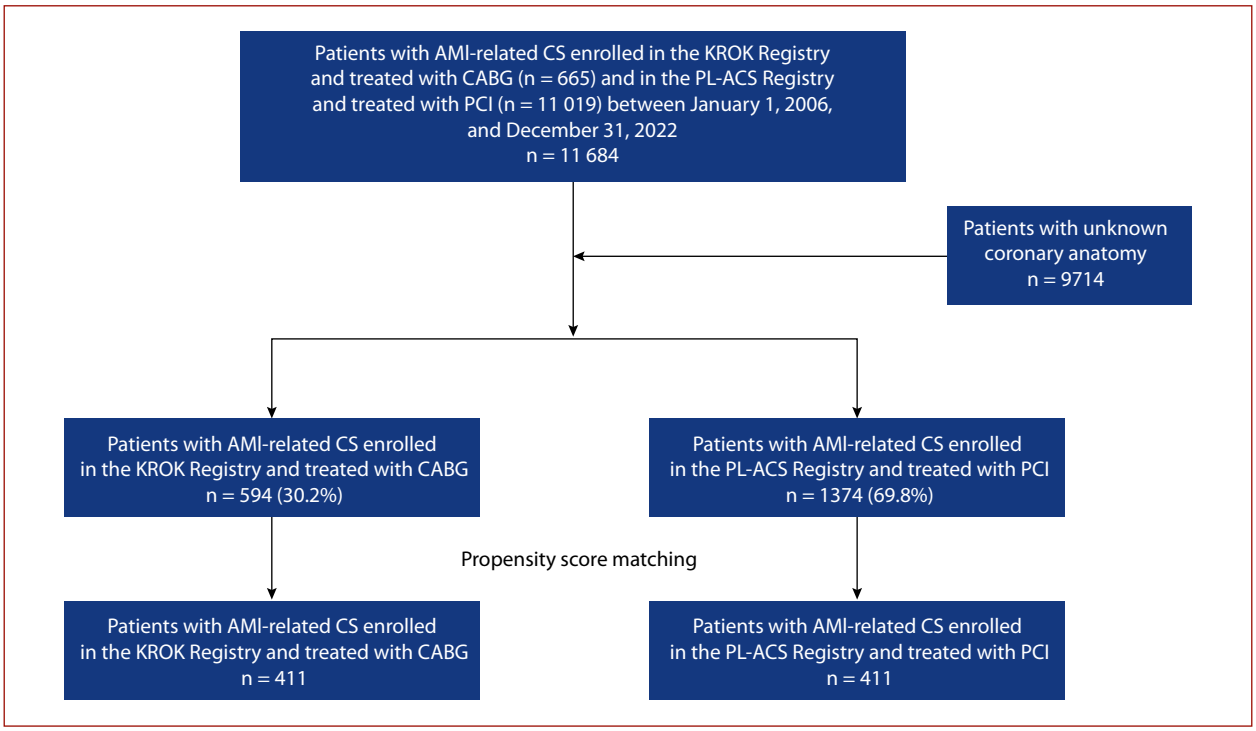


Figure 1. Study flowchart. Graphical presentation of the patients included in the analysis

Abbreviations: AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; CS, cardiogenic shock; KROK, Polish National Registry of Cardiac Surgical Procedure; PCI, percutaneous coronary intervention; PL-ACS, Polish Registry of Acute Coronary Syndromes

Table 1. Baseline patient characteristics by study groups

Variable	Before matching			After matching		
	CABG n = 594	PCI n = 1376	*P*-value	CABG n = 411	PCI n = 411	*P*-value
Sex (female), n (%)	177 (29.8)	493 (35.8)	0.01	137 (33.3)	114 (27.7)	0.1
Age, years (mean, SD)	67.6 (9.4)	69.4 (11.8)	0.001	67.9 (9.4)	69.2 (11.2)	0.07
Current smoker, n (%)	154 (25.9)	368 (26.7)	0.7	106 (25.8)	108 (26.3)	0.9
Hypertension, n (%)	493 (83)	825 (60)	<0.001	316 (76.9)	321 (78.1)	0.74
Hyperlipidemia, n (%)	330 (56)	516 (37)	<0.001	203 (49.4)	206 (50)	0.89
Diabetes, n (%)	192 (32.3)	424 (31.1)	0.6	142 (34.5)	129 (31)	0.4
Body mass index[a] (mean, SD)	27.7 (4.4)	27.9 (5)	0.4	27.6 (4.3)	27.7 (4.9)	0.8
Previous PCI, n (%)	168 (28.3)	224 (16.3)	<0.001	103 (25.1)	104 (25.3)	1.0
Previous CABG, n (%)	7 (1.2)	58 (4.2)	<0.001	7 (1.7)	11 (2.7)	0.5
Atrial fibrillation, n (%)	58 (9.8)	270 (19.6)	0.001	49 (11.9)	46 (11.2)	0.8
Previous stroke, n (%)	32 (5.4)	108 (8.7)	0.02	24 (5.8)	24 (5.8)	0.8
Chronic kidney disease, n (%)	115 (19.4)	170 (13.7)	0.002	71 (17.3)	72 (17.5)	1.0
Peripheral artery disease, n (%)	117 (19.7)	133 (10.7)	<0.001	63 (15.3)	56 (13.6)	0.5
COPD, n (%)	57 (9.6)	64 (5.2)	0.001	35 (8.5)	33 (8.03)	0.9
1VD, n (%)	31 (5.2)	317 (23.0)	<0.001	28 (6.8)	28 (6.8)	0.9
2VD, n (%)	63 (10.6)	329 (23.9)	<0.001	57 (13.9)	57 (13.9)	0.9
3VD, n (%)	139 (23.4)	302 (21.9)	0.5	117 (28.5)	117 (28.5)	0.9
Left main+1VD, n (%)	86 (14.5)	180 (13.1)	0.44	74 (18)	74 (18)	0.9
Left main + 2/3VD, n (%)	275 (46.3)	248 (18)	<0.001	135 (32.8)	135 (32.8)	0.9
No. of vein grafts (mean, SD)	0.6 (0.6)	–		0.7 (0.6)	–	
No. of arterial grafts (mean, SD)	1.7 (0.9)	–		1.7 (0.9)	–	
No. of all grafts (mean, SD)	2.4 (0.9)	–		2.4 (0.9)	–	
No. of vessels treated with PCI (mean, SD)	–	1.4 (0.7)		–	1.6 (0.8)	
No. of stents used (mean, SD)	–	1.6 (1.1)		–	1.7 (1.2)	

[a]The body mass index is the weight in kilograms divided by the square of the height in meters

Abbreviations: CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention; SD, standard deviation; VD, vessel disease

Table 2. In-hospital outcomes: 30-day and 12-month mortality

Variable	Before matching			After matching		
	CABG n = 594	PCI n = 1376	*P*-value	CABG n = 411	PCI n = 411	*P*-value
Stroke, n (%)	40 (6.7)	8 (0.6)	<0.001	27 (6.6)	1 (0.24)	<0.001
IABP, n (%)	342 (57.6)	125 (9.1)	<0.001	228 (55.5)	31 (7.5)	<0.001
ECMO, n (%)	5 (0.8)	2 (0.07)	0.03	3 (0.7)	0 (0)	0.27
Pacemaker placement, n (%)	1 (0.2)	11 (0.8)	0.14	1 (0.2)	2 (0.5)	0.9
In-hospital stay, days median (IQR)	10.6 (7.1–15.6)	6.8 (3.1–11.0)	<0.001	10.6 (7.1–15.0)	6.7 (3.8–9.9)	<0.001
In-hospital stay, days median (IQR)[b]	2.7 (0.5–8.8)	0.4 (0.1–2.2)	<0.001	2.7 (0.5–10.2)	0.3 (0.1–3.0)	<0.001
In-hospital death from any cause, n (%)	190 (32)	593 (43.1)	<0.001	130 (31.6)	169 (41.1)	0.006
30-day death from any cause, n (%)	198 (33.3)	683 (49.6)	<0.001	138 (33.6)	198 (48.2)	<0.001
12-month death from any cause, n	250 (42.1)	788 (57.3)	<0.001	169 (41.1)	220 (53.5)	<0.001

[a]Patients who survived and were discharged. [b]Patients who died during index hospitalization

Abbreviations: ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; IQR, interquartile range; other — see Table 1

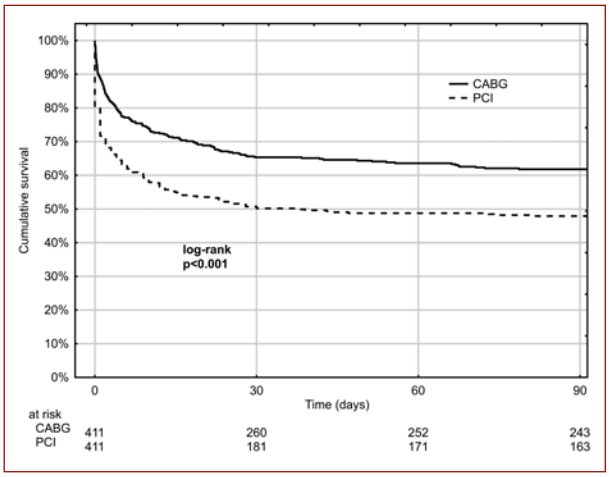


Figure 2. Kaplan–Meier estimates for all-cause 30-day survival. Free from all-cause mortality at 30 days

Abbreviations: see Figure 1

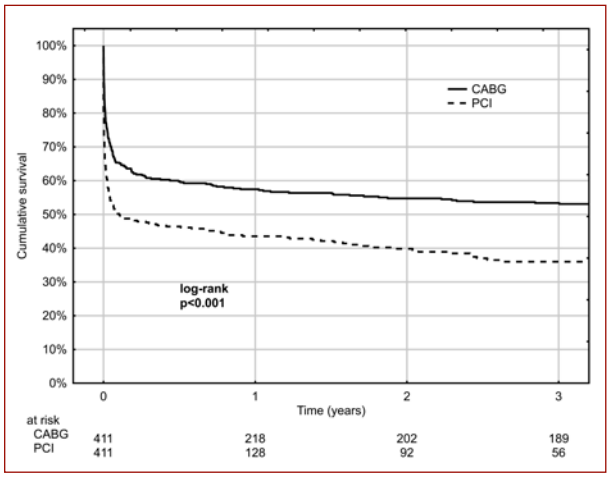


Figure 3. Kaplan–Meier estimates for all-cause one-year survival. Free from all-cause mortality at one year

Abbreviations: see Figure 1

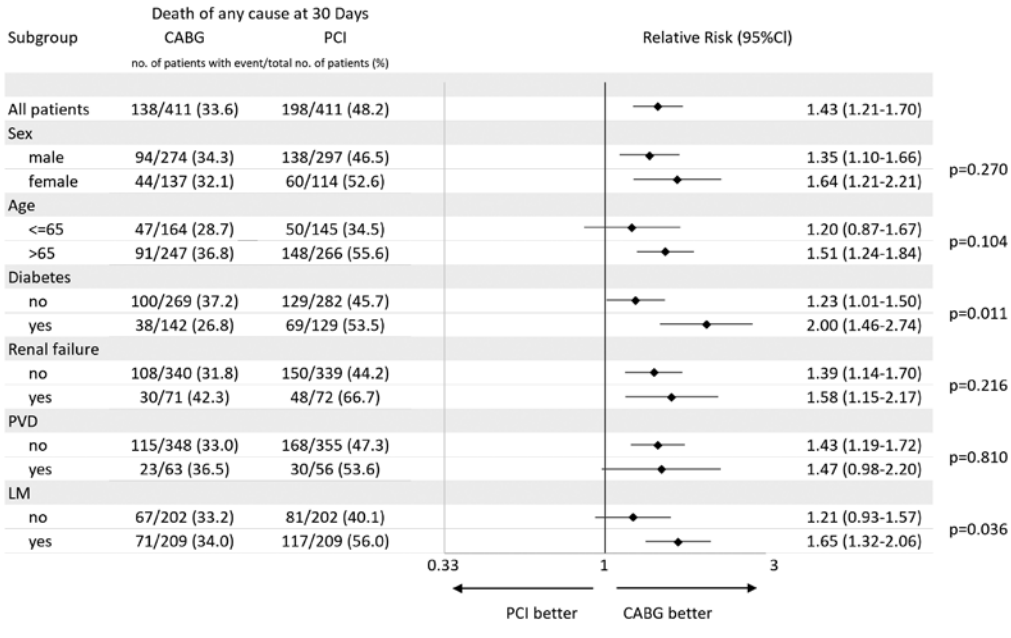
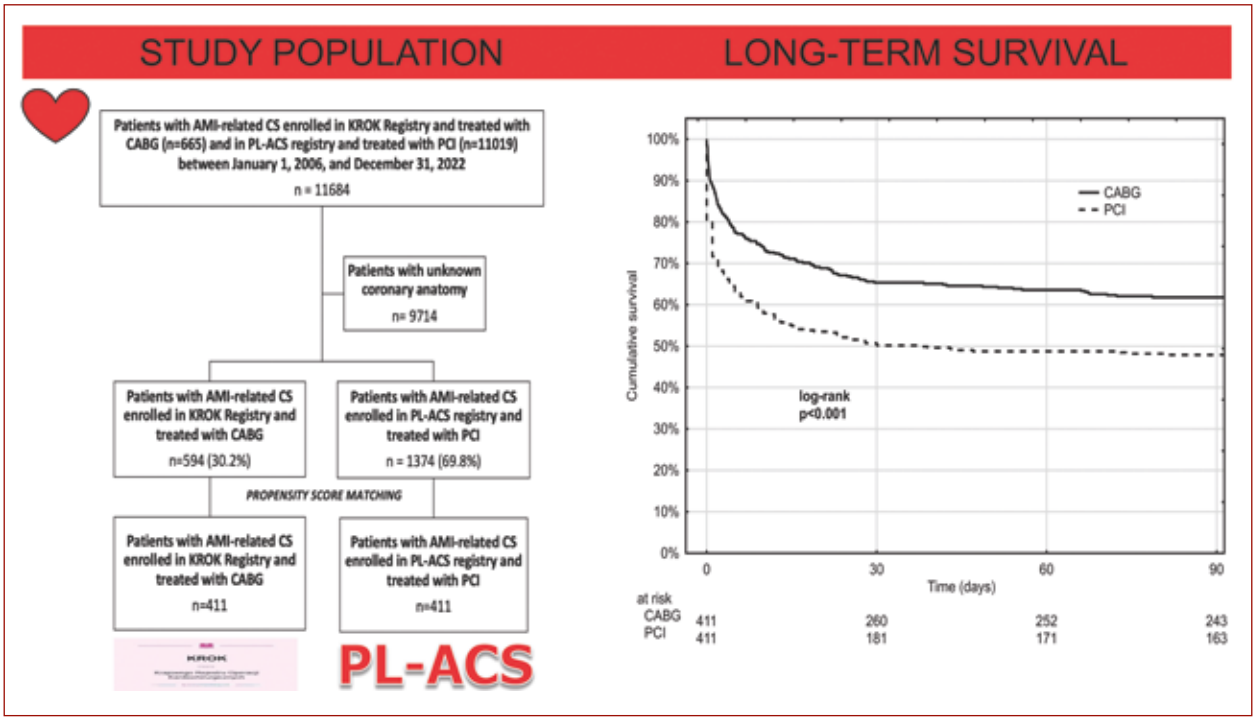


Figure 4. Subgroup analysis of the primary outcome. The forest plot illustrates the relative risk of death from any cause at 30 days (the primary outcome) in prespecified subgroups

Abbreviations: LM, left main; PVD, peripheral artery disease; other — see Figure 1



Graphical abstract. Among patients with AMI affected by CS, those treated with CABG had a higher survival rate at 30 days and one year as compared to those treated with PCI. Graphical presentation of the major findings coming from the presented study

Abbreviations: AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; CS, cardiogenic shock; KROK, Polish National Registry of Cardiac Surgical Procedure; PCI, percutaneous coronary intervention; PL-ACS, Polish Registry of Acute Coronary Syndromes

outcomes may be the fact that clinical gaps in knowledge regarding optimal revascularization strategies are present.

Currently, immediate coronary angiography and PCI of the IRA are recommended in this population regardless of time delay. Emergency CABG is recommended if PCI of the IRA is not possible and/or failed [21, 22]. However, bearing in mind that over 70% of patients with AMICS have a complex form of CAD, involving the LM multivessel, which is a strong and independent predictor of mortality, and given the very high mortality of patients with unsuccessful PCI, CABG should still be viewed as a valuable option of complete revascularization in patients with AMICS [23]. This is in line with the subanalysis of the SHOCK trial, published nearly two decades ago, in which White et al. [8] revealed that CABG vs. PCI in AMICS patients showed comparable survival rates. However, those patients allocated for CABG had much a more complex coronary anatomy, higher prevalence of diabetes, and a longer time to revascularization (0.9 hours for PCI vs. 2.7 hours for CABG). The authors concluded that the next "logical step" needs to be to design and perform RCTs comparing PCI and CABG in patients with AMICS [8]. To the best of our knowledge, no such RCT has yet been conducted. Moreover, the utility of CABG in the setting of AMI complicated by CS remains rare. In the Intra-aortic Balloon Pump in Cardiogenic Shock (IABP-Shock II) trial and registry, for example, where 52% of patients had a three-vessel disease and the left main was the IRA in approximately 9%, only 3.5 % of patients had immediate CABG [5].

Taking into consideration all facts mentioned above, the present study aimed to compare PCI and CABG regarding survival rates in patients with AMI complicated by CS. We strongly believe that conducting such an analysis using PSM could reignite a debate about the optimal revascularization methods in this highly demanding patient population. This may include expediting the process of designing and conducting dedicated RCTs or prospective registries. Additionally, this holds significant importance, particularly in light of recently published RCTs that have failed to demonstrate any benefits with regards to changes in current clinical practices. These include the routine use of intra-aortic balloon pump [5], routine immediate complete revascularization [6], and routine use of extracorporeal life support treatment [7].

The primary finding of this investigation is the significantly higher survival rates at both 30 days and one year in patients with AMI complicated by CS who underwent CABG compared to those who underwent PCI. The results of this study align with other observational data, although the inclusion of a small number of subjects [24] and limitation to in-hospital outcomes [25] should be noted. Of note, this was recorded despite of significantly higher rate of in-hospital stroke in CABG group. Although cardiopulmonary bypass was thought to be the primary cause of stroke in all cardiac surgeries, the development of off pump CABG surgery has made it possible to directly compare the risk of stroke with and without bypass, and no discernible difference has been observed [26].

Considering the latitude and potential of surgical coronary revascularization, the superiority of CABG over PCI in patients with AMICS regarding survival may be reasonably explained. This assumption may be corroborated by several findings. Firstly, CABG can accomplish one-stage complete revascularization even in the presence of chronic total occlusion or complex and calcified coronary anatomy. A propensity score-matching analysis compared a smaller set of patients who underwent PCI followed by CABG with patients who underwent PCI alone. This analysis showed no difference in mortality at 7 days (15.9% vs. 25%; $P = 0.29$) but a substantial difference favoring PCI + CABG at 30 days (20.5% vs. 40.9%; $P = 0.03$) [24]. Secondly, CABG using cardio-pulmonary bypass aids in arresting the heart with cardioplegia, cooling the myocardium, and ventricular unloading with adequate circulatory and hemodynamic support. These effects may be attributed to myocardial rest during surgery and a reduction in the myocardium's oxygen demand before revascularization, consequently preserving ischemic myocardium. Moreover, cardio-pulmonary bypass during surgery reverses global ischemia and sustains perfusion of vital organs, thus halting the cascade of events that can precipitate systemic inflammation and progressive hemodynamic deterioration in CS [27].

Study limitations

There are several limitations to our analysis that warrant acknowledgment. Firstly, this is a retrospective cohort study and we were constrained by the data available in the PL-ACS and KROK Registry, which are databases with different designs. The convergence of collected data, including the type of MI, is incomplete. Unfortunately, we did not record the timing between the onset of MI, the onset of cardiogenic shock, and the timing of coronary revascularization. Additionally, our follow-up analysis was limited to all-cause mortality. Due to the observational nature of the study and the limited number of patients, these results should be interpreted as hypothesis-generating and could be used for sample size calculation in randomized controlled trials comparing PCI with CABG in AMICS patients. Moreover, despite data adjustment in the propensity score matching, the results could still be biased by potentially important parameters that were not available in the PL-ACS and KROK registries. Finally, as this is a single-country study, its findings may not be generalizable to other populations.

However, a key strength of the present study lies in the assessment of all-cause mortality, which was conducted using a centralized, national database. This approach ensured a thorough and comprehensive capture of all deaths. Additionally, the data presented originates from a large administrative database, potentially identifying a representative cohort of patients with cardiogenic shock in terms of real-life clinical practice.

CONCLUSIONS

Our study indicates that CABG, when compared to PCI, was linked to higher 30-day and one-year survival rates in patients with AMICS. This underscores the need for further validation through multi-center, adequately powered randomized studies and/or prospective registries to conclusively evaluate the absolute benefits and risks of CABG in this patient population.

Article information

Conflict of interest: None declared.

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Allergic reactions during coronary angiography or PCI in Poland: Occurrence, trends, and long-term perspective based on the Polish ORPKI registry

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ABSTRACT

Background: Allergic reactions during coronary angiography and percutaneous coronary intervention (PCI) in patients with acute coronary syndromes can affect their outcomes.

Aims: We aimed to investigate the incidence of allergic reactions and predictors of their occurrence in the catheterization laboratory.

Material and methods: The study included 1 812 994 treatment cases available in the ORPKI Polish National Registry, of which 659 372 were for women and 1 144 689 for men. Data were collected from 161 interventional cardiology centers in Poland between 2014 and 2022 and included in the retrospective analysis. An allergic reaction was defined as any hypersensitive response of the immune system manifesting as bronchospasm, asthma exacerbation, conjunctivitis, urticaria, eczema, angioedema, or anaphylactic shock.

Results: There was a decreasing incidence of allergic reactions overall, in both sexes and all age subgroups. The incidence of allergic reactions each year oscillated between 0.02% and 0.11% (P <0.001), and the most recent one was 0.02% in 2022. The incidence of allergic reaction was associated with low-molecular-weight heparin (LMWH) (OR, 23.5 [95% CI, 18.92–29.19]), glycoprotein IIb/IIIa inhibitors (GPI IIb/IIIa) (OR, 2.31 [95% CI, 1.92–2.78]), previous PCI (OR, 1.55 [95% CI, 1.34–1.8]), radiation dose (OR, 1.25 per 1000 mGy [95% CI, 1.19–1.31]), and contrast dose (OR, 1.17 per 100 ml [95% CI, 1.08–1.28]).

Conclusions: The overall incidence of acute allergic reactions in the cath lab is low and decreased significantly between 2014 and 2022. The decrease in frequency did not depend on age or sex. Independent predictors of allergic reaction incidence were the use of GPI IIb/IIIa, LMWH, and dose of contrast agent and radiation.

Key words: allergic reaction, anaphylaxis, coronary angiography, iodinated contrast media, myocardial infarction, percutaneous coronary intervention

INTRODUCTION

Despite variable reports, the overall number of revascularization procedures has been increasing in recent years, the clinical profile of the patient has been changing, and higher risk procedures (left main coronary artery revascularization, rotablation and chronic total occlusion revascularization) are being performed more frequently [1–4].

Patients undergoing revascularization procedures are increasingly older and have more risk factors for atherosclerosis [2, 5]. Assessing the frailty of elderly patients remains crucial in selecting an appropriate revascularization strategy [6]. Despite these changes in patient profile, peri-procedural mortality in percutaneous coronary intervention (PCI) remains steady [3–5]. The rate of PCI complications,

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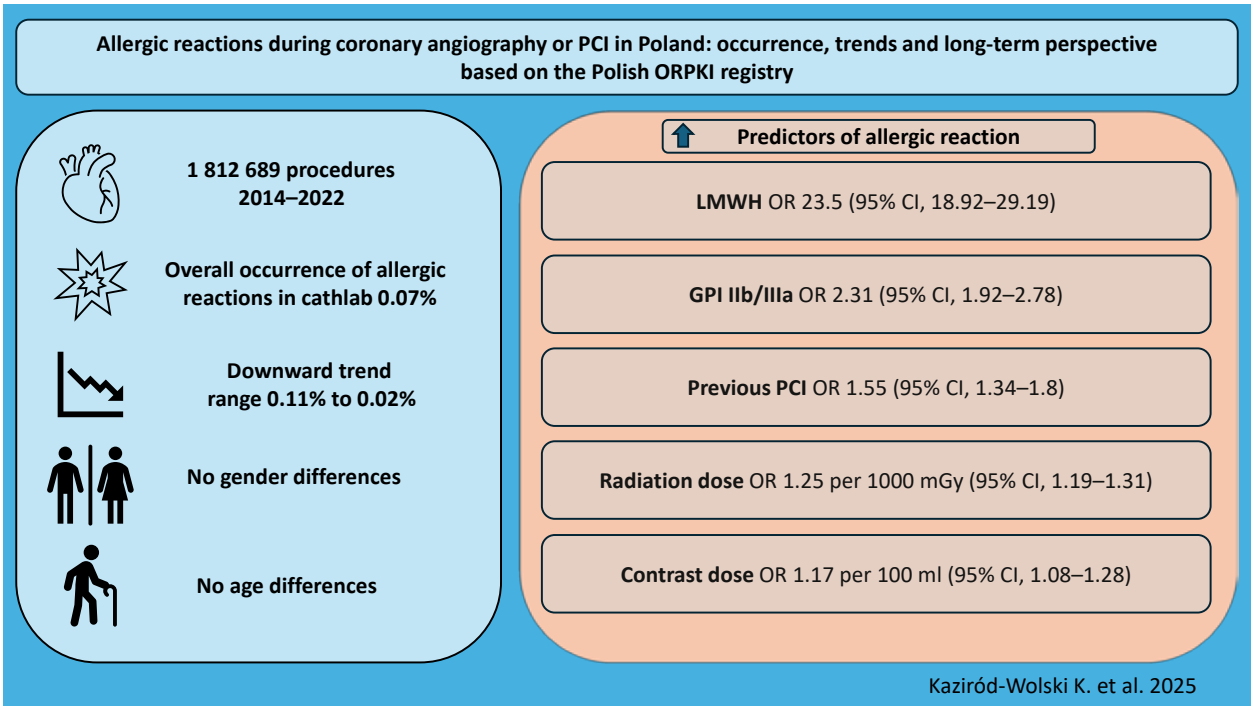
We present a retrospective study based on ORPKI (National Registry of Invasive Cardiology Procedures), which is the latest report on acute allergic reactions during coronary angiography and percutaneous coronary interventions. The overall incidence of acute allergic reactions in the cath lab is low and decreased significantly between 2014 and 2022. Recent data from other studies suggest that their incidence is higher. The decrease in frequency did not depend on age or sex. Independent factors that significantly increased the risk of allergic reaction were the use of glycoprotein IIb/IIIa inhibitors, low-molecular-weight heparin, contrast agents, and radiation.

such as coronary artery perforation and major vascular access complications, remains constant [7, 8]. Other complications, such as allergic reactions, are less studied. Based on available data, the incidence of allergic reactions during PCI is estimated to be 0.08% in patients without psoriasis and 0.4% in patients with psoriasis [9]. Allergic reactions during PCI can be caused by antiplatelet and anticoagulant drugs, as well as drug-eluting stents and contrast alone [10–12]. The incidence of contrast reactions, regardless of study type and mechanism of the allergic reaction, varies between 1% and 3% [13].

The purpose of this study is to accurately analyze the incidence of allergic reactions during coronary angiography and/or PCI, to select the most sensitive groups, and to identify predictors of such reactions.

MATERIAL AND METHODS

The National Registry of Invasive Cardiology Procedures (ORPKI) was launched in 2004 by the Association of Cardiovascular Interventions of the Polish Cardiac Society. Currently, the registry is coordinated by the Jagiellonian University College of Medicine in Krakow [14]. The data used in the statistical analysis in our study were accessed on January 10, 2024. All consecutive patients who underwent coronary angiography or coronary angiography with immediate PCI at 161 interventional cardiology centers in Poland between 2014 and 2022 were included in this retrospective analysis. The total number of patients referred to all assessed patients in consecutive years of the registry. Patients with incomplete data on baseline characteristics were excluded. No methods were used to impute missing data. An allergic reaction was defined as any hypersensitive response of the immune system manifesting as bronchospasm, asthma exacerbation, conjunctivitis, urticaria, eczema, angioedema, or anaphylactic shock. All of these symptoms had to be detected during the patient's stay in the catheterization laboratory and had not been present before admission to the hospital. Other complications or adverse events were diagnosed at the operator's discretion according to the current European Society of Cardiology



Graphical abstract

Abbreviations: CI, confidence interval; GPI, glycoprotein inhibitor; LMWH, low-molecular-weight heparin; OR, odds ratio; PCI, percutaneous coronary intervention

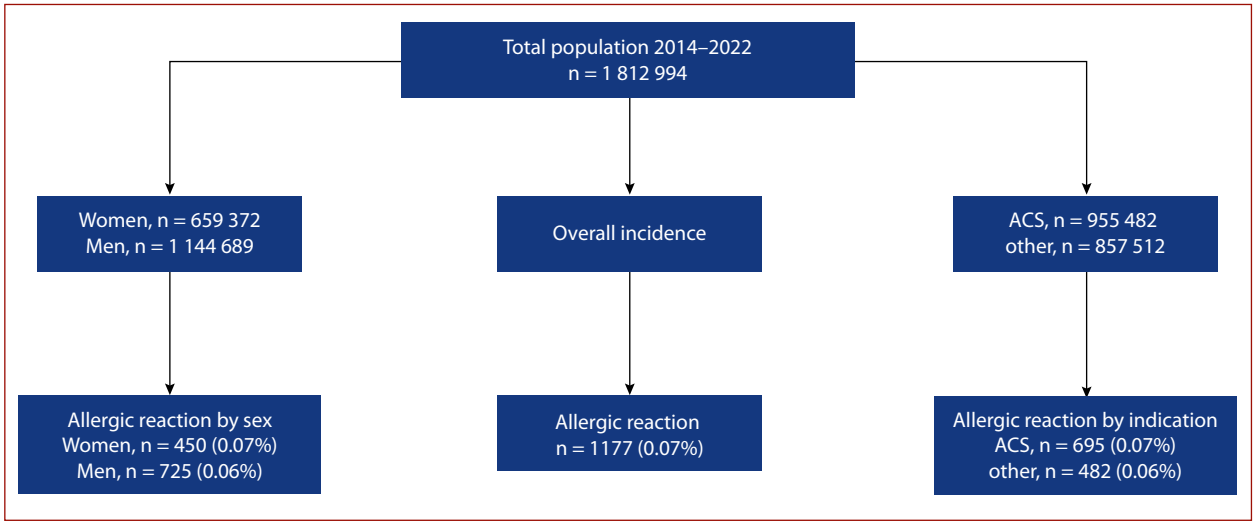


Figure 1. Incidence of allergic reactions in study population

Abbreviations: ACS, acute coronary syndrome

definitions. No further evaluation or follow-up of patients was performed. ORPKI is a national PCI registry in which all PCI patients from various hospitals are enrolled. The signed informed consent for PCI hospitalization contains consent for data transfer to the ORPKI registry. Since this is a mandatory and central national registry, ethics committee approval was waived. The study complied with the ethical principles of clinical research based on the Declaration of Helsinki, as amended. We had access to information that could identify individual participants during or after data collection, and this information was used only for long-term observation, which does not apply to the current study. No external funding was used to support this registry.

Clinical variables such as arterial hypertension, diabetes mellitus, chronic obstructive pulmonary disease, active smoking status, kidney disease, and history of stroke or myocardial infarction were defined as positive if confirmed by the patient during clinical history taking or based on documentation. Kidney disease was defined by a reduced estimated glomerular filtration rate of <60 ml/min/1.73 m^2. The use of unfractionated heparin (UFH), therapeutic doses of low-molecular-weight heparin (LMWH), glycoprotein IIb/IIIa inhibitor (GPI IIb/IIIa), and thrombolysis during angiography or PCI was determined by documentation. Cardiac arrest at baseline referred to cases where this event occurred before the procedures were performed. Using the Killip–Kimball classification, the severity of heart failure was determined (I — no clinical evidence of left ventricular failure, II — mild-to-moderate failure, III — severe failure, pulmonary edema, IV — cardiogenic shock) [15]. Variable "angiography" referred to cases in which only coronary angiography was performed, and variable "PCI" referred to all types of revascularization procedures. Variable "stent" indicated implantation of a specific type of stent (drug-eluting stent, bare metal stent, bioabsorbable stent). Variable "drug-eluting balloon" concerned the use of antimitotic drug-releasing balloons. Variable "chronic total occlusion" referred to procedures during which chronic total occlusion of at least one vessel was found. Variable "TIMI" (Thrombolysis in Myocardial Infarction) refers to perfusion in the culprit vessel: 0 — no perfusion, 1 — penetration without perfusion, 2 — partial perfusion, 3 — complete perfusion) [16].

Statistical analysis

In this study, nominal variables were represented as percentages along with their respective counts. The temporal variation in the proportion of allergic reactions was analyzed using the Cochran–Armitage test for trend. The logistic regression model was employed to identify the predictors of periprocedural allergic reactions. All potential demographic, baseline, and procedural characteristics were incorporated into a multivariable model if the *P*-value in a univariable model was less than 0.2 or if they were considered to have clinical significance. The final model was derived by minimizing the Akaike information criterion. The robustness of the model was validated using bootstrap resampling. To evaluate the presence of multicollinearity, variance inflation factors were analyzed. The results were expressed as odds ratios with 2-sided 95% confidence intervals. The entire statistical analysis was conducted using R software (version 4.3.1)

RESULTS

The study included 1 812 994 coronary and PCI procedures available in the ORPKI registry, of which 659 372 were for women and 1 144 689 for men (Figure 1). We found a declining incidence of allergic reactions overall, as well as in subgroups of men and women, between 2014 and 2022. The overall incidence of allergic reactions oscillated between 0.02% and 0.11% (p<0.001), and the most recent one, noted in 2022, was 0.02% (Table 1). When assessing the incidence of allergic reactions according to the indications for coronary/PCI, there was a decrease in the frequency of allergic reactions regardless of acute

Table 1. Incidence of allergic reaction in general and according to gender and indication

Variable	Year	2014, n (%)	2015, n (%)	2016, n (%)	2017, n (%)	2018, n (%)	2019 (n, %)	2020 (n, %)	2021 (n, %)	2022 (n, %)	Total	*P*-value
Total	Yes	221 0.10	244 0.11	231 0.10	200 0.09	148 0.07	34 0.02	30 0.02	31 0.02	38 0.02	1177	<0.001
	Total	227 971	224 642	230 324	226 484	210 836	199 230	150 924	166 096	176 487	1 812 994	
Gender	Year	2014	2015	2016	2017	2018	2019	2020	2021	2022	Total	
Women	Yes	93 0.11	93 0.11	84 0.1	68 0.08	54 0.07	15 0.02	13 0.02	12 0.02	18 0.03	450	<0.001
	Total	85 266	83 102	84 790	83 411	77 154	72 139	52 945	58 288	62 277	659 372	
Men	Yes	128 0.09	150 0.11	147 0.1	132 0.09	94 0.07	19 0.02	17 0.02	19 0.02	19 0.02	725	<0.001
	Total	142 625	140 763	142 566	142 989	132 817	125 935	97 176	107 060	112 758	1 144 689	
Indication	Year	2014	2015	2016	2017	2018	2019	2020	2021	2022	Total	
ACS	Yes	162 0.12	153 0.12	119 0.1	112 0.09	85 0.08	12 0.01	18 0.02	16 0.02	18 0.02	695	<0.001
	Total	135 410	129 203	124 830	120 862	105 443	97 686	78 689	81 909	81 450	955 482	
Other	Yes	59 0.06	91 0.1	112 0.11	88 0.08	63 0.06	22 0.02	12 0.02	15 0.02	20 0.02	482	<0.001
	Total	92 561	95 439	105 494	105 622	105 393	101 544	72 235	84 187	95 037	857 512	

Table 2. Incidence of allergic reaction according to age decades

Age, decades	Count	Row %	2014, n (%)	2015, n (%)	2016, n (%)	2017, n (%)	2018, n (%)	2019, n (%)	2020, n (%)	2021, n (%)	2022, n (%)	Total	*P*-value
10–19	Yes		0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0	NA
	Total		82	77	73	47	59	45	16	18	21	438	
20–29	Yes		0 0	0 0	1 0.33	0 0	0 0	0 0	0 0	0 0	0 0	1	0.28
	Total		348	326	304	309	287	233	175	232	201	2415	
30–39	Yes		2 0.1	1 0.05	1 0.05	2 0.1	3 0.15	0 0	0 0	0 0	0 0	9	0.047
	Total		1969	1996	2010	1967	1950	1911	1427	1520	1600	16350	
40–49	Yes		9 0.08	18 0.18	7 0.07	10 0.1	10 0.11	2 0.02	2 0.03	1 0.01	1 0.01	60	<0.001
	Total		10 661	10 242	10 491	10 063	9417	9231	7169	8067	8203	83 544	
50–59	Yes		52 0.11	65 0.15	43 0.11	40 0.1	21 0.06	4 0.01	3 0.01	2 0.01	10 0.04	240	<0.001
	Total		46 806	43 427	40 776	38 340	33 590	30 667	22 658	23 938	24 417	304 619	
60–69	Yes		81 0.1	72 0.09	84 0.1	76 0.09	49 0.06	13 0.02	10 0.02	15 0.03	15 0.02	415	<0.001
	Total		81 549	83 160	86 718	85 850	79 457	73 732	55 467	59 426	61 482	666 841	
70–79	Yes		51 0.09	49 0.08	66 0.11	40 0.07	39 0.07	9 0.02	12 0.03	8 0.02	7 0.01	281	<0.001
	Total		59 620	57 671	60 470	61 071	59 189	57 780	45 323	52 654	59 290	513068	
80–89	Yes		26 0.1	38 0.15	26 0.09	30 0.11	24 0.1	6 0.03	2 0.01	5 0.03	5 0.03	162	<0.001
	Total		25 388	26 117	27 478	27 007	24 980	23 646	17 220	18 719	19 450	210 005	
90–99	Yes		0 0	1 0.07	2 0.12	2 0.12	2 0.12	0 0	1 0.08	0 0	0 0	8	0.18
	Total		1363	1467	1661	1689	1667	1652	1273	1374	1477	13 623	
100–109	Yes		0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0	NA
	Total		27	18	32	28	22	19	19	26	18	209	
110–119	Yes		0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0	NA
	Total		5	4	9	10	3	7	6	10	8	62	

coronary syndromes (ACS) (Table 1). In the analysis of age subgroups by decades, a significant decrease in the incidence of allergic reactions was found in the age range of 30-90 years; in other groups, the number of recorded allergic reactions was very low, which influenced the lack of significance of the difference in years (Table 2). Among clinical and pharmacological factors, the risk of allergic reactions was increased by a history of myocardial infarction, a history of coronary artery by-pass grafting, a diagnosis of ST-segment elevation myocardial infarction (STEMI), a diagnosis of ACS, the use of IIb/IIIa glycoprotein inhibitor (GPI IIb/IIIa), low molecular weight heparin (LMWH), and earlier PCI. The risk of allergic reaction was reduced by active smoking, renal disease, chronic obstructive pulmonary disease, UFH, and performing coronary angiography only (Table 3).

Among perioperative factors, the use of drug-eluting balloons decreased the risk of allergic reaction, and the amount of contrast and radiation increased the risk of allergic reaction (Table 4). Based on multivariable regression analysis of selected variables, we found that independently the risk of allergic reaction was increased by LMWH (25-fold increase in risk), GPI IIb/IIIa (2-fold increase in risk), previous PCI (1.5-fold increase in risk), each 1000 mGy of radiation (29% increase in risk) and each 100 ml of contrast (20% increase in risk) and. Independently, the risk of allergic reaction was reduced by factors such as active smoking, diabetes (21% decrease in risk), and UFH (50% decrease in risk) (Figure 1). The distribution of the variables used in the regression analysis is shown in Supplementary material, *Table S1*.

Table 3. Clinical and periprocedural factors affecting incidence allergic reaction

Variables	Univariable	
	OR (95% CI)	*P*-value
Male sex	0.93 (0.83–1.04)	0.21
Age, years	1 (0.99–1)	0.24
Weight, kg	1 (1–1)	0.49
Diabetes	0.87 (0.75–1)	0.06
Previous stroke	1.14 (0.83–1.57)	0.42
Previous myocardial infarction	1.27 (1.12–1.44)	<0.001
Previous PCI	1.37 (1.22–1.55)	<0.001
Previous CABG	0.89 (0.68–1.16)	0.37
Smoking status (active)	0.8 (0.68–0.94)	0.01
Arterial hypertension	0.96 (0.85–1.09)	0.56
Kidney disease	0.68 (0.5–0.92)	0.01
COPD	0.46 (0.27–0.78)	0.003
ACS (yes/no)	1.29 (1.15–1.45)	<0.001
UFH during angiogram	0.67 (0.52–0.87)	0.003
LMWH during angiogram	0.53 (0.2–1.41)	0.21
Cardiac arrest at baseline	1.24 (0.62–2.48)	0.55
Direct transport to cathlab	0.64 (0.41–0.99)	0.045
UFH	0.34 (0.3–0.39)	<0.001
LMWH	49.18 (43.85–55.15)	<0.001
GPI IIb/IIIa	4.46 (3.79–5.24)	<0.001
Killip IV vs. Killip I	1.09 (0.57–2.11)	0.79
Thrombolysis during angiogram	11.67 (1.63–83.46)	0.01
Angiography	0.33 (0.29–0.37)	<0.001
PCI	2.74 (2.4–3.12)	<0.001
CTO	0.94 (0.7–1.25)	0.67
Bifurcation lesion	1.18 (0.96–1.45)	0.12
DES	1.18 (0.97–1.44)	0.11
BVS	1.25 (0.56–2.8)	0.58
BMS	0.73 (0.44–1.19)	0.21
Implanted stent (any)	1.15 (0.92–1.42)	0.22
DEB	0.43 (0.2–0.9)	0.03
TIMI 0-1 PRE	0.93 (0.8–1.07)	0.31
TIMI 3 POST	0.89 (0.68–1.16)	0.38
Contrast per 100 ml	1.53 (1.46–1.6)	<0.001
Radiation per 1000 mGy	1.5 (1.46–1.55)	<0.001

Abbreviations: ACS, acute coronary syndrome; BMS, bare metal stent; BVS, bioresorbable vascular scaffold; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CTO, chronic total occlusion; DEB, drug-eluting balloon; DES, drug-eluting stent; GPI IIb/IIIa, IIb/IIIa glycoprotein inhibitor; LMWH, low molecular weight heparin; PCI, percutaneous coronary intervention; UFH, unfractionated heparin; TIMI, thrombolysis in myocardial infarction

DISCUSSION

Our study showed a declining incidence of allergic reactions during invasive ACS treatment. The incidence of allergic reactions was 0.02% during the 176 487 coronary angiography and PCI procedures performed in 2022. This study did not include a breakdown of the etiology of these reactions, therefore, the reported frequency refers to reactions to contrast agents and drugs together. Our multivariable logistic regression analysis showed that GPI IIb/IIIa, LMWH, previous PCI, contrast dose, and x-ray dose were independent predictors of allergic reaction occurrence. According to recent data, the incidence of immediate allergic reactions to non-ionic iodine contrast agents is 0.02%–1%, and late reactions are 1%–3% [17–19]. In patients with a history of radiocontrast allergy, the risk of recurrence is 16%–35% [20]. Contrast reactions in most cases (29%) are rash-like skin reactions, while anaphylaxis occurs in about 8.6% of patients [21]. Confirmed methods for managing patients with a history of allergic reactions to contrast are to routinely check for a history of such reactions, use skin tests, avoid triggers, and premedicate [22]. Recommended protocols for managing patients with a history of allergic reaction to contrast help prevent complications in predisposed individuals [23].

Dery et al. [24], in a study involving 1342 patients, showed that re-administration of abciximab was associated with a very low incidence of allergic reaction (5 patients) and did not require interruption of the drug infusion. In contrast, Masood et al. [23], in a study involving 37 patients receiving eptifibatide, reported allergic reactions in 3 patients (10.75%). These reactions can be characterized as anaphylaxis and require urgent interventions [26, 27]. The incidence of allergic reactions during the use of tirofiban is very rare, but anaphylactic reactions and rash can occur even during the first exposure (similar to apixaban) [28].

In our study, the strongest predictor of allergic reaction was the use of LMWH. In the available literature, cutaneous allergic reactions as adverse reactions to this group of drugs occur with a frequency of 7.5% to 39.5% [29–31].

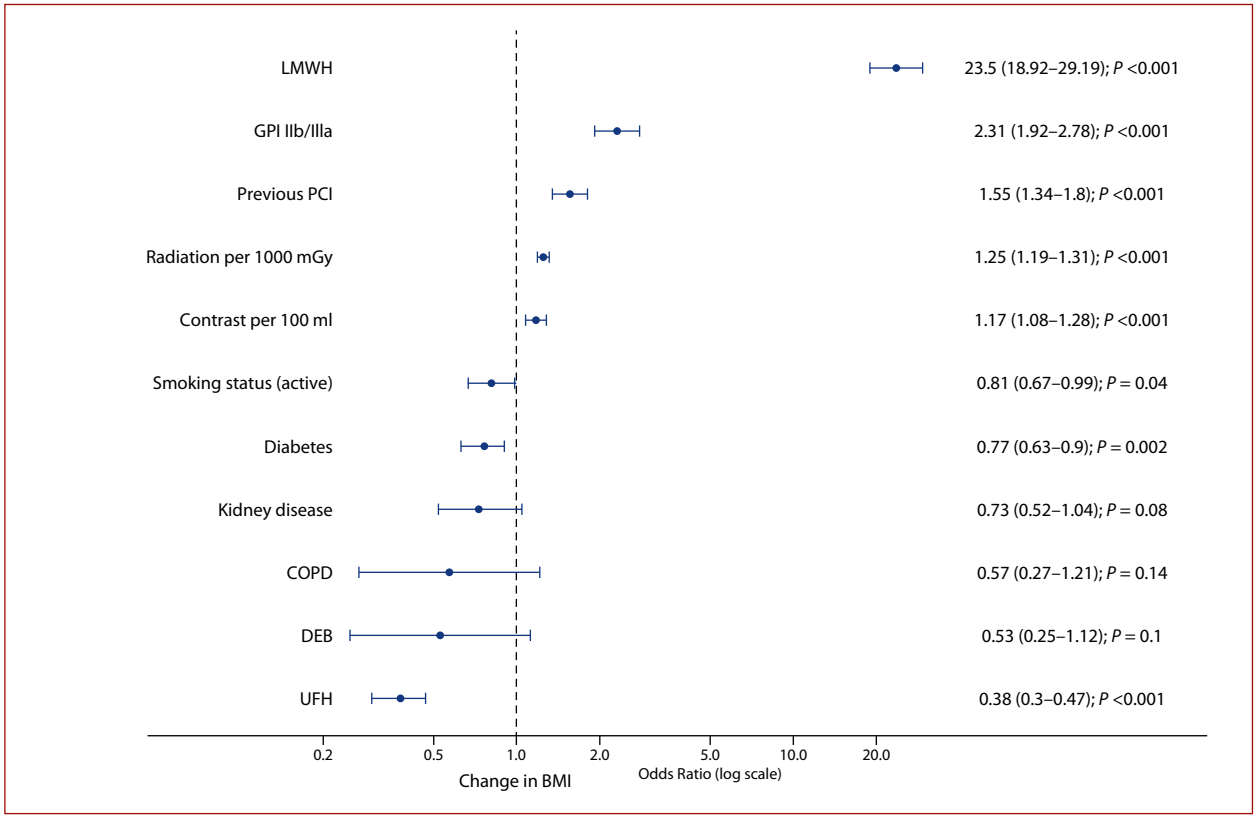


Figure 2. Independent predictors of allergic reactions during procedure adjusted to consecutive years

Abbreviations: COPD, chronic obstructive pulmonary disease; DEB, drug-eluting balloon; GPI IIb/IIIa, IIb/IIIa glycoprotein inhibitor; LMWH, low molecular weight heparin; UFH, unfractionated heparin

These reactions are most often delayed-type hypersensitivity reactions [30, 32] but can also appear immediately [33]. In addition, clinically, these reactions can manifest as pustulosis, urticaria, bullous eruptions, necrosis, and heparin-induced thrombocytopenia [34]. Of all LMWHs, nadroparin has the highest risk of late cutaneous reactions [35]. The association of the occurrence of allergic reaction with LMWH use may be due to the subcutaneous route of administration of the drug. So far, it has been established that the heparin molecule itself is not immunogenic, while it may be a hapten that gains immunogenicity when combined with previously unrecognized proteins after intradermal or subcutaneous administration [36].

Radiation does not cause allergic reactions but leads to direct damage to the skin [37]. Skin lesions can appear immediately after exposure and pathophysiologically are usually dermatitis with a rash or blistering eruptions [38]. An earlier study [9] and our results confirmed the effect of rentgen radiation on the occurrence of allergic reactions; however, the mechanism of this phenomenon has not been clarified. A possible reason is the dependence of the radiation dose on the duration of the procedure and, thus, the increased likelihood of revascularization with the drugs used during the procedure. Although Killip–Kimball class IV did not affect the onset of allergic reaction, it remains one of the strongest predictors of poor short- and long-term prognosis [39]. As Cazzola et al. [40] pointed out, the presence of a history of bronchial asthma may affect cardiovascular mortality; however, the registry presented here does not provide information on the prevalence of this disease or other allergic diseases in those undergoing coronary angiography and PCI. Currently, patients undergoing interventional cardiology procedures with a history of allergic reactions receive prophylactic antihistamines and corticosteroids, which significantly reduce the risk of recurrence of such reactions [41]. The above procedure, as well as the widespread use of low osmolality contrast agents, has significantly reduced the incidence of allergic reactions during contrast procedures [42]. If, despite adequate prophylaxis, a severe anaphylactic allergic reaction leading to shock develops, it is advisable to administer epinephrine by the intramuscular or even intravenous route in patients with severe hypotension [43].

Each predictor directly or indirectly influences the occurrence of allergic reactions. The results of this study can be used in direct clinical practice when performing invasive cardiac procedures. However, the study has some limitations. This is a multi-center national registry. Observation for allergic reaction included the duration of the patient's stay in the hemodynamics laboratory. The registry does not provide accurate information on the symptoms of an allergic reaction, type of allergic reaction, severity of the course, number of deaths due to an allergic reaction

or treatment of allergic reactions, as well as the type of LMWH or GPI IIb/IIIa that were used during the treatments.

CONCLUSIONS

The overall incidence of acute allergic reactions in the cath lab is low and decreased significantly between 2014 and 2022. The decrease in frequency did not depend on age or sex. Independent strong predictors of allergic reaction were the use of GPI IIb/IIIa, LMWH, high dose of contrast agent, and radiation. To reduce the risk of allergic reaction, one should consider avoiding these treatments if possible and minimizing contrast and radiation doses.

Supplementary material

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

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Rationale, objectives, and design of the HEart failuRe ObsErvational Study of the Polish Cardiac Society (HEROES)

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INTRODUCTION

Heart failure (HF) has become one of the most important contemporary medical challenges. A report from the Polish Cardiac Society states that 1.2 million people in Poland have HF, characterized by a 40% 5-year mortality rate, annual treatment costs of PLN 1.7 billion, and a total expenditure of PLN 6.2 billion on direct costs [1].

There is a lack of up-to-date data on risk factors, clinical symptoms, pharmacotherapy, use of devices, as well as the clinical indicators of re-exacerbations and prognosis [2]. Therefore, through the Scientific Platform of the Polish Cardiac Society, we conducted an observational study, the HEart failuRe ObsErvational Study of the Polish Cardiac Society (HEROES).

The main objective of the HEROES was to obtain comprehensive and contemporary clinical data in a representative population of Polish HF patients in both outpatient and hospital settings in cardiology and internal medicine departments. One of the most important aims of the study was to describe current treatment, including adherence to the latest European and Polish HF guidelines [3]. Moreover, the European HF Registry [4] has introduced novel methods of treatment. The HEROES database allowed not only the examination of the impact of those novel methods on prognosis but also exploration of current topics in modern HF management (i.e., frailty).

METHODS

This was a prospective, multi-center, observational study, which was designed to describe the clinical status of HF patients in a representative national sample. The study design and selection of centers were based on the Long-term Registry on Patients with Heart Failure endorsed by the European Society of Cardiology and overseen by 25 national societies of cardiology, including the Polish Cardiac Society [4–6]. The acquired data were the basis for more than 30 publications [7–15].

The Bioethical Committee at the Medical University of Lodz approved the HEart failuRe ObsErvational Study of the Polish Cardiac Society (No.RNN/316/20/KE with the amendment KE/762/23). The study received funding from the Polish Cardiac Society (contract No.CRU0120-KCKB-2023).

Scientific Committee

The Scientific Committee included the authors of this article. The current President of the Polish Cardiac Society and the National Consultant for Cardiology were added to the team.

Centers

The centers applying for the HEROES were analyzed in terms of geographical representation and their equipment in accordance with the principles developed by the EURObservational Research Program of the European Society of Cardiology:

1. representation of all areas of Poland;
2. representation of centers with varizus levels of specialist facilities:
   — 25% of centers with on-site cardiac surgery,
   — 25% of centers with a hemodynamics laboratory but without cardiac surgery,
   — 50% of centers without hemodynamics or cardiac surgery;
3. consent from the center to share unmodified, full profile of clinical data.

Forty-one centers were approved for the HEROES, including 32% with on-site cardiac surgery, 22% with a cath-lab but without cardiac surgery, and 46% without a cath-lab or cardiac surgery.

Data collection

To facilitate consecutive enrollment, patients were enrolled in the registry on a one-day-per-week basis. The detailed inclusion and exclusion criteria and the objectives of the data collection are presented in Supplementary material, *Appendix 2*.

Clinical data sheet

The electronic case report form (eCRF) was developed by the Scientific Committee. The eCRF was supplemented by the investigator's brochure, which contained descriptions of procedures and definitions necessary to properly conduct the study and complete the form. Patient data handling remained compliant with applicable regulations on the protection of data and sensitive data (including the GDPR).

The eCRF was used to collect complete and qualitatively valuable clinical data. Its scope depended only on the availability of routine diagnostic and therapeutic tests. None of the elements of eCRF required any examina-

tion or treatment other than those related to the individual decision of the attending physician based on the current clinical situation. Each diagnostic or therapeutic item in the eCRF contained the option of stating "Not performed". The most important clinical variables collected in the eCRF are presented in Supplementary material, *Appendix 3*.

Signed written informed consent was obtained from all participants. In the case of hospitalized patients, the range of the data was supplemented on discharge. The analysis of the current condition of the patients could be carried out based on data from ambulatory or hospital records.

Follow-up

Data on overall mortality during the follow-up, provided in accordance with the GDPR, were sourced from the Polish Ministry of Digital Affairs and included only the exact date of death from all causes. The document was dated May 21, 2024, which was established as the fixed "end-of-follow-up date" for the HEROES database. There were no follow-up visits planned according to the protocol, and no other endpoints than all-cause death were estimated.

Statistical analysis and data publications

All data reported by the centers underwent professional statistical analysis. The published results of the analyzes will not apply to any center or their subgroup other than those of equipment facilities in accordance with the description listed above in the subsection "Centers". Clinical data will be the only criteria used to subgroup patients.

No individual data of specific patients and selected data of a specific center will be made available to any party other than the strict group of informatics specialists responsible proper functioning of the eCRF and the principal investigator in a given center.

The planned statistical analysis of gathered data will include methods of descriptive statistics. Categorical variables will be presented as numbers and corresponding percentages, while quantitative variables as means (with standard deviations) or medians (with interquartile ranges) depending on data distribution. For comparisons of subgroups, tests of independence and risk factors identification methods of regression (linear/logistic; uni-/multivariate) will be used. Further statistical methods (i.e., survival analysis) will be performed depending on the particular sub-analysis and will be precisely described in each manuscript.

Completion and first results of the study

Based on the HEROES database and further sub-analysis, over 30 publications are planned, including: on population characteristics, quality of life, frailty, HF with supranormal ejection fraction, patients with HF and cancer, antithrombotic treatment in HF, atrial fibrillation, and other conditions.

The project was launched on April 2, 2022, and patient recruitment was completed on March 27, 2024, which allowed obtaining clinical and survival data on all 1422 patients (no patients lost to follow-up). During the mean follow-up of 16 months (median: 485 days, interquartile range: 397–599 days), 246 patients died (17.3%). The annual mortality rate was 12.9%.

Supplementary material

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

Article information

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Study URL: https://heroes.umed.pl

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Transesophageal echocardiography in corroborating aortic stenosis severity in patients with low-gradient aortic stenosis with preserved ejection fraction

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INTRODUCTION

In approximately 50% of cases, severe aortic stenosis (AS) is classified as low-gradient (LGAS), and in 35% of patients, it is low-flow (LF) LGAS [1].

The aim of this study was to determine the usefulness of two-dimensional transoesophageal echocardiography (2D-TOE) in assessing aortic valve area by planimetry (AVAPlaniTOE) in patients with severe LGAS with preserved ejection fraction (LGAS pEF) diagnosed by 2D transthoracic echocardiography (2D-TTE).

METHODS

Patient population

From a database of patients treated at the National Institute of Cardiology in Warsaw between 2013 and 2022, a group of 102 patients with symptomatic severe LGAS with pEF were selected, who also had 2D-TOE. Clinical data were retrieved from patient records. The study group included patients with normal sinus rhythm and permanent atrial fibrillation (AFib) (n = 26), as well as with normal-flow and LF (n = 35).

Echocardiography

2D-TTE examinations were performed according to current guidelines [1–3] using the Vivid E95™ device with an M5SC-D probe (GE HealthCare; Vingmed Ultrasound, Horten, Norway). Right ventricular systolic pressure, stroke volume (SV), aortic valve area (AVA) and doppler velocity index were calculated using standard methods [1]. AVA and SV were indexed to body surface area. Energy loss coefficient (ELCo) was calculated using the formula:

$$ELCo = \frac{AVA \times AoA}{AVA - AoA}$$

where AoA = cross-sectional area of the ascending aorta at the sinotubular (STJ) level.

Energy loss index (ELI) was calculated by the following formula (indexed for body surface area):

$$ELI = \frac{(AVA \times AoA)/AoA - AVA}{BSA}$$

2D-TOE examinations were performed according to current guidelines [4] also using the same device. A 6VT-D probe was used. AVAPlaniTOE was measured in the transverse short-axis plane of aortic valve, in the mid-systole, in zoom mode, by manually tracing the anatomical orifice area at the blood-cusp interface (Supplementary material, *Figure S1*). At least 5 measurements were made (for cases with permanent AFib and significant calcifications, up to 10 measurements were performed).

Echocardiographic measurements were made using EchoPAC software (v. 204; GE HealthCare; Vingmed Ultrasound, Horten, Norway). In 2D-TTE severe LGAS was diagnosed based on AVA ≤1.0 cm^2 and mean aortic gradient (mAG) <40 mm Hg. LF was

diagnosed when indexed stroke volume (SVi) was <35 ml/m^2. In 2D-TOE true-severe LGAS was diagnosed based on AVAPlaniTOE ≤1.0 cm^2.

The comparison between pseudo-severe and true-severe AS subgroups based on AVAPlaniTOE, as well as between four groups categorized by 2D-TOE and SVi values, was performed. A sub-analysis of the normal-flow and LF groups, as well as those with permanent AFib and normal sinus rhythm, was also conducted.

The study protocol was approved by the Regional Bioethics Committee at the National Institute of Cardiology in Warsaw.

Statistical analysis

Normality of numerical variables was tested using the Shapiro–Wilk test. Data were presented as mean (SD) for normally distributed variables or as median and quartiles for non-normal data. Where relevant, the standard error of the mean (SE) was also reported to provide an estimate of the variability of the sample mean. Differences between groups were tested using Student's t-test, Mann–Whitney test, or analysis of variance with Tukey–Kramer or Dwass–Steel–Critchlow–Fligner tests for multiple comparisons. Categorical variables were analyzed using the χ^2 or Fisher exact test. Pearson's correlation coefficient was used to assess linear correlations. A two-sided *P*-value <0.05 was considered significant. All analyses were conducted using SAS software, version 9.4 (SAS Institute, Cary, NC, US).

Intra- and inter-observer variability and method agreement

Intra- and inter-observer variability for AVAPlaniTOE assessment were evaluated in 20 randomly selected patients using the Intraclass Correlation Coefficient (ICC [2,1]) with a two-way random effects model. Variability was assessed with 95% confidence intervals (CI). The agreement between AVA by continuity equation and AVAPlaniTOE was analyzed using Bland–Altman plots. All analyses were conducted using MedCalc software (version 19.4.1, MedCalc Software Ltd, Ostend, Belgium).

RESULTS AND DISCUSSION

The baseline demographic and clinical characteristics of the patients and echocardiographic characteristics of the group are shown in Supplementary material, *Table S1* and *S2*.

In 57 (55.9%) patients, AVA by continuity equation in 2D-TTE was lower than AVAPlaniTOE; in 22 (21.6%) it was larger, and in 23 (22.5%) it was equal (data not shown), with 2D-TTE generally overestimating AVA by a mean of –0.07 (0.02) (SE) cm^2 compared to AVAPlaniTOE (Supplementary material *Figure S2A* and *S2B*). Based on these findings, 16 (15.7%) patients were reclassified as having pseudo-severe AS (AVAPlaniTOE >1.0 cm^2).

Baseline demographic and clinical characteristics (Supplementary material, *Table S3*) did not show differences across the groups. However, several echocardiographic variables exhibited significant variation among them (Supplementary material, *Table S4*).

In patients with LF and permanent AFib, there was no difference in mean AVAPlaniTOE (*P* = 0.18 and *P* = 0.70, respectively).

The ICC for inter-observer reliability was 0.934 (95% CI, 0.844–0.973) for AVAPlaniTOE, indicating substantial agreement between observers. The mean intra-observer reliability was also substantial at 0.942 (95% CI, 0.889–0.976).

To the best of our knowledge, no study has specifically addressed the evaluation of AVA by planimetry in 2D-TOE in patients with severe LGAS pEF based on 2D-TTE.

We believe that the planimetric assessment of AVA in 2D-TOE can complement the integrated staging algorithm for determining AS severity proposed by Baumgartner et al. [1], and it can be implemented in the so-called LG AS "difficult track". Stoddard et al. [5] demonstrated that planimetric measurement of AVA in 2D-TOE is an effective method for determining the severity of AS, similar to the findings of Kim et al. [6].

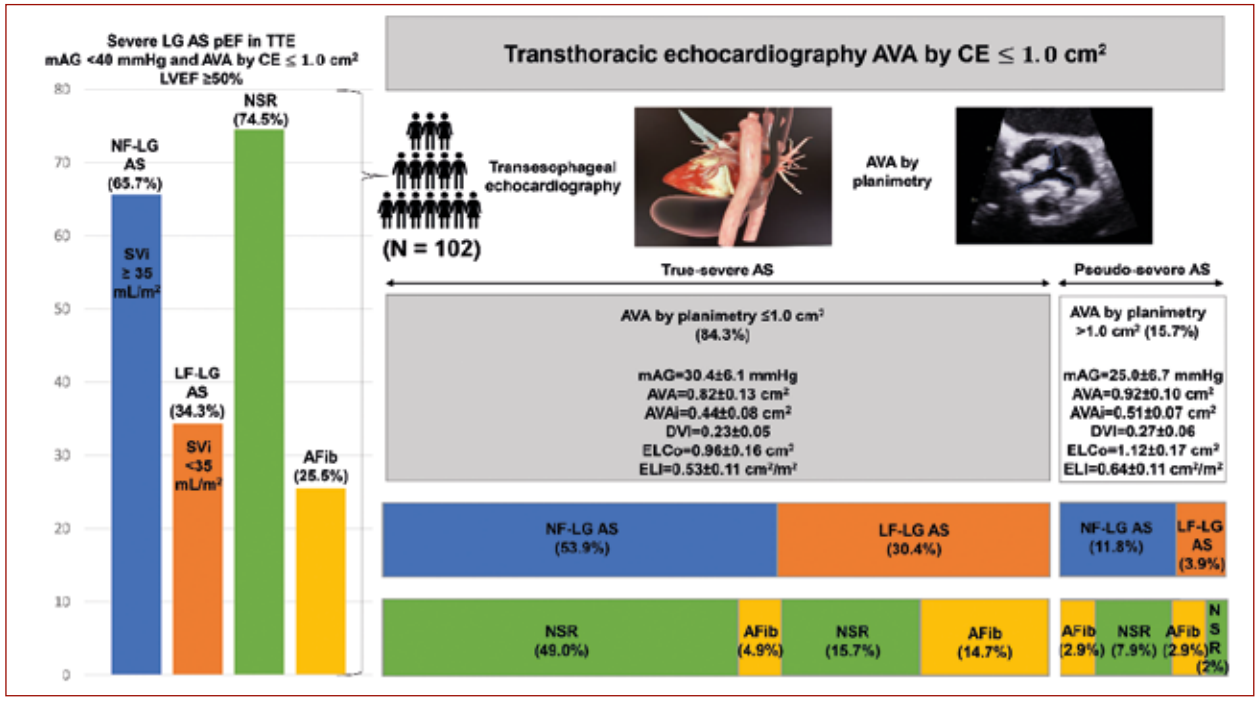
Although our study demonstrated 100% feasibility of 2D-TOE for determining AVA by planimetry, this may be an overestimation. However, LGAS patients typically have lower aortic valve calcium score [1], which facilitates AVAplaniTOE measurements. Due to the fact that only 52.9% of the study patients underwent cardiac computed tomography, including just 3 patients reclassified into the pseudo-severe AS group, a comparative analysis between the groups was not performed.

The correctness of our AVAPlaniTOE measurements and the exact diagnosis are supported by the higher mAG in the group with true-severe AS (30.4 [6.1] vs. 25.0 [6.7] mm Hg; *P* = 0.002), as well as the lower AVA (0.82 [0.13] vs. 0.92 [0.10] cm^2; *P* = 0.006). According to Baumgartner et al. [1], mAG ≥30 mm Hg and AVA by continuity equation ≤0.8 cm^2 increase the likelihood of severe AS in patients with LGAS pEF. Additionally, the significantly reduced doppler velocity index value, supports the accuracy of our AVAPlaniTOE assessment.

As 68.6% of patients in the study group had an STJ diameter of less than 3.0 cm, we calculated the ELI [1, 7], and a value of 0.53 (0.11) cm^2/m^2 [8, 9] confirmed the accuracy of AS severity assessment by planimetry in 2D-TOE. Additionally, we calculated the ELCo [10], with a value of 0.96 (0.18) (*P* <0.001), which further supports our findings.

No significant difference was observed in AVAPlaniTOE assessment for patients with LF (34.3%; Supplementary material, *Table S5* and *S6*) or for those with permanent AFib (25.5%; Supplementary material, *Table S7* and *S8*), further supporting the usefulness of 2D-TOE.

Finally, the comparison of the four groups with different AVAPlaniTOE and SVi values suggests that patients with smaller AVA and reduced SVi, particularly those in the group with AVAPlaniTOE ≤1.0 cm^2 and SVi <35 ml/m^2, exhibit worse ventricular function, smaller LVOT and aor-



Graphical abstract.

Abbreviations: AFib, atrial fibrillation; AS, aortic stenosis; AVA, aortic valve area; AVAi, aortic valve area index; DVI, doppler velocity index; ELCo, energy loss coefficient; ELI, energy loss index; LG, low-gradient; mAG, mean aortic gradient; NSR, normal sinus rhythm; pEF, preserved ejection fraction; TTE, transthoracic echocardiography

tic annulus diameters, and greater energy loss across the aortic valve. In interpreting the results, it is important to note that group 2 (n = 9; with AVAPlaniTOE >1.0 cm^2 and SVi <35 ml/m^2) had a smaller sample size, which may affect the robustness of the comparisons.

Limitations

This was a retrospective, single-center study conducted on a small, heterogeneous patient population. Only 52.9% of patients underwent cardiac computed tomography, limiting our ability to correlate aortic valve calcium scores with AVAPlaniTOE, preventing the establishment of a clear relationship between valvular calcification and planimetric measurements.

Conclusions and clinical implications

Patients with LGAS pEF and a planimetric AVA ≤1.0 cm^2, as assessed by 2D-TOE, exhibit stenosis severity parameters in 2D-TTE that meet the criteria for severe AS. 2D-TOE offers a reliable approach for AVA assessment by planimetry, even in patients with LF, permanent AFib, or reduced STJ diameter.

Supplementary material

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

Article information

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Heart failure epidemiology and outcomes in Poland from 2010 to 2021: A marked decline in HF hospitalization rate during the COVID-19 pandemic

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INTRODUCTION

The COVID-19 pandemic affected healthcare performance. This nationwide study evaluated trends in heart failure (HF) epidemiology and patient outcomes during the first 2 years of the COVID-19 pandemic in Poland.

METHODS

This retrospective study included all adult HF patients treated from January 1, 2010, to December 31, 2021, in the public healthcare sector in Poland. Data were based on the Nationwide Polish Ministry of Health Registry. This cross-sectional investigation included all patients with inpatient or outpatient diagnosis of HF. Co-morbid conditions were identified based on ICD-10 diagnoses and incorporated into the Charlson Comorbidity Index (CCI). Data on unplanned hospital admissions were collected. The investigation conformed to the principles outlined in the Declaration of Helsinki. The Regional Ethical Review Board approved the study.

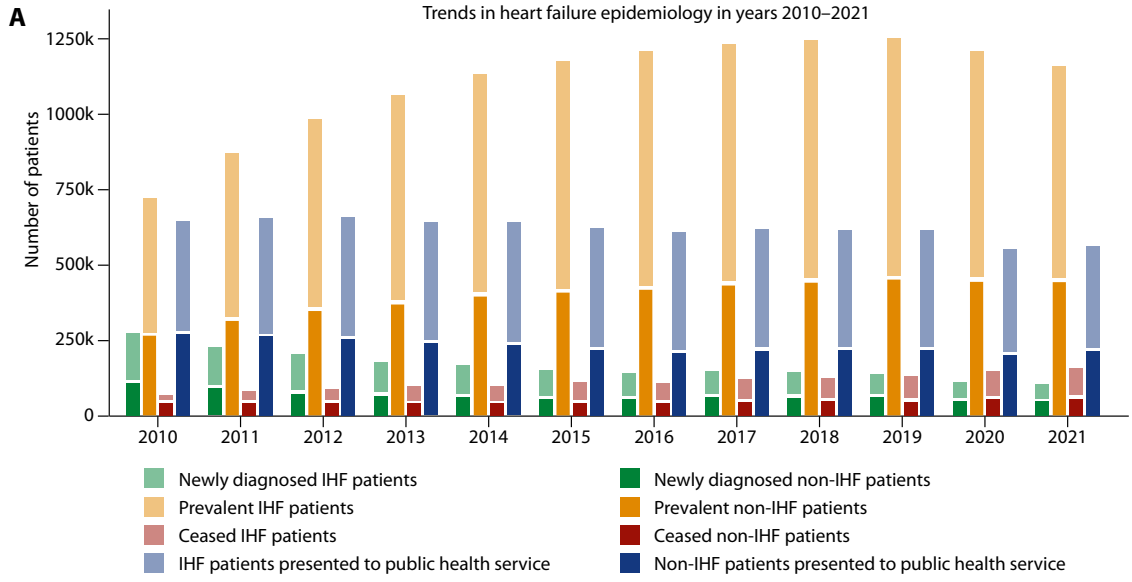
Data were presented as mean values or percentages. The study did not use a random sample. All patients using the public healthcare sector in Poland participated in the study. Therefore, statistical significance cannot be verified. All analyses and plots were performed using free-license R.

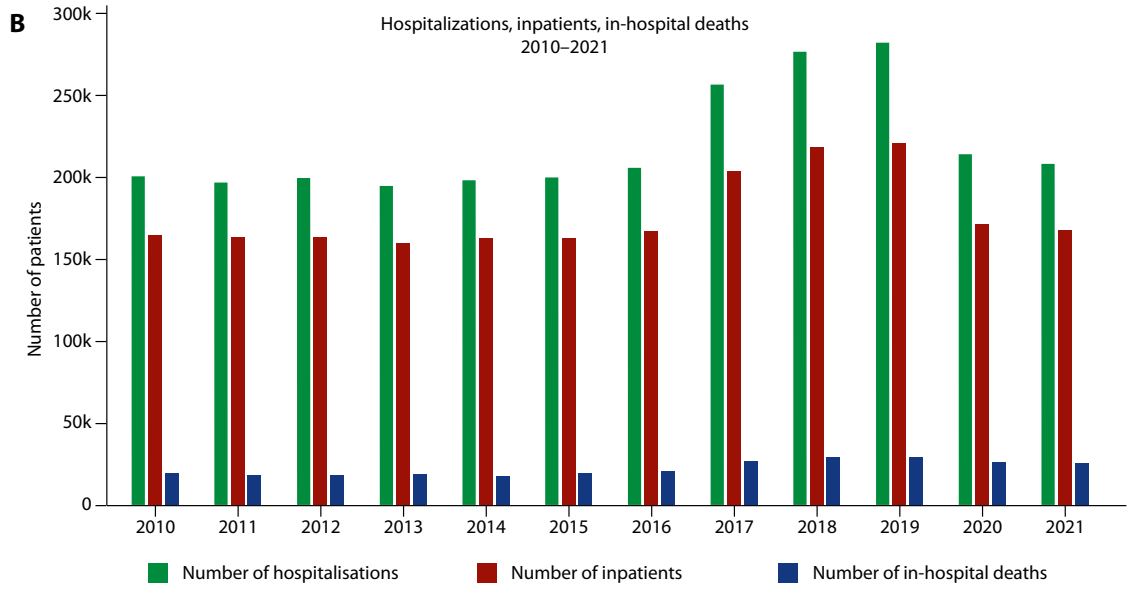
RESULTS AND DISCUSSION

Heart failure epidemiology

Heart failure incidence declined from 0.39% in 2019 to 0.2% in 2020 and 0.3% in 2021 (Supplementary material, *Table S1*). This reflects an absolute decline in new HF cases of 18% and 22% in 2020 and 2021, respectively (Figure 1A; Supplementary material, *Table S2*). Given the average yearly drop of 7% in the last decade, this was the greatest decline (Figure 1A; Supplementary material, *Table S2*). The change was mainly driven by a decline in the number of patients with ischemic HF (Figure 1A; Supplementary material, *Table S2*). As a result, 2020 was the first year over a decade when ischemic etiology accounted for the minority of incident HF (Figure 1A; Supplementary material, *Table S2*). The CCI score of incident patients has slightly increased from 1.23 to 1.25 (Supplementary material, *Table S1*).

The prevalence decreased from 3.63% in 2019 to 3.59% in 2020 and 3.48% in 2021 (Supplementary material, *Table S1*). It was the first decline in the last decade (Figure 1A; Supplementary material, *Table S2*). This reflected a drop of 7.6% in the total number of HF patients by the end of 2021 (Figure 1A; Supplementary material, *Table S2*). Ischemic HF prevalence decreased from 2.26% to 2.11%





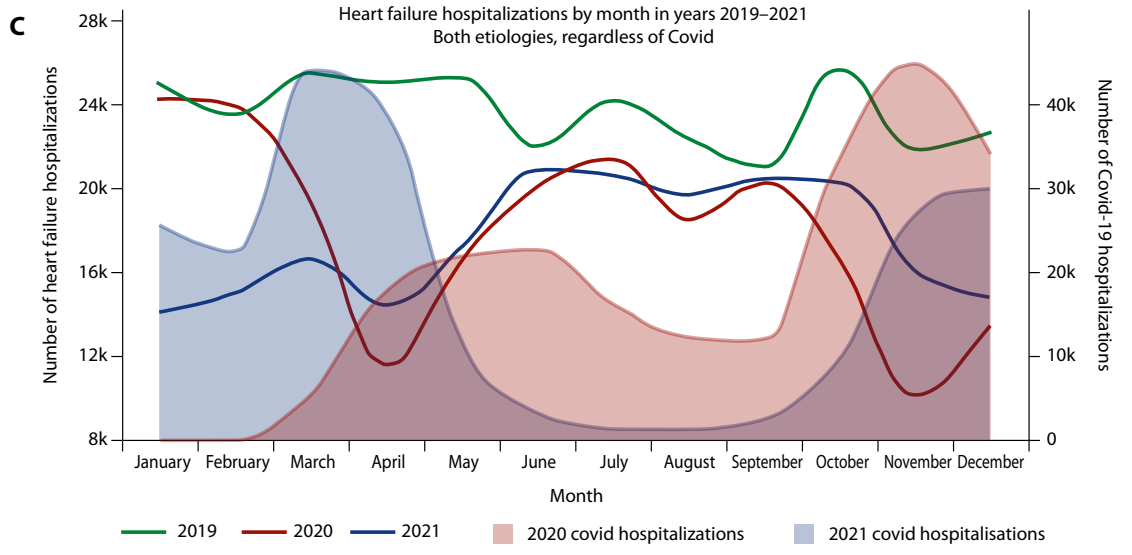


Figure 1. A. Trends in heart failure epidemiology in the years 2010–2021. **B.** Hospital admissions and inpatient deaths in the years 2010–2021. **C.** Heart failure hospital admissions by month in the years 2019–2021

Abbreviations: IHF, ischemic heart failure

in 2021, and non-ischemic HF remained steady (Supplementary material, *Table S2*).

Mortality increased from 9.92% in 2019 to 11.54% in 2020 and 12.47% in 2021 (Supplementary material, *Table S1*). In comparison to 2019, an excess of 20 088 (14.5%) and 27 087 (19.5%) HF patient deaths was recorded in 2020 and 2021, respectively. It was the first time over the last decade that the number of deaths exceeded the number of newly diagnosed HF cases (Figure 1A; Supplementary material, *Table S2*). Total mortality among ischemic HF patients increased from 9.13% to 12.18% in 2021 and from 11.26% to 12.93% among non-ischemic HF patients (Supplementary material, *Table S2*). Regardless of etiology, mortality increased remarkably among patients with CCI >5 points (Supplementary material, *Table S1*).

Patient presentation and outcomes

The number of HF patients who presented at least once to the public healthcare system in Poland dropped by 10.97% in 2020 and 9.16% in 2021 compared to 2019 (Figure 1A; Supplementary material, *Table S2*). The number of patients with ischemic HF dropped by 12.2% in 2020 and 13.3% in 2021, and by 8.8% and 2% for non-ischemic HF (Figure 1A). This decline was mainly driven by the reduction in hospital admissions (Figure 1B). There were 24% and 26% fewer hospital admissions in 2020 and 2021 (Figure 1B; Supplementary material, *Table S3*). Admissions to cardiac units declined by 19% and 9%, respectively (Supplementary material, *Table S4*), while admissions to non-cardiac departments plummeted by 23% and 31%. (Supplementary material, *Table S4*). The number of outpatient visits dropped only by 11% in 2020 and 5% in 2021, with significant recovery in cardiac secondary care (Supplementary material, *Table S4*). Every month, the number of admissions reflected pandemic fluctuation (Figure 1C; Supplementary material, *Table S3)*.

The number of patients hospitalized at least once dropped from 17.63% (222 426) to just above 14% (172 960 and 169 153) in 2020 and 2021 (Figure 1B; Supplementary material, *Table S5*). Patients hospitalized during the pandemic years were slightly younger and more often resided in nonurban areas compared to 2019 (Supplementary material, *Table S5*). There was a greater drop in the number of ischemic HF patients being hospitalized in 2019 (27% vs. 18% for non-ischemic). The comorbidity burden (CCI) of hospitalized patients increased from 1.33 to 1.37 in 2021 (Supplementary material, *Table S5*). The mean length of hospital stay was comparable.

In-hospital mortality rose and reached 16% in 2020 and 15.72% in 2021 compared to 14.07% in 2019 (Supplementary material, *Table S5*). Monthly, the percentage of hospital stays that ended with death varied in parallel with COVID-19 waves (Supplementary material, *Figure S1* and *Table S3*). Additionally, the rate of hospital admissions ending with death within the day from admission increased to 1.11% in 2020 compared to 0.93% in 2019 and improved to 0.97% in 2021 (Supplementary material, *Table S3*). In-hospital mortality of ischemic HF patients increased from 11.69% in 2019 to 13.8% in 2021, while non-ischemic patients experienced only a transient rise in 2020 (Supplementary material, *Table S5*).

This nationwide study displays challenges met by the Polish healthcare system over the years 2010–2021. By the end of 2019, there was a gradual uptrend in HF prevalence accompanied by a downtrend in incidence and leveled-off mortality. During the first 2 years of COVID-19, significant shifts in epidemiology occurred. HF incidence and prevalence decreased for the first time in the decade. This was accompanied by a remarkable reduction in HF hospital admissions and an incremental increase in total and in-hospital mortality, with ischemic HF patients being mostly affected.

Yearly reduction in the total number of hospital admissions exceeded 20%. The drop in non-cardiac unit admissions was markedly greater compared to cardiac units. Worldwide declines in HF hospital admissions followed by decreased incidence were reported [1]. The outpatient visits were less affected, which could be the result of high use of tele-visits in Poland [2].

Total and in-hospital mortality in Poland was on the rise in the first 2 years of the COVID-19 pandemic. Limited access to healthcare services and patients' reluctance to seek help could have contributed. During the COVID-19 pandemic, as many as 28% of Polish residents admitted having unmet needs for medical examination or treatment [3]. Access to the most effective treatment became available late into the pandemic [4]. Kubica et al. [5] reported a significant reduction in self-referrals and an increased number of acute HF patients brought by ambulance. Finally, quick protective measures such as lockdowns could limit virus spread in Poland but, on the other hand, could prevent people from seeking help.

The ischemic HF subpopulation experienced a profound decline in incidence and prevalence along with a mortality increase compared to barely changed epidemiology of non-ischemic HF.

Limited data refer to differences in outcomes between HF etiology during the COVID-19 pandemic. A significant drop in percutaneous coronary interventions could contribute to unfavorable outcomes in ischemic HF patients. According to Drożdż et al. [6], in Lodz Voivodship, by the end of 2020, the number of percutaneous coronary interventions dropped below 85% in 2019. Secondly, it can be assumed that ischemic patients were reluctant to seek help or could not receive it early, as Hawranek et al. [7] reported a decrease in the number of cases of myocardial infarction along with the rise in cases of cardiac arrest before admission. Finally, patients with acute coronary syndromes presented in pandemics, similar to HF patients analyzed in this study, had a greater comorbidity burden [8].

This study has the limitations inherent to a registry of unaudited procedures, and the results may not necessarily be generalizable outside the study period. However, they

may indicate changes in HF epidemiology in the coming years. The study is awaiting continuation with an overview of the HF population by the end of 2024 to assess if the pandemic had long-term effects.

To sum up, during the two years of the COVID-19 pandemic, significant shifts in epidemiology were noted. Interestingly, ischemic HF patients experienced worse outcomes compared to non-ischemic. The pandemic reshaped the HF population, and at the beginning of 2022, it was reduced by 7.7% and became younger with fewer comorbidities. In light of the above facts and the ongoing COVID-19 pandemic beyond 2022, an increase in HF incidence in the years following pandemics might be anticipated in Poland as a tidal effect to delay or deferral of care for patients with HF or other cardiac symptoms.

Supplementary material

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

Article information

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Single Perclose ProGlide vs. figure-of-eight suture technique for closure of large-bore sheaths in venous transcatheter procedures

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INTRODUCTION

The use of large-bore sheaths for femoral venous access has increased in recent years [1]. The figure-of-eight suture (FOES) and Perclose ProGlide™ (Abbott Vascular Device, CA, US) constitute 2 alternative strategies commonly employed to achieve early hemostasis following venous access using large-bore sheaths [2–4]. Although the Perclose ProGlide can be used with venous sheaths with an outer diameter of up to 29 French, the manufacturer discourages the use of a single device for sheaths larger than 8 French, where a double Perclose ProGlide (DPP) approach is then recommended [3, 5]. However, there are limited data regarding results in procedures with a single Perclose ProGlide (SPP) [1]. The aim of the present study is to compare the effectiveness and safety of a SPP when compared to FOES after a large-bore venous access.

METHODS

This is a single-center observational study conducted at a high-volume, tertiary referral center for complex cardiovascular structural interventions. We included all consecutive adult patients between January 2021 and December 2023 who underwent a transcatheter procedure in which a sheath with an outer diameter ≥14 French was used. The choice of vascular closure strategy (SPP or FOES) was at the discretion of the operator. Routine DPP was not performed during the study period. Patients with missing data or those in whom manual compression was exclusively used were excluded from the analysis. Ultrasound-guided puncture was routinely used. Success was defined as achieving complete hemostasis within one minute of the vascular closure. Early mobilization was initiated at 6 hours for patients with Perclose ProGlide closure and at 12 hours for those with FOES sutures. The main outcomes were major and minor vascular complications according to the Valve Academic Research Consortium-2 (VARC-2) criteria and re-bleeding during hospitalization or within the first month, assessed through an in-person visit [6]. In a consecutive patient subgroup, the femoral vein diameter was assessed pre-procedure and before discharge to rule out stenosis linked to the vascular closure type.

Categorical variables are presented as counts and percentages and compared using the χ^2 or Fisher's test. All continuous variables were evaluated for normality using the Shapiro–Wilk test, and none exhibited a normal distribution. These variables are presented as median and interquartile range and were compared using the Mann–Whitney U test. Univariate logistic regression was performed to identify variables associated with closure failure or rebleeding. A two-tailed *P*-value <0.05 was considered statistically significant for all analyses. Statistical analyses were performed using Stata for Mac, version 15.1 (StataCorp, College Station, TX, US). The study was approved by the local Institutional Review Board (PR [AG] 122/2023) and registered on https://www.clinicaltrials.gov (NCT05859503).

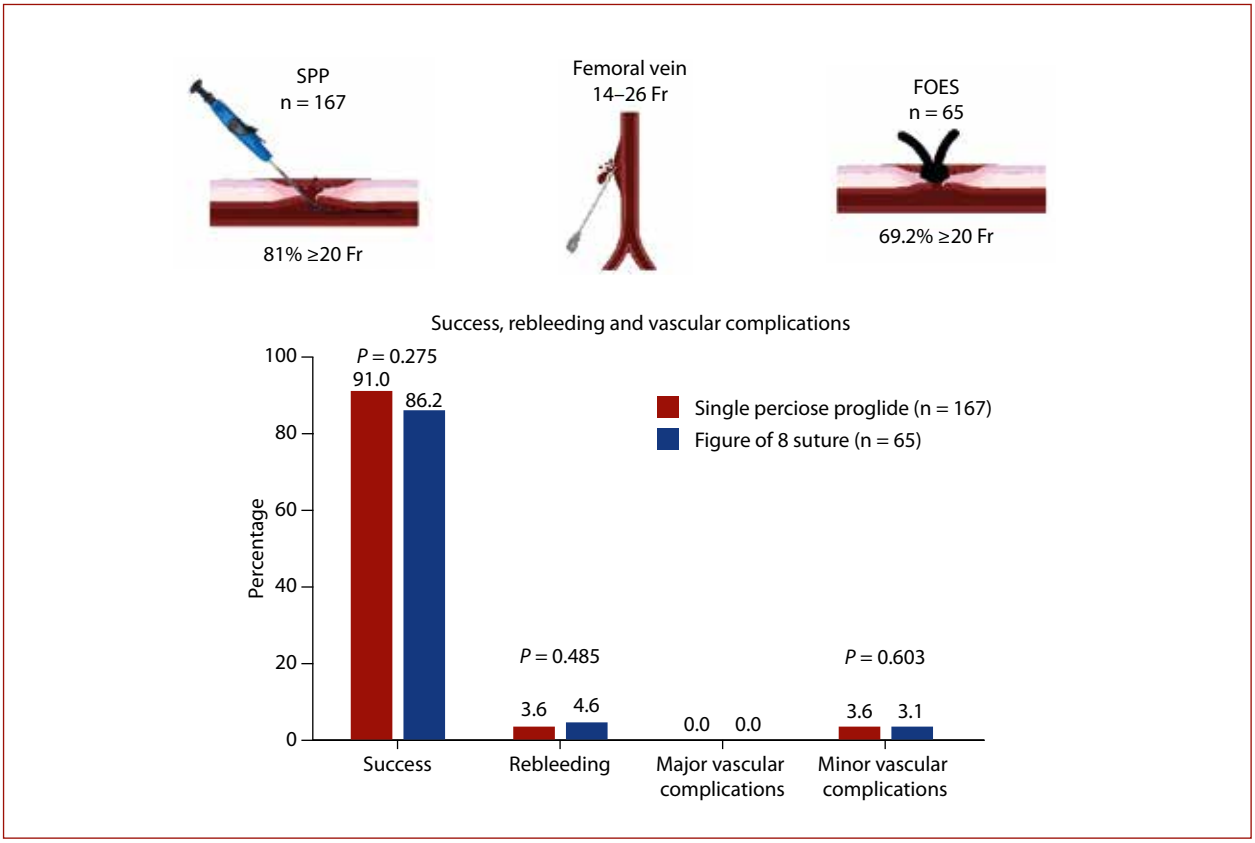


Figure 1. Success and vascular complications based on venous vascular closure strategy

Abbreviations: SPP, single Perclose Proglide; FOES, figure-of-eight suture

RESULTS AND DISCUSSION

Out of 283 patients initially selected during the study period, a total of 232 patients were included for analysis (43 were excluded because of exclusive manual compression, and 8 due to missing data). In 167 patients, a SPP strategy was attempted, and 65 patients had FOES. The median age was 68.0 years (interquartile range 52.6–81.1), and 45.3% of the patients were female. The median body mass index was 25.9 kg/m^2 (interquartile range 22.7–29.4). Hypertension was present in 58.6% of the patients, diabetes in 25.4%, and 29.7% had chronic kidney disease in stages III–V. Additionally, 71.6% of the patients were on anticoagulant therapy, and 97% of the access procedures were performed under ultrasound guidance. No significant differences in baseline or procedural characteristics were observed between the 2 groups, except for higher rates of very large bore utilization (≥20 French) in the SPP group compared to FOES (85.6% vs. 69.2%; $P = 0.004$) and the type of procedure performed ($P < 0.01$). Edge-to-edge mitral or tricuspid valve repair was more common in the SPP group (60.5% vs. 32.1%), whereas pulmonary valve replacement (25.1% vs. 36.9%), left atrial appendage closure (7.2% vs. 18.5%), and PFO/ASD closure (7.2% vs. 12.3%) were more frequent in the FOES group. Supplementary material, *Table S1* provides information about patient characteristics and procedural features.

Procedural success was attained in 91.0% and 86.2% of the SPP and FOES group, respectively ($P = 0.28$), with no significant differences observed in terms of rebleeding rates (3.6% vs. 4.6%; $P = 0.49$). There were no major vascular complications, and rates of minor vascular complications were similar between groups (3.6% and 3.1%; $P = 0.60$), all of which were uncomplicated hematomas (Figure 1). In the SPP group, 1.8% of patients and 1.5% of patients in the FOES group required blood transfusions during their hospital stay, with none of the cases linked to vascular access complications. In 12.1% of cases, a 5–6 French femoral arterial access ipsilateral to the venous access was used, with no vascular complications reported. In the SPP group, 13 of 15 procedural failures (86.7%) were managed with manual compression, while 2 cases (13.3%) required a second Perclose device. All failures in the FOES group were managed with manual compression. No predictors of suture failure or rebleeding were found for either group. The vascular closure strategy was not associated with immediate hemostasis or rebleeding (OR 1.50; 95% CI, 0.67–3.34; $P = 0.32$). A subgroup of 51 (22%) patients (29 in the SPP group and 22 in the FOES group) underwent ultrasound Doppler studies. No significant vein stenosis at discharge was observed with either closure technique, and no significant differences were observed in terms of diameter of the common femoral vein before and after the

procedure in any group (median change in diameter after SPP –0.1 mm; $P = 0.61$; and after FOES 0.2 mm; $P = 0.12$).

In this study we have demonstrated the high efficacy (91.0%) and safety (no major complications and 3.6% of minor bleeding) of an initial SPP strategy for vascular closure in patients with large-bore venous access, with similar outcomes to those observed with FOES, despite the use of larger-bore sheaths in the SPP group. Other definitions, different from no bleeding in less than a minute, have been used to define procedural success in the literature, such as no rebleeding without vascular complications, or early mobilization after the procedure [7]. Unfortunately, although we are unable to report the time until first mobilization due to the retrospective nature of the study, Figure 1 shows comparable rates of bleeding or any type of vascular complication, suggesting that other clinical definitions of procedural success would have been equivalent between techniques.

The FOES strategy has been compared to manual compression following large venous sheath removal, demonstrating that the FOES method reduces hemostasis time, immobility duration, length of hospitalization, and the incidence of vascular complications [8]. Despite the lack of knowledge regarding the SPP strategy, the results observed in our cohort are aligned with those reported by other groups using a DPP approach [3, 5].

Smaller studies have reported the use of SPP with similar success rates, but with up to 34.8% rates of mild bleeding [9] and up to a 12.5% rate of bleeding requiring transfusions [2]. The absence of vein stenosis after SPP when measured by ultrasound, as observed in a quarter of our cohort, were also previously suggested by other groups [3, 9]. A recent small trial randomized 40 patients with a 14–24 French venous access to vascular closure using SPP or FOES, and there were no differences between strategies in terms of efficacy or safety, but cost-effectiveness favored FOES [10]. However, the SPP or DPP closure strategy may offer certain advantages that may offset the costs, such as early mobilization and increased patient comfort [2, 7], which was not specifically assessed in our study.

This study has several limitations inherent to its observational, retrospective, and single-center design, as is subjected to potential confounding factors arising from differences in procedure types and sheath calibers. The choice of closure technique, left to the operator's discretion, may introduce selection bias, yet very large-bore procedures (>20 French) were more often performed using the SPP strategy, showing no differences in outcomes, which reinforces its safety. Although early mobilization (6 hours for Perclose ProGlide and 12 hours for FOES) is part of our protocol, the time to ambulation was not recorded and could not be compared between strategies. Also, SPP has not been compared to DPP, and its non-inferiority cannot be inferred.

In conclusion, SPP after a large-bore venous access is feasible, highly effective, and associated with low bleeding rates, offering similar results to FOES.

Supplementary material

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

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Is etiology the dominant modifier of prognosis in all heart failure phenotypes?

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INTRODUCTION

In general the most common phenotype of heart failure is heart failure with reduced ejection fraction (HFrEF) followed by either heart failure with mildly reduced ejection fraction (HFmrEF) or heart failure with preserved ejection fraction (HFpEF) (depending on population studied) [1–4]. In literature, the influence of ischemic etiology (IE) on the prognosis of HF regardless of the phenotype is a critical area of study, as ischemic heart disease is a prevalent cause of HF. Across all heart failure phenotypes, IE is a major determinant of prognosis, often leading to worse outcomes compared to non-ischemic etiology (non-IE) [5, 6]. However, the impact of IE on prognosis is influenced by various factors, including comorbidities and age, which can exacerbate the risk of adverse outcomes [7]. Therefore the aim of our study was to evaluate the survival of patients with HF according to the ischemic etiology in different HF phenotypes.

METHODS

It was a retrospective study using data from an electronic database of patients with hospitalization coded as HF billing codes, at the National Institute of Cardiology in Warsaw. We analyzed all patients hospitalized between January 2014 and May 2019 coded as HF hospitalization. For individuals with multiple hospitalizations, we used the first event for further analysis. We excluded patients who underwent heart transplantation/implantation of left ventricular assist devices or were misdiagnosed and individuals with missing data on EF. Patients who underwent left ventricular assist device implantation or heart transplantation during hospitalization were censored as alive. All patients were phenotyped based on the EF assessed during an echocardiography examination. Individuals with EF below 40% were labeled as HFrEF, those with EF between 40% and 49%, as HFmrEF, and those with EF equal or greater than 50%, as HFpEF, following the recommendations in force at the time. Medical history, such as comorbidities or invasive procedures performed, was based on medical records provided by the attending physicians and supplemented with data from the National Health Fund database. Data on their survival status were obtained from the Central Informatics Center, with the censoring date set at May 25, 2023 [1]. The study protocol was approved by the Biomedical Ethics Committee of the National Institute of Cardiology (No. IK-NPIA-0021/1799/2019; 11.06.2019).

Statistical analysis

The distribution of quantitative data was verified by the Shapiro–Wilk test in all subgroups. It did not follow a normal distribution and is therefore presented as median with interquartile range. The distribution of qualitative variables is presented as numbers and percentages. Patient characteristics were compared in subsamples by HF phenotype and etiology using the Mann–Whitney test for quantitative data and the χ^2 test for qualitative data. Survival probability was assessed and graphically presented using Kaplan–Meier survival curves with the log-rank test for comparison. Using, Cox proportional hazards methods, hazards ratios were calculated with 95% confidence intervals, first comparing by etiology in the whole group and then adjust-

ing for age, sex, and number of comorbidities. All data analyses were performed with STATA (StataCorp. 2023. Stata Statistical Software: Release 18. College Station, TX, US: StataCorp LLC). The significance level was set at a *P*-value of less than 0.05.

RESULTS AND DISCUSSION

Between January 2014 and May 2019, 2597 patients were hospitalized with a hospitalization coded as HF. Among them, 1040 patients had an IE including 798 with HFrEF (49.8% within subgroup), 114 HFmrEF (34.4% within subgroup), and 128 with HFpEF (19.3% within subgroup). Patient characteristics by HF phenotype and IE vs. non-IE are presented in Supplementary material, *Table S1*. The median age in the overall HF group was significantly higher in the IE group compared to the non-IE group and male sex was more prevalent. Similar trends were observed across all HF phenotypes. These results for HF resemble those from other studies [3, 6]. Chronic HF was more frequent in IE, with comparable patterns observed in HFrEF and HFpEF.

Among the recorded comorbidities, hypertension was more prevalent in IE, and this trend persisted across all HF phenotypes. Diabetes was also more frequent in IE, with nearly 70% higher percentage of patients in all HF subtypes within the IE group. Renal dysfunction and stroke were also more common in IE, with similar patterns seen in all HF phenotypes. In contrast, atrial fibrillation was less frequent in IE, with this pattern observed only in the HFrEF group [1]. In general, our findings regarding comorbidities, resemble the observation from previous studies [3, 6]. The median number of comorbidities was higher in IE than in non-IE with nearly identical distribution across all HF phenotypes [7].

There was no significant difference between IE and non-IE in terms of asthma/chronic obstructive pulmonary disease or cancer, across all HF phenotypes. However, the highest prevalence of cancer was noted in HFpEF can be partially explained by an older age in this phenotype [1].

Pharmacology trends showed that angiotensin converting enzyme inhibitors, beta blockers and loops diuretics were used more often in IE compared to non-IE. However, angiotensin converting enzyme inhibitors and loops diuretics recommendations were only more prevalent in HFpEF, whereas beta blockers only in HFmrEF. On the contrary the use of mineralocorticoid receptor antagonists did not differ between IE and non-IE, but were less likely in HFrEF, with similar distribution in other phenotypes (Supplementary material, *Table S1*)

During a median (interquartile range) follow-up of 4.26 (1.56–5.47) years the mortality rate was significantly higher in the IE group compared to the non-IE group, similar to previous reports [3, 6, 8], with survival rates of 43.03% vs. 57.15% (P <0.001) at 5 years post hospitalization, respectively. Survival in the IE group was consistently worse than in the non-IE group across all HF phenotypes. As previously demonstrated, survival was worse for HFrEF compared to HFpEF and HFmrEF, which had similar outcomes [9].

Based on the current data, the risk of death was 52% higher in the IE group compared to the non-IE group (P <0.001) (Figure 1A). When stratified by HF phenotypes in the IE group, survival was worse in HFrEF and HFpEF compared to HFmrEF, with no significant difference between the former two phenotypes (Figure 1B). In the non-IE group, survival was worse in HFrEF compared to both HFmrEF and HFpEF, with latter having similar outcomes (Figure 1C). A comparison of survival by etiology within each HF phenotype revealed that survival was worse in IE compared to non-IE for all phenotypes (Figure 1D).

These findings suggest that IE was the strongest modifier of survival, regardless of HF phenotype, what confirms previous findings [3]. However, in a paper from the Italian network IE was not an independent factor in all phenotypes after adjustment for other variables [10]. Therefore, to further explore this issue, we constructed multivariable models for each phenotype, incorporating sex, age, number of comorbidities, and etiology (Supplementary material, *Table S2*). In these models, ischemic etiology was no longer a significant predictor of prognosis for any HF phenotype. However, age remained a significant risk factor for death across all phenotypes. Similarly the number of comorbidities was associated with increased mortality in all phenotypes. On the other hand, female gender was associated only with HFrEF, showing a better prognosis. Therefore, our data indicate that providing information on prognosis solely based on etiology might be misleading, as this association is often biased by significant differences in the characteristics of the analyzed groups [10]. To our knowledge, this is the first study to provide such information for the Polish HF population across diverse HF phenotypes and etiologies. In conclusion, the observed differences in survival, with worse outcomes for IE across all phenotypes, were largely influenced by patient characteristics, like age, number of comorbidities in the IE subgroups, rather than ischemic etiology alone.

Supplementary material

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

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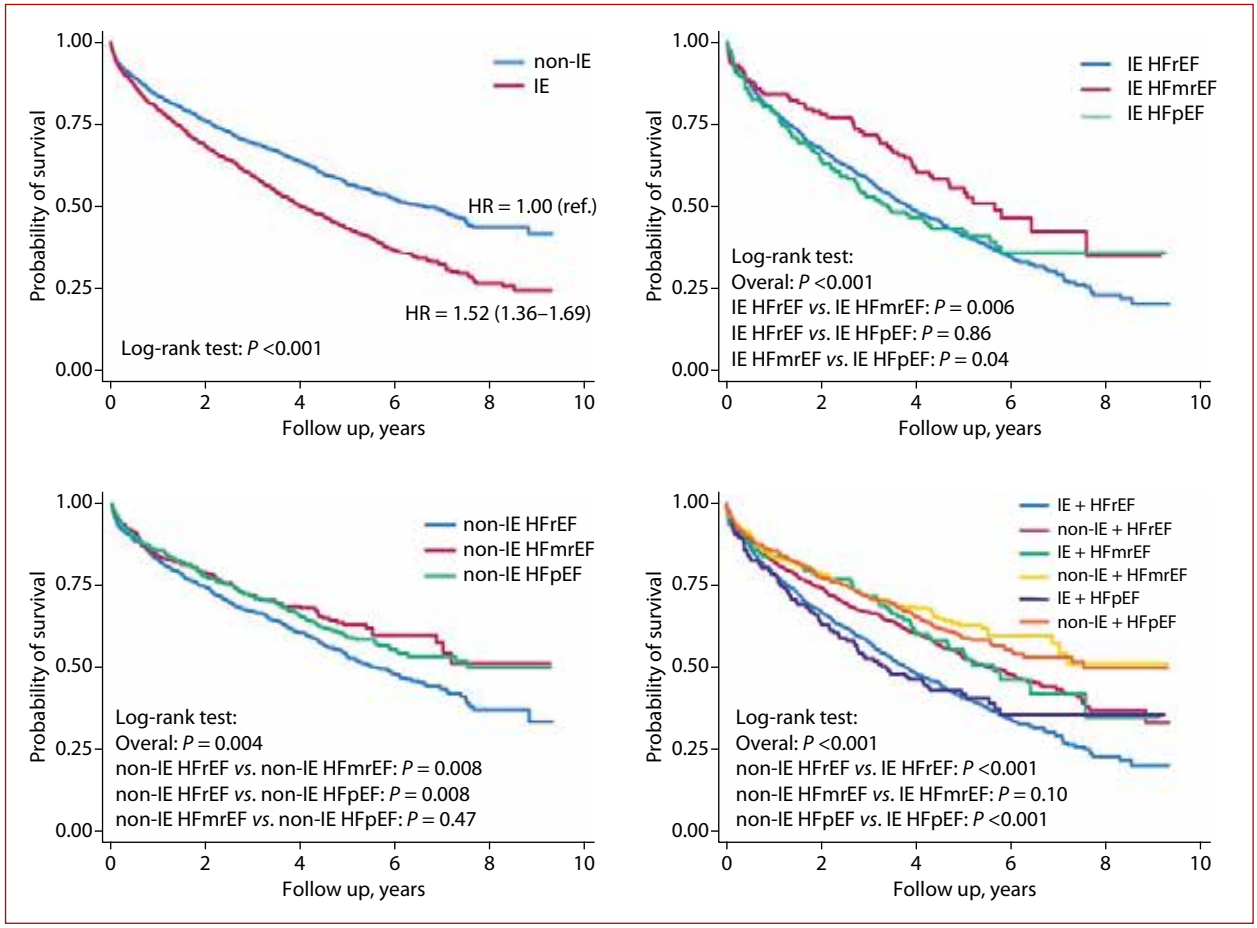


Figure 1. Kaplan–Meier survival estimates by phenotypes and etiology from univariable modeling

Abbreviations: HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction HR, hazard ratio; IE, ischemic etiology; non-IE, non-ischemic etiolog

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Initial experience with transvenous lead extraction in patients with left ventricular assist devices

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INTRODUCTION

Left ventricular assist devices (LVADs) are an essential treatment for patients with advanced heart failure. Many of these patients may have previously received an implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy with a defibrillator before LVAD implantation. Combining electrical and mechanical support has been shown to significantly benefit heart failure management [1]. However, a common complication with both devices is the risk of infection, including lead-dependent infective endocarditis (LDIE), making patients with LVADs and cardiac implantable electronic devices (CIEDs) particularly vulnerable to infections in one or both devices [2]. Additionally, the presence of a cardioverter-defibrillator lead increases the risk of CIED dysfunction [3, 4]. The increasing prevalence of patients with both LVADs and CIEDs has led to a corresponding rise in the need for transvenous lead extraction (TLE) procedures, driven by a range of clinical indications. Currently, data on TLE procedures in patients with LVADs are limited.

Our study aims to evaluate the effectiveness and safety of TLE procedures in patients with LVADs using mechanical extraction systems from the perspective of a reference center.

METHODS

A prospective analysis was conducted, including all patients with LVADs who underwent TLE between October 2011 and December 2023. The Research and Ethics Committee of Jagiellonian University approved the study protocol (KBET/259/B/2011), and written informed consent was obtained from all patients for the use of their anonymized data in this study. The study protocol adhered to the Declaration of Helsinki and followed Good Clinical Practice guidelines. Patients with endocardial leads implanted less than one year prior to the procedure were excluded from the analysis.

Data were collected from a prospectively maintained database, which included records of device implantation, follow-up visits at device and cardiology clinics, medical information from the index admissions for TLE, and data on 30-day post-procedure complications as well as one-year follow-up after TLE. We analyzed data related to the age of extracted leads, fluoroscopy time, extraction techniques, effectiveness of TLE, complete/incomplete lead removal for each targeted lead, and complications occurring intra-operatively and within 30 days post-operatively. The effectiveness of TLE procedures was defined based on current HRS and EHRA consensus guidelines [5, 6]. A detailed description of the TLE procedure has been provided in our previous study [7].

Statistical analysis

Continuous variables were presented as median and interquartile range (IQR) or minimum and maximum values. Categorical variables were presented as counts and percentages.

Table 1. Baseline clinical and procedural characteristics

Patient	1	2	3	4	5	6	7	8	9
Gender	M	M	F	M	M	M	M	M	M
Age, years	53.0	62.8	62.3	50.2	67.9	62.8	64.9	50.9	63.6
Pacing system	ICD-VR	ICD-VR	CRT-D	ICD-VR	ICD-DR	ICD-VR	ICD-VR	CRT-D	CRT-D
Prevention of SCD	Primary	Primary	Primary	Primary	Primary	Secondary	Secondary	Primary	Primary
Etiology of CM	Ischemic	Non-ischemic	Ischemic	Ischemic	Ischemic	Ischemic	Ischemic	Ischemic	Non-ischemic
Diabetes mellitus	No	No	No	Yes	No	Yes	Yes	Yes	Yes
Creatinine clearance, ml/min/1.73 m^2	44	49	67	77	44	31	59	78	43
BMI, kg/m^2	30.08	29.05	22.76	22.84	31.71	25.83	25.43	36.93	26.08
LVAD type	HW	HM3	HW2	HW2	HW2	HW2	HM3	HM3	HM3
LVAD indication	DT	DT	DT	DT	DT	DT	DT	DT	DT
Indication for TLE	PI	Lead dysfunction	LDIE	LDIE	Lead dysfunction	LDIE	PI	High defibrillation threshold	LDIE
Time from LVAD implant to CIED removal, months	28.3	1.0	0.9	37.1	53.6	24.6	51.9	6.9	62.6
Number of extracted leads, n	1	1	3	1	2	1	1	2	4
Oldest extracted lead, years	4.1	7.0	4.7	3.7	11.4	9.5	11.8	5.0	10.8
Sum of age of extracted leads, years	4.1	7.0	14.0	3.7	12.8	9.5	11.8	10.0	37.5
Tools	TS	TS	TS, Evo	TS	TS, Evo	TS, Evo	TS, Evo	TS	Evo
Total fluoroscopy time during extraction of all leads, min	4.67	2.27	6.16	1.00	23.88	5.92	5.00	1.15	12.65
Results of TLE procedure	FS	FS	FS	FS	FS	FS	FS	FS	FS
Major complications	None	None	None	None	None	None	None	None	None
Minor complications	None	None	None	None	None	None	None	None	None
30-day complications after the procedure	None	None	None	None	None	None	None	None	None
Follow-up duration, months	76.9	75.3	63.8	43.4	39.7	39.4	37.2	22.0	10.5
1-year follow-up after TLE	Dead	Alive	Alive	Dead	Alive	Dead	Dead	Alive	NA
Survival after TLE, months	7.1	42.0	still alive	0.7	30.2	3.4	7.8	still alive	4.0

Abbreviations: BMI, body mass index; CM, cardiomyopathy; CRT-D, cardiac resynchronization therapy with defibrillator; DT, destination therapy; FS, full success; Evo, Evolution mechanical system; F, female; HW, HeartWare; HW2, HeartWare2; HM3, HeartMate 3; ICD-DR, dual chamber implantable cardioverter-defibrillator; ICD-VR, single chamber implantable cardioverter-defibrillator; LDIE, lead-dependent infective endocarditis; LVAD, left ventricular assist device; M, male; NA, not applicable; PI, pocket infection; SCD, sudden cardiac death; TS, telescopic sheaths

RESULTS AND DISCUSSION

The study included 9 patients who met the inclusion criteria, one of whom was female, with a median (IQR) age of 62.8 (53.0–63.6) years, ranging from 50.2 to 67.9 years. All patients had CIEDs with high-voltage therapy, with 6 patients having an ICD and 3 having cardiac resynchronization therapy with a defibrillator. All CIEDs were implanted on the left side of the chest, for primary prevention in 7 patients (78%) and secondary prevention in 2 patients (22%). TLE was performed due to LDIE in 4 patients, pocket infection in 2 patients, and non-infectious indications in 3 patients. Among those with non-infectious indications, 2 required TLE due to an increased ICD lead threshold, while one underwent TLE due to a high defibrillation threshold with ineffective defibrillation. A total of 16 leads were extracted: 9 ICD leads, 5 pacing leads, and 2 left ventricular leads, with a median (IQR) lead dwell time of 4.4 (4.2–4.8) years. Most of the leads were over 4 years old. The median (IQR) fluoroscopy time was 2.75 (1.21–4.83) minutes per lead. No major or minor complications occurred during the procedure or within the 30-day post-procedure period (Table 1). All patients with infectious indications for TLE received appropriate antibiotic therapy.

The overall median (IQR) follow-up duration after the TLE procedure was 3.3 (3.1–5.3) years (Table 1). During the one-year follow-up, 5 patients (55.6%) died — 3 with LDIE and 2 with pocket infections. Notably, only one patient with LDIE and all patients with non-infectious indications for TLE survived the one-year follow-up period (Table 1).

Guidelines for managing CIED infections recommend the immediate extraction of all leads and devices as a class I indication [5]. However, there are no data on the management of non-infectious indications for TLE in this patient group. To perform TLE in patients with both LVADs and CIEDs for non-infectious indications remains controversial. While it increases the risk of complications, including infection, it may not offer the same therapeutic benefits as in patients without LVADs. In our study, despite the absence of TLE-related complications and a 100% procedural success rate, 5 patients (83.3%) who underwent TLE for infectious indications died within the 12-month follow-up. In contrast,

Black-Maier et al. reported a lower one-year mortality rate of 22% in a similar patient group [8].

In contrast, Krishnamoorthy et al. [9] reported an 83.3% (5 out of 6) mortality rate due to early recurrence of bloodstream infections within one year of the procedure in patients with CIED- and LVAD-associated infections, which aligns with our findings. Notably, among patients with non-infectious indications for TLE, there were no deaths or CIED reinfections during the 12-month follow-up.

Our initial experience suggests that TLE in patients with LVADs is both safe and effective. However, patients undergoing TLE for infectious indications face a high 12-month mortality rate, despite satisfactory procedural outcomes. In contrast, TLE in patients with LVADs for non-infectious indications is not associated with an increased risk of infection at the 12-month follow-up. Nonetheless, the risks, benefits, and optimal management strategies for TLE in this patient population warrant careful consideration and further research.

Article information

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EP-Heart Team approach with sinus node sparing ablation for complex inappropriate sinus tachycardia and postural orthostatic tachycardia syndrome: A first experience in Central Europe

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We present the case of a 19-year-old woman (body mass index, 19 kg/m^2) who was referred with a 4-year history of dizziness, fatigue, palpitation, exercise and orthostatic intolerance, dyspnea, presyncope, and syncope. Besides sinus tachycardia (ST) over 110 bpm when the patient was in the supine position, her resting electrocardiography (ECG) was normal. Other evident causes for ST were excluded by comprehensive interdisciplinary exams. On 24-hour-ECG-Holter monitoring, the mean sinus rate above 90 bpm was documented for 71% of time (103 bpm on average). Moreover, several episodes of symptomatic ST (>130–150 bpm) were associated with bed rest, upright position, and mild stress.

Several non-pharmacological recommendations (including exercise training, compressive garments, etc.) and pharmacological treatment (bisoprolol 2.5 mg bid, metoprolol 25 mg bid, ivabradine 7.5 bid [2 months], verapamil or combination of ivabradine 5 mg bid and bisoprolol 2.5 mg bid titrated to the highest tolerated doses), according to guidelines, had failed. The patient suffered from progressive severe disabling symptoms during mild activity [1].

The baseline cardiovascular autonomic test confirmed the criteria for normal autonomic reaction. On head-up tilt test with beat-to-beat blood pressure monitoring (Finapress Nova, Enschede, the Netherlands), the criteria for postural orthostatic tachycardia syndrome (POTS) (increase of sinus rhythm from 78–95 to 135–140 bpm within 10 min of test without hypotension) and late vasodepressive vasovagal syncope were confirmed. In the electrophysiological study, the diagnosis of inappropriate ST (IST) was confirmed by excluding other arrhythmias.

The current case report constitutes to the ongoing HEAL-IST registry (NCT05280093) that includes IST and POTS patients and was approved by the institutional ethics board.

After shared decision-making, the patient was referred for sinus node sparing hybrid ablation with typical right-sided video-assisted thoracoscopic surgical (VATS) ablation (Figure 1A–D) [2, 3] according to a structured protocol, as described previously in the SUS-

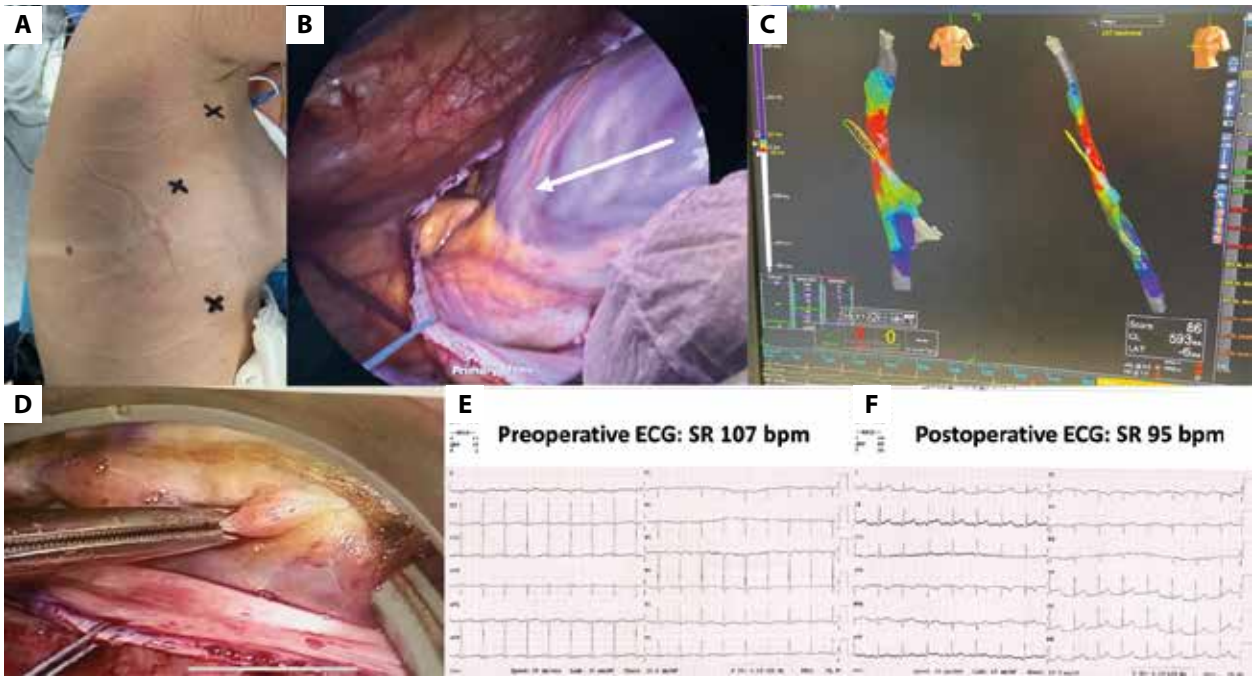


Figure 1. A. Right VATS from 3 ports at the midaxillary line. After opening of pericardial sack, significant signs of right atrial lateral wall fibrosis were revealed (white arrow). **B.** High-density endocardial activation map was performed from femoral access to validated the earliest activation of SN (Advisor HD Grid catheter and Ensite Precision, Abbott, St Paul, MN, US). **C.** Then, 4 lines (right superior and inferior pulmonary veins isolation, *superior vena cava* isolation, *crista terminalis* line, inferior *vena cava* isolation) were created by bipolar Isolator Synergy Surgical Ablation System (AtriCure, Mason, OH, US). **D.** *Crista terminalis* line. During general anesthesia stable ST 102–105 bpm were observed (EP-System, Ep-Tracer, Schwarzer Cardiotek, Heilbronn, Germany) similarly to preop. 107 bpm on ECG. **E**. After completing lines, drop in sinus rhythm 95 bpm. **F.** Were observed with shift of P wave and shortening of PQ interval (precordial leads with modified position in the first intercostal space

Abbreviations: ECG, electrocardiogram; ST, sinus tachycardia; VATS, video-assisted thoracoscopic surgical

RUTA-IST Registry [4]. Finally, combined endocardial and epicardial remapping with a zero-fluoroscopy approach showed consistent isolations of the superior vena cava, right pulmonary veins, and *crista terminalis*. An additional endocardial RF ablation was completed to achieve cavo-tricuspid isthmus bidirectional block [5]. Sinus rate changed from 107 to 96 bpm (Figure 1E–F). After 5 days, the patient was discharged and underwent a 2-week on-site cardiac rehabilitation program. Between the second and fourth post-procedural week, intermittent asymptomatic pericardial effusion (max. 13 mm) was diagnosed despite prophylactic treatment with ibuprofen and colchicine. Moreover, the patient was offered a 2-week tele-rehabilitation program with a hybrid multi-recorder smart-phone-based platform (DrEryk Kardio, Kraków, Poland). One year follow-up confirmed persistence of normal sinus rhythm (87 bpm on average on 24-hour-ECG-Holter monitoring) and disappearance of all earlier symptoms. The control cardiovascular autonomic test and 12-month follow-up did not find any symptoms meeting the criteria for IST/POTS and vasodepressive vasovagal syncope. Finally, the patient became a voluntary consultant of other candidates for that procedure and started her first job with heavy physical activity.

Our case documented the first case in Central Europe of sinus node sparing hybrid ablation and EP-Heart-Team approach for complex IST/POTS. That procedure is the further area of a hybrid approach for treatment of cardiac arrhythmia [4], especially in centers familial with minimally invasive VATS for arrhythmias [6]. Moreover, an individualized comprehensive approach for cardiac rehabilitation program (on-site and tele-rehabilitation) is yet to be developed to ensure patient improvement of exercise performance with possible early intermittent pericardial effusion, risk of pericarditis, exercise and/or orthostatic intolerance, as well as long-lasting deconditioning.

Article information

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Conflict of interest: PS and MLM are consultants for AtriCure; all authors are investigators for the HEAL-IST trial. No other conflicts of interest are relevant to the current contribution.

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Atrial tachycardia during pregnancy: Postnatal treatment

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A 32-year-old woman presented to the Emergency Department with heart palpitations and increased fatigue. She was at 26 weeks' gestation. An electrocardiogram showeda narrow complex tachycardia, at an approximate rate of 150 beats per minute, with visible P waves (Figure 1A). The patient's preliminary laboratory investigations showed no abnormalities, and no structural changes were seen on echocardiography. There were no signs of fetal distress. An attempt was made to terminate the tachycardia with vagal maneuvers, but it was ineffective, and so intravenous adenosine was administered. The arrhythmia failed to convert to sinus rhythm after the first dose of 6 mg adenosine; however, the second dose of 12 mg was successful (Figure 1B). She was discharged home in good condition with a recommendation for 25 mg of metoprolol daily. In later weeks of pregnancy and the perinatal period, the patient did not report any similar symptoms, and no further tachycardia was documented. The patient's child was born at term with no complications. Unfortunately, the arrhythmia returned in the postpartum period. An electrophysiological study with low fluoroscopy technique was performed to determine the substrate of the arrhythmia, which induced atrial tachycardia at 352 ms cycle length. Using the CARTO electroanatomical mapping system, potential and activation maps were made of the right atrium, which revealed the earliest activation site in the anterolateral tricuspid annulus (Figure 1C). A series of radiofrequency ablation applications were performed, resulting in termination of the tachycardia. The patient made a full recovery and was discharged home. During a 10-month follow-up period 2 arrhythmia episodes were reported, each lasting approximately a couple of seconds.

Hospitalizations due to arrhythmia are not common and it is estimated that out of 100 000 hospitalizations in pregnant women, 68–166 are caused by arrhythmia. The most common cases reported are common arrhythmias, such as atrial fibrillation and paroxysmal supraventricular tachycardia, which account for approximately 14% [1]. Gestational arrhythmias usually affect mothers giving birth at the age from 41 to 50 years, and the incidence of atrial tachycardia and AVNRT increases with age. The patient's history, i.e., previous episodes of SVT or structural heart disease, can also indicate a higher risk of SVT during pregnancy. Dangerous cardiac arrhythmias during pregnancy include supraventricular and ventricular tachycardia with hemodynamic symptoms. Patient care requires a multidisciplinary approach by cardiology, pediatric electrophysiology, anesthesiology, and neonatology specialists [2–4].

If a patient is experiencing episodes of supraventricular tachycardia before pregnancy and is planning to get pregnant, the best option is to perform an ablation before the planned pregnancy. During pregnancy, standard catheter ablation using fluoroscopy is not recommended. The first treatment option in hemodynamically stable patients with symptomatic or prolonged SVT confirmed by electrocardiography should be vagal maneuvers and further administration of adenosine if these prove ineffective [5].

In the case of the patient described above, the source of the arrhythmia was a focus at the lateral wall of the tricuspid annulus without low amplitude potentials in the bipolar map.

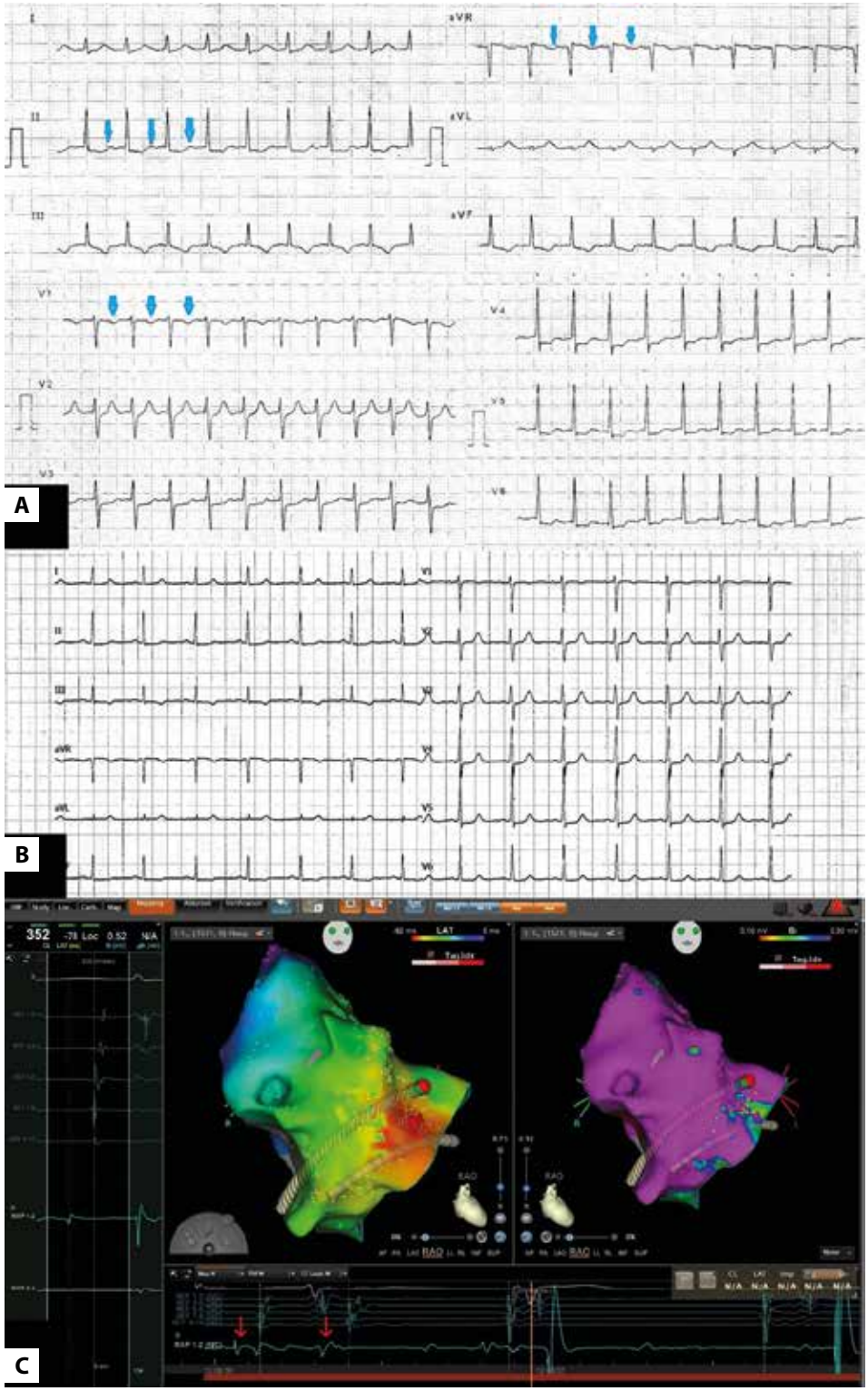


Figure 1. A. Electrocardiogram of atrial tachycardia — visible P waves in lead V1, II and aVR (blue arrows). **B.** Electrocardiogram of sinus rhythm after the administration of adenosine. **C.** High density activation ablation map (LAT) and bipolar map of the tricuspid annulus in left anterior oblique (LAO) and right (RAO) projection. The red arrows point to the earliest activation and the location of tachycardia cessation. The mapping catheter electrocardiogram under the maps presents two last beats (pointed with red arrows) of the tachycardia and its cessation during application with the following sinus rhythm

The symptoms first appeared in the second trimester of pregnancy, which led to the suspicion of gestational etiology of the arrhythmogenic focus.

Article information

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Swan–Ganz catheter-induced pulmonary artery rupture with massive bronchial hemorrhage treated by implantation of cover stents

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A 60-year-old man with heart failure and reduced ejection fraction (of 20%) due to ischemic heart disease was admitted for a hemodynamic assessment. His medical history included 2 myocardial infarctions, a cardioverter-defibrillator implantation, and MitraClip implantation. A few weeks prior, he had a mild COVID-19 infection accompanied by persistent paroxysmal cough.

Right heart catheterization was performed *via* the right internal jugular vein access with a 7Fr Swan–Ganz catheter (SGC) (Edwards Lifesciences, US). The systolic (s)/ /diastolic (d)/mean (m) right atrial pressures were 24/15/20 mm Hg, respectively. Right ventricular pressures s/d/end diastolic (ed) were 80/10/22 mm Hg, and PA pressures were s/d/m 80/36/54 mm Hg, respectively. The mean pulmonary capillary wedge pressure was 36 mm Hg. As the inflated balloon reached the branch of the PA, the patient coughed, resulting in perforation of the distal PA with sudden massive bronchial hemorrhage and subsequent hypoxia after balloon deflation. Selective bronchial intubation was urgently performed, and the patient was sedated. The SGC balloon was repositioned proximally and inflated to create a tamponade effect to stop the hemoptysis, but unsuccessfully. The common femoral vein was accessed, and selective angiography of the right PA using a 6Fr multipurpose guiding catheter (Cordis, US) showed significant contrast extravasation from the inferoanterior segmental PA (Figure 1A and Supplementary material, *Video S1*). The guiding catheter was advanced to achieve selective intubation of the ruptured segmental PA, and a semi-compliant balloon 4.0 × 15 mm (Artemis, Brosmed, Netherlands) was distally introduced over the 0.014 guidewire (Sion Blue, Asahi, Japan) (Figure 1B). The balloon was inflated for approximately an hour with periodic deflations and imaging to assess whether the rupture would seal. Subsequently, 5000 IU/5 ml of bovine thrombin (Pfizer, US) was injected through a Fine Cross microcatheter (Terumo, Japan) (Figure 1C). Unfortunately, the ruptured PA did not seal, as shown by continuous contrast medium extravasation (Figure 1D), necessitating an escalation of interventional therapy. Under angiographic guidance, 2 cover stents measuring 3.5 mm × 20 mm and 3.0 mm × 20 mm (PK Papyrus, Biotronik, Germany) were deployed in the inferoanterior segmental PA (Figure 1E), resulting in the complete closure of the feeding artery (Figure 1F and Supplementary material, *Video S2*).

The right pleural cavity hemothorax was also drained, with 1000 ml of blood evacuated. A follow-up high-resolution chest computed tomography performed several days later showed retained hemothorax without any signs of acute bleeding or pulmonary emboli, leading to the decision for surgical thoracotomy. The patient died 3 months later due to septic shock.

The PA rupture during SGC placement is rare (0.03%–0.2%) and may be attributed to excessive distal catheter tip advancement, its migration during balloon deflation, retraction of the inflated balloon, and high-pressure

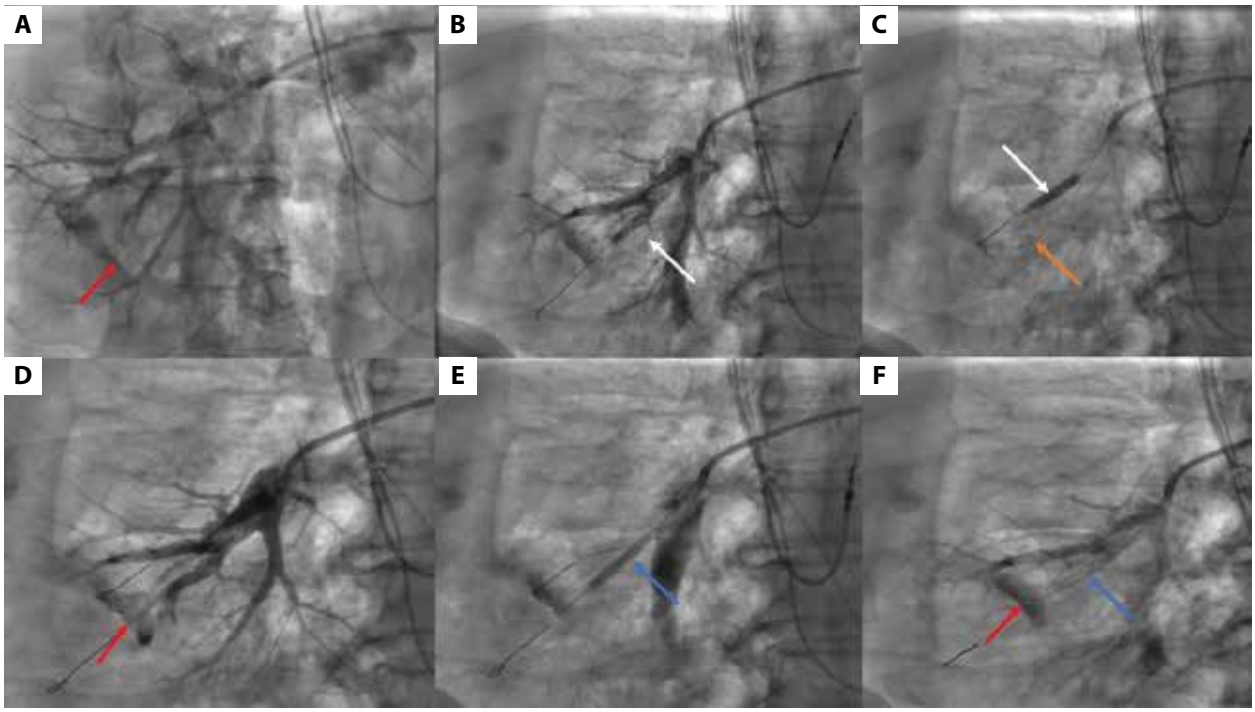


Figure 1. A. Selective angiography revealing pulmonary artery rupture and arterial blood leakage (red arrow). **B.** One-hour occlusion of the feeding artery with semi-compliant balloon 4.0 × 15 mm (Artemis, Brosmed, Netherlands) (white arrow). **C.** Thrombin injection through a Fine Cross microcatheter (orange arrow). The white arrow indicates simultaneous occlusion of the proximal segmental artery. **D.** Selective angiography showing active bleeding despite balloon occlusion and thrombin administration (red arrow). **E.** Deployment of the covered stents (PK Papyrus, Biotronik Germany) 3.5 mm × 20 mm (proximally) and 3.0 mm × 20 mm (blue arrow). **F.** Selective angiography showing interruption of the bleeding. The blue arrow indicates covered stents, and the red arrow indicates staining of contrast dye in the lung parenchyma

inflation exceeding the tensile strength of the vessel wall [1–3]. Specifically, repeated inflation and deflation during the wedge position pose a risk of PA rupture. ThePA rupture constitutes an extreme emergency situation associated with a mortality rate of 50%–70% [1, 4]. Several endovascular occlusive techniques have been described to achieve adequate hemostasis, including thrombin injection, coiling, or vascular plug implantation [3–5]. This case supports cover stent implantation as a viable option for managing PA rupture, allowing blood flow to bypass the stent and isolate the injury site. Moreover, it emphasizes the critical need for operators with high expertise and technical proficiency in the right catheterization laboratories, who can manage such life-threatening complications.

Supplementary material

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

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Long road to success. Endocardial radiofrequency ablation of septal hypertrophy using three-dimensional electroanatomic mapping guided by echocardiography in a patient with hypertrophic obstructive cardiomyopathy and severe aortic stenosis

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As far as the literature is concerned, approximately 75% of patients with hypertrophic cardiomyopathy have resting or latent obstruction (hypertrophic obstructive cardiomyopathy [HOCM]) of the left ventricle outflow tract (LVOT). Standard procedures for septal reduction include alcohol septal ablation and septal myectomy [1, 2]. However, the scenario in which HOCM coexists with severe aortic stenosis (AS) remains challenging, and septal myectomy with valve replacement seems to be the most favorable option. However, if the patient is ineligible for cardiac surgery, which strategy might be beneficial remains an open question.

A 77-year-old woman who had previously undergone coronary artery bypass grafting (CABG) 7 years earlier, with well-controlled arterial hypertension, hypercholesterolemia, and body mass index of 24 kg/m^2, was admitted to the cardiology department due to angina pectoris.

Transthoracic echocardiography (TTE) was conducted before the CABG procedure. However, the results did not indicate the presence of HOCM. The examination showed the absence of valvular defects and normal contractility. Based on these, the patient was promptly transferred from the regional cardiology department to the cardiac surgery department. Her imaging findings were not confirmed, and the cardiosurgical procedure included only CABG.

Her subsequent TTE exam revealed significant hypertrophy and LVOT obstruction (resting peak gradient over 100 mm Hg) (Figure 1A), AS, and mitral regurgitation (MR) caused by systolic-anterior motion (SAM). The aortic valve area (0.81 cm^2) on transesophageal echocardiography and calcium score (>2000 AgU) on computed tomography confirmed severe AS diagnosis. Coronary angiography showed patent bypass grafts, including the left internal mammary artery-left anterior descending coronary artery, which was the cause of her disqualification from surgical treatment.

Despite favorable conditions (occlusion of the septal branch perfusing the basal segment of the interventricular septum), there were no significant effects of septal ablation (Figure 1B). Before the implantation of a cardioverter-defibrillator, magnetic resonance imaging revealed the presence of fibrotic foci, which may have been associated with hypertrophic cardiomyopathy. The gradient reduction after implantation of the cardioverter-defibrillator was not achieved using optimal atrio-ventricular delay.

The subsequent intervention was transcatheter aortic valve implantation. Hemodynamic measurements performed immediately after the procedure demonstrated persistent

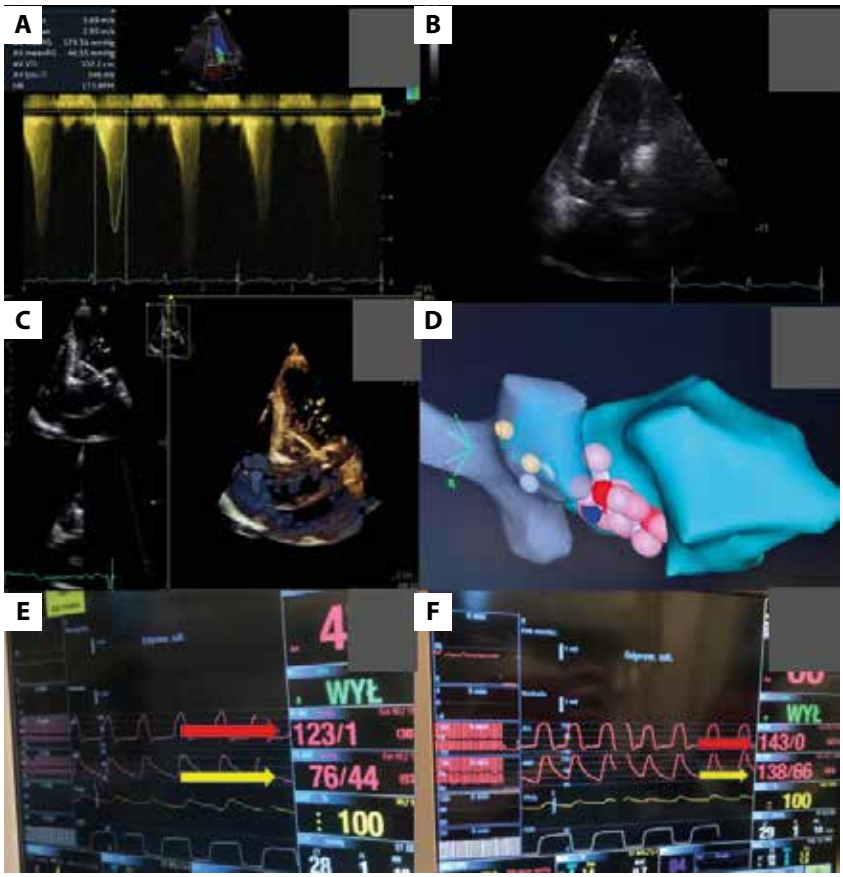


Figure 1. A. Severe obstruction of the left ventricular outflow tract (2D echocardiography, CW Doppler resting gradient). **B.** Alcohol septal ablation, optimal perfusion of the basal segment of the interventricular septum. **C.** 3D-echocardiography, position of the ablation catheter. **D.** 3D-mapping system, area of ablation. **E.** Hemodynamic measurements at the beginning of the procedure; the red arrow indicates the left ventricular pressure; the yellow arrow indicates the pressure in the ascending aorta. **F.** Hemodynamic measurements at the end of the procedure; the red arrow indicates the left-ventricular pressure; the yellow arrow indicates the pressure in the ascending aorta

high LVOT obstruction, and at the 3-month follow-up, the prosthetic valve exhibited good functionality with persistent LVOT (peak gradient of 100 mm Hg), and the patient remained symptomatic.

As the previous procedures failed, we decided to perform endocardial radiofrequency ablation of septal hypertrophy. Under general anesthesia using right-femoral-vein access *via* transseptal-puncture, left-atrium and mitral-annulus, an irrigated, contact-force ablation catheter (Thermocool-Smart-Touch-SF, Biosense-Webster) was introduced into the LV. Current hemodynamic measurements were conducted with two pig-tail catheters in the LV-apex and the ascending aorta (Figure 1E–F). Combining TTE, transesophageal echocardiography, and 3D-mapping system (CARTO-3, Biosense-Webster) determined the best placement of ablation over the SAM-septal contact area and electroanatomic-mapping allowed marking conduction system preventing thus its damage.

The target area was designated on the maximal contact zone between the basal septum and the mitral valve (Figure-1C). A total of 30 applications of radiofrequency energy (power 40–45 W, 60 sec duration) were delivered to the target area. The estimated lesion area was 2.5 cm^2 (Figure 1D), which resulted in a significant reduction in the LVOT gradient: to 5 mm Hg measured invasively and to 20 mm Hg on TTE. There were no complications, including atrio-ventricular block or arrhythmias.

At the 12-month follow-up, the TTE revealed persistent reduction in the LVOT gradient, regression of the SAM, with reduction of the mitral regurgitation, and the patient remained asymptomatic.

Although this method is not included in the guidelines, several cases have demonstrated that endocardial radiofrequency ablation of septal hypertrophy may lead to a significant and constant LVOT obstruction reduction [3–5]. This intervention may provide an option to treat HOCM in patients in whom septal reduction therapy has failed or in those who are not good candidates for such treatment. Combining echocardiography with 3D electro-anatomical mapping is crucial for choosing the optimal target.

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A persistent cough after cryoballoon ablation as an initial symptom of *Bordetella pertussis* respiratory tract infection

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A 47-year-old female patient with a history of highly symptomatic paroxysmal atrial fibrillation (EHRA III) and peripheral artery disease (occlusion of the right middle cerebral artery trunk, history of endovascular treatment of the left internal carotid artery aneurysm) was scheduled for cryoballoon ablation (CB). The procedure was conducted according to the standard institutional protocol (Figure 1A, details of the procedure available in Supplementary material, *Table S1*). The patient was discharged the next day without complication.

After 2 weeks the patient was readmitted due to a persistent dry cough exacerbated during low physical activity and at night. The cough had started 3 days after ablation. There was no hemoptysis, fever, or other signs of respiratory tract or general infection. A transesophageal echocardiography (TEE) (Figure 1B–C) and chest computed tomography were performed to exclude possible complications of CB: pulmonary vein stenosis, phrenic nerve palsy, or atrio-esophageal fistula. A chest computed tomography scan indicated no evident signs of bronchial damage or infection, and the patient was referred to a pulmonologist for differential diagnosis of chronic cough. The spirometry showed features of moderate obstruction, and an initial suspicion of asthma was raised. However, based on positive *Bordetella pertussis* IgM antibody count (Figure 1D) and negative history of *B. pertussis* vaccination, the pulmonologist diagnosed pertussis and initiated successful antibiotic treatment with clarithromycin. The cough persisted for another 3 weeks but with gradually decreasing intensity and frequency. The patient remained free of symptomatic AF for 17 months and was followed-up using repetitive 24-h Holter monitoring.

Cryoballoon ablation is a well-established and effective technology for pulmonary vein isolation in a wide range of patients [1–3]. CB is generally considered a safe procedure; however, some very rare complications like pulmonary vein stenosis or damage to the bronchi may require careful differential diagnosis [4, 5]. Due to their location adjacent to pulmonary veins, ostia bronchi can be damaged by an unintentional ice formation, which may manifest as chronic cough or hemoptysis. However, in this case, persistent cough was a symptom of respiratory tract infection by *B. pertussis* and not a complication of CB. Differential diagnosis may be challenging, but some symptoms are more characteristic for a specific diagnosis. Symptoms associated with pertussis comprise paroxysmal cough, often without other signs of infection and exacerbated at night, while symptoms associated with pulmonary vein stenosis or bronchial damage rather comprise cough, hemoptysis, and exercise dyspnea. Detailed diagnostic workout and multidisciplinary cooperation resulted in a correct diagnosis and successful treatment.

Supplementary material

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

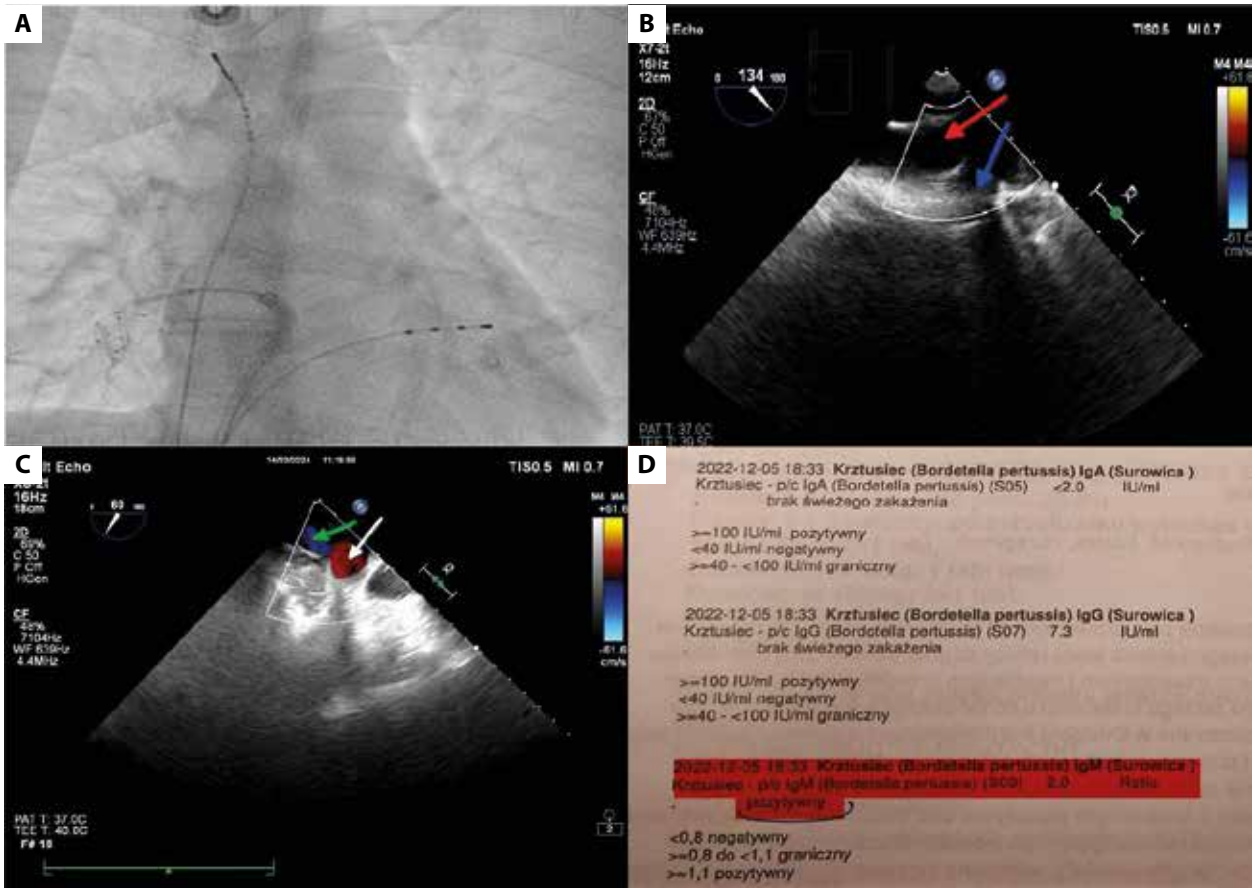


Figure 1. A. Venography of right inferior pulmonary vein before application. Decapolar catheter in vena cava superior prepared to phrenic nerve stimulation, diagnostic 4-pole catheter in right ventricle. **B.** A 2D TEE midesophageal view of the normal left pulmonary veins: superior (red arrow) and inferior (blue arrow). **C.** A TEE image of the right pulmonary veins: superior (green arrow) and inferior (white arrow). The TEE was conducted during the hospitalization for differential diagnosis of chronic cough to exclude pulmonary veins' narrowing. **D.** Serum antibodies of Bordetella pertussis in IgM class — positive

Abbreviations: TEE, transesophageal echocardiography

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Orthotopic liver transplantation due to primary biliary cholangitis in a patient with ventricular septal defect: A cardiological perspective

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We present a 49-year-old female suffering from primary biliary cholangitis (PBC), with a history of a congenital heart disease (CHD), who was evaluated before liver transplantation (LTx) due to liver cirrhosis.

The score on the MELD (Model for End-stage Liver Disease) scale was 9 and on Child–Pugh scale was B (7 points). On physical examination a loud systolic murmur over the heart at Erb's point was audible (5/6 on Levin's scale). Symptoms of overt heart failure and arrhythmias were not observed. ECG did not show any disturbing abnormalities (Figure 1A).

Transthoracic echocardiography (TTE) showed a left-to-right shunt through the interventricular septum (Figure 1B; Supplementary material, *Video S1*) with Vmax 5.6 m/s and PG 126 mm Hg (Figure 1B). The Qp:Qs ratio was 1.3. The short-axis view confirmed a 4-mm ventricular septal defect (VSD) in the aneurysm of the membranous interventricular septum (Figure 1C; Supplementary material, *Video S2*). The shunt was also clearly visible in the apical 5-chamber view (Figure 1D). There was no evidence of significant left ventricular (LV) overload, pulmonary hypertension (PH), aortic regurgitation, or a doublechambered right ventricle. To assess the left and right ventricular systolic functions more precisely, a myocardial deformation analysis was performed. The average global longitudinal strain for the LV was –22% (Figure 1E; Supplementary material, *Video S3*), and the free wall strain for the right ventricle was –26% (Figure 1F), which were within the normal range. There were no indications for closing the VSD.

The patient was scheduled for LTx with a recommendation to prevent infective endocarditis. LTx was successfully performed after 4 months without cardiovascular complications, and she was discharged on 3 immunosuppressive drugs.

Adult patients with CHD are rarely in the group of patients for organ transplantation. Depending on the type and severity of defect and type of surgery, their perioperative risk is assessed. LTx is classified as a high surgical risk procedure (>5%) [1].

The role of TTE is unquestionable in patients with heart murmurs before high-risk non-cardiac surgery. Patients with confirmed CHD require a specialist consultation before intermediate- or high-risk surgery [1]. A group of high-risk patients include those with uncorrected cyanotic heart disease, PH, complex CHD, or significant ventricular dysfunction, who require treatment in experienced centers [1].

Patients with VSDs closed in childhood or small unoperated VSDs, without LV volume overload, are usually asymptomatic [2]. In the presented patient, VSD had not been previously considered for cardiac surgery. Unfortunately, she developed a rare autoimmune liver disease, and non-cardiac surgery was necessary.

TTE did not showed LV volume overload or PH, and the novel speckle tracking analysis confirmed proper systolic functions of both ventricles, so the patient-related perioperative risk was low.

In cases of non-significant VSD, endocarditis prophylaxis is not routinely recommended,

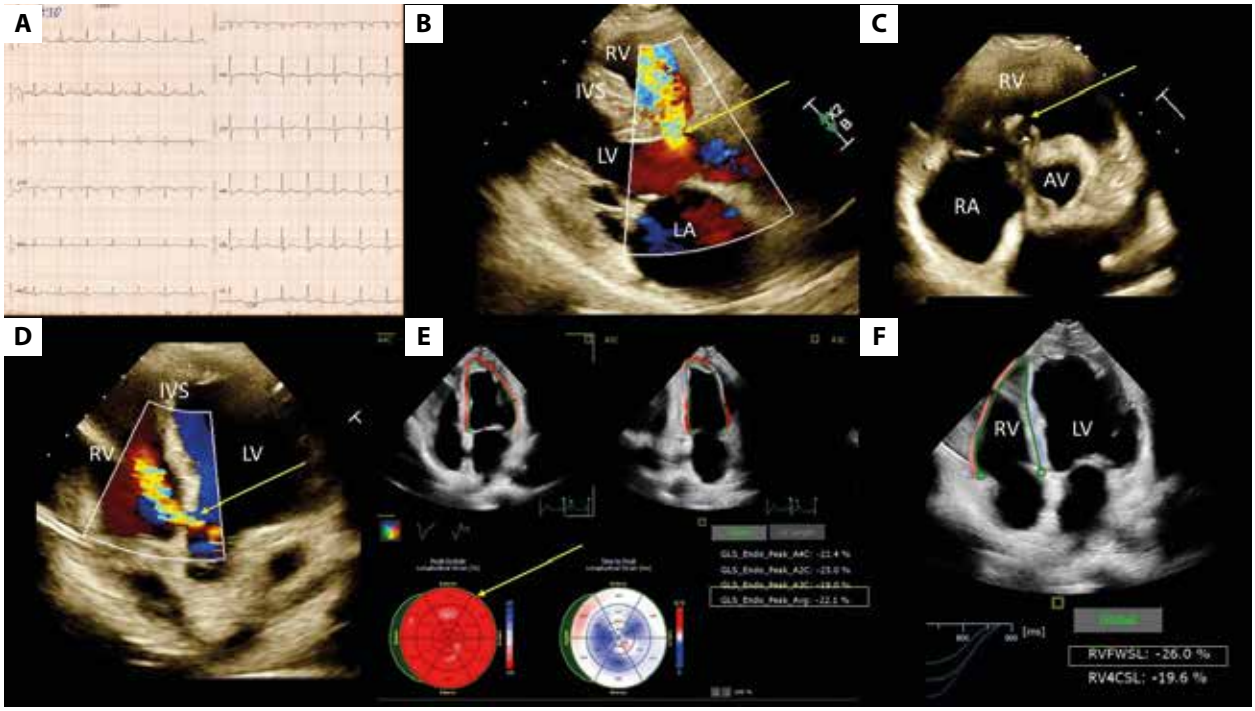


Figure 1. A. Resting ECG of the described patient. **B.** Left-to-right shunt through the interventricular septum, at the site of the membranous part (arrow), long axis view, color Doppler. **C.** Aneurysmal deformation of the upper part of the interventricular septum with a small defect at the top (arrow), short axis view. **D.** Left-to-right shunt through the interventricular septum (arrow), 5-chamber apical view, color Doppler. **E.** Speckle tracking analysis of the left ventricular myocardial deformation. Average global longitudinal strain value (frame) and the "bulls eye" (arrow). **F.** Speckle tracking analysis of the right ventricular myocardial deformation. Free wall longitudinal strain value in the frame

Abbreviations: AV, aortic valve; IVS, interventricular septum; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle

but in our patient it was administered due to the rapid initiation of immunosuppression [3].

It is well known that liver disease may be secondary to CHD [4]; however, data on the incidence of CHD in patients with PBC are limited [5]. Therefore, patients with a rare coexistence of liver disease (i.e., PBC) and congenital problems (i.e., VSD) prepared for transplant surgery always require a specialized approach.

Supplementary material

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

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Cor medusae trinity: Unraveling congenital coronary artery fistula complications through multimodality imaging

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We report a case of a 62-year-old woman presenting with acute resting dyspnea, palpitations, and chest discomfort. She also reported progressive dyspnea and unintentional weight loss over the last 3 months. Her history included overweight, dyslipidemia, and a positive ischemic stress test demonstrating a small reversible defect in the left ventricle (LV), and dilation of atria and the LV on transthoracic echocardiography (TTE) (Figure 1A–C). Examination revealed a diastolic heart murmur and bi-basal crackles on lung auscultation. B-type natriuretic peptide was 1512 pg/ml, and high-sensitivity troponin I was 543 pg/ml. Electrocardiogram showed atrial fibrillation; chest computed tomography angiography (CTA) ruled out pulmonary embolism or aortic syndrome. TTE revealed severe aortic regurgitation, moderate mitral regurgitation, LV dilation (ejection fraction [EF] 53%), right chamber dilation, and an abnormal flux in a dilated coronary sinus (CS) (Figure 1D–E; Supplementary material, *Video S1–S4*). Transesophageal echocardiogram identified a vegetation (5 × 4 mm) on the right coronary cusp, causing 2 eccentric regurgita-

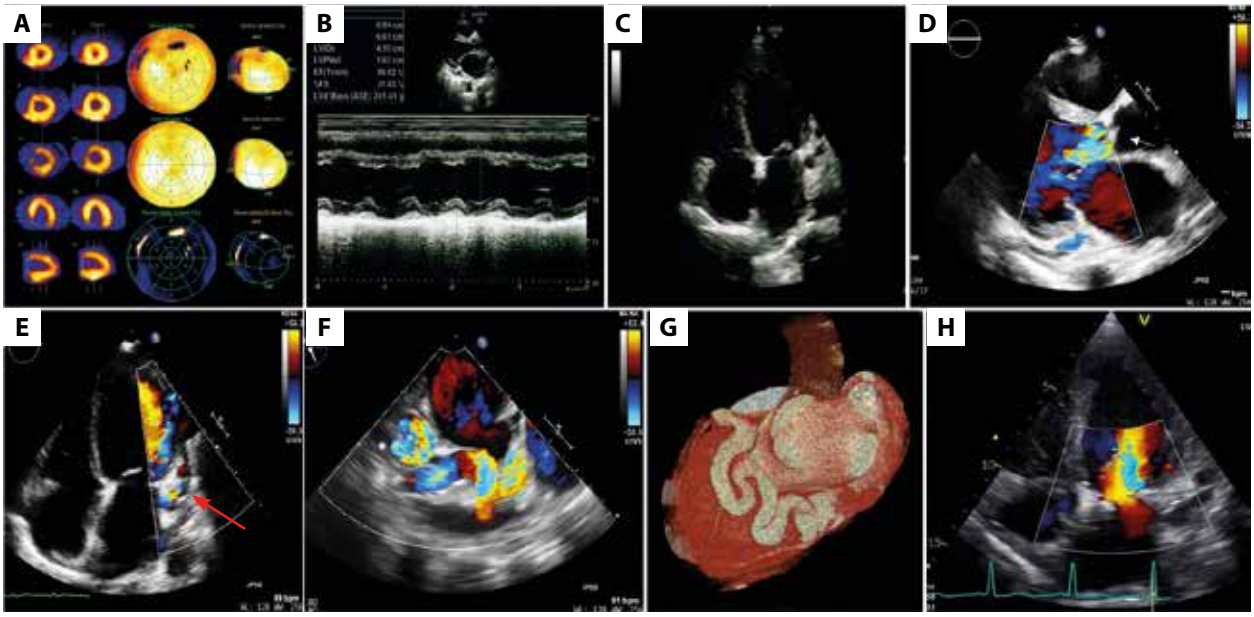


Figure 1. Concomitant complications of a giant congenital coronary artery fistula (CCAF) of the left circumflex coronary artery (LCx). **A.** Myocardial scintigraphy with mild reversible perfusion defect involving the anterior wall of the left ventricle (LV), consistent with a steal phenomenon in the left anterior descending artery, performed prior to infective endocarditis. **B** and **C.** Transthoracic echocardiography (TTE) demonstrating dilation of the atria and LV prior to infective endocarditis. **D.** TTE showing aortic vegetation (white arrow) associated with severe eccentric aortic regurgitation, and the abnormal flux in a dilated coronary sinus (CS; red arrow). **E.** TTE revealing LV dilatation with mild systolic dysfunction, right cardiac chamber enlargement, and an abnormal flow in the posterolateral LV wall. **F.** Transesophageal echocardiography showing a turbulent and tortuous inflow into CS originating from an aneurysmal LCx fistula (asterisk). **G.** Coronary computed tomography angiography showing CCAF of the LCx draining into the CS (14 × 17 mm) and in the right atrium. **H.** Four-month control TTE after surgical repair and medical therapy for HF demonstrating reverse remodeling of the LV and absence of abnormal flux in the posterolateral LV wall

tion jets (right coronary cusp perforation and noncoronary cusp prolapse). An aneurysmal left coronary artery with a turbulent flow to the CS was also noted (Figure 1F; Supplementary material, *Video S5*). Blood cultures identified penicillin-sensitive *Streptococcus mutans*. Coronary computed tomography angiography confirmed a congenital coronary artery fistula (CCAF; 14 × 17 mm) from an aneurysmal left circumflex (LCx) coronary artery draining into the CS and right atrium (Figure 1G). After discussion among the Heart Team, bioprosthetic aortic valve replacement, mitral and tricuspid annuloplasty, and LCx ligation with saphenous vein graft bypass were performed. Postoperative LVEF was 40%, prompting up-titration of medical therapy for heart failure with reduced ejection fraction. At 4 months, LV function improved (Figure 1H; Supplementary material, *Video S6*), and at one year, the patient remained stable with no signs of heart failure.

CCAFs are abnormal connections between coronary arteries and surrounding epithelialized structures due to anomalous epicardial and myocardial development, forming low-resistance pathways that may interfere with coronary hemodynamics [1]. With an estimated prevalence of 0.1% [2], CCAF-related complications such as myocardial ischemia, infective endocarditis (IE), and ventricular dysfunction are exceptionally rare [1], but they more often seen in larger CCAF draining into CS or right cardiac chambers [2]. In this case, LV remodeling was likely driven by volume overload secondary to CCAF and left-to-right shunt [3]. The coexistence of CCAF and IE is increasingly reported, but whether CCAF predisposes to IE or acts as a coincidental finding remains uncertain. *Streptococcus* species was the most frequent isolated agent, with either right- or left-sided valves affected regardless of CCAF anatomy [4]. Closure of CCAFs can be performed *via* percutaneous or surgical techniques. Surgery was chosen due to required intervention in the aortic valve. Surgical closure would still be preferred in isolated CCAF intervention because catheter-based closure of fistulas originating from distal coronary arteries with diameter exceeding 10 mm has a heightened risk of myocardial infarction due to thrombosis caused by stagnant flow in the aneurysmatic bed [1].

This case uniquely illustrates 3 simultaneous CCAF-related complications: myocardial ischemia, ventricular dysfunction, and IE — and it emphasizes the key role of multimodality imaging in diagnosing and managing such rare anomalies.

Supplementary material

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Severe bicuspid aortic valve regurgitation with ascending aortic aneurysm in a 53-year-old female patient with Turner syndrome

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Turner syndrome is a genetic disorder caused by missing or abnormal structure of the X chromosome. The incidence is estimated at 1:2500–1:3000 female births. The women, apart from typical phenotypic features and delayed mental development, present several cardiovascular disorders, which are coarctation, dilatation of the arch of the aorta, aortic aneurysms, and a bicuspid aortic valve. The average age at diagnosis is 9–10 years. The prognosis is usually good if regular monitoring and treatment of concomitant diseases are provided [1–3].

We present the case of a 53-year-old female patient admitted to the Cardiology Department for increasing shortness of breath and significant deterioration in exercise tolerance. The patient showed signs of mild intellectual disability. According to her documentation, the woman was diagnosed with Turner syndrome in her teenage years. For almost 40 years of her life, she remained without specialist monitoring and never had cardiological diagnostics for social reasons.

In the laboratory tests, elevated concentrations of N-terminal pro-B-type natriuretic peptide and troponin were noted. Sinus tachycardia with features of left ventricular hypertrophy and overload were noticed on the electrocardiogram. Transthoracic echocardiography showed good systolic function of the left ventricle and no signs of right ventricular overload or segmental contractility disorders. No pericardial effusion was also detected. However, we detected severe insufficiency (Figure 1A) of the bicuspid aortic valve (Sievers type 1a, left coronary cusp and right coronary cusp fusion) (Figure 1B) with an ascending aortic aneurysm measuring 57 mm and dilation of the main artery arch to 41 mm (Figure 1C). Additionally, below the origin of the left subclavian artery, aortic stenosis of 12 mm with a maximum gradient of 28 mm Hg was noticed (Figure 1D). These disorders had not been previously diagnosed. Computed tomography angiography excluded signs of dissection, estimated the dilation dimension at 63 × 60 mm (Figure 1E), and the narrowing of the main artery isthmus to 13 mm, with subsequent bending of the vessel at a right angle (Figure 1F). A horseshoe kidney was also found. Based on these findings, prognostic indicators were calculated: the aortic height index (AHI — 38 mm/m) and the aortic size index (ASI — 35.6 mm/m^2). The patient was classified as high-risk and had a consultation with the Heart Team, which resulted in qualification for a surgical procedure. The last element of the diagnostic process was a coronary angiography, in which no significant stenosis was found.

During her hospitalization in the Cardiac Surgery Center, the patient was implanted with a biological aortic valve and ascending aortic prosthesis. The stenosis of the aortic isthmus qualified for conservative treatment.

After the procedure, the patient was transferred to the Cardiac Rehabilitation Department. During her hospitalization, she remained in good condition. Control echocardiography showed normal function of the prosthesis and a decrease in the gradient at the site of the stenosis of the descending aorta, which was associated with a decrease

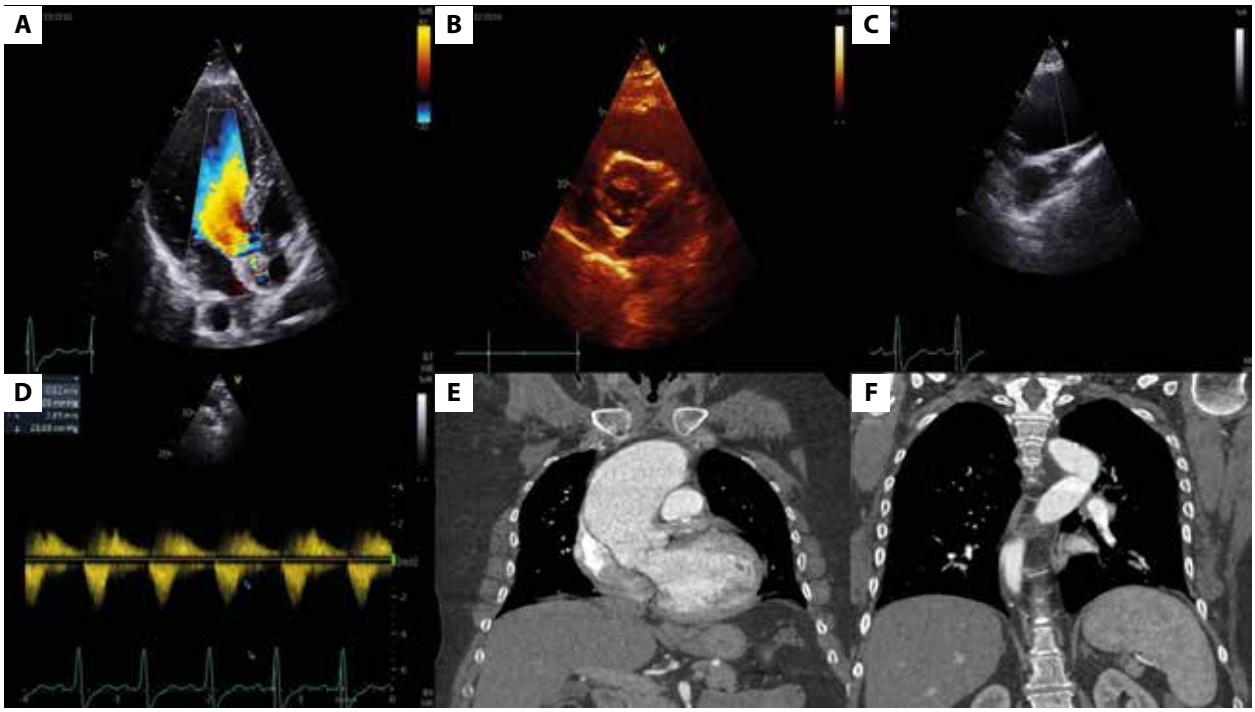


Figure 1. A. Severe aortic occlusion regurgitation. **B.** Bicuspid aortic valve. **C.** Ascending aortic aneurysm. **D.** Gradient at the site of narrowing of the descending aorta. **E.** Aortic aneurysm on computed tomography. **F.** Aortic isthmus stenosis on computed tomography

in cardiac output resulting from the correction of aortic regurgitation. A complication of the surgical treatment was pericarditis, which was treated with colchicine.

The presented case is a rare example of a congenital heart defect diagnosed at a relatively late age. It also illustrates the key role of echocardiography in the diagnosis and control of patients with Turner syndrome. These patients also require regular follow-up [4, 5].

Article information

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Right atrial anomalous muscle bundle. Clinical implications

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Right atrial muscle bundle (RAMB) is a congenital anomaly of unknown origin, probably deriving from the right venous valve [1]. So far, only four patients with RAMB have been reported, including two children [1–4]. Similar malformations were found much more frequently in the left atrium. In an impressive study by Yamashita et al. (Supplementary material, [5]) of 1100 autopsies, left atrial muscle bundle (LAMB) was observed in 2% of cases and coexisted with other abnormalities, such as premature atrial complexes (41%), Chari's network (27%), or patent foramen ovale (23%). LAMB may also cause mitral valve prolapse and its regurgitation. Potential arrhythmogenicity of LAMB remains unknown.

A 60-year-old male with a 3-month history of hemoptysis, rest dyspnea, and deterioration of exercise tolerance was admitted with suspicion of pulmonary embolism (PE). His previous medical history included heart failure and stable coronary artery disease. He also underwent implantation of a double-chamber pacemaker due to tachycardia-bradycardia syndrome 6 years earlier, aortic valve replacement (St. Jude prosthesis) with coronary artery bypass grafting twelve years earlier, and supracoronary prosthesis implantation due to aneurysm of the ascending aorta with two re-do operations due to post-operative complications 6 years earlier. On admission, there were no signs of local or generalized infection (normal device pocket, body temperature within normal limits, no elevated inflammatory biomarkers). Transthoracic echocardiography (TTE) showed dilated both ventricles, significantly reduced left ventricular ejection fraction (20%), and elevated pulmonary artery systolic pressure (90 mm Hg). Moreover, an additional echo was seen on the ventricular electrode in the right atrium, suggesting an old organized thrombus. Cardiac computed tomography (cCT) showed a structure with dimensions of 55 × 5 mm, resembling a thrombus and located between the superior vena cava (SVC) and the right atrial appendage (Figure 1). No thrombi in the pulmonary arteries were visualized.

The patient was treated with an intravenous infusion of tissue plasminogen activator, heparin (initially unfractionated and subsequently low-molecular weight), and diuretics, which led to clinical improvement.

On repeated cCT examination one month later, the additional structure looked virtually identical. Therefore, a strong suspicion was raised that it was not a thrombus but RAMB. Three years later, the patient underwent an uneventful pacemaker upgrade to cardiac resynchronization therapy-defibrillator. The clinical follow-up two years later was also unremarkable.

The clinical significance of RAMB remains largely unclear. Philip et al. reported that RAMB precluded percutaneous closure of atrial septal defect (ASD) [2]. Madjarov et al. [3] presented a patient with RAMB, who developed SVC syndrome with pulmonary embolism. Recently, Kofler et al. [4] described a fourth case of a patient with RAMB, who presented with two ASD and supraventricular tachycardia (both were successfully treated percutaneously).

In our case, we wish to emphasize that visualization of RAMB may be challenging, especially in patients with pacemakers (none of the previously reported patients had a pacemaker). Cardiac device-related infective endocarditis, lead-thrombosis, or another thrombus [5] must be excluded. Thus, careful evaluation of inflammatory biomarkers (like white blood cells, C-reactive protein, and procalcitonin)

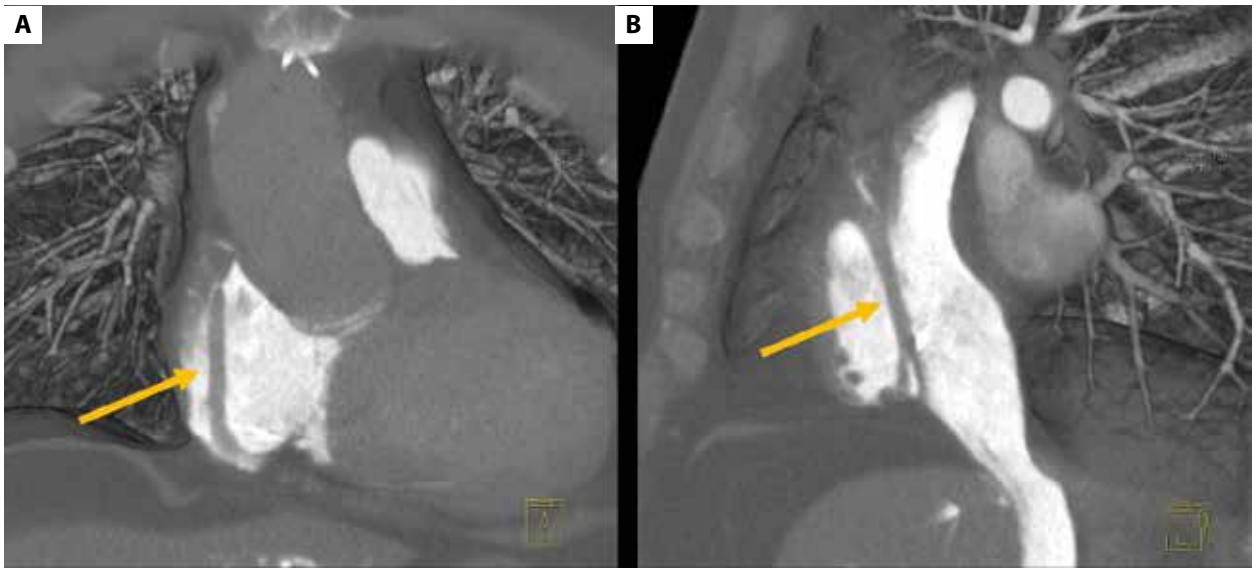


Figure 1. Cardiac computed tomography. Muscle bundle in the right atrium (yellow arrow): Coronal (**A**) and sagital (**B**) view

and blood cultures, as well as multimodality visualization by TTE, transesophageal echocardiography, cCT, or even positron emission tomography, may be indispensable in dubious cases. In previously reported cases, RAMB was visualized by TTE/transesophageal echocardiography, not by cCT or positron emission tomography.

Supplementary material

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

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Leadless pacing combined with extraction of an infected epicardial single chamber pacemaker in an 11-year-old girl

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An eleven-year-old girl (150 cm, 37 kg, body mass index 16 kg/m^2) was admitted to our clinic for a pacemaker exchange. She had received an epicardial single chamber pacemaker for a congenital complete atrioventricular block in the first month of life. Four years later, she underwent box exchange. Apart from the elective replacement indicator, we observed correct pacing parameters and lack of intrinsic cardiac activity. A new Vitatron SR pacemaker was connected to the existing lead under general anesthesia and placed in the abdominal pocket.

Two weeks later, the patient returned due to a superficial infection of the wound. The swab was negative. Empiric antibiotic therapy was initiated with amoxicillin and clavulanic acid, and surgical intervention was postponed because of the SARS-CoV-2 infection. We performed surgical revision of the infected wound as soon as the isolation was completed. *Pseudomonas aeruginosa* was found in the culture from the pocket. We started local treatment with vacuum dressing and targeted antibiotic treatment (ceftazidime and cefepime). Pacemaker extraction was planned. Due to complete atrioventricular block with no intrinsic rhythm and a high risk of infection, we chose to implant a leadless system in line with the available guidelines [1, 2]. Ultrasound assessment of possible access veins was performed. The femoral veins were 3 and 4 mm in diameter (right and left, respectively). The common iliac veins were 7 and 3 mm (right, left). The right internal jugular vein was 8 mm in diameter. Therefore, we decided to choose the jugular approach. A Leadless Micra AV pacemaker (Medtronic, US) was implanted under general anesthesia (Figure 1). A detailed description of the device selection process is provided in the Supplementary material. Appropriate pacing and sensing parameters were achieved in the first attempted location (R wave — 10 mV, threshold — 1.13 V/0.24 ms, impedance — 680 Ohm) with no complications. The radiation dose was 5 mGy, and the fluoroscopy time was 3.4 min. The vascular access site was closed with hemostatic subcutaneous and cutaneous sutures.

Extraction of the infected epicardial pacing system was planned 2 weeks later to stabilize pacemaker parameters (R wave 11 mV, threshold 0.63 V/0.24 ms, impedance 630 Ohm, poor atrioventricular synchrony due to low atrial mechanical signals). The subxyphoid approach was chosen to avoid sternotomy. The pacemaker and a part of the epicardial lead were removed. Complete lead extraction was not possible due to anatomical limitations.

Three months later, a positron emission tomography scan of the mediastinum revealed an ongoing infective process along the remnants of the lead. Another surgical procedure with sternotomy was undertaken, and all the remnants of the epicardial lead were removed. The bacteriological culture was again positive for *Pseudomonas aeruginosa* (the carbapenem-resistant strain, CRPA+). Antibiotic therapy with ceftazidime (6 weeks)

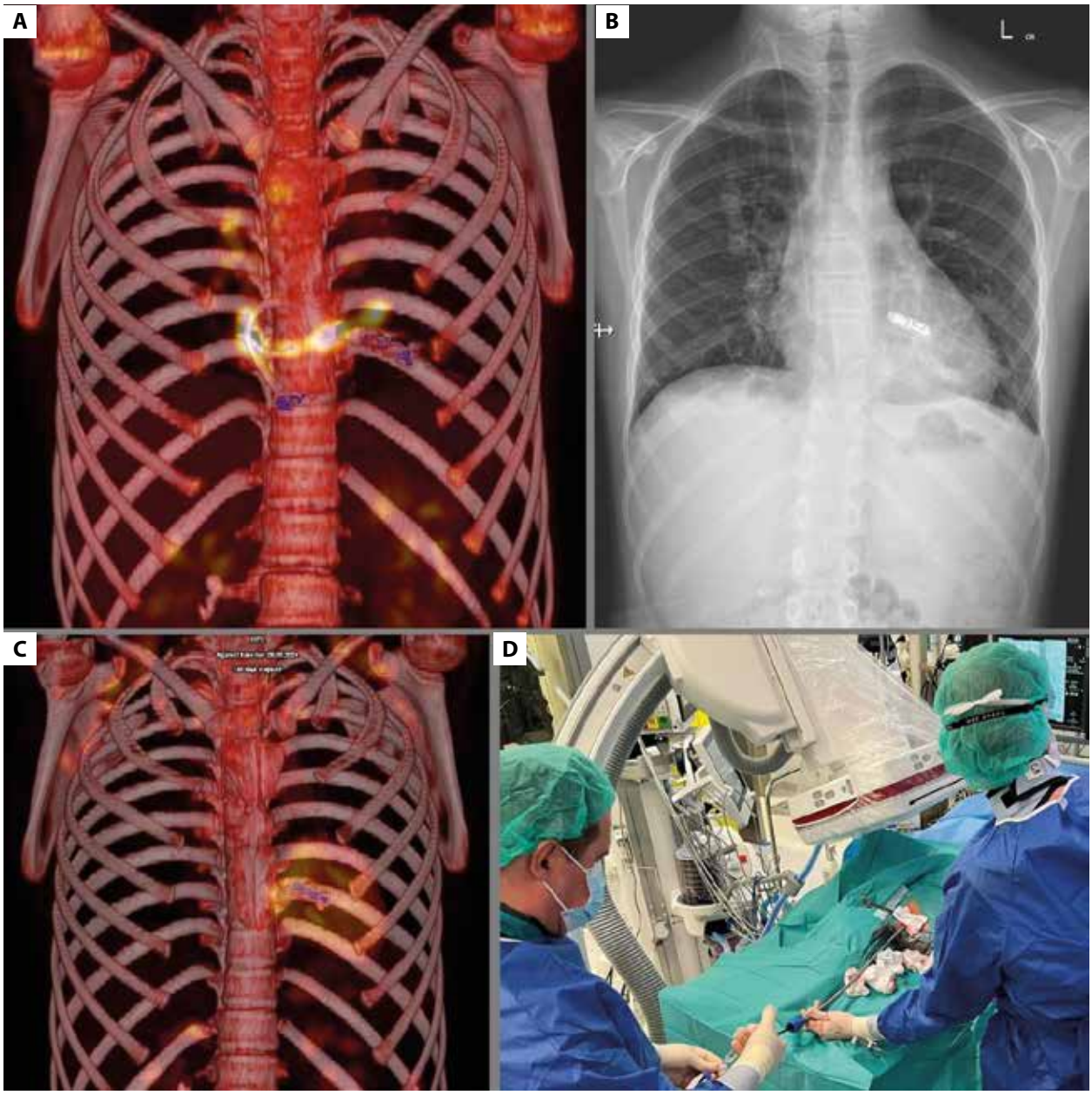


Figure 1. A. Positron emission tomography (PET) scan of the thorax with signs of infection spreading along the remnants of the epicardial pacing lead. **B.** X-ray of the thorax in the postero-anterior view with a leadless pacemaker implanted in the right ventricle. **C.** PET scan of the thorax with no signs of persistent mediastinal infection after the last surgical procedure and with the leadless pacemaker visible in the projection of the right ventricle. **D.** Modified organization of the operating room for leadless pacemaker implantation using the right jugular approach

and amikacin (4 weeks) was then continued along with hyperbaric oxygen therapy (4 weeks). Seven weeks later, no infection was found in the mediastinum on another positron emission tomography scan. The stability of pacemaker parameters was confirmed ten months after leadless pacemaker implantation. Atrioventricular synchrony could not be obtained; therefore, the device operated in VVI mode.

This clinical case shows the feasibility of leadless pacing in children using the jugular approach. It is the first such procedure performed in Poland [3].

Supplementary material

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

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Vulnerable atherosclerotic plaque and iron homeostasis: the role of intraplaque erythrophagocytosis, ferroptosis, and heme oxygenase-1 overexpression

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We have read with great interest the article by Oleksiak et al. [1] on the relationship between iron levels and the type and composition of coronary atherosclerotic plaques. The authors found that higher iron levels were associated with the presence of low-attenuation plaque and greater vulnerable component of coronary plaques, as assessed by computed tomography angiography.

Iron is an essential trace element involved in numerous fundamental biologic processes, including heme synthesis, iron-dependent catalytic reaction, mitochondrial respiration, and DNA synthesis. To our knowledge, only one organism is known so far on Earth that does not require iron to live and relies on manganese for its metabolism. This is the gram-negative spirochete *Borrelia burgdorferi*, which causes Lyme disease, the most common anthropozoonosis in the Northern Hemisphere.

Growing evidence suggests a close relationship between atherogenesis and iron metabolism [1, 2]. The understanding of the pathomechanisms of hereditary hemochromatosis, as well as the results of many experimental and clinical studies, confirm that not only iron deficiency but also iron overload have adverse health effects.

However, we would like to highlight some important issues in the paper by Oleksiak et al. [1] that may affect the clinical interpretation of the study results and conclusions. First, it seems unlikely that this study really assessed non-transferrin-bound iron (NTBI) or highly toxic free iron levels. Although the manuscript lacks detailed information regarding the methodology for iron measurements, considering the presented reference values (33–193 µg/dl), it can be assumed that serum/plasma iron levels were evaluated using a routine colorimetric method. The term NTBI refers to a group of circulating toxic forms of iron that are bound to ligands other than transferrin, ferritin, or heme (i.e., serum albumin, citrate, and other undefined, negatively charged ligands) and result from iron overload or other rare conditions associated with severe dysregulation of iron metabolism [3]. Increased NTBI levels have been found in sickle cell anemia, thalassemia, hemochromatosis, cancer, and in patients receiving myeloablative chemotherapy, but their measurement required other methodologies, e.g., chelation of iron with nitrilotriacetic acid [3]. Population-based studies have shown that NTBI levels in healthy individuals usually do not exceed 1 µmol/l or are undetectable by most methods.

Second, it is worth noting that in humans, as in all mammals, serum iron levels show a significant diurnal variation, with the highest levels usually occurring in the morning and after many hours (>5–6 h) of fasting, and the lowest in the evening. This may have affected the study results, particularly if blood samples were collected at different times of the day.

Third, the complex metabolism of iron was not evaluated in detail in this study. Assessment of iron levels in isolation from other parameters of iron metabolism and hemogram is very difficult to interpret and can be misleading. More attention should also have been paid to biomarkers of inflamma-

tion, which is closely related to iron homeostasis, ferritin (a positive acute phase reactant and marker of acute and chronic inflammation), transferrin (a negative acute phase reactant), and NTBI. Importantly, human tissues present an iron-restricted environment for bacterial pathogens, and during infection and inflammation, further sequestration of iron ions by the host to limit pathogenicity by invading microorganisms occurs, underlying the evolutionarily conserved defense mechanism of "nutritional immunity", which is common to vertebrates but also invertebrates and even plants.

There is increasing evidence that intraplaque neovascularization and hemorrhages are a key feature of advanced/vulnerable atherosclerotic plaques [4]. The newly formed immature intraplaque neovessels are fragile and leaky, which leads to the release of erythrocytes and their phagocytosis by macrophages (erythrophagocytosis). This is accompanied by overexpression of heme oxygenase-1 (HO-1, EC 1.14.14.18), an inducible cytoprotective enzyme, which protects cells from toxic free heme by catalyzing the first and rate-limiting step in the oxidative cleavage of heme to biliverdin, carbon monoxide (CO), and ferrous iron (Fe^{2+}) [4]. However, the iron accumulation in phagocytes, increased intracellular oxidative stress, and lipid peroxidation trigger a cascade of mechanisms of non-canonical ferroptosis, a form of iron-dependent, non-apoptotic programmed cell death, which seems to contribute significantly to plaque destabilization. Interestingly, ferroptosis can be inhibited pharmacologically, e.g., by ferrostatin-1 (Fer-1) and its analogs, which is explained by their ability to scavenge free radicals, especially in lipid bilayers/biomembranes [4].

Therefore, it would be extremely valuable to continue research on the role of iron metabolism in atherogenesis and atherosclerotic plaque destabilization, also using imaging methods, such as magnetic resonance imaging and optical coherence tomography, to assess intraplaque hemorrhage [5].

In conclusion, we congratulate the authors of this very interesting and inspiring article.

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A hope to save Esperanza. Robert Bartlett and the 50th anniversary of the first neonatal ECMO patient

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In 1965, Dr. Robert Bartlett was a resident at a hospital in Boston, where Robert Gross was the chief of surgery. One day the pupil asked his master a question about the possibility of treating acute respiratory failure using a heart-lung machine. Less than a decade later, this former pupil had an extracorporeal oxygenation device ready and able to keep dogs alive for five days. As Robert Bartlett recalled, his main motivation was the very high mortality rate after complex surgeries for congenital heart defects. Low cardiac output, respiratory failure, and finally death occurred in 50% of children after surgery for complex heart defects [1–3].

The first success with the use of extracorporeal oxygenation is credited to Donald Hill from Santa Barbara (US). It was in 1971, and the patient was a 24-year-old man with multi-organ trauma and acute respiratory distress syndrome. During the next 4 years, 150 people (only adults) were treated in this way, and a several percent of them survived [1, 3].

One night in the year 1975, Dr Robert Bartlett from the University of California — Irvine was asked for help by neonatologists caring for a newborn with severe respiratory distress due to meconium aspiration. The baby was born full-term on April 29, 1975, weighing 3370 g. The mother was a 29-year-old Mexican woman from Baja. It was her seventh pregnancy and sixth delivery. As an illegal immigrant, she had crossed the Mexico — US border to give her child a chance for a better life. But during the journey, the labor began. The baby was born with central cyanosis, with an Apgar score of 6 and 7 (at 1 and 3 minutes, respectively). The desperate mother signed a consent form for an experimental therapy that had never been used in neonates before. The woman was discharged soon after giving birth and never returned to the hospital. The nurses named the child "Esperanza," meaning "Hope"… (Figure 1)[1–3].

It was a hopeless case, meaning there was nothing to lose, because the partial pressure of oxygen in the newborn's arterial blood (pO_2) was only 17 mm Hg. Cardiac catheterization and angiocardiography revealed significantly limited blood flow through the lungs, a wide pulmonary trunk, and a patent ductus arteriosus with a right-to-left shunt (i.e., persistent fetal circulation). The patent ductus arteriosus was closed and extracorporeal membrane oxygenation (ECMO) support was continued (venoarterial bypass was begun 20 hours after birth). Pulmonary function gradually



Figure 1. Esperanza Pineda ("Baby Esperanza") at the age of 14 (courtesy: Dr Robert Bartlett)

improved from minimal gas exchange (due to a high pulmonary vascular resistance) to adequate gas exchange. After 7 days, the child was disconnected from ECMO, and after 9 days, mechanical ventilation was discontinued. Baby Esperanza was discharged 10 weeks after birth. At 12 months of age, she had a growth curve in the 10th percentile and normal psychomotor function [1, 2].

A case report was prepared for publication, but interestingly the work was rejected. This is how Robert Bartlett recalled it years later: *In 1975, we successfully used prolonged extracorporeal support for a newborn infant with severe respiratory failure. At the time, we thought the single case was worth reporting to demonstrate the feasibility and technology of ECMO in neonatal respiratory failure. Journal editors disagreed, and the report was never published* [1, 2]

This work, rejected by the editors, was published only in 2017 with the author's commentary [2]. Photos of 21-year-old Esperanza-Hope and her doctor, Robert Bartlett, who met at The Extracorporeal Life Support Organization conference in 1996 went down in the history of cardiac surgery and intensive care (Figure 2). Today, Esperanza Pineda is a happy wife, a mother of three children, and an advocate for ECMO patients and their families [3].

Robert Bartlett (born May 8, 1939) graduated from the University of Michigan Medical School. *I wanted to be a professional hockey player, but I could see that wasn't going to work. And then I thought about being a professional musician*, he recalled in an interview years later.

As a young doctor Bartlett started a team for medical students named "Hockey Docs". He played until the age of 50. He still plays the bass violin and the euphonium. Professor emeritus (aged 86) is still active in research; with his team he is working on the next generation of life-support extracorporeal devices like wearable artificial lungs or artificial placentas [4].

The era of circulatory support started by John Gibbon in 1953 with his successful correction of an atrial septal defect using an extracorporeal circuit was continued almost a quarter of a century later by the first use of ECMO in a newborn as a method of treating cardiorespiratory failure. There are now over 170 000 cases (children and adults) in the Extracorporeal Life Support Organization Registry (ELSO, formed in 1989) [5].



Figure. 2. The patient and the doctor, Esperanza Pineda (at the age of 21) and Robert Bartlett (courtesy: Dr Robert Bartlett)

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Guidelines for the management of hypertension in Poland 2024 — the position paper of the Polish Society of Hypertension and Polish Cardiac Society experts

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TABLE OF CONTENTS

List of abbreviations
1. Introduction 373
2. BP measurements 373
   2.1. BP classification 373
   2.2. Office BP 374
   2.3. Home BP 374
   2.4. Ambulatory blood pressure monitoring 374
   2.5. Situational hypotension 376
   2.6. Opportunistic BP measurements and BP measurements in pharmacies 377
   2.7. Night-time BP 377
3. HT diagnosis 377
4. Clinical assessment, diagnostic tests and assessment of target organ damage 378
   4.1. Clinical assessment of the HT patient 378
   4.2. Routine and addtional evaluation 378
   4.3. Electrocardiographic assessment in a patient with HT 381
   4.4. Echocardiographic evaluation of a hypertensive patient 382
   4.5. Renal function assessment in a patient with HT 382
   4.6. Other diagnostic tests in a patient with HT 383
   4.7. Assessment for secondary forms of HT 383
5. Cardiovascular risk assessment in a patient with HT 384
6. Hypertension as a component of the metabolic syndrome 384
7. Initiation of treatment and target values 386
   7.1. Initiation of HT treatment 386
   7.2. Antihypertensive treatment in patients with elevated BP 386
   7.3. BP target values 386
   7.4. Dimensions of antihypertensive effectiveness 388
8. Non-pharmacological management in patients with HT 388
9. Basic algorithm for the treatment of HT 389
   9.1. Dosage of antihypertensive drugs versus intensification of therapy 391
10. The place of beta-blockers in HT therapy 391
11. Differences in hypertension management 392
   11.1. Hypertension in women 392
   11.2. The "metabolic" patient with hypertension on a continuum of obesity → MS → diabetes → HFpEF 394
   11.3. The "cardiac" patient with HT and a continuum of atherosclerotic cardiovascular disease 398
   11.4. Hypertension in patients with a history of stroke 399
   11.5. Hypertension in patients with peripheral artery disease 399
   11.6. Hypertension in patients with chronic kidney disease 400
   11.7. Hypertension in patients with atrial fibrillation 401
   11.8. Gestational hypertension 402
   11.9. Hypertension in young adults 402
   11.10. Hypertension in cancer patients 403
   11.11. Hypertension in elderly patients with frailty and/or multimorbidity 404
12. Management of emergencies 405
   12.1. Management of asymptomatic significantly elevated BP 407
   12.2. Management of emergencies 407
13. Perioperative treatment of HT 407
   13.1. Qualification for surgery and preoperative management 407
   13.2. Intraoperative management 408
   13.3. Postoperative period 408
14. Uncontrolled hypertension 408
   14.1. Definition, characteristics and causes of uncontrolled and resistant HT 408
   14.2. Diagnostic and therapeutic management of patients with suspected resistant HT 408
   14.3. Antihypertensive therapy of truly resistant HT 409
15. Interventional treatment of HT 410
16. Importance of patient co-operation in long-term BP control 410
17. Editorial Committee, Opinion Committee and Reviewers 411

LIST OF ABBREVIATIONS

ABI	ankle-brachial index
ABPM	ambulatory blood pressure monitoring
ACEI	angiotensin-converting enzyme inhibitor
ACR	albumin-creatinine ratio
AF	atrial fibrillation
ARB	angiotensin II receptor AT1 blocker
ARNI	angiotensin receptor-neprilysin inhibitor
ASA	acetylsalicylic acid
BARKH	brain, arteries, retina, kidneys, heart
BB	beta-blocker
BMI	body mass index
BP	blood pressure
CAC	calcium score
CCB	calcium channel blocker
CKD	chronic kidney disease
COVID-19	coronavirus disease 2019
COX-2	cyclooxygenase 2
CPAP	continuous positive airway pressure
CT	computed tomography
CV	cardiovascular
DBP	diastolic blood pressure
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
ESC	European Society of Cardiology
ESH	European Society of Hypertension
FMD	fibromuscular dysplasia
GLP-1	glucagon-like peptide 1
HbA1c	glycated hemoglobin
HELLP	hemolysis, elevated liver enzymes, low platelets
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HMOD	hypertension-mediated organ damage
HR	heart rate
HRT	hormone replacement therapy
HT	hypertension
ISH	isolated systolic hypertension
KCCQ-CCS	Kansas City Cardiomyopathy Questionnaire — The Clinical Summary Score
LEAD	lower extremity arterial disease
LVH	left ventricular hypertrophy
MAP	mean arterial hypertension
MMM	May Measurement Month
MRA	mineralocorticoid receptor antagonist
MS	metabolic syndrome
NSAID	non-steroidal anti-inflammatory drug
NT-proBNP	N-terminal pro-B-type natriuretic peptide
op-BP	opportunistic blood pressure measurements
OC	oral contraceptive
OGTT	oral glucose tolerance test
OSA	obstructive sleep apnea
PA	primary hyperaldosteronism
PAD	peripheral arterial disease
PCOS	polycystic ovary syndrome
PCSK9	proprotein convertase subtilisin/kexin 9
PE	pre-eclampsia
PRES	posterior reversible encephalopathy syndrome
PTD	Polish Diabetes Association
PTK	Polish Cardiac Society
PTNT	Polish Society of Hypertension
PUFA	polyunsaturated fatty acid
PWV	brachial-ankle PWV
RRI	renal resistive index
SBP	systolic blood pressure
SCD	sudden cardiac death
SPC	single-pill combination
TIA	transient ischemic attack
TLD/TD	thiazide-like diuretic/thiazide diuretic
TSH	thyrotropin-stimulating hormone
UACR	urine albumin-creatinine ratio
USG	ultrasonography
X-ray	radiological examination

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1. INTRODUCTION

For years, hypertension (HT) has remained one of the most common risk factors leading to cardiovascular disease (CVD) and death both in Poland and worldwide [1–5]. Therefore, its effective treatment has become a priority for hypertensiologists, cardiologists, general practitioners (GPs) and physicians from other specialities. In the past, the ESH and ESC cooperated on publishing the joint version of the HT treatment guidelines; however, the two societies created the most recent publications separately [3–5, 7, 8]. To increase the effectiveness of HT therapy, the activities of all specialists should be coordinated and based on common guidelines. Therefore, the Board of the Polish Society of Hypertension (PTNT) and the Board of the Polish Cardiac Society (PTK) agreed to develop a joint document Guidelines for the management of hypertension in Poland 2024 — the position of PTNT/PTK Experts. The text was first assessed by reviewers and then submitted to the Committee of 30 Polish HT Experts for opinion. Each controversial statement had to be supported by at least 23 of the 30 Committee members to be included in the final document.

Based on the analysis of the National Health Fund (NFZ) data from 2018–2022, the number of HT patients in Poland remains stable and it is approximately 11 million people (Figure 1.1). The disease affects 34%–35% of adults [9]. Additionally, global data show that HT affects a total of approximately 5% of the population aged 0–18 [10]. The disease is rarely diagnosed in the first years of life, but during puberty, the incidence of HT increases significantly, especially in boys. Polish data indicate that in adolescents aged 18 years, HT affects 9% of the population and it is almost 16% in boys, which corresponds to the prevalence of HT in young adults [11].

The 2019–2021 analysis, excluding patients with heart failure (HF), found that 9.5–10.3 million people are taking antihypertensive medication [12]. In Poland, the incidence of HT is among the highest in Europe, in both women and men [13]. Monotherapy still remains the most common treatment (54% of patients in 2021). Beta-blockers (BBs) remain the most commonly used group of drugs. The popularity of single-pill combinations (SPCs) increased in the period from 2019 to 2021. In 2021, 30% of patients taking antihypertensive drugs used SPCs combining two drugs and 3% used SPCs combining three drugs. Among patients undergoing combination treatment (2 drugs or more), 46% used SPCs combining two drugs. Among patients treated with three or more antihypertensive drugs, the share of patients using SPCs combining three drugs was 20%. There is no current data on the effectiveness of HT treatment in Poland. The 2013–2014 WOBASZ study showed that effective HT therapy was achieved in 23% of the participants [14]. In contrast, the 2018–2019 POLSENIOR2 study revealed that HT affected three out of four people aged 60 and older. HT control was achieved in one-third of the population — 33%, including 39% receiving antihypertensive medication [15]. A slightly higher share of patients aged 65 and older who achieved blood pressure (BP) control was confirmed in the 2017–2018 NOMED-AF study [16]. In 2021, during the May Measurement Month (MMM) campaign, BP was measured/assesed in 1699 persons. The control was achieved by 31% of HT patients, including 60% undergoing treatment [17]. The BP control may have been negatively affected by the coronavirus disease 2019 (COVID-19) [18–21].

In this document, the level of recommendation is not provided. Instead, the assessed recommendations and degrees of recommendation were taken from the ESH and ESC guidelines and presented in the figures. The purpose of this approach is to make it easier to understand what should definitely be done and what is worth considering. The graphical representation of the recommendations seems more useful in practice.

2. BP MEASUREMENTS

BP measurements (Figure 2.1) should be taken using validated devices. This means that their accuracy was assessed in a clinical trial in accordance with accepted protocols and the results were published in a peer-reviewed scientific journal. A list of such devices can be found at: www.dobrzemierze.pl and www.stridebp.org [3, 5].

BP measurements at the doctor's office are considered crucial in diagnosing and evaluating the effectiveness of HT treatment [4, 5]. However, studies indicate that out-of-office measurements have greater prognostic value [23, 24]. More than 90% of HT patients in Poland take home BP measurements [22], which, together with access to ambulatory blood pressure measurements (ABPM) through the National Cardiac Network and Coordinated Care, allows to consider out-of-office methods as the main means of BP monitoring [25]. Office BP measurements play an additional and verifying role.

2.1. BP classification

The correlation between BP values and cardiovascular risk in persons without blood lowering therapy is linear, starting from values as low as 100–110 mm Hg for systolic BP [26–28]. For this reason, describing BP values as "normal" may be misleading in terms of their association with cardiovascular risk. In the presented document, three BP categories (systolic and diastolic BP values for office measurements) are introduced:

- **optimal BP**: below 120 and below 70 mm Hg;
- **elevated BP**: 120 to 139 and/or 70 to 89 mm Hg;
- **HT**: 140 and/or 90 mm Hg or greater.

The purpose of the new BP classification is not only to simplify BP categories used so far, but also to promote preventive measures against HT development and to reduce CV disease risk in people with elevated BP. In the ESC guidelines, the lowest BP category is referred to as "non-elevated" BP [5]. This may imply that BP values in this category are incorrect; moreover, such a term is not motivating to

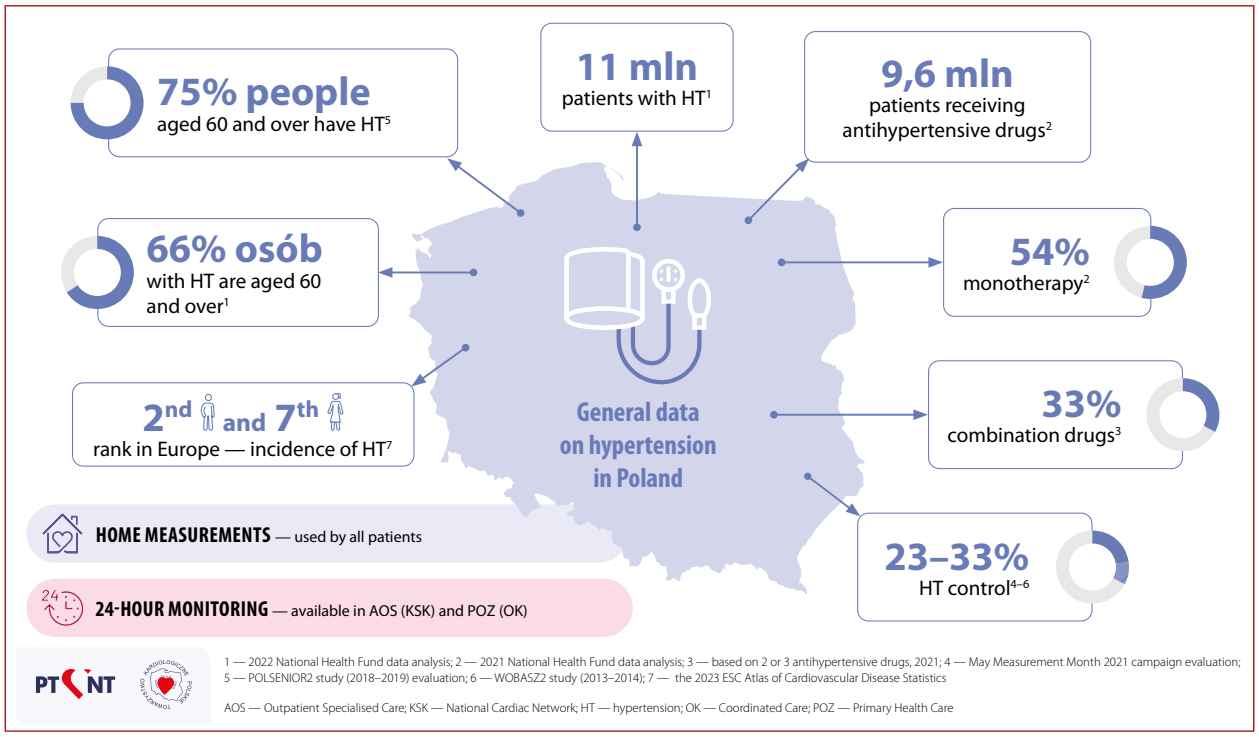


Figure 1.1. The prevelance of hypertension (HT) in Poland. Developed based on [9, 12, 14, 15, 17, 22]

pursue healthy lifestyle. Therefore, it is proposed to refer to the BP values below 120 and below 70 mm Hg as "optimal".

Detailed cut-off values for each category for the different BP measurement methods are presented in Figure 2.2. As the white coat effect becomes gradually less evident along with lower BP values, the criteria for "optimal BP" are the same for office and out-of-office BP [5]. Table 2.1 shows the present and new classification of BP categories.

2.2. Office BP

BP measurements taken in healthcare facilities or by medical staff are referred to as office BP. For decades, office BP constituted basic method of BP assessment. However, the wide availability of out-of-office BP measurement methods that better illustrate CV disease risk is gradually reducing role of office BP. Office measurements can be performed with an aneroid sphygmomanometer or using a validated automatic device. The cuff should be adjusted according to arm circumference and at least two, preferably three, measurements should be taken on the same arm, one minute apart. The result is presented as the average of the last two measurements [2, 4, 5, 29].

Unattended automatic office BP measurements, due to the lack of clearly defined BP thresholds for this method and the fact that they do not increase the accuracy of the cardiovascular risk assessment compared to office measurements, are not currently recommended [30, 31].

2.3. Home BP

Home BP measurements are self-measurements taken by the patient or another person. In Poland, almost all patients with HT have an access to personal BP measurement devices. Home BP monitoring over several consecutive days provides more comprehensive insight into HT control than a single 24-hour recording. Reliable home measurements help to identify patients with elevated BP. Additionally, self BP monitoring engage patients which translates to better adherence to therapy. Automatic validated devices with an appropriately selected arm cuff are recommended. Validated wrist BP measuring devices are also available, including those for overnight measurements [2, 4, 5, 29]. Interpretation of the results is shown in Figures 2.2 and 2.3.

What is the optimal regimen for home BP measurements?

- HT diagnosis, treatment control and pre-visit recommendations: BP measurements on 7 consecutive days (not less than 3 days) should be taken following the 2 × 2 scheme, i.e. two measurements in the morning and two in the evening , before meals and medications. The measurements should be tak en one after the other on the same arm.
- Outside the 7-day period: the frequency of measurements is determined individually, usually several times a week or month, at different times. Two measurements should always be taken, one after the other, and both results should be recorded.

2.4. Ambulatory blood pressure monitoring

Ambulatory blood pressure monitoring (ABPM) is a method of monitoring the BP 24 hours a day using a device worn by

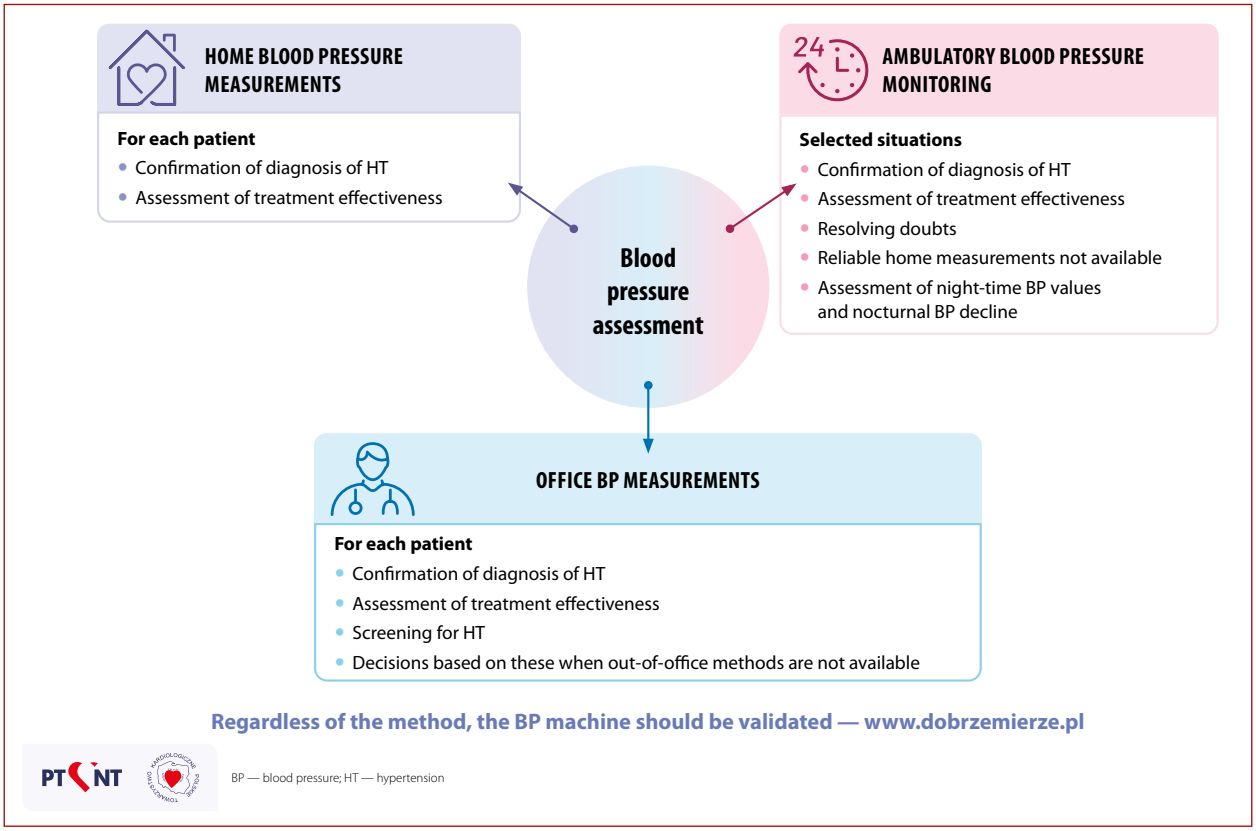


Figure 2.1. Selection of blood pressure (BP) measurement method

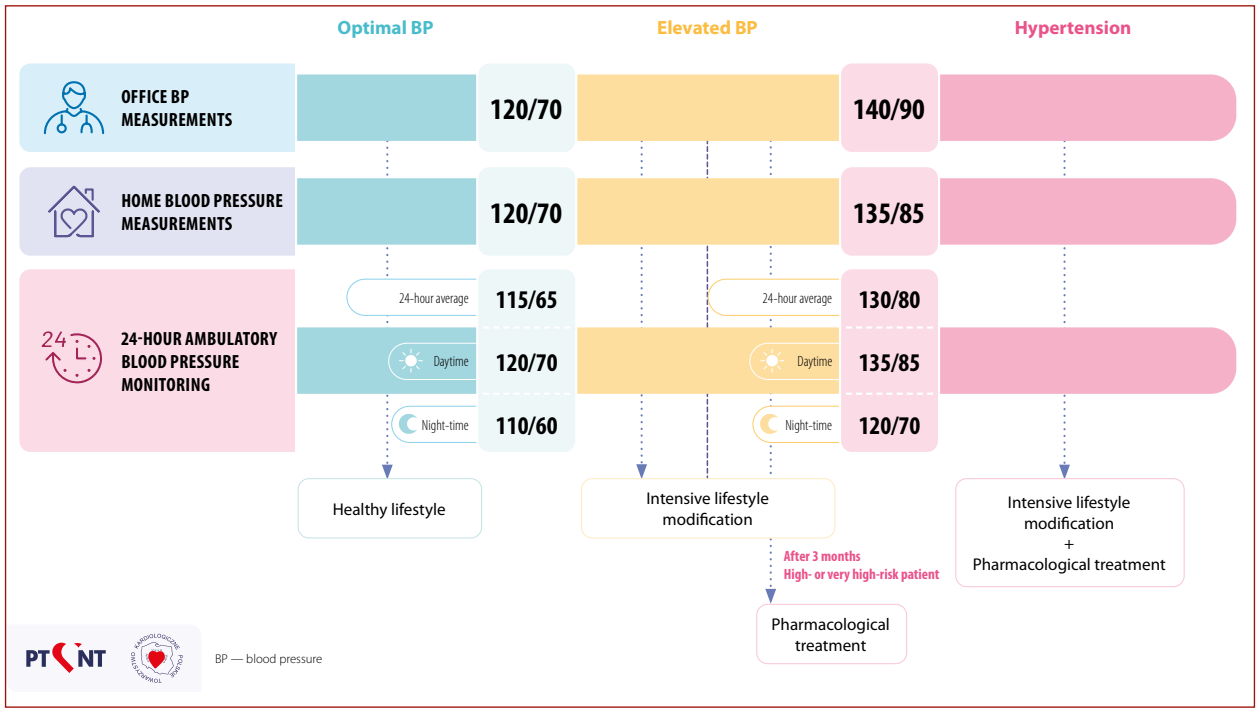


Figure 2.2. Blood pressure (BP) cut-off values and initiation of hypertension (HT) treatment. Based on [2, 4, 5, 29]

Table 2.1. Present and new classification of blood pressure (BP) categories. Based on [4, 5]

Systolic and diastolic BP values [mm Hg]		Present BP categories	New BP categories
< 120 and < 120 and/or	< 70	Optimal BP	Optimal BP
	70–79		Elevated BP
120–129 and/or 80–84		Normal BP	
130–139 and/or 85–89		Normal high BP	
≥ 140 and/or ≥ 90		HT grade 1.	HT
≥ 160 and/or ≥ 100		HT grade 2.	
≥ 180 and/or ≥ 110		HT grade 3.	

Where BP values fall into different categories, the higher category should be considered

Abbreviations: HT, hypertension

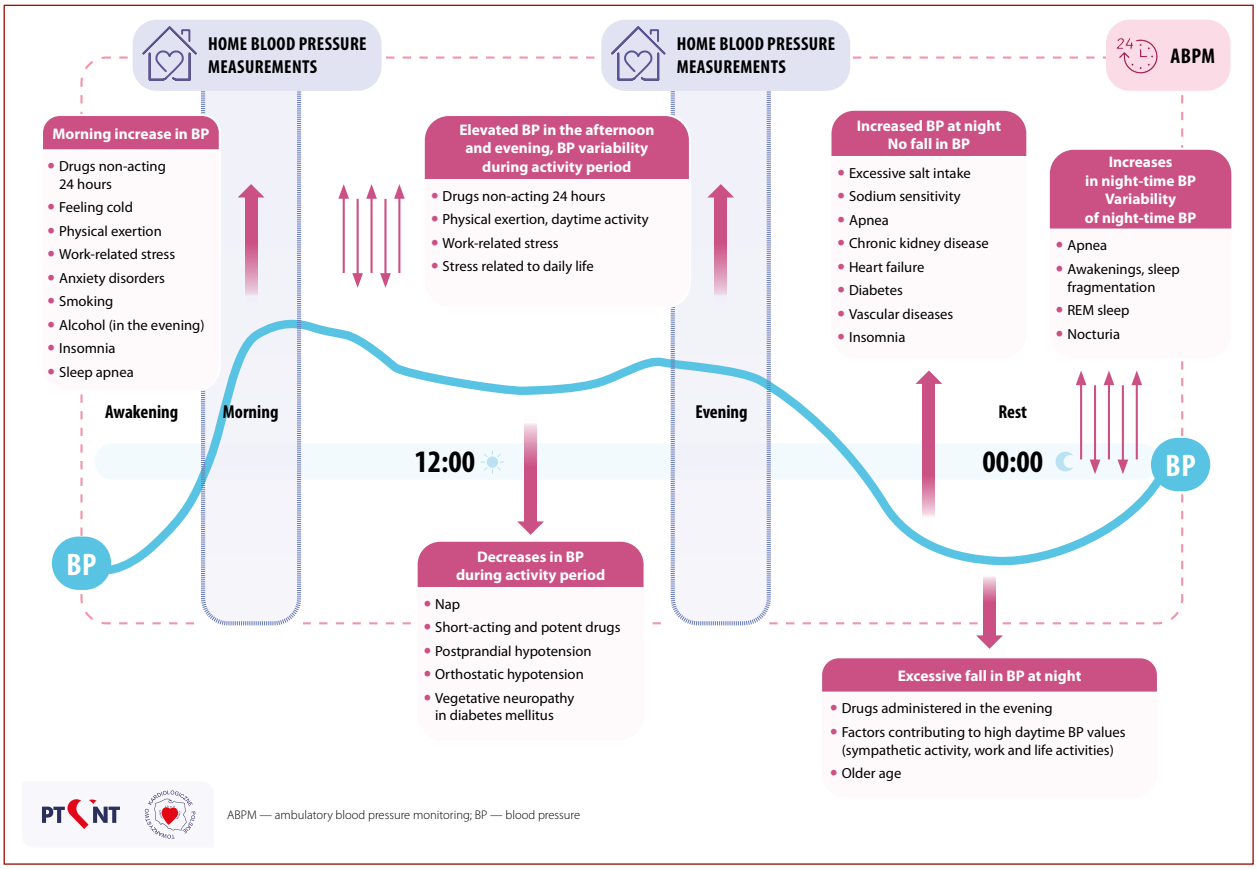


Figure 2.3. Interpretation of blood pressure (BP) values and profile in out-of-office measurements. Based on [35–40]

the patient under everyday conditions. It is a key method for verifying BP values obtained during office and out-of-office BP measurements (Figure 2.1). It also allows the verification of BP values at night. Validated devices with an appropriately sized cuff should be used for that purpose. The measurements should be taken every 15–20 minutes during the day and every 30 minutes at night. Day and night are determined after registration is completed based on the rest time reported by the patient. For the registration to be considered valid, at least 70% of the measurements must provide reliable results. The results are interpreter according to Figures 2.2 and 2.3.

2.5. Situational hypotension

Conditions which may evoke hypotension and further confer CV events and premature death risks include the following:

- orthostatic hypotension;
- postprandial hypotension;
- post-exercise hypotension;
- sleeptime hypotension.

Confirmation of situational hypotension as listed above usually require individualized antihypertensive therapy.

As part of the initial assessment of patients, it is recommended to perform an orthostatic test by measuring BP

1 and 3 minutes after changing the position from sitting/lying to standing (the patient should stay in a sitting/lying position for ≥5 minutes). Orthostatic hypotension is diagnosed when there is a decrease in systolic BP of ≥20 mm Hg or diastolic BP of ≥10 mm Hg. It is recommended to repeat the orthostatic test when suggestive symptoms of orthostatic hypotension occur [5].

2.6. Opportunistic BP measurements and BP measurements in pharmacies

BP measurements that do not meet the criteria of the categories described above are referred to as opportunistic (op-BP) measurements. Examples of op-BP are BP measurements carried out during health awareness events (e.g. White Saturdays, the international MMM campaign, the World Heart Day, etc.) [17]. The non-standard course of the op-BP measurements makes the BP readings difficult to clearly interpret, but this type of activities engage participants in preventive actions. It is recommended that the op-BP measurement organisers consider the following:

- printing/saving the op-BP measurement result;
- name of the device used and the size of the cuff;
- recommending the person to consult the result with the physician during the next visit (or, in the case of an abnormal result, a recommendation to contact the physician urgently — in the case of BP >180/110 mm Hg).

Systematic incorporation of op-BP into non-medical services, such as hairdressing services, have additional potential. Regular visits to barbershops during which clients measure their BP and receive feedback on HT have been shown to increase the effectiveness of blood-lowering treatment, especially in high CV risk populations [32].

A special category of op-BP measurements are those performed in pharmacies; the procedure which was not regulated in Poland until 2023. Currently, pharmacists are authorized to measure BP according to the office measurement standard. The aim of that service, together with drug review as part of the pharmaceutical care is to improve therapeutic safety and adherence to blood lowering therapy [33, 34].

2.7. Night-time BP

Lack of BP fall during sleep, or the so-called non-dipping, is a condition in which BP does not fall at night by a physiological 10%–20% compared to daytime values. Such a condition, as well as elevated BP at night, excessive night-time fall or morning surge, is associated with a higher risk of cardiovascular diseases such as HT, HF, stroke or myocardial infarction. The most favourable BP profile that is associated with the lowest CV events risk is characterized by a moderate reduction in BP during sleep and no excessive surge in the morning [35–40].

How to assess BP values at night?

- Ensure that ABPM has been carried out correctly using a validated device.
- Ask the patient if the quality and length of sleep were adequate and if BP measurements did not interrupt their sleep.
- Check whether the rest period specified in the result matches the actual rest time.
- Assess the absolute BP values at night, the night-time fall and morning increase.
- A useful addition to the ABPM machines is the motor activity assessment function [consider the use of the available ABPM machine function as a supplement], which helps to assess the quality and quantity of the patient's sleep during the recording.

3. HT DIAGNOSIS

BP tends to rise with age. The initial BP rise is mainly driven by genetic factors, whereas the environmental factors play a pivotal role later in life. The cut-off values that define HT are set arbitrary. It is BP value beyond which its' reduction results in longer predicted life span and better quality of life. In recent years, a large body of evidence has emerged showing the benefits of lower target BP values (<130/80 mm Hg). However, the European guidelines uphold the cut-off for the diagnosis of HT at 140/90 mm Hg [4, 5].

The authors of this document confirm 140/90 mm Hg in office BP to be diagnostic for HTN (and corresponding values in out-of-office measurements; Figure 2.2). However, it is emphasized that BP in the ranges of 120–139/70–89 mm Hg, referred to as "elevated BP", require intensive lifestyle changes and, in some clinical settings, also pharmacotherapy [5].

Hypertension is diagnosed based on:

- a reliable history indicating high BP or use of antihypertensive therapy;
- BP values on home BP measurements (see section 2);
- BP values on ABPM (see section 2);
- office BP, only if confirmed by home measurements/ABPM or when office BP is ≥180/110 mm Hg after excluding reversible causes (see Figure 3.1).

Figure 2.2 presents the BP cut-off values for the diagnosis of HT depending on the method of measurement. BP defined as elevated is also associated with a higher cardiovascular risk. Figure 3.1 presents the principles for the HT diagnosis.

The white coat effect occurs when BP in office measurements is within the range of values consistent with HT, but remains within the range of elevated BP or optimal BP values during home measurements or ABPM. Patients with that condition may be at increased cardiovascular risk and should be monitored regularly, i.e. every 6–12 months. In

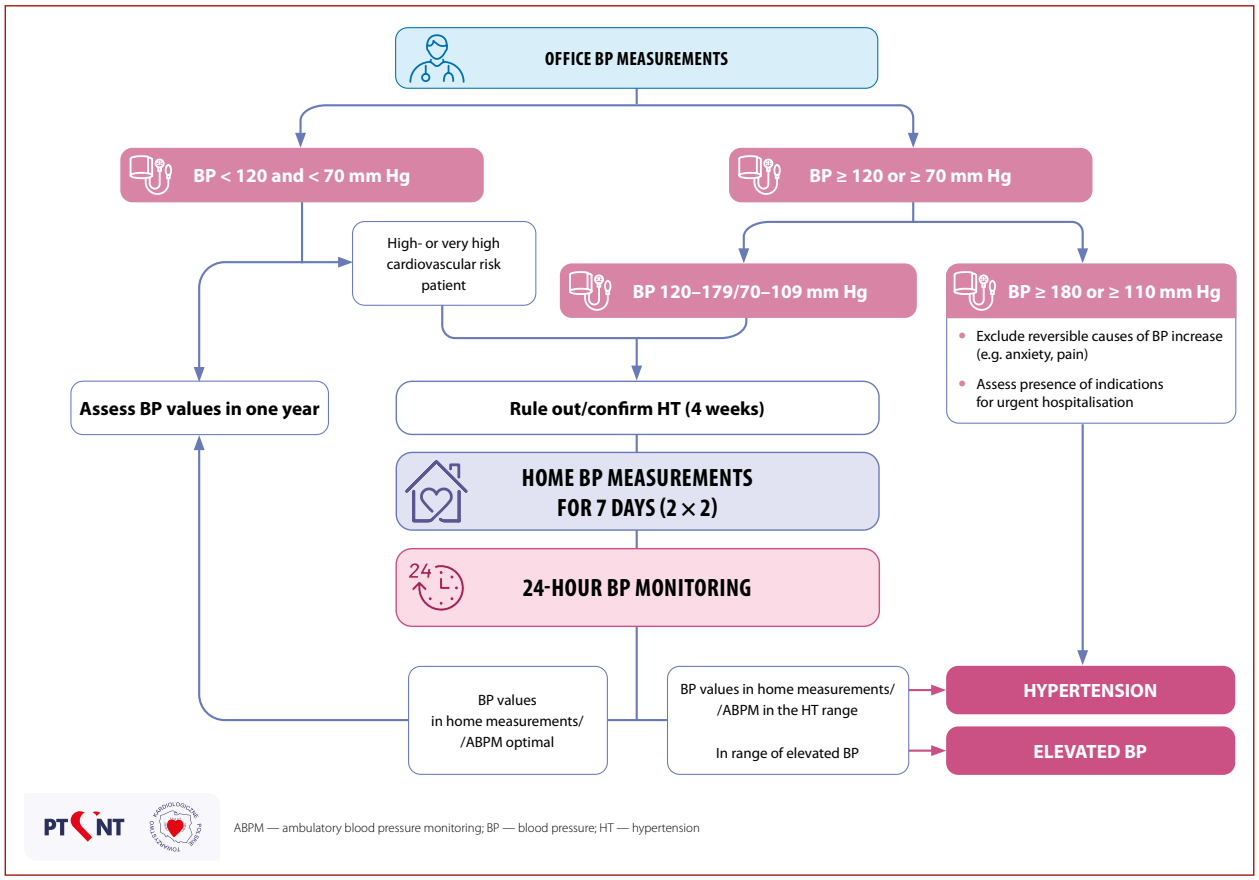


Figure 3.1. Principles of hypertension diagnosis

specific cases, especially in patients with organ complications or diagnosed CV disease, the initiation of antihypertensive treatment should be considered.

How often to assess BP values to detect HT?

Since BP increases throughout life and the rate of increase depends on many factors, BP measurement (office or at home) should be performer at least once a year in every adult.

People with elevated BP who are not on antihypertensive treatment should have their BP measured every three months. In the last case, it is also worth considering annual 7-day home measurements to get a more accurate picture of BP changes.

Masked HT is defined by office BP readings lower than 140/90 mm Hg which coincide with elevated home or 24-h ambulatory values. Such a condition should be treated as HT and requires appropriate treatment (Figure 3.1).

4. CLINICAL ASSESSMENT, DIAGNOSTIC TESTS AND ASSESSMENT OF TARGET ORGAN DAMAGE

4.1. Clinical assessment of the HT patient

Clinical assessment of a patient with HT includes patient's medical history, physical examination, as well as routine and extended tests/evaluation. The purpose is to detect the increased risk of CV diseases and to identify specific comorbidities and potential causes of secondary HT. Additionally, the aim of the assessment is to identify HT-mediated organ damage (HMOD). The key information on HT to be obtained from the anamnesis and physical examination is summarized in Tables 4.1 and 4.2.

4.2. Routine and addtional evaluation

Routine evaluation

Routine medical assessment and additional tests to be performed at the diagnosis and monitored as indicated are summarized in Figure 4.1 and Table 4.3.

Table 4.1. Key information on hypertension (HT) to be obtained during a medical interview

Patient's history of HT
• Age at which HT was diagnosed (disease duration) • Stable versus rapidly increasing BP (or increasing need for antihypertensive medication) • Record of current and past BP values obtained during home measurements • Current/previous use of antihypertensive medications, including their effectiveness and tolerability • Adherence to therapy • Past history of HT during pregnancy/pre-eclampsia/eclampsia
Risk factors
• Family history of hypertension, especially in grade one relatives <50 years of age • Family history of renal disease and premature atherosclerosis (in men <55 years of age, in women <65 years of age) • Smoking, including e-cigarettes — currently and in the past — number of pack-years • Inappropriate diet, amount of salt intake, alcohol consumption — amount and type • Lack of regular physical activity/sedentary lifestyle • Increase or loss of weight in the past • Erectile dysfunction • Sleep disturbance: sleep length and quality, snoring, sleep apnea (information also from the partner) • Stress related to work or personal life (subjective stress level) • In women, premature menopause (natural/iatrogenic) • Low weight at birth, premature birth • Pregnancy-related events — recurrent miscarriages, stillbirths • Chronic inflammatory diseases, frequent and prolonged infections, especially COVID-19 and influenza • Long-term oncological treatment
History and symptoms of HMODs, cardiovascular diseases, strokes and kidney disease
• Brain and eyes: headache, dizziness, fainting, visual impairment, TIA, sensory or motor deficits, stroke, carotid revascularisation, cognitive function impairment, memory impairment, dementia (in older people) • Heart: chest pain, dyspnea, syncope, peripheral edema, history of myocardial infarction, coronary revascularisation, symptoms or diagnosis of arrhythmia (especially atrial fibrillation), heart failure • Kidney: thirst, polyuria, nycturia, hematuria, recurrent urinary tract infections, patient or family history of CKD (e.g. polycystic kidney disease), history of urological surgery, congenital abnormalities of the urinary tract (in young patients), overuse of NSAIDs. • Peripheral arteries: cold extremities — observed asymmetry of temperature and/or skin colour, intermittent claudication (painless claudication, pain at rest), ulceration or necrosis of the skin of the lower limbs, previous peripheral revascularisation
Assessment for secondary HT
• Young age of onset of HT (<40 years of age) and >160 mm Hg systolic BP values or sudden development of HT or rapidly deteriorating BP control in older patients • Recurrent renal/urinary tract diseases • Paroxysmal symptoms suggestive of pheochromocytoma • History of spontaneous or diuretic-induced hypokalemia, episodes of weakness/painful muscle cramps (hyperaldosteronism) • Recurrent elevated BP with pulmonary edema with unstable renal function parameters (renal artery stenosis) • Symptoms suggestive of thyroid disease or hyperparathyroidism • Use of hormonal contraception or hormone replacement
Drug treatment (other than antihypertensive drugs)
• Psychostimulant/recreational drug abuse, concomitant therapies, e.g. glucocorticosteroids, including over-the-counter paracetamol, NSAIDs/COX-2 inhibitors, immunosuppressants, anticancer drugs, vasoconstrictors

Abbreviations: COVID-19, coronavirus disease 2019; COX-2, cyclooxygenase 2; HMOD, hypertension-mediated organ damage; NSAIDs, non-steroidal anti-inflammatory drugs; CKD, chronic kidney disease; BP, blood pressure; CV, cardiovascular; TIA, transient ischemic attack

Table 4.2. Essential elements of the physical examination associated with hypertension (HT)

Body structure
• Body weight and height measured on a calibrated scale, with the calculation of BMI • Waist circumference, neck circumference
Symptoms of organ damage caused by HT
• Neurological examination and assessment of cognitive functions • Auscultation of the heart and carotid, renal, femoral arteries • • Palpation of carotid and peripheral arteries
Secondary HT symptoms
• Assessment of skin lesions: café-au-lait spots associated with neurofibromatosis (pheochromocytoma) • Palpation of the kidneys to detect enlargement in polycystic kidney disease • Auscultation of the heart and renal arteries to look for murmurs indicative of aortic stenosis or renovascular HT • Symptoms (phenotypic features) of Cushing's disease or acromegaly • Symptoms of thyroid disease

Abbreviation: BMI, body mass index

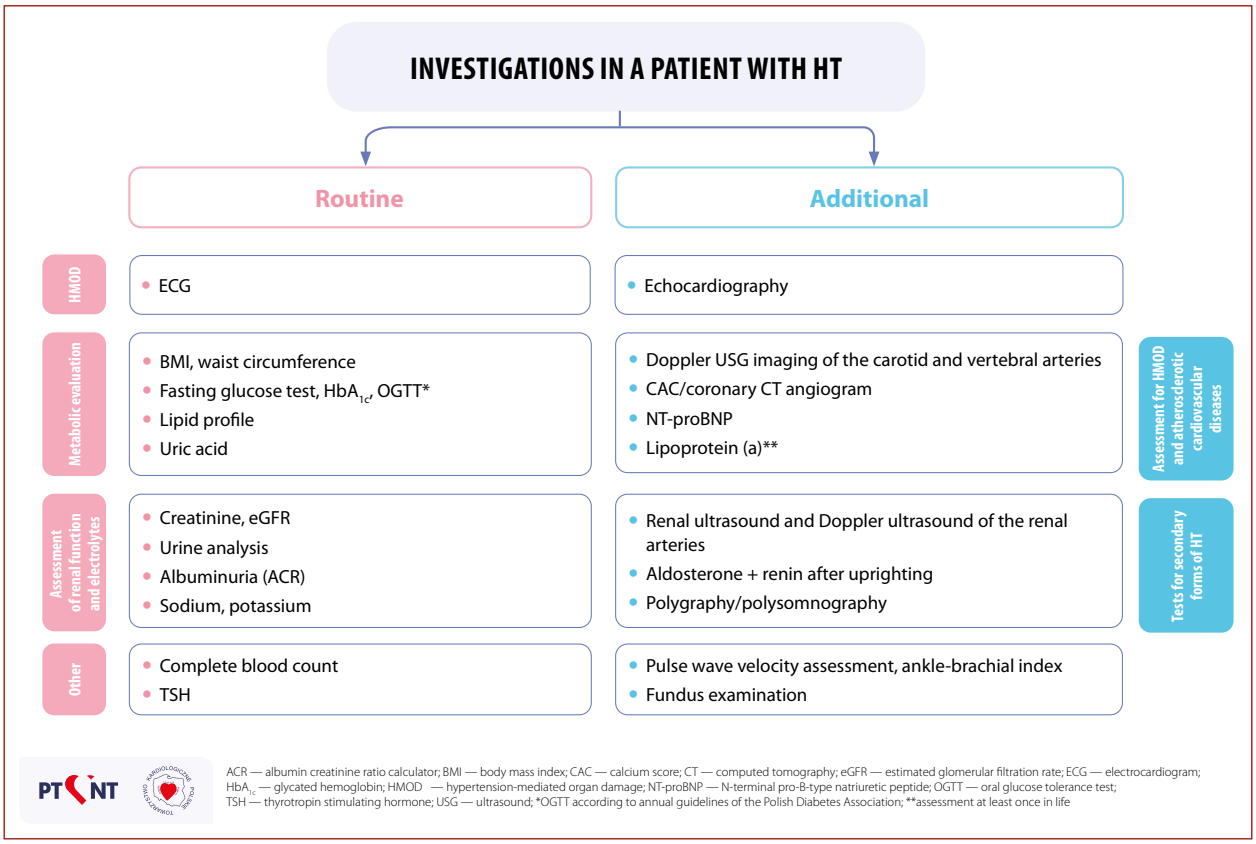


Figure 4.1. Basic and extended medical examinations in a patient with hypertension (HT)

Table 4.3. Basic medical examinations in patients with hypertension (HT)

Routine medical examination	Clinical significance	Frequency
Peripheral blood morphology — hemoglobin and/or hematocrit	Screening for causes of secondary HT (polycythemia, e.g. in the course of sleep apnea, secondary polycythemia, polycythemia vera)	Depending on the results and indications
Fasting glucose test, HbA1c, OGTT*	Cardiovascular risk assessment and comorbidities, diagnosis of diabetes and prediabetes	According to PTD guidelines
Lipoprotein profile: total cholesterol, HDL cholesterol, LDL, non-HDL cholesterol and triglycerides	Cardiovascular risk assessment	In patients on lipid lowering therapy — once a year, in others — according to PTL guidelines
Potassium, serum sodium	Assessment before and after initiation/modification of antihypertensive treatment Screening for secondary HT (hyperaldosteronism, Cushing's disease)	At least annually and after modification of antihypertensive treatment
Serum uric acid	Cardiovascular risk assessment	Depending on obtained results
Serum creatinine to assess eGFR Urine — general examination and mandatory urine albumin to creatinine ratio (ACR)	Cardiovascular and HMOD risk assessment Screening for secondary HT (parenchymal kidney disease, and renal vascular disease) Assessment before and after initiation/modification of antihypertensive treatment	Serum creatinine with eGFR assessment at least once a year and after modification of antihypertensive treatment ACR at least once a year and depending on the results and indications
TSH	Screening for secondary HT — hypothyroidism or hyperthyroidism	Depending on the results and indications
12-lead ECG	Assessment of HMOD (hypertensive heart disease, left ventricular hypertrophy) Assessment of comorbidities (atrial fibrillation, history of myocardial infarction)	Once a year

*OGTT as recommended by PTD

Abbreviations: ACR, albumin creatinine ratio calculator; eGFR, estimated glomerular filtration rate; ECG, electrocardiogram; HbA1c, glycated hemoglobin; HMOD, hypertension-mediated organ damage; HT, hypertension; OGTT, oral glucose tolerance test; PTD, Polish Diabetes Association; PTL, Polish Lipid Association; cardiovascular; TSH, thyrotropin stimulating hormone

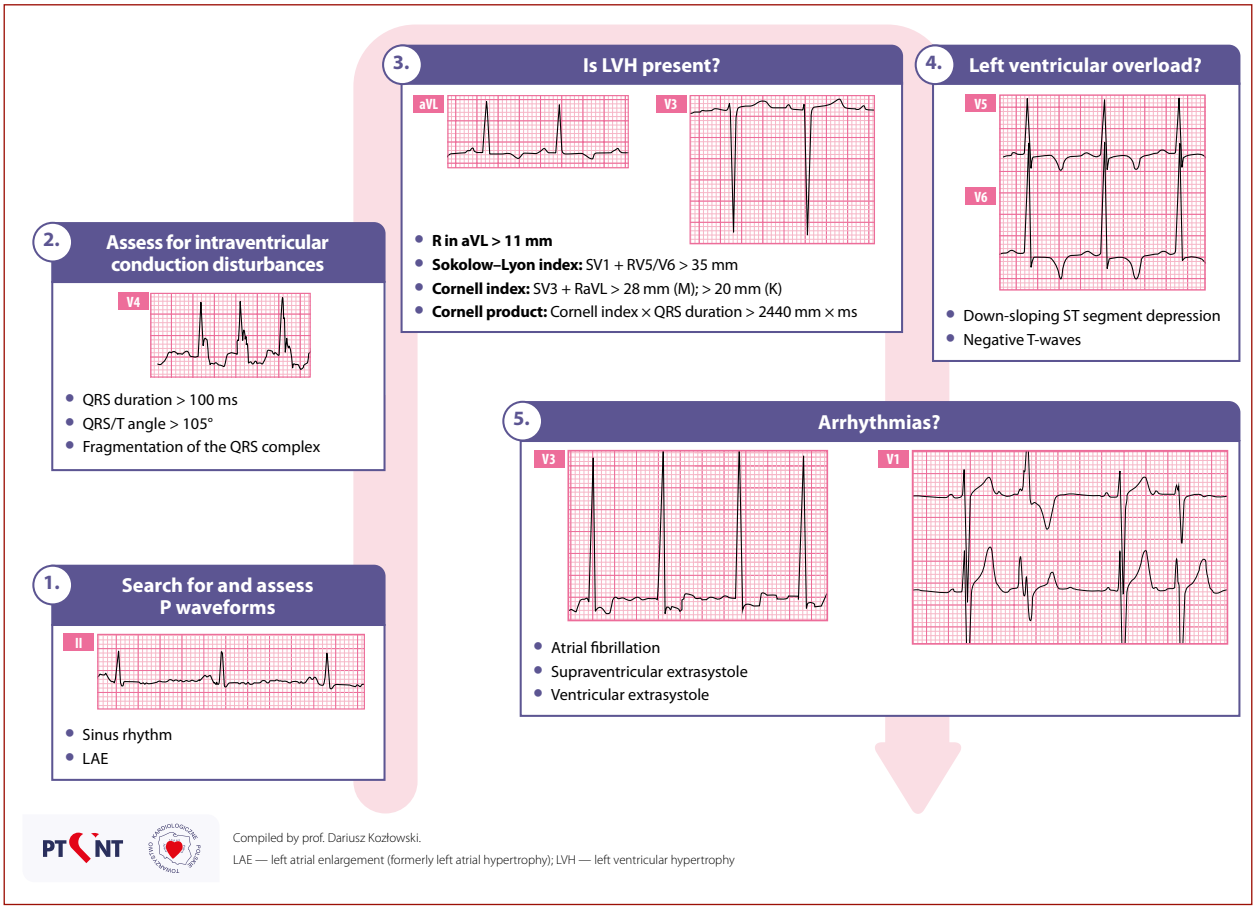


Figure 4.2. Interpretation of an electrocardiographic examination in a patient with hypertension (HT). The criteria for diagnosing left ventricular hypertrophy (LVH) presented in the figure authorise the diagnosis of LVH, i.e. organ damage due to HT, which affects the patient's assessment and prognosis

Additional medical examination

Additional medical examination is to be considered at the initial assessment of a patient with HT, whenever the results may influence further treatment (Figure 4.1). The aim of the examination is primarily to optimise cardiovascular disease risk assessment and to assess HMOD and secondary HT risk [41]. Plasma lipoprotein(a) concentration should be assessed in every adult once in their life [42]. Tests such as non-contrast-enhanced computed tomography (CT) scans to assess calcification index, coronary artery CT scans, ankle-brachial index (ABI), carotid artery ultrasound and echocardiography may document HMOD and confirm the presence of atherosclerotic cardiovascular disease. These test results are important in the risk re-classification (to high or very high risk category) which further justifies the redefinition of therapeutic goals. Based on the results of additional evaluation, the initiation of pharmacotherapy in elevated BP category may be justified.

4.3. Electrocardiographic assessment in a patient with HT

The 12-lead ECG is a key tool in the routine evaluation of patients with HT (Figure 4.2). The development of left ventricular hypertrophy (LVH), a significant HMOD, which becomes more probable along with the duration and severity of HT. ECG recording not only helps to predict cardiovascular risk but also provides valuable information for the clinical assessment of the patient i.e.: detection of atrial fibrillation (AF), history of coronary events. However, the sensitivity of ECG in the diagnosis of LVH is substantially lower as compared to echocardiography.

The Sokolow–Lyon and Cornell indices are key ECG-derived criteria for the diagnosis of LVH. Based on Sokolow–Lyon index criteria, LVH is more commonly diagnosed in people with higher BP, older persons, and males vs. females. In contrast, with reference to the Cornell index criteria, LVH is more common in people with lower BP, younger people, women and obese people. Abnormal ST-segment, and T-wave documented in the lateral precordial leads are the most pronounced signs of LVH. Left ventricular hypertrophy on ECG is a strong indicator of the risk of arrhythmia, including sudden cardiac death (SCD), AF, heart failure and stroke [4].

In addition to the LVH assessment, the ECG provides information on heart rate (HR), type of rhythm, atrioventricular conduction and repolarisation phase disturbances. These data can help to choose an appropriate antihypertensive therapy [4].

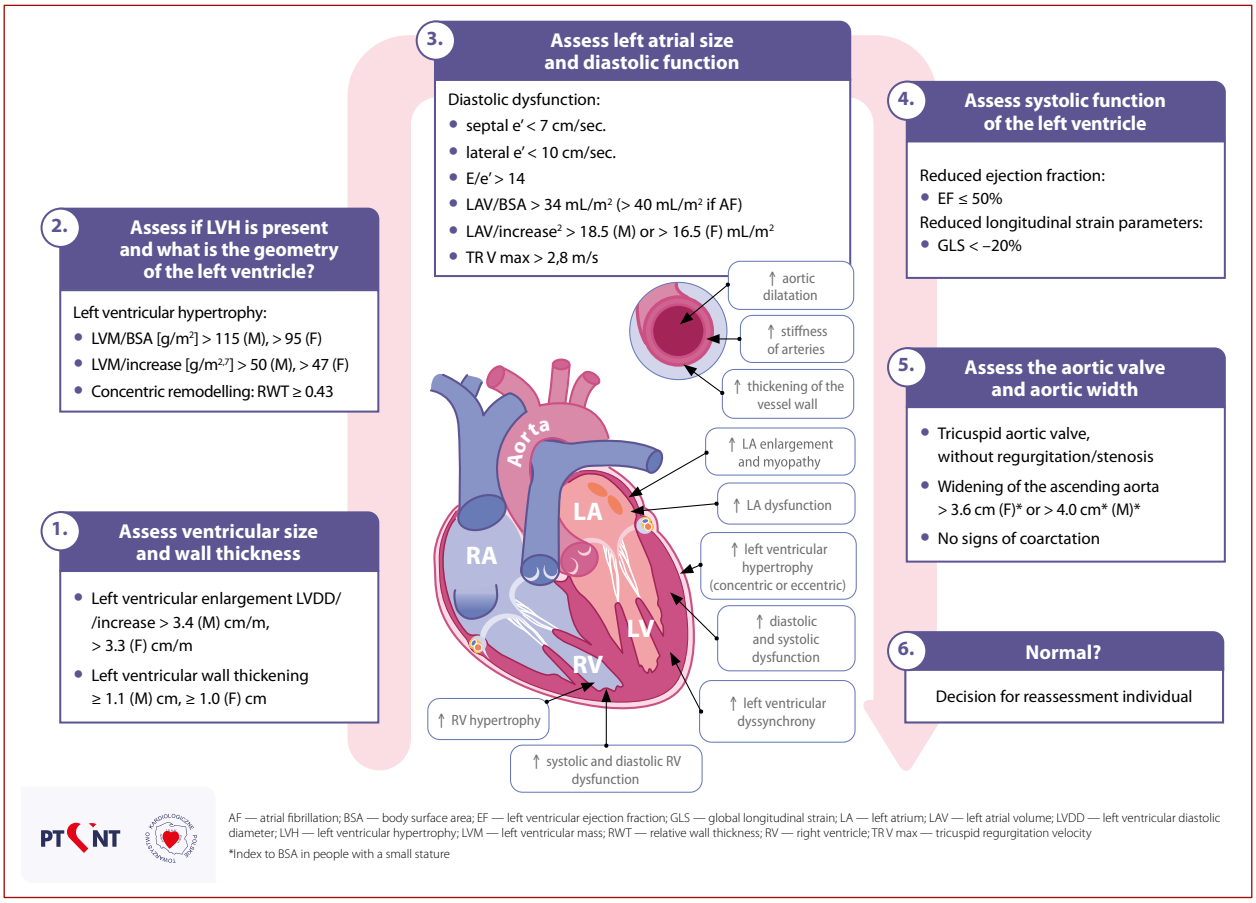


Figure 4.3. Interpretation of an echocardiographic examination in a patient with hypertension (HT) [4, 5, 45]. Abnormal parameters allow for the diagnosis of left ventricular hypertrophy (LVH) (point 2), diastolic dysfunction (point 3) or systolic dysfunction (point 4), i.e. organ damage due to HT, which affects the patient's assessment and prognosis

4.4. Echocardiographic evaluation of a hypertensive patient

Studies show that LVH documented in the echocardiographic examination is an independent risk factor for cardiovascular events, while its regression is associated with a risk reduction [43].

The echocardiographic examination should be considered in all patients with HT. It allows to detect subclinical changes such as LVH, left ventricular remodeling, assessment of systolic and diastolic function, as well as the morphology and function of valves and increased aorta diameter (Figure 4.3). In hypertensive patients with heart murmurs, heart failure symptoms, chest pain, syncope or palpitations, the echocardiographic examination becomes a key diagnostic tool. Occasionally, echocardiography bears the potential to detect secondary forms of HT, such as coarctation of the aorta.

Parameters of left ventricular structure and function considered as subclinical changes in the course of HT (Figure 4.3) are the same as those assessed in patients with heart failure with preserved ejection fraction (HFpEF). This highlights the continuity of cardiovascular risk and the role of HT in the development of clinically overt disease. The basis of diagnosis in such cases is the echocardiographic examination [44].

4.5. Renal function assessment in a patient with HT

Hypertension constitutes the second most common cause of chronic kidney disease (CKD) after diabetes. Inversely, hypertension may also result from primary kidney disease. Deterioration of renal function can be detected by routine laboratory tests using estimated glomelural filtration rate (eGFR) based on either serum creatinine or cystatin C (if available) [46]. Serum creatinine poorly illustrates impaired kidney function, as significant deterioration of renal function can occur with creatinine concentrations remaining within the broad laboratory normal range. Chronic kidney disease is classified based on eGFR, using 2009 CKD-Epidemiology Collaboration formula, and the presence and severity of albuminuria [47, 48]. The albumin–creatinine ratio (ACR) is assessed in a urine sample (preferably in the morning) and is the preferred method for measuring urinary albumin excretion [49]. A single negative strip test result as well as a single normal ACR result do not rule out moderately increased albuminuria [50]. To confirm the diagnosis of moderately or severely increased albuminuria,

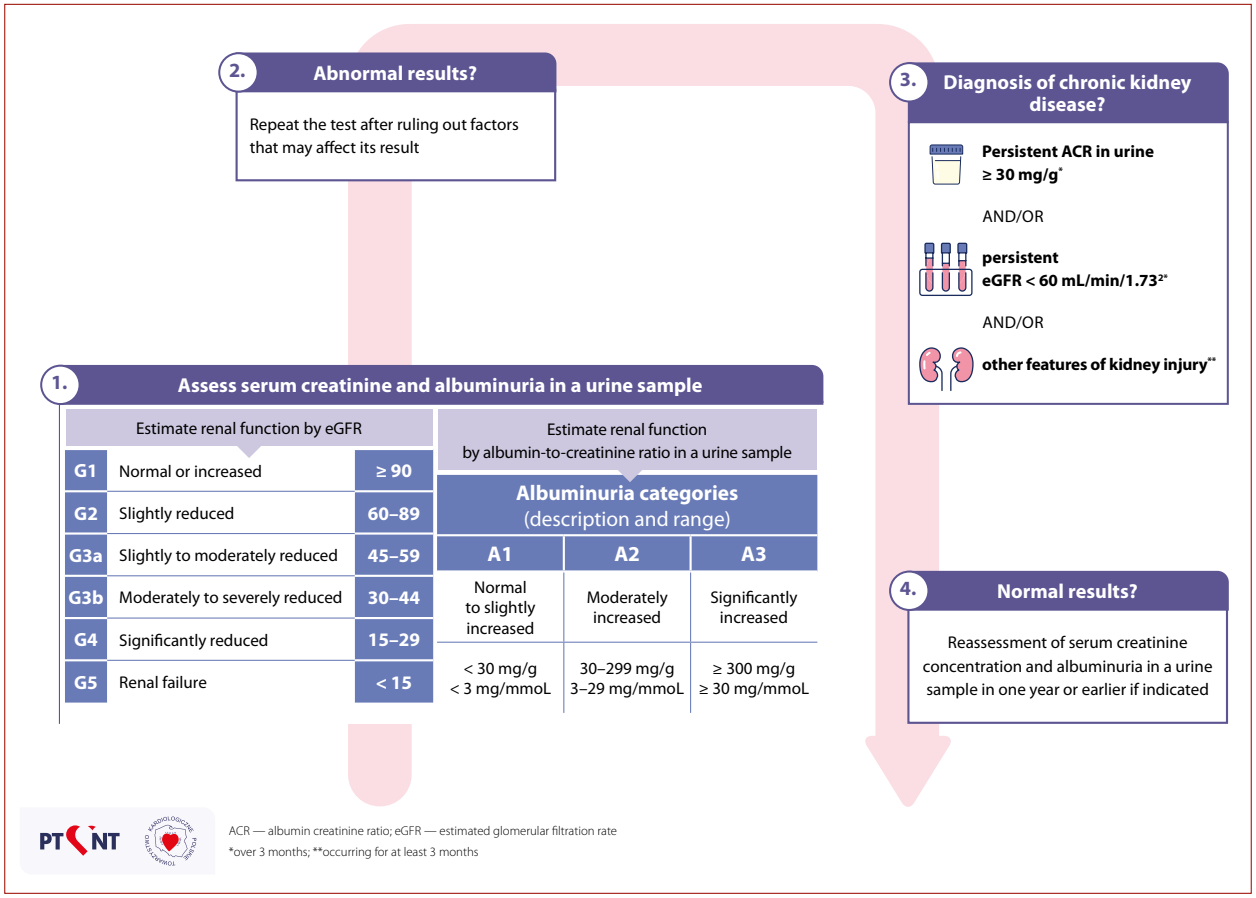


Figure 4.4. Renal function assessment in a patient with hypertension (HT)

two results within this range taken three months apart are required [48]. Serum creatinine, eGFR and ACR should be monitored in all patients with HT (Figure 4.4). The tests should be repeated at least once a year.

Renal ultrasound

Owing to relatively low cost and wide availability renal ultrasound is often utilized to assess kidneys morphology [51, 52]. It is a valuable method for diagnosing CKD and detecting renal artery stenosis [53]. Doppler imaging can be used to assess hemodynamic alterations in the renal artery and the kidney. Doppler spectral ultrasound allows for the measurement of the renal resistive index (RRI), which is a non-invasive and repeatable way to assess the compliance or resistance of the kidneys and systemic arteries [54]. In healthy adults, the RRI ranges from 0.58 to 0.64. A value below 0.7 is considered normal [4, 55]. In relation to age, high RRI values may indicate renal parenchymal disease (e.g. diabetic or hypertensive nephropathy). A difference in RRI between the kidneys may indicate renal artery stenosis [56, 57].

4.6. Other diagnostic tests in a patient with HT

In different settings, hypertensive patients' evaluation may be extended with tests that aim at the HMOD assessment and risk reclassification (HMOD criteria are given in brackets) [2, 5, 58–59]:

- ultrasound examination of the carotid, vertebral or femoral arteries for risk stratification (presence of atherosclerotic plaques, focal wall thickening >1.5 mm);
- assessment of the coronary artery calcification (>100 Agatston score);
- assessment of thyroid-stimulating hormone (TSH);
- N-terminal pro-B-type natriuretic peptide (NT-proBNP) (>125 pg/ml <75 years of age or >450 pg/ml >75 years of age);
- ABI assessment;
- pulse wave velocity (PWV): carotid femoral PWV (cfPWV) >10 m/s and brachial-ankle PWV (baPWV) >14 m/s.

In specific settings, the evaluation of hypertensive patients may be extended to include:

- 24-hour ECG recording (to evaluate arrhythmias);
- fundoscopy (suspition of malignat HT).

4.7. Assessment for secondary forms of HT

Symptoms that may indicate the presence of secondary HT and the screening tests are shown in Figure 4.5. Heart morphology and functional abnormalities specific for secondary forms of HT are also presented.

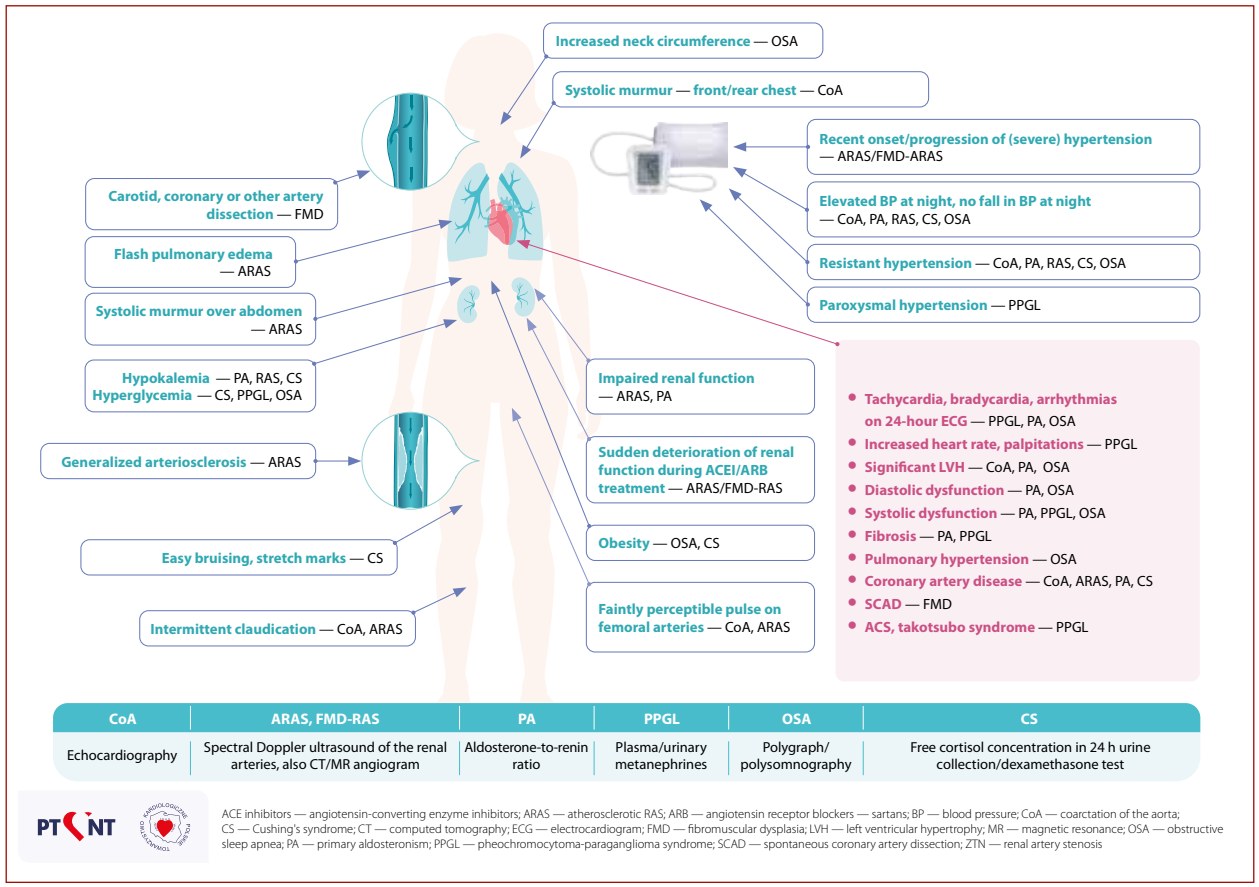


Figure 4.5. Symptoms that may indicate the presence of secondary hypertension (HT) and the screening tests. Based on [4, 5, 60, 61]

5. CARDIOVASCULAR RISK ASSESSMENT IN A PATIENT WITH HT

In most patients, HT coexists with other diseases and risk factors that affect cardiovascular health [62, 63]. In daily practice, priority should be given to patients at high and very high cardiovascular risk. A tool which allows to identify patients at high and very high cardiovascular risk are risk scorecards such as SCORE2, SCORE2-OP, SCORE2-Diabetes, as well as a scale based on "10 for Heart" being developed for the Polish population. We recommend that patients at high and very high cardiovascular risk are identified according to the scorecards, as well as using a range of risk factors and comorbid conditions, as illustrated in Figure 5.1. In patients at high and very high cardiovascular risk, it is essential to take immediate action to substantially reduce the risk, which includes blood lowering pharmacotherapy if BP ranges between 130–139 for systolic BP, and/or 80–89 mm Hg for diastolic BP [4, 25, 41, 42, 64].

In addition to the risk factors shown in Figure 5.1, other risk factors and clinical conditions affecting cardiovascular risk should be considered [4, 65], such as:

- malignant HT/resistant HT;
- increased HR (resting HR >80/min);
- hepatic steatosis;
- chronic obstructive pulmonary disease;
- obstructive sleep apnea (OSA) and other sleep disorders;
- chronic inflammatory disease;
- migraine with aura;
- depressive disorders/chronic stress;
- premature and early menopause;
- frailty;
- other psychosocial and environmental factors (noise and pollution exposure), migration.

6. HYPERTENSION AS A COMPONENT OF THE METABOLIC SYNDROME

Hypertension is one of the most common risk factors for cardiovascular diseases in Poland. In most cases, patients with HT have additional cardiovascular risk factors such as obesity, dyslipidemia or glucose metabolism disorders. In response to that, in 2022, Polish experts proposed a new definitione of metabolic syndrome (MS) [64].

The primary criterion for the diagnosis of MS is obesity as determined by waist circumference and/or BMI. Additional criteria are HT or elevated BP, atherogenic dyslipidemia and pre-diabetes or diabetes. Obesity and two of the three additional criteria allow the diagnosis of MS (Figure 6.1). Waist circumference cut-off values for the diagnosis of abdominal obesity are debated; in

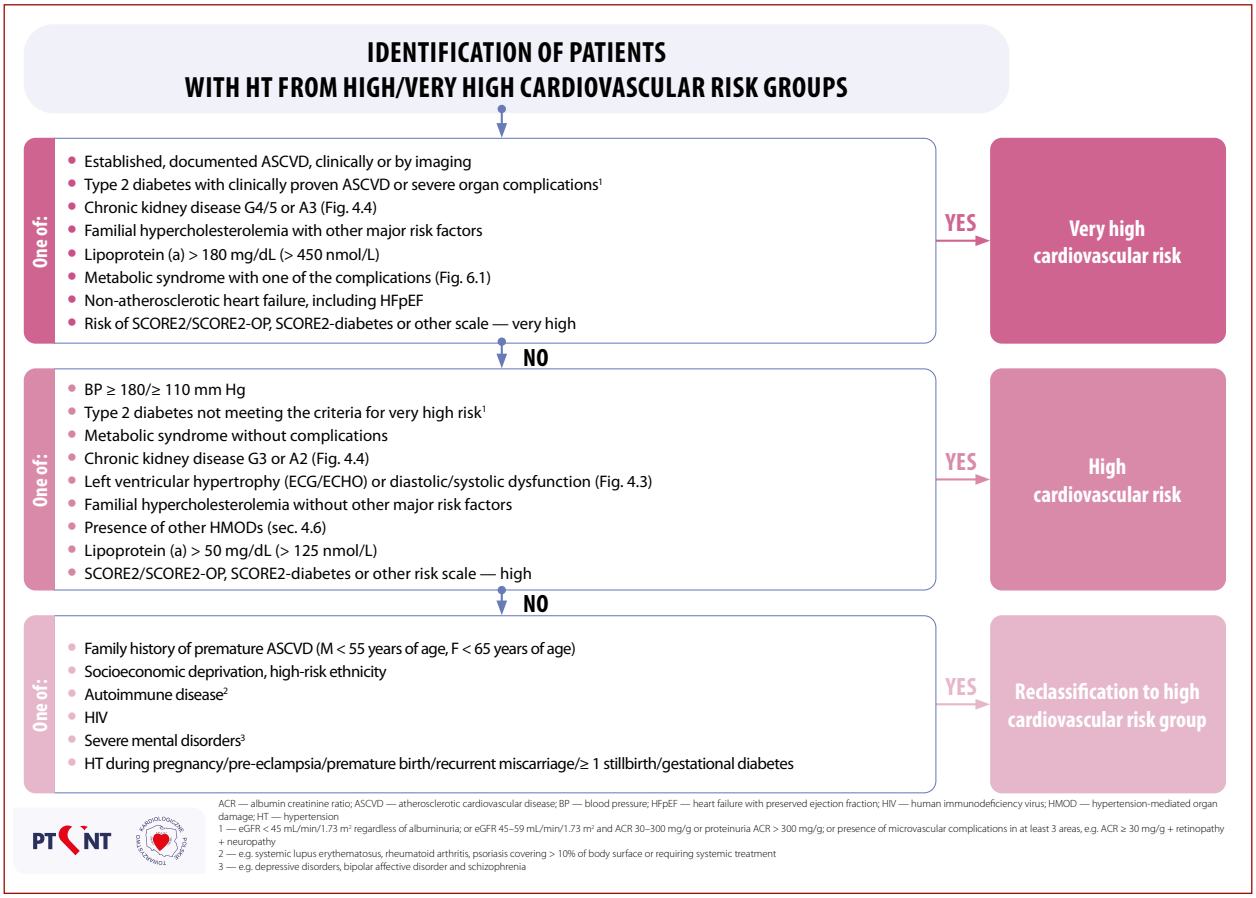


Figure 5.1. Distinction of hypertension (HT) patients at high and very high cardiovascular risk. Developed based on [4, 25, 41, 42, 64]

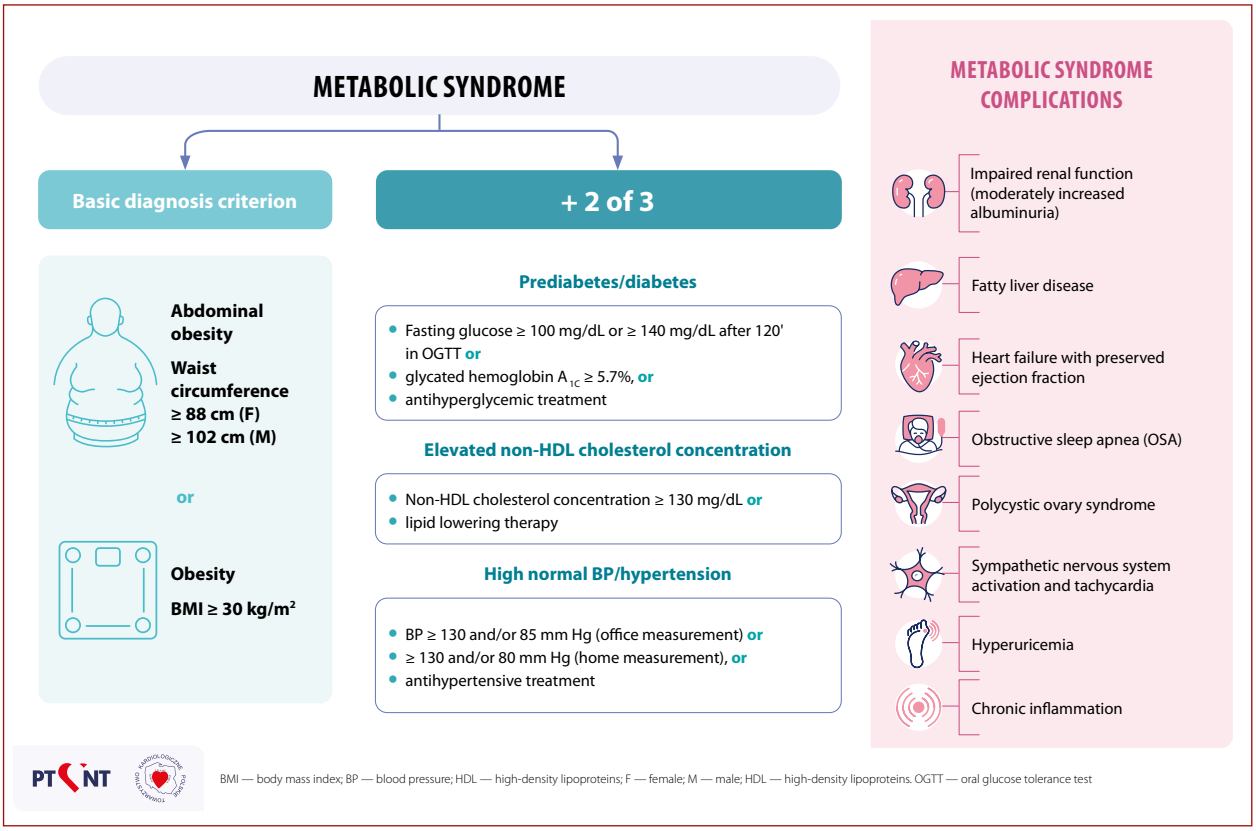


Figure 6.1. Criteria for the diagnosis of metabolic syndrome and its complications. Based on [64]

young people, a waist circumference >80 cm in women and >94 cm in men may already indicate abdominal obesity [64].

The WOBASZ II study shows that 32% of the adult Polish population meets the criteria for the diagnosis of MS [66]. Its most common component is BP ≥130/85 mm Hg or the use of antihypertensive treatment (94% of WOBASZ II participants). Atherogenic dyslipidemia was found in 91% and prediabetes or diabetes in 61% of subjects. The increasing prevalence of obesity may lead to more frequent cases of MS.

Every patient with HT should be assessed for the remaining components of MS. Effective non-pharmacological and pharmacological treatment of each of the four components of MS can substantially reduce cardiovascular risk. Attention should also be paid to complications associated with MS, such as moderately increased albuminuria, hepatic steatosis, OSA or HFpEF, the presence of which further confer cardiovascular risk (Figure 5.1); prevention and treatment of MS reduces the risk of development of abovementioned complications of MS [64].

7. INITIATION OF TREATMENT AND TARGET VALUES

7.1. Initiation of HT treatment

Lowering BP is a key action that significantly reduces cardiovascular risk in patients with HT. Therefore, it is important not to delay the initiation of antihypertensive treatment in patients with a confirmed BP above 140/90 mm Hg [67]. Regardless of baseline BP values, all patients with elevated BP or HT should initiate non-pharmacological measures (section 8) aimed at lowering BP. At the same time, antihypertensive pharmacotherapy should be introduced in all patients with HT and considered in patients with BP within 130–139/80–89 mm Hg who are at high or very high cardiovascular risk after 3 months of non-pharmacological management (Figure 2.2).

7.2. Antihypertensive treatment in patients with elevated BP

The basis of the inclusion of antihypertensive pharmacotherapy in patients with a systolic BP in the range 130–139/80–89 mm Hg is the results of studies showing that such treatment is effective in reducing the risk of developing HT [68–70]. Studies indicate that long-term exposure to elevated BP and other major factors contributing to cardiovascular diseases significantly increases the overall cardiovascular and death risk [71]. It is therefore reasonable to subject patients with elevated BP who are at high or very high cardiovascular risk (criteria in Figure 5.1) to antihypertensive intervention if changes in their lifestyle do not result in BP lowering, despite the lack of hard end-point studies in that group. A decision to introduce pharmacotherapy should be made after 3 months of ineffective non-pharmacological treatment. It is then recommended to start with monotherapy while continuing with the implementation of lifestyle changes (Figure 7.1).

7.3. BP target values

Data from both observational and randomized studies support the recommendation to reduce BP below 130/80 mm Hg, but not lower than 120/70 mm Hg (Figure 7.2) [4, 5, 72, 73]. In this document, the decision-making patterns are simplified, the previous proposals are abandoned in favour of a single, clearer algorithm — it should be assumed that the patient is to be treated considering that goal unless "exceptions" presented later in the section is met. The previous guidelines were revised, the importance of age in determining BP targets was reduced [2]. The basic strategy of pharmacologically lowering systolic BP to 120–129 mm Hg is now recommended for most patients. There are several reasons for that:

- the health status and life expectancy of Poles have improved, thanks to, e.g. better BP control in older people;
- frailty is one of the most common reasons for modifying antihypertensive treatment goals. Therefore, rather than just taking age into account, it is important to consider frailty more broadly. Using only the age criterion leaves out a significant proportion of the population: 6.6% of Poles aged 60–64 may suffer from frailty and 51.7% are at risk of it. In turn, 11.8% of people aged 75–79 are healthy and do not require mitigating therapeutic targets [15]. The assessment for the presence of frailty (using the 9-item Canadian scale or more specific tools) should become a standard at the initial and annual screening of patients at the age of >60.
- the results of intervention studies such as STEP, SPRINT or ESPRIT, which included elderly patients with systolic BP targets below 120 mm Hg, showed a reduction in cardiovascular morbidity and mortality [74–76]. However, the criticism of these studies concerns the enrollment of relatively healthy patients, which does not necessarily reflect the actual health condition of the majority of the elderly population, including in Poland [15]. This confirms that the decision on BP targets should be based on frailty risk and not only on the age of the patient.

Before starting HT pharmacotherapy, it is important to make a clinical decision as to whether the standard target of lowering BP to 120–129/70–79 mm Hg is appropriate for the patient [77]. It is sometimes necessary to set individual, more liberal targets, for example a systolic BP in the range 130–139 mm Hg, in some clinical settings:

- in patients at the age of ≥80;
- when a reduction to 120–129/70–79 mm Hg is not well tolerated; then the rule of thumb is "as low as reasonably achievable" [5];
- in patients with at least mild frailty, regardless of age (in patients with severe/very severe frailty, therapy goals should be determined individually) — see also Figure 11.9;

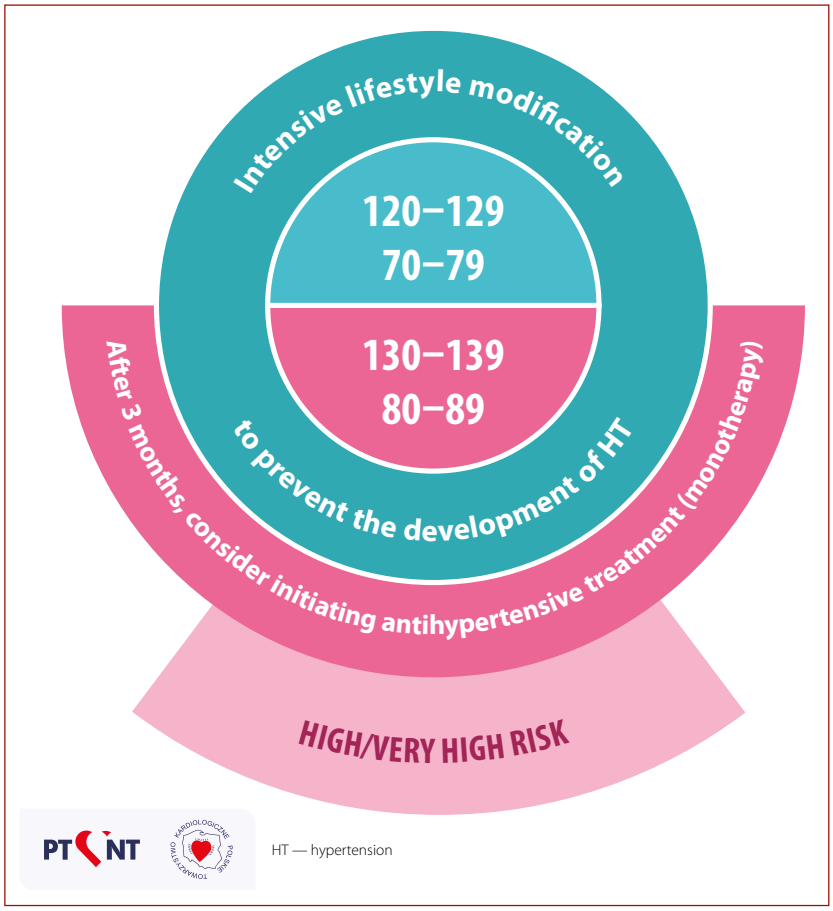


Figure 7.1. Management of patients with elevated blood pressure

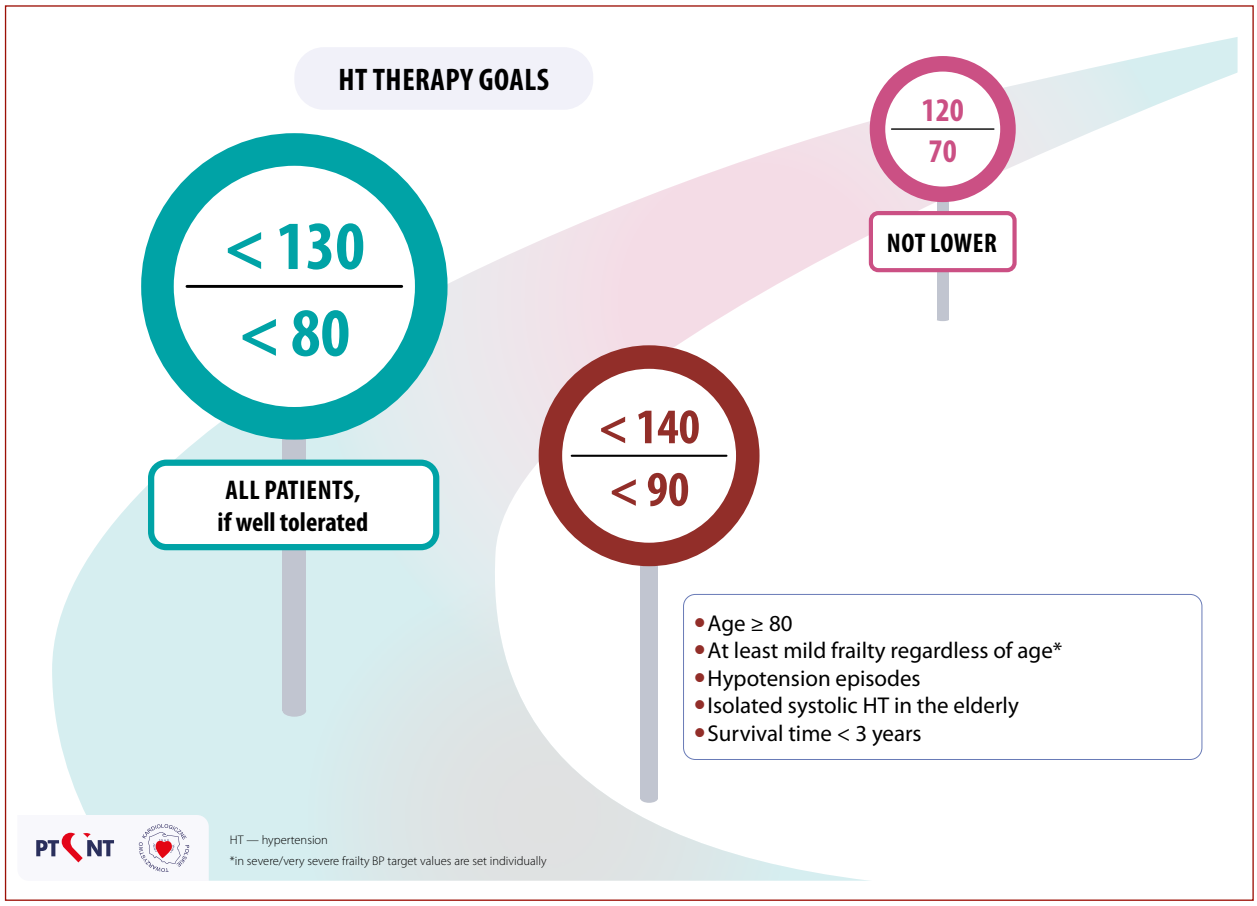


Figure 7.2. Blood pressure (BP) target values

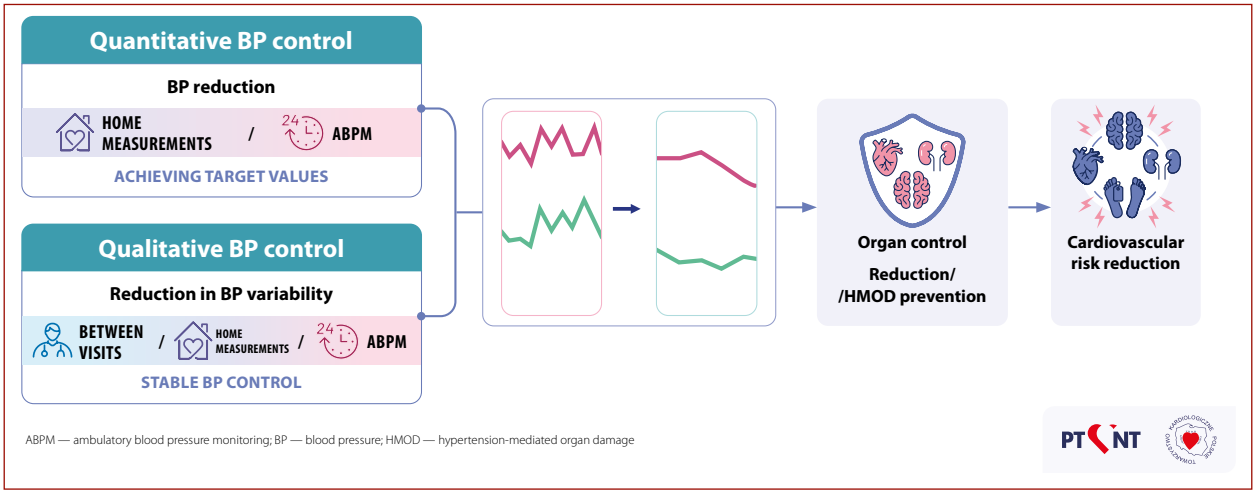


Figure 7.3. Dimensions of antihypertensive effectiveness

- in the case of hypotension syndromes, e.g., orthostatic, post-exercise or postprandial hypotension or occurring during sleep;
- in elderly patients with isolated systolic hypertension (ISH);
- in patients with a life expectancy of less than 3 years.

When it comes to office BP measurements, it is worth follwoing the "trust but verify" principle. This means that, where possible, it is advisable to take BP measurements outside the office before starting therapy and while monitoring its effectiveness [5].

7.4. Dimensions of antihypertensive effectiveness

Achieving target BP is only part of effective HT control. In addition to achieving BP targets ("quantitative" control), the effect of antihypertensive treatment on BP variability ("qualitative" control) — achieving stable HT control — is also important. A growing body of data indicates that increased BP variability in ABPM, home measurements and office measurements (between visits) is associated not only with a higher risk of HMOD and cardiovascular events but also with a higher risk of cognitive impairment (Figure 7.3). Assessing the effect of the treatment used on BP variability is, therefore, an additional exponent of the quality of HT control. Studies show that the use of long-acting antihypertensive drugs may have a beneficial effect on BP variability [78–81].

8. NON-PHARMACOLOGICAL MANAGEMENT IN PATIENTS WITH HT

Non-pharmacological management in patients with HT is a key component of therapy. It is the basis for preventing the development of HT in people with elevated BP. It helps to reduce cardiovascular risk and improves prognosis and quality of life. Lifestyle changes result in lower BP, slow the progression of atherosclerosis and may delay the onset of HMOD and clinical signs of atherosclerosis. Non-pharmacological recommendations (lifestyle measures) with documented efficacy in the treatment of HT are shown in Figure 8.1.

A common belief regarding non-pharmacological management is that coffee consumption should be reduced in patients with HT. Coffee consumption does not increase the risk of HT in the general population. In fact, higher coffee consumption may even lower this risk [82]. Therefore, limiting coffee consumption in HT patients is not necessary. In addition, higher consumption of coffee or tea may reduce the risk of type 2 diabetes [83]. The relationship is different with unfiltered, Turkish-brewed or boiled coffee. It contains higher concentrations of caffestol and kahweol, which may slightly increase serum LDL cholesterol concentrations. However, increased cardiovascular risk was observed in cases of consumption of nine or more such drinks per day [84, 85].

In contrast, the consumption of two or more servings of sugar-sweetened beverages per day is associated with a 35% higher risk of coronary heart disease in women [86]. Consumption of such drinks also increases the risk of all-cause mortality. In children and adolescents, sugar-sweetened beverages raise systolic BP and increase the risk of developing HT [87, 88]. From an early age, sugar-sweetened beverages should not account for more than 10% of daily energy intake.

Excessive alcohol consumption is one of the main causes of premature mortality. Increased alcohol consumption is linearly associated with a higher risk of cancer, liver disease, AF, stroke and HF. Although many scientific societies recommend limiting alcohol consumption and set limits, there is no proven safe amount of alcohol for the general population. Findings show a strong linear correlation between alcohol consumption and higher BP, while also suggesting that low consumption may be associated with a lower cardiovascular risk than total abstinence. However, potential cardioprotective benefits may arise from the overall healthier lifestyle of moderate alcohol drinkers. The risk of HT increases in both sexes when daily consumption is one to two drinks, or 10–20 g of alcohol. Reducing alco-

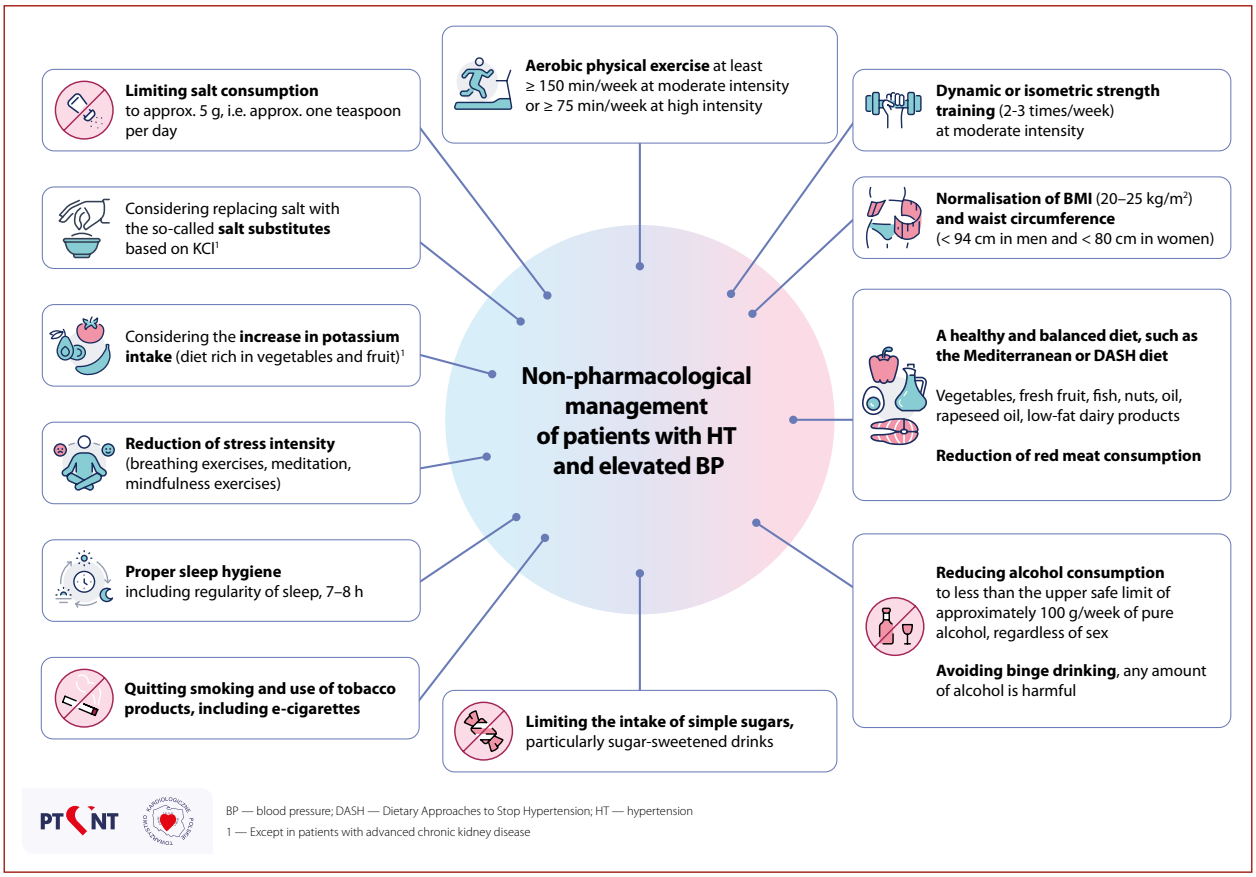


Figure 8.1. Non-pharmacological (changing lifestyle) recommendations with documented efficacy in the treatment of hypertension (HT). Developed based on [4, 5, 41]

hol consumption close to abstinence can lower systolic and diastolic BP by 3.3 and 2.0 mm Hg. Binge drinking is particularly dangerous and, together with uncontrolled HT, it increases the risk of hemorrhagic stroke. Reducing or stopping alcohol consumption, especially in Poland, is recommended for better BP control and overall health [89, 90].

9. BASIC ALGORITHM FOR THE TREATMENT OF HT

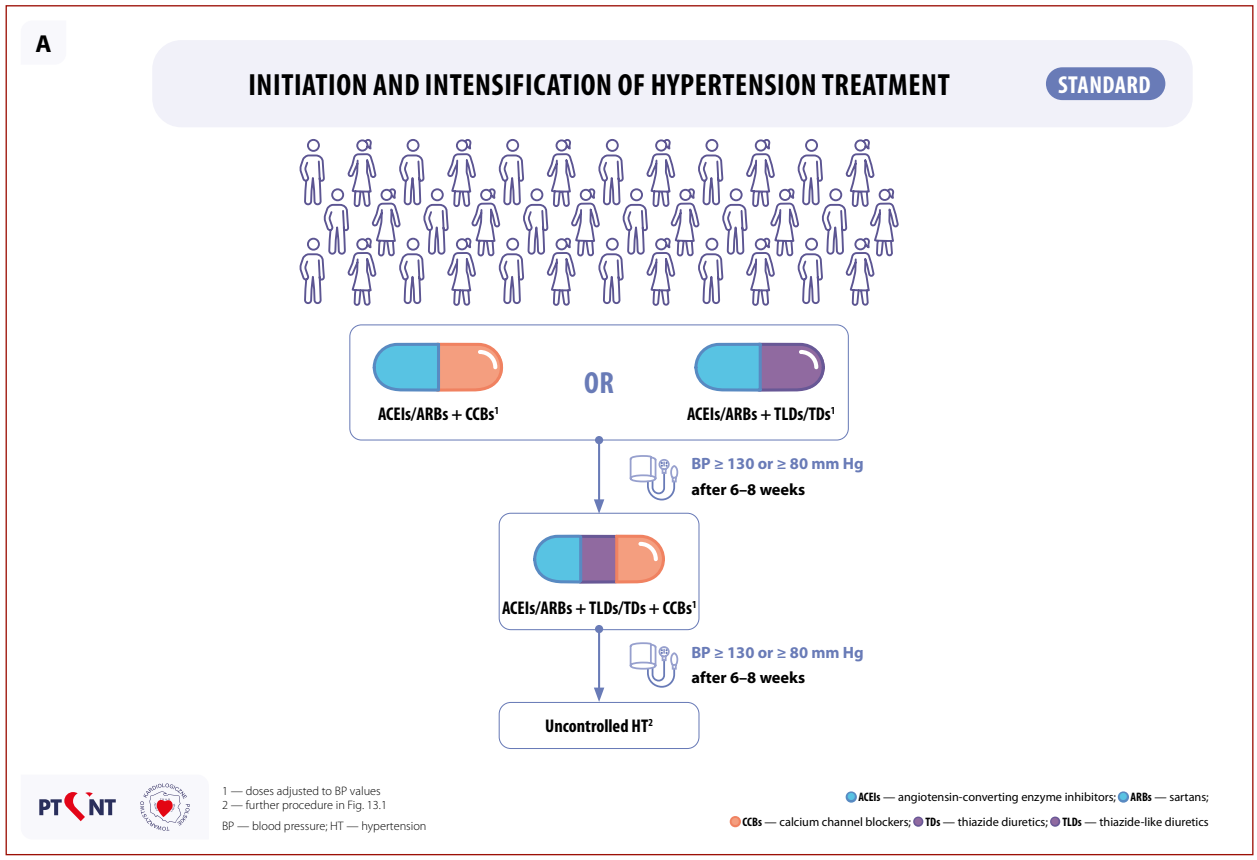
Most antihypertensive drugs used in monotherapy lower BP by less than 20/10 mm Hg and only in approximately half of patients. For that reason, most people with HT require combination therapy. Due to the limited efficacy of monotherapy, it is recommended to start HT therapy with combination therapy, preferably in the form of SPCs. Exceptions are patients in poor general condition, with at least mild frailty (Figure 11.9) or with no HT but with elevated BP, in whom the treatment decision is made on an individual basis, generally starting with monotherapy (Figure 9.1). One to two months after starting two-drug therapy its effectiveness should be assessed and, if target BP values are not achieved, intensification should be considered by adding a third drug to achieve target BP values within three months [2–6, 58, 91]. In recent years, data has been published indicating the effectiveness and safety of starting therapy with a combination of three or four antihypertensive drugs, including the use of SPCs, at low or very low doses. However, this regimen cannot currently be recommended as a routine in daily practice [92].

The use of appropriately selected combinations of two or three drugs, especially in the form of SPCs, can control BP in most patients. The treatment algorithm based on SPCs is effective and better tolerated, promotes patient cooperation and ensures rapid achievement of BP targets. This reduces cardiovascular risk, which is a key goal of HT therapy [2–6, 58, 91, 93].

Groups of antihypertensive drugs that effectively reduce the incidence of cardiovascular events are angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin II receptor AT1 blockers (ARBs, also known as sartans), calcium channel blockers[1] (CCBs), thiazide-like diuretics/thiazide diuretics (TLDs/TDs) and beta-blockers (BBs). The first three groups (the so-called "basic three") are recommended as first-line solutions for the initiation of HT therapy due to their superior efficacy in reducing cardiovascular risk [2–6, 58, 91]. It should be noted that in Poland, among patients using two or three antihypertensive drugs, only 34% use a regimen based on the recommended combinations [12].

The basic treatment strategy should include (Figure 9.1) [2–6, 58, 91]:

[1]For simplicity, unless otherwise stated in the document, the term CCB refers to dihydropyridine CCBs



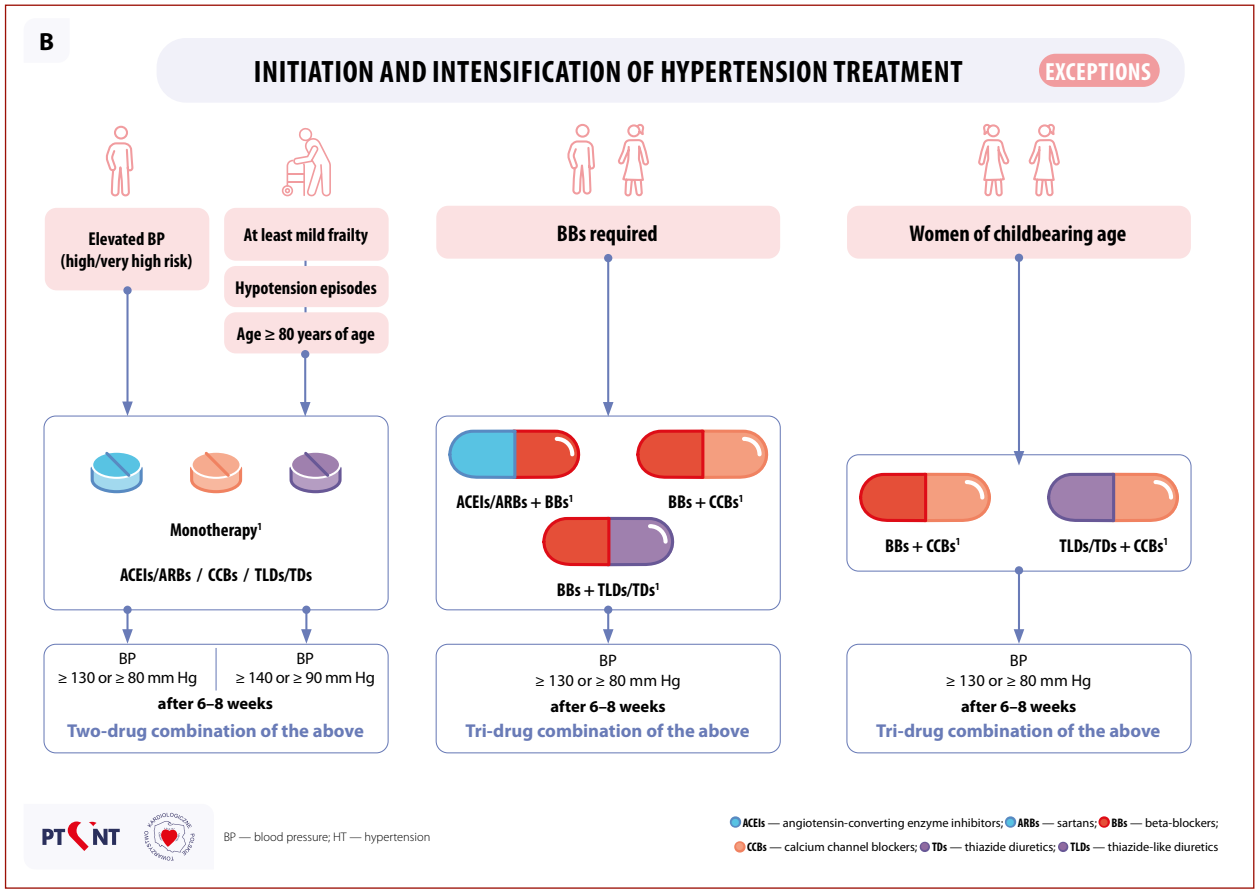


Figure 9.1. Basic strategy for the treatment of hypertension (HT) (**A**) and exceptions to this strategy (**B**)

- ACEIs or ARBs with CCBs or TLDs/TDs (step 1);
- ACEIs or ARBs and CCBs and TLDs/TDs (step 2).

Beta-blockers should be used in selected clinical situations in combination with other drugs or independently of the use of the "basic three" (section 10). When choosing drugs, one should take into account their ability to significantly lower BP, reduce its variability and reduce the risk of developing or worsening HMOD and cardiovascular diseases, as well as their tolerability profile [2–6, 58, 91]. Exceptions to the use of the „basic three" are shown in Figure 9.1.

9.1. Dosage of antihypertensive drugs versus intensification of therapy

As part of the basic algorithm of HT therapy, two approaches to the selection and intensification of doses of antihypertensive drugs are proposed. The first involves starting with lower doses of a two-drug combination, increasing them to maximum doses and then adding a third drug. The second involves starting therapy with low doses of two drugs and moving on to three drugs in low doses. Based on a practical approach in daily practice, it is recommended:

- the use of SPCs at every stage of therapy — the wide availability of doses and combinations allows to modify the doses and numer of drugs while still remaining on SPCs, which translates into better therapeutic persistence [2–6, 58, 91, 94–96]. In the search for available drug combinations in the form of SPCs in Poland, an app developed by PTNT is helpful — mniejlekow.pl;
- matching doses to the patient's BP values and following the principle that adding another drug is more effective than increasing the doses of the drugs already in use [91, 95, 97–100];
- avoiding increasing doses of drugs such as CCBs, as this may increase the risk of side effects [101];
- taking advantage of the benefits of increasing doses of TLDs/TDs when diuretic treatment needs to be intensified, especially indapamide and chlortalidone [92, 102, 103];
- using full doses of ACEIs/ARBs, especially in patients with cardiovascular disease based on atheromatosis or CKD, in line with data from large clinical trials [104–106].

When to use antihypertensive drugs: in the morning or evening?

- With regard to long-acting antihypertensive drugs, no differences have been reported in terms of efficacy in lowering BP depending on whether they are administered in the morning or evening. Randomized trials indicate that there is no difference in the reduction of cardiovascular risk between morning and evening drug administration [107–110].
- However, the use of medication in the evening may be associated with a higher rate of skipping it compared to taking the drugs in the morning. It is recommended to use long-acting drugs once a day, in the form of SPCs, and adjust the time of taking drugs to the patient's habits. The most frequently chosen time is the morning hours [109, 110].
- The TIME study showed no difference in the rate of glaucoma-related hospitalisations, but it did not thoroughly analyse glaucoma-related complications. In the BED-MED study, in turn, glaucoma was an exclusion criterion. Therefore, the administration of antihypertensive drugs in the evening should be avoided in patients with glaucoma [109–112].
- In patients with elevated BP at night, an increase in the dose of diuretic in the morning may be considered, especially in cases of coexisting CKD, diabetes or OSA. In the case of OSA, a mineralocorticoid receptor antagonist (MRA) and/or BBs may also be considered [113, 114].

10. THE PLACE OF BETA-BLOCKERS IN HT THERAPY

In previous guidelines, BBs were mainly recommended for exceptional indications [2, 6]. Despite this, BBs are the most commonly used group of antihypertensive drugs in Poland [12]. Numerous studies have shown that BBs significantly reduce the risk of HF and serious cardiovascular events in HT patients compared with placebo. BBs are also comparatively effective in preventing serious CV events, as are other classes of antihypertensive drugs. The exception is stroke prevention, where they are less effective. This difference may be due to small differences in the BP achieved, including central systolic BP, which has a particular impact on cerebrovascular events [115–119].

Beta-blockers are a diverse group of drugs. Of particular interest are their beta1 selectivity and vasodilatory properties. Studies on nebivolol (additional vasodilatory effect) and bisoprolol, which have higher beta-1 selectivity, showed that these drugs have a more favourable side-effect profile, including a lower incidence of erectile dysfunction [120–122]. Studies using carvedilol, bisoprolol, metoprolol succinate and nebivolol have confirmed their beneficial effects on prognosis in patients with HFrEF [123]. Beta-blockers such as metoprolol and bisoprolol are also effective in treating cardiac arrhythmias. In addition, metoprolol and propranolol are used for non-cardiac conditions such as essential tremor, prevention of migraine attacks or psychosomatic disorders [4, 116, 124].

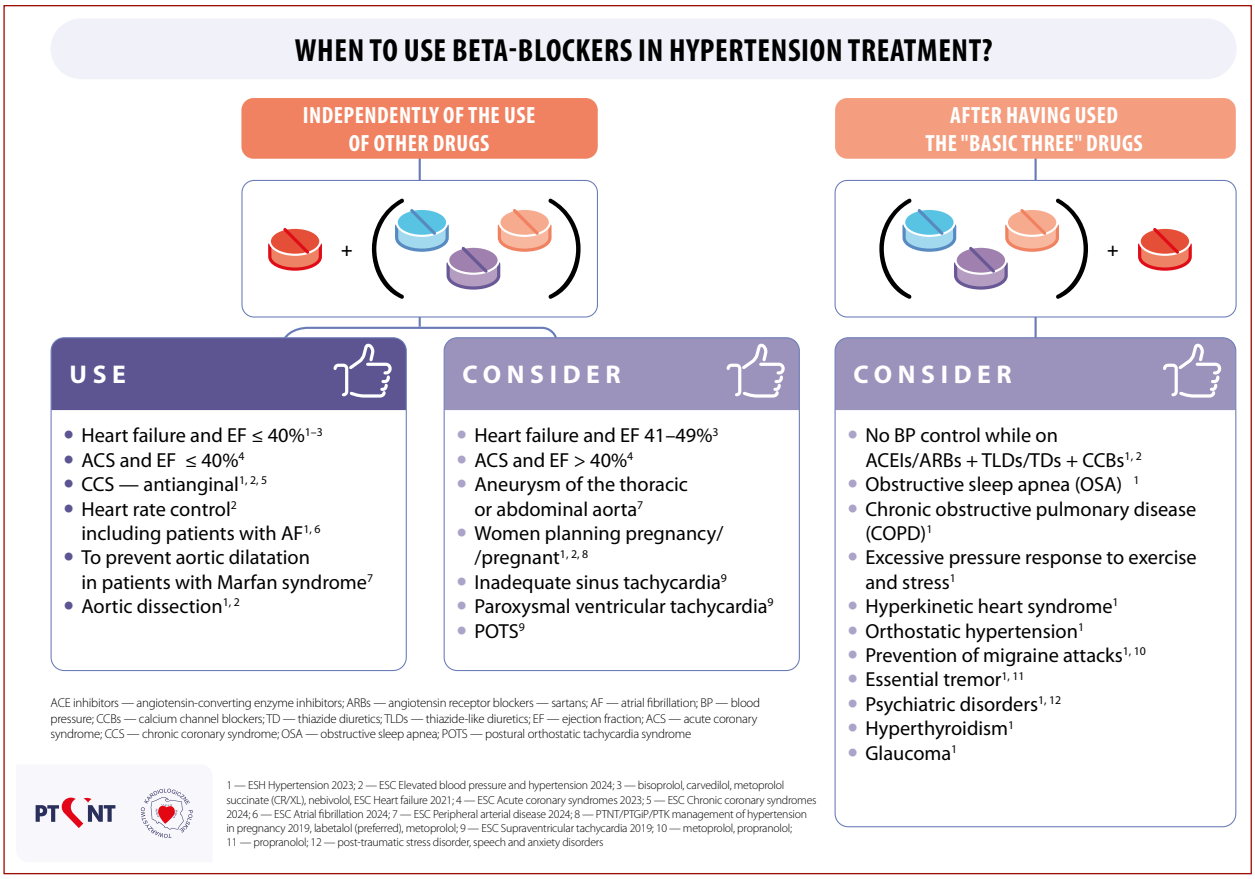


Figure 10.1. Use of beta-blockers (BBs) in hypertension (HT) treatment

A resting HR above 80 beats per minute is common in HT and indicates increased sympathetic nervous system activity [125]. An increase in resting HR is directly associated with a higher risk of AF, HF and increased mortality, both in the general population and in patients with HT. Although the evidence for the benefit of lowering HR in HT is mainly based on post hoc analyses, some data suggest that patients with HT and elevated HR may particularly benefit from BB therapy [124, 126–128]. The use of BBs in HT therapy is illustrated in Figure 10.1 by introducing a three-category division: (1) BBs should or (2) can be considered in specific clinical situations, independent of other drugs, and (3) BBs can be considered after the basic three antihypertensive drugs (ACEIs/ARBs, CCBs and TLDs/TDs) have been used as primary therapy [4, 58].

11. DIFFERENCES IN HYPERTENSION MANAGEMENT

11.1. Hypertension in women

Hypertension in women is associated with a higher risk of myocardial infarction than in men at comparable BP values. Women are more likely to develop concentric LVH and HFpEF and have a higher risk of developing renal failure [129, 130]. Women are also more likely to report adverse effects of antihypertensive drugs, such as edema, cough, hyponatremia and hypokalemia. Although they are more likely to start treatment, it is less likely to be effective. Treatment regimens for HT in women vary according to the patient's age, reproductive plans and metabolic and hemodynamic profile (Figure 11.1).

Hypertension in women of childbearing age

When taking a medical history, attention should be paid to female-specific risk factors such as early menarche, menstrual disorders, polycystic ovary syndrome (PCOS) features, history of pregnancy and use of oral contraceptives (OCs). The clinical assessment should also consider the secondary causes of HT, like fibromuscular dysplasia (FMD) or primary hyperaldosteronism (PA), as well as the quantive assessment of proteinuria [131].

The drug choice in this patients group includes CCBs, BBs and TLDs/TDs. It is recommended to start treatment with a two-drug combination therapy using SPCs (Figure 9.1).

The use of ACEIs, ARBs and MRAs in uncomplicated HT is not recommended due to their teratogenicity. The prescription of these drugs should be limited to female patients with diabetic kidney disease, hypertensive nephropathy, or heart failure, with the provision of effective contraception methods. Patients should be informed about the risks and give their informed consent.

If a woman with HT is planning a pregnancy, her treatment may be continued or changed to drugs dedicated

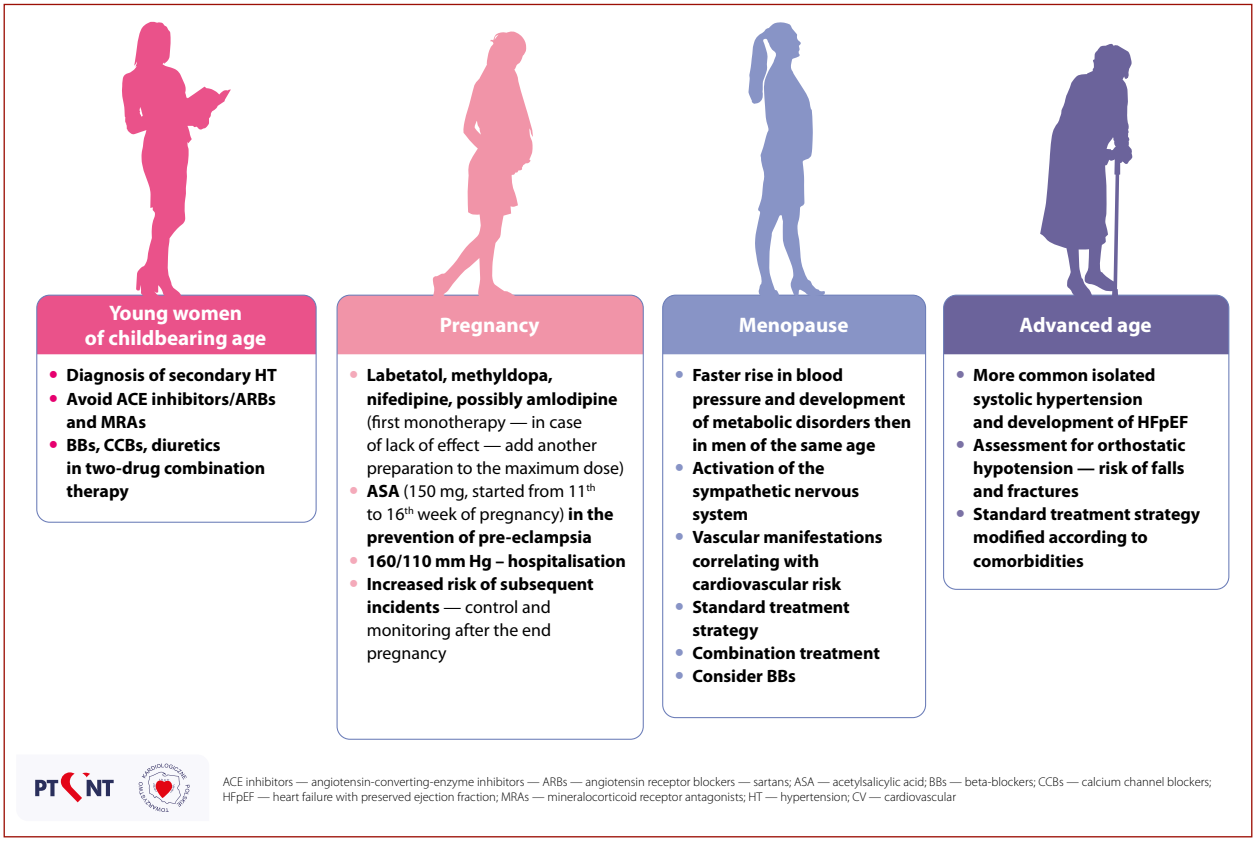


Figure 11.1. Hypertension (HT) management in women by age

to hypertension treatment during pregnancy, such as labetalol, metoprolol, methyldopa or extended-release nifedipine (possibly amlodipine). This is particularly recommended for women planning to use assisted reproduction technologies, as in vitro fertilisation may increase the risk of developing pre-eclampsia (PE) and gestational HT [132].

Oral contraceptives may slightly elevate BP by an average of 5 mm Hg, which applies to systolic and diastolic BP. It is estimated that 2% of women using OCs for four years may develop HT. Their use is also associated with a higher thromboembolic risk and a slight increase in the risk of arterial thrombosis. The described relationship depends on other risk factors present in the patient [133].

A patient using oral contraceptives develops HT: how to manage her?

It is recommended to discontinue oral contraceptives, as it usually lowers BP, and to consider other contraceptives. If BP does not return to normal within three to six months, a comprehensive diagnostic evaluation for HT is required. The initiation of treatment depends on the patient's overall cardiovascular risk.

Menopause

After menopause, BP in women increases more rapidly than in men of the same age. Vasomotor symptoms may indicate future cardiovascular risk [135]. Activation of the sympathetic nervous system plays a role in the pathogenesis of HT and vasomotor symptoms. Patients may benefit from combining ACEIs/ARBs with BBs.

Postmenopausal treatment of HT in women is similar to that used in men and based on the individual characteristics of the patient, such as metabolic and hemodynamic profile and concomitant diseases.

HRT may be used to relieve the menopausal symptoms in women with HT, but it is not

recomended for primary prevention of cardiovascular diseases. It does not affect BP but may improve lipid profile and endothelial function. HRT is contraindicated in women after cardiovascular events and at high thrombotic risk.

What contraceptive can be used in a patient with chronic HT?

Progestogen-only pills are safe for women with well-controlled HT as they do not affect BP [134].

Combined oral contraceptive pills can be used if more suitable methods are not available or acceptable. The risk of cardiovascular diseases depends on the dose of estrogen and risk factors such as obesity, smoking and lipid disorders. They should not be used by women over 35 who smoke, patients with diagnosed cardiovascular diseases, uncontrolled HT or those at very high risk of cardiovascular diseases [45].

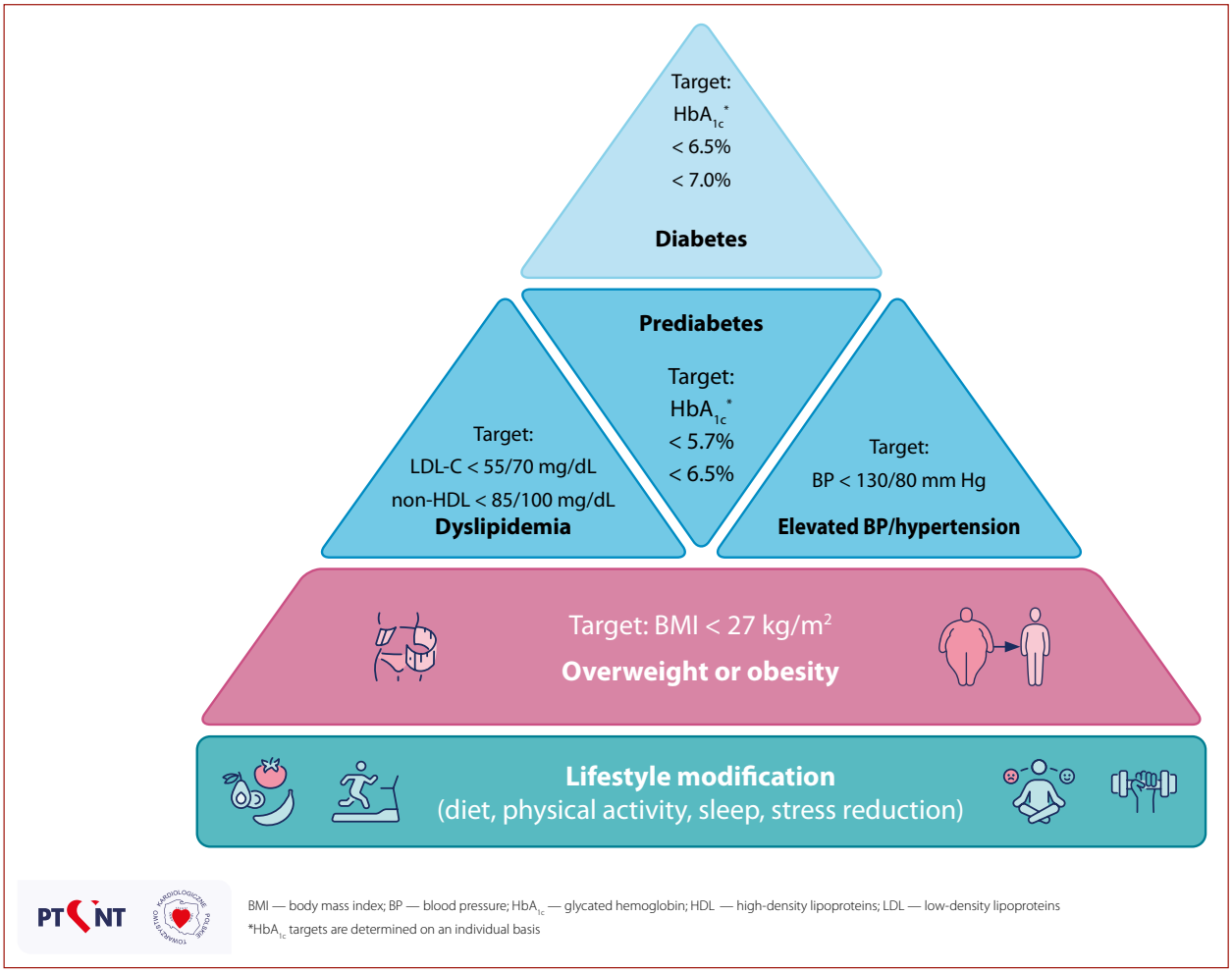


Figure 11.2. Therapy goals of hypertension (HT) and comorbid conditions on the continuum of obesity → metabolic syndrome → diabetes → HFpEF

Intrauterine devices (with copper or levonorgestrel) are an effective and safe option for women with HT. **Progestogen-only subdermal implants** (e.g. etonogestrel), effective for three years, are also a good alternative.

11.2. The "metabolic" patient with hypertension on a continuum of obesity → MS → diabetes → HFpEF

Obesity is a significant gateway to the development of cardiovascular diseases. One of its first consequences is the development of HT, prediabetes, diabetes and atherogenic dyslipidemia [64]. These early complications of obesity, which are the main risk factors for cardiovascular disease, make up MS. This leads to further sequelae of obesity, such as LVH, moderately increased albuminuria, hepatic steatosis and OSA. Left ventricular diastolic dysfunction also occurs, which can result in AF and HFpEF.

This sequence of adverse events can be referred to as the obesity cardiovascular continuum, in which treatment of obesity is crucial (Figure 11.2). The processes along the chain of obesity → MS → diabetes → HFpEF may progress at different rates. Therefore, these patients require an individualized approach to treating HT, taking into account the different severity of obesity complications.

Heart failure with preserved ejection fraction can be considered one of the sequelae of obesity-induced MS [64]. Metabolic syndrome is a significant risk factor for HFpEF. Hypertension leads to concentric LVH (with reduced compliance), and obesity and metabolic disorders, through inflammation and microcirculatory dysfunction, exacerbate left ventricular diastolic dysfunction [64].

Heart failure with preserved ejection fraction is not a homogeneous condition. One can differentiate between its phenotypes associated with obesity and MS and those associated with older age, arterial stiffness or CKD. The co-occurrence of obesity and HFpEF increases the risk of hospitalisation for HF exacerbations [136].

The treatment of obesity improves HT and diabetes control, which is evidence of the importance of the sequence of events outlined above. Reducing the BMI by 10 kg/m^2, for example, through bariatric surgery, allows

some patients with HT to achieve normal BP without antihypertensive medication [137, 138]. Recent studies indicate that bariatric surgery reduces the incidence of AF episodes, and pharmacological treatment of obesity improves exercise tolerance in patients with HFpEF and reduces the severity of OSA [139–141].

Management of the patient in the continuum of obesity → MS → diabetes → HFpEF is based on intensive implementation of lifestyle modification principles and measures to achieve treatment goals in four dimensions: (1) weight reduction, (2) glycemic control, (3) BP reduction and (4) control of serum LDL and non-HDL cholesterol levels (Figure 11.2) [64, 142–145].

Obesity treatment

- To reduce body weight by approximately 0.5 kg per week, it is recommended to introduce a balanced calorie-restricted diet with a daily defficit of 500 kcal to daily requirements. In patients with obesity with concomitant HT, the treatment goal is to reduce body weight by at least 5%–15%. In patients with coexisting prediabetes and diabetes, the goal is to reduce body weight respectively by at least 10% and 5%–15% [64, 146].
- Pharmacotherapy is an obesity treatment option for patients with a BMI ≥30 kg/m^2 who have not achieved significant weight reduction or therapeutic goals through dietary and behavioural management and for overweight patients with a BMI of 27–29.9 kg/m^2 and the coexistence of at least one obesity-related disease [64, 146].
- Five drugs are registered for treating obesity: orlistat, a combination of naltrexone hydrochloride and bupropion hydrochloride; liraglutide; semaglutide and tirzepatide [64, 146].
- In patients with obesity and HT, especially those with MS and its complications, liraglutide, semaglutide or tirzepatide are worth trying because of their BP-lowering effects. The choice of drug should depend on the need for the drug efficacy and the expected therapy outcomes. In patients with cardiovascular disease, semaglutide at a target dose of 2.4 mg/week should be considered first and foremost, as it has been shown to reduce the incidence of serious cardiovascular events. In patients experiencing emotional eating or planning to quit smoking at the same time, naltrexone therapy with bupropion may be considered as an initial treatment. Pharmacological treatment of obesity should be part of a management plan that includes lifestyle modification and changes in eating habits [146–148].
- In a study involving obese patients, 36% of whom had HT, the use of semaglutide reduced BMI by 5.5 kg/m^2, resulting in a 7 mm Hg reduction in systolic BP [149]. Further analysis of studies with semaglutide indicates that a 15% BMI reduction was associated with a decrease in systolic BP of approximately 5 mm Hg. In patients with HT, including resistant HT, such an effect is additionally observed with a reduction in the intensity of antihypertensive treatment [150]. In another study with tirzepatide, involving patients with BP below 140/90 mm Hg, a significant dose-dependent reduction in systolic daytime and night-time BP of 7–11 mm Hg and 6–9 mm Hg in ABPM was observed throughout antihypertensive therapy. This effect was 70% associated with a reduction in body weight [151]. In addition, it has been shown that in patients with moderate-to-severe OSA, a 16%–17% reduction in body weight as a result of tirzepatide therapy led to a 48%–56% apnea-hypopnea index (AHI) reduction, a decrease in OSA severity to a level not requiring continuous positive airway pressure (CPAP) therapy in 42%–50% of patients, and a significant reduction in BP [139].
- Qualification for bariatric surgery based on BMI applies to patients with a BMI >40 kg/m^2 and with a BMI of 35–39.9 kg/m^2 with at least one obesity-related disease (e.g. type 2 diabetes, HT, severe joint disorders, lipid disorders, acute OSA) [146].
- A 5% reduction of body mass, over three months of treatment with a full therapeutic dose, confirms the efficacy of pharmacotherapy [64, 146].

Treatment of prediabetes/diabetes

- Lifestyle modifications, including changes in dietary habits and increased physical activity, are recommended for patients with prediabetes, regardless of their BMI [152]. In patients with a BMI ≥35 kg/m^2, those under 60 and women with gestational diabetes in their history, treatment with metformin for the prevention of type 2 diabetes should be considered [64, 153]. In addition, glucagon-like peptide-1 (GLP-1) receptor agonists or dual GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptor agonists, registered for the treatment of overweight and obesity, can be used in patients with a BMI ≥27 kg/m^2 to reduce the risk of progression of prediabetes to type 2 diabetes [154].
- According to the guidelines of the Polish Diabetes Association, metformin is the base of pharmacotherapy in patients with type 2 diabetes. In the case of coexisting overweight and obesity, cardiovascular disease, HF, CKD or very high cardiovascular risk, at the treatment initiation, drugs with proven beneficial effects on cardiovascular risk from the GLP-1 receptor agonist group or dual GLP-1 and GIP receptor agonists or sodium-glucose cotransporter 2 (SGLT2) inhibitors should be added to it [153].
- In patients with type 2 diabetes and atherosclerotic cardiovascular disease, the use of SGLT2 inhibitors and/or GLP-1 receptor agonists is recommended to reduce cardiovascular risk independently of the antihyperglycemic drugs used and the level of glycemic control [25].
- The use of GLP-1 receptor agonists or dual GLP1 and GIP receptor agonists, as well as SGLT2 inhibitors, is associated with BP reduction. Meta-analyses indicate

Table 11.1. Characteristics of hypertension (HT) in patients on the continuum of obesity → MS → diabetes → HFpEF and implications for HT management. Developed based on [64, 142–145, 187]

Characteristics of HT in "metabolic" patients on the continuum of obesity → MS → diabetes → HFpEF	Impact on management
Larger arm circumference	BP measurement using a wider cuff [usually designated L (32–42 cm) or combining two sizes: M–L (22–42 cm)]
Larger increase in systolic BP, higher pulse pressure*	Combination treatment in virtually all patients, starting therapy with two drugs
Greater BP variability	Use of long-acting drugs
Elevated night-time BP, no drop in night-time BP	Use of long-acting drugs Adequate therapy with TLDs/TDs, MRAs, and, if necessary, loop diuretics Prevention and treatment of OSA
HT sodium sensitivity, hypervolemia	Use of TLDs/TDs
Increased risk of hyperkalemia	Periodic assessment of potassium levels
Orthostatic and postprandial hypotension	Need to assess BP after standing up and after meals, adjust the intensity of pharmacotherapy
Difficulties in achieving HT control, frequent resistant HT	Use of multiple groups of antihypertensive drugs, including BBs and MRAs
More frequent "hidden HT" than in the general population	Performance of out-of-office BP measurements, especially in patients with diabetes and elevated BP

*Difference between systolic and diastolic BP

Abbreviations: BBs, beta-blockers; TLDs/TDs, thiazide-like diuretics/thiazide diuretics; HFpEF, heart failure with preserved ejection fraction; MRAs, mineralocorticoid receptor antagonists; HT, hypertension; OSA, obstructive sleep apnea; BP, blood pressure; MS, metabolic syndrome

that SGLT2 inhibitors lower BP by approximately 3.6/1.7 mm Hg at ABPM [155].

Hypertension treatment

Table 11.1 shows the characteristics of HT patients with relation to a continuum of obesity → MS → diabetes → HFpEF. The principles of HT treatment on a continuum of obesity → MS → diabetes → HFpEF are described below (Figure 11.3) [64, 142–145]:

- primary HT treatment is based on a combination of ACEIs/ARBs with TLDs/TDs and/or CCBs;
- as a first step, the combination of ACEIs/ARBs with TLDs/TDs is justified due to the importance of sodium sensitivity and hypervolemia in the development of HT in patients with obesity and MS/diabetes;
- the recommended drug combinations within the "basic three" are equally effective in patients with and without obesity [156];
- indapamide and chlorthalidone are the preferred drugs among diuretics (for eGFR ≥30 ml/min/1.73 m^2, and in the case of chlorthalidone for eGFR <30 ml/min/1.73 m^2), while loop diuretics [should be included for indications such as symptoms of congestion, or the absence of BP control as a fifth antihypertensive drug [157, 158];
- the use of ACEIs/ARBs positively influences glucose metabolism and reduces the risk of developing new cases of diabetes [159];
- in patients with diabetes over 55 years of age, and other cardiovascular risk factors, ACEIs should be considered in order to reduce cardiovascular risk regardless of BP [153]. A higher BMI is linked to greater benefits from using these drugs [160];
- if basic antihypertensive drugs are ineffective, the addition of MRAs may be considered not only because of the cardio- and nephroprotective effects described below but also because their antihypertensive efficacy is higher the greater the waist circumference [161–163];
- when indicated, BBs are recommended for the control of excessive sympathetic nervous system activity, especially nebivolol, carvedilol or bisoprolol, due to their metabolic profile [64]. This is beneficial for patients with increased resting heart rate, which is common in obese or diabetic patients [142]. The use of BBs in patients with HFpEF is under discussion; their effect on exercise tolerance should be assessed during use [164–166].

Treatment of lipid disorders

Pharmacotherapy of lipid disorders in patients on a continuum of obesity → MS → diabetes → HFpEF is based on the following principles [64, 167, 168]:

- the use of potent statins (atorvastatin, rosuvastatin) at the highest tolerated dose to achieve the target serum LDL cholesterol concentration set for the specific risk level;
- if targets are not achieved at the maximum tolerated statin dose, then a combination with ezetimibe is recommended;
- in primary prevention, if the goal of lowering serum LDL cholesterol levels is not achieved despite the maximum tolerated dose of statin and ezetimibe, a combination with a proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitor may be considered;
- in secondary prevention, if the goal of lowering serum LDL cholesterol is not achieved despite the maximum tolerated dose of statin and ezetimibe, a combination with a PCSK9 inhibitor (available under B.101 treatment program) or bempedoic acid is recommended; inclisiran is also available under B.101 treatment program;
- once target serum LDL cholesterol levels have been achieved, target non-HDL cholesterol levels may be considered (Figure 11.2);
- in patients with serum triglyceride levels of 2.3 mmol/l (200 mg/dl) or more despite treatment with statins, the use of omega-3 fatty acids (polyunsaturated fatty acids [PUFAs] at a dose of 2–4 g/day) in combination with

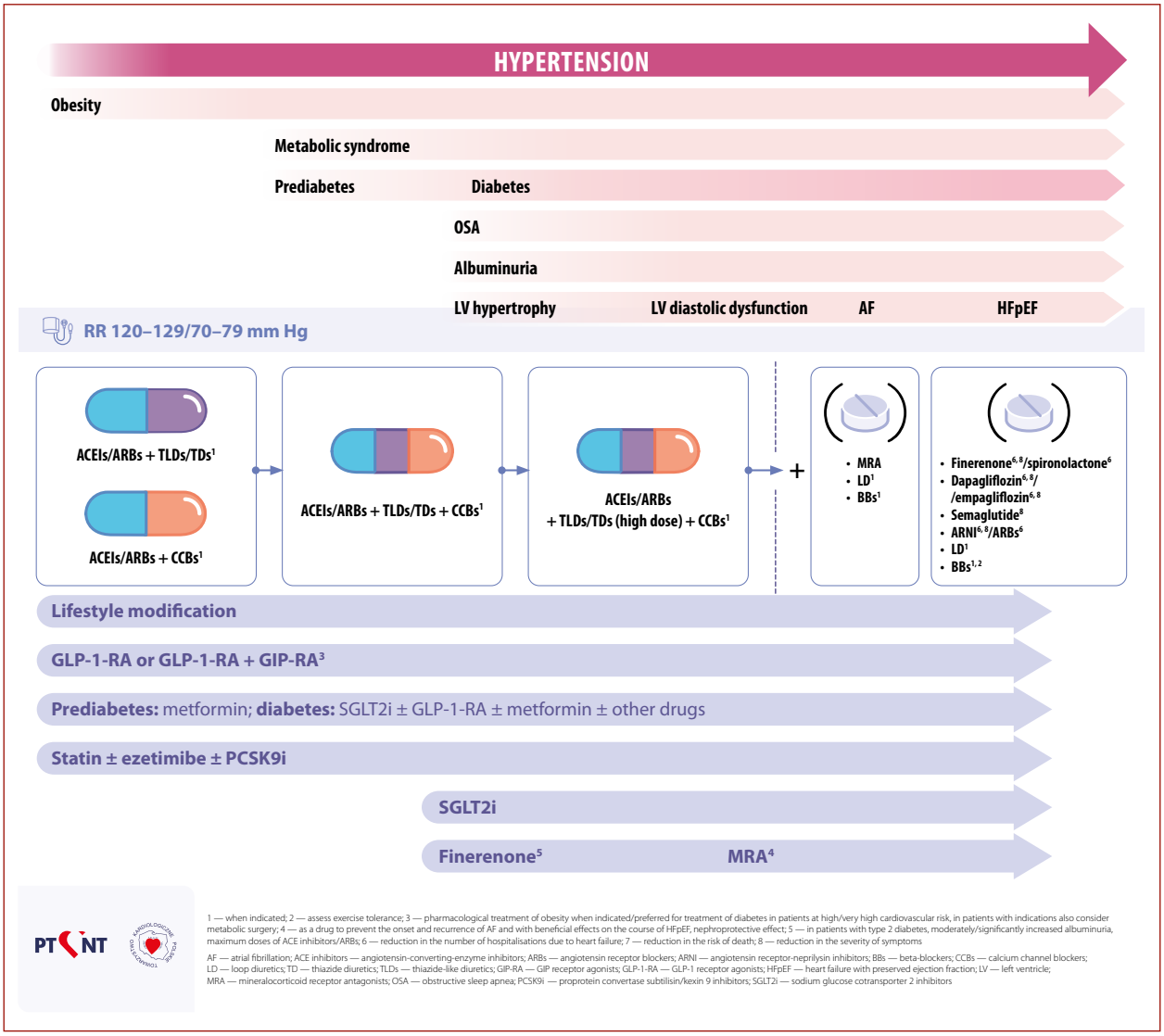


Figure 11.3. Treatment of hypertension (HT) and comorbid conditions on the continuum of obesity → metabolic syndrome → diabetes → HFpEF

a statin may be considered; the use of omega-3 fatty acids at doses of 2 g and above is associated with a higher AF risk;

- in primary prevention in patients who have reached their target serum LDL cholesterol levels with persistent serum triglyceride levels >2.3 mmol/l (>200 mg/dl), fenofibrate in combination with statins may be considered, particularly in patients with low HDL;
- in high-risk patients who have reached their target serum LDL cholesterol levels with persistent serum triglyceride levels >2.3 mmol/l (>200 mg/dl), fenofibrate in combination with statins should be considered, particularly in patients with low HDL.

Additional drugs in the continuum of obesity → MS → diabetes → HFpEF with cardio- and nephroprotective effects

As shown in Figure 11.3, the use of SGLT2 inhibitors, GLP-1 receptor agonists, and MRAs plays an important role in the obesity → MS → diabetes → HFpEF continuum.

The use of SGLT2 inhibitors carries important cardioprotective benefits. In addition, they are well-established in the treatment of HFpEF, where they lower the risk of hospitalisation for HF. These benefits include reduction of left atrial volume and left ventricular mass, improved left ventricular diastolic function, reduced AF risk, a significant decrease in NT-proBNP levels and reduced risk of major ventricular arrhythmias, cardiac arrest and sudden death in patients with HT [169–176].

In patients with CKD, SGLT2 inhibitors further reduce the risk of a composite endpoint, including a 50% or greater reduction in eGFR, development of end-stage renal failure and death from renal causes [177, 178]. In addition, they reduce albuminuria, regardless of glycemic status, eGFR level or baseline severity of albuminuria [179].

There is also increasing evidence supporting the cardioprotective and nephroprotective benefits of GLP-1 re-

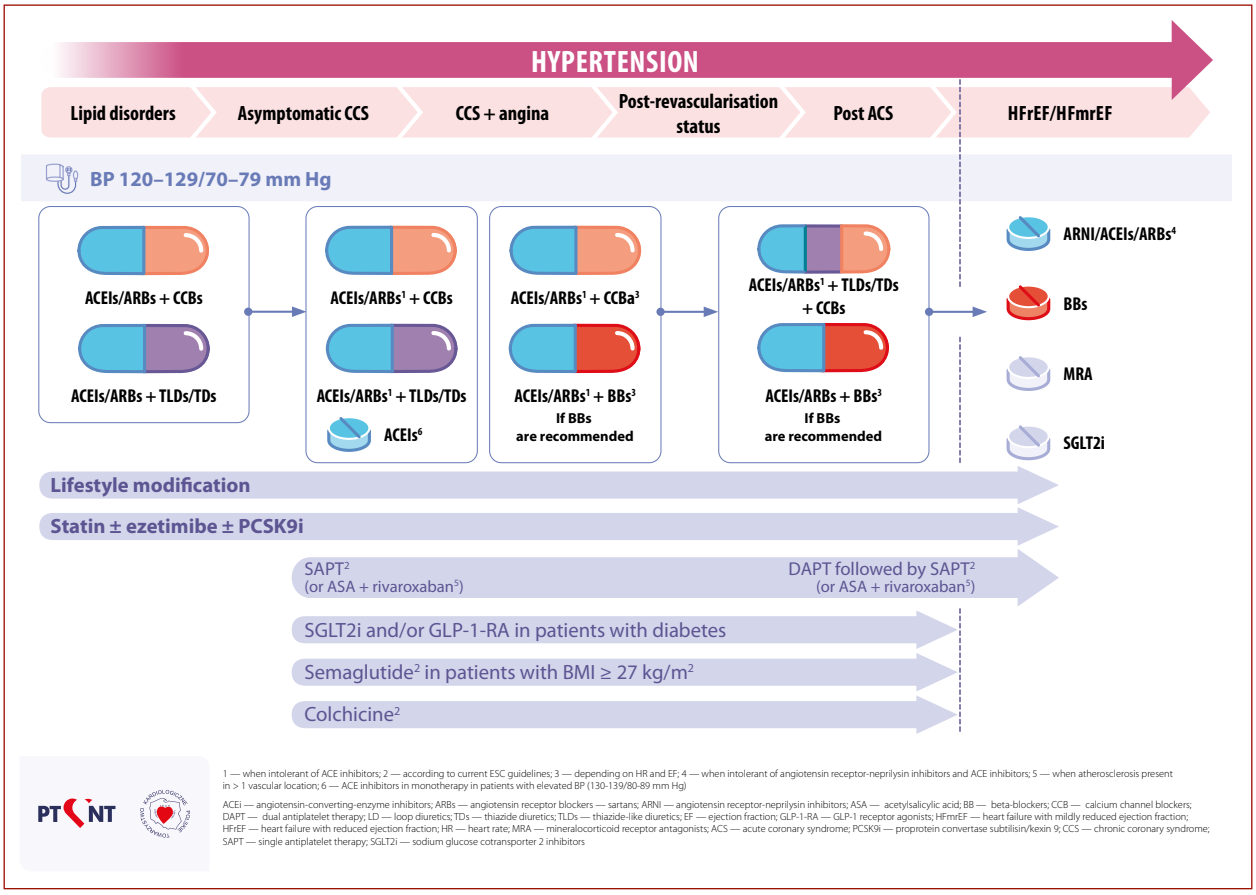


Figure 11.4. Treatment of hypertension (HT) in the continuum of atherosclerotic cardiovascular disease

ceptor agonists [180]. In studies involving patients with HFpEF and obesity, semaglutide significantly reduced the severity of HFpEF symptoms according to the Kansas City Cardiomyopathy Questionnaire — The Clinical Summary Score (KCCQ-CCS), increased the distance in the 6-minute walk test and had a beneficial effect on echocardiographic parameters, including a reduction in left atrial volume [140, 141, 181].

Mineralocorticoid receptor antagonists are also an important component of therapy in the obesity → metabolic syndrome → diabetes → HFpEF continuum. In the FINEARTS-HF trial, finerenone demonstrated the ability to reduce the risk of hospitalisation for HF in patients with HFpEF and a composite endpoint including deaths and hospitalisations. Previous studies indicate that MRAs reduce albuminuria and inhibit the progression of CKD in patients with diabetes and CKD (finerenone), reduce the frequency of AF attacks, reduce left ventricular hypertrophy and inhibit myocardial fibrosis [161, 180, 182–186].

11.3. The "cardiac" patient with HT and a continuum of atherosclerotic cardiovascular disease

The change in approach to coronary artery disease through the concept of chronic coronary syndromes (CCS) allows a holistic view of atherosclerosis-induced cardiovascular disease. This process starts with atherosclerosis risk factors, leads to subclinical coronary atherosclerosis, CCS with angina, acute coronary syndrome (ACS) and ends with heart failure with reduced ejection fraction (HFrEF) (Figure 11.4) [5, 148, 188].

Management of HT in patients on the continuum of cardiovascular disease secondary to atherosclerosis

- Therapy aims to lower the systolic BP to 120–129 mm Hg, provided the patient tolerates the treatment well [5, 148].
- In patients with CCS, ACEIs (or ARBs, if intolerant) are recommended, especially in cases of coexisting HT, diabetes or HF [5, 148].
- ACEIs should be considered in CCS patients at very high risk of cardiovascular events regardless of BP [5, 148].
- Antihypertensive treatment should be initiated at BP of 130–139/80–89 mm Hg (ACEI monotherapy) or combination therapy for HT [5, 148].
- In HT therapy, one should stick to the basic algorithm, using the "basic three" drugs [5, 148]. The combination of ACEIs and CCBs (using SPCs) is preferred. If there is an indication for BBs, the combination of ACEIs and BBs (using SPCs) may be considered [5, 148, 189].
- Patients with CCS and angina may benefit from CCBs and BBs [5, 148].

- Patients with HFrEF should be treated with angiotensin receptor-neprilysin inhibitors ARNIs) or ACEIs (or ARBs, if intolerant), BBs, MRAs and SGLT2 inhibitors [5, 148].

Other drugs reducing cardiovascular risk in patients with CCS

- Potent statins (atorvastatin, rosuvastatin) are recommended to achieve LDL cholesterol targets. If statins alone are insufficient, then ezetimibe is included. If targets are still not met, then bempedoic acid or a PCSK9 inhibitor (available under the B.101 programme) is considered. Inclisiran is also available under the B.101 programme [148].
- Antiplatelet therapy (single or dual), anticoagulant therapy and their combination (including acetylsalicylic acid (ASA) with low-dose rivaroxaban), is used according to the ESC guidelines [148, 190].
- In patients with type 2 diabetes, SGLT2 inhibitors and/or GLP-1 receptor agonists are recommended, irrespective of baseline or target glycated hemoglobin (HbA1c) levels and antihyperglycemic drugs used [148].
- Low-dose colchicine (0.5 mg daily) can be considered in patients with atherosclerotic coronary artery disease [148].
- Semaglutide can be considered in overweight (BMI >27 kg/m^2) or obese patients, even without diabetes, to reduce cardiovascular risk [148].

11.4. Hypertension in patients with a history of stroke

Hypertension is a key and modifiable risk factor for vascular damage to the central nervous system. The association of HT with stroke risk is stronger than for other complications such as ischemic heart disease [191, 192]. Observational studies have shown an almost linear relationship between BP values and its variability and the risk of ischemic stroke, intracerebral hemorrhage and vascular dementia [191–194]. HT is estimated to cause at least 45% of ischemic strokes and 74% of primary intracerebral hemorrhages [191, 192]. Diabetes and HT sequelae such as AF and heart failure (HFpEF and HFrEF) further increase the risk of stroke in patients with HT [195, 196].

In the context of long-term stroke prevention, several placebo-controlled studies have shown that HT pharmacotherapy is effective in reducing the risk of first and subsequent acute cerebrovascular events, regardless of the drugs used [58, 197–200]. Fewer data are available for dementia risk reduction [201, 202].

Patients who benefit more from antihypertensive therapy in terms of stroke risk are those who:

- achieve a greater reduction in BP;
- experience less BP variability;
- use diuretics (especially TLDs), CCBs and ARBs/ACEIs;
- use combination therapy rather than monotherapy [58, 197, 199, 203–211].

Principles of hypertension therapy

- Available data from randomized trials and data from observational studies suggest that in patients with HT after TIA (transient ischemic attack) or after ischemic stroke, the target BP should be similar to that recommended for people with HT [212, 213]. In chronic BP control in patients after TIA, ischemic stroke and cerebral hemorrhagic stroke, a target of less than 130/80 mm Hg, but not less than 120/65 mm Hg is aimed for, provided good clinical tolerance [211] [214–216]. The exception is patients with symptomatic intracranial artery stenosis, in whom it is recommended to achieve values below 140/90 mm Hg [217]. Antihypertensive treatment is initiated immediately after a TIA incident and after the onset of intracerebral hemorrhage, whereas in patients after ischemic stroke, it is deferred for a few days after clinical stabilisation has been achieved [218, 219].
- In patients without established HT prior to an episode of TIA/cerebral ischemic stroke, in whom values ≥130/80 mm Hg are maintained in office measurements after the above-mentioned episode, antihypertensive treatment may be beneficial in terms of reducing recurrent vascular episodes. Target systolic BP values are in the range of 120–129 mm Hg, subject to good tolerance [5, 214, 215, 220].
- Therapy should be individualized, taking into account the patient's degree of functionality and the effect of reduced BP on daily functioning [221].
- It is advisable to monitor BP outside the office (e.g. BP at night, BP after meals) and verify the readings with an orthostatic test, especially in patients who function independently.
- The findings of new randomized trials in stroke patients are awaited [222], but extrapolated evidence suggests that SPC-based pharmacotherapy from the start of treatment is more effective in reducing cardiovascular risk (including stroke risk) than using several separate tablets [223].
- The greatest benefit in secondary prevention comes from a strategy based on controlling HT and all other risk factors associated with cerebrovascular disease.

11.5. Hypertension in patients with peripheral artery disease

Antihypertensive therapy in patients with peripheral artery disease (PAD) should holistically consider other cardiovascular diseases, treating HT as a concomitant disease. It is crucial to minimise the use of symptomatically acting drugs that do not affect the patient's life expectancy and overall morbidity. A patient with PAD should have BP measured in both arms at each visit. In patients with lower extremity arterial disease (LEAD), it is also important to determine the AHI. Because of the risk of atherosclerotic changes in the small vessels, including the retinal microcirculation, patients with LEAD should have an ABPM performed once a year to assess the degree of BP control and diurnal profile.

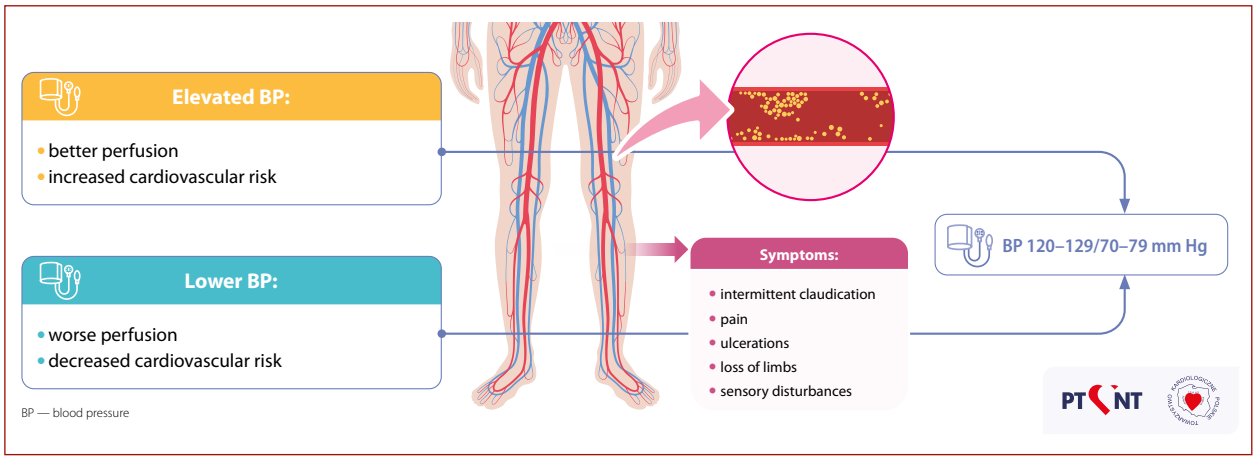


Figure 11.5. Blood pressure (BP) and the risk of worsening limb perfusion and increasing cardiovascular risk. Based on [224, 225]

This is especially important in those with glaucoma (risk of excessive night-time BP drops).

Treatment of HT with coexisting PAD raises concerns of worsening ischemia and increasing the risk of stroke or amputation. However, therapy strives to balance the benefits of BP control and not exacerbate ischemia (Figure 11.5). Effective antihypertensive therapy significantly reduces the long-term risk of cardiovascular events [224–226]. With good tolerance, lowering BP to 120–129/70–79 mm Hg is recommended in most patients [225]. The principles of pharmacotherapy are similar to those used in uncomplicated HT [4].

Myths about the risk of deterioration of limb blood supply by BBs need to be dispelled [227]. Meta-analyses indicate that these drugs do not worsen the symptoms of intermittent claudication or increase the risk of ischemia. On the contrary, BBs may improve prognosis, especially in patients with HFrEF. BBs can be safely used for HT coexisting with LEAD and specific indications. The guideline emphasises that especially those with vasodilatory effects may prolong the distance in the intermittent claudication and improve the clinical condition of the patient [228, 229].

11.6. Hypertension in patients with chronic kidney disease

Hypertension is a key risk factor for the development and progression of CKD. Effective treatment of HT and achievement of target BP slow the progression of CKD and reduce cardiovascular risk. HT and nephroprotective treatment in patients with CKD should start immediately after diagnosis. SGLT2 inhibitors have a strong nephroprotective effect, especially in patients with moderately/significantly increased albuminuria. They also have, as described above, a weak antihypertensive effect [230, 231].

Nephroprotective treatment should be implemented in CKD patients with elevated BP (Figure 11.6) [230, 231]. If BP remains elevated, additional antihypertensive drugs should be considered in addition to the ACEIs/ARBs used, especially with an ACR ≥30 mg/g [4, 5, 48]. Target BP in patients with CKD is controversial and varies in guidelines [4, 5, 48]. Generally, it should be 120–129/70–79 mm Hg with regular control of serum creatinine, avoiding too-low BP [4, 5]. SPRINT and ESPRIT trials, for instance, have shown that intensive BP control was associated with increased rates of acute kidney injury (SPRINT) and renal events (ESPRIT) but reduced the risk of death and cardiovascular events [75, 76].

Principles of HT therapy (Figure 11.6)

- Combination of ACEIs/ARBs with CCBs and/or TLDs/TDs using SPCs [4, 5].
- In patients with albuminuria >30 mg/g, ACEIs/ARBs should be used at the maximum tolerated dose [4, 5, 48].
- The choice of diuretic should depend on the eGFR.
  - — therapy is based on TLDs/TDs for an eGFR ≥30 ml/min/1.73 m^2, and loop diuretics should be included in the absence of BP control or other indications;
  - — therapy is based on chlortalidone for eGFR <30 ml/min/1.73 m^2, and loop diuretics should be included in the absence of BP control or other indications. When loop diuretics are concerned, torasemide is recommended due to its longer duration of action and better tolerability profile than furosemide [4, 5, 157].
- It is common for patients with CKD to have elevated BP at night and without its decrease during sleep. This may be due to inadequate treatment with diuretics. Depending on the eGFR (see above), treatment with TLDs/TDs or loop diuretics, as well as spironolactone, should be intensified [4, 5, 48, 114, 157].
- Finerenone is used as a nephroprotective drug in CKD patients with type 2 diabetes mellitus and an eGFR ≥25 ml/min/1.73 m^2 who have persistent albuminuria ≥30 mg/g despite full-dose ARBs or ACEIs and are not prone to hyperkalemia. It has a significant (but lower than spironolactone) risk of hyperkalemia and an moderate (lower in office measurements, higher in ABPM) reduction in BP. In patients with an eGFR

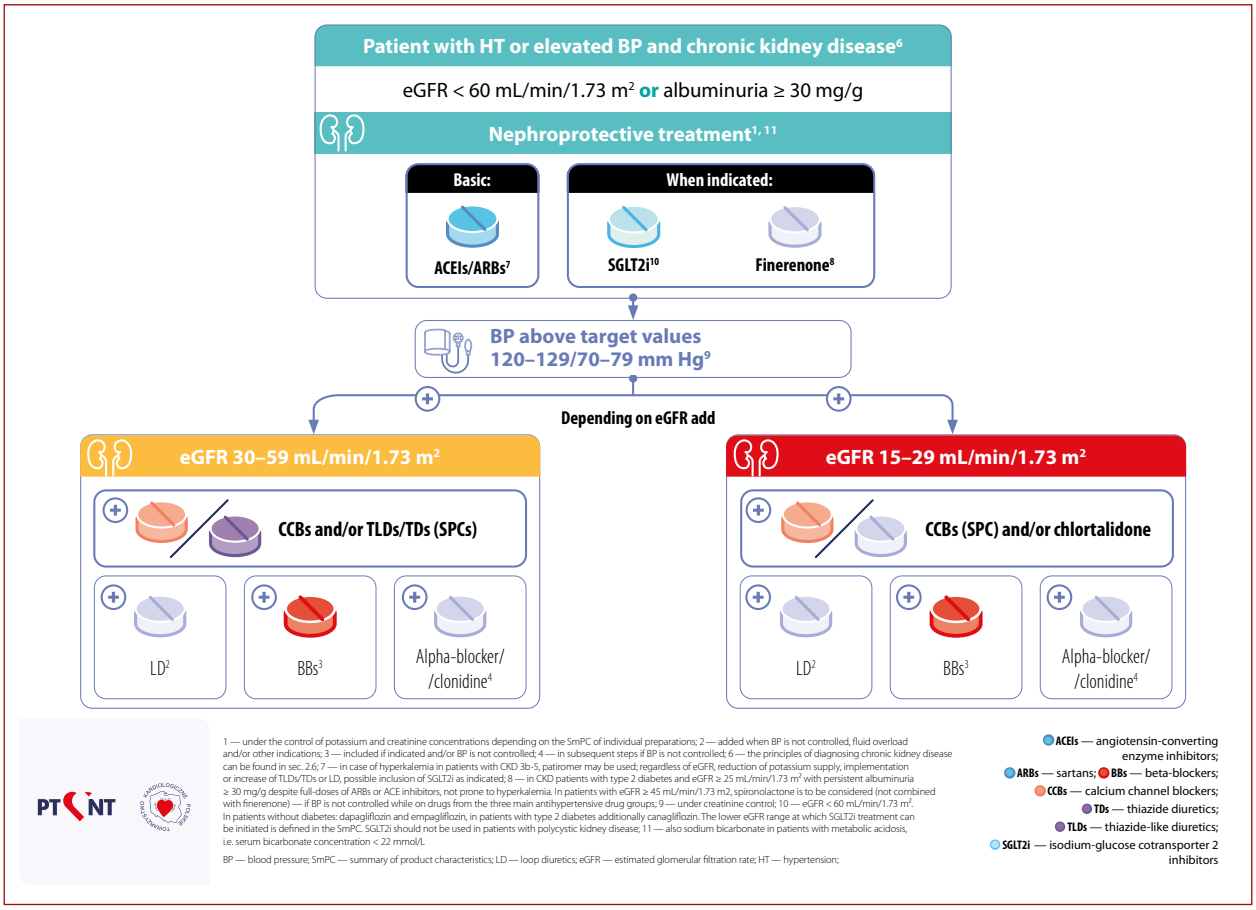


Figure 11.6. Management of patients with hypertension (HT) and chronic kidney disease. Developed based on [4, 5, 48]

≥45 ml/min/1.73 m², in whom the basic three antihypertensive drugs are ineffective, the addition of spironolactone is recommended because of its proteinuria-reducing effect and more pronounced antihypertensive effect. In patients with an eGFR below 45 ml/min/1.73 m² or a potassium concentration of more than 4.5 mmol/l, spironolactone should be used with caution due to the risk of hyperkalemia. Spironolactone should not be combined with finerenone [4, 5, 48, 232, 233].

When to discontinue ACEIs/ARBs in patients with CKD?

ACEI/ARB discontinuation increases cardiovascular and renal risk and should be avoided [234]. Inclusion of these drugs can lower the eGFR by 10%–15%. If the decrease exceeds 30%, then withdrawal should be considered, and renal artery stenosis or other causes should be ruled out [4]. For hyperkalemia in patients with an eGFR <45 ml/min/1.73 m², potassium-binding drugs such as patiromer, available in Poland, may be considered, preventing the need to discontinue ACEIs/ARBs [235]. Regardless of the eGFR, one should try to reduce dietary potassium supply, use or increase doses of TLDs/TDs or loop diuretics, and consider including SGLT2 inhibitors as indicated.

11.7. Hypertension in patients with atrial fibrillation

Patients with HT are almost twice as likely to develop AF as those with normal BP [236, 237]. Regular screening for AF in patients with HT is therefore recommended [238]. In patients with paroxysmal AF and HT, optimal pressure control is crucial, reducing the risk of recurrent AF and cardiovascular events [238–240]. Studies indicate that patients with AF whose BP is adequately controlled are less likely to experience strokes [241, 242]. Target BP in patients with HT and AF is 120–129/70–80 mm Hg [243, 244].

Appropriate pharmacological treatment of HT and HF can prevent AF. It works by limiting atrial stretch, and drugs that inhibit the renin–angiotensin system may further protect against electrical and structural remodelling of the heart. As an outcome and marker of atrial remodelling, AF is closely associated with atrial cardiomyopathy. Drugs affecting atrial remodelling may prevent new episodes of AF and act as unconventional antiarrhythmics [238].

ACEIs or ARBs are preferred in the treatment of patients with AF and HT, but MRAs should also be considered. Effective combinations of ACEIs/ARBs with CCBs or TLDs/TDs are recommended for optimal BP control. Beta-blockers are recommended to control HR [238]. In patients with HT and AF, anticoagulant treatment is necessary for the prevention of ischemic stroke. HT increases both the risk

of stroke and the risk of hemorrhagic complications. HT is not a contraindication to anticoagulant treatment, whereas poor BP control increases the risk of hemorrhages.

11.8. Gestational hypertension

Hypertensive disorders of pregnancy include [4, 131]:

- **pre-existing** (chronic) HT: diagnosed before pregnancy or up to the 20th week of gestation;
- **gestational HT**: developing after the 20th week of gestation; it often resolves within six weeks postpartum. It is not accompanied by proteinuria or biochemical abnormalities;
- **PE**;
- **eclampsia**;
- **HELLP** (hemolysis, elevated liver enzymes, low platelets) syndrome: characterized by clotting abnormalities, liver damage and thrombocytopenia.

If women with pre-existing HT after the 20th week of gestation experience an exacerbation of HT and develop symptoms typical of pre-eclampsia, such as proteinuria or significant organ dysfunction, a diagnosis of HT with superimposed pre-eclampsia is made [4, 131].

The cut-offs values for diagnosing HT in pregnant women are the same as in the general population: ≥140/90 mm Hg, confirmed by out-of-office measurements within seven days in the first trimester and up to three days in the second and third trimesters [4, 131].

Antihypertensive drugs and the prevention of AF

- Studies in which AF was an additional endpoint suggest that ACEIs and ARBs may prevent the first occurrence of AF in patients with left ventricular dysfunction, LVH or HT. ACEIs and ARBs are beneficial as first-line drugs in patients with AF; however, ARBs do not reduce AF severity in patients without structural heart disease [238].
- Recent studies using Mendelian randomisation indicate that BBs are as effective as other classes of antihypertensive drugs [245].
- Aldosterone plays a role in the induction and perpetuation of AF, and the use of MRAs reduces the burden of AF. Meta-analyses have shown that MRAs significantly reduce the incidence of first occurrence and recurrence of AF, although they do not reduce the risk of postoperative AF. In contrast, MRAs reduce the incidence of AF in both HFrEF and HFpEF patients [183, 236, 237, 246, 247].

Gestational hypertension

Management of gestational HT includes [4, 131, 248, 249]:

- maintaining a normal diet without significant salt restriction. Women with chronic HT should continue a low-sodium diet;
- physical activity: at least 140 minutes of moderate exercise per week (30–60 min, 3–4 times per week).
- pharmacological treatment of HT is initiated when BP is ≥140/90 mm Hg (according to the principles shown in Figure 11.7).
- maintaining BP during therapy in the range of 110––140/80–85 mm Hg;
- ASA at a dose of 150 mg daily administered in the evening, started by the 16th week of gestation to prevent pre-eclampsia;
- in case of BP ≥160/110 mm Hg or symptoms indicative of pre-eclampsia, hospitalisation is indicated.

Pre-eclampsia

Pre-eclampsia develops after the 20th week of gestation in women with previously normal BP or exacerbates pre-existing HT; it is accompanied by proteinuria and/or a risk to fetal or maternal well-being. It rarely develops in the puerperium. It is caused by increased vascular resistance, platelet propensity to aggregate, activation of the coagulation system, impaired endothelial function, and placental abnormalities. Risk factors are shown in Table 11.2 [4, 131, 248].

In women at high risk of PE, ASA at 150 mg daily, started by the 16th week of gestation, and moderate physical activity are recommended as prophylaxis. Women with a history of gestational HT or PE have an increased risk of HT, HF, cardiovascular events and premature death. They should be regularly assessed for risk factors, and intensive treatment should be instituted if they develop [4, 131, 248].

11.9. Hypertension in young adults

Diagnosis of HT at a young age increases the risk of death and accelerates the occurrence of HMOD. High BP in young adults often persists also in later years of life, which is known as "tracking". This phenomenon is associated with an unfavourable prognosis in both short and medium-term follow-up and increases the risk of cardiovascular events [250].

Selected patients should be referred to specialist centres for detailed assessment for secondary causes of HT. In young adults, it is worth considering early introduction of pharmacological treatment alongside lifestyle modifications. Patient education and close collaboration between GPs, hypertensiologists, cardiologists and the patients are crucial. This integration of efforts increases the effectiveness of HT diagnosis and therapy in young adults.

Recent studies indicate that ISH is most common in older adolescents and young adults with primary HT. This type is diagnosed in 66% of patients, mainly among boys and men. Systolic-diastolic HT was found in 30% of patients and isolated diastolic HT in 4% [251]. Among young adults aged 18 to 40 (mean 25 years), ISH predominates in men. Women are more commonly affected by systolic-diastolic HT or isolated diastolic HT [252].

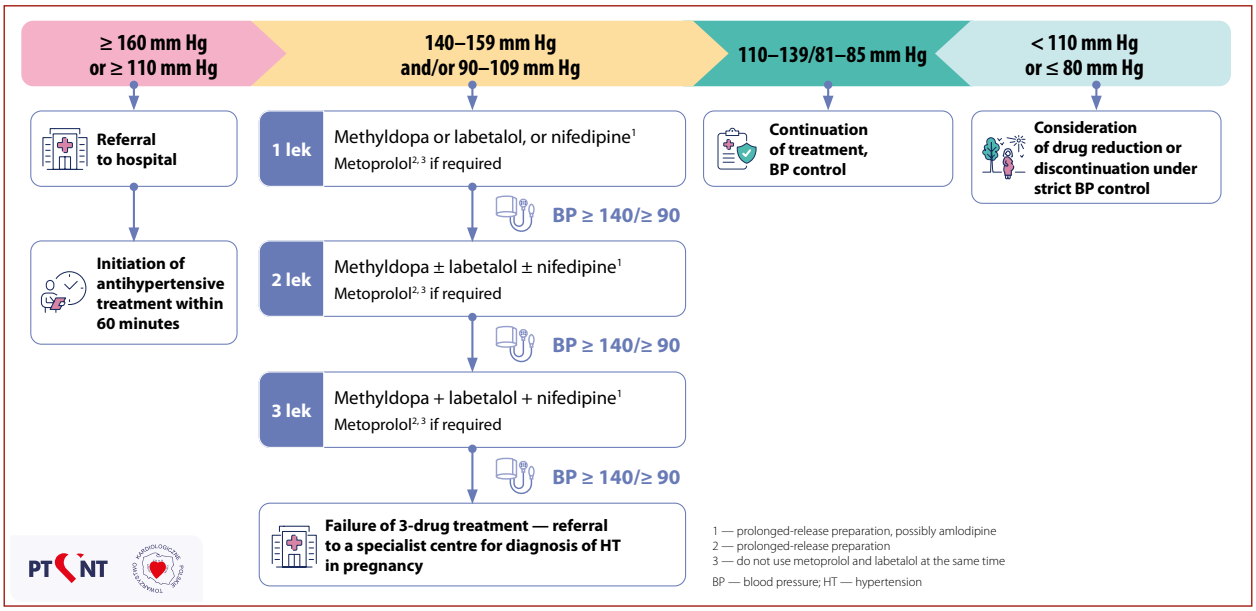


Figure 11.7. Treatment of gestational hypertension (HT). Based on [131]

Table 11.2. Risk factors for pre-eclampsia (PE) [4, 131, 248]

Intermediate risk	High risk
First pregnancy	History of gestational HT
Age >40 years	Chronic kidney disease
In between pregnancy interval >10 years	Systemic lupus
	Antiphospholipid syndrome
Pre-pregnancy BMI of >35 kg/m^2	Type 1 or type 2 diabetes
History of PE in the patient's mother	Chronic HT
Multiple pregnancy	

Abbreviations: BMI, body mass index; HT, hypertension

Isolated systolic HT in young people is a complex phenomenon. In some, particularly tall and physically active men, it may result from pulse pressure amplification. Despite a normal central BP in the aorta, it may reflect an extreme physiology, called pseudohypertension. This type of HT is also sometimes the result of increased cardiac output with not yet increased peripheral resistance (hyperkinetic circulation).

The management of young people with ISH follows the following principles:

- treatment should be based on the general principles of HT management;
- non-invasive measurement of central BP may be valuable, although it is rarely available and not mandatory;
- for ISH patients with systolic BP values between 140 and 159 mm Hg and no HMOD or cardiovascular risk factors, non-pharmacological treatment for 6–12 months is recommended;
- for ISH with systolic BP values ≥160 mm Hg or with coexisting HMOD or cardiovascular risk factors, initiation of pharmacotherapy is indicated.

11.10. Hypertension in cancer patients

Hypertension is the most common comorbidity in cancer patients. Unhealthy diet, obesity, physical inactivity, smoking and alcohol consumption are common risk factors that contribute to the prevalence of HT in this group. In cancer patients, HT, like other cardiovascular risk factors and recognized cardiovascular disease, increases the risk of cardiotoxicity of anticancer treatment (Figure 11.8).

Increases in BP during the use of VEGF pathway inhibitors

- BP rise occurs within hours or days. It is dose-dependent and usually resolves when treatment is stopped. With small-molecule TKIs, such as sorafenib and sunitinib, this happens within a few days. With antibodies such as bevacizumab, it may take several weeks.
- The risk of elevated BP is increased in patients with existing HT or cardiovascular diseases. It is higher in patients previously treated with anthracyclines, at advanced age, who are smokers, or have hyperlipidemia or obesity.
- BP usually decreases after completion of VEGF inhibitor therapy. The dose of antihypertensive drugs should then be reduced accordingly or treatment discontinued.

Hypertension may develop or worsen due to malignancy (stress, pain) or treatment such as vascular endothelial growth factor receptor (VEGF) inhibitors, second- and third-generation BCR-ABL tyrosine kinase inhibitors (TKIs), brigatinib, ibrutinib, fluoropyrimidines, cisplatin, abiraterone, bicalutamide, enzalutamide and non-cancer therapies such as corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) [253].

The management of HT in cancer patients should follow standard principles for other patient groups. It is important

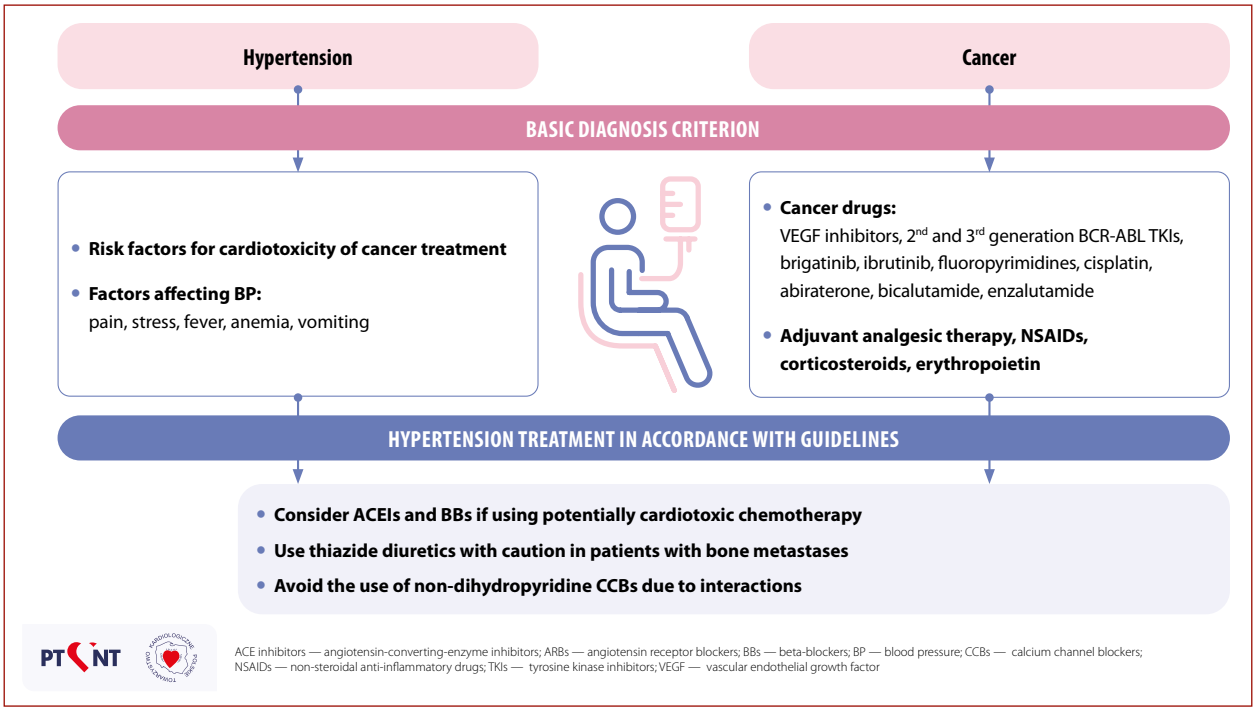


Figure 11.8. Management of hypertension (HT) in cancer patients

to optimise BP control before starting cancer treatment and to monitor it closely. The choice of treatment should take into account the type of cancer treatment and the risk of drug interactions.

Drugs from the ACEI/ARB and CCB groups are preferred. In contrast, TLDs/TDs, which are the mainstay of treatment in the general HT patient population, should be used with caution in this group. In patients with bone metastases, TLDs/TDs may increase the risk of hypercalcemia, and in patients with gastrointestinal symptoms (vomiting, diarrhea) during cancer treatment, TLDs/TDs may exacerbate electrolyte disturbances. In patients treated with androgen synthesis inhibitors or androgen receptor antagonists, MRAs may be effective [253, 254].

Diltiazem and verapamil are not recommended during anticancer treatment as their metabolism is *via* the cytochrome P450 3A4 system, which may lead to interactions with chemotherapeutics and increase drug concentrations in the blood [253].

The inclusion of ACEIs or ARBs and BBs — recommended in HF — should be considered for primary prevention in high-risk patients, especially when targeted drugs are used that may induce heart failure [253].

A distinctive form of HT is observed during treatment with angiogenesis inhibitors, whose main target is the VEGF receptor. When using VEGF inhibitors, close monitoring of BP during the first cycle of treatment is recommended — daily home measurements are preferred. An increase in BP during therapy with these drugs is observed in the majority of patients; antihypertensive treatment often needs to be intensified during cancer treatment and then reduced after the end of the cycle. The aims of monitoring BP values and optimising treatment are to reduce cardiovascular risk and to allow continuation of cancer treatment. The threshold values for withholding cancer treatment are a rise in BP ≥180/110 mm Hg [253].

11.11. Hypertension in elderly patients with frailty and/or multimorbidity

The changing age structure in Western societies, better health and longer life expectancy of the elderly lead to a discussion on the arbitrariness of the definitione of old age. As a result, this position paper refrains from setting specific boundaries for old age [5, 15, 41]. Instead, priority is given to assessing the fitness of patients, regardless of age, in the diagnostic and therapeutic process of HT.

In light of the unequivocal intervention studies that have shown benefits of antihypertensive treatment even after the age of 80, elderly HT patients should be treated similarly to younger patients in decision-making algorithms [206]. This means using the same diagnostic criteria and decision-making BP values for pharmacotherapy. However, in the case of elderly patients, specific conditions that are more common in this age group should be taken into account, such as:

- frailty (in Poland it affects 15.9% of people over 60 years of age) [15];
- multimorbidity, including polypragmasia or short life expectancy [255, 256];
- situational hypotension (orthostatic, postprandial, exercise-induced, nocturnal);
- ISH (affects 26.8% of people over 60 years of age in Poland) [15, 257].

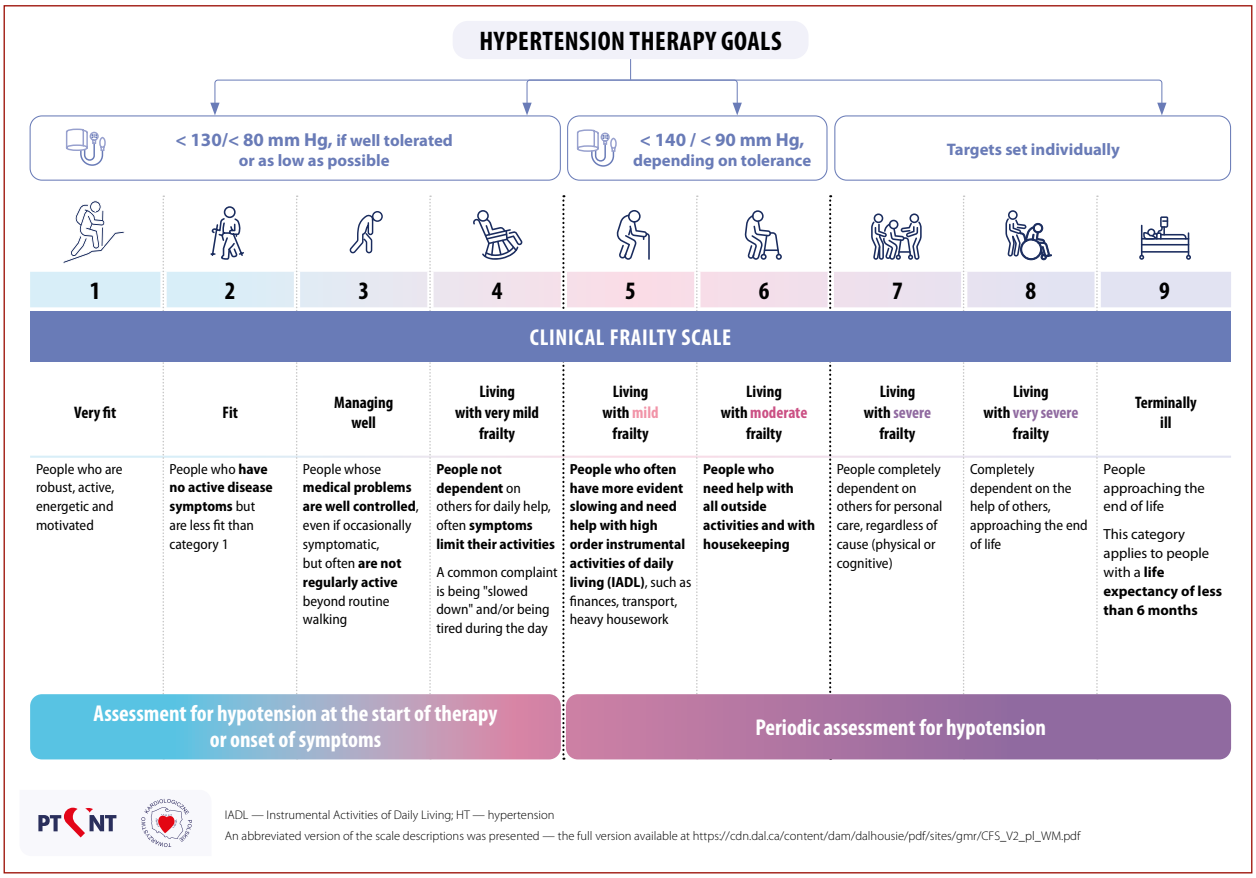


Figure 11.9. Management of hypertension (HT) in elderly patients

Each of these situations requires an individual approach to therapy, which makes it difficult to formulate uniform recommendations. It should also be borne in mind that problems such as frailty or multimorbidity are not just a matter of age and may also be present in people under 60 years of age.

Management in elderly patients

- A key part of the assessment of elderly patients during the diagnosis of HT is a thorough hemodynamic assessment. This includes the risk of orthostatic and postprandial hypotension and excessive BP fall during sleep and after exercise. It is also important to assess the risk of frailty, which is defined as a multidimensional loss of the body's physical, cognitive or social reserves and capabilities [15, 258]. In clinical practice, validated questionnaires are used to assess the presence and severity of frailty, of which the easiest-to-use 9-item scale is recommended (Figure 11.9) [206, 259–262].
- Elderly patients with HT should be provided with a complete set of information on non-pharmacological treatment, which is recommended to be implemented to the maximum extent possible. Recommendations for adequate fluid supply should also be kept in mind.
- Due to the higher risk of polypragmasy in the elderly, with its negative consequences, long-acting drugs administered in an SPC formulation should be preferred in the complex therapy of HT in elderly patients [255]. Exceptions are patients with at least mild frailty, aged ≥80 years, with orthostatic hypotension or a life expectancy of less than 3 years, in whom HT therapy is started with monotherapy.
- The mainstay of antihypertensive therapy in most elderly patients are ACEIs/ARBs in combination with CCBs or low-dose TLDs/TDs (preferentially TLDs). BBs should be considered if indicated, with a preference for SPC preparations. In patients with ISH in whom BBs are not indicated, drugs other than BBs should be considered due to their weaker effect on central BP than other drugs [5].

12. MANAGEMENT OF EMERGENCIES

Emergencies — are characterized by severe HT (≥180/≥110–120 mm Hg) accompanied by acute signs of organ damage (Table 12.1). Such cases are life-threatening and in most patients require immediate intervention (intravenous pharmacotherapy). The key in such circumstances is a rapid lowering of BP with intravenous pharmacotherapy (Figure 12.1) [2, 4, 263].

Typical emergencies:

- **severe HT** in acute conditions: refers to situations requiring urgent BP lowering, such as acute (hemorrhagic

Table 12.1. Emergencies in hypertension (HT) — organ damage. Based on [263]

	Type of organ damage (BARKH)				
	B — brain	**A — arteries**	**R — retina**	**K — kidneys**	**H — heart**
Acute conditions indicative of a hypertensive emergency	a) ischemic stroke b) PRES c) cerebral hemorrhage	a) acute aortic dissection b) pre-eclampsia, HELLP, eclampsia	Keith–Wagener–Barker grade III–IV hypertensive retinopathy	Acute kidney injury Thrombotic microangiopathy	a) acute heart failure b) pulmonary edema c) acute coronary syndrome
Initial BP target	a) when reperfusion treatment (thrombolysis/thrombectomy): lower BP <185/110 mm Hg and maintain within <180/105 mm Hg for at least 24 h • when conservative treatment: gently lower when BP>220/120 mm Hg — ↓ MAP by 15% within 24 h • when coexisting non-cerebral emergency conditions — individual BP targets b) immediately ↓ MAP by 20%–25% c) when spontaneous intracranial hemorrhage of mild to moderate severity and SBP in the range 150–220 mm Hg in the first 6 h, lower SBP <140 mm Hg and maintain in the range 130–150 mm Hg for the following 7 days • in other cases, individual BP targets	a) immediately ↓ SBP <120 mm Hg and HR <60/min b) immediately ↓ SBP <160 mm Hg and DBP <105 mm Hg	SBP <180 mm Hg ↓ MAP by 15%	↓ MAP by 20%–25% over several hours	a) SBP <180 mm Hg or immediate MAP by 25% b) immediately SBP <140 mm Hg c) immediately SBP <140 mm Hg
Treatment	Labetalol, nicardipine, sodium nitroprusside (alternative)	Esmolol (alternatively labetalol/metoprolol) and nitroglycerin or sodium nitroprusside or nicardipine Labetalol or nicardipine, magnesium sulphate, urapidyl when needed		Labetalol, nicardipine, urapidil, sodium nitroprusside (alternative)	Nitroglycerine with a loop diuretic Nitroglycerine or sodium nitroprusside and possibly a loop diuretic Nitroglycerine, labetalol or esmolol; alternatively urapidyl

Abbreviations: BARKH — brain, arteries, retina, kidneys, heart; DBP — diastolic blood pressure; HELLP — hemolysis, elevated liver enzymes, low platelets; HR — heart rate; MAP — mean arterial hypertension; PRES — posterior reversible encephalopathy syndrome; SBP — systolic blood pressure

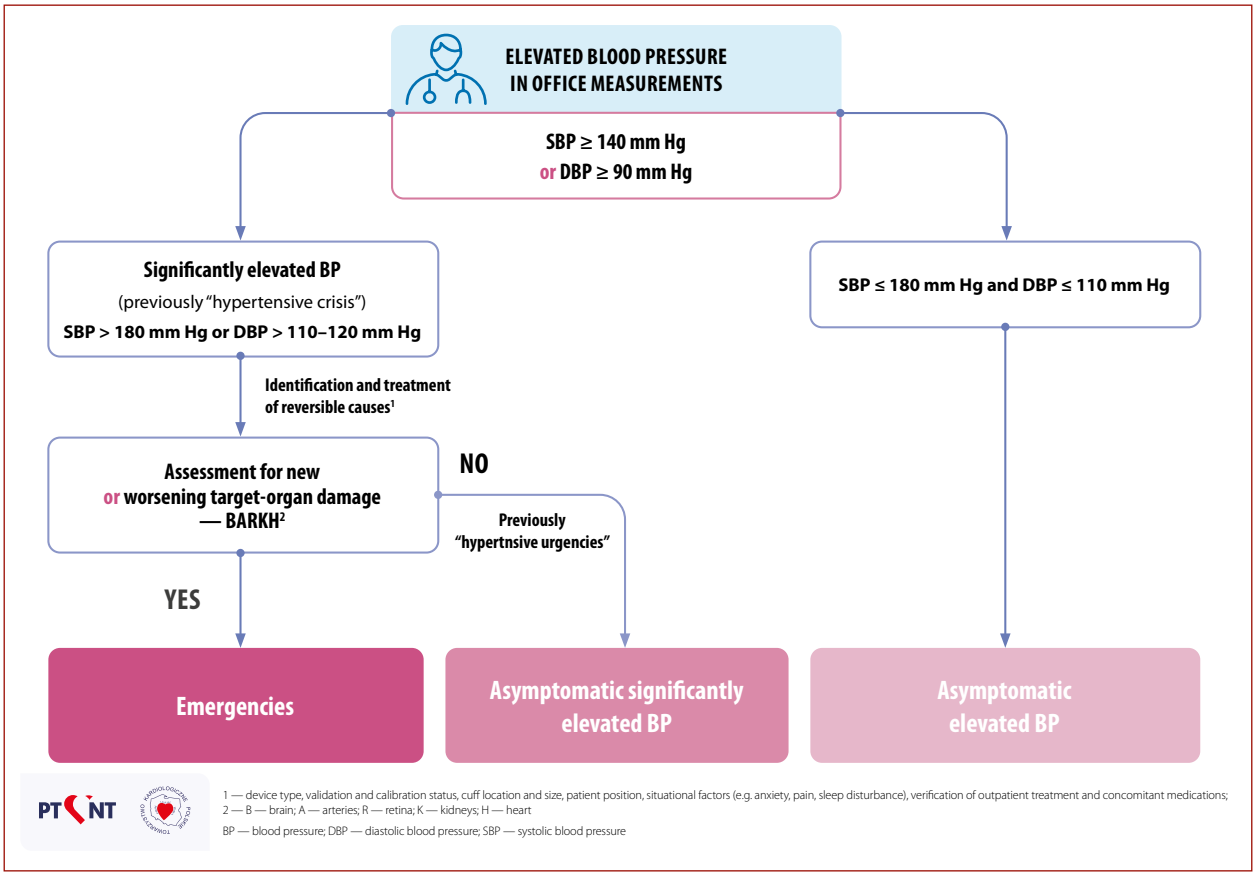


Figure 12.1. Clinical conditions with elevated blood pressure (BP) values in office measurements. Based on [263]

Table 12.2. Diagnosis of emergencies and asymptomatic significantly elevated blood pressure (BP). Based on [4]

Commonly performed tests	Specific examinations
Fundus examination	Troponin, NT-proBNP (suspicion of heart failure and/or acute coronary syndrome)
12-lead ECG	Chest X-ray or ultrasound (lung densities and fluid overload)
Hemoglobin, platelet count, fibrinogen, peripheral blood smear	Echocardiography (heart failure, acute ischemia, aortic dissection)
Creatinine, eGFR, electrolytes, LDH, haptoglobin	CT angiogram of the chest and/or abdomen when aortic disease is suspected (aortic dissection)
ACR, evaluation of urine sediment for red blood cells, leukocytes and/or casts	Brain CT or MR (nervous system involvement)
Pregnancy test in women of childbearing age	Renal ultrasound renal impairment or suspected renal artery stenosis
	Urine sampling for the presence of drugs (cocaine or methamphetamine use)

Abbreviations: eGFR, estimated glomerular filtration rate; ECG, electrocardiogram; LDH, lactate dehydrogenase; MRI, magnetic resonance; NT-proBNP, N-terminal pro-B-type natriuretic peptide; X-ray, radiological/X-ray examination; ACR, albumin/creatinine ratio; CT, computed tomography; ultrasound, ultrasound examination

or ischemic) stroke, aortic aneurysm or dissection, acute HF, ACS and renal failure. In such cases, even a small increase in BP can significantly exacerbate organ failure;

- **HT induced by specific factors**: can be caused by a tumour secreting catecholamines or by exogenous sympathomimetics such as psychoactive substances.
- **severe HT in pregnant women**: includes PE, eclampsia and HELLP syndrome.

The term "**urgent cases**" — currently proposed as **asymptomatic significantly elevated BP** — refers to HT with significantly elevated BP values that are not associated with acute organ damage at the time of the patient's assessment (Figure 12.1).

Malignant HT is a distinct form of emergency in HT characterized by a very poor prognosis when left untreated. It is defined as the coexistence of very high BP and thrombotic microangiopathy and acute renal failure. It is an emergency in which there is fibrinoid necrosis of small arteries and arterioles in the kidneys, retina and brain. Lesions of the fundus, microangiopathy, disseminated intravascular coagulation, encephalopathy or acute heart failure are also possible. Symptoms depend on the organs involved. They may include headaches, visual disturbances, dizziness and other neurological deficits, as well as chest pain and dyspnea. Patients with hypertensive encephalopathy may experience drowsiness, lethargy, tonic-clonic seizures and cortical disorders; blindness may precede loss of consciousness [4, 264]. The management of malignant HT is discussed in detail in a recently published paper [264].

12.1. Management of asymptomatic significantly elevated BP [4, 263]

- Patients generally do not require hospitalisation.
- The range of diagnostic investigations is shown in Table 12.2.
- It is necessary to gradually lower BP with oral antihypertensive drugs, which can be achieved by resuming or intensifying treatment (choice of drugs according to the basic strategy). This process should last 24–48 hours.
- For *ad hoc* BP lowering, short-acting drugs: clonidine, captopril or nitrendipine.
- Significantly elevated BP is one of the most common reasons for presenting to hospital emergency departments. A domestic analysis of these admissions indicates that there is a significant problem of inadequate antihypertensive therapy in this group of patients [265]. The patient should be advised by the treating physician for urgent consultation to modify HT therapy.

12.2. Management of emergencies [4, 263]

- All patients, including pregnant women with BP ≥160/110 mm Hg, should be hospitalized.
- The range of diagnostic investigations is shown in Table 12.2.
- It is important to determine which organs are involved, whether they require specialist intervention beyond lowering BP and to understand the cause of the sudden rise in pressure, which may influence the treatment plan.
- Determine the time scale and extent of BP lowering needed, and select appropriate pharmacological treatment (Table 12.1).
- Use intravenous drugs with a short half-life, which allows fine-tuning of treatment with close monitoring of the patient.
- Oral treatment with ACEIs, ARBs or BBs (with low initial doses and careful escalation) is sometimes effective in malignant HT, as the renin–angiotensin system may be activated by renal ischemia associated with this condition.

13. PERIOPERATIVE TREATMENT OF HT

13.1. Qualification for surgery and preoperative management

The basic recommendations for preoperative management [4, 266] are as follows:

- non-cardiac surgery should be performed when systolic BP is below 180 mm Hg and diastolic BP is below 110 mm Hg.
- surgical treatment should not be postponed in patients with untreated HT whose BP is 140–159/90–99 mm Hg or in those with controlled or almost controlled BP;
- if a patient is untreated and has a BP of at least 160/100 mm Hg, surgery should be postponed until BP control is achieved, unless it is an urgent operation;
- antihypertensive treatment, including BBs, should not be discontinued during the perioperative period. How-

ever, the patient should be monitored for electrolyte disturbances, arrhythmias, bradycardia and hypotension as possible consequences of treatment. BB therapy should not be started in <1 week before surgery;

- ACEIs/ARBs and diuretics can be discontinued on the day of surgery, while SGLT2 inhibitors should be discontinued three days before the planned surgery. Although discontinuation of ACEIs/ARBs on the day of surgery compared with continued therapy has been shown to be associated with fewer episodes of intraoperative hypotension, no differences were found in terms of the incidence of postoperative complications [267].

Changes in BP values may occur during perioperative management. Increases in BP may be induced by induction of anesthesia, intubation, pain associated with surgery and vasopressors, and decreases — by continued anesthesia, volume loss and blood loss.

13.2. Intraoperative management

During surgery, both low and high BP values may increase the risk of complications due to impaired autoregulation of blood flow, especially in older patients. There are no clear guidelines as to the specific BP values that should be maintained during surgery. It is important to try to keep them within a safe range, avoiding large fluctuations, especially episodes of hypotension, and aim for hemodynamic stability [4, 266].

13.3. Postoperative period

In the initial two hours after surgery, it is common to see an elevation in BP values, which usually resolves when antihypertensive treatment is reintroduced. Oral BBs should be restarted as soon as possible. Oral diuretics and ACEIs/ARBs should be restarted within 48 hours, after a thorough assessment of BP and the hydration status of the patient, taking into account the type of surgery performed, i.e. whether it was cardiac or non-cardiac surgery [4, 266].

14. UNCONTROLLED HYPERTENSION

14.1. Definition, characteristics and causes of uncontrolled and resistant HT

Hypertension is considered resistant when, despite the use of three drugs, including a diuretic, in appropriate combinations (ACEIs/ARBs and TLDs/TDs and CCBs) and at maximum tolerated doses, BP values in office measurements remain ≥140/90 mm Hg. Resistant HT defined in this way affects 10%–20% of patients. However, after taking into account ABPM to exclude the white coat effect and adherence to therapeutic recommendations (taking at least 80% of medication doses), the incidence of truly resistant HT is lower at around 5% [2, 4, 5, 268].

The reduction of target BP values to below 130/80 mm Hg means that many patients, although not meeting the definition of resistant HT, have uncontrolled HT. This is an increasingly common clinical problem. Patients with uncontrolled HT, especially those with resistant HT, have a higher incidence of HMOD and a higher cardiovascular risk. This risk also depends on the number of antihypertensive drugs used.

The pathophysiology of resistant HT includes overexpression of vasoconstrictive neurohormonal factors, renal dysfunction with fluid overload and, in the elderly, aortic and large artery stiffness. Common clinical conditions associated with resistant HT include obesity, alcohol abuse, salt-rich diet, CKD and diseases causing secondary HT [2, 4, 268, 269].

14.2. Diagnostic and therapeutic management of patients with suspected resistant HT

Figure 14.1 shows the algorithm for the diagnostic and therapeutic management of patients with suspected resistant HT.

The first step is to verify the appropriate choice of HT pharmacotherapy. The best option is to replace the current treatment with a single pill triple drug combination containing ACEIs/ARBs, TLDs/TDs and CCBs at maximum tolerated doses. This improves BP control in many patients [2, 4, 5, 268].

The second step is to check whether BP is indeed inadequately controlled, by taking home measurements (correctly taken) or ABPM. This helps to rule out the white coat effect, which is the second most common cause of pseudo-resistant HT [270].

The third step: in conversation with the patient, it is also worth verifying compliance with therapeutic recommendations (non-adherence is the most common cause of pseudo-resistant HT), including regular medication and lifestyle changes. Weight reduction, regular physical activity, reduction of salt and alcohol intake are important. A significant antihypertensive effect of intensive implementation of lifestyle modification recommendations has been shown in patients with resistant HT [271, 272]. Common reasons for non-adherence to therapeutic recommendations are: forgetting to take medication, poor motivation due to lack of awareness of the effects of HT, side effects of medication (including so-called multiple drug intolerance), poor tolerance of lower BP values and lack of symptoms at the onset of HT, too many medications used [273, 274]. Improvements in adherence can be achieved by using SPCs [2, 4, 5, 268, 269].

The fourth step: it is important to review the medications and substances taken by the patient, including those taken ad hoc, which may increase BP. These include drugs such as NSAIDs, corticosteroids, pseudoephedrine and combined contraceptives, theophylline, as well as substances such as liquorice and cocaine and other stimulants and dietary supplements.

The fifth step: often carried out already in reference centres, is screening for secondary causes of HT, which often lead to resistant HT. If a secondary form of HT is diagnosed, the key is to treat the underlying disease (Figure 4.5,

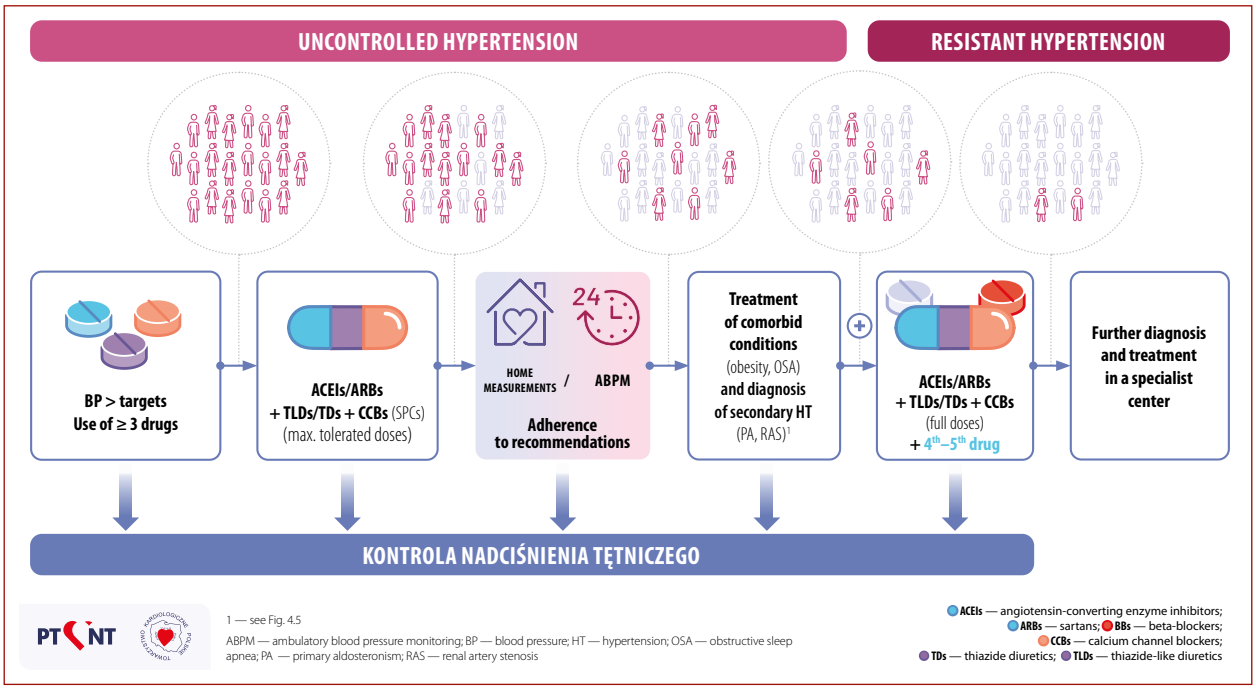


Figure 14.1. Algorithm for the management of patients with suspected resistant hypertension (HT)

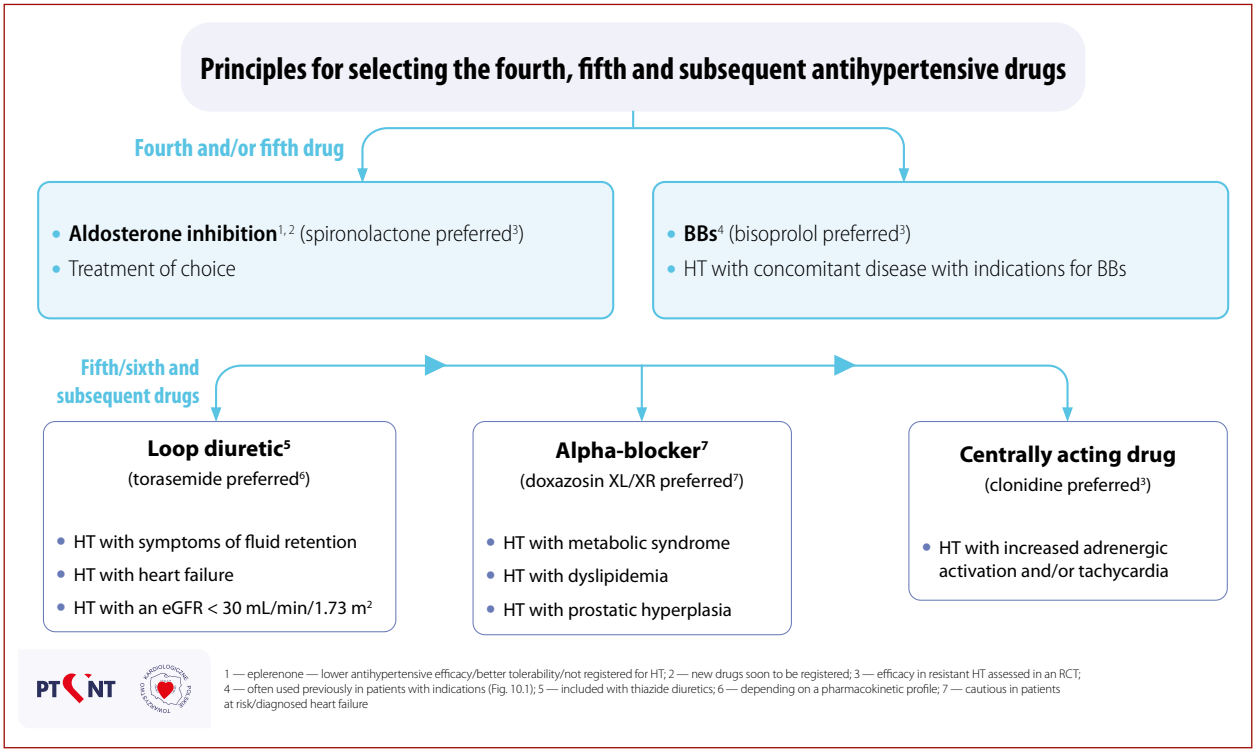


Figure 14.2. Algorithm for the treatment of resistant hypertension (HT)

section 4.7) [2, 4, 5, 268]. This diagnostic step is carried out in parallel with intensification of antihypertensive therapy for resistant HT.

14.3. Antihypertensive therapy of truly resistant HT

For truly resistant HT, a fourth antihypertensive drug should be added. According to current recommendations, aldosterone-inhibiting drugs and BBs are recommended (Figure 14.2). The treatment of choice is the use of MRAs, especially spironolactone, even at low doses (25–50 mg/day). In the PATHWAY-2 study, spironolactone was shown to have a stronger antihypertensive effect than bisoprolol or doxazosin [275]. Its effect can be attributed to the inhibition of aldosterone, the concentration of which is often elevated in resistant HT (increased secretion after an initial reduction due to renin-angiotensin system blockade or undiagnosed

primary hyperaldosteronism). In patients with an eGFR below 45 ml/min/1.73 m^2 or a potassium concentration of more than 4.5 mmol/l, spironolactone should be used with caution due to the risk of hyperkalemia. If spironolactone is not tolerated, eplerenone may be an alternative, although it is not currently registered for the treatment of HT and its efficacy is significantly lower [2, 4, 276]. Approval of the selective aldosterone synthesis inhibitor, baxdrostat, which has shown efficacy in the BrighHTN trial in patients with resistant HT can be expected soon [277]. Due to the high incidence of cardiac complications in resistant HT, BBs, especially bisoprolol, are also a recommended fourth drug [275, 278]. In clinical practice, patients with indications for BBs receive them earlier. It has been shown to be effective in intensifying ineffective therapy based on three essential drugs with an SPC containing four antihypertensive drugs using bisoprolol — ACEIs, TLDs/TDs, CCBs and BBs [279]. A vasodilating BB such as nebivolol (10 mg dose) may also be considered for selection.

In subsequent treatment steps, an increase in the number of drugs to five-seven may be considered, including:

- a loop diuretic (torasemide preferred) as an adjunct to TLDs/TDs (chlortalidone in patients with an eGFR <30 ml/min/1.73 m^2), especially in patients with CKD or with signs of sodium and water retention [4, 5, 48, 157];
- an alpha-blocker (doxazosin XL preferred) [270];
- a centrally acting drug (clonidine preferred) [280];
- a direct vasodilator (dihydralazine) [2, 4, 5, 268];
- a double endothelin inhibitor (aprocicentan), whose moderate efficacy was shown in the PRECISION trial [281].

In patients with resistant HT, drugs often need to be administered twice daily. In the case of refractory HT, which cannot be controlled despite treatment with five to seven drugs, and in the case of suspected secondary forms of HT, patients should be referred to a specialist HT centre [282]. In Poland, the diagnosis of resistant HT allows the patient to access priority hospital treatment within the National Cardiac Network.

15. INTERVENTIONAL TREATMENT OF HT

Renal artery denervation stands out among interventional treatments for HT in terms of the greatest evidence of antihypertensive efficacy from clinical trials, including those in which sham surgery was performed. However, there is a lack of data on its long-term efficacy, especially in terms of cardiovascular risk reduction [283–288]. Also worth noting are domestic studies on the efficacy of cardioneuromodulation in BP lowering. The cardioneuromodulation is the alghorithm available on a pacemaker that affects the autonomic system through changes in the PQ interval. This method requires further research [289].

Currently, only in centres with suitably experienced staff renal artery denervation can be considered as a therapeutic option, in patients with HT uncontrolled with at least three drugs in full doses, including TDLs/TDs. The decision to perform the procedure is made by a team of specialists, consisting of a hypertensiologist and an interventional cardiologist, after a detailed discussion with the patient about the potential benefits and risks. The procedure is not recommended in patients with an eGFR below 40 ml/min/1.73 m^2 [4, 5].

Although patients with an eGFR below 40 ml/min/1.73 m^2 were not eligible for randomized trials with the sham procedure, the results of observational studies demonstrate the safety and nephroprotecitive effect of the procedure in patients with CKD.

In patients who do not adhere to therapeutic recommendations or who cannot tolerate many antihypertensive drugs, especially the three essential ones, are at least at high cardiovascular risk and have not achieved target BP values, renal denervation may also be considered. The prerequisite is that patients are willing to undergo this procedure following a shared decision-making process. This process requires that patients are fully informed of the benefits, limitations and risks of renal denervation [5].

The issue of renal artery denervation will be discussed in detail in a forthcoming position paper of PTK and PTNT experts.

16. IMPORTANCE OF PATIENT CO-OPERATION IN LONG-TERM BP CONTROL

Non-adherence to therapeutic recommendations, including both lifestyle modifications and pharmacotherapy, is increasingly recognized as a major cause of failure to achieve therapeutic goals. This leads to increased morbidity and mortality from cardiovascular causes and increases healthcare costs, i.a. avoidable hospitalisations. This problem particularly concerns HT [290].

Two groups of patients are particularly vulnerable: the young and middle-aged, who, according to research, show the least persistence with therapy, and those who are just starting therapy with cardiovascular risk reducing drugs, including antihypertensive drugs. Early discontinuation of such treatment, for example with antihypertensive drugs and statins, is associated with a higher risk of morbidity and death from cardiovascular causes [291–293].

To increase adherence to treatment in cardiovascular diseases, there are several key areas to focus on. Improving communication skills and building a partnership between patient and clinician are a key. This allows for a fully informed decision by the patient and acceptance of the actions taken. Patient education, dispelling myths and misinformation from the internet, and the use of electronic reminder methods such as SMS can help. Eliminating economic barriers and monitoring treatment progress are also important. Simplifying treatment regimens through SPCs also promotes better adherence [294–296].

Multidirectional interventions to improve adherence, including building physician–patient partnerships so that all therapeutic decisions are autonomously made by the patient, can significantly increase treatment persistence

and reduce morbidity and mortality from cardiovascular causes in society.

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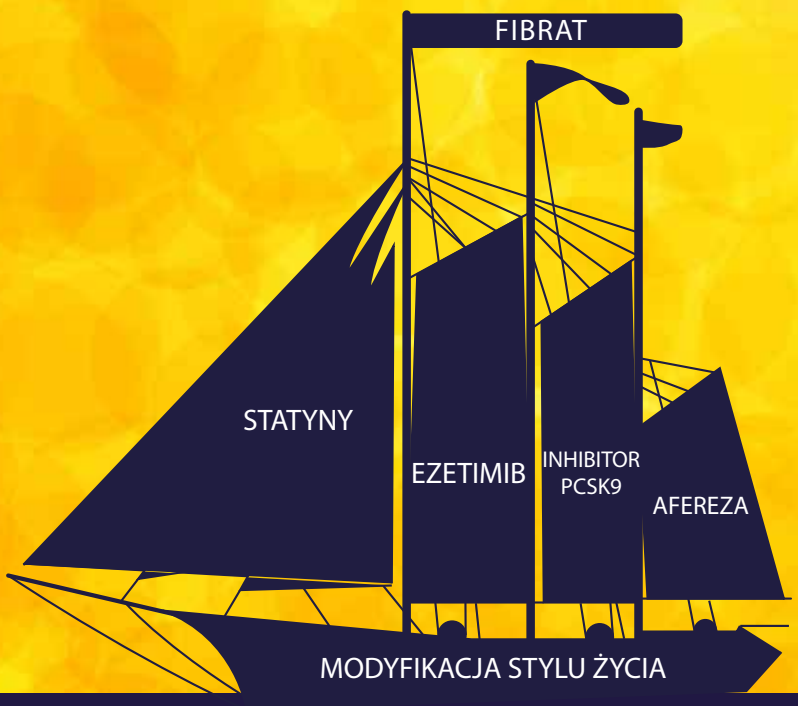
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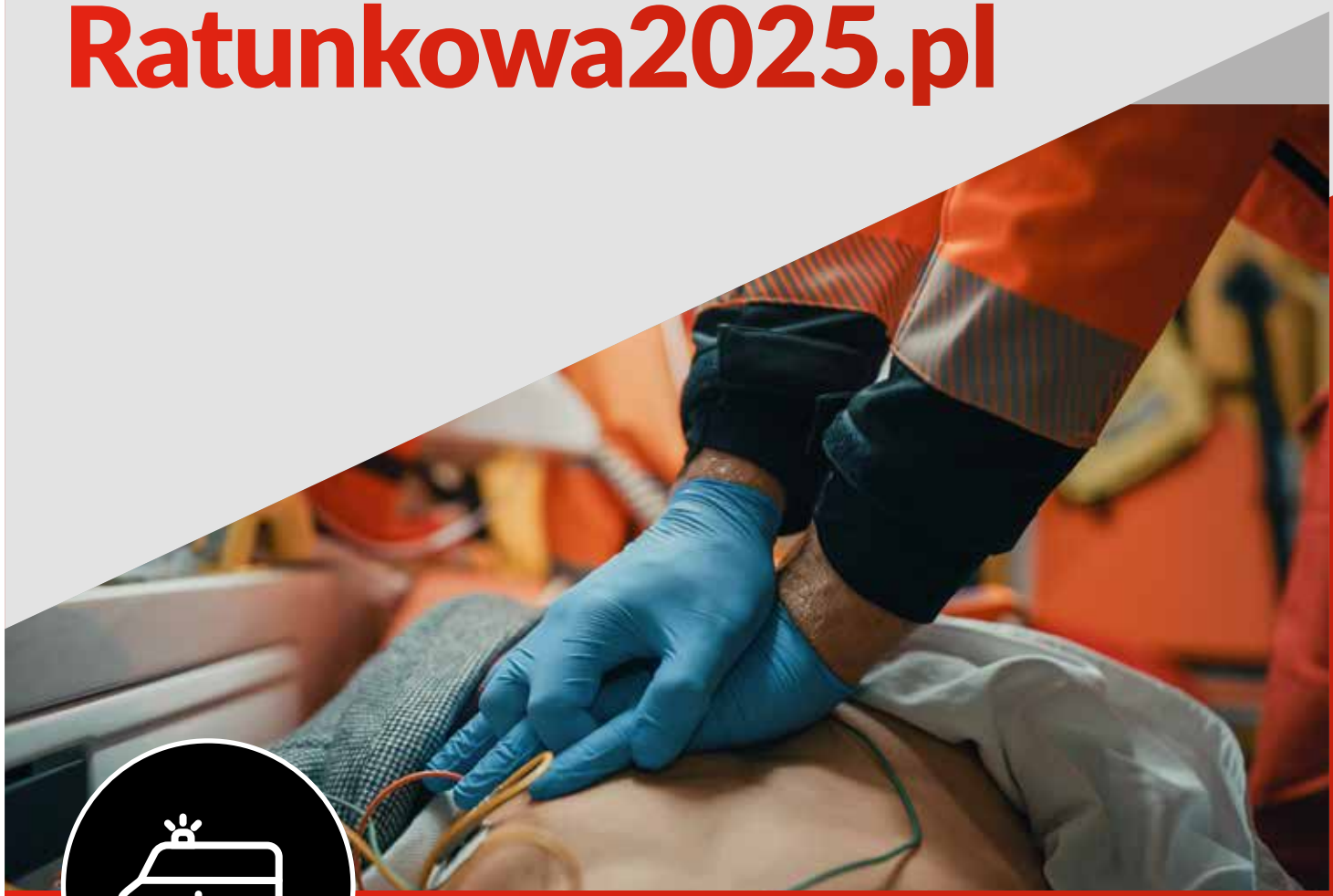
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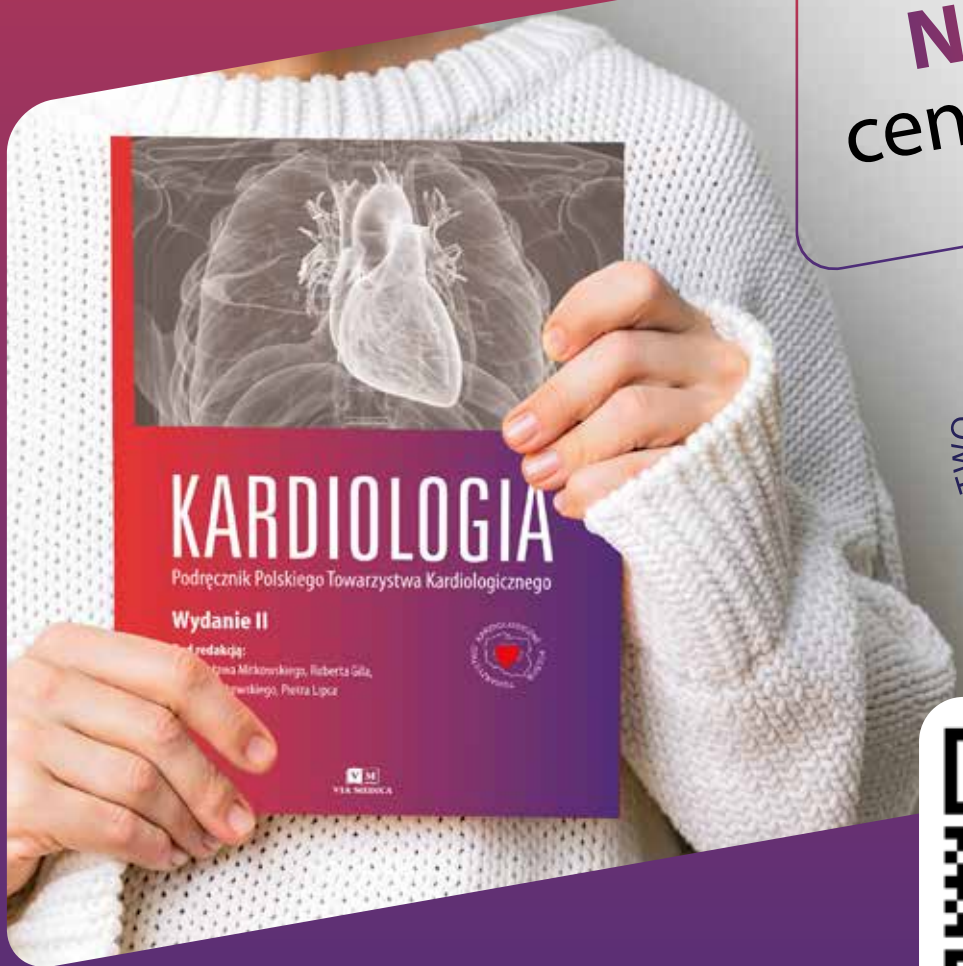
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