ISSN 0022–9032

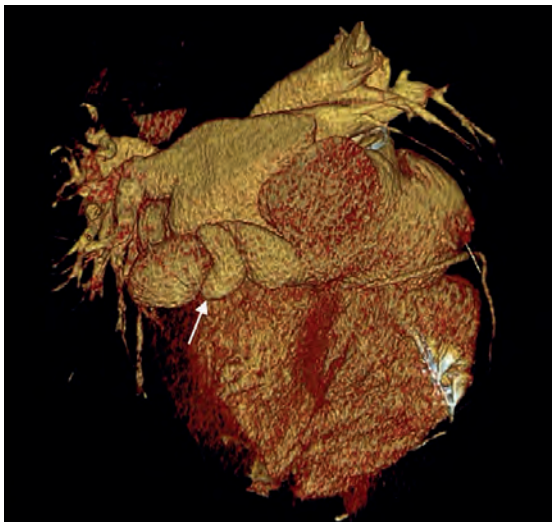
e-ISSN 1897–4279

December 2023, vol. 81, number 12

KARDIOLOGIA POLSKA

Polish Heart Journal

The Official Peer-reviewed Journal
of the Polish Cardiac Society
since 1957



Coronary artery fistula (arrow) between the circumflex artery and the coronary sinus on computed tomography, see p. 1219

https://journals.viamedica.pl/kardiologia_polska

VIA MEDICA

Kieszonkowe wytyczne ESC

APLIKACJA MOBILNA
KIESZONKOWE WYTYCZNE ESC

- Wszystkie wytyczne od 2014 roku dostępne w jednym miejscu
- Bieżąca aktualizacja o nowo ukazujące się wytyczne ESC
- Możliwość korzystania przy łóżku pacjenta
- Łatwa nawigacja
- Możliwość tworzenia zakładek z wybranymi przez użytkownika zagadnieniami
- Możliwość skalowania tekstu

APLIKACJA DOSTĘPNA BEZPŁATNIE DLA WSZYSTKICH UŻYTKOWNIKÓW:

Pobierz w App Store

POBIERZ Z Google Play

21-0050.019.005

VIA MEDICA

KARDIOLOGIA POLSKA

Polish Heart Journal

The official peer-reviewed journal of the Polish Cardiac Society since 1957

Indexed in Chemical Abstract Service (CAS), CrossRef, EBSCO, EMBASE, Free Medical Journals, Google Scholar, Index Copernicus (IC), Index Scholar, MEDLINE, Polish Medical Library (GBL), Scopus, Polish Ministry of Education and Science, Ulrich's Periodicals Directory, Web of Science

Address
Kardiologia Polska
ul. Prądnicka 80, bud. M–IX
31–202 Kraków
phone: +48 126 143 004
e-mail: kardiologiapolska@ptkardio.pl
www.kardiologiapolska.pl

Polskie Towarzystwo Kardiologiczne
ul. Stawki 3 A lok. 1–2
00–193 Warszawa

Publisher

VIA MEDICA

VM Media Group sp. z o.o.,
Grupa Via Medica
ul. Świętokrzyska 73
80–180 Gdańsk
phone: +48 58 320 94 94
e-mail: journals@viamedica.pl
https://journals.viamedica.pl

ISSN 0022-9032
e-ISSN 1897-4279

Subscription rates: Paper subscription, 12 issues incl. package and postage individual 150€
Paper subscription, 12 issues incl. package and postage institutional 250€
Payment should be made to: BNP Paribas Bank Polska SA, Gdańsk, Poland,
Acc.: PL 41 1600 1462 0008 1377 1035 9168.
Single issues, subscriptions orders and requests for sample copies should be send to e-mail: prenumerata@viamedica.pl Electronic orders option available at: https://journals.viamedica.pl/kardiologia_polska/user/subscriptions

Advertising: For details on media opportunities within this journal please contact the Advertising Sales Department, ul. Świętokrzyska 73, 80–180 Gdańsk, Poland, phone: +48 58 320 94 94; e-mail: dsk@viamedica.pl.

Editorial policy and information for authors available on https://journals.viamedica.pl/kardiologia_polska/about/submissions#authorGuidelines.

Polish Ministry of Education and Science score: 100 pts.

The project on the development of the journal „Kardiologia Polska" is co-financed from the state budget under the „Development of Scientific Journals" program as per the Regulation of the Minister of Education and Science of August 3, 2021 on the „Development of Scientific Journals" program (Journal of Laws of 2021, item Scientific Journals").

Dni Nadciśnienia Tętniczego i Cukrzycy

Gdańsk, 17 lutego 2024 roku

Hotel Scandic
ul. Podwale Grodzkie 9

Przewodniczący Komitetu Naukowego
dr hab. n. med. Jacek Wolf
dr hab. n. med. Michał Hoffmann

ORGANIZATOR

VIA MEDICA

www.dntic.viamedica.pl

Konferencja jest skierowana tylko do osób uprawnionych do wystawiania recept lub osób prowadzących obrót produktami leczniczymi — podstawa prawna: ustawa z dnia 6 września 2001 r. Prawo farmaceutyczne (t.j. Dz.U. z 2020 r. poz. 944).

KARDIOLOGIA POLSKA
Polish Heart Journal

Table of contents

SHORT COMMUNICATION

CLINICAL VIGNETTE

Congenital Coronary Artery Fistulas, a Polish single-center computed tomographic registry

Sérgio Madeira, António Rocha Almeida, Miguel Domingues

Hospital de Santa Cruz — Centro Hospitalar de Lisboa Ocidental, Carnaxide, Portugal

Related article
by Michałowska et al.

Correspondence to:
Sérgio Madeira, MD,
Hospital de Santa Cruz
— Centro Hospitalar de Lisboa
Ocidental,
Av. Prof. Dr. Reinaldo dos Santos,
2790–134 Carnaxide, Portugal
phone: 21 043 10 00,
e-mail:
serg.lou.madeira@gmail.com

DOI: 10.33963/v.kp.98517

Received:
December 10, 2023

Accepted:
December 10, 2023

Early publication date:
December 12, 2023

Congenital coronary artery fistulas (CAF) are aberrant connections between the coronary arteries and contiguous structures like non-coronary vessels or cardiac chambers. In patients undergoing coronary computed tomography (CT) angiography, the prevalence of CAFs ranges from 0.2 to 0.9% [1–3].

CAF is often found incidentally during a study for other reasons [4], however depending on the anatomy (donor vessel, recipient vessel or chamber, size and length) and patient characteristics (concomitant heart disease), it may cause symptoms and lead to life-threatening complications like acute ischemia, congestive heart failure, pulmonary hypertension, endarteritis and rupture [5, 6]. Usually small incidentally found CAFs are asymptomatic and do not require intervention [1, 4, 7]. Some CAF may remain clinically silent for decades, however once it becomes hemodynamic significant (myocardial ischemia through a steal phenomenon, left ventricle volume overload or significant left to right shunt leading to congestive heart failure or pulmonary hypertension) treatment must be considered [8]. Percutaneous treatment is currently the mainstay of therapy when technically feasible and there are no other indications for heart surgery [4, 8]. Patients that underwent intervention should be followed up more frequently early after closure to recognize the possible recurrence of the fistula, persistent dilatation of the coronary artery, thrombus formation, calcification, arrhythmias, and myocardial infarction [8]. Regarding medical therapy, antiplatelet therapy is recommended empirically to prevent thrombosis when there is coronary artery or fistula dilatation, anti-anginal drugs should be used to alleviate angina, and most authors recommend endocarditis prophylaxis.

In this issue of the *Polish Heart Journal*, Michałowska et al. [9] reported the prevalence, anatomic characteristics, and clinical significance of congenital CAFs, of 42 patients diagnosed as having at least one CAF among 39 066 unselected adults, that had a cardiac CT assessment over a period of 12 year in a tertiary single center. It is the largest, CT diagnosed congenital CAF series, ever reported. Overall, the findings regarding anatomy and clinical manifestations are in line with other international series, however some points deserve a thoughtful reflection. The prevalence of CAF in the present report was 0.11%, which is within the range of invasive angiography registries, but bellow most of the largest CT series (0.19%–0.9%) [1–3]. This may be due to: 1) the retrospective nature of the study and the methodology that the authors used to identify CAF cases; 2) exclusion of CAFs suspected to be acquired and non-diagnostic CTs, (nevertheless, it accounted only for 10 patients, and the prevalence would have been otherwise 0.13%, still bellow most of the CT series); and 3) finally a possible difference in CAFs prevalence among distinct populations, with higher prevalence in eastern population, where the largest CT reports were derived from [1–3]. There was an association between CAF size and drainage site (namely, low pressure right sided vessels/chambers — superior vena cava, right atrium, coronary sinus) with fistula calcification, infective endocarditis, pulmonary hypertension, and clinical significance (as defined by the authors). Clinical significant

CAF were more common in younger and male patients. This results should be interpreted with caution, given the small sample size, prone to type II error. Also, mortality at a median follow up of 22.5 months was very high, 16.7% (7/42) in the overall CAF population, 43% (3/7) in patients with clinically significant CAFs, and 11% (4/35) in patients with non-significant CAF, the mean ages of these groups were 57.5, 47.1 and 59.5 years old, respectively.

The present results add up to the evidence that already exists, reinforcing that CAF is a rare entity, and clinically significant CAF is even rarer; in adults the diagnosis is usually made "incidentally" by CT as an investigation for other causes of chest pain, and heart failure; and that anatomical factors influence the clinical presentation. In addition the current findings, raise some hypothesis, namely: 1) the possibility that CAF prevalence may vary in different populations; 2) that CAFs draining into right sided structures may increase in size and progress to larger shunts with clinical repercussion at younger ages, and 3) that mortality in CAF patients is high, even in patients with non-clinically significant CAFs. This issues deserve further investigation, to clarify if there are differences in the prevalence and presentation in different populations; if CAFs draining into right sided structures deserve a different approach, namely and more preemptive follow up and treatment; and if CAF presence is associated with higher risk of mortality. Furthermore, the role of other diagnostic modalities, namely functional cardiac magnetic resonance and invasive hemodynamic assessment, in establishing a mechanistic correlation between the anatomical characteristics and clinical repercussion, needs to be clarified. Finally, given the high anatomical and clinical variability, therapy should always be individually tailored, however it is not known when is the sweet spot for intervention nor what is the best therapeutic option for incidentally found CAFs. This kind of reports highlight the need for larger prospective multicenter international registries. An effort should be made to incite physicians collaboration in reporting the natural history and management of all types of CAFs, so that a more comprehensive characterization of this rare and highly heterogeneous condition can be made.

Article information

Conflict of interest: None declared.

Funding: None.

REFERENCES

1. Zhou K, Kong L, Wang Y, et al. Coronary artery fistula in adults: evaluation with dual-source CT coronary angiography. Br J Radiol. 2015; 88(1049): 20140754, doi: 10.1259/bjr.20140754, indexed in Pubmed: 25784320.
2. Ouchi K, Sakuma T, Ojiri H. Coronary artery fistula in adults: Incidence and appearance on cardiac computed tomography and comparison of detectability and hemodynamic effects with those on transthoracic echocardiography. J Cardiol. 2020; 76(6): 593–600, doi: 10.1016/j.jjcc.2020.06.005, indexed in Pubmed: 32636129.
3. Lim JJ, Jung JI, Lee BY, et al. Prevalence and types of coronary artery fistulas detected with coronary CT angiography. AJR Am J Roentgenol. 2014; 203(3): W237–W243, doi: 10.2214/AJR.13.11613, indexed in Pubmed: 25148179.
4. Albeyoglu S, Aldag M, Ciloglu U, et al. Coronary arteriovenous fistulas in adult patients: surgical management and outcomes. Braz J Cardiovasc Surg. 2017; 32(1): 15–21, doi: 10.21470/1678-9741-2017-0005, indexed in Pubmed: 28423125.
5. Bauer HH, Allmendinger PD, Flaherty J, et al. Congenital coronary arteriovenous fistula: spontaneous rupture and cardiac tamponade. Ann Thorac Surg. 1996; 62(5): 1521–1523, doi: 10.1016/0003-4975(96)00757-6, indexed in Pubmed: 8893601.
6. Buccheri D, Chirco PR, Geraci S, et al. Coronary artery fistulae: anatomy, diagnosis and management strategies. Heart Lung Circ. 2018; 27(8): 940–951, doi: 10.1016/j.hlc.2017.07.014, indexed in Pubmed: 29503240.
7. Warnes C, Williams R, Bashore T, et al. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease. J Am Coll Cardiol. 2008; 52(23): e143–e263, doi: 10.1016/j.jacc.2008.10.001, indexed in Pubmed: 19038677.
8. Karazisi C, Eriksson P, Dellborg M. Coronary artery fistulas: case series and literature review. Cardiology. 2017; 136(2): 93–101, doi: 10.1159/000447445, indexed in Pubmed: 27577264.
9. Michałowska A, Skowroński J, Michałowska I, et al. Computed tomographic characteristics of congenital coronary artery fistulas in an adult population. Kardiol Pol. 2023; 81(12): 1217–1226, doi: 10.33963/v.kp.97829.

Restrictive cardiomyopathies: The need for better characterization of a deadly disease

Daniele Masarone, Luigi Falco

Heart Failure Unit, Department of Cardiology, AORN dei Colli-Monaldi Hospital, Naples, Italy

Related article
by Szczygieł et al.

Correspondence to:
Daniele Masarone MD, PhD,
Heart Failure Unit- AORN dei Colli-
-Monaldi Hospital,
80121 Naples, Italy,
phone: +39 081 706 28 15,
e-mail: daniele.masarone@
ospedalideicolli.it

DOI: 10.33963/v.kp. 98518

Received:
December 10, 2023

Accepted:
December 10, 2023

Early publication date:
December 12, 2023

An abrupt rise in filling pressure is the landmark feature of restrictive cardiomyopathies (RCM). Non-dilated but stiffened ventricles underpin diastolic dysfunction, atrial enlargement, and heart rate dependency due to fixed stroke volume. However, several knowledge gaps persist despite a thorough understanding of the underlying pathophysiology. The main reason is that pure RCM is the rarest cardiomyopathy phenotype, and its prevalence is still unclear [1]. In addition, a wide spectrum of diseases, both genetic and acquired, can manifest as RCM. Finally, to further complicate the RCM landscape, restrictive phenotypes can be transient or permanent; they even overlap with other phenotypes [2].

Nevertheless, this was a favorable year for management of cardiomyopathies, with the publishing of the first comprehensive cardiomyopathy guidelines by the European Society of Cardiology (ESC) [3]. The relevance of meticulous etiological research of RCM was emphasized since disease-modifying therapies are now available, especially for transthyretin cardiac amyloidosis (TTR-CA). On the other hand, only a few management recommendations were suggested, highlighting the lack of data on RCM. Indeed, except for TTR-CA, a few studies focused on RCM in recent years [4–7].

In this issue of *Kardiologia Polska*, Szczygieł and colleagues [8] provide interesting etiological, genetic, and prognostic insights (Figure 1) on a prospective cohort of patients enrolled in a single tertiary center. Thirty-six consecutive patients received a diagnosis of RCM from 2015 to 2016. Patients with hypertrophic cardiomyopathy features were excluded. Then, the entire cohort underwent cardiac amyloidosis screening, including medical history, physical examination, cardiovascular, digestive, and neurological assessment, laboratory tests, electrocardiography, echocardiography, and cardiovascular magnetic resonance. Novel non-invasive imaging features, such as impaired global longitudinal strain with the relative apical sparing pattern and increased T1 mapping, were not assessed in the entire population. A positive result of CA screening prompted amyloid typing through evaluation of serum-free light chains and immunofixation of both serum and urine.

According to recent position papers [9, 10], invasive tests are mandatory for the diagnosis of cardiac light chain amyloidosis (AL-CA), while a cardiac uptake on diphosphonate scintigraphy of at least grade 2 of Perugini score in the absence of a monoclonal protein allows non-invasive TTR-CA diagnosis. In non-amyloid RCM (na-RCM), genetic testing identified pathogenic or likely pathogenic (P/LP) variants in the majority of patients (86%), underscoring that RCM may be mostly a genetic disorder, especially after careful exclusion of infiltrative diseases. In this regard, similar results (60%) were found in a Spanish study including 32 patients with end-stage RCM [3]. All-cause mortality for the overall cohort was 56%. The poor prognosis was consistent with a previous multicenter Korean study, where five-year overall survival was 64% [5].

The recent EURObservational Research Programme Cardiomyopathy registry designed by the ESC provided further intriguing information [6, 7]. Patients with RCM showed the highest annual rates of major cardiovas-

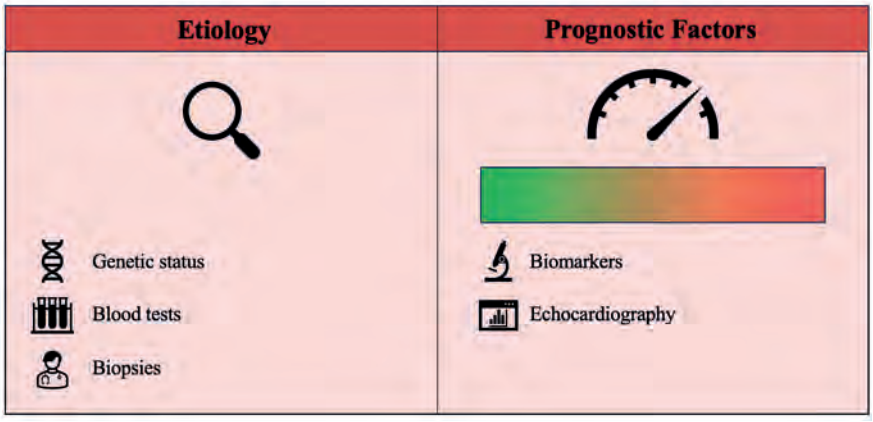


Figure 1. Key aspects of the study by Szczygieł et al. [7]. Left panel: etiologic evaluation. Right panel: assessment of biomarkers and echocardiographic findings as prognostic factors

cular events (P <0.001) as compared to those with other cardiomyopathies. Moreover, except for RCM, all cardiomyopathy phenotypes were more prevalent in males. Finally, RCM patients were more symptomatic, and their functional status was less likely to improve. Subsequently, biomarkers and echocardiographic findings were tested as predictors of outcomes. N-terminal proB-type natriuretic peptide (NT-proBNP) is included in every proposed prognostic staging score for both AL-CA and TTR-CA [3]. Interestingly, the authors evaluated NT-proBNP, high-sensitive troponin T (hs-TnT), soluble suppression of tumorigenicity 2 (sST2), and growth differentiation factor-15 (GDF15) in both amyloid and na-RCM. Univariate Cox models identified GDF15 as the strongest predictor among biomarkers (hazard ratio [HR], 1.45; confidence interval [CI], 1.12–1.88; P = 0.004). NT-proBNP and hs-TnT were also significantly associated with reduced survival (HR, 1.17; CI, 1.08–1.28; P <0.001 and HR, 1.10; CI, 1.04–1.16; P <0.001, respectively). Pericardial effusion was three-fold more frequent in AL-CA than na-RCM (P <0.001) and was the most important predictor of death (HR, 5.49; CI, 1.94–15.51; P = 0.001). It is important to note that the prognosis is still poor, as in previous reports [4, 6]. Additionally, the limited number of patients prevented further analyses.

In conclusion, while authors need to be congratulated for their effort to assess new biomarkers through a wide spectrum of well-characterized RCM, we believe that emerging targeted therapies are paving the way to a proactive approach aiming at precision medicine as a cornerstone of RCM management. We acknowledge that this is a difficult task to achieve, considering RCM epidemiology. Thus, further studies are required to improve the characterization and prognosis of such a deadly disease.

Article information

Conflict of interest: None declared.

Funding: None.

REFERENCES

1. Masarone D, Kaski JP, Pacileo G, et al. Epidemiology and clinical aspects of genetic cardiomyopathies. Heart Fail Clin. 2018; 14(2): 119–128, doi: 10.1016/j.hfc.2017.12.007, indexed in Pubmed: 29525641.
2. Rapezzi C, Aimo A, Barison A, et al. Restrictive cardiomyopathy: definition and diagnosis. Eur Heart J. 2022; 43(45): 4679–4693, doi: 10.1093/eurheartj/ehac543, indexed in Pubmed: 36269634.
3. Arbelo E, Protonotarios A, Gimeno JR, et al. 2023 ESC Guidelines for the management of cardiomyopathies. Eur Heart J. 2023; 44(37): 3503–3626, doi: 10.1093/eurheartj/ehad194, indexed in Pubmed: 37622657.
4. Gallego-Delgado M, Delgado JF, Brossa-Loidi V, et al. Idiopathic restrictive cardiomyopathy is primarily a genetic disease. J Am Coll Cardiol. 2016; 67(25): 3021–3023, doi: 10.1016/j.jacc.2016.04.024, indexed in Pubmed: 27339502.
5. Hong JA, Kim MS, Cho MS, et al. Clinical features of idiopathic restrictive cardiomyopathy: A retrospective multicenter cohort study over 2 decades. Medicine (Baltimore). 2017; 96(36): e7886, doi: 10.1097/MD.0000000000007886, indexed in Pubmed: 28885342.
6. Charron P, Elliott PM, Gimeno JR, et al. The Cardiomyopathy Registry of the EURObservational Research Programme of the European Society of Cardiology: baseline data and contemporary management of adult patients with cardiomyopathies. Eur Heart J. 2018; 39(20): 1784–1793, doi: 10.1093/eurheartj/ehx819, indexed in Pubmed: 29378019.
7. Gimeno JR, Elliott PM, Tavazzi L, et al. Prospective follow-up in various subtypes of cardiomyopathies: insights from the ESC EORP Cardiomyopathy Registry. Eur Heart J Qual Care Clin Outcomes. 2021; 7(2): 134–142, doi: 10.1093/ehjqcco/qcaa075, indexed in Pubmed: 33035297.
8. Szczygieł JA, Michałek P, Truszkowska G, et al. Clinical features, etiology and survival in patients with restrictive cardiomyopathy: A single center experience. Kardiol Pol. 2023; 81(12): 1227–1236, doi: 10.33963/v.kp.97879, indexed in Pubmed: 37937352.
9. Garcia-Pavia P, Rapezzi C, Adler Y, et al. Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases. Eur Heart J. 2021; 42(16): 1554–1568, doi: 10.1093/eurheartj/ehab072, indexed in Pubmed: 33825853.
10. Kittleson MM, Ruberg FL, Ambardekar AV, et al. 2023 ACC Expert Consensus Decision Pathway on Comprehensive Multidisciplinary Care for the Patient With Cardiac Amyloidosis: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2023; 81(11): 1076–1126, doi: 10.1016/j.jacc.2022.11.022, indexed in Pubmed: 36697326.

Social relationships and health: What do we know and where do we go from here?

Thomas Rutledge[1, 2], Nicole Virzi[1, 3]

[1]VA San Diego Healthcare System, San Diego, California, United States
[2]Department of Psychiatry, University of California, San Diego, California, United States
[3]Department of Clinical Psychology, San Diego State University/University of California, San Diego Joint Doctoral Program, San Diego, California, United States

Related article
by Piwońska et al.

Correspondence to:
Thomas Rutledge, PhD,
Department of Psychiatry,
University of California,
San Diego, California, United States,
phone: (858) 552 85 85,
e-mail: thomas.rutledge@va.gov

DOI: 10.33963/v.kp.98351

Received:
November 24, 2023

Accepted:
November 29, 2023

Early publication date:
November 29, 2023

In one of the latest studies describing associations between social relationships and health, Piwońska and colleagues [1] provide further evidence for a conclusion now backed by greater than 50 years of research: social relationships appear to be important — perhaps even essential — for optimizing our healthspans and lifespans.

Since the publication of the original groundbreaking social network studies in the 1970s, linking larger social networks to a reduced risk of premature death [2], the field has evolved tremendously in both size and quality. Beyond the now widely replicated findings connecting social relationships and numerous health indicators, there are, for example, compelling empirical arguments for at least all the following theses:

- Social relationship quality and perceived social support — not just social network size — are associated with improved health and longevity.
- The health benefits associated with social relationships are surprisingly robust across culture, age, and gender groups.
- Social relationships may be as important to mental health and quality of life as they are to physical health.
- Social relationship effects on health may be gradual — perhaps manifesting slowly over decades — or sudden, as demonstrated in life-threatening cases of takotsubo cardiomyopathy (broken heart syndrome) [3].
- The relationship between social networks and health is probably bidirectional — health may affect the number and quality of social relationships and social relationships (depending on quality) may improve or worsen health.
- Even in the absence of randomized controlled trials, there is an increasingly strong case — based on traditional Bradford-Hill criteria [4], experimental animal models [5], and even Mendelian randomization studies [4], that at least some of the associations between social relationships and health are causal rather than merely correlative.

This is an impressive resume of research-based social relationship findings. Yet amidst this still growing literature, perhaps the most vexing scientific and public health challenge regarding social relationships and health is what we still do not know: what to do about loneliness and social isolation.

Thankfully, this practical constraint may slowly be changing. As summarized in the paper by Piwońska and their team [1], the evidence supporting both statistically and clinically significant associations between social relationships and health is compelling. In fact, the quality of evidence is now so persuasive that the World Health Organization (WHO) [6] and US Surgeon General [7] each took unprecedented steps in 2023 to highlight the importance of social relationships to public health and begin the difficult process of translating social relationship and health science into solution-based initiatives. In the former case, the WHO tasked a commission of international experts to identify strategies to

promote increased social connectedness [6]. The Surgeon General report [7], meanwhile, contains a comprehensive summary of social relationships and health research and proposes a "six pillar" strategy for enhancing social connections at different levels of society in the US.

The convergence of scientific support by leading health organizations towards the cause of promoting social relationships for improved public health should be a cause for celebration among researchers. It represents a multi-decade process of scientific case-building involving hundreds of investigators and many thousands of research participants. However, the path forward for social relationships and health scientists arguably remains no less daunting than before.

The landscape of social relationships has changed greatly since the days of the Alameda County study and the initial Social Network Index. Relationships in the categories that formerly comprised the most common examples of social relationships on the Social Network Index — such as marriage, church attendance, children, and community involvement — have since plummeted in many advanced countries. Novel relationship categories based on technology, such as video conferencing and social media interactions, have emerged so rapidly that their short- and long-term consequences for health remain unclear while nonetheless being accelerated by the COVID-19 pandemic.

Finally, even while organizations such as the WHO and the US Surgeon General grapple with the already multilayered complexities of promoting healthy social relationships in the present, the future appears ready to offer even more dynamic challenges. What role, for instance, will relationships with artificial intelligence companions play in reducing loneliness and social isolation [8] or relationships that exist only on virtual and extended reality platforms [9]? As abruptly and disruptively as social media and video relationships emerged in the early 21st century, the next wave of technology-based social relationships may arrive even faster and with even greater public health implications. Current and future generations of social relationship and health scientists must be ready to explore these new frontiers.

Article information

Conflict of interest: None declared.

Funding: None.

REFERENCES

1. Piwońska AM, Piwoński J, Cicha-Mikołajczyk A, et al. Identifying associations between the social network index, its components, and the prevalence of cardiovascular diseases in Polish adults. Results of the cross-sectional WOBASZ II study. Kardiol Pol. 2023; 81(12): 1237–1246, doi: 10.33963/v.kp.98066, indexed in Pubmed: 37997823.
2. Berkman LF, Syme SL. Social networks, host resistance, and mortality: a nine-year follow-up study of Alameda County residents. Am J Epidemiol. 1979; 109(2): 186–204, doi: 10.1093/oxfordjournals.aje.a112674, indexed in Pubmed: 425958.
3. Díaz-Navarro R. Takotsubo syndrome: the broken-heart syndrome. Br J Cardiol. 2021; 28(1): 11, doi: 10.5837/bjc.2021.011, indexed in Pubmed: 35747479.
4. Zheng C, He MH, Huang JR, et al. Causal relationships between social isolation and osteoarthritis: a Mendelian randomization study in European population. Int J Gen Med. 2021; 14: 6777–6786, doi: 10.2147/IJGM.S331864, indexed in Pubmed: 34703283.
5. Cacioppo JT, Cacioppo S, Cole SW, et al. Loneliness across phylogeny and a call for comparative studies and animal models. Perspect Psychol Sci. 2015; 10(2): 202–212, doi: 10.1177/1745691614564876, indexed in Pubmed: 25910390.
6. https://www.who.int/news/item/15-11-2023-who-launches-commission-to-foster-social-connection. (accessed: November 23, 2023).
7. https://www.hhs.gov/sites/default/files/surgeon-general-social-connection-advisory.pdf (accessed: November 23, 2023).
8. Chaturvedi R, Verma S, Das R, et al. Social companionship with artificial intelligence: Recent trends and future avenues. Technological Forecasting and Social Change. 2023; 193: 122634, doi: 10.1016/j.techfore.2023.122634.
9. Kenyon K, Kinakh V, Harrison J. Social virtual reality helps to reduce feelings of loneliness and social anxiety during the Covid-19 pandemic. Sci Rep. 2023; 13(1): 19282, doi: 10.1038/s41598-023-46494-1, indexed in Pubmed: 37935718.

Atrial fibrillation therapy and stroke prevention in hemodialysis patients

Václav Melenovský[1, 2], Pavel Osmančík[1, 2]

[1]Department of Cardiology, Kralovske Vinohrady University Hospital, Prague, Czech Republic
[2]Department of Cardiology, 3rd Faculty of Medicine, Charles University, Prague, Czech Republic

Correspondence to:
Prof. Pavel Osmancik, MD, PhD, Department of Cardiology, Kralovske Vinohrady University Hospital and 3rd Faculty of Medicine, Charles University, Šrobárova 50, 100 34 Prague, Czech Republic, phone: +420 267 162 621, e-mail: pavel.osmancik@fnkv.cz

DOI: 10.33963/v.kp.98424

Received:
October 20, 2023

Accepted:
December 6, 2023

Early publication date:
December 14, 2023

ABSTRACT

The prevalence of atrial fibrillation (AF) in patients with chronic kidney disease (CKD), especially on hemodialysis (HD) is higher compared to the general population without CKD and reaches ~20%. The risk of ischemic stroke in CKD patients is also significantly increased. However, since the risk of bleeding is also significantly increased in CKD patients and the number of bleeding events exceeds the number of thrombotic events, there are great concerns regarding the routine use of anticoagulation in this patient population. No randomized studies were performed to compare anticoagulation with placebo in patients with advanced CKD and AF. This lack of knowledge is reflected in international guidelines which refrain from clear recommendations. The use of anticoagulation for stroke prevention in HD patients with AF should be strictly individualized for each patient. Anticoagulation for stroke prevention in HD patients with AF seems justified only in selected patients with high stroke and low bleeding risk. Reduced-dose direct oral anticoagulants (especially apixaban) may prove beneficial. In patients with high thrombotic and bleeding risk, left atrial appendage closure could be considered. In this article, the results of the most relevant observational studies with anticoagulation in CKD/HD patients with AF have been presented and discussed. Furthermore, results of randomized studies comparing vitamin K antagonists with non-vitamin K antagonists in CKD patients have been discussed in detail. Finally, ongoing randomized studies with reduced doses of apixaban, factor XI inhibitors, and left atrial appendage closure in CKD patients are mentioned. A brief summary of rhythm control strategies in AF is given.

Key words: anticoagulation, atrial fibrillation, bleeding, dialysis, renal failure

INTRODUCTION — EPIDEMIOLOGY AND PATHOPHYSIOLOGY OF ATRIAL FIBRILLATION AND CHRONIC KIDNEY DISEASE

Atrial fibrillation (AF) is characterized by rapid and uncoordinated electrical and mechanical activity of atrial cardiomyocytes. AF is considered the most commonly sustained arrhythmia with an estimated worldwide prevalence of 600 per 100 000 in men and 370 per 100 000 in women, with significant regional and ethnic variations [1, 2]. AF prevalence is mostly determined by age, with the prevalence spanning from 0.1% among adults under 55 years to 9.0% in those 80 years or older [3]. The overall prevalence of AF may increase significantly after thorough screenings with new rhythm monitoring devices [4]. AF is associated with increased mortality, mainly due to the increased risk of stroke and worsening of heart failure [5, 6]. Recently, AF has also been linked to increased risk of cognitive impairment and dementia [7].

Chronic kidney disease (CKD) is divided into 5 stages according to glomerular filtration rate, with CKD 5 treated by dialysis as end-stage chronic kidney disease. Novel, more patient-centered, nomenclature is now being used for patients with glomerular filtration rate (GFR) <15 ml/min/1.73 m^2 or on dialysis treatment; terms like "kidney failure" are replacing terms such as (end-stage kidney disease" (ESKD) or "end-stage renal disease" (ESRD) [8]. The prevalence of stage 5 CKD worldwide is reported to be 0.1%; the number of patients treated by hemodialysis varies significantly worldwide and is substantially higher in wealthier countries [9]. Hemodia-

lysis is the most used form of kidney replacement therapy (KRT) and accounts for nearly 70% of all patients on kidney replacement therapy and nearly 90% of dialyses (the rest being peritoneal dialysis) [10].

There is a close and bidirectional relationship between CKD and AF since patients with CKD are at higher risk of AF and AF patients are more prone to develop CKD [11–13]. AF is also associated with a significant increase in mortality of CKD patients [14]. Estimates of the prevalence of AF differ by study cohorts. For example, the nationwide United States Renal Data System states a prevalence of 21% and 16% in hemodialysis (HD) and peritoneal dialysis patients, respectively [15]. Just as in the general population, the use of novel rhythm monitoring devices has increased the number of AF patients diagnosed with kidney failure. In a study of HD patients with implanted loop recorders, 31% (18 of 59 patients) had *de novo* detection of AF episodes lasting ≥6 minutes during a 6-month follow-up [16].

The increased prevalence of AF in HD patients is not surprising given the shared risk factors for both AF and CKD, factors associated directly with advanced kidney disease, and finally with the effects of the dialysis procedure itself.

Age is one of the greatest risk factors for both AF and CKD [3] Other frequently shared risk factors are hypertension, obesity, and diabetes mellitus, all of which pose a rising global health burden [17]. The most common primary renal diagnosis (cause of kidney failure in HD patients) in the Western world is diabetes, followed by hypertension [18, 19].

The mechanisms associated with advanced kidney disease that are involved in AF development include oxidative stress, chronic inflammation, transforming growth factor-β1 (TGF-β1) signaling, hyperactivation of the renin-angiotensin-aldosterone system, and altered mineral and bone metabolism associated with CKD, most of which ultimately play a role in myocardial fibrosis [20–22].

The role of mineral and bone abnormalities in chronic kidney disease and their impact on cardiovascular disease is increasingly more recognized. Levels of fibroblast growth factor-23 (FGF-23), a circulating peptide produced by osteoblasts and osteocytes that is crucial for serum phosphate control, rise in the early stages of CKD. This cytokine activates intracellular signaling leading to cardiac hypertrophy [23]. The presumed vicious cycle is left ventricular hypertrophy leading to diastolic dysfunction, increase in left ventricular filling pressure, and then left ventricular strain with fibrosis and dilatation, which creates a substrate for AF. Thus, and not surprisingly, concentrations of FGF-23 were shown to be strongly and independently associated with increased risk of AF incidents [24]. This situation is similar to heart failure with preserved ejection fraction (HFpEF), which is, by far, the most common heart failure phenotype in HD patients [25]. It is widely known that AF and HFpEF often coexist; AF is seen in about two-thirds of HFpEF patients and is linked to a worse prognosis [26].

Finally, the dialysis procedure itself is associated with large changes in plasma constituents and volume status, which can also play a significant role in triggering atrial arrhythmias. In a study of dialysis patients with implanted cardioverter defibrillators capable of continuous rhythm monitoring, AF occurrence was analyzed in relation to the HD procedure [27]. Of all AF episodes occurring on HD days, 8% occurred before the dialysis procedure, 48% during, and 43% after dialysis. AF also occurred more often around HD with higher ultrafiltration and lower dialysate potassium concentrations (which can serve as a surrogate for a potassium shift with lower dialysate concentrations indicating higher shifts between dialysate and plasma).

Hemodialysis significantly contributes to changes in serum electrolytes: serum potassium concentration changes by a mean of 1.2 mmol/l during HD, and 40% of patients experience hypokalemia immediately after HD, and a significant post-HD decrease was also seen in magnesium and phosphate concentrations [28]. Pre-dialysis hypokalemia and lower dialysate potassium (below 2 mmol/l) are independently associated with increased risk of AF [29].

STROKE RISK ASSOCIATED WITH KIDNEY FAILURE

There are several reasons why patients with advanced kidney disease are at higher risk of stroke. The numbers of both ischemic and hemorrhagic strokes are increased in the HD population. Although ischemic stroke is more frequent than hemorrhagic (also in the HD population), the proportion of hemorrhagic to ischemic strokes is higher in HD patients compared to the general population [30].

At the pathophysiological level, the increased ischemic stroke risk and overall increased thrombogenesis involve primary and secondary hemostasis. Platelet activation and interaction, altered platelet transcriptome and secretome, platelet-derived microparticles, and endothelial dysfunction all seem to play a role, with most effects being mediated by uremic toxins [31]. A higher burden of atherosclerosis in CKD patients, including the carotid arteries, is well established [32]. Interestingly, oxidative stress, inflammation, and endothelial dysfunction associated with CKD alter brain vascular reactivity and function of the blood-brain barrier, making the brain more susceptible to ischemia and aggravating brain injury secondary to ischemia [33].

The increased risk of hemorrhagic stroke is primarily caused by platelet dysfunction discussed later. Additionally, arterial hypertension (AH) plays a role. The majority of HD patients have AH, which is often poorly controlled and resistant to pharmacotherapy [34]. AH is a leading risk factor for hemorrhagic stroke in the general and HD populations [35, 36].

All these pathophysiological circumstances have major clinical implications and lead to an increase in the number of both ischemic and hemorrhagic strokes. A meta-analysis of cohort studies focusing on stroke risk

in relation to kidney function pooling over 2 million patients found that the stroke rate increases by 7% for every 10 ml/min/1.73 m^2 decrease in GFR [37] In HD patients, the stroke risk was found to be 3–10 times higher than in the general population [35, 36]. HD was also linked to a worse prognosis, longer in-hospital stays, worse functional status, and worse response to rehabilitation after stroke [38, 39]. Furthermore, CKD was found to be associated with higher risk of hemorrhagic transformation of ischemic stroke and with underutilization of evidence-based therapies for acute stroke patients [39, 40].

BLEEDING RISK IN HEMODIALYSIS PATIENTS

The bleeding diathesis in kidney failure is a complex phenomenon, but most abnormalities are present on the platelet count. Disturbed platelet adhesion, disturbed endothelial-thrombocyte interplay, defective platelet aggregation, an imbalance in secretory granule content, and even defects in the platelet cytoskeletal structure have been demonstrated in HD patients [31]. Most of the aberrations seem to be mediated by uremic toxins, which explains the beneficial effect of dialysis [41]. Aspirin, often prescribed to HD patients for cardiovascular primary or secondary event prevention, has an amplified impact on hemostasis compared to healthy individuals [42]. Finally, anticoagulation (most often heparin-based) used during HD to prevent blood clotting in the extracorporeal circuit also contributes to the pro-hemorrhagic milieu.

The risk of bleeding in CKD and, especially, HD patients is higher compared to the general population. For instance, a retrospective cohort study with 11 000 patients (>80% on HD) found that the annualized incidence of hospitalization for bleeding was 5.3 per 100 patient-years [43] The most frequent bleeding site was the lower gastrointestinal (GI) tract, with an incidence of 3.1 per 100 patient-years, followed by upper GI bleeding (2.1 per 100 patient-years) and intra-cerebral and subarachnoid bleeding (0.3 per 100 patient-years). In another prospective cohort study with nearly 50 000 patients, the observed rate of bleeding requiring hospitalization was 8 per 100 patients-years [44]. Bleeding rates were dramatically higher in HD patients with a history of GI bleeding in the past 12 months. A prospective cohort study of over 200 000 European dialysis patients (84% on hemodialysis) found a 12.8-fold increased risk of death caused by bleeding compared to the general population [45]. In this cohort, older age at the start of dialysis, primary kidney diseases including renal vascular disease, AH, and diabetes mellitus were all associated with an increased risk of bleeding. Older age and associated frailty affect outcomes of anticoagulated patients, irrespective of renal function [46]. A meta-analysis of studies on anticoagulation in elderly (age ≥65 years) AF patients with CKD found similar rates of ischemic stroke/transient ischemic attack in anticoagulated vs. nonanticoagulated patients (risk ratio [RR], 1.18; 95% confidence interval [CI], 0.88–1.58 for dialysis patients) and increased risk of bleeding in dialysis (RR, 1.37; 95% CI, 1.09–1.74) but not in non-dialysis patients [47]. Another large cohort study of HD patients found that current smoking, history of coronary vascular disease, and inability to walk without assistance (a sign of overall frailty) were predictive of upper GI bleeding [48].

An observational study of over 200 000 dialysis patients examined death caused by bleeding and stroke and compared the data to the general population [49]. The study found that bleeding-associated mortality was 12.8 times higher, and stroke-related mortality was 12.4 times higher than in the general population. On an absolute scale, however, mortality rates for bleeding were lower than for stroke (6.2 vs. 14.3 per 1000 person-years, respectively).

STROKE AND BLEEDING RISK-STRATIFICATION SCORES IN HEMODIALYSIS PATIENTS

In non-CKD patients, the CHA_2DS_2-VASc score has become a standard for stroke risk stratification in patients with AF and is widely used in decision-making [50, 51]. Data on the usefulness of CHA_2DS_2-VASc in CKD patients are far less substantial than for non-CKD patients; nonetheless, studies have confirmed that higher CHA_2DS_2-VASc scores are also associated with higher stroke risk in HD patients. A Taiwanese study examined the predicted risk accuracy of CHA_2DS_2-VASc scores in 11 000 non-anticoagulated HD patients with AF; the authors found that an increased score significantly predicted stroke risk [52]. In HD patients, the median score was 5; but importantly only 3.8% of this HD population had a score of 0 or 1 (compared to 20% in the population in which the scores were validated) [53]. Additionally, even low-risk patients (CHA_2DS_2-VASc score = 0) had an annualized risk of ischemic stroke of 2.1 per 100 patient-years. Thus, the score is not considered useful in clinical practice since its aim is to differentiate between low and high-stroke-risk patients (to accordingly start, or not, anticoagulation treatment), and most HD patients are automatically deemed to be at high risk.

The situation is even more complicated for scoring systems predicting bleeding risk, and evidence to support routine use of bleeding risk scores in HD patients is lacking. Two prospective cohort studies performed in 1745 and 625 patients showed that established bleeding risk scores (such as HAS-BLED, ATRIA, $HEMORR_2HAGES$, and others), performed poorly in predicting future bleeding events [54, 55].

RATE AND RHYTHM CONTROL STRATEGIES IN HEMODIALYSIS PATIENTS

In the general population without CKD, the clear prognostic benefit of rhythm control strategies was confirmed in randomized studies only in patients with left ventricular dysfunction. Therefore, in patients with preserved left ventricular function, the rhythm control strategy is recommended primarily to improve symptoms related to AF. Due to the absence of specific evidence for the CKD population, the

general recommendations are not different from the recommendations for the non-CKD population. Nonetheless, due to important distinctions in CKD patients (i.e., altered drug elimination or possible renal improvement in sinus rhythm), the following paragraph sums up the treatment possibilities of the rhythm control strategy in CKD patients.

With regard to antiarrhythmic drugs, amiodarone does not require dose-renal function adjustment, nor does propafenone, which should, however, be dosed with caution in advanced CKD, and ECG and plasma level monitoring is recommended. On the other hand, dronedarone and sotalol are contraindicated in advanced CKD, and flecainide requires careful dosing with plasma level monitoring [56].

Electrical cardioversion has a high success rate in acute rhythm control, but the maintenance of sinus rhythm (SR) in the long-term is low and the presence of CKD or even HD presents a very significant negative prognostic factor in SR maintenance [57] Compared to patients with normal eGFR, patients with eGFR less than 30 ml/min/1.73 m^2 have a 5-fold higher risk of AF recurrence within one year.

Catheter ablation presents the most effective treatment modality for the AF rhythm control strategy. No randomized study compared the effect of antiarrhythmics to catheter ablation specifically in the population of CKD patients. However, data from observational studies have shown that the efficacy of catheter ablation is approximately 2-fold lower in patients with advanced CKD compared to the general population. In the meta-analysis of observational studies by Chung et al. [58], patients with CKD had a significantly higher risk of AF recurrence (RR, 2.34; 95% CI, 1.36–4.02; P <0.01). The risk of AF recurrence continuously increases with decreasing renal function. Furthermore, patients with less impaired renal function (CKD 3) compared to the more severely impaired (CKD 4–5) not only have a better effect in terms of SR maintenance but also an improvement in renal function was observed in patients who maintained SR. For instance, in the cohort of 368 CKD-3 patients published by Takahashi et al., freedom from AF achieved by catheter ablation was associated with eGFR improvement, and similar findings were reported by others [59, 60]

In conclusion, catheter ablation in CKD patients should be considered in the same circumstances as in the general population, i.e., with the presence of symptoms or with left ventricular dysfunction. If catheter ablation is considered, it should not be postponed but performed in the early stages of renal impairment due to better efficacy and a chance of improving renal function due to SR maintenance.

STRATEGIES TO PREVENT ATRIAL-FIBRILLATION-RELATED STROKE IN KIDNEY FAILURE PATIENTS

Vitamin K antagonists

In non-CKD patients, the effect of vitamin K antagonists (VKAs; namely warfarin), was tested in several randomized studies, and all of them confirmed the superiority of VKA over placebo in terms of ischemic stroke reduction. Unfortunately, stage 4 and 5 CKD and HD patients were excluded from these seminal trials.

As such, the effect of VKAs in kidney failure patients has only been assessed using observational studies, and often with conflicting results. A meta-analysis of 15 observational studies with nearly 50 000 patients (22% on warfarin) showed that warfarin use, compared to no anticoagulation, was not associated with a significant reduction in ischemic strokes (hazard ratio [HR], 0.96; 95% CI, 0.82–1.13) and had no effect on mortality (HR, 0.95; 95% CI, 0.83–1.09) [61]. The risk of hemorrhagic stroke was significantly increased (HR, 1.49; 95% CI, 1.03–1.94), but surprisingly, the increase of all-cause major bleeding did not reach statistical significance (HR, 1.2; 95% CI, 0.99–1.47). In another observational study of older dialysis patients (over 65 years), a significant increase in major bleeding was reported [62]. VKA treatment must be interpreted relative to long-term international normalized ratio values; a higher time in the therapeutic range (TTR) is associated with a reduction in the number of strokes [63]. Real-world data show that international normalized ratio values in dialysis patients are often subtherapeutic, with a low TTR even in closely monitored clinical trial patients [64]. In addition, a rare but serious complication in kidney failure is calcific uremic arteriolopathy (sometimes wrongly called calciphylaxis). It presents as extensive, painful ischemic skin lesions caused by skin arteriole wall calcification and obstruction, with 1-year mortality nearing 50% [65]. Warfarin treatment is linked to this condition and is possibly causal, with VKAs antagonizing the action of matrix Gla protein (MGP), a protein that inhibits arterial wall calcification.

Direct oral anticoagulants in renal kidney patients

In the non-CKD population, direct oral anticoagulants (DOACs) have replaced VKAs due to similar efficacy in terms of ischemic stroke reduction, and a significantly lower intracranial bleeding risk. All DOACs are excreted by the kidneys to some extent, with approximate renal clearance being 80% for dabigatran, 50% for edoxaban, 35% for rivaroxaban, and 25% for apixaban [66]. Furthermore, 60% of dabigatran, 9% of edoxaban, 7% of apixaban, and 1% of rivaroxaban are removed by hemodialysis. Essentially, from the pharmacokinetic perspective, apixaban presents the potentially most favorable DOAC for CKD patients.

Regrettably, patients with advanced CKD (i.e., CrCl <30 ml/min; <25 ml/min for apixaban) have been excluded from the landmark trials. Table 1 summarizes currently completed randomized trials on anticoagulation strategies in HD patients.

Apixaban — the most promising DOAC in hemodialysis patients

Due to its aforementioned pharmacokinetics, apixaban has garnered the greatest attention in the search for the "best"

Table 1. Published randomized studies on anticoagulation strategies in dialysis patients

First author, study name	Cohort	Comparison (number of patient)	Endpoints	Outcomes and conclusions	Comment
De Vriese et al. *The Valkyrie study* (76)	HD patients *Mean CHA_2DS_2-VASc score = 5*	VKA n = 44 vs. rivaroxaban n = 45 vs. rivaroxaban + vitamin K2 = 42	*Primary*: vascular calcification measures *Secondary*: mortality, stroke, bleeding, modified MACE, valve calcification	No significant changes in vascular calcification. All cause death, stroke, and cardiovascular event rates similar between the groups. Bleeding outcomes not significantly different (except for a lower number of life-threatening and major bleeding episodes in rivaroxaban arms vs. VKA arm)	Not designed or powered to compare VKA vs. DOAC in stroke prevention or bleeding
Pokorney et al. *Renal-AF trial* (70)	HD patients *Mean CHA_2DS_2-VASc score = 4.5*	Apixaban n = 82 vs. VKA n = 72	*Primary:* major or clinically relevant nonmajor bleeding (ISTH definitions) *Secondary:* SSE, death, medication adherence, pharmacokinetics	Trial stopped prematurely for enrollment challenges Inadequate power to draw conclusions regarding primary bleeding outcomes Clinically relevant bleeding events were ≈10-fold more frequent than stroke or systemic embolism Death was the most common major event in the apixaban and warfarin arms The AUC for the 2.5 mg dose in RENAL-AF did not differ from the AUC for patients with eCrCl ≥15 and <90 ml/min from the ARISTOTLE trial	Initial targeted sample size 762 patients Reduce dose apixaban in 29% of apixaban patient. Median TTR in VKA patient = 44%
Reinecke et al. *The AXADIA-AF-NET 8 Study* (64)	HD patients *Mean CHA_2DS_2-VASc score = 4.0*	Apixaban n =48 vs. VKA n = 49	*Primary:* composite of all-cause death, major bleeding, clinically relevant nonmajor bleeding (ISTH definitions) *Secondary:* composite of MI, ischemic stroke, all cause death, DVT, PE	No significant differences in primary or secondary outcomes Non-inferiority of apixaban could not be shown because of insufficient enrollment	Original sample size 222 patients Median TTR in VKA patients = 50.7%

Abbreviations: DVT, deep vein thrombosis; HD, hemodialysis; ISTH, International Society on Thrombosis and Haemostasis; MACE, major adverse cardiovascular events; MI, myocardial infarction; PD, peritoneal dialysis; PE, pulmonary embolism; SSE, stroke and systemic embolism; TTR, time in therapeutic range; VKA, vitamin K antagonist

anticoagulant in HD patients. A pharmacokinetic study in eight HD patients found that apixaban 2.5 mg b.i.d. resulted in a comparable drug exposure as the standard dose (5 mg b.i.d.) in patients without renal impairment; however, 5 mg b.i.d. in HD patients produced supratherapeutic levels [67]. A retrospective cohort study of over 25 thousand Medicare beneficiaries with kidney disease and anticoagulation for AF compared apixaban and warfarin patients matched at a ratio of 1:3 based on prognostic scores (dabigatran and rivaroxaban prescriptions were negligible and thus not tracked) [68]. There was no difference in stroke and systemic embolism (SSE) between apixaban and warfarin (HR, 0.88; 95% CI, 0.69–1.12), but apixaban was associated with significantly lower risk of major bleeding (HR, 0.72; 95% CI, 0.59–0.87). In sensitivity analyses, the standard dose of apixaban was associated with significantly lower risk of SSE and death compared to the reduced dose or warfarin treatment. This study served as the background for the American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) guidelines recommending the use of standard-dose apixaban in HD patients [51]. Due to the observational nature of the study, these results must be interpreted cautiously. The positive effect of the higher (i.e., standard) dose may be explained by selection bias caused by prescribing standard doses of apixaban to healthier patients who are less prone to bleeding (and *vice versa*), along with an overall worse prognosis for patients meeting criteria for dose reduction.

A later smaller retrospective study analyzed outcomes in 500 HD patients receiving apixaban and 1500 matched non-anticoagulated HD patients [69]. Compared to no anticoagulation, apixaban did not lower the risk of new stroke (ischemic or hemorrhagic), transient ischemic attack, or systemic embolism. However, treatment with apixaban was associated with a 2.7 higher risk of fatal/intracranial bleeding, with rates translating to fatal/intracranial bleeding occurring in 1 in 30 patients on apixaban per year. In subgroup analyses, a significantly higher rate of SSE and a significantly higher incidence of fatal or intracranial bleeding was seen in the subgroup of patients treated with the standard dose, compared to no anticoagulation at all. This did not apply to the reduced dose. As in the previous study, apixaban was connected to lower all-cause mortality. However, the authors also analyzed the incidence of hip fractures and pneumonia, which were lower in apixaban-treated patients. Since these clinical events are definitively associated with frailty and cannot be directly affected by apixaban, it emphasizes the systematic selection bias associated with the observational nature of the study.

The first randomized trial addressing anticoagulation strategies in HD patients was the RENAL-AF trial [70]. Study details can be found in Table 1. This trial enrolled

HD patients with AF and randomized them to apixaban or warfarin treatment. The primary endpoints were stroke or clinically relevant non-major bleeding; secondary outcomes were stroke, mortality, and apixaban pharmacokinetics. Unfortunately, the trial was stopped prematurely due to slow enrollment (the target sample was 760 patients, but only 154 patients were enrolled), which resulted in a lack of statistical power. Nevertheless, several findings from the study are noteworthy. Pharmacokinetic data revealed that the standard dose of 2 × 5 mg in HD patients in the RENAL-AF study resulted in significantly higher area under the curve (AUC) 0–12 values (12-hour area under the curve; a pharmacokinetic measure describing maximum exposure to the drug on a non-dialysis day) than in patients on the same dose of apixaban but with normal renal function in the ARISTOTLE trial. Interestingly, the AUC of patients on 2 × 5 mg apixaban on HD in the RENAL study was similar to the AUC of CKD 3b-4 patients on 2 × 5 mg apixaban in the ARISTOTLE trial, but CKD 5 patients without HD on apixaban 2 × 5 mg in the ARISTOTLE had an even higher AUC than HD patients on apixaban 2 × 5 mg in the RENAL study. On the other hand and very importantly, the AUC of apixaban at 2.5 mg dose in HD patients in the RENAL-AF study did not differ from the AUC of 2.5 mg dose in patients with only mild CKD in the ARISTOTLE trial. Interestingly, there was a relation between pharmacokinetic values of patients with and without bleeding, whereas higher levels of apixaban correlated with more bleeding and *vice versa*. In the RENAL AF study, the primary outcome of major or clinically relevant non-major bleeding (as defined by the International Society on Thrombosis and Hemostasis) occurred at similar frequencies in both groups, i.e., 26% of patients on apixaban and 22% of patients on warfarin, which documented the high risk of bleeding in this population. There was only one hemorrhagic stroke in each group. SSE occurred in 3% of apixaban patients and 3.3% of warfarin patients. Bleeding was 10-fold more frequent than SSE, and HD access site bleeding events comprised the majority of clinically relevant non-major bleeding. The use of a standardized bleeding definition in this study must be appreciated since many observational studies use different definitions of bleeding and bleeding severity, thus hindering data comparison. The low and slow enrollment seen in RENAL-AF is, unfortunately, common in trials with HD patients. In the RENAL-AF trial, a partial explanation for its insufficient enrollment was that some patients were not deemed suitable for the trial by their treating physicians (a factor that can potentially introduce an unintended selection bias). The situation in which physicians prevent patients from participating in trials because they are deemed "clinically unstable" has also been seen in other HD trials [71]. HD patients also experience a high burden of treatment side effects, which partially explains the high drop-out rates, leading to reduced statistical power [71, 72]. Moreover, high mortality in this group is one of the leading causes of low retention rates in trials involving HD patients.

AXADIA-AFNET 8 is the most recent randomized trial on stroke prevention in HD patients with AF [64]. As with the RENAL-AF trial, the study also suffered from insufficient enrollment (for details, see Table 1). In this trial, HD patients were randomized either to reduced-dose apixaban or warfarin treatment. The annualized incidence of the primary outcome, i.e., International Society on Thrombosis and Haemostasis major/non-major bleeding or all-cause death, was similar in both groups and occurred in 36.1% of apixaban patients and 36.6% of warfarin patients. All-cause mortality was also similar between groups (14.8%/year in the apixaban group vs. 17.6%/year in the warfarin group). However, due to insufficient enrollment, apixaban did not meet the non-inferiority criteria.

Rivaroxaban in hemodialysis patients

After apixaban, rivaroxaban is the second most studied DOAC in stroke prevention in HD patients, also due to its relatively low renal clearance (30%) and very low hemodialysis removal (<1%). In the largest observational study comparing 1896 stage 4 or 5 CKD patients (88% on HD), rivaroxaban (39% on reduced doses) did not significantly reduce the risk of SSE but was associated with a significant reduction in major bleeding compared to warfarin [73]. On the contrary, a smaller observational study comparing (n = 173) these two drugs found similar rates of major bleeding but lower rates of SSE (90% of patients on reduced-dose rivaroxaban) [74]. A multinational observational registry of 1461 patients with advanced CKD (eGFR between 15 and 49 ml/min/1.73 m^2) compared outcomes of AF patients treated with rivaroxaban vs. warfarin. After one year of follow-up, rivaroxaban was associated with net clinical benefit, lower event rates for stroke, major bleeding, and all-cause mortality [75]. However, the study was observation and non-randomized, and again, the results have to be interpreted with caution.

The Valkyrie study was so far the only randomized study to compare the effect of VKAs and rivaroxaban on vascular calcifications and observe SSE and bleeding as secondary outcomes [76]. Patients (n = 143) were randomized to VKA, rivaroxaban 10 mg, or rivaroxaban 10 mg + vitamin K2 supplement treatment. The 10 mg dose was chosen based on a pharmacokinetics study by the same group, which showed similar drug exposure of rivaroxaban 10 mg in HD patients compared to healthy individuals, with no accumulation after multi-day dosing [77]. The primary outcome (extent of vascular calcifications) did not differ between the two groups. Interestingly, the rate of stroke was also similar in the groups. A significantly smaller number of life-threatening and major bleeding episodes was observed in rivaroxaban compared to VKA-treated patients. Analogous to other studies, the bleeding rate

was substantially higher than the stroke rate (22/100 person-years vs. 1.22/100 person-years, respectively). It should be noted that the study was not designed or powered to compare DOACs vs. VKAs in HD patients.

Low-molecular-weight heparins

Low-molecular-weight heparin (LMWH), typically given as a single intravenous bolus into the arterial limb when starting dialysis, is used to prevent blood clot formation in the extracorporeal dialysis circuit. LMWH application on non-HD days is also used as a primary stroke prevention strategy for specific patients (in the US and Austria) and is the most preferred option, for instance, in the Czech Republic [78, 79]. However, there is no evidence to support this praxis.

Novel therapeutic stroke prevention approaches

Two promising novel therapeutic approaches are currently being tested. The first is a pharmacological intervention that enompasses of coagulation factor (F)XI inhibition. The development of synthetic FXI inhibitors was based on observations that patients with inherited FXI deficiency, also known as hemophilia C, have a decreased risk of venous thromboembolism and strokes and a relatively low risk of spontaneous bleeding [80]. In the PACIFIC study on AF patients, asundexian (a direct inhibitor of activated FXI) showed reduced bleeding compared to apixaban [81]. However, very recently, a large study (OCEANIC-AF; NCT05643573) comparing asundexian with apixaban was stopped due to the inferiority of asundexian in SSE prevention. In CKD or HD patients, the risk-benefit profile seems appropriate, and, currently, there are two ongoing drug-testing clinical trials in HD patients (NCT04523220 and NCT04534114).

The other approach is based on the fact that the left atrial appendage is the source of cardiac emboli in the majority of cases. Left atrial appendage closure (LAAC) is a procedure offering the potential for long-term stroke prophylaxis without the need for long-term anticoagulation therapy. A meta-analysis of three trials comparing LAAC with anticoagulation showed similar rates of stroke compared to OAC; however, there was a significant reduction in hemorrhagic stroke, non-procedure-related bleeds, cardiovascular death, and all-cause death [82]. LAAC would appear to be an ideal alternative for patients at high risk of bleeding including HD patients, although patients must endure an invasive procedure with appreciable complications and a period of antithrombotic treatment (usually 3 months of dual antiplatelet treatment and life-long aspirin), which is required for epithelialization of the LAAC device. In an observational cohort study, 92 dialysis patients with AF on HD who underwent LAAC were compared to two similarly sized cohorts of HD patients with AF either on warfarin or without antithrombotic treatment [83]. No difference in bleeding was present between LAAC and warfarin patients during the first three months after the procedure; however, there was a significantly higher risk of bleeding in warfarin patients over the next 21 months (HR, 6.4; 95% CI, 1.21–31.72). Overall mortality was higher in both the warfarin (HR, 2.76; 95% CI, 1.31–5.86) and no-antithrombotic therapy (HR, 3.09; 95% CI, 1.59–5.98) arms compared to LAAC patients.

On the other hand, observational data show that older age, impaired eGFR, diabetes, and heart failure are independently associated with increased risk of death within 1 year of the procedure [84]. Therefore, whether this procedure conveys a long-term benefit in the highly comorbid and frail HD population, with its many competing causes of death, remains a question. Fortunately, a randomized controlled trial comparing LAAC with the best medical treatment (LAA-KIDNEY) in HD patients with AF is currently ongoing (NCT05204212).

ANTICOAGULATION IN KIDNEY FAILURE PATIENTS WITH ATRIAL FIBRILLATION — SUMMARY OF THE CURRENT GUIDELINES

The distinctiveness of the HD population is apparent throughout the international guidelines on anticoagulation treatment in those with AF; many societies refrain from making specific statements on the topic. The ESC 2020 guidelines for diagnosis and management of AF state that up-to-date knowledge is "limited and to some extent controversial" and restate the lack of approval of NAOCs in patients with CrCl <15 ml/min or on dialysis [50]. The 2021 European Heart Rhythm Association (EHRA) Practical Guide on DOAC treatment in AF patients summarizes the existing data and states that "given the lack of strong evidence the decision to anticoagulate and (if so) whether to use a NOAC or VKA in patients with end-stage renal failure or on dialysis requires a high degree of individualization" [85]. EHRA goes on to state that DOAC plasma level measurement also lacks robust evidence and should be reserved to highly specialized centers; EHRA also emphasizes the need for shared decision-making between physicians and patients regarding off-label use of anticoagulants. Based on a small pharmacokinetic study on eight patients, the Food and Drug Administration approved apixaban in HD patients in 2012 [86]. Reflecting this, the 2019 AHA/ACC/HRS guidelines updated recommendations for AF management by stating that either warfarin or apixaban "*might be reasonable*" in patients with ESKD (CrCl <15 ml/min) or on dialysis with a IIb class of recommendation and moderate quality evidence based on non-randomized data. These guidelines go as far as to not recommend the use of rivaroxaban and edoxaban in ESKD/dialysis patients for "lack of evidence from clinical trials that benefit exceeds risk" [51]. The 2018 guidelines from Australia and New Zealand advise that the decision to anticoagulated in ESKD should be individualized "with knowledge that an estimate of benefits and harms cannot be provided" and suggest the use of warfarin in severe

Table 2. Upcoming randomized studies on anticoagulation strategy in dialysis patients

Study name, NCT number	Cohort	Endpoints	Comparison	Original estimated enrollment	Actual enrollment	Recruitment status	Estimated study completion date
Oral Anticoagulation in Haemodialysis Patients (AVKDIAL) *NCT02886962*	HD patients	Cumulative incidence of severe bleedings and thrombosis	No anticoagulation vs. VKA	n = 855	n = 50	Active, not recruiting	December 2023
Strategies for the Management of Atrial Fibrillation in patiEnts Receiving Dialysis (SAFE-D) *NCT03987711*	HD / PD patients	*Primary*: adequate recruitment and retainment (evaluation of feasibility of conducting a RCT comparing anticoagulation strategies in dialysis patients) *Secondary:* major bleeding, SSE, all-cause mortality, dialysis access site events, non-fatal MI	Warfarin vs. Apixaban vs. No anticoagulation	n = 150	n = 151	Completed	December 2022
The Danish Warfarin-Dialysis Study — Safety and Efficacy of Warfarin in Patients With Atrial Fibrillation on Dialysis (DANWARD) *NCT03862859*	HD patients	*Primary:* TIA, ischemic stroke, unspecified stroke; fatal or non-fatal major bleeding (ISTH definitions) *Secondary:* number of participants with stroke, number of deaths	Warfarin vs. No anticoagulation	n = 718	-	Recruiting	December 2025
Stroke Prophylaxis With Apixaban in Chronic Kidney Disease Stage 5 Patients With Atrial Fibrillation (SACK) *NCT05679024*	HD patients, CKD5 nonHD	*Primary:* ischemic stroke; intracranial bleeding and fatal bleeding *Secondary*: all-cause mortality, cardiovascular events, major bleeding (modified ISTH definitions)	Apixaban (reduced dose) vs. No anticoagulation	n = 1400	-	Recruiting	December 2028

Abbreviations: CKD, chronic kidney disease; TIA, transient ischemic attack; other — see Table 1

CKD (low quality of evidence, strong recommendation), emphasizing that DOACs are contraindicated [87]. The Canadian guidelines recommend against the routine use of antithrombotic therapy for stroke prevention in AF patients in stage 5 CKD (weak recommendation, low quality of evidence) but also state that therapy should be individualized and anticoagulation "might be appropriate for some patients in whom the benefit of preventing stroke outweighs the increased risk of bleeding" [88]. Nephrology guidelines directly on anticoagulation treatment in advanced CKD are scarce. A 2011 Kidney Disease Improving Global Outcomes (KDIGO) clinical update on cardiovascular disease states that in contradiction to previous recommendations, routine use of anticoagulation in stroke prevention in stage 5 CKD patients is not indicated [89]. The 2012 KDIGO guidelines suggest using lower doses of warfarin with close monitoring of eGFR <30 ml/min/1.73 m^2. A KDIGO international interdisciplinary conference on CKD and arrhythmias took place in 2016, and the conference report stated that there is insufficient high-quality evidence to recommend VKAs for stroke prevention in stage 5 CKD patients [90]. The attendees suggested considering reduced doses of apixaban b.i.d.

The lack of clear recommendations and discrepancies in various guidelines only emphasize the unknowns surrounding AF treatment in HD patients.

CURRENT PRACTICE OF ANTITHROMBOTIC TREATMENT IN KIDNEY FAILURE PATIENTS WITH ATRIAL FIBRILLATION

As indicated above, most of our knowledge of anticoagulation strategies for stroke prevention in HD patients comes from observational studies. No randomized study comparing anticoagulation (either VKA or DOAC) vs. placebo has been conducted in stage 4–5 CKD or HD patients. Several randomized studies comparing anticoagulants have been conducted but all were finished prematurely due to low enrollment, and none had a placebo arm. Furthermore, the stroke risk and bleeding risk stratification scores that are used in non-CKD patients are not applicable to renal failure patients. As a consequence of the aforementioned reasons, an evidence-based approach to the anticoagulation treatment in stage 4–5 CKD patients is not possible. Currently, in surveys on real-world treatment, some HD patients are treated with VKAs, some by DOACs (mostly apixaban) or LMWH; some HD patients receive antiplatelet drugs instead of anticoagulants and some patients go without anticoagulation treatment.

A crucial question is whether to initiate anticoagulation at all, and randomized trials exploring anticoagulation therapy versus no anticoagulation are desperately needed. Fortunately, several ongoing trials to explore this issue are currently ongoing (Table 2).

Clinical perspective on stroke prevention in HD patients with AF

Fundamentally, HD patients' preferences must be taken into account. In a survey of HF patients' preferences, "mortality" was ranked 14th, after outcomes such as dialysis-free time, fatigue, and ability to travel [91]. From this perspective, preventing the probabilistically less likely event of stroke at the cost of more frequent bleeding episodes that are inherently associated with increased medical care is of questionable justification, especially since HD patients have high co-morbidity, and many competing causes of morbidity and mortality result in longer hospitalization with more frequent complications [92, 93].

Translating the current data into clinical practice, routine prescription of anticoagulation for stroke prevention in HD patients with AF does not seem warranted due to the potential for net clinical harm. Anticoagulation should be reserved for those with a high risk of stroke, which is not offset by high bleeding risk, with careful consideration of patients' preferences and treatment goals. Reduced-dose apixaban seems superior to other anticoagulants in this population. Non-pharmacological approaches (i.e., LAAC) should be considered in selected patients. Furthermore, physicians involved in HD patient care should contribute to broadening knowledge by enrolling their patients in ongoing trials.

CONCLUSION

Kidney failure patients with atrial fibrillation are a distinct cohort of patients. Current knowledge on stroke prevention in atrial fibrillation patients in the general population does not apply to kidney failure patients. Data on the most suitable anticoagulant in HD patients are mostly observational and show that VKA treatment is not desirable and that the reduced-dose apixaban is the most promising agent. However, left atrial appendage closure or the new class of FXI inhibitors may prove beneficial. The frequency of clinically significant bleeding in HD patients greatly surpasses the frequency of ischemic strokes. Keeping in mind the dictum of medical ethics, "*primum non nocere*" or "first, do no harm," care for these patients must be individualized to prevent unnecessary harm from overtreatment. To resolve this lack of guidance, randomized studies assessing either pharmacological or non-pharmacological treatments vs. placebo are badly needed.

Article information

Conflict of interest: None declared.

Funding: Supported by the project National Institute for Research of Metabolic and Cardiovascular Diseases (CarDia), Programme EXCELES, ID Project No. LX22NPO5104. Funded by European Union – Next Generation EU, and by the Charles University Research program „Cooperatio – Cardiovascular Science".

REFERENCES

1. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation. 2014; 129(8): 837–847, doi: 10.1161/CIRCULATIONAHA.113.005119, indexed in Pubmed: 24345399.
2. Kornej J, Börschel CS, Benjamin EJ, et al. Epidemiology of atrial fibrillation in the 21st century: novel methods and new insights. Circ Res. 2020; 127(1): 4–20, doi: 10.1161/CIRCRESAHA.120.316340, indexed in Pubmed: 32716709.
3. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA. 2001; 285(18): 2370–2375, doi: 10.1001/jama.285.18.2370, indexed in Pubmed: 11343485.
4. Svendsen JH, Diederichsen SZ, Højberg S, et al. Implantable loop recorder detection of atrial fibrillation to prevent stroke (The LOOP Study): a randomised controlled trial. Lancet. 2021; 398(10310): 1507–1516, doi: 10.1016/S0140-6736(21)01698-6, indexed in Pubmed: 34469766.
5. Chen LY, Sotoodehnia N, Bůžková P, et al. Atrial fibrillation and the risk of sudden cardiac death: the atherosclerosis risk in communities study and cardiovascular health study. JAMA Intern Med. 2013; 173(1): 29–35, doi: 10.1001/2013.jamainternmed.744, indexed in Pubmed: 23404043.
6. Benjamin EJ, Wolf PA, D'Agostino RB, et al. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation. 1998; 98(10): 946–952, doi: 10.1161/01.cir.98.10.946, indexed in Pubmed: 9737513.
7. Papanastasiou CA, Theochari CA, Zareifopoulos N, et al. Atrial fibrillation is associated with cognitive impairment, all-cause dementia, vascular dementia, and alzheimer's disease: a systematic review and meta-analysis. J Gen Intern Med. 2021; 36(10): 3122–3135, doi: 10.1007/s11606-021-06954-8, indexed in Pubmed: 34244959.
8. Levey AS, Eckardt KU, Dorman NM, et al. Nomenclature for kidney function and disease: report of a Kidney Disease: Improving Global Outcomes (KDIGO) Consensus Conference. Kidney Int. 2020; 97(6): 1117–1129, doi: 10.1016/j.kint.2020.02.010, indexed in Pubmed: 32409237.
9. Thurlow JS, Joshi M, Yan G, et al. Global epidemiology of end-stage kidney disease and disparities in kidney replacement therapy. Am J Nephrol. 2021; 52(2): 98–107, doi: 10.1159/000514550, indexed in Pubmed: 33752206.
10. Bello AK, Okpechi IG, Osman MA, et al. Epidemiology of haemodialysis outcomes. Nat Rev Nephrol. 2022; 18(6): 378–395, doi: 10.1038/s41581-022-00542-7, indexed in Pubmed: 35194215.
11. Alonso A, Lopez FL, Matsushita K, et al. Chronic kidney disease is associated with the incidence of atrial fibrillation: the Atherosclerosis Risk in Communities (ARIC) study. Circulation. 2011; 123(25): 2946–2953, doi: 10.1161/CIRCULATIONAHA.111.020982, indexed in Pubmed: 21646496.
12. Watanabe H, Watanabe T, Sasaki S, et al. Close bidirectional relationship between chronic kidney disease and atrial fibrillation: the Niigata preventive medicine study. Am Heart J. 2009; 158(4): 629–636, doi: 10.1016/j.ahj.2009.06.031, indexed in Pubmed: 19781424.
13. Bansal N, Fan D, Hsu Cy, et al. Incident atrial fibrillation and risk of end-stage renal disease in adults with chronic kidney disease. Circulation. 2013; 127(5): 569–574, doi: 10.1161/CIRCULATIONAHA.112.123992, indexed in Pubmed: 23275377.
14. Massicotte-Azarniouch D, Kuwornu JP, Carrero JJ, et al. Incident atrial fibrillation and the risk of congestive heart failure, myocardial infarction, end-stage kidney disease, and mortality among patients with a decreased estimated GFR. Am J Kidney Dis. 2018; 71(2): 191–199, doi: 10.1053/j.ajkd.2017.08.016, indexed in Pubmed: 29153994.
15. Annual Data Report | USRDS n.d. https://usrds-adr.niddk.nih.gov/2022/end-stage-renal-disease/1-incidence-prevalence-patient-characteristics-and-treatment-modalities (accessed: May 2, 2023).
16. Koplan BA, Winkelmayer WC, Costea AI, et al. Implantable loop recorder monitoring and the incidence of previously unrecognized atrial fibrillation in patients on hemodialysis. Kidney Int Rep. 2022; 7(2): 189–199, doi: 10.1016/j.ekir.2021.10.001, indexed in Pubmed: 35155858.

17. Kazancioğlu R. Risk factors for chronic kidney disease: an update. Kidney Int Suppl (2011). 2013; 3(4): 368–371, doi: 10.1038/kisup.2013.79, indexed in Pubmed: 25019021.
18. Annual Data Report | USRDS n.d. https://usrds-adr.niddk.nih.gov/2022/end-stage-renal-disease/1-incidence-prevalence-patient-characteristics-and-treatment-modalities (accessed: August 25, 2023).
19. Astley ME, Boenink R, Abd ElHafeez S, et al. The ERA Registry Annual Report 2020: a summary. Clin Kidney J. 2023; 16(8): 1330–1354, doi: 10.1093/ckj/sfad087, indexed in Pubmed: 37529647.
20. Akhtar Z, Leung LW, Kontogiannis C, et al. Arrhythmias in chronic kidney disease. Eur Cardiol. 2022; 17: e05, doi: 10.15420/ecr.2021.52, indexed in Pubmed: 35321526.
21. Ding WY, Gupta D, Wong CF, et al. Pathophysiology of atrial fibrillation and chronic kidney disease. Cardiovasc Res. 2021; 117(4): 1046–1059, doi: 10.1093/cvr/cvaa258, indexed in Pubmed: 32871005.
22. Everett TH, Olgin JE. Atrial fibrosis and the mechanisms of atrial fibrillation. Heart Rhythm. 2007; 4(Suppl 3): S24–S27, doi: 10.1016/j.hrthm.2006.12.040, indexed in Pubmed: 17336879.
23. Grabner A, Faul C. The role of fibroblast growth factor 23 and Klotho in uremic cardiomyopathy. Curr Opin Nephrol Hypertens. 2016; 25(4): 314–324, doi: 10.1097/MNH.0000000000000231, indexed in Pubmed: 27219043.
24. Mehta R, Cai X, Lee J, et al. Association of fibroblast growth factor 23 with atrial fibrillation in chronic kidney disease, from the chronic renal insufficiency cohort study. JAMA Cardiol. 2016; 1(5): 548–556, doi: 10.1001/jamacardio.2016.1445, indexed in Pubmed: 27434583.
25. Malik J, Valerianova A, Pesickova SS, et al. Heart failure with preserved ejection fraction is the most frequent but commonly overlooked phenotype in patients on chronic hemodialysis. Front Cardiovasc Med. 2023; 10: 1130618, doi: 10.3389/fcvm.2023.1130618, indexed in Pubmed: 37324637.
26. Zakeri R, Chamberlain AM, Roger VL, et al. Temporal relationship and prognostic significance of atrial fibrillation in heart failure patients with preserved ejection fraction: a community-based study. Circulation. 2013; 128(10): 1085–1093, doi: 10.1161/CIRCULATIONAHA.113.001475, indexed in Pubmed: 23908348.
27. Buiten MS, de Bie MK, Rotmans JI, et al. The dialysis procedure as a trigger for atrial fibrillation: new insights in the development of atrial fibrillation in dialysis patients. Heart. 2014; 100(9): 685–690, doi: 10.1136/heartjnl-2013-305417, indexed in Pubmed: 24670418.
28. Correa S, Scovner KM, Tumlin JA, et al. Electrolyte changes in contemporary hemodialysis: a secondary analysis of the monitoring in dialysis study. Kidney360. 2021; 2(4): 695–707, doi: 10.34067/KID.0007452020, indexed in Pubmed: 34676372.
29. Hu A, Liu S, Montez-Rath ME, et al. Associations of serum and dialysate potassium concentrations with incident atrial fibrillation in a cohort study of older US persons initiating hemodialysis for kidney failure. Kidney Int Rep. 2023; 8(2): 305–316, doi: 10.1016/j.ekir.2022.11.003, indexed in Pubmed: 36815107.
30. Wang HH, Hung SY, Sung JM, et al. Risk of stroke in long-term dialysis patients compared with the general population. Am J Kidney Dis. 2014; 63(4): 604–611, doi: 10.1053/j.ajkd.2013.10.013, indexed in Pubmed: 24290244.
31. Lutz PD, Jurk PdD. Platelets in advanced chronic kidney disease: two sides of the coin. Semin Thromb Hemost. 2020; 46(3): 342–356, doi: 10.1055/s-0040-1708841, indexed in Pubmed: 32259877.
32. Yu FP, Zhao YC, Gu B, et al. Chronic kidney disease and carotid atherosclerosis in patients with acute stroke. Neurologist. 2015; 20(2): 23–26, doi: 10.1097/NRL.0000000000000044, indexed in Pubmed: 26280286.
33. Chelluboina B, Vemuganti R. Chronic kidney disease in the pathogenesis of acute ischemic stroke. J Cereb Blood Flow Metab. 2019; 39(10): 1893–1905, doi: 10.1177/0271678X19866733, indexed in Pubmed: 31366298.
34. Hörl MP, Hörl WH. Hemodialysis-associated hypertension: pathophysiology and therapy. Am J Kidney Dis. 2002; 39(2): 227–244, doi: 10.1053/ajkd.2002.30542, indexed in Pubmed: 11840363.
35. Wang HH, Hung SY, Sung JM, et al. Risk of stroke in long-term dialysis patients compared with the general population. Am J Kidney Dis. 2014; 63(4): 604–611, doi: 10.1053/j.ajkd.2013.10.013, indexed in Pubmed: 24290244.
36. Power A, Chan K, Singh SK, et al. Appraising stroke risk in maintenance hemodialysis patients: a large single-center cohort study. Am J Kidney Dis. 2012; 59(2): 249–257, doi: 10.1053/j.ajkd.2011.07.016, indexed in Pubmed: 21944665.
37. Masson P, Webster AC, Hong M, et al. Chronic kidney disease and the risk of stroke: a systematic review and meta-analysis. Nephrol Dial Transplant. 2015; 30(7): 1162–1169, doi: 10.1093/ndt/gfv009, indexed in Pubmed: 25681099.
38. Cohen-Hagai K, Nacasch N, Rozenberg I, et al. Clinical outcomes of stroke in hemodialysis patients: a retrospective single-center study. Int Urol Nephrol. 2019; 51(8): 1435–1441, doi: 10.1007/s11255-019-02218-x, indexed in Pubmed: 31264088.
39. Ovbiagele B, Schwamm LH, Smith EE, et al. Patterns of care quality and prognosis among hospitalized ischemic stroke patients with chronic kidney disease. J Am Heart Assoc. 2014; 3(3): e000905, doi: 10.1161/JAHA.114.000905, indexed in Pubmed: 24904017.
40. Lee JG, Lee KB, Jang IM, et al. Low glomerular filtration rate increases hemorrhagic transformation in acute ischemic stroke. Cerebrovasc Dis. 2013; 35(1): 53–59, doi: 10.1159/000345087, indexed in Pubmed: 23428997.
41. Remuzzi G, Livio M, Marchiaro G, et al. Bleeding in renal failure: altered platelet function in chronic uraemia only partially corrected by haemodialysis. Nephron. 1978; 22(4-6): 347–353, doi: 10.1159/000181474, indexed in Pubmed: 740096.
42. Gaspari F, Viganò G, Orisio S, et al. Aspirin prolongs bleeding time in uremia by a mechanism distinct from platelet cyclooxygenase inhibition. J Clin Invest. 1987; 79(6): 1788–1797, doi: 10.1172/JCI113020, indexed in Pubmed: 3108321.
43. Sood MM, Bota SE, McArthur E, et al. The three-year incidence of major hemorrhage among older adults initiating chronic dialysis. Can J Kidney Health Dis. 2014; 1: 21, doi: 10.1186/s40697-014-0021-x, indexed in Pubmed: 25780611.
44. Sood MM, Larkina M, Thumma JR, et al. Major bleeding events and risk stratification of antithrombotic agents in hemodialysis: results from the DOPPS. Kidney Int. 2013; 84(3): 600–608, doi: 10.1038/ki.2013.170, indexed in Pubmed: 23677245.
45. Ocak G, Noordzij M, Rookmaaker MB, et al. Mortality due to bleeding, myocardial infarction and stroke in dialysis patients. J Thromb Haemost. 2018; 16(10): 1953–1963, doi: 10.1111/jth.14254, indexed in Pubmed: 30063819.
46. Liao JN, Chan YH, Kuo L, et al. Optimal anticoagulation in elderly patients with atrial fibrillation: Which drug at which dose? Kardiol Pol. 2022; 80(2): 128–136, doi: 10.33963/KP.a2022.0046, indexed in Pubmed: 35167115.
47. He W, Zhang H, Zhu W, et al. Effect of anticoagulation therapy in older patients with chronic kidney disease and atrial fibrillation: A meta-analysis. Medicine (Baltimore). 2019; 98(42): e17628, doi: 10.1097/MD.0000000000017628, indexed in Pubmed: 31626146.
48. Wasse H, Gillen DL, Ball AM, et al. Risk factors for upper gastrointestinal bleeding among end-stage renal disease patients. Kidney Int. 2003; 64(4): 1455–1461, doi: 10.1046/j.1523-1755.2003.00225.x, indexed in Pubmed: 12969166.
49. Ocak G, Noordzij M, Rookmaaker MB, et al. Mortality due to bleeding, myocardial infarction and stroke in dialysis patients. J Thromb Haemost. 2018; 16(10): 1953–1963, doi: 10.1111/jth.14254, indexed in Pubmed: 30063819.
50. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J. 2021; 42(5): 373–498, doi: 10.1093/eurheartj/ehaa612, indexed in Pubmed: 32860505.
51. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in collaboration with the Society of Thoracic Surgeons. Circulation. 2019; 140(2): e125–e151, doi: 10.1161/CIR.0000000000000665, indexed in Pubmed: 30686041.
52. Chao TF, Liu CJ, Wang KL, et al. Incidence and prediction of ischemic stroke among atrial fibrillation patients with end-stage renal disease requiring dialysis. Heart Rhythm. 2014; 11(10): 1752–1759, doi: 10.1016/j.hrthm.2014.06.021, indexed in Pubmed: 24952148.

53. Olesen JB, Lip GYH, Hansen ML, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. BMJ. 2011; 342: d124, doi: 10.1136/bmj.d124, indexed in Pubmed: 21282258.
54. Ocak G, Ramspek C, Rookmaaker MB, et al. Performance of bleeding risk scores in dialysis patients. Nephrol Dial Transplant. 2019; 34(7): 1223–1231, doi: 10.1093/ndt/gfy387, indexed in Pubmed: 30608543.
55. Nopp S, Spielvogel CP, Schmaldienst S, et al. Bleeding risk assessment in end-stage kidney disease: validation of existing risk scores and evaluation of a machine learning-based approach. Thromb Haemost. 2022; 122(9), doi: 10.1055/a-1754-7551, indexed in Pubmed: 35098518.
56. Khouri Y, Stephens T, Ayuba G, et al. Understanding and managing atrial fibrillation in patients with kidney disease. J Atr Fibrillation. 2015; 7(6): 1069, doi: 10.4022/jafib.1069, indexed in Pubmed: 27957157.
57. Schmidt M, Rieber J, Daccarett M, et al. Relation of recurrence of atrial fibrillation after successful cardioversion to renal function. Am J Cardiol. 2010; 105(3): 368–372, doi: 10.1016/j.amjcard.2009.09.037, indexed in Pubmed: 20102950.
58. Chung I, Khan Y, Warrens H, et al. Catheter ablation for atrial fibrillation in patients with chronic kidney disease and on dialysis: a meta-analysis and review. Cardiorenal Med. 2022; 12(4): 155–172, doi: 10.1159/000525388, indexed in Pubmed: 35820393.
59. Navaravong L, Barakat M, Burgon N, et al. Improvement in estimated glomerular filtration rate in patients with chronic kidney disease undergoing catheter ablation for atrial fibrillation. J Cardiovasc Electrophysiol. 2015; 26(1): 21–27, doi: 10.1111/jce.12530, indexed in Pubmed: 25142836.
60. Takahashi Y, Takahashi A, Kuwahara T, et al. Renal function after catheter ablation of atrial fibrillation. Circulation. 2011; 124(22): 2380–2387, doi: 10.1161/CIRCULATIONAHA.111.047266, indexed in Pubmed: 22042886.
61. Randhawa MS, Vishwanath R, Rai MP, et al. Association between use of warfarin for atrial fibrillation and outcomes among patients with end-stage renal disease: a systematic review and meta-analysis. JAMA Netw Open. 2020; 3(4): e202175, doi: 10.1001/jamanetworkopen.2020.2175, indexed in Pubmed: 32250434.
62. Tan J, Bae S, Segal JB, et al. Warfarin use and the risk of stroke, bleeding, and mortality in older adults on dialysis with incident atrial fibrillation. Nephrology (Carlton). 2019; 24(2): 234–244, doi: 10.1111/nep.13207, indexed in Pubmed: 29219209.
63. Friberg L, Benson L, Lip GYH. Balancing stroke and bleeding risks in patients with atrial fibrillation and renal failure: the Swedish Atrial Fibrillation Cohort study. Eur Heart J. 2015; 36(5): 297–306, doi: 10.1093/eurheartj/ehu139, indexed in Pubmed: 24722803.
64. Reinecke H, Engelbertz C, Bauersachs R, et al. A randomized controlled trial comparing apixaban with the vitamin K antagonist phenprocoumon in patients on chronic hemodialysis: the AXADIA-AFNET 8 study. Circulation. 2023; 147(4): 296–309, doi: 10.1161/circulationaha.122.062779.
65. Nigwekar SU, Kroshinsky D, Nazarian RM, et al. Calciphylaxis: risk factors, diagnosis, and treatment. Am J Kidney Dis. 2015; 66(1): 133–146, doi: 10.1053/j.ajkd.2015.01.034, indexed in Pubmed: 25960299.
66. Chan KE, Giugliano RP, Patel MR, et al. Nonvitamin K anticoagulant agents in patients with advanced chronic kidney disease or on dialysis with AF. J Am Coll Cardiol. 2016; 67(24): 2888–2899, doi: 10.1016/j.jacc.2016.02.082, indexed in Pubmed: 27311528.
67. Mavrakanas TA, Samer CF, Nessim SJ, et al. Apixaban pharmacokinetics at steady state in hemodialysis patients. J Am Soc Nephrol. 2017; 28(7): 2241––2248, doi: 10.1681/ASN.2016090980, indexed in Pubmed: 28302754.
68. Siontis KC, Zhang X, Eckard A, et al. Outcomes associated with apixaban use in patients with end-stage kidney disease and atrial fibrillation in the United States. Circulation. 2018; 138(15): 1519–1529, doi: 10.1161/CIRCULATIONAHA.118.035418, indexed in Pubmed: 29954737.
69. Mavrakanas TA, Garlo K, Charytan DM. Apixaban versus no anticoagulation in patients undergoing long-term dialysis with incident atrial fibrillation. Clin J Am Soc Nephrol. 2020; 15(8): 1146–1154, doi: 10.2215/CJN.11650919, indexed in Pubmed: 32444398.
70. Pokorney SD, Chertow GM, Al-Khalidi HR, et al. Apixaban for patients with atrial fibrillation on hemodialysis: a multicenter randomized controlled trial. Circulation. 2022; 146(23): 1735–1745, doi: 10.1161/CIRCULATIONAHA.121.054990, indexed in Pubmed: 36335914.
71. Roberts MA, Pilmore HL, Ierino FL, et al. The β-blocker to lower cardiovascular dialysis events (BLOCADE) feasibility study: a randomized controlled trial. Am J Kidney Dis. 2016; 67(6): 902–911, doi: 10.1053/j.ajkd.2015.10.029, indexed in Pubmed: 26717861.
72. Fellström BC, Jardine AG, Schmieder RE, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med. 2009; 360(14): 1395–1407, doi: 10.1056/NEJMoa0810177, indexed in Pubmed: 19332456.
73. Coleman CI, Kreutz R, Sood N, et al. Rivaroxaban versus warfarin in patients with nonvalvular atrial fibrillation and severe kidney disease or undergoing hemodialysis. Am J Med. 2019; 132(9): 1078–1083, doi: 10.1016/j.amjmed.2019.04.013, indexed in Pubmed: 31054829.
74. Lin YC, Chen BL, Shih CM, et al. Effectiveness and safety of rivaroxaban versus warfarin in Taiwanese patients with end-stage renal disease and nonvalvular atrial fibrillation: A real-world nationwide cohort study. PLoS One. 2021; 16(4): e0249940, doi: 10.1371/journal.pone.0249940, indexed in Pubmed: 33831130.
75. Kreutz R, Deray G, Floege J, et al. Rationale and design of XARENO: XA inhibition in RENal patients with non-valvular atrial fibrillation. Observational registry. Kardiol Pol. 2021; 79(11): 1265–1267, doi: 10.33963/KP.a2021.0134, indexed in Pubmed: 34643264.
76. De Vriese AS, Caluwé R, Pyfferoen L, et al. Multicenter randomized controlled trial of vitamin K antagonist replacement by rivaroxaban with or without vitamin K2 in hemodialysis patients with atrial fibrillation: The Valkyrie study. J Am Soc Nephrol. 2020; 31(1): 186–196, doi: 10.1681/ASN.2019060579, indexed in Pubmed: 31704740.
77. De Vriese AS, Caluwé R, Bailleul E, et al. Dose-finding study of rivaroxaban in hemodialysis patients. Am J Kidney Dis. 2015; 66(1): 91–98, doi: 10.1053/j.ajkd.2015.01.022, indexed in Pubmed: 25804678.
78. Pon TK, Dager WE, Roberts AJ, et al. Subcutaneous enoxaparin for therapeutic anticoagulation in hemodialysis patients. Thromb Res. 2014; 133(6): 1023–1028, doi: 10.1016/j.thromres.2014.03.036, indexed in Pubmed: 24718051.
79. Königsbrügge O, Posch F, Antlanger M, et al. Prevalence of atrial fibrillation and antithrombotic therapy in hemodialysis patients: cross-sectional results of the vienna investigation of atrial fibrillation and thromboembolism in patients on hemodialysis (VIVALDI). PLoS One. 2017; 12(1): e0169400, doi: 10.1371/journal.pone.0169400, indexed in Pubmed: 28052124.
80. Seligsohn U. Factor XI deficiency in humans. J Thromb Haemost. 2009; 7 (Suppl 1): 84–87, doi: 10.1111/j.1538-7836.2009.03395.x, indexed in Pubmed: 19630775.
81. Piccini JP, Caso V, Connolly SJ, et al. Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): a multicentre, randomised, double-blind, double-dummy, dose-finding phase 2 study. Lancet. 2022; 399(10333): 1383–1390, doi: 10.1016/S0140-6736(22)00456-1, indexed in Pubmed: 35385695.
82. Turagam MK, Osmancik P, Neuzil P, et al. Left atrial appendage closure versus oral anticoagulants in atrial fibrillation: a meta-analysis of randomized trials. J Am Coll Cardiol. 2020; 76(23): 2795–2797, doi: 10.1016/j.jacc.2020.08.089, indexed in Pubmed: 33272374.
83. Genovesi S, Porcu L, Slaviero G, et al. Outcomes on safety and efficacy of left atrial appendage occlusion in end stage renal disease patients undergoing dialysis. J Nephrol. 2021; 34(1): 63–73, doi: 10.1007/s40620-020-00774-5, indexed in Pubmed: 32535831.
84. Mesnier J, Cruz-González I, Arzamendi D, et al. Incidence and predictors of early death in patients undergoing percutaneous left atrial appendage closure. JACC Clin Electrophysiol. 2022; 8(9): 1093–1102, doi: 10.1016/j.jacep.2022.06.012, indexed in Pubmed: 36137713.
85. Steffel J, Collins R, Antz M, et al. External reviewers. 2021 European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Europace. 2021; 23(10): 1612–1676, doi: 10.1093/europace/euab065, indexed in Pubmed: 33895845.
86. Apixaban FDA approval 2012 n.d. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202155s002lbl.pdf (accessed: May 9, 2023).
87. Brieger D, Amerena J, Attia J, et al. National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand: Australian clinical guidelines for the diagnosis and management of atrial fibrillation 2018. Heart Lung Circ. 2018; 27(10): 1209–1266, doi: 10.1016/j.hlc.2018.06.1043, indexed in Pubmed: 30077228.

88. Andrade JG, Aguilar M, Atzema C, et al. The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society Comprehensive Guidelines for the management of atrial fibrillation. Can J Cardiol. 2020; 36(12): 1847–1948, doi: 10.1016/j.cjca.2020.09.001, indexed in Pubmed: 33191198.
89. Herzog CA, Asinger RW, Berger AK, et al. Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2011; 80(6): 572–586, doi: 10.1038/ki.2011.223, indexed in Pubmed: 21750584.
90. Turakhia MP, Blankestijn PJ, Carrero JJ, et al. Chronic kidney disease and arrhythmias: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) controversies conference. Eur Heart J. 2018; 39(24): 2314–2325, doi: 10.1093/eurheartj/ehy060, indexed in Pubmed: 29522134.
91. Urquhart-Secord R, Craig JC, Hemmelgarn B, et al. Patient and caregiver priorities for outcomes in hemodialysis: an international nominal group technique study. Am J Kidney Dis. 2016; 68(3): 444–454, doi: 10.1053/j.ajkd.2016.02.037, indexed in Pubmed: 26968042.
92. D'Agata EM, Mount DB, Thayer V, et al. Hospital-acquired infections among chronic hemodialysis patients. Am J Kidney Dis. 2000; 35(6): 1083–1088, doi: 10.1016/s0272-6386(00)70044-8, indexed in Pubmed: 10845821.
93. Tam-Tham H, Ravani P, Zhang J, et al. Association of initiation of dialysis with hospital length of stay and intensity of care in older adults with kidney failure. JAMA Netw Open. 2020; 3(2): e200222, doi: 10.1001/jamanetworkopen.2020.0222, indexed in Pubmed: 32108896.

REVIEW

Neutrophil extracellular traps (NETs) in cardiovascular diseases: From molecular mechanisms to therapeutic interventions

Joanna Natorska*, Michał Ząbczyk*, Anetta Undas

[1]Department of Thromboembolic Disorders, Institute of Cardiology, Jagiellonian University Medical College, Kraków, Poland
[2]St. John Paul II Hospital, Kraków, Poland
*Both authors equally contributed to the study.

Correspondence to:
Joanna Natorska, MD, PhD,
Department of Thromboembolic Disorders,
Institute of Cardiology,
Jagiellonian University Medical College,
Prądnicka 80, 31–202 Kraków, Poland,
phone: +48 12 614 21 08,
fax: +48 12 614 21 20,
e-mail: joanna.natorska@uj.edu.pl

DOI: 10.33963/v.kp98520

Received:
November 10, 2023

Accepted:
December 8, 2023

Early publication date:
December 18, 2023

ABSTRACT

Neutrophil extracellular traps (NETs), which are net-like structures composed of DNA, histones, and antimicrobial proteins, in particular myeloperoxidase (MPO) and elastase, have been demonstrated in bacterial, viral, protozoal, and fungal infections as a potent innate immunity mechanism of pathogen elimination associated with enhanced inflammation. Growing evidence indicates the contribution of NETs formation (NETosis), driven by protein-arginine deiminase type 4, to thrombosis, ischemia, and atherosclerosis. NETs are considered new players involved in the development and progression of cardiovascular diseases (CVDs), including coronary artery disease (CAD) and its acute manifestations in particular acute myocardial infarction (MI), peripheral artery disease (PAD) along with ischemic stroke, heart failure, aortic stenosis, and atrial fibrillation (AF). Formation of NETs and elevated levels of their circulating markers, e.g. citrullinated histone 3 and MPO-DNA complexes, have been observed in chronic and acute manifestations of CVD. NETs accumulation was associated with plaque rupture, infarct size, and impaired myocardial function. NETs have been identified within human stenotic aortic valves, like in atherosclerotic plaques and arterial thrombi. Moreover, circulating NETs markers in association with prothrombotic markers, including fibrin clot properties, predicted adverse clinical events in AF. Several NETs inhibitors, including recombinant human DNase, an enzyme degrading NETs, reactive oxygen species scavengers, together with antithrombotic and antiplatelet drugs, have been shown to reduce uncontrolled NETosis. This review summarizes the current evidence on the role of NETosis in CVDs, its significance as a risk factor for clinical outcomes, and finally, the potential of NETs as a target for future therapeutic interventions.

Key words: atherosclerosis, atrial fibrillation, myocardial infarction, NETs, stroke

INTRODUCTION

Cardiovascular diseases (CVDs) represent a range of common conditions being the leading cause of death worldwide, accounting for about one-third of all death in 2019, as reported by the World Health Organization [1]. CVDs encompass coronary artery disease (CAD) and its acute manifestations, in particular acute coronary syndrome, myocardial infarction (MI), and peripheral artery disease (PAD), increasing the risk of ischemic stroke, as well as heart failure (HF) and atrial fibrillation (AF). The prevalence of CVD rises with age, starting at around 1% of individuals aged 20–39 and increasing to 42.9% among males and 31.3% among females aged 80 years and older, excluding cases related to hypertension [2]. In 2019, the primary cause of CVD-related deaths was CAD, which accounts for 41.3% of fatalities, followed by stroke at 17.2%, high blood pressure at 11.7%, HF at 9.9%, and arterial diseases at 2.8% of all deaths [2]. It is worth mentioning that CVD risk factors, such as obesity and diabetes, were more frequently associated with CVD-related deaths, as became evident during the COVID-19 pandemic [3].

Chronic inflammation within the arterial wall is a key pathophysiological mechanism underlying the development and progression of CVDs [2]. Extremely intricate and

intertwined processes involved in atherosclerosis, which are still incompletely elucidated encompass enhanced oxidative stress, lipid accumulation, immune responses, fibrosis, calcification and many others [4].

While monocytes have been extensively studied in the context of CVD, neutrophils, the most abundant white blood cells, play a crucial role in innate defense against infections. Their functions include phagocytosis, the process of engulfing and ingesting pathogens like bacteria, fungi, and cellular debris [5].

Neutrophils migrate to sites of infection or inflammation in response to chemical signals, such as chemokines and cytokines, through a process called chemotaxis [5]. In response to specific stimuli neutrophils can produce large amounts of reactive oxygen species (ROS) upon activation of NADPH oxidase 2 (NOX2) [6]. ROS are toxic to pathogens and destroy bacteria and fungi inside the neutrophil. As inflammation subsides, neutrophils undergo apoptosis (programmed cell death), and then macrophages remove the apoptotic neutrophils [6].

In 2004 Brinkmann et al. [7] described a new activity of neutrophils called neutrophil extracellular traps (NETs) formation, suggesting that this mechanism of the innate immunity is of key importance in pathogen elimination. NETs are web-like structures composed of DNA, histones, and antimicrobial proteins [7]. Initially it was thought that NETs exclusively capture and immobilize microbes, such as bacteria, fungi, and some viruses, and thus preventing their spread [7]. However, in the following years growing evidence supported the concept that NETosis is implicated in sepsis, autoimmune diseases, venous thromboembolism, cancer, and also CVDs [8]. It is important to emphasize that neutrophil activation and NETosis are two different processes involving neutrophils. Neutrophil activation is associated with their degranulation, oxidative burst, and phagocytosis. Prolonging neutrophil activation associated with enhanced ROS production leads to NETs generation [9].

In this review we summarized available data on the role of NETosis in a broad spectrum of CVDs involving CAD, acute arterial thromboembolism, and AF in search for novel biomarkers and potential treatment options targeting NETosis inhibition.

Molecular mechanisms of NETosis

The molecular basis of NETosis involves a series of complex events. Neutrophil activation triggers intracellular signaling pathways that lead to the activation of an enzyme called nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. NADPH generates ROS, including singlet oxygen ($1O_2$), hydrogen peroxide (H_2O_2), hypochlorous acid, and others, which are about to destroy microbes [9]. It is important to note that ROS, apart from its bactericidal function, play a crucial role in the process of "suicidal" NETosis, which persists for 3–4 hours and is fatal for neutrophils [9]. An enzyme, called myeloperoxidase (MPO), activated by H_2O_2, leads to the release of neutrophil elastase (NE) from neutrophil azurophilic granules. NE migrates to the cell nuclei to induce chromatin decondensation and degrade neutrophil actin filaments, thereby inhibiting neutrophil chemotaxis [10]. After nucleus disintegration, neutrophils release NETs into the extracellular environment and both MPO and NE on chromatin fibers stabilize NETs and ensure their antibacterial properties [11]. Complexes of cell free DNA and MPO or NE are considered as specific biomarkers of NETs, while citrullinated histones H3 (citH3), although associated with NETosis, covers only protein arginase deiminase 4 (PAD4)-dependent citrullination of H3 histones [9]. Moreover, Kenny et al. [9] reported that NETosis can occur without histone H3 citrullination and pharmacological inhibition of PADs did not inhibit NETosis.

PAD4, catalyzes the conversion of arginine residues in histones to citrulline, which weakens their interaction with DNA, promoting chromatin decondensation [11]. Citrullinated histones have been demonstrated to exert antimicrobial properties [11]. Of note, several proteins, including fibrinogen, can be citrullinated by PAD4. Citrullinated fibrinogen, together with citrullinated vimentin were observed within human atherosclerotic plaques [12]. Moreover, *in vitro* fibrinogen citrullination led to formation of more compact clots with reduced porosity and susceptibility to fibrinolysis [13].

An alternative form of NETosis is the "vital" or NOX-independent pathway. In contrast to the "suicidal", the "vital" NETosis occurs in about 30 minutes [14]. "Vital" NETosis is ROS-independent and can be induced by activated platelets, microorganisms, and complement proteins. This leads to the influx of Ca^{2+} *via* the small conductance potassium channel member three [14], which activates PAD4, and results in histone citrullination and chromatin decondensation [15]. Neutrophils remain viable after this form of NETosis [8].

NETs are eliminated by deoxyribonucleases (DNases), Ca^{2+}/Mg^{2+}-dependent enzymes degrading circulating DNA, and phagocyted by macrophages [16]. There are three main types of DNases: DNase-I, DNase-II, and DNase-1L3. DNase-I preferentially digests cell-free DNA (cfDNA), DNase-II degrades DNA from apoptotic bodies, while DNase-1L3 degrades chromatin and chromatin-bound DNA [17, 18]. It was shown that genetic defects in the DNase-I or DNase-1L3 genes are associated with severe forms of autoimmune diseases e.g. rheumatoid arthritis and scleroderma [19]. Insufficient clearance of NETs may contribute to the development of autoimmune diseases primarily because of the exposure to intracellular antigens present on NETs [20]. Moreover, in mouse models, DNase deficiency was associated with massive NET-related thrombosis in lungs, liver or kidneys [21].

Factors triggering NETosis

NETosis is triggered by a variety of factors, primarily associated with the recognition of pathogens such as pathogen-associated molecular patterns (PAMPs), like bacterial

lipopolysaccharides, lipoproteins, viruses, and fungal cell wall components. NETosis can also be activated by receptors, including toll-like receptors (TLRs), C-type lectin receptors (CLRs), complement receptors (CRs), receptors for immunoglobulin c-terminal fragment (FcR) and Cys-X-Cys motif chemokine receptors. Recently nucleotide-binding oligomerization domain-like receptors have been shown to activate NETosis [22]. Moreover, cytokines released upon inflammation, such as interleukin-1β (IL-1β), tumor necrosis factor alpha (TNF-α), and interleukin-8 (IL-8) that can activate neutrophils trigger NETosis [23]. The complement system, a component of the immune system, was also shown to induce NETosis. It has been demonstrated that complement component 3 (C3) knock-out mice and receptor for C3a fragment (C3aR) knock-out mice display reduced NETs formation [24]. Other complement components such as C3b or C5a were shown to stimulate NETosis by binding to their receptors on neutrophils, while C1q can prevent NETs from DNases. Moreover, physical factors such as shear stress and mechanical stretching can contribute to NETosis. Factors like hypoxia (low oxygen levels) and nutrient deprivation can also induce NETosis, especially during tissue damage or inflammation.

Platelets in NETosis

Platelets are the interface between blood coagulation and inflammation in atherosclerosis [25]. Neutrophils and platelets interact together *via* the glycoprotein Ib. Moreover, neutrophils recognize P-selectin expressed by activated platelets, which was shown to facilitate NETosis [25] but P-selectin blockage does not inhibit NETs formation [26]. Another platelet-derived protein, high mobility group box 1 (HMGB1), was independently associated with NETs formation. A study by Maugeri et al. [26] performed on 26 patients with acute MI showed that besides activated platelets, NETing neutrophils were a main cellular component of thrombi. Additionally, studies have demonstrated that platelets are recruited to NETs and bind to them in a histone-dependent manner via complement component C3b deposited on NETs and CR1 receptor expressed by platelets [27, 28]. Histones H3 and H4 have been shown to activate platelets, which in turn stimulated NETosis in a positive-feedback loop [27, 28]. Moreover, those histones induced secretion of platelet-derived polyphosphate (poly P) and activated blood coagulation by factor XII (FXII) and render fibrin clots more compact [28, 29]. Factors triggering NETosis and receptors involved are summarized in Figure 1.

A link between NETosis and coagulation

NETs formed after neutrophil activation provide a scaffold for thrombus formation [30]. Interestingly, only DNA and histones alone can induce thrombin generation, while these components in a complex of nucleosomes did not have the same effect [28]. Moreover, the selective exposure of tissue factor (TF), which initiates blood coagulation *in vivo*, on NETs determines the ability to initiate coagulation. However, it is important to note that not all NETs exhibit TF. It has been shown that neutrophils treated with cytokines increased the expression of TF mRNA and its release on NETs [31]. Therefore, the exposure of TF on NETs appears to be contingent on the specific stimulus used to induce NETosis, which may explain an importance of the experimental approach used to research. On the other hand, another mechanisms of direct coagulation activation by NETs is that they provide a negatively charged surface to activate FXII, the initial factor of the intrinsic coagulation pathway [32]. FXII or FXI inhibition attenuated thrombin generation on NETs [33]. Finally, it was shown that fibrinogen binds to DNA-rich NETs [34]. It is plausible that fibrin formation takes place on NETs following coagulation activation regardless of the pathway involved. Fibrin may serve to stiffen the structure of NETs, creating a mesh that entraps pathogens, thus preventing their dissemination. Using scanning electron microscopy imaging it has been demonstrated that fibrin clots formed *in vitro* in the presence of NET components displayed denser structure, which is more resistant to lysis [35].

It is worth mentioning that positively-charged nucleosomes located at the site of injury can attract negatively-charged tissue factor pathway inhibitor (TFPI) [2]. NET-associated proteins, namely NE and cathepsin G, play a role in promoting fibrin formation on NETs, since they have been demonstrated to inhibit TFPI, a major inhibitor of the extrinsic coagulation pathway [2]. Further research is needed to clarify the role of TFPI in the cross-talk between NETosis and blood coagulation.

Enhanced NETosis exerts potent proinflammatory effects. An overabundant discharge or malfunction of NETs may initiate and enhance inflammatory reactions, leading to potential harm to tissues and various disease conditions. Components of NETs, such as histones, of circulating DNA, can transform into self-antigens, resulting in inflammation, tissue toxicity and thrombosis [29]. Therefore, maintaining a balance between NETosis activation and inhibition seems to be of major importance in a variety of disease states, including atherosclerotic vascular disease and its thrombotic manifestations.

NETosis in CVDs

Growing evidence has established a link between enhanced NETs formation or insufficient NETs degradation and the underlying mechanisms of various CVDs driven by inflammatory responses (Figure 2).

Coronary artery disease (CAD)

The involvement of NETosis in atherosclerosis may result from infections and stimulation of neutrophils by bacterial components [36] or from a non-infectious activation of neutrophils within atherosclerotic plaques by cholesterol crystals and the interplay between neutrophils and macrophages, amplifying the immune response [37].

In 2012, Megens and co-workers [38] were the first to report the presence of NETs within atherosclerotic plaques,

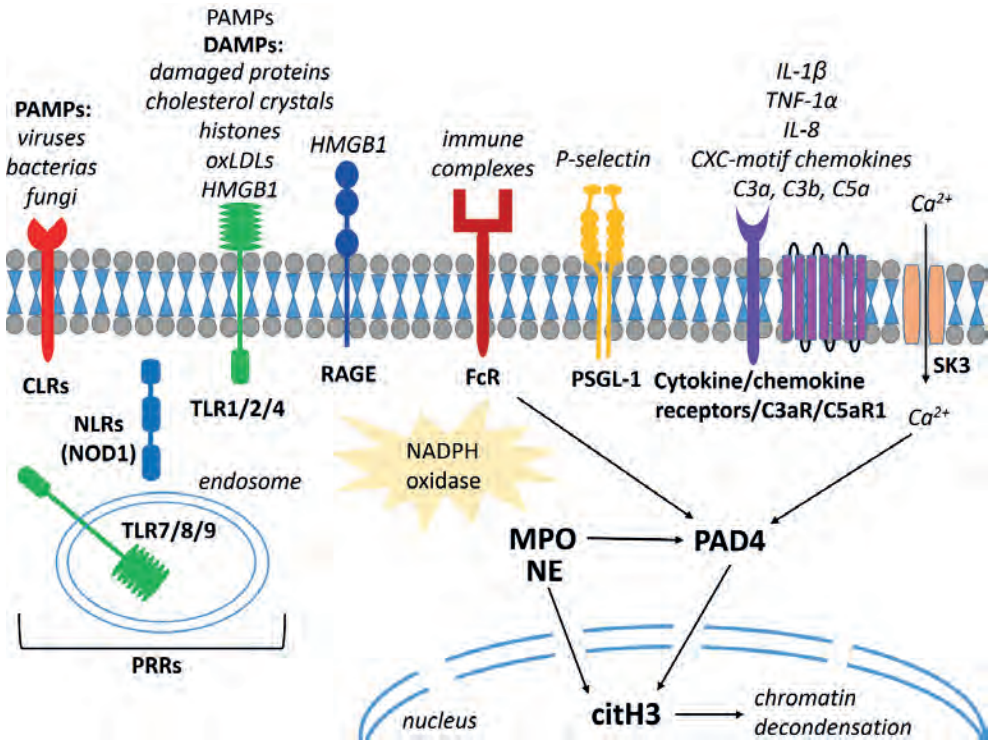


Figure 1. Receptors and corresponding stimuli activating the release of neutrophil extracellular traps (NETs). Pathogen-associated molecular patters (PAMPs) and damage-associated molecular patterns (DAMPs) activate receptors such as C-type lectin (CLRs), cytoplasmic nucleotide-binding oligomerization domain (NOD)-like receptors as well as toll-like receptors (TLRs), called together as pathogen-recognition receptors (PRRs). Moreover, transmembrane receptors such as receptor for advanced glycation end products (RAGE) binding platelet-derived high mobility group box 1 (HMGB1) protein, Fc fragments receptors (FcR), P-selectin glycoprotein ligand-1 (PSGL-1) binding P-selectin released by activated platelets, and cytokine (for interleukin [IL]-1β, tumor necrosis factor-1α [TNF-1α], and IL-8) or chemokine receptors, including receptors for complement components C3a and C5a (C3aR and C5aR1) are able to activate enzymes involved in NETs generation, such as myeloperoxidase (MPO), neutrophil elastase (NE), and protein arginine deiminase 4 (PAD4) in nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase)-dependent mechanism. PAD4 can be also activated directly by an influx of calcium ions (Ca^{2+}) through the small conductance potassium channel member three (SK3). MPO, NE, and PAD4 are responsible for chromatin decondensation and histone citrullination, leading to NETs formation

precisely in the luminal region. Borissoff et al. [39] in a study comprising 282 individuals with CAD showed associations between elevated levels of circulating DNA, nucleosomes, citrullinated histone H4, and MPO-DNA complexes with thrombin-antithrombin complexes. These were linked to the severity of CAD and the occurrence of major adverse cardiac events. This study strongly suggested that NETs contribute to the progression of atherosclerosis.

Fibrin forms the primary matrix of thrombi intertwined with DNA, derived from NETs, which has been shown in intracoronary thrombi from acute MI patients, particularly within fresh and lytic but not in organized thrombi [40]. Two studies provided additional evidence that NETs are involved in acute MI and the no-reflow phenomenon after reperfusion [41, 42]. Savchenko et al. [42] showed in a mouse model that cardiac ischemia induced NETs formation and DNase treatment reduced NETs accumulation. Similarly, Ge et al. [41] reported that addition of DNase I to thrombolytic therapy reduced NETosis, limited the no-reflow area, and showed beneficial effects for left ventricular function in rats. Mangold et al. [43] investigated 111 patients with ST-segment elevation MI (STEMI) who were undergoing primary percutaneous coronary intervention. They found that markers of NETosis and neutrophil activation, including nucleosomes, double-stranded DNA, NE, and MPO, are elevated in the culprit lesion site. NETs were identified within coronary thrombi retrieved during thrombectomy and the extent of NETosis was positively associated with the infarct size and negatively with ST-segment resolution [43]. Stakos et al. [44] in 18 patients with STEMI showed that thrombi from the culprit artery were rich in NETs expressing TF. The largest study performed on 253 thrombi from patients with stent thrombosis revealed the presence of NETs in 23% of samples, highlighting the role of NETs in coronary thrombosis [45]. It is unclear as to whether NETosis markers can predict major adverse coronary events in CAD.

Peripheral arterial disease (PAD)

PAD, often secondary to atherosclerosis, coexists commonly with CAD and shows association with a prothrombotic state [46]. Little is known about the role of NETosis in PAD. In 79 patients with PAD citH3 and cell-free DNA levels tended to be higher compared to healthy controls [47]. Circulating citH3 were associated with P-selectin

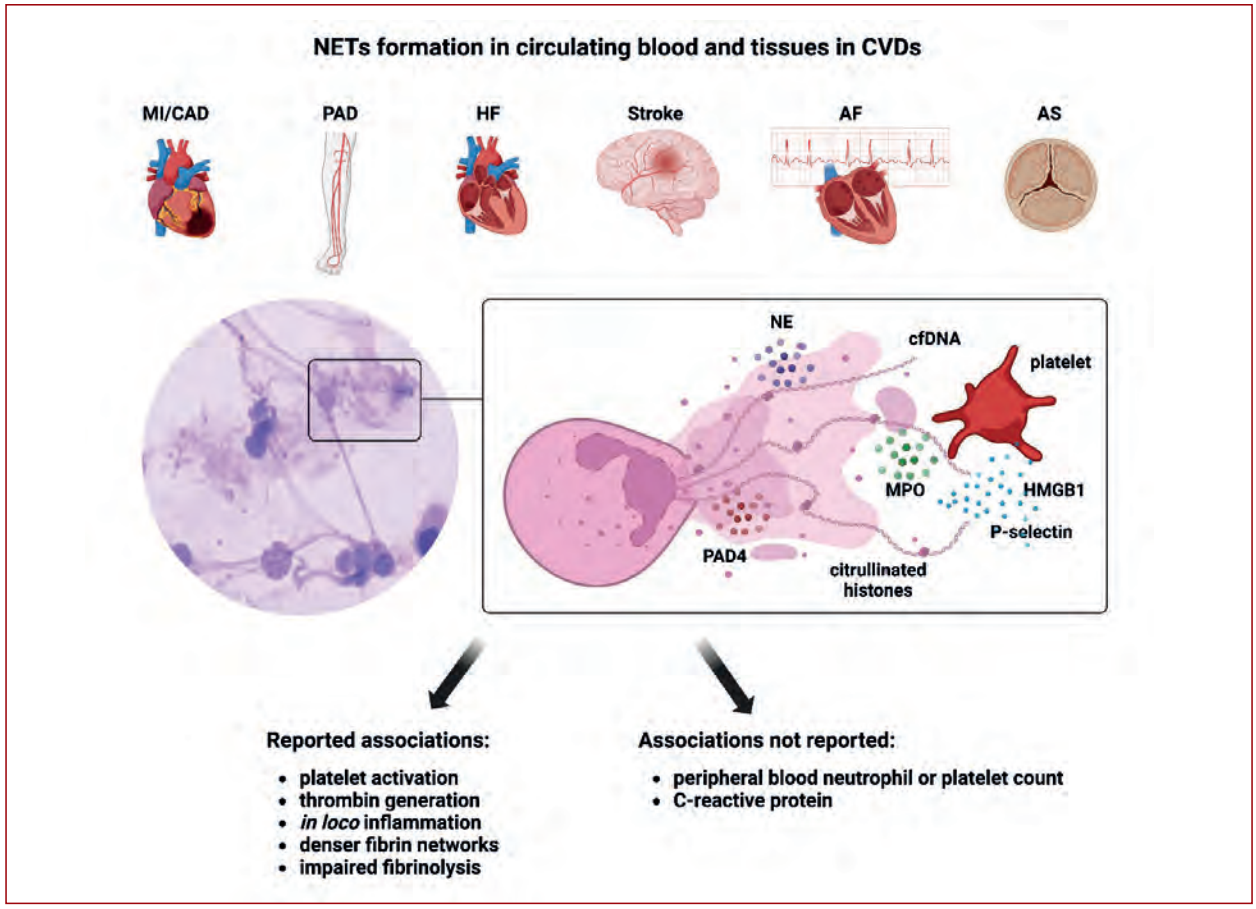


Figure 2. The involvement of NETosis in cardiovascular diseases (CVDs). NETs formation in circulating blood or tissues contributes to platelet activation, thrombin generation, and *in loco* inflammation in myocardial infarction (MI), coronary artery disease (CAD), and stroke. In peripheral arterial disease (PAD) no differences in circulating NETs markers were observed compared to controls, however, levels of cell-free DNA (cfDNA) and citrullinated histone H3 (citH3) correlated with P-selectin following platelet activation. Myeloperoxidase (MPO) was identified as an independent predictor of heart failure (HF) development. In ischemic stroke MPO-DNA complexes were associated with platelet-derived high mobility group box 1 (HMGB1) levels and neurological function. Prothrombotic fibrin clot phenotype, involving formation of more compact fibrin network and reduced susceptibility to fibrinolysis, in association with enhanced NETosis predisposed to cerebrovascular events in atrial fibrillation (AF). In aortic stenosis (AS) elevated plasma citH3 levels, together with increased valvular expression of citH3, MPO, and neutrophil elastase (NE) were observed. The image presents human neutrophils stimulated for 180 min with phorbol 12-myristate 13-acetate (PMA, final concentration 600 nM) and hematoxylin stained after stimulation. Magnification, 40×. Created with BioRender.com (agreement No. YZ262U4X94)

expression in response to exogenous thrombin-receptor activating peptide or arachidonic acid, while cell-free DNA was associated with P-selectin expression and activated glycoprotein IIb/IIIa after *in vitro* platelet activation using arachidonic acid [47]. Following infrainguinal angioplasty with stent implantation, increased levels of citH3 and cell-free DNA on admission predicted ischemic outcomes during 2-year follow-up [47]. Toth et al. [48] assessed 19 PAD and 18 CAD patients and reported that in PAD and CAD patients with dyslipidemia (n = 15) and high prevalence of atherothrombosis, DNA content was positively associated with the amounts of von Willebrand factor within thrombi.

No difference in circulating MPO-DNA levels was shown between symptomatic PAD patients compared with healthy controls. However, increased neutrophil degranulation was found to be related with PAD along with its prognostic role for major adverse cardiac events [49].

Heart failure

Mechanisms leading to HF involve inflammation, endothelial dysfunction, abnormal cardiac metabolism, cardiomyocyte hypertrophy or cardiac fibrosis [50, 51]. To the best of our knowledge there are few reports linking HF with NETosis.

Increased circulating MPO levels were identified as an independent risk factor for the onset and persistence of chronic HF [52, 53]. La Rocca et al. [54] suggested that this phenomenon is associated with MPO-associated chlorination or nitration of protein tyrosine, resulting in protein malfunction and endothelial damage. In an animal experiment involving lipodystrophic mice, which are prone to development of HF with preserved EF, showed that NETs-associated interstitial fibrosis contributes to ventricular stiffness. Moreover, NETs can be deposited within cardiac tissue as large amorphous structures [55]. A role of NETs in cardiac fibrosis has been demonstrated

in PAD4-knockout mice [56]. The authors showed that in this model protection from heart/lung fibrosis and improvement in left ventricular ejection fraction was found compared to wild-type mice, with a similar effect after DNase 1 supplementation [56]. Langseth et al. [57] reported in 61 STEMI patients with symptomatic acute HF that circulating levels of cell free DNA, MPO-DNA complexes, and IL-8 correlated with myocardial function but not myocardial recovery.

Ischemic stroke

Neutrophils are the initial immune cells that enter into the brain tissue shortly following an acute ischemic stroke (AIS), and contribute to brain injury within the ischemic region [58]. In 2012 De Meyer et al. [59] showed increased levels of circulating NETs components, such as nucleosomes, cell-free DNA, and histones in mice with experimental ischemic stroke. Moreover, histones contributed to cerebral ischemia/reperfusion injury and targeting of histones and DNA improved stroke outcome [59]. Laridan et al. [60] have shown for the first time that NETs are present in cerebral thrombi during AIS. Interestingly, NETs amount was largely higher in strokes of cardioembolic compared to non-cardioembolic origin. Additionally, thrombi older than 1 day exhibited higher neutrophil count compared to fresh thrombi [60].

In the study by Vallés et al. [61] performed on 243 AIS patients who were compared to 27 healthy controls, the highest quartile of citH3 (>0.284 AU) was independently associated with all-cause mortality at one-year follow-up (odds ratio [OR], 7.06; 95% confidence interval [CI], 1.63–30.5). In contrast, no associations with cfDNA or nucleosomes were found [61].

Elevated citH3 along with higher von Willebrand factor levels assessed on admission predicted AF-related cerebrovascular ischemic events, including ischemic stroke or transient ischemic attack during long-term anticoagulation [62]. This observation suggests a potential predictive value of NETosis markers in AF. Kollikowski et al. [63] showed in AIS patients that MPO concentrations assessed in cerebral arterial blood samples correlated positively with the number of neutrophils infiltrating the ischemic brain area, local platelet count, and neutrophil-activating peptide 2 (NAP-2), a primary platelet-derived neutrophil chemoattractant. Moreover, brain MPO levels were associated with functional clinical outcome assessed using modified Rankin scale. A recent study by Denorme et al. [64] performed in AIS patients and on a mouse model supported a pathological role of NETs in AIS. NETs were detected in the brain tissue samples of patients, irrespectively of stroke severity, and platelet-derived HMGB1 was correlated with NETs formation in this group of patients [64]. This study also showed on a model of HMGB1-knockout mice that platelets are a critical source of HMGB1 and that HMGB1-knockout mice had reduced plasma NETs and improved stroke outcomes [64]. In conclusion, NETs contribute to AIS and further studies are needed to elucidate whether therapeutic strategies aimed at NETosis inhibition may be beneficial to reduce stroke severity or improve stroke outcomes.

Atrial fibrillation

Little is known about the role of NETs in AF. Both experimental and clinical data have shown that MPO, an enzyme released upon neutrophil activation, plays a role in the pathogenesis of AF [62, 65]. In experiments involving right atrial electrophysiological stimulation, mice deficient in MPO did not develop AF [65]. However, when MPO was administered, this protective effect was reversed, leading to a similar degree of atrial fibrosis as observed in wild type mice treated with MPO for 7 days [65]. This observation suggests that MPO is a vital factor in myocardial remodeling, ultimately increasing susceptibility to AF. Also NE was shown to be elevated in AF patients compared to healthy subjects and the highest NE concentrations (>55.3 ng/ml) predicted ACEs (HR, 1.84; 95% CI, 1.01–3.76) in this group of patients [66]. Increased levels of NETs markers, including elevated citH3 concentrations characterized AF patients at high thromboembolic risk during long-term follow-up (Figure 3) [62]. Moreover, citH3 levels were associated with formation of denser fibrin clots, explaining about 5% of variation in clot porosity [62]. More compact fibrin clots were composed of thinner fibers and were more resistant to fibrinolysis [62]. These observations suggest that enhanced NETosis may contribute to a prothrombotic state observed in AF patients. Of note, in AF patients positive correlations between citH3 levels, 3-nitrotyrosine, as a marker of protein oxidation, and NAP-2 were found, emphasizing the role of oxidative stress and an interplay between neutrophils and platelets in AF [67]. Whether NETosis may be involved in the pathogenesis of AF remains to be established.

Aortic stenosis

Aortic stenosis (AS) is the most common acquired valvular heart disease in the adult population [68]. AS is closely linked to atherosclerosis, with similar risk factors and underlying pathomechanisms, such as chronic inflammation driven by oxidatively modified low-density lipoproteins (oxLDLs) followed by an influx of monocytes transforming into macrophages and the resulting calcification [68]. Moreover, prothrombotic state and hypofibrinolysis have been shown to contribute to AS progression [69]. The activity of MPO can also contribute to LDL modifications, which can effectively function as damage-associated molecular patterns (DAMPs) known to initiate atherosclerosis [70]. Awasthi et al. [71] reported that oxLDLs, especially lysophosphatidylcholine, facilitate NETs formation in humans, which favored endothelial inflammation in a vicious cycle. In 2019 Kopytek et al. [72] showed that AS patients compared to healthy controls had above 80% higher plasma citH3 levels and the presence of citH3/MPO- and citH3/NE-positive NETs was demonstrated within stenotic aortic valves

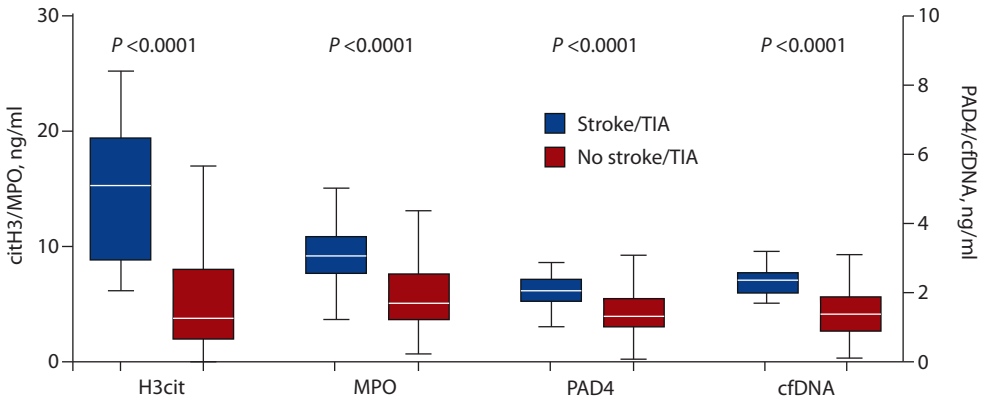


Figure 3. Elevated levels of circulating NETosis-related markers in patients with AF who experienced thrombotic cerebrovascular events during long-term follow-up. Circulating NETs markers were assessed in 243 AF patients (aged, 69 [64–75], 44% women) off anticoagulation. As many as 20 patients (8.2%) experienced thrombotic cerebrovascular events (ischemic stroke or transient ischemic attacks) during a median follow-up of 53 months despite anticoagulation (based on [62])

Abbreviations: TIA, transient ischemic attack; other — see Figures 1 and 2

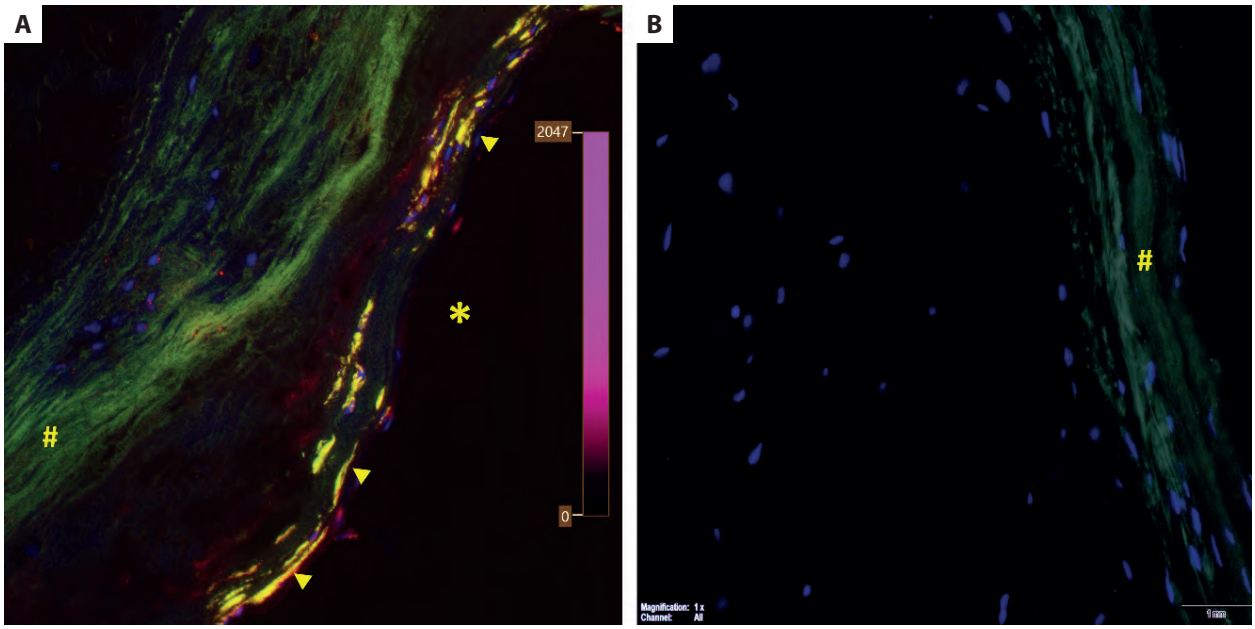


Figure 4. Specific biomarkers of neutrophil extracellular traps (NETs) within stenotic aortic valves. Aortic valve samples, dissected during surgical aortic valve replacement, were embedded in Tissue Tec-OCT compound (Sakura, Torrance, CA, USA) and cryosectioned onto SuperFrost slides (5 µm) (Menzel-Glaser, Braunschweig, Germany) by a Leica CM 1520 cryostat (Wetzlar, Germany). Single-label fluorescence was performed using monoclonal antibodies against citrullinated histones H3 (citH3; 1:250; Abcam, Cambridge, UK, cat. No. ab219407) or myeloperoxidase (MPO; 1:1000; GeneTex, Irvine, CA, USA, cat. No. GTX75318). Primary antibodies, incubated overnight at 4°C, were followed by the corresponding secondary antibodies conjugated with AlexaFluor 488 or AlexaFluor 594 (1:1500, Abcam, Cambridge, UK, cat. No. ab150073 and ab150116) at room temperature for 1 hour. Double-label immunofluorescence was performed using the same antibodies. A negative control (without primary antibody) was included. The semi-quantitative analyses were performed using Olympus BX 43 microscope equipped with software Cell Sense Standard (version 11.0.06). citH3 stained in green, MPO stained in red, Δ merged citH3 and MPO stained in yellow (**A**). A negative control stained without citH3 primary antibody (**B**). Cell nuclei are stained in blue (DAPI, Sigma Aldrich, Co, St. Louis, MO, US). Images were performed for the purposes of the study described previously [72]. #Autofluorescence of collagen fibers; *Aortic site of the leaflet. Original magnification 40×

(Figure 4). Importantly, the valvular expression of NETs markers correlated with AS severity. The authors concluded that the small amount of valvular NETs may contribute to AS progression [72]. Further studies are needed to establish whether valvular NETosis results from neutrophil interaction with oxLDL or with platelets/macrophages.

Therapeutic interventions to suppress NETosis

Controlling NETosis could present a promising approach for the treatment of NETs-associated cardiovascular manifestations especially in cases resistant to available strategies. The use of agents that can inhibit NETosis or degrade NETs to reduce inflammation and prevent thrombosis has

been assessed in cardiovascular patients or animal models of CVD. However until now there have been no reliable studies able to confirm that any of the therapies tested can substantially suppress NETosis in such patients leading to clinical benefits, though a few candidates deserve further investigation.

Recombinant human DNase-I (rhDNase-I)

Elevated double stranded-DNA levels within the 2nd to 4th quartiles were independently linked to a two-fold increase in the risk of experiencing the composite outcome of unstable angina, non-hemorrhagic stroke, acute MI, or all-cause mortality. This relationship was observed independently of the specific treatment received and markers associated with hypercoagulability [73]. DNase-I, an enzyme that selectively cleaves extracellular DNA, serves multiple roles, such as reducing neutrophil infiltration, regulating biofilm formation, assisting in pathogen invasion, degrading DNA matrices, and modulating immune functions via effective break down of DNA-nucleoprotein complexes and immune complexes [74]. Studies have demonstrated that rhDNase-I provides therapeutic benefits in conditions like lupus nephritis or systemic lupus erythematosus. Despite numerous studies evaluating the effect of rhDNase on NETs, which showed reduced NETosis and inflammatory response [75–77], to our knowledge, there have been no studies investigating DNases in CVD patients. This approach may be controversial due to studies showing that neutrophil components can limit inflammatory response, restrict the area of myocardial injury or initiate repair in a process of conversion macrophages to a reparative phenotype [78]. Moreover, a mouse model showed that neutrophil depletion impairs myocardial function and HF development [78]. However, it was demonstrated in HF patients that statins [79] and metformin [80] can effectively decrease NETosis by exerting anti-inflammatory effects and additionally by their ability to reduce plasma MPO levels. Metformin also reduced the levels of NE, proteinase-3, histones, and cfDNA, while a similar effect was not observed for glucose control with insulin [80].

Acetylsalicylic acid (Aspirin)

This antiplatelet agent can also affect NETs formation. Platelets take part in activating NETosis, therefore the inhibition of this action, using antiplatelet therapy, has the potential to inhibit NET formation [81]. Lapponi et al. [82] demonstrated that aspirin prevented NETs formation by inhibiting a transcriptional pathway controlled by nuclear factor kappa B (NFκB). Interestingly, dexamethasone had no effect on NETosis in this model [83]. On the other hand, dexamethasone, an inhibitor of TLR-2 and 4, reduced NETosis in COVID patients [83].

Antithrombotic drugs, such as heparin have been shown to suppress histone-induced diseases, e.g., sepsis [84]. Unfractionated heparin, low-molecular-weight heparin (parnaparin) and non-anticoagulant heparin protected from organ damage and death, neutralizing a toxic effect of circulating histones [85, 86]. Heparin, especially the non-anticoagulant type, represents a novel and promising approach to treating patients with high levels of circulating histones without increasing the bleeding risk [84].

Activated protein C (APC), a serine protease displaying anticoagulant, cytoprotective, and anti-inflammatory activities, has been demonstrated to cleave extracellular histones. Moreover, pretreatment of neutrophils with APC prevented activated platelets from adhering to neutrophils and from NETosis [87], suggesting that APC could serve as NETosis inhibitor. Recombinant human thrombomodulin (rhTM) can also inhibit NETosis. Helms et al. [88] showed in a rat model of septic shock that rhTM reduced NETosis and protected inner organs from dysfunction.

Chlor-amidine (Cl-amidine), a pharmacological inhibitor of PAD4, administered daily for 11 weeks, reduced thrombosis and the size of atherosclerotic lesions in a mouse model of atherosclerosis [89]. In a murine model of systemic lupus erythematosus, Cl-amidine protected against NET-induced kidney injury, endothelial dysfunction, and vascular damage [90]. Another therapeutic option to suppress PAD4 activity is hydroxychloroquine [91], used to treat malaria. Hydroxychloroquine has been shown to inhibit NETs formation in a mouse model of hepatic ischemia/reperfusion injury [91]. PAD4 inhibitors as a therapeutic option are an area of ongoing research with unclear safety and efficacy in humans.

Anti-HMGB1 antibodies also diminished NET formation in the bronchoalveolar lavage fluid of lipopolysaccharide-treated mice, measured as decreased levels of TNF-α, cell-free DNA and citH3 [92]. This observation allows to consider anti-HMGB1 antibodies as a potential therapy against excessive NETosis, though their value in CVDs is unknown.

C1 esterase inhibitor (C1INH), an endogenous inhibitor of C1 component of the complement system and a regulator of the contact activation pathway, has been reported to bind histones *in vitro* as well as C1INH-histone complexes were detected in the bronchoalveolar lavage fluid from acute respiratory distress syndrome patients [93]. The positive charge of histones could be used to deliver negatively charged inhibitors, which might not only bind to and neutralize histones but also be coupled with other potential therapeutic agents to augment their effectiveness at the site of inflammation [94].

N-acetylcysteine used primarily in patients with chronic obstructive pulmonary disease, was shown to exert antioxidant properties, consequently diminishing ROS-associated NETosis, however, its effect was not observed in the presence of H_2O_2 [95]. N-acetylcysteine reduced thrombus formation *in vivo* and decreased NETs formation in human neutrophils obtained from patients with hematologic malignances and healthy controls [96]. Also ROS scavengers, like octyl gallate [97] or methotrexate (NCT00470522) have been shown to reduce NETosis.

Antibiotics, such as chloramphenicol, azithromycin, and gentamicin, were shown to reduce NETs formation,

probably by decreased cytokine release and respiratory burst in a concentration-dependent manner [98].

Statins, potent cholesterol-lowering agents with pleiotropic effects used in primary and secondary CVD prevention [99], have shown anti-inflammatory effects in part by reducing NETosis, along with several antithrombotic and anti-inflammatory actions [79, 100].

SUMMARY

NETosis is a crucial part of the innate immune response and now is considered as the important mediator in atherothrombosis and atherosclerosis. The most compelling evidence supports the role of enhanced NETs formation in STEMI and ischemic stroke in particular in the context of resistance to thrombolysis. The role of NETosis in the progression of atherosclerotic plaques and AS appears to be less pronounced. Of importance is a potential predictive value of circulating NETs markers in AF despite anticoagulation. Further work is needed to develop more refined and well standardized diagnostic tools to detect excessive NETosis in cardiovascular patients. Modulation of NETosis attracts attention though the development of such targeted therapies may take some time, but it holds promise for improving the treatment and management of thromboembolic manifestations of CVDs in the future. It is tempting to speculate that combining NETosis-targeted treatment with existing therapies for CVD, such as aspirin, statins or antithrombotic drugs, could maximize the benefits. Large clinical trials to evaluate the safety and efficacy of NETosis-targeted treatments, alone or in combination, also in patients with CVDs are warranted in the next years.

Article information

Conflict of interest: None declared.

Funding: This study was supported by the Jagiellonian University Medical College (grant number N41/DBS/001040, to AU and N41/DBS/000906, to MZ).

REFERENCES

1. Dobrosielski DA. How can exercise reduce cardiovascular disease risk? A primer for the clinician. Pol Arch Intern Med. 2021; 131(10): 16122, doi: 10.20452/pamw.16122, indexed in Pubmed: 34706491.
2. Massberg S, Grahl L, von Bruehl ML, et al. Reciprocal coupling of coagulation and innate immunity via neutrophil serine proteases. Nat Med. 2010; 16(8): 887–896, doi: 10.1038/nm.2184, indexed in Pubmed: 20676107.
3. Pająk A, Jankowski P, Zdrojewski T. The burden of cardiovascular disease risk factors: A current problem. Kardiol Pol. 2022; 80(1): 5–15, doi: 10.33963/KP.a2022.0018, indexed in Pubmed: 35137945.
4. Libby P. Inflammation during the life cycle of the atherosclerotic plaque. Cardiovasc Res. 2021; 117(13): 2525–2536, doi: 10.1093/cvr/cvab303, indexed in Pubmed: 34550337.
5. Amulic B, Cazalet C, Hayes GL, et al. Neutrophil function: from mechanisms to disease. Annu Rev Immunol. 2012; 30: 459–489, doi: 10.1146/annurev-immunol-020711-074942, indexed in Pubmed: 22224774.
6. Kolaczkowska E, Kubes P. Neutrophil recruitment and function in health and inflammation. Nat Rev Immunol. 2013; 13(3): 159–175, doi: 10.1038/nri3399, indexed in Pubmed: 23435331.
7. Brinkmann V, Reichard U, Goosmann C, et al. Neutrophil extracellular traps kill bacteria. Science. 2004; 303(5663): 1532–1535, doi: 10.1126/science.1092385, indexed in Pubmed: 15001782.
8. Jayaseelan VP, Paramasivam A. Emerging role of NET inhibitors in cardiovascular diseases. Hypertens Res. 2020; 43(12): 1459–1461, doi: 10.1038/s41440-020-0527-9, indexed in Pubmed: 32733104.
9. Kenny EF, Herzig A, Krüger R, et al. Diverse stimuli engage different neutrophil extracellular trap pathways. Elife. 2017; 6: e24437, doi: 10.7554/eLife.24437, indexed in Pubmed: 28574339.
10. Metzler KD, Goosmann C, Lubojemska A, et al. A myeloperoxidase-containing complex regulates neutrophil elastase release and actin dynamics during NETosis. Cell Rep. 2014; 8(3): 883–896, doi: 10.1016/j.celrep.2014.06.044, indexed in Pubmed: 25066128.
11. Li P, Li M, Lindberg MR, et al. PAD4 is essential for antibacterial innate immunity mediated by neutrophil extracellular traps. J Exp Med. 2010; 207(9): 1853–1862, doi: 10.1084/jem.20100239, indexed in Pubmed: 20733033.
12. Sokolove J, Brennan MJ, Sharpe O, et al. Brief report: citrullination within the atherosclerotic plaque: a potential target for the anti-citrullinated protein antibody response in rheumatoid arthritis. Arthritis Rheum. 2013; 65(7): 1719–1724, doi: 10.1002/art.37961, indexed in Pubmed: 23553485.
13. Varjú I, Tóth E, Farkas ÁZ, et al. Citrullinated fibrinogen forms densely packed clots with decreased permeability. J Thromb Haemost. 2022; 20(12): 2862–2872, doi: 10.1111/jth.15875, indexed in Pubmed: 36083779.
14. Douda DN, Khan MA, Grasemann H, et al. SK3 channel and mitochondrial ROS mediate NADPH oxidase-independent NETosis induced by calcium influx. Proc Natl Acad Sci U S A. 2015; 112(9): 2817–2822, doi: 10.1073/pnas.1414055112, indexed in Pubmed: 25730848.
15. Leshner M, Wang S, Lewis C, et al. PAD4 mediated histone hypercitrullination induces heterochromatin decondensation and chromatin unfolding to form neutrophil extracellular trap-like structures. Front Immunol. 2012; 3: 307, doi: 10.3389/fimmu.2012.00307, indexed in Pubmed: 23060885.
16. Jiménez-Alcázar M, Rangaswamy C, Panda R, et al. Host DNases prevent vascular occlusion by neutrophil extracellular traps. Science. 2017; 358(6367): 1202–1206, doi: 10.1126/science.aam8897, indexed in Pubmed: 29191910.
17. Sisirak V, Sally B, D'Agati V, et al. Digestion of chromatin in apoptotic cell microparticles prevents autoimmunity. Cell. 2016; 166(1): 88–101, doi: 10.1016/j.cell.2016.05.034, indexed in Pubmed: 27293190.
18. Napirei M, Wulf S, Eulitz D, et al. Comparative characterization of rat deoxyribonuclease 1 (Dnase1) and murine deoxyribonuclease 1-like 3 (Dnase1l3). Biochem J. 2005; 389(Pt 2): 355–364, doi: 10.1042/BJ20042124, indexed in Pubmed: 15796714.
19. Martin M, Leffler J, Blom AM. Annexin A2 and A5 serve as new ligands for C1q on apoptotic cells. J Biol Chem. 2012; 287(40): 33733–33744, doi: 10.1074/jbc.M112.341339, indexed in Pubmed: 22879587.
20. Hakkim A, Fürnrohr BG, Amann K, et al. Impairment of neutrophil extracellular trap degradation is associated with lupus nephritis. Proc Natl Acad Sci U S A. 2010; 107(21): 9813–9818, doi: 10.1073/pnas.0909927107, indexed in Pubmed: 20439745.
21. Jiménez-Alcázar M, Rangaswamy C, Panda R, et al. Host DNases prevent vascular occlusion by neutrophil extracellular traps. Science. 2017; 358(6367): 1202–1206, doi: 10.1126/science.aam8897, indexed in Pubmed: 29191910.
22. Alyami HM, Finoti LS, Teixeira HS, et al. Role of NOD1/NOD2 receptors in Fusobacterium nucleatum mediated NETosis. Microb Pathog. 2019; 131: 53–64, doi: 10.1016/j.micpath.2019.03.036, indexed in Pubmed: 30940608.
23. Huang J, Hong W, Wan M, et al. Molecular mechanisms and therapeutic target of NETosis in diseases. MedComm (2020). 2022; 3(3): e162, doi: 10.1002/mco2.162, indexed in Pubmed: 36000086.
24. Yipp BG, Petri B, Salina D, et al. Infection-induced NETosis is a dynamic process involving neutrophil multitasking in vivo. Nat Med. 2012; 18(9): 1386–1393, doi: 10.1038/nm.2847, indexed in Pubmed: 22922410.
25. Clark SR, Ma AC, Tavener SA, et al. Platelet TLR4 activates neutrophil extracellular traps to ensnare bacteria in septic blood. Nat Med. 2007; 13(4): 463–469, doi: 10.1038/nm1565, indexed in Pubmed: 17384648.
26. Maugeri N, Campana L, Gavina M, et al. Activated platelets present high mobility group box 1 to neutrophils, inducing autophagy and promoting

the extrusion of neutrophil extracellular traps. J Thromb Haemost. 2014; 12(12): 2074–2088, doi: 10.1111/jth.12710, indexed in Pubmed: 25163512.
27. Hamzeh-Cognasse H, Damien P, Chabert A, et al. Platelets and infections — complex interactions with bacteria. Front Immunol. 2015; 6: 82, doi: 10.3389/fimmu.2015.00082, indexed in Pubmed: 25767472.
28. Noubouossie DF, Whelihan MF, Yu YB, et al. In vitro activation of coagulation by human neutrophil DNA and histone proteins but not neutrophil extracellular traps. Blood. 2017; 129(8): 1021–1029, doi: 10.1182/blood-2016-06-722298, indexed in Pubmed: 27919911.
29. Semeraro F, Ammollo CT, Morrissey JH, et al. Extracellular histones promote thrombin generation through platelet-dependent mechanisms: involvement of platelet TLR2 and TLR4. Blood. 2011; 118(7): 1952–1961, doi: 10.1182/blood-2011-03-343061, indexed in Pubmed: 21673343.
30. Fuchs TA, Brill A, Duerschmied D, et al. Extracellular DNA traps promote thrombosis. Proc Natl Acad Sci U S A. 2010; 107(36): 15880–15885, doi: 10.1073/pnas.1005743107, indexed in Pubmed: 20798043.
31. Kambas K, Mitroulis I, Apostolidou E, et al. Autophagy mediates the delivery of thrombogenic tissue factor to neutrophil extracellular traps in human sepsis. PLoS One. 2012; 7(9): e45427, doi: 10.1371/journal.pone.0045427, indexed in Pubmed: 23029002.
32. von Brühl ML, Stark K, Steinhart A, et al. Monocytes, neutrophils, and platelets cooperate to initiate and propagate venous thrombosis in mice in vivo. J Exp Med. 2012; 209(4): 819–835, doi: 10.1084/jem.20112322, indexed in Pubmed: 22451716.
33. Gould TJ, Vu TT, Swystun LL, et al. Neutrophil extracellular traps promote thrombin generation through platelet-dependent and platelet-independent mechanisms. Arterioscler Thromb Vasc Biol. 2014; 34(9): 1977–1984, doi: 10.1161/ATVBAHA.114.304114, indexed in Pubmed: 25012129.
34. Healy LD, Puy C, Itakura A, et al. Colocalization of neutrophils, extracellular DNA and coagulation factors during NETosis: Development and utility of an immunofluorescence-based microscopy platform. J Immunol Methods. 2016; 435: 77–84, doi: 10.1016/j.jim.2016.06.002, indexed in Pubmed: 27286714.
35. Longstaff C, Varjú I, Sótonyi P, et al. Mechanical stability and fibrinolytic resistance of clots containing fibrin, DNA, and histones. J Biol Chem. 2013; 288(10): 6946–6956, doi: 10.1074/jbc.M112.404301, indexed in Pubmed: 23293023.
36. Rangé H, Labreuche J, Louedec L, et al. Periodontal bacteria in human carotid atherothrombosis as a potential trigger for neutrophil activation. Atherosclerosis. 2014; 236(2): 448–455, doi: 10.1016/j.atherosclerosis.2014.07.034, indexed in Pubmed: 25173070.
37. Warnatsch A, Ioannou M, Wang Q, et al. Inflammation. Neutrophil extracellular traps license macrophages for cytokine production in atherosclerosis. Science. 2015; 349(6245): 316–320, doi: 10.1126/science.aaa8064, indexed in Pubmed: 26185250.
38. Megens RTA, Vijayan S, Lievens D, et al. Presence of luminal neutrophil extracellular traps in atherosclerosis. Thromb Haemost. 2012; 107(3): 597–598, doi: 10.1160/TH11-09-0650, indexed in Pubmed: 22318427.
39. Borissoff JI, Joosen IA, Versteylen MO, et al. Elevated levels of circulating DNA and chromatin are independently associated with severe coronary atherosclerosis and a prothrombotic state. Arterioscler Thromb Vasc Biol. 2013; 33(8): 2032–2040, doi: 10.1161/ATVBAHA.113.301627, indexed in Pubmed: 23818485.
40. de Boer OJ, Li X, Teeling P, et al. Neutrophils, neutrophil extracellular traps and interleukin-17 associate with the organisation of thrombi in acute myocardial infarction. Thromb Haemost. 2013; 109(2): 290–297, doi: 10.1160/TH12-06-0425, indexed in Pubmed: 23238559.
41. Ge L, Zhou X, Ji WJ, et al. Neutrophil extracellular traps in ischemia-reperfusion injury-induced myocardial no-reflow: therapeutic potential of DNase-based reperfusion strategy. Am J Physiol Heart Circ Physiol. 2015; 308(5): H500–H509, doi: 10.1152/ajpheart.00381.2014, indexed in Pubmed: 25527775.
42. Savchenko AS, Borissoff JI, Martinod K, et al. VWF-mediated leukocyte recruitment with chromatin decondensation by PAD4 increases myocardial ischemia/reperfusion injury in mice. Blood. 2014; 123(1): 141–148, doi: 10.1182/blood-2013-07-514992, indexed in Pubmed: 24200682.
43. Mangold A, Alias S, Scherz T, et al. Coronary neutrophil extracellular trap burden and deoxyribonuclease activity in ST-elevation acute coronary syndrome are predictors of ST-segment resolution and infarct size. Circ Res. 2015; 116(7): 1182–1192, doi: 10.1161/CIRCRESAHA.116.304944, indexed in Pubmed: 25547404.
44. Stakos DA, Kambas K, Konstantinidis T, et al. Expression of functional tissue factor by neutrophil extracellular traps in culprit artery of acute myocardial infarction. Eur Heart J. 2015; 36(22): 1405–1414, doi: 10.1093/eurheartj/ehv007, indexed in Pubmed: 25660055.
45. Riegger J, Byrne RA, Joner M, et al. Histopathological evaluation of thrombus in patients presenting with stent thrombosis. A multicenter European study: a report of the prevention of late stent thrombosis by an interdisciplinary global European effort consortium. Eur Heart J. 2016; 37(19): 1538–1549, doi: 10.1093/eurheartj/ehv419, indexed in Pubmed: 26761950.
46. Carlin S, de Vries TAC, Budaj A, et al. Dual pathway inhibition for atherosclerotic cardiovascular disease: Recent advances. Kardiol Pol. 2022; 80(12): 1200–1210, doi: 10.33963/KP.a2022.0283, indexed in Pubmed: 36601884.
47. Demyanets S, Stojkovic S, Mauracher LM, et al. Surrogate markers of neutrophil extracellular trap formation are associated with ischemic outcomes and platelet activation after peripheral angioplasty and stenting. J Clin Med. 2020; 9(2): 304, doi: 10.3390/jcm9020304, indexed in Pubmed: 31979010.
48. Tóth E, Beinrohr L, Gubucz I, et al. Fibrin to von Willebrand factor ratio in arterial thrombi is associated with plasma levels of inflammatory biomarkers and local abundance of extracellular DNA. Thromb Res. 2022; 209: 8–15, doi: 10.1016/j.thromres.2021.11.011, indexed in Pubmed: 34844046.
49. Buso G, Faggin E, Bressan A, et al. Biomarkers of neutrophil activation in patients with symptomatic chronic peripheral artery disease predict worse cardiovascular outcome. Biomedicines. 2023; 11(3): 866, doi: 10.3390/biomedicines11030866, indexed in Pubmed: 36979845.
50. Sierpiński R, Franczuk P, Tkaczyszyn M, et al. Burden of multimorbidity in a Polish cohort of ambulatory and hospitalized heart failure patients from 2 large European registry programs: prognostic implications. Pol Arch Intern Med. 2021; 131(11): 16101, doi: 10.20452/pamw.16101, indexed in Pubmed: 34585879.
51. Rywik TM, Doryńska A, Wiśniewska A, et al. Epidemiology and clinical characteristics of hospitalized patients with heart failure with reduced, mildly reduced, and preserved ejection fraction. Pol Arch Intern Med. 2022; 132(5), doi: 10.20452/pamw.16227, indexed in Pubmed: 35253416.
52. Ng LL, Pathik B, Loke IW, et al. Myeloperoxidase and C-reactive protein augment the specificity of B-type natriuretic peptide in community screening for systolic heart failure. Am Heart J. 2006; 152(1): 94–101, doi: 10.1016/j.ahj.2005.09.020, indexed in Pubmed: 16824837.
53. Tang WH, Tong W, Troughton RW, et al. Prognostic value and echocardiographic determinants of plasma myeloperoxidase levels in chronic heart failure. J Am Coll Cardiol. 2007; 49(24): 2364–2370, doi: 10.1016/j.jacc.2007.02.053, indexed in Pubmed: 17572253.
54. La Rocca G, Di Stefano A, Eleuteri E, et al. Oxidative stress induces myeloperoxidase expression in endocardial endothelial cells from patients with chronic heart failure. Basic Res Cardiol. 2009; 104(3): 307–320, doi: 10.1007/s00395-008-0761-9, indexed in Pubmed: 19030913.
55. Bai Bo, Yang W, Fu Y, et al. Seipin knockout mice develop heart failure with preserved ejection fraction. JACC Basic Transl Sci. 2019; 4(8): 924–937, doi: 10.1016/j.jacbts.2019.07.008, indexed in Pubmed: 31909301.
56. Martinod K, Witsch T, Erpenbeck L, et al. Peptidylarginine deiminase 4 promotes age-related organ fibrosis. J Exp Med. 2017; 214(2): 439–458, doi: 10.1084/jem.20160530, indexed in Pubmed: 28031479.
57. Langseth MS, Andersen GØ, Husebye T, et al. Neutrophil extracellular trap components and myocardial recovery in post-ischemic acute heart failure. PLoS One. 2020; 15(10): e0241333, doi: 10.1371/journal.pone.0241333, indexed in Pubmed: 33119664.
58. Bonaventura A, Liberale L, Vecchié A, et al. Update on inflammatory biomarkers and treatments in ischemic stroke. Int J Mol Sci. 2016; 17(12): 1967, doi: 10.3390/ijms17121967, indexed in Pubmed: 27898011.
59. De Meyer SF, Suidan GL, Fuchs TA, et al. Extracellular chromatin is an important mediator of ischemic stroke in mice. Arterioscler Thromb Vasc Biol. 2012; 32(8): 1884–1891, doi: 10.1161/ATVBAHA.112.250993, indexed in Pubmed: 22628431.
60. Laridan E, Denorme F, Desender L, et al. Neutrophil extracellular traps in ischemic stroke thrombi. Ann Neurol. 2017; 82(2): 223–232, doi: 10.1002/ana.24993, indexed in Pubmed: 28696508.

61. Vallés J, Lago A, Santos MT, et al. Neutrophil extracellular traps are increased in patients with acute ischemic stroke: prognostic significance. Thromb Haemost. 2017; 117(10): 1919–1929, doi: 10.1160/TH17-02-0130, indexed in Pubmed: 28837206.
62. Mołek P, Ząbczyk M, Malinowski KP, et al. Markers of NET formation and stroke risk in patients with atrial fibrillation: association with a prothrombotic state. Thromb Res. 2022; 213: 1–7, doi: 10.1016/j.thromres.2022.02.025, indexed in Pubmed: 35276507.
63. Kollikowski AM, Pham M, März AG, et al. Platelet activation and chemokine release are related to local neutrophil-dominant inflammation during hyperacute human stroke. Transl Stroke Res. 2022; 13(3): 364–369, doi: 10.1007/s12975-021-00938-w, indexed in Pubmed: 34455571.
64. Denorme F, Portier I, Rustad JL, et al. Neutrophil extracellular traps regulate ischemic stroke brain injury. J Clin Invest. 2022; 132(10): e154225, doi: 10.1172/JCI154225, indexed in Pubmed: 35358095.
65. Rudolph V, Andrié RP, Rudolph TK, et al. Myeloperoxidase acts as a profibrotic mediator of atrial fibrillation. Nat Med. 2010; 16(4): 470–474, doi: 10.1038/nm.2124, indexed in Pubmed: 20305660.
66. Arroyo AB, de Los Reyes-García AM, Rivera-Caravaca JM, et al. MiR-146a regulates neutrophil extracellular trap formation that predicts adverse cardiovascular events in patients with atrial fibrillation. Arterioscler Thromb Vasc Biol. 2018; 38(4): 892–902, doi: 10.1161/ATVBAHA.117.310597, indexed in Pubmed: 29437577.
67. Ząbczyk M, Natorska J, Matusik PT, et al. Neutrophil-activating peptide 2 as a novel modulator of fibrin clot properties in patients with atrial fibrillation. Transl Stroke Res. 2023: 1–11, doi: 10.1007/s12975-023-01165-1, indexed in Pubmed: 37294500.
68. Natorska J. Diabetes mellitus as a risk factor for aortic stenosis: from new mechanisms to clinical implications. Kardiol Pol. 2021; 79(10): 1060–1067, doi: 10.33963/KP.a2021.0137, indexed in Pubmed: 34643267.
69. Jaworska-Wilczyńska M, Natorska J, Siudut J, et al. Patients scheduled for TAVI tend to form abnormal fibrin clots more resistant to lysis: the impact of age. Kardiol Pol. 2021; 79(7-8): 796–803, doi: 10.33963/KP.a2021.0005, indexed in Pubmed: 34002842.
70. Itabe H, Obama T, Kato R. The dynamics of oxidized LDL during atherogenesis. J Lipids. 2011; 2011: 418313, doi: 10.1155/2011/418313, indexed in Pubmed: 21660303.
71. Awasthi D, Nagarkoti S, Kumar A, et al. Oxidized LDL induced extracellular trap formation in human neutrophils via TLR-PKC-IRAK-MAPK and NADPH-oxidase activation. Free Radic Biol Med. 2016; 93: 190–203, doi: 10.1016/j.freeradbiomed.2016.01.004, indexed in Pubmed: 26774674.
72. Kopytek M, Kolasa-Trela R, Ząbczyk M, et al. NETosis is associated with the severity of aortic stenosis: Links with inflammation. Int J Cardiol. 2019; 286: 121–126, doi: 10.1016/j.ijcard.2019.03.047, indexed in Pubmed: 30952530.
73. Langseth MS, Opstad TB, Bratseth V, et al. Markers of neutrophil extracellular traps are associated with adverse clinical outcome in stable coronary artery disease. Eur J Prev Cardiol. 2018; 25(7): 762–769, doi: 10.1177/2047487318760618, indexed in Pubmed: 29473463.
74. Yadav R, Momin A, Godugu C. DNase based therapeutic approaches for the treatment of NETosis related inflammatory diseases. Int Immunopharmacol. 2023; 124(Pt A): 110846, doi: 10.1016/j.intimp.2023.110846, indexed in Pubmed: 37634446.
75. Meng W, Paunel-Görgülü A, Flohé S, et al. Deoxyribonuclease is a potential counter regulator of aberrant neutrophil extracellular traps formation after major trauma. Mediators Inflamm. 2012; 2012: 149560, doi: 10.1155/2012/149560, indexed in Pubmed: 22315507.
76. Gray RD, McCullagh BN, McCray PB. NETs and CF lung disease: current status and future prospects. Antibiotics (Basel). 2015; 4(1): 62–75, doi: 10.3390/antibiotics4010062, indexed in Pubmed: 27025615.
77. Mohanty T, Fisher J, Bakochi A, et al. Neutrophil extracellular traps in the central nervous system hinder bacterial clearance during pneumococcal meningitis. Nat Commun. 2019; 10(1): 1667, doi: 10.1038/s41467-019-09040-0, indexed in Pubmed: 30971685.
78. Horckmans M, Ring L, Duchene J, et al. Neutrophils orchestrate post-myocardial infarction healing by polarizing macrophages towards a reparative phenotype. Eur Heart J. 2017; 38(3): 187–197, doi: 10.1093/eurheartj/ehw002, indexed in Pubmed: 28158426.
79. Al-Ghoul WM, Kim MS, Fazal N, et al. Evidence for simvastatin anti-inflammatory actions based on quantitative analyses of NETosis and other inflammation/oxidation markers. Results Immunol. 2014; 4: 14–22, doi: 10.1016/j.rinim.2014.03.001, indexed in Pubmed: 24809006.
80. Menegazzo L, Scattolini V, Cappellari R, et al. The antidiabetic drug metformin blunts NETosis in vitro and reduces circulating NETosis biomarkers in vivo. Acta Diabetol. 2018; 55(6): 593–601, doi: 10.1007/s00592-018-1129-8, indexed in Pubmed: 29546579.
81. Ortiz-Muñoz G, Mallavia B, Bins A, et al. Aspirin-triggered 15-epi-lipoxin A4 regulates neutrophil-platelet aggregation and attenuates acute lung injury in mice. Blood. 2014; 124(17): 2625–2634, doi: 10.1182/blood-2014-03-562876, indexed in Pubmed: 25143486.
82. Lapponi MJ, Carestia A, Landoni VI, et al. Regulation of neutrophil extracellular trap formation by anti-inflammatory drugs. J Pharmacol Exp Ther. 2013; 345(3): 430–437, doi: 10.1124/jpet.112.202879, indexed in Pubmed: 23536315.
83. Wan T, Zhao Y, Fan F, et al. Dexamethasone inhibits-induced neutrophil extracellular pathogen-killing mechanism, possibly through toll-like receptor regulation. Front Immunol. 2017; 8: 60, doi: 10.3389/fimmu.2017.00060, indexed in Pubmed: 28232829.
84. Wildhagen KC, García de Frutos P, Reutelingsperger CP, et al. Non-anticoagulant heparin prevents histone-mediated cytotoxicity in vitro and improves survival in sepsis. Blood. 2014; 123(7): 1098–1101, doi: 10.1182/blood-2013-07-514984, indexed in Pubmed: 24264231.
85. Iba T, Hashiguchi N, Nagaoka I, et al. Heparins attenuated histone-mediated cytotoxicity in vitro and improved the survival in a rat model of histone-induced organ dysfunction. Intensive Care Med Exp. 2015; 3(1): 36, doi: 10.1186/s40635-015-0072-z, indexed in Pubmed: 26715580.
86. Manfredi AA, Rovere-Querini P, D'Angelo A, et al. Low molecular weight heparins prevent the induction of autophagy of activated neutrophils and the formation of neutrophil extracellular traps. Pharmacol Res. 2017; 123: 146–156, doi: 10.1016/j.phrs.2016.08.008, indexed in Pubmed: 28161237.
87. Healy LD, Puy C, Fernández JA, et al. Activated protein C inhibits neutrophil extracellular trap formation and activation. J Biol Chem. 2017; 292(21): 8616–8629, doi: 10.1074/jbc.M116.768309, indexed in Pubmed: 28408624.
88. Helms J, Clere-Jehl R, Bianchini E, et al. Thrombomodulin favors leukocyte microvesicle fibrinolytic activity, reduces NETosis and prevents septic shock-induced coagulopathy in rats. Ann Intensive Care. 2017; 7(1): 118, doi: 10.1186/s13613-017-0340-z, indexed in Pubmed: 29222696.
89. Knight JS, Luo W, O'Dell AA, et al. Peptidylarginine deiminase inhibition reduces vascular damage and modulates innate immune responses in murine models of atherosclerosis. Circ Res. 2014; 114(6): 947–956, doi: 10.1161/CIRCRESAHA.114.303312, indexed in Pubmed: 24425713.
90. Gordon RA, Herter JM, Rosetti F, et al. Lupus and proliferative nephritis are PAD4 independent in murine models. JCI Insight. 2017; 2(10): e92926, doi: 10.1172/jci.insight.92926, indexed in Pubmed: 28515361.
91. Zhang S, Zhang Q, Wang F, et al. Hydroxychloroquine inhibiting neutrophil extracellular trap formation alleviates hepatic ischemia/reperfusion injury by blocking TLR9 in mice. Clin Immunol. 2020; 216: 108461, doi: 10.1016/j.clim.2020.108461, indexed in Pubmed: 32437924.
92. Tadie JM, Bae HB, Jiang S, et al. HMGB1 promotes neutrophil extracellular trap formation through interactions with Toll-like receptor 4. Am J Physiol Lung Cell Mol Physiol. 2013; 304(5): L342–L349, doi: 10.1152/ajplung.00151.2012, indexed in Pubmed: 23316068.
93. Wygrecka M, Wujak L, Markart P, et al. Antihistone properties of C1 esterase inhibitor protect against lung injury. Am J Respir Crit Care Med. 2017; 196(2): 186–199, doi: 10.1164/rccm.201604-0712OC, indexed in Pubmed: 28005404.
94. Lefrançais E, Looney MR. Neutralizing extracellular histones in acute respiratory distress syndrome. A new role for an endogenous pathway. Am J Respir Crit Care Med. 2017; 196(2): 122–124, doi: 10.1164/rccm.201701-0095ED, indexed in Pubmed: 28707972.
95. Aldini G, Altomare A, Baron G, et al. N-Acetylcysteine as an antioxidant and disulphide breaking agent: the reasons why. Free Radic Res. 2018; 52(7): 751–762, doi: 10.1080/10715762.2018.1468564, indexed in Pubmed: 29742938.
96. Craver BM, Ramanathan G, Hoang S, et al. N-acetylcysteine inhibits thrombosis in a murine model of myeloproliferative neoplasm. Blood Adv. 2020; 4(2): 312–321, doi: 10.1182/bloodadvances.2019000967, indexed in Pubmed: 31978215.

97. Haute GV, Luft C, Pedrazza L, et al. Octyl gallate decrease lymphocyte activation and regulates neutrophil extracellular traps release. Mol Biol Rep. 2022; 49(2): 1593–1599, doi: 10.1007/s11033-021-06937-2, indexed in Pubmed: 34783987.
98. Bystrzycka W, Manda-Handzlik A, Sieczkowska S, et al. Azithromycin and chloramphenicol diminish neutrophil extracellular traps (NETs) release. Int J Mol Sci. 2017; 18(12): 2666, doi: 10.3390/ijms18122666, indexed in Pubmed: 29292737.
99. Strandberg TE. Benefits and limitations of statin use in primary cardiovascular prevention: recent advances. Pol Arch Intern Med. 2022; 132(5): 16258, doi: 10.20452/pamw.16258, indexed in Pubmed: 35635404.
100. Undas A. Statins in prevention of thromboembolic events: from seminal studies to recent advances. Pol Arch Intern Med. 2022; 132(2): 16208, doi: 10.20452/pamw.16208, indexed in Pubmed: 35226441.

Computed tomographic characteristics of congenital coronary artery fistulas in an adult population

Anna Maria Michałowska[1, 2], Jarosław Skowroński[3], Ilona Michałowska[4], Paweł Tyczyński[3], Ilona Kowalik[5], Rafal Wolny[3], Maksymilian Przemysław Opolski[3], Marcin Demkow[6], Piotr Hoffman[7], Hubert Lazarczyk[1], Mariusz Kruk[6], Cezary Kepka[6], Mariusz Kusmierczyk[8], Adam Witkowski[3], Jerzy Pręgowski[2]

[1]National Institute of Cardiology, Warszawa, Poland
[2]Department of Diagnostic Radiology, The National Institute of Medicine of the Ministry of Interior and Administration, Warszawa, Poland
[3]Department of Interventional Cardiology and Angiology, National Institute of Cardiology, Warszawa, Poland
[4]Department of Radiology, National Institute of Cardiology, Warszawa, Poland
[5]Department of Coronary Artery Disease and Cardiac Rehabilitation, National Institute of Cardiology, Warszawa, Poland
[6]Department of Coronary and Structural Heart Diseases, National Institute of Cardiology, Warszawa, Poland
[7]Congenital Heart Diseases Department, National Institute of Cardiology, Warszawa, Poland
[8]Department of Cardiac Surgery, Medical University of Warsaw, Warszawa, Poland

Editorial
by Madeira et al.

Correspondence to:
Ilona Michałowska, MD, PhD, Department of Radiology, National Institute of Cardiology Alpejska 42, 04–628 Warszawa, Poland,
phone: +48 22 343 41 67,
e-mail: imichalowska@ikard.pl

DOI: 10.33963/v.kp.97829

Received:
July 15, 2023

Accepted:
October 13, 2023

Early publication date:
October 16, 2023

ABSTRACT

Background: Coronary artery fistulas (CAFs) are usually congenital coronary artery anomalies of termination.

Aims: This study aimed to assess the prevalence, anatomic characteristics, and clinical significance of CAFs detected by computed tomography (CT) in an adult population.

Methods: We performed 45 817 CT examinations in 39 066 subjects between 2008 and 2020. The electronic database was manually checked using specific keywords to identify patients with CAFs. The CT characteristics of CAFs were evaluated. CAF was defined as clinically significant if it was the most plausible cause of myocardial infarction, infective endocarditis, heart failure, death during follow-up, hospitalization, or if it required either percutaneous or surgical intervention.

Results: Of 39 066 patients, 56 CAFs were detected in 42 subjects (20 men, 47.6%) with a prevalence of 0.11%. Most CAFs originated from the right coronary artery (RCA) (48.2%) and drained into the pulmonary artery (PA) (58.9%). CAFs terminating in the PA were more frequently multiple (P <0.001) and tortuous (P <0.001) as compared to CAFs without PA drainage. Clinically significant CAFs, identified in 7 of 42 patients, were more common in younger (P = 0.03) and male (P = 0.04) subjects and had larger lumen area and diameter at the site of origin (P = 0.03, P = 0.03, respectively).

Conclusions: In the unselected adult population undergoing coronary CT angiography, the RCA and the PA are the most common sites of origin and termination of CAFs, respectively. CAFs draining into the PA are more often multiple and tortuous. Clinically meaningful CAFs are larger and most frequently detected in younger and male patients.

Key words: computed tomography, congenital coronary artery anomalies, coronary artery anomalies of termination, coronary artery fistulas, non-invasive diagnostic technique

INTRODUCTION

Coronary artery fistulas (CAFs) are rare and usually congenital coronary artery anomalies of termination, involving either vessels (coronary-vascular fistula [CVF]) or cardiac chambers (coronary-cameral fistula [CCF]) [1, 2]. With CAF prevalence varying across prior angiographic studies (0.05%–0.17%), their detection has increased with the use of computed tomography (CT) up to 0.91%

WHAT'S NEW?

Congenital coronary artery fistulas (CAFs) are rare coronary artery anomalies of termination, usually detected incidentally. Although CAFs are mainly asymptomatic, some of them might be of clinical importance and lead to myocardial infarction, heart failure, infective endocarditis, or even death. Clinically significant CAFs are not only more frequently detected in younger and male patients but are also larger, and often with wall calcifications. To our knowledge, the current study represents the largest computed tomographic study on congenital coronary artery fistulas in an adult population to date.

[3–6]. Although the vast majority of CAFs are asymptomatic, clinical manifestation of CAFs depends on their size along with the direction and volume of blood flow [7, 8]. Our study aimed to assess the prevalence, anatomic characteristics, and clinical significance of CAFs diagnosed with CT in adults.

METHODS

The study was approved by the Local Ethics Committee and complied with the Declaration of Helsinki. Between February 2008 and November 2020, there were 45 817 coronary CT examinations performed in 39 066 subjects in a single high-volume cardiac center. To select patients with CAF, the electronic database of all coronary CT reports was manually screened with the use of specific keywords. Based on that electronic database, all demographic and clinical data were collected. Information about clinical conditions during follow-up time was obtained based on a telephone survey (February–April 2021). Heart failure (HF) with at least mildly reduced ejection fraction was diagnosed based on the coexistence of classical signs and symptoms of HF together with impaired left ventricular ejection fraction (LVEF) <50% [9, 10]. The probability of pulmonary hypertension (PH) was estimated based on the systolic pulmonary arterial pressure (sPAP) [11]. To assess sPAP, the peak tricuspid regurgitation velocity (TRV) and the TRV-derived regurgitation pressure gradient were measured, after excluding pulmonary stenosis [11]. Exclusion criteria were as follows: (1) poor diagnostic quality of coronary CT; (2) truncated part of fistula on CT examination; (3) known or suspected acquired etiology of fistula; (4) coronary CT performed after surgical or percutaneous treatment of CAF.

In the course of the study, 3 generations of dual-source CT scanners were used: from 2008 to May 2011 (6414 CT examinations [14%]) – the Somatom Definition; from June 2011 to May 2015 (13 745 CT examinations [30%]) – the Somatom Definition Flash; and from June 2015 to November 2020 (25 658 CT examinations [56%]) – the Somatom Force (all Siemens Healthcare, Forchheim, Germany). The following CT acquisition parameters were used: slice collimation of 64 × 0.6 mm (Definition), 128 × 0.6 mm (Flash), and 192 × 0.6 mm (Force); gantry rotation time of 330 ms (Definition), 280 ms (Flash), and 250 ms (Force); tube voltage of 80–140 kV (Definition, Flash), and 70–120 kV (Force); tube current of 300–550 mAs. Prospective (including high-pitch flash acquisition) or retrospective ECG-gated CT angiography was used. The study protocol was selected by the supervising physician depending on the heart rhythm and clinical indications. A dose modulation technique was used to limit the radiation exposure. Data were routinely reconstructed in the mid- or end-systolic and diastolic phases (35% to 45% and 65% to 75% of the RR intervals). Unless contraindicated, nitroglycerin in a dose of 0.8 mg was administered sublingually immediately before the examination. To achieve a heart rate of 60–75/min (depending on the scanner generation) metoprolol in fractionated doses of 2.5 mg was injected intravenously. After administration of a 10 ml bolus of contrast, the start time of the study acquisition was calculated. The contrast agent (Iomeron 400; Bracco Altana Pharma, Ultravist 370; Bayer Pharma AG; Omnipaque 350 GE) was injected intravenously in two phases — 45–60 ml of contrast and 30 ml of the contrast and saline (30/70%) mixture at the rate of 4.5–6 ml/s (depending on the generation of the CT scanner).

The analysis of the CT scans was performed on a dedicated workstation by a single experienced observer. CAF was defined as an anomalous direct connection between ≥1 coronary artery and a cardiac chamber or a vessel [1]. All CAFs were evaluated based on their site of origin (≥1 main coronary artery: the right coronary artery [RCA], left anterior descending [LAD], or circumflex artery [Cx]) and termination (Figures 1 and 2), as well as morphology: (1) number of CAFs; (2) complexity; (3) size; (4) tortuosity; (5) intramuscular course; and (6) presence of aneurysms, calcifications, vegetations, thrombus in CAF or dissection of CAF (Figure 3). The following definitions of CAF morphologies have been adopted: (1) coronary-cameral fistula — a CAF draining into ≥1 cardiac chamber (right atrium [RA], left atrium, right ventricle [RV], LV); (2) coronary-vascular fistula — a CAF terminating in ≥1 vascular structure (pulmonary trunk [PA], right pulmonary artery, left pulmonary artery, coronary sinus [CS], superior vena cava, inferior vena cava, cardiac veins) [2]; (3) simple CAF — a CAF with 1 origin, consisting of 1 vessel and terminating in 1 structure [6]; (4) complex CAF — a CAF with >1 origin and/or consisting of >1 vessel, and/or terminating in >1 structure [6]; (5) bilateral CAF — a CAF originating from both the RCA and left coronary artery with only 1 termination site [4]; (6) tortuous CAF — presence of ≥3 consecutive bends, i.e., changes in the direction of the vessel by ≥45° in relation to the main stem [12]. In addition, all CAFs were categorized according to their size: small CAF — maximal lumen diameter (LD) of the CAF <2 mm, medium CAF — 2–10 mm, and large CAF — >10 mm [13].

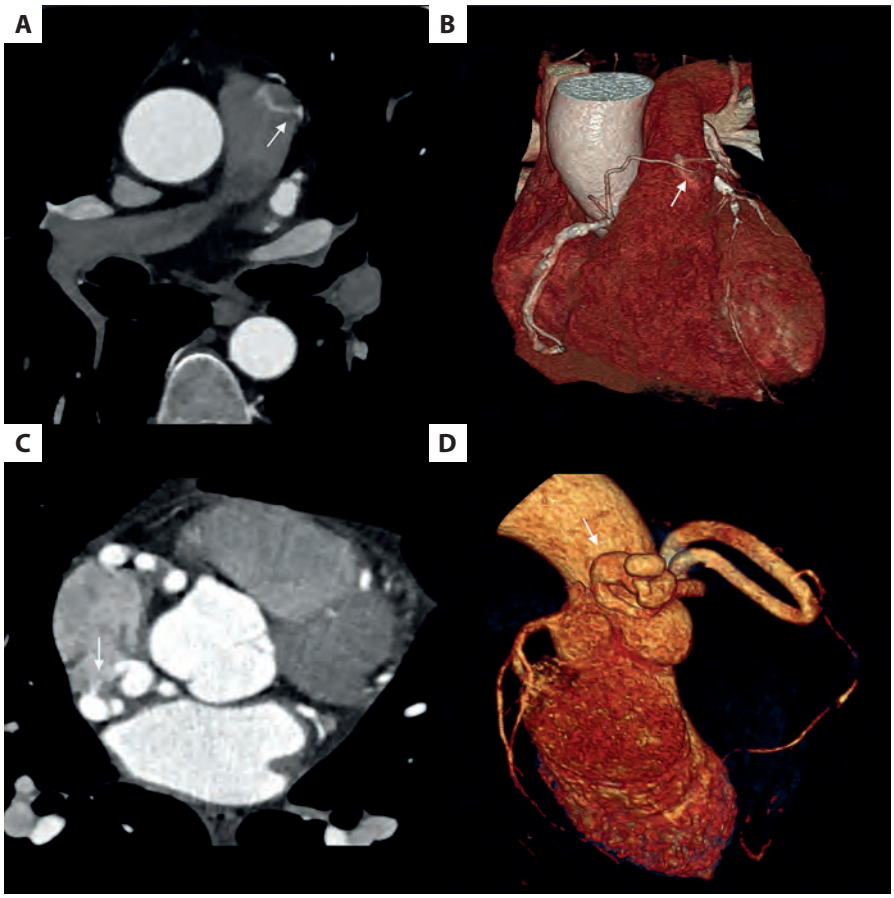


Figure 1. Coronary computed tomography (CT). **A.** Multiplanar reconstruction (MPR). **B.** volume-rendered reconstruction, the coronary artery fistula (CAF) between the right coronary artery (RCA) and the pulmonary artery (white arrows). **C.** MPR. **D.** volume-rendered reconstruction, CAF between the RCA and the superior vena cava (white arrows)

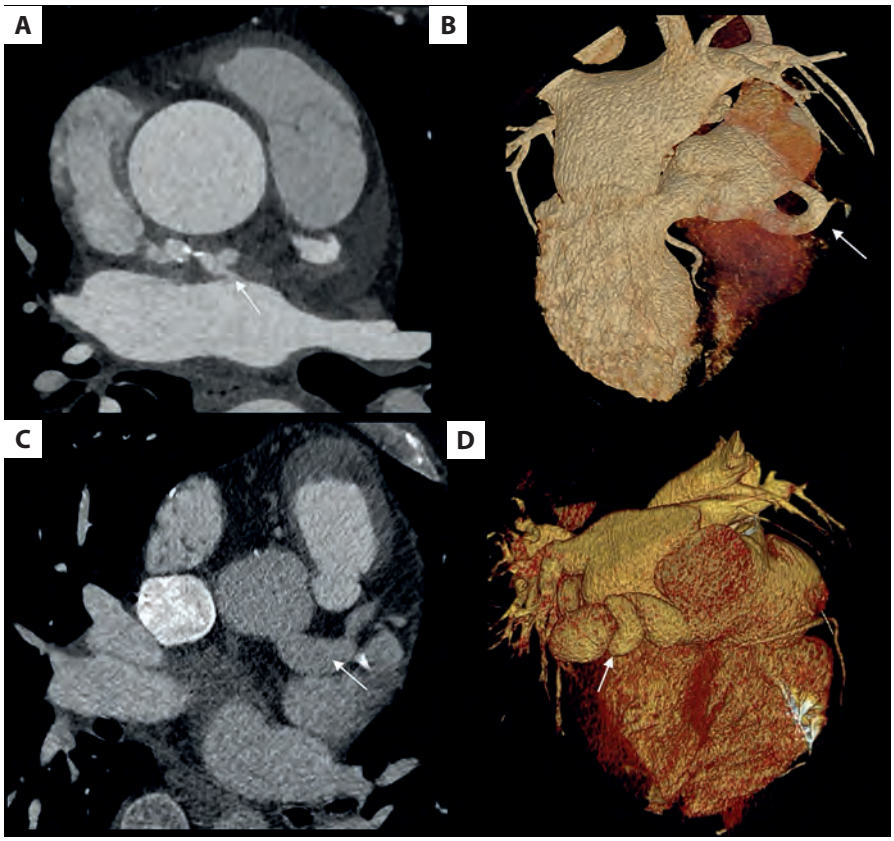


Figure 2. Coronary CT. **A.** MPR. **B.** Volume-rendered reconstruction, CAF between the RCA and the left atrium (white arrows). **C.** MPR. **D.** Volume-rendered reconstruction, CAF between the circumflex artery and the coronary sinus (white arrows)

Abbreviation: see Figure 1

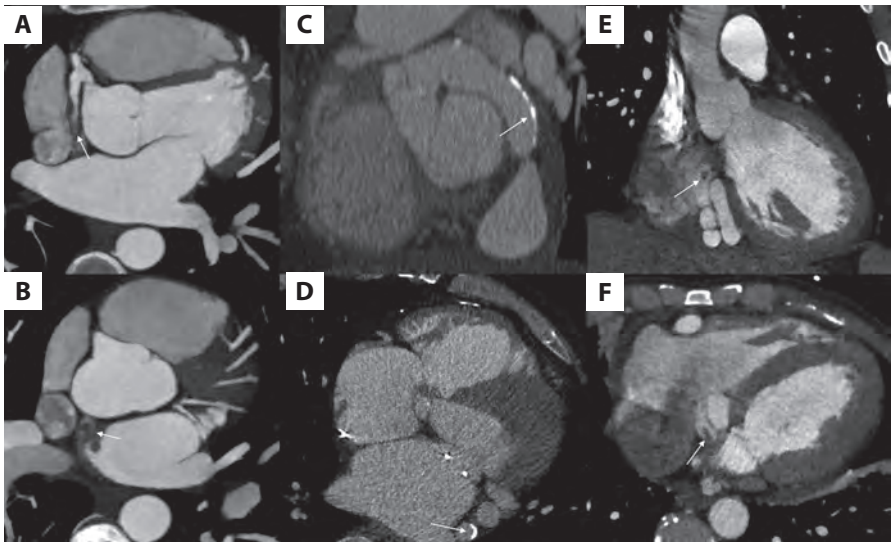


Figure 3. Coronary CT, MPR. **A.** Cross-sectional view, CAF between the RCA and the LA (arrow). **B.** Distal segment of CAF with thrombus (arrow). **C.** Oblique cross-section, calcification within CAF (arrow). **D.** Cross-sectional view, calcification within CAF (arrow). **E–F.** Vegetation at the site of termination of CAF draining into the right atrium (arrow), frontal view (**E**), cross-sectional view (**F**)

Abbreviation: see Figure 1

Within every CAF, the following morphological features were described: (1) aneurysm — segmental dilatation of the artery ≥50% of the reference vessel diameter [13]; (2) calcification — presence of regions with >130 Hounsfield units attenuation in the fistula wall [14]; (3) vegetation — hypodense, homogeneous, irregular mass in the lumen of the fistula [15]; (4) thrombus – low-attenuated structure within the lumen of the fistula [16]; (5) dissection — linear, hypodense structure within the vessel lumen, separating the false and true canals [17]. To distinguish between vegetation and a thrombus, clinical data were used — in patients with clinical signs of infective endocarditis (IE), vegetation was diagnosed.

The minimal and maximal LD and lumen area (LuA) of CAFs were measured at the site of origin and termination, as well as at the narrowest and widest segments of the CAFs. In addition, the end-diastolic RV and LV dimensions were measured in a four-chamber CT view, and the ratio of RV/LV dimensions was calculated to identify RV enlargement as an indicator of its volume overload (RV/LV ≥1.0) [18].

CAF was defined as clinically significant if it was the most plausible cause of myocardial infarction, IE, HF, death within the follow-up time, hospitalization, or if it required either percutaneous or surgical intervention.

The presence and severity of atherosclerotic lesions in coronary arteries were assessed according to the Coronary Artery Disease — Reporting and Data System (CAD-RADS), which ranges from CAD-RADS 0 (no atherosclerosis) to CAD-RADS 5 (total occlusion in at least one vessel) [19].

Statistical analysis

Normality was assessed with the Shapiro-Wilk test and visual evaluation of histogram skewness. Continuous variables with normal distribution were presented as means (standard deviations, SD) and non-normally distributed variables as medians with interquartile ranges (IQR). The significance of differences between the mean values of the three groups was verified by one-way analysis of variance and Tukey's post-hoc test, applied when the null hypothesis of the general test was rejected. The significance of differences between the mean values of the 2 groups was analyzed using Student's t-test. To assess the conformity of skewed distributions of continuous variables for 3 or 2 groups, non-parametric analysis of variance Kruskal-Wallis, non-parametric multiple comparison tests, and Mann-Whitney tests were used. To assess the difference within the group, the Wilcoxon rank-sum test was used.

The results of categorical variables were shown as counts and relative frequencies (percentages). The χ^2 test of independence or Fisher's exact test were used for binary comparison. The χ^2 test for equal proportion was used to verify the homogeneity of proportion. The Cochran-Mantel-Haenszel modified ridit score was applied to the analysis of categorical variables, with >2 categories (whereby nominal variables were compared using General Association *P*-value and ordinal variables were compared using row mean score *P*-value).

All *P*-values were two-tailed and a *P*-value of <0.05 was considered statistically significant. Statistical analysis was performed using SAS, version 9.4. (SAS Institute Inc, Cary, NC, US).

RESULTS

Among 39 066 patients, CAFs were diagnosed in 52 subjects. After exclusion of 10 patients due to the potentially acquired nature of CAFs (n = 7) and non-diagnostic evaluation of the site of termination of CAFs (n = 3), the final study cohort included 42 patients (20 men, 47.6%) with 56 CAFs. The prevalence of CAFs was 0.11% (42/39 066). In the majority of subjects (73.8%), CAFs were incidental findings. Table 1 displays the baseline characteristics, while Table 2 shows CT morphology of CAFs. Six of 42 (14.3%) patients required surgical or percutaneous closure of CAFs, whereas the remaining patients were treated conservatively. During the median 22.5-month (4.75–103.5) follow-up, 7 (16.7%) patients died.

Table 1. Baseline characteristics

	CAF (n = 42)
Age[a], years	57.5 (13.8)
Sex, male	20 (47.6)
BMI, kg/m^2	27.8 (7.2)
Hypertension	23 (54.8)
Diabetes mellitus	4 (9.5)
Dyslipidemia	13 (31.0)
Smoking history	5 (11.9)
Presence of atherosclerosis:	
CAD-RADS <3	30 (71.4)
CAD-RADS 3 (50%–69%)	6 (14.3)
CAD-RADS 4/5 (≥70%)	6 (14.3)
Concomitant congenital heart diseases	2 (4.8)
Previous history of AF (acute/chronic)	10 (23.8)
Supraventricular arrhythmias	5 (11.9)
Ventricular arrhythmias	2 (4.8)
Heart failure	12 (28.6)
Previous history of myocardial infarction	4 (9.5)
Pulmonary hypertension	5 (11.9)
Previous history of IE	3 (7.1)
Previous history of sudden cardiac arrest	1 (2.4)
Previous history of PCI	4 (9.5)
Death during follow-up	7 (16.7)
Follow-up, months	22.5 (4.75–103.5)

Values are presented as n (%), means (SD), or medians (IQR)

[a]Age of the patients at which the CT examination was performed

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CAF, coronary artery fistula; CAD-RADS, Coronary Artery Disease – Reporting and Data System; CT, computed tomography; IE, infective endocarditis; IQR, interquartile range; n, number of patients; PCI, percutaneous coronary intervention; SD, standard deviation

Table 2. CAF morphology evaluated with computed tomography

CAFs		n (%)
Fistula origin	RCA	27 (48.2)
	LAD	19 (33.9)
	Cx	10 (17.9)
Fistula drainage site		
	PA	33 (58.9)
	CS	6 (10.7)
	LA	5 (8.9)
	RPA	3 (5.4)
	SVC	3 (5.4)
	LPA	2 (3.6)
	RA	2 (3.6)
	IVC	1 (1.8)
	MCV	1 (1.8)
Number of CAFs per patient	1	30 (71.4)
	>1	12 (28.6)
Size of CAF	<2 mm	1 (1.8)
	2–10 mm	45 (80.4)
	>10 mm	10 (17.9)
Type of CAF	CVF	48 (85.7)
	CCF	8 (14.3)
Complexity of CAF	Simple	29 (51.8)
	Complex	27 (48.2)
Tortuosity of CAF		44 (78.6)
Intramuscular course		0
Presence within CAF	Aneurysmal formation	9 (16.1)
	Calcification	5 (8.9)
	Vegetation	2 (3.6)
	Thrombus	1 (1.8)
	Dissection	0

Values are presented as n (%)

Abbreviation: CCF, coronary-cameral fistula; CS, coronary sinus; CVF, coronary-vascular fistula; Cx, circumflex artery; IVC, inferior vena cava; LA, left atrium; LAD, left anterior descending; LPA, left pulmonary artery; MCV, middle cardiac vein; n, number; PA, pulmonary artery; RA, right atrium; RCA, right coronary artery; RPA, right pulmonary artery; SVC, superior vena cava; other — see Figure 1

The most common origin of CAFs was the RCA (48.2%), followed by the LAD (33.9%) and the Cx (17.9%) (Table 2). The site of origin was neither related to demographic characteristics, clinical presentation, nor CAF morphology (Table 3 and Supplementary material, *Table S1*). Additionally, there was no significant relationship between the site of origin and the size of the CAF. The pulmonary artery (PA) was the predominant drainage site of CAFs (58.9%). Furthermore, IE was more often diagnosed in patients with CAFs draining into the right-side cardiac structures compared with CAFs with drainage in the left-side cardiac structures as well as with CAFs terminating in the pulmonary arteries ($P = 0.006$). CAFs terminating in the PA as well as into the right and left pulmonary arteries were more often multiple (63.2% vs. 11.1%; $P < 0.001$), complex (71.1% vs. 0%; $P < 0.001$), tortuous (92.1% vs. 50.0%; $P < 0.001$), and bilateral (57.9% vs. 0%; $P < 0.001$) as compared to CAFs draining into either the left-side or right-side cardiac structures. CAFs draining into the right structures and vasculatures of the heart were significantly larger at the site of origin (average lumen diameter [LD_{avg}]: 6.8 vs. 2.4; $P = 0.008$), site of termination (LD_{avg} 18.7 vs. 3.94; $P < 0.01$) as well as at their narrowest segment (LD_{avg} 4.65 vs. 1.55; $P = 0.004$) in comparison to CAFs terminating in the pulmonary vasculature or the left-side structures of the heart (Table 3).

Supplementary material, *Table S2* displays the comparison between CAFs ≤10 mm and >10 mm. Large CAFs were not only more often found in younger patients ($P = 0.03$), subjects with PH ($P = 0.03$) and/or IE ($P = 0.004$), but also were more frequently treated by surgical or percutaneous closure ($P = 0.04$). Furthermore, CAFs >10 mm were more often calcified and usually drained into the CS ($P < 0.001$ for both). The site of origin and termination of CAFs ≤10 mm and >10 mm are shown in Figure 4.

Atherosclerosis was detected in 22 of 42 (52.4%) subjects with CAFs, in whom 6 (27.3%) atherosclerotic lesions were classified as CAD-RADS 1, 4 (18.2%) as CAD-RADS 2, 6 (27.3%) as CAD-RADS 3, 5 (22.7%) as CAD-RADS 4, and 1 (4.5%) as CAD-RADS 5. Percutaneous coronary intervention (PCI) was performed in 4 subjects (18.2%). The comparison between clinical manifestation of patients with versus without atherosclerosis is shown in Supplementary material, *Table S3*, while *Figure S1* depicts the presence of atherosclerotic lesions based on the sites of origin and termination of CAFs.

Clinically significant CAFs were diagnosed in 7 of 42 patients (16.7%), of whom 3 subjects died (42.9%). Four of 7 of these patients (57.1%) had HF resulting from CAFs while in 3 patients (42.9%) IE was confirmed. Of all patients with clinically significant CAFs, 3 patients required percutaneous

Table 3. Tomographic characteristics of coronary artery fistulas based on their site of origin and termination

Tomographic evaluation	CAFs originating from RCA (n_F = 27)	CAFs originating from LAD (n_F = 19)	CAFs originating from Cx (n_F = 10)	*P*-value	CAFs terminating in the right structures of the heart (n_F = 13)	CAFs terminating in the pulmonary trunk and pulmonary arteries (n_F = 38)	CAFs terminating in the left structures of the heart (n_F = 5)	*P*-value
	(1)	(2)	(3)		(4)	(5)	(6)	
Number of CAFs, >1	13 (48.1)	10 (52.6)	3 (30.0)	0.500	1 (7.7)	24 (63.2)	1 (20.0)	0.001
Large CAFs, >10 mm	6 (22.2)	1 (5.3)	3 (30.0)	0.19	8 (61.5)	1 (2.6)	1 (20.0)	<0.001
Complex CAF	13 (48.1)	12 (63.2)	2 (20.0)	0.09	0	27 (71.1)	0	<0.001
Tortuous CAF	21 (77.8)	16 (84.2)	7 (70.0)	0.67	7 (53.8)	35 (92.1)	2 (40.0)	0.001
Aneurysm formation	5 (18.5)	3 (15.8)	1 (10.0)	0.82	1 (7.7)	7 (18.4)	1 (20.0)	0.65
Vascular calcification within CAF wall	2 (7.4)	1 (5.3)	2 (20.0)	0.39	3 (23.1)	1 (2.6)	1 (20.0)	0.06
Presence of thrombus in CAF	1 (3.7)	0	0	0.58	0	0	1 (20.0)	0.09
CAF origin site								
LuA, mm^2	7.2 (4.1–14.0)	3.6 (2.4–6.2)	7.6 (3.8–31.0)	0.08	36.0 (5.5–95.0)	4.4 (3.0–7.8)	7.5 (2.1–29.0)	0.02 4 vs. 5: 0.02
LD_{avg}, mm	3.05 (2.2–4.3)	2.05 (1.8–2.8)	3.3 (2.0–6.3)	0.08	6.8 (2.3–11.0)	2.4 (1.9–3.2)	3.15 (1.5–6.5)	0.02 4 vs. 5: 0.02
CAF drainage site								
LuA, mm^2	4.4 (3.2–12.9)	3.5 (2.7–7.2)	4.7 (1.3–18.7)	0.51	18.7 (4.4–38.0)	3.7 (2.8–6.7)	5.7 (1.3–8.5)	0.04 4 vs. 5: 0.03
LD_{avg}, mm	2.35 (2.1–4.1)	2.15 (1.75–3.1)	2.55 (1.3–4.9)	0.40	4.9 (2.3–7.5)	2.2 (1.9–3.1)	2.5 (1.3–3.3)	0.04 4 vs. 5: 0.03
Widest segment of CAF								
LuA, mm^2	10.4 (5.7–63.0)	12.0 (5.2–19.0)	8.8 (3.8–124.0)	0.79	124.0 (7.8–213.0)	10.1 (5.4–14.5)	7.8 (5.7–47.0)	0.13
LD_{avg}, mm	3.65 (2.65–8.95)	3.6 (2.6–4.8)	3.35 (2.15–13.15)	0.74	13.15 (3.2–16.4)	3.5 (2.6–4.3)	3.25 (2.5–8.0)	0.11
Narrowest segment of CAF								
LuA, mm^2	2.6 (1.7–5.5)	1.8 (1.5–2.8)	2.4 (1.3–11.1)	0.15	15.0 (3.0–36.0)	2.2 (1.4–2.2)	2.1 (1.3–5.5)	0.008 4 vs. 5: 0.006
LD_{avg}, mm	1.85 (1.45–2.6)	1.55 (1.2–2.0)	1.45 (1.3–3.75)	0.23	4.65 (2.0–6.8)	1.58 (1.3–1.8)	1.55 (1.3–2.6)	0.01 4 vs. 5: 0.01
RV, cm	4.1 (0.7)	4.1 (0.7)	4.5 (0.9)	0.31	4.4 (0.8)	4.1 (0.7)	4.1 (0.8)	0.33
LV, cm	4.6 (0.9)	4.7 (1.0)	4.5 (0.9)	0.92	4.8 (0.8)	4.6 (1.0)	4.3 (1.1)	0.62
RV/LV	0.9 (0.2)	0.9 (0.2)	1.0 (0.2)	0.20	0.9 (0.1)	0.9 (0.2)	1.0 (0.3)	0.51

Values are presented as n (%), means (SD), or medians (IQR)

Abbreviations: avg, average; LuA, lumen area; LD, lumen diameter; LV, left ventricle, transverse diameter in the 4-chamber view; n_F, number of fistulas; RV, right ventricle, transverse diameter in the 4-chamber view; RV/LV, right-to-left ventricular diameter ratio; SD, standard deviation; other — see Figures 1 and 2

closure of CAFs, 2 subjects with coexisting structural heart diseases underwent surgical repair of CAFs, and in 2 cases, CAFs were treated conservatively due to active IE (n = 1) or the presence of a thrombus within CAF (n = 1). The comparison between clinically significant and clinically insignificant CAFs is shown in Table 4. The presence of clinically significant CAFs was more common in younger (P = 0.03) and male (P = 0.04) patients and was associated with PH (P = 0.03). Also, the CT analysis revealed larger lumen area and diameter at the site of origin (P = 0.03, P = 0.03, respectively) and higher wall calcifications (P = 0.003) in clinically meaningful CAFs.

In 15 patients (35.7%) stress myocardial perfusion imaging was performed – predominantly in subjects with moderate CAFs (12/15). Eight patients underwent magnetic resonance imaging, 6 single-photon emission computed tomography, and 1 both magnetic resonance imaging and single-photon emission computed tomography. In all subjects, no significant myocardial perfusion defects were detected.

DISCUSSION

In this study, we evaluated the prevalence, clinical significance, and anatomic characteristics of CAFs detected on coronary CT in the unselected adult population. Our main findings are as follows: (1) the most common site of origin and termination of CAFs are the RCA and PA, respectively; (2) large CAFs are usually single and calcified, and most commonly drain into the CS, whereas CAFs terminating in the PA are frequently multiple, tortuous, and complex; (3) clinically significant CAFs are usually large, mainly terminate in the RA or CS and are most frequently found in younger and male patients.

The prevalence of CAFs differs based on the study group, diagnostic methods, and applied definitions. To our knowledge, our report represents the largest computed

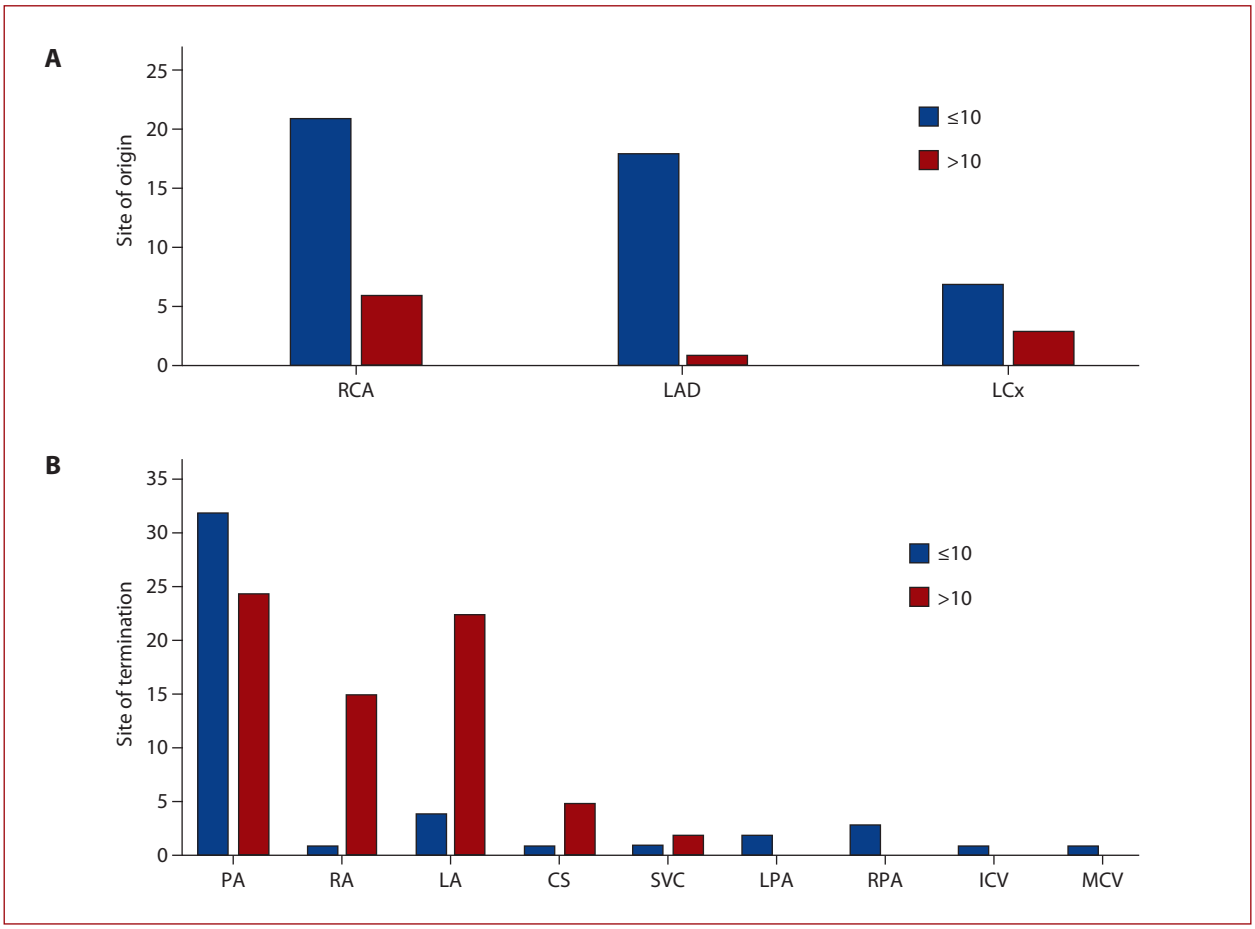


Figure 4. Site of origin (**A**) and termination (**B**) of CAFs ≤10 mm and >10 mm

Abbreviations: CS, coronary sinus; Cx, circumflex artery; IVC, inferior vena cava; LAD, left anterior descending; LA, left atrium; LPA, left pulmonary artery; MCV, middle cardiac vein; PA, pulmonary artery; RA, right atrium; RCA, right coronary artery; RPA, right pulmonary artery; SVC, superior vena cava

tomographic study to date in adults, and the CAF prevalence of 0.11% is in line with the previous tomographic and angiographic studies [3–6, 19–21].

CAFs usually drain into the low-pressure right-sided structures of the heart and less frequently into those on the left. Importantly, there are contradictory data regarding the most common site of origin (RCA or LAD) and termination (RV or PA) of CAFs [1, 4–5, 7, 21–23]. In our study, the most frequent site of origin of CAFs was the RCA, whereas the most common site of termination was the PA. Moreover, most of our CAFs including clinically significant CAFs were single, which corroborates the earlier report [4].

The fistula drainage site rather than the site of origin has more clinical significance [1, 24]. Indeed, PH and IE were more often observed in patients with CAFs terminating in right-sided structures of the heart in our cohort replicating previous reports [2]. Valente et al. in their study noted that most CAF patients with clinically significant complications, such as myocardial infarction, HF, or thrombus formation, had CAFs draining into the CS [25], which was similar to our findings. Of all CAFs terminating in the CS in this study, 50% were clinically significant, and the CS was more often the drainage site of large CAFs.

The size of the fistula has clinical significance — small CAFs are usually incidental findings due to their asymptomatic clinical course, whilst large CAFs often cause symptoms and are related to progressive enlargement of the native vessel [1, 8, 26–28]. In our study, the predominance of medium-sized CAFs was observed. The most common drainage site of CAFs ≤10 mm was the PA, while CAFs >10 mm mostly drained into the CS, which is in line with earlier echocardiographic studies [28]. Large CAFs are not only clinically significant but also more common in younger patients. In addition, CAFs >10 mm were more often calcified and usually drained into the CS.

Clinical manifestations in CAF patients may be related to the presence of atherosclerosis and/or valvular heart disease [8, 29]. In contrast, clinical symptoms of myocardial ischemia in patients with CAFs and without any or with non-significant atherosclerotic lesions might be explained by decreased myocardial perfusion resulting from the coronary steal phenomenon [24]. Interestingly, 4 of 42 patients (9.5%) in our cohort had myocardial infarction despite not having coronary atherosclerosis. Another potential but rare cause of acute myocardial infarction or ventricular arrhythmia in CAF patients is thrombus

Table 4. Comparison between clinically significant and clinically insignificant CAFs

	Clinically insignificant CAFs (n_P = 35)	Clinically significant CAFs (n_P = 7)	*P*-value
Age[a], years	59.5 (13.0)	47.1 (13.8)	**0.03**
Sex, male	14 (40.0)	6 (85.7)	**0.04**
BMI, kg/m^2	29.1 (7.5)	24.1 (4.2)	0.1
Hypertension	18 (51.4)	5 (71.4)	0.43
Diabetes mellitus	4 (11.4)	0	>0.99
Dyslipidemia	13 (37.1)	0	0.08
Smoking history	3 (8.6)	2 (28.6)	0.19
Presence of atherosclerosis:			
CAD-RADS <3	23 (65.7)	7 (100)	0.19
CAD-RADS 3 (50%–69%)	6 (17.1)	0	
CAD-RADS 4/5 (≥70%)	6 (17.1)	0	
Concomitant congenital heart diseases	2 (5.7)	0	>0.99
Clinical presentation			
Previous history of AF (acute/chronic)	7 (20.0)	3 (42.9)	0.33
Supraventricular arrhythmia	4 (11.4)	1 (14.3)	>0.99
Ventricular arrhythmia	2 (5.7)	0	>0.99
Pulmonary hypertension	2 (5.7)	3 (42.9)	**0.03**
Previous history of sudden cardiac arrest	0	1 (14.3)	0.17
Previous history of PCI	4 (11.4)	0	>0.99
Tomographic evaluation	(n_F = 46)	(n_F = 10)	
Large CAFs, >10 mm	5 (10.9)	5 (50.0)	**0.03**
Type of CAF, CVFs	43 (93.5)	5 (50.0)	**0.003**
Complex CAF	24 (52.2)	3 (30.0)	0.3
Bilateral CAF	20 (43.5)	2 (20.0)	0.29
Tortuous CAF	37 (80.4)	7 (70.0)	0.43
Aneurysm formation	7 (15.2)	2 (20.0)	0.65
Vascular calcification within CAF	1 (2.2)	4 (40.0)	**0.003**
Presence of visible thrombus	0	1 (10.0)	0.18
CAF origin site			
LuA, mm^2	4.92 (2.5–9.1)	18.25 (4.4–96.0)	**0.03**
LD_{avg}, mm	2.4 (1.9–3.4)	4.8 (2.4–11.0)	**0.03**
CAF drainage site			
LuA, mm^2	3.9 (2.8–8.4)	16.7 (2.8–38.0)	0.12
LD_{avg}, mm	2.3 (2.0–3.0)	4.6 (1.9–7.2)	0.11
Widest segment of CAF			
LuA, mm^2	8.9 (4.2–14.5)	75.0 (25.0–213.0)	**0.003**
$LD_{avg,}$ mm	3.4 (2.3–4.3)	10.2 (5.9–16.4)	**0.002**
Narrowest segment of CAF			
LuA, mm^2	2.3 (1.4–3.2)	4.25 (1.8–34.0)	0.06
LD_{avg}, mm	1.6 (1.3–2.0)	2.3 (1.7–6.5)	**0.02**
RV, cm	4.01 (0.70)	4.73 (0.73)	**0.005**
LV, cm	4.51 (0.96)	5.16 (0.47)	**0.004**
RV/LV	0.91 (0.17)	0.92 (0.14)	0.88

Values are presented as n (%), means (SD,) or medians (IQR)
[a]Age of the patients at which the CT examination was performed
Abbreviations: avg, average; LuA, lumen area; LD, lumen diameter; LV, left ventricle, transverse diameter in the 4-chamber view; n_F, number of fistulas; n_P, number of patients; RV, right ventricle, transverse diameter in the 4-chamber view; RV/LV, right-to-left ventricle diameter ratio; other — see Table 1

formation within CAF, which, in our study, was observed in 1 patient [30].

Despite the mostly asymptomatic clinical course of CAFs, the probability of clinical manifestations increases with age due to the development of atherosclerosis in coronary arteries [7, 8, 24]. Canga et al. suggested that CAFs >1.5 mm, originating from the proximal segments of coronary arteries might increase the progression of coronary atherosclerosis and further the risk of myocardial infarction [22]. However, there was no association between the site of origin and termination and the presence as well as the severity of atherosclerotic lesions in our study. Significant coronary artery disease (≥50%) was more often seen in patients with smaller CAFs.

Clinically relevant complications of CAFs, such as IE, HF, myocardial infarction, or rupture of aneurysm, might be the first clinical manifestation of CAFs and may even lead to sudden cardiac death [1, 2, 7, 8, 26]. According to a 10-year analysis of available literature conducted by Said et al., clinically significant complications of CAF more often

occur in men [2]. This is in line with our results, whereby clinically relevant CAFs were more frequently found in younger male subjects.

Coronary artery aneurysms associated with fistula develop in up to 26% of cases of congenital CAFs detected by coronary angiography [1, 4, 29]. While tomographic analysis of CAFs conducted by Ouchi et al. reported the prevalence of aneurysms at 48.4%, in our study, aneurysms associated with CAFs were found in 16.1% of cases [6]. Although rupture of CAF aneurysms is extremely rare, it is associated with very high mortality [27]. In the present study, all CAFs with aneurysms were tortuous.

The presence of CAFs predisposes to IE, which is seen in up to 12% of patients with CAFs and might be the cause of death [8, 26]. While IE could be the first clinical manifestation of CAFs, the development of IE is seen in both coronary-cameral and coronary-vascular fistulas [26]. In our study, IE was present in 7.1% of patients and was more often seen in CAFs draining into the right-side structures of the heart as well as in large CAFs.

Due to the most common asymptomatic clinical course, the majority of CAFs do not require invasive treatment [31]. In our study patients with clinically relevant CAFs and with large CAFs required surgical or interventional treatment. According to the American College of Cardiology/American Heart Association (ACC/AHA) guidelines patients with symptomatic small and medium CAFs should undergo CAF closure, as well as patients with large CAFs regardless of clinical manifestation [32]. Percutaneous interventions are less invasive and usually better tolerated [33]. Surgical treatment is preferable in patients with CAFs and structural heart diseases necessitating surgical repair and in subjects with large CAFs, CAFs with high blood flow as well as in cases of complex CAFs or the presence of large aneurysms [34]. Albeit, in some cases, the closure of CAFs might be challenging and require a multi-disciplinary approach [35, 36].

This research did not receive any specific grant from funding agencies from the public, commercial, or not-for-profit sectors.

In conclusion, although CAFs are usually asymptomatic incidental findings on CT scans, clinically significant CAFs are larger and more frequently detected in younger and male patients.

This study has several limitations. First, it was a single-center and retrospective report of patients referred to tertiary sites. Second, three generations of dual-source CT with similar spatial resolution but different time resolution were used during the study. Finally, CT examinations were selected manually from the electronic database based on the predefined keywords.

Supplementary material

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

Article information

Conflict of interest: None declared.

Funding: None.

REFERENCES

1. Gowda RM, Vasavada BC, Khan IA. Coronary artery fistulas: clinical and therapeutic considerations. Int J Cardiol. 2006; 107(1): 7–10, doi: 10.1016/j.ijcard.2005.01.067, indexed in Pubmed: 16125261.
2. Am Said S. Current characteristics of congenital coronary artery fistulas in adults: A decade of global experience. World J Cardiol. 2011; 3(8): 267–277, doi: 10.4330/wjc.v3.i8.267, indexed in Pubmed: 21876777.
3. Cebi N, Schulze-Waltrup N, Frömke J, et al. Congenital coronary artery fistulas in adults: concomitant pathologies and treatment. Int J Cardiovasc Imaging. 2008; 24(4): 349–355, doi: 10.1007/s10554-007-9277-x, indexed in Pubmed: 17965946.
4. Said SAM, van der Werf T. Dutch survey of coronary artery fistulas in adults: congenital solitary fistulas. Int J Cardiol. 2006; 106(3): 323–332, doi: 10.1016/j.ijcard.2005.01.047, indexed in Pubmed: 16337040.
5. Lim JJ, Im Jung J, Lee BY, et al. Prevalence and types of coronary artery fistulas detected with coronary CT angiography. AJR Am J Roentgenol. 2014; 203(3): W237–W243, doi: 10.2214/AJR.13.11613, indexed in Pubmed: 25148179.
6. Ouchi K, Sakuma T, Ojiri H. Coronary artery fistula in adults: Incidence and appearance on cardiac computed tomography and comparison of detectability and hemodynamic effects with those on transthoracic echocardiography. J Cardiol. 2020; 76(6): 593–600, doi: 10.1016/j.jjcc.2020.06.005, indexed in Pubmed: 32636129.
7. Balanescu S, Sangiorgi G, Castelvecchio S, et al. Coronary artery fistulas: clinical consequences and methods of closure. A literature review. Ital Heart J. 2001; 2(9): 669–676, indexed in Pubmed: 11666095.
8. Liberthson RR, Sagar K, Berkoben JP, et al. Congenital coronary arteriovenous fistula. Report of 13 patients, review of the literature and delineation of management. Circulation. 1979; 59(5): 849–854, doi: 10.1161/01.cir.59.5.849, indexed in Pubmed: 428095.
9. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022;145:e895-e1032. Erratum in: Circulation. 2022; 145: e1033.
10. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2016; 18(8): 891–975, doi: 10.1002/ejhf.592, indexed in Pubmed: 27207191.
11. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2022; 43(38):3618-3731. Erratum in: Eur Heart J. 2023; 44: 1312.
12. Li Y, Shen C, Ji Y, et al. Clinical implication of coronary tortuosity in patients with coronary artery disease. PLoS One. 2011; 6(8): e24232, doi: 10.1371/journal.pone.0024232, indexed in Pubmed: 21904618.
13. Kim H, Beck KS, Choe YH, et al. Coronary-to-Pulmonary artery fistula in adults: natural history and management strategies. Korean J Radiol. 2019; 20(11): 1491–1497, doi: 10.3348/kjr.2019.0331, indexed in Pubmed: 31606954.
14. Agatston AS, Janowitz WR, Hildner FJ, et al. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol. 1990; 15(4): 827–832, doi: 10.1016/0735-1097(90)90282-t, indexed in Pubmed: 2407762.
15. Kim IC, Chang S, Hong GR, et al. Comparison of cardiac computed tomography with transesophageal echocardiography for identifying

vegetation and intracardiac complications in patients with infective endocarditis in the era of 3-dimensional images. Circ Cardiovasc Imaging. 2018; 11(3): e006986, doi: 10.1161/CIRCIMAGING.117.006986, indexed in Pubmed: 29555833.
16. Kim DH, Choi SII, Choi JA, et al. Various findings of cardiac thrombi on MDCT and MRI. J Comput Assist Tomogr. 2006; 30(4): 572–577, doi: 10.1097/00004728-200607000-00004, indexed in Pubmed: 16845286.
17. Singh N, Goel P, Singh Y. Pictorial essay: Computed tomography findings in acute aortic syndromes. SA J Radiol. 2018; 22(1): 1309, doi: 10.4102/sajr.v22i1.1309, indexed in Pubmed: 31754495.
18. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). Eur Respir J. 2019; 54(3), doi: 10.1183/13993003.01647-2019, indexed in Pubmed: 31473594.
19. Cury R, Leipsic J, Abbara S, et al. CAD-RADS™ 2.0 - 2022 Coronary Artery Disease-Reporting and Data System. Journal of Cardiovascular Computed Tomography. 2022; 16(6): 536–557, doi: 10.1016/j.jcct.2022.07.002.
20. Zhou K, Kong L, Wang Y, et al. Coronary artery fistula in adults: evaluation with dual-source CT coronary angiography. Br J Radiol. 2015; 88(1049): 20140754, doi: 10.1259/bjr.20140754, indexed in Pubmed: 25784320.
21. Podolec J, Wiewiórka Ł, Siudak Z, et al. Presence and characteristics of coronary artery fistulas among patients undergoing coronary angiography. Kardiol Pol. 2019; 77(11): 1034–1039, doi: 10.33963/KP.14963, indexed in Pubmed: 31486416.
22. Canga Y, Ozcan KS, Emre A, et al. Coronary artery fistula: review of 54 cases from single center experience. Cardiol J. 2012; 19(3): 278–286, doi: 10.5603/cj.2012.0050, indexed in Pubmed: 22641547.
23. Yun H, Zeng MS, Yang S, et al. Congenital coronary artery fistulas: dual-source CT findings from consecutive 6,624 patients with suspected or confirmed coronary artery disease. Chin Med J (Engl). 2011; 124(24): 4172–4177, indexed in Pubmed: 22340382.
24. Buccheri D, Chirco PR, Geraci S, et al. Coronary artery fistulae: anatomy, diagnosis and management strategies. Heart Lung Circ. 2018; 27(8): 940–951, doi: 10.1016/j.hlc.2017.07.014, indexed in Pubmed: 29503240.
25. Valente AM, Lock JE, Gauvreau K, et al. Predictors of long-term adverse outcomes in patients with congenital coronary artery fistulae. Circ Cardiovasc Interv. 2010; 3(2): 134–139, doi: 10.1161/CIRCINTERVENTIONS.109.883884, indexed in Pubmed: 20332380.
26. Am Said S. Characteristics of congenital coronary artery fistulas complicated with infective endocarditis: analysis of 25 reported cases. Congenit Heart Dis. 2016; 11(6): 756–765, doi: 10.1111/chd.12392, indexed in Pubmed: 27414233.
27. Am Said S, Schroeder-Tanka JM, Mulder BJM. Female gender and the risk of rupture of congenital aneurysmal fistula in adults. Congenit Heart Dis. 2008; 3(1): 63–68, doi: 10.1111/j.1747-0803.2007.00144.x, indexed in Pubmed: 18373752.
28. Vinograd CA, Ostermayer S, Lytrivi ID, et al. Prevalence and outcomes of coronary artery ectasia associated with isolated congenital coronary artery fistula. Am J Cardiol. 2014; 114(1): 111–116, doi: 10.1016/j.amjcard.2014.04.015, indexed in Pubmed: 24819906.
29. Said SA, el Gamal MI. Coronary angiographic morphology of congenital coronary arteriovenous fistulas in adults: report of four new cases and review of angiograms of fifteen reported cases. Cathet Cardiovasc Diagn. 1995; 35(1): 29–35, doi: 10.1002/ccd.1810350106, indexed in Pubmed: 7614537.
30. Feltes TF, Bacha E, Beekman RH, et al. Indications for cardiac catheterization and intervention in pediatric cardiac disease: a scientific statement from the American Heart Association. Circulation. 2011; 123(22): 2607–2652, doi: 10.1161/CIR.0b013e31821b1f10, indexed in Pubmed: 21536996.
31. Challoumas D, Pericleous A, Dimitrakaki IA, et al. Coronary arteriovenous fistulae: a review. Int J Angiol. 2014; 23(1): 1–10, doi: 10.1055/s-0033-1349162, indexed in Pubmed: 24940026.
32. Warnes C, Williams R, Bashore T, et al. ACC/AHA 2008 Guidelines for the Management of Adults With Congenital Heart Disease. Circulation. 2008; 118(23), doi: 10.1161/circulationaha.108.190690.
33. Latson LA. Coronary artery fistulas: how to manage them. Catheter Cardiovasc Interv. 2007; 70(1): 110–116, doi: 10.1002/ccd.21125, indexed in Pubmed: 17420995.
34. Buccheri D, Chirco PR, Geraci S, et al. Coronary artery fistulae: anatomy, diagnosis and management strategies. Heart Lung Circ. 2018; 27(8): 940–951, doi: 10.1016/j.hlc.2017.07.014, indexed in Pubmed: 29503240.
35. Zalewska J, Skowronski J, Witkowski A, et al. The percutaneous embolization of the coronary artery fistula after edge-to-edge repair of mitral and tricuspid valve regurgitation. Kardiol Pol. 2022; 80(5): 610–611, doi: 10.33963/KP.a2022.0091, indexed in Pubmed: 35380008.
36. Wolny R, Pręgowski J, Cyran K, et al. Acute myocardial infarction due to embolisation from the thrombosed coronary artery fistula between the right coronary artery and the left atrium. Kardiol Pol. 2017; 75(7): 720, doi: 10.5603/KP.2017.0126, indexed in Pubmed: 28703270.

Clinical features, etiology, and survival in patients with restrictive cardiomyopathy: A single-center experience

Justyna A Szczygieł[1], Piotr Michałek[2], Grażyna Truszkowska[3], Joanna Drozd-Sokołowska[4], Aleksandra Wróbel[5], Maria Franaszczyk[3, 6], Monika Gawor-Prokopczyk[1], Łukasz Mazurkiewicz[1], Mateusz Ziarkiewicz[4], Anna Waszczuk-Gajda[4], Marta Legatowicz-Koprowska[7], Ewa Walczak[7], Piotr Stawiński[6], Anna Lutyńska[3, 5], Rafał Płoski[6], Wiesław W Jędrzejczak[4], Zofia T Bilińska[8], Jacek Grzybowski[1]

[1]Department of Cardiomyopathy, National Institute of Cardiology, Warszawa, Poland
[2]Rapid Diagnosis Department, National Institute of Cardiology, Warszawa, Poland
[3]Department of Medical Biology, Molecular Biology Laboratory, National Institute of Cardiology, Warszawa, Poland
[4]Department of Hematology, Transplantology and Internal Medicine, Medical University of Warsaw, Warszawa, Poland
[5]Department of Medical Biology, National Institute of Cardiology, Warszawa, Poland
[6]Department of Medical Genetics, Medical University of Warsaw, Warszawa, Poland
[7]Department of Pathomorphology, National Institute of Geriatrics, Rheumatology and Rehabilitation, Warszawa, Poland
[8]Unit for Screening Studies in Inherited Cardiovascular Diseases, National Institute of Cardiology, Warszawa, Poland

Editorial
by Masarone et al.

Correspondence to:
Justyna A. Szczygieł, MD, PhD, Department of Cardiomyopathy, National Institute of Cardiology, Alpejska 42, 04–628 Warszawa, Poland,
phone: +48 22 34 34 671,
fax: +48 22 34 34 515,
e-mail: j.szczygiel@ikard.pl

DOI: 10.33963/v.kp.97879

Received:
May 23, 2023

Accepted:
October 17, 2023

Early publication date:
October 20, 2023

ABSTRACT

Background: Numerous prognostic factors have been proposed for cardiac amyloidosis (CA). The knowledge about other subtypes of restrictive cardiomyopathy (RCM) is scant.

Aims: This study aimed to elucidate the etiology and prognostic factors of RCM as well as assess cardiac biomarkers: high-sensitive troponin T (hs-TnT), growth differentiation factor-15 (GDF-15), N-terminal pro-B-type natriuretic peptide (NT-proBNP), and soluble suppression of tumorigenicity 2, as mortality predictors in RCM.

Methods: We enrolled 36 RCM patients in our tertiary cardiac department. All patients were screened for CA. Genetic testing was performed in 17 patients without CA.

Results: Pathogenic or likely pathogenic gene variants were found in 86% of patients, including 5 novel variants. Twenty patients died, and 4 had a heart transplantation during the study. Median overall survival was 29 months (8–55). The univariate Cox models analysis indicated that systolic and diastolic blood pressure, GDF-15, hs-TnT, NT-proBNP, left ventricular stroke volume, the ratio of the transmitral early peak velocity (E) estimated by pulsed wave Doppler over the early mitral annulus velocity (e'), tricuspid annulus plane systolic excursion, early tricuspid valve annular systolic velocity, the presence of pulmonary hypertension, and pericardial effusion influenced survival (P <0.05). A worse prognosis was observed in patients with GDF-15 >1316 pg/ml, hs-TnT >42 ng/l, NT-proBNP >3383 pg/ml, and pericardial effusion >3.5 mm (Kaplan-Meier analysis, log-rank test, P <0.001).

Conclusions: Genetic testing should be considered in every RCM patient where light-chain amyloidosis has been excluded. Survival remains poor regardless of etiology. Increased concentrations of GDF-15, hs-TNT, NT-proBNP, and pericardial effusion are associated with worse prognosis. Further studies are warranted.

Key words: genetic testing, growth differentiation factor-15, light-chain amyloidosis, restrictive cardiomyopathy, soluble suppression of tumorigenicity 2

WHAT'S NEW?

This is the first report about clinical utility of new cardiac biomarkers, growth differentiation factor-15 (GDF-15) and soluble suppression of tumorigenicity 2, in the whole spectrum of restrictive cardiomyopathy (RCM). We have preliminarily identified GDF-15, high-sensitive troponin T, N-terminal pro B-type natriuretic peptide, and pericardial effusion as relevant predictors of death in RCM. We have described an easily applicable diagnostic workup for RCM, which may be useful in countries where there are no diagnostic centers for amyloidosis. We have presented an insightful analysis of RCM etiology including up-to-date genetic testing results with five novel genetic variants.

INTRODUCTION

Restrictive cardiomyopathy (RCM) occurs with an incidence of only 2% of all cardiomyopathies in adults, and although heterogeneous, is the rarest cardiomyopathy according to the European Registry [1]. Cardiac amyloidosis (CA) is a traditional paradigm of RCM [2]. Numerous prognostic factors in CA have been proposed. N-terminal pro-B-type natriuretic peptide (NT-proBNP) and troponin T have been included in the light-chain (AL) amyloidosis staging system since 2012 [3]. The role of the right ventricular (RV) dimension and function in CA is considered important [4, 5]. Growth differentiation factor-15 (GDF-15) and soluble suppression of tumorigenicity 2 (sST2) have proved to be encouraging biomarkers in AL amyloidosis [6, 7]. The following prognostic factors have been described in non-amyloid RCM (na-RCM): male sex, age >70 years, the New York Heart Association Functional Classification (NYHA class) ≥III, left atrial (LA) diameter >60 mm, and low cardiac output [8]. Recent studies underline the role of left ventricular end-diastolic diameter (LVEDD) and tricuspid regurgitation [9].

GDF-15 is considered a cardioprotective hormone due to its antioxidative, anti-inflammatory, and antiapoptotic properties [10]. In heart failure (HF) with preserved ejection fraction, a positive correlation of GDF-15 concentrations with echocardiographic parameters of left ventricular (LV) diastolic dysfunction was observed [11].

In patients with acute dyspnea assessed in the emergency unit, sST2 concentrations correlated with systolic pressure in the right ventricle and early diastolic myocardial velocities (e') [12].

Pathogenic mutations in nineteen different genes have been identified in patients with primary RCM [13]. On the other hand, Anderson-Fabry disease, transthyretin (ATTR) amyloidosis, or glycogenosis may also demonstrate RCM phenotype [2], so screening of genes associated with these diseases should be considered if clinically reasonable.

This study aimed to describe the etiology of RCM, including the genetic background of na-RCM, to identify prognostic factors and to assess whether new cardiac biomarkers, GDF-15 and sST2, may be useful in clinical evaluation of this group.

METHODS

The study enrolled 36 consecutive RCM patients diagnosed in a tertiary cardiac department from January 2015 to August 2016. Patients were followed up until April 2021. Features of RCM including biatrial enlargement, normal LV cavity size, and systolic function with severe diastolic dysfunction were assessed on echocardiography by an experienced cardiologist. Severe diastolic dysfunction was defined by criteria presented in Table 1 based on the current recommendations [14]. Patients with the following echocardiographic presentations of hypertrophic cardiomyopathy (HCM) were not included: profuse asymmetric LV hypertrophy without features of amyloidosis, systolic anterior motion of mitral valve leaflet, and LV outflow tract obstruction.

Lack of informed consent (n = 1), dialysis treatment (n = 1), and neoplastic disease other than AL amyloidosis (n = 0) were the exclusion criteria (see Figure 1).

On presentation, levels of serum NT-proBNP, high-sensitive troponin T (hs-TnT), GDF-15, sST2, and creatinine were measured. Concentrations of GDF-15 and sST2 were measured using R&S Quantikine ELISA Kits (Minneapolis, MN, US).

Echocardiography

In order to obtain a reliable assessment of LV diastolic dysfunction, echocardiography with tissue Doppler imaging (TDI) was performed. The dimensions and functions of both ventricles and the LA volume index (LAVI) were assessed according to current guidelines [15, 16]. Atrial dimensions were also presented as their areas.

Table 1. Criteria for severe diastolic dysfunction

Sinus rhythm + LVEF ≥50%	Sinus rhythm + LVEF <50%	Atrial fibrillation
E/e' ratio >14	E/e' ratio >14	E/e' septal ≥11
e' septal <7 cm/s and e' lateral <10 cm/s	TRPV >2.8 m/s	IVRT ≤65 ms
TRPV >2.8 m/s	LAVI >34 ml/m^2	DT <160 ms
LAVI >34 ml/m^2		

Abbreviations: DT, deceleration time; e' lateral, mitral annular early diastolic lateral velocity; e' septal, mitral annular early diastolic septal velocity; E/e' ratio, the ratio of the transmitral early peak velocity (E) estimated by pulsed wave Doppler over the early mitral annulus velocity (e'); IVRT, isovolumic relaxation time; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; TRPV, tricuspid regurgitation peak velocity

Left ventricular function was assessed by modified Simpson's method as LV ejection fraction (LVEF). Maximal systolic velocities of LV longitudinal fibers (LV S') were assessed in apical views by TDI [17]. RV function was described by tricuspid annular plane systolic excursion (TAPSE) measured in M-mode presentation in a four-chamber view and by the longitudinal myocardial velocity of the right ventricle (RV S') measured on TDI. The ratio of the transmitral early peak velocity (E) estimated by pulsed wave Doppler over average e' velocity estimated by TDI (E/e' ratio) was used to assess LV diastolic dysfunction.

Pericardial effusion was defined as an echo-free space between the two layers of the pericardium. The amount of pericardial effusion was assessed as small (<10 mm) or moderate (10–20 mm).

Pulmonary hypertension (PH) was assessed using tricuspid regurgitation peak velocity (TRPV) [18]. Values of TRPV >3.4 m/s indicated a high PH possibility. Additional criteria were used for values of TRPV between 2.8 and 3.4 m/s: inferior vena cava (IVC) diameter >21 mm with decreased inspiratory collapse; RV/LV basal diameter or area ratio >1.0; interventricular septum flattering; pulmonary artery (PA) diameter >25 mm or PA diameter >aortic root; RV outflow tract acceleration time <105 ms and/or mid-systolic notching.

Cardiac amyloidosis screening

Every patient enrolled in the study was screened for CA. The full list of analyzed amyloidosis features is presented in the Supplementary material, *Table S1*. The main clinical data taken into consideration were as follows: age >30 years, no family history of cardiomyopathy, a short history of HF symptoms (≤12 months), rapidly progressing HF, early satiety, loss of appetite (particularly aversion to meat dishes), weight loss (at least 10 kg), persistent diarrhea or constipation, hoarseness, and macroglossia. Medical history and typical features of amyloidosis, such as a low amplitude and pseudo-infarct pattern on 12-lead electrocardiogram, hyperechogenicity of the myocardium on echocardiography, right atrial enlargement, thickening of the interatrial septum and valve leaflets, or characteristic late gadolinium enhancement and abnormal gadolinium kinetics on cardiovascular magnetic resonance (CMR) resulted in further investigations for amyloidosis, including biopsy.

Amyloid typing

Cardiac AL amyloidosis was diagnosed using free light chain (sFLC) concentrations in the serum (Binding Site test, Birmingham, United Kingdom), the serum and urine immunofixation, and at least two biopsies: endomyocardial biopsy, labial salivary gland biopsy, gastric biopsy, surgical fat tissue biopsy, and hematologic consultation including bone marrow biopsy.

Immunohistochemistry (IHC) was performed for amyloid typing. Four monoclonal antibodies were used: against serum amyloid A, transthyretin, kappa, and lambda light chains (DAKO, Glostrup, Denmark).

Cardiac ATTR amyloidosis was confirmed with tissue biopsy and Technetium-based diphosphono-1,2-propanodicarboxylic acid (Tc-99m-DPD) scintigraphy. In every patient with ATTR amyloidosis, genetic analysis was performed and coding regions of the transthyretin (*TTR)* gene were screened by Sanger sequencing (SGS).

Genetic testing

Commercial testing of the galactosidase alpha (*GLA*) gene was performed in two patients with clinical features of Anderson-Fabry disease (SGS, CENTOGENE, Rostock, Germany). DNA was extracted from the peripheral blood by phenol extraction or salting-out method in 15 patients. In 12 patients, Next Generation Sequencing (NGS) was performed using the TruSight One (TSO) sequencing panel consisting of >4800 disease-associated genes (Illumina, San Diego, California, CA, US) on Illumina HiSeq 1500. Whole exome sequencing (WES) was performed in 2 patients. WES libraries were prepared using the TruSeq Exome Enrichment Kit (Illumina San Diego, CA, US) and sequenced on Illumina HiSeq1500. Library preparation, sequencing, and data analysis were performed as described previously [19]. SGS was performed in one patient and the presence of a gene variant detected previously in a relative was confirmed (Patient 18 in Table 2).

Results were inspected for rare (minor allele frequency <0.001 for dominant and <0.05 for recessive disorders) protein-coding or splicing variants in HCM- and RCM-associated genes including genes causative for genetic amyloidosis and storage diseases (Supplementary material, *Table S2*). The identified variants were classified according to the American College of Medical Genetics and Genomics guidelines [20]. Pathogenic and likely pathogenic variants identified with NGS were followed up in probands and their relatives with SGS using BigDye Terminator v3.1 or v1.1 Cycle Sequencing Kit (Life Technologies, Carlsbad, CA, US) according to the manufacturer's instructions and the 3500xL or 3130xl Genetic Analyzer (Life Technologies, Carlsbad, CA, US). The results were analyzed with Variant Reporter 1.1 Software (Life Technologies, Carlsbad, CA, US).

Statistical analysis

The Shapiro-Wilk test was used for data distribution assessment. Data were presented as mean with SD or as medians with interquartile ranges (IQR) depending on data distribution. The quantitative variables of two groups (the AL amyloidosis group and the na-RCM group) were compared with the independent samples t-test or the Mann-Whitney test. Fisher's exact test was used for the comparison of categorical variables. The Pearson or the Spearman correlation analysis was used depending on data distribution. All-cause mortality was the only one analyzed endpoint. Four na-RCM patients who underwent heart transplantation were excluded from the survival

Table 2. Diagnostics of 18 patients with non-amyloid restrictive cardiomyopathy

No.	Age (yrs) and sex	Amyloidosis diagnostics			Genetic testing		Survival (mos.)
		sFLC	CMR	biopsy	Gene and ACMG classification	Variant position (hg38), nucleotide, and amino acid change	
1.	45, F	N/A	(–)	N/A	*GLA*[c] Pathogenic	chrX-101407766-G-T, NM_000169.3:c.138C>A (p.His46Gln)	1, OHT
					GLA Pathogenic	chrX-101407751-C-G, NM_000169.3:c.153G>C (p.Met51Ile)	
					GLA Pathogenic	chrX-101407737-C-A, NM_000169.3:c.167G>T (p.Cys56Phe)	
2.	27[a]	N/A	(–)	(–) EMB	*TTN*[c] Likely pathogenic	chr2-178534401-A-G, NM_001267550.2:c.102214T>C (p.Trp34072Arg), rs375159973	11, OHT
3.	35[a], F	(–)	(–)	(–) EMB	*MYH7* Pathogenic	chr14-23429005-G-A, NM_000257.4:c.1357C>T (p.Arg453Cys), rs121913625	10, OHT
4.	65	N/A	(–)	N/A	N/A (systemic sclerosis – genetic testing not performed)		28[d]
5.	57[a], F	N/A	(–)	(–)	*GLA* Pathogenic	chrX-101403846-G-A, NM_000169.3:c.334C>T (p.Arg112Cys)	70
6.	20[a], F	N/A	(–)	N/A	*MYH7* Likely pathogenic	14:23418243-G-T, NM_000257.4:c.4136C>A (p.Ala1379Asp)	69
7.	33, F	(–)	(?)	(–) EMB	*TNNI3*[c] Likely pathogenic	19:55151904-A-C, NM_000363.5:c.563T>G (p.Val188Gly)	66
8.	42, F	N/A	(–)	N/A	*FLNC*[c] Likely pathogenic	7:128851562-T-G, NM_001458.5:c.5776T>G p.Tyr1926Asp	10[d]
					TTN[c] VUS	2:178776534-C>T, NM_001267550.2:c.5330G>A (p.Cys1777Tyr)	
9.	55[a]	N/A	(–)	N/A	*FLNC*[c] VUS	7:128849405-G>A, NM_001458.5:c.5026G>A (p.Gly1676Arg)	36[d]
10.	49, F	N/A	(–)	(–) EMB	*PRKAG2* Likely pathogenic	7:151576440-A>G, NM_016203.4:c.877T>C (p.Phe293Leu)	58
					BAG3 VUS	10:119676965-G>A, NM_004281.4:c.1411G>A (p.Glu471Lys), rs778496291	
11.	63	(?)	(–)	(–)	MYBPC3 Pathogenic	11:047332813-C>A, NM_000256.3:c.3490+1G>T, rs397516020	5[d]
12.	44[a]	(–)	(–)	N/A	*MYH7*[c] Likely pathogenic	14:023425363-A>T, NM_000257.4:c.2342T>A (p.Leu781Gln)	58
13.	63	N/A	(–)	(–) EMB	*MYBPC3* Pathogenic	chr11-47341990 C-G, NM_000256.3:c.1790+1G>C	18[d]
					ACTN2[c] VUS	chr1-236762528 G-C, NM_001103.4:c.2594G>C	
14.	40, F	(–)	(–)	(–)		Nothing to report	57
15.	50, F	N/A	(–)	(–) EMB	*TNNI3*[c] Likely pathogenic	19:055151859-C-T, NM_000363.4:c.608G>A (p.Gly203Asp)	7, OHT[d]
16.	52	N/A	(–)	(–) EMB	*TNNI3*[c] Likely pathogenic	19:055154073-A-G, NM_000363.5:c.506T>C (p.Leu169Pro)	55[d]
17.	18, F	N/A	(–)	N/A	*BAG3* Pathogenic	chr10-119672373 C-T, NM_004281.4:c.626C>T (p.Pro209Leu) rs121918312	50[d]
18.	37[a,b]	N/A	(–)	N/A	*MYBPC3* Pathogenic	11:047332813-C>A, NM_000256.3:c.3490+1G>T, rs397516020	61

[a]Family history of cardiomyopathy; [b]Patient 18 is a relative of Patient 11; [c]Novel variant; [d]Patient died during the study

Abbreviations: ACMG, American College of Medical Genetics and Genomics; *ACTN2*, actinin alpha 2; *BAG3*, BAG cochaperone 3; F, female; *FLNC*, filamin C; *GLA*, galactosidase alpha; hg38, Genome Reference Consortium Human Build 38; *MYBPC3*, myosin binding protein C3; *MYH7*, myosin heavy chain 7; N/A, not applicable — the test was not performed; OHT, orthotopic heart transplantation; *PRKAG2*, protein kinase AMP-activated non-catalytic subunit gamma 2; *TNNI3*, cardiac troponin I; *TTN*, titin; (–), the test excluded amyloidosis; (?), the test did not exclude amyloidosis; other — see Figure 1

analysis. Survival was defined as the time between entry to the study and death for deceased patients (medical documentation or relatives' reports) and time to last follow-up in April 2021 for patients who stayed alive (personal contact or phone call). The univariate Cox proportional models were prepared. Kaplan-Meier curves analysis with log-rank tests were performed for overall survival predictors provided that the sample size was large enough. Patients were assigned into two subgroups using the median values of predictors. Statistical analysis was performed with MedCalc v. 22.009 and PQstat v.1.8.2.

The study conformed to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Cardinal Wyszynski National Institute of Cardiology in December 2014. All patients provided written informed consent to participate in the study.

RESULTS

Thirty-six patients (median age 52 years, 18 females) were enrolled (Figure 1). The clinical details of the 8 patients with negative CA screening results are presented in the Supplementary material, *Table S3*. Fourteen patients were

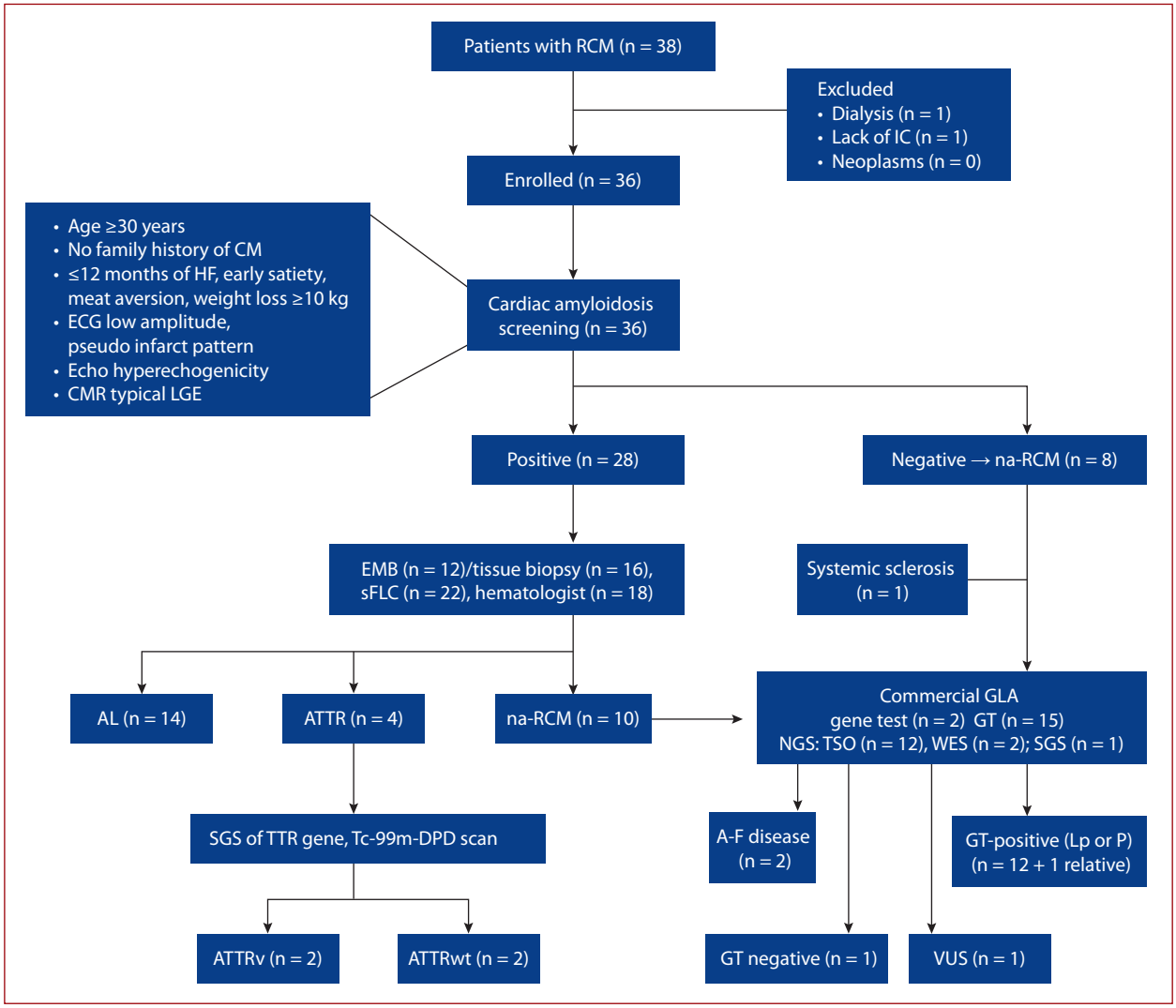


Figure 1. Patient flowchart

Abbreviations: A-F, Anderson-Fabry; AL, light-chain amyloidosis; ATTR, transthyretin amyloidosis; CM, cardiomyopathy; CMR, cardiovascular magnetic resonance; EMB, endomyocardial biopsy; sFLC, serum free light chains; *GLA*, alpha-galactosidase A; GT, genetic testing; HF, heart failure; IC, informed consent; LGE, late gadolinium enhancement; Lp, likely pathogenic gene variant; n, number of patients; na-RCM, non-amyloid RCM; NGS, next generationsequencing; P, pathogenic gene variant; RCM, restrictive cardiomyopathy; SGS, Sanger sequencing; Tc-99m-DPD scan, Technetium-based diphosphono-1,2-propanodicarboxylic acid scintigraphy; TSO, TruSight One; *TTR*, transthyretin; VUS, gene variant of uncertain significance; WES, whole exome sequencing

diagnosed with AL amyloidosis, 4 patients had ATTR amyloidosis, and 18 patients had na-RCM.

Two patients were diagnosed with variant ATTR amyloidosis, and the following gene variants were identified: NM_000371.4:c.157T>C(p.Phe53Leu) known as Phe33Leu, and NM_000371.4:c.302C>T(p.Ala101Val) known as Ala81Val, rs1555631417. Two patients were diagnosed with wild-type ATTR amyloidosis.

Genetic testing (GT) was performed in 15 patients with na-RCM, excluding two commercial tests of the *GLA* gene used for confirmation of Anderson-Fabry disease. Systemic sclerosis was the cause of na-RCM in one patient, so no GT was indicated (Figure 1). Detailed diagnostics of the na-RCM group with GT results are depicted in Table 2 (additional information — see the Supplementary material, *Table S4*). Positive GT results were observed in 12 of 14 patients (86%), who underwent NGS, and in one relative (Patient 18 see Table 2). Five novel pathogenic or likely pathogenic gene variants were detected in 5 patients.

The median follow-up time was 31.5 months (interquartile range [IQR]: 6.7–58.5) for all patients included in the survival analysis (n = 32) and 63.5 months (IQR: 58–67.5) for surviving patients (n = 12). At data cutoff, 20 patients (56%) had died with a median survival time of 9 months (IQR: 3.5–28.5). The median overall survival for all 32 patients included in the survival analysis was 29 months (IQR: 8–55). The main cause of death was advanced HF, and the main cause of death in AL amyloidosis was pulseless electrical activity.

General characteristics of the total cohort and comparison of the AL and na-RCM groups are presented in Table 3.

Table 3. General characteristics of the total cohort and comparison of the non-amyloid restrictive cardiomyopathy (na-RCM) group and the light-chain (AL) amyloidosis group

Variable	Total cohort n = 36	na-RCM n = 18	AL amyloidosis n = 14	*P*-value
Demographical and clinical data				
Age, years, median (IQR)	52 (43–63)	45 (35–55)	58 (50–65)	0.008
HF symptoms, months, median (IQR)	16 (12–37)	57 (34–84)	12 (6–14)	<0.001
Heart rate, n/min, median (IQR)	77 (67–90)	69 (60–80)	80 (75–96)	0.1
Atrial fibrillation, n (%)	15 (42)	10 (56)	3 (21%)	0.08
Systolic blood pressure, mm Hg, median (IQR)	113 (99–125)	112 (100–123)	106 (90–125)	0.3
Diastolic blood pressure, mm Hg, median (IQR)	74 (61–80)	71 (60–80)	68 (60–80)	0.5
Laboratory investigations				
Creatinine, µmol/l, median (IQR)	91 (80–110)	81 (78-107)	93 (81–117)	0.5
eGFR, ml/min/1.73 m^2, median (IQR)	66 (51–77)	69 (55–83)	64 (49–70)	0.3
GDF-15, pg/ml, median (IQR)	1316 (654–2204)	972 (420–2188)	1656 (1344–2472)	0.04
hs-TnT, ng/l, median (IQR)	39 (24–90)	25 (18–42)	112 (36–145)	<0.001
NT-proBNP, pg/ml, median (IQR)	3384 (1998–6578)	2074 (1064–3288)	7091 (4048–10028)	<0.001
sST2, ng/ml, median (IQR)	23 (17–39)	19 (12–27)	37 (23–62)	0.01
Echocardiography				
e' lateral, cm/s, median (IQR)	7 (5–9)	9 (6–11)	5 (3–7)	0.02
e' septal, cm/s, median (IQR)	5 (3–6)	5 (3–6)	4 (4–6)	0.4
E/e' ratio, median (IQR)	15 (12–21)	14 (11–18)	20 (12–25)	0.1
Left atrial area, cm^2, median (IQR)	29 (25–35)	35 (32–41)	27 (23–28)	<0.001
LAVI, ml/m^2, median (IQR)	67 (46–76)	86 (61–108)	48 (42–57)	0.02
LV IVS, mm, median (IQR)	16 (14–19)	14 (12–16)	18 (15–19)	0.02
LV posterior wall, mm, median (IQR)	14 (13–16)	13 (10–14)	16 (15–16)	<0.001
LV s', cm/s, median (IQR)	6 (5–7)	6 (5–7)	5 (4–8)	0.2
LVEF, %, median (IQR)	55 (45–65)	59 (45–65)	55 (50–70)	0.5
LV stroke volume, ml, median (IQR)	35 (31–52)	48 (33–62)	34 (22–40)	0.03
LV end-diastolic diameter, mm, median (IQR)	45 (41–48)	48 (43–49)	42 (39–45)	0.02
PASP, mm Hg, median (IQR)	45 (40–55)	55 (43–73)	44 (40–48)	0.07
Pulmonary hypertension, n (%)	25 (69)	11 (61)	12 (86)	0.2
Right atrial area, cm^2, median (IQR)	24 (20–30)	28 (24–39)	20 (18–21)	0.002
RV s', cm/s, median (IQR)	9 (8–11)	10 (8–11)	9 (7–11)	0.6
RV end-diastolic diameter, mm, mean (SD)	38 (6)	39 (8)	37 (4)	0.2
RV wall, mm, median (IQR)	8 (5–9)	5 (5–8)	8 (6–9)	0.08
TAPSE, mm, mean (SD)	16 (5)	18 (5)	14 (5)	0.03
TRPV, m/s, mean (SD)	3.1 (0.6)	3.3 (0.7)	2.8 (0.4)	0.04
Pericardial effusion, n (%)	19 (53)	6 (33%)	13 (93%)	<0.001
Pericardial effusion, mm, median (IQR)	3.5 (0.0–8.0)	0.0 (0.0–6.4)	8.0 (5.4–11.0)	0.009

Abbreviations: eGFR, estimated glomerular filtration rate; GDF-15, growth differentiation factor-15; hs-TnT, high-sensitive troponin T; IQR, interquartile range; LV, left ventricle; LV s', early mitral valve annular systolic velocity; NT-proBNP, N-terminal-proB-type natriuretic peptide; PASP, pulmonary artery systolic pressure; RV, right ventricle; RV s', early tricuspid valve annular systolic velocity; sST2, soluble suppression of tumorigenicity 2; TAPSE, tricuspid annulus plane systolic excursion; others — see Table 1

The prognostic factors for overall survival identified by univariate Cox models are presented in Table 4.

The sample size was big enough to perform Kaplan-Meier analysis with the log-rank test for four predictors of overall survival: GDF-15, hs-TnT, NT-proBNP, and pericardial effusion, considered as continuous variables (Figure 2).

The Kaplan-Meier analysis of the total cohort, excluding the recipients of heart transplants (n = 32), is presented in Figure 3.

Significant correlations of GDF-15 and sST2 with other variables observed in the entire group of 36 patients are presented in the Supplementary material, *Table S5*.

DISCUSSION

We describe a thorough analysis of the etiology, clinical characteristics, and prognostic factors of the rarest cardiomyopathy subtype. Cardiac amyloidosis screening should start diagnostic workup for every RCM patient [21]. We preferred an early invasive strategy and performed a biopsy in 77.8% of patients. Today, CA screening should include sFLC assessment with serum and urine immunofixation and DPD scan in the event of negative laboratory results. However, positive hematological tests should result in a prompt biopsy.

It is worth emphasizing that a high percentage of positive GT results was observed in the na-RCM group (86%). This justifies the inclusion of GT in diagnostic management of na-RCM. Such a high proportion of positive GT results, namely the identification of pathogenic or likely pathogenic gene variants, may have resulted from careful group selection and identification of specific heart muscle diseases. Notably, in that group, there were two patients

Table 4. Univariate Cox models analysis in 32 patients with restrictive cardiomyopathy

Univariate Cox model	Hazard ratio	95% confidence interval of hazard ratio	*P*-value
Systolic blood pressure	0.97	0.95–0.99	0.03
Diastolic blood pressure	0.95	0.91–0.99	0.01
GDF-15 (per 1000 pg/ml increase)	1.45	1.12–1.88	0.004
hs-TnT (per 10 ng/l increase)	1.10	1.04–1.16	<0.001
NT-proBNP (per 1000 pg/ml increase)	1.17	1.08–1.28	<0.001
LV stroke volume	0.95	0.92–0.99	0.007
E/e' ratio	1.06	1.01–1.11	0.01
TAPSE	0.84	0.75–0.94	0.002
RV s'	0.74	0.59–0.92	0.006
Pulmonary hypertension (yes vs. no)	4.33	1.26–14.90	0.02
Pericardial effusion (yes vs. no)	5.49	1.94–15.51	0.001
Pericardial effusion (per 1 mm increase)	1.13	1.04–1.22	0.003

Abbreviations: see Tables 1 and 3

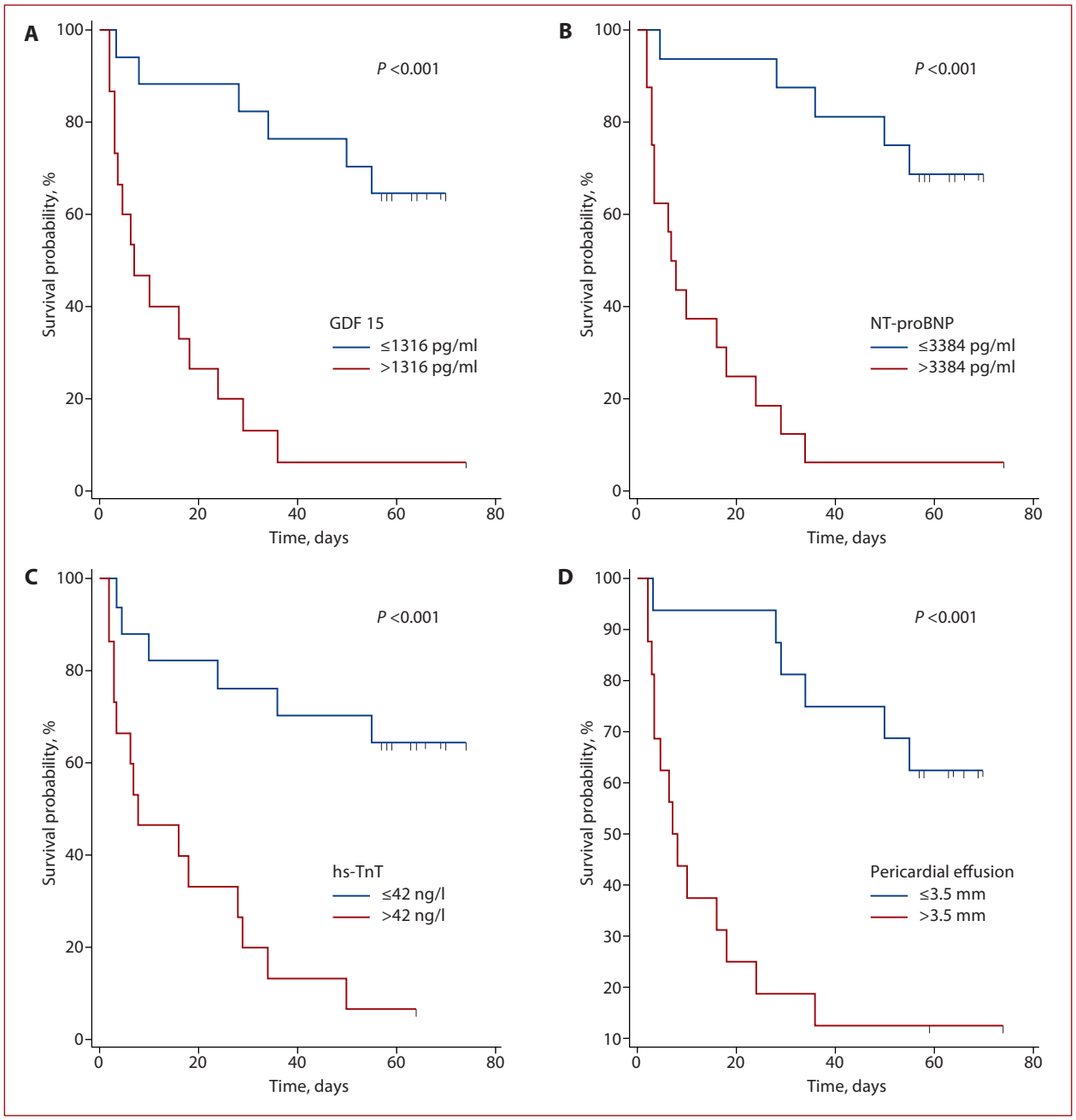


Figure 2. Prognostic factors for survival in restrictive cardiomyopathy. Kaplan-Meier survival curves stratified by the median of GDF-15 (**A**), NT-proBNP (**B**), high-sensitive troponin T (**C**), and pericardial effusion (**D**)

Abbreviations: see Table 2

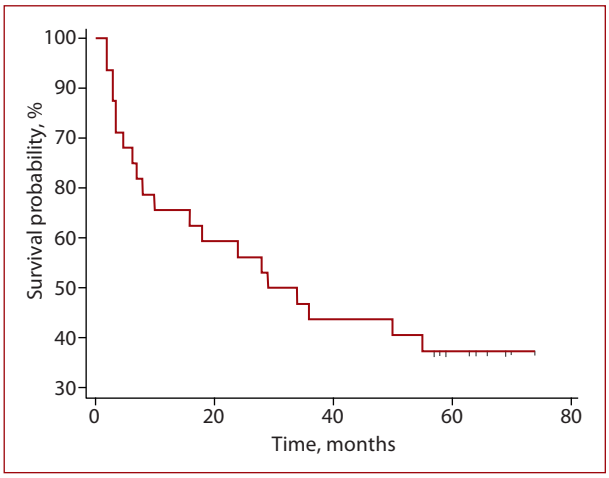


Figure 3. Overall survival in restrictive cardiomyopathy. Kaplan-Meier survival curve for 32 patients

with Anderson-Fabry disease – one with protein kinase AMP-activated non-catalytic subunit gamma 2 (*PRKAG2*) cardiomyopathy and one with myofibrillar myopathy related to the Bcl2-associated athanogene 3 (*BAG3*) Pro209Leu variant. Similarly, as in the literature, pathogenic sarcomeric variants were the most common. The study was conducted in a tertiary cardiac department, so patient selection bias should also be considered.

Importantly, we identified five novel gene variants, with further genetic research on RCM. Restrictive cardiomyopathy is still a lesser-known cardiomyopathy subtype. Data about the genetic background of RCM in Polish patients are scant.

As LVEF remains normal or slightly decreased in RCM patients for a long time [2], it is important to include amyloidosis [22] and na-RCM in differential diagnosis of HF with preserved ejection fraction. Although LVEF is commonly used in clinical practice, it is less suitable for assessing prognosis in RCM than RV function. Only ten patients (28%) in the study had decreased LVEF <50%. The lowest LVEF value was 40%, and this was observed in four patients. Whereas decreased RV function defined as TAPSE <17 mm [16] was present in 19 patients (53%).

Results concerning atrial areas were serendipitous. Atrial dilation is considered a reliable marker of increased pressure in the left ventricle and diastolic dysfunction [14]. Meanwhile, in our study, patients with AL amyloidosis had smaller LA dimensions than in the na-RCM group; they had also lower lateral mitral annular e' velocities. The latter variable suggested more advanced diastolic dysfunction. Similarly, the higher values of the E/e' ratio in the AL group could indicate a more restrictive filling pattern although the latter difference was not significant. We suggest that amyloid deposits gathering in the atrial wall prevent further atrial dilation. Thus, LA dimension in AL amyloidosis may not actually reflect diastolic dysfunction.

Troponin T, NT-proBNP [23], GDF-15 [6], and pericardial effusion [24] were proposed as prognostic factors in AL amyloidosis. We observed a relevant prognostic value of these parameters in RCM regardless of disease etiology. Small (<10 mm; n = 12) to moderate (10–20 mm; n = 7) amounts of pericardial effusion were observed, with no cases of cardiac tamponade. Interestingly, just 3.5 mm of pericardial effusion indicated worse survival.

Recent studies showed that GDF-15 levels may be used in early determination of anthracycline-induced cardiomyopathy during treatment of childhood cancers [25] and are positively correlated with myocardial fibrosis parameters in systemic sclerosis [26]. Soluble ST2 predicts negative outcomes for patients with Chagas disease [27].

However, according to our knowledge, this is the first analysis of GDF-15 and sST2 concentrations in the whole spectrum of RCM. The advantage of GDF-15 above sST2 in RCM prognosis needs to be confirmed in further studies. Correlations observed between GDF-15 and RV function demonstrate the utility of this biomarker in right ventricular assessment in RCM (Supplementary material, *Table S5*).

Limitations

Patients were diagnosed from January 2015 to August 2016. Current guidelines concerning amyloidosis [28, 29] were not available at that time, so we needed to refine our own diagnostic algorithm to achieve an indisputable diagnosis. The early invasive strategy with endomyocardial or surrogate tissue biopsy, as presented in the study, is gaining ground today, especially in the case of high AL amyloidosis suspicion [29, 30].

Amyloid typing was performed by immunohistochemistry instead of mass-spectrometry, which is considered the gold standard. Still, it is accepted that referral centers use a method with which they are familiar [28, 29]. Each amyloidosis diagnosis was confirmed by two tissue/organ biopsies and further testing: DPD scan and genetic evaluation of the *TTR* gene, or hematological assessment for AL amyloidosis.

The limited size of the study group is a serious drawback. Prognostic factors for overall survival identified by the univariate Cox model may be thrown into question. The study group was not large enough to perform multivariate Cox model analysis (n <33), which reduced the value of survival analysis. However, given limited data about RCM, which is an extremely rare disease, we decided to report the results of our study. For comparison purposes, the Cardiomyopathy Registry of the EURObservational Research Programme included 66 RCM patients [1].

Nevertheless, it should be emphasized that all patients met the recent RCM criteria proposed by the European Society of Cardiology, which require several months of persistence of a restrictive filling pattern to confirm RCM diagnosis [2]. However, we suggest being wary of postponing RCM diagnosis because any delay in confirming AL amyloidosis may be fateful.

It would be very interesting to include CMR parameters in survival analysis. Unfortunately, performing CMR in five

patients with AL amyloidosis was unfeasible due to clinical and technical difficulties.

Treatment analysis was not performed because of the limited size of the study group and the different schemes of chemotherapy for AL amyloidosis.

Since 2015, when the study started, new variants in RCM-associated genes have been identified [13]. We re-analyzed our data in 2023 in light of these new findings. However, only two of our patients had WES performed (Patients 3 and 9 in Table 2) and the discoidin CUB and LCCL domain-containing protein 2 (*DCBLD2)* gene variants assessment since the TSO panel does not allow this analysis. Variants of unknown significance of the filamin C (*FLNC)* gene were detected in two patients, and further studies would be warranted.

CONCLUSIONS

Light-chain amyloidosis is the most common cause of RCM. Primary RCM with genetic background is the second most frequent cause of RCM, what justifies including genetic testing in the diagnostic workup of RCM patients after exclusion of AL amyloidosis. Although we have found relevant differences in clinical pictures of AL amyloidosis and non-amyloid restrictive cardiomyopathy, the prognosis of both RCM subtypes remains poor. GDF-15 concentration upon hospital admission, but not sST2 concentration, should be considered as prognostic factor in RCM patients. Remaining predictors of death that are worth further studies include NT-proBNP and hs-TnT concentrations and pericardial effusion.

Supplementary material

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

Article information

Acknowledgments: This work was supported by the National Institute of Cardiology in Warsaw, Poland (Grant No. 2.48/VII/15).

We would like to give special thanks to Ewa Żółtowska for obtaining labial salivary gland biopsies, to Andrzej Bieganowski for performing endoscopic biopsies of the gastric mucosa, and to the CENTOGENE Team for performing free-of-charge genetic analysis of two patients with Anderson-Fabry disease.

Anna Waszczuk-Gajda did not manage to accept the final version of the manuscript.

Conflict of interest: None declared.

Funding: None.

REFERENCES

1. Charron P, Elliott PM, Gimeno JR, et al. The Cardiomyopathy Registry of the EURObservational Research Programme of the European Society of Cardiology: baseline data and contemporary management of adult patients with cardiomyopathies. Eur Heart J. 2018; 39(20): 1784–1793, doi: 10.1093/eurheartj/ehx819, indexed in Pubmed: 29378019.
2. Rapezzi C, Aimo A, Barison A, et al. Restrictive cardiomyopathy: definition and diagnosis. Eur Heart J. 2022; 43(45): 4679–4693, doi: 10.1093/eurheartj/ehac543, indexed in Pubmed: 36269634.
3. Kumar S, Dispenzieri A, Lacy MQ, et al. Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements. J Clin Oncol. 2012; 30(9): 989–995, doi: 10.1200/JCO.2011.38.5724, indexed in Pubmed: 22331953.
4. Ghio S, Perlini S, Palladini G, et al. Importance of the echocardiographic evaluation of right ventricular function in patients with AL amyloidosis. Eur J Heart Fail. 2007; 9(8): 808–813, doi: 10.1016/j.ejheart.2007.05.006, indexed in Pubmed: 17586091.
5. Szczygieł JA, Wieczorek PZ, Drozd-Sokołowska J, et al. Impaired right ventricular function as a predictor of early mortality in patients with lightchain cardiac amyloidosis assessed in a cardiology department. Pol Arch Intern Med. 2017; 127(12): 854–864, doi: 10.20452/pamw.4135, indexed in Pubmed: 29112180.
6. Kastritis E, Papassotiriou I, Merlini G, et al. Growth differentiation factor-15 is a new biomarker for survival and renal outcomes in light chain amyloidosis. Blood. 2018; 131(14): 1568–1575, doi: 10.1182/blood-2017-12-819904, indexed in Pubmed: 29386197.
7. Dispenzieri A, Gertz MA, Saenger A, et al. Soluble suppression of tumorigenicity 2 (sST2), but not galactin-3, adds to prognostication in patients with systemic AL amyloidosis independent of NT-proBNP and troponin T. Am J Hematol. 2015; 90(6): 524–528, doi: 10.1002/ajh.24001, indexed in Pubmed: 25753178.
8. Ammash NM, Seward JB, Bailey KR, et al. Clinical profile and outcome of idiopathic restrictive cardiomyopathy. Circulation. 2000; 101(21): 2490–2496, doi: 10.1161/01.cir.101.21.2490, indexed in Pubmed: 10831523.
9. Hong JA, Kim MS, Cho MS, et al. Clinical features of idiopathic restrictive cardiomyopathy: A retrospective multicenter cohort study over 2 decades. Medicine (Baltimore). 2017; 96(36): e7886, doi: 10.1097/MD.0000000000007886, indexed in Pubmed: 28885342.
10. Rochette L, Dogon G, Zeller M, et al. GDF15 and cardiac cells: current concepts and new insights. Int J Mol Sci. 2021; 22(16): 8889, doi: 10.3390/ijms22168889, indexed in Pubmed: 34445593.
11. Stahrenberg R, Edelmann F, Mende M, et al. The novel biomarker growth differentiation factor 15 in heart failure with normal ejection fraction. Eur J Heart Fail. 2010; 12(12): 1309–1316, doi: 10.1093/eurjhf/hfq151, indexed in Pubmed: 20837635.
12. Shah RV, Chen-Tournoux AA, Picard MH, et al. Serum levels of the interleukin-1 receptor family member ST2, cardiac structure and function, and long-term mortality in patients with acute dyspnea. Circ Heart Fail. 2009; 2(4): 311–319, doi: 10.1161/CIRCHEARTFAILURE.108.833707, indexed in Pubmed: 19808354.
13. Brodehl A, Gerull B. Genetic insights into primary restrictive cardiomyopathy. J Clin Med. 2022; 11(8): 2094, doi: 10.3390/jcm11082094, indexed in Pubmed: 35456187.
14. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular imaging. J Am Soc Echocardiogr. 2016; 29(4): 277–314, doi: 10.1016/j.echo.2016.01.011, indexed in Pubmed: 27037982.
15. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015; 28(1): 1–39.e14, doi: 10.1016/j.echo.2014.10.003, indexed in Pubmed: 25559473.
16. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society

of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr. 2010; 23(7): 685–713; quiz 786, doi: 10.1016/j.echo.2010.05.010, indexed in Pubmed: 20620859.
17. Pellerin D, Sharma R, Elliott P, et al. Tissue Doppler, strain, and strain rate echocardiography for the assessment of left and right systolic ventricular function. Heart. 2003; 89(Suppl 3): iii9–ii17, doi: 10.1136/heart.89.suppl_3.iii9, indexed in Pubmed: 14594870.
18. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2022; 43(38): 3618–3731, doi: 10.1093/eurheartj/ehac237, indexed in Pubmed: 36017548.
19. Ploski R, Pollak A, Müller S, et al. Does p.Q247X in TRIM63 cause human hypertrophic cardiomyopathy? Circ Res. 2014; 114(2): e2–e5, doi: 10.1161/CIRCRESAHA.114.302662, indexed in Pubmed: 24436435.
20. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015; 17(5): 405–424, doi: 10.1038/gim.2015.30, indexed in Pubmed: 25741868.
21. Asher CR, Klein AL. My approach to the evaluation of restrictive cardiomyopathy. Trends Cardiovasc Med. 2017; 27(1): 74–75, doi: 10.1016/j.tcm.2016.04.017, indexed in Pubmed: 27989285.
22. Murat S, Cavusoglu Y, Yalvac HE, et al. Assessment of clinical characteristics of cardiac amyloidosis as a potential underlying etiology in patients diagnosed with heart failure with preserved ejection fraction. Kardiol Pol. 2022; 80(6): 672–678, doi: 10.33963/KP.a2022.0098, indexed in Pubmed: 35390167.
23. Dispenzieri A, Gertz M, Kyle R, et al. Serum cardiac troponins and N-terminal pro-brain natriuretic peptide: a staging system for primary systemic amyloidosis. J Clin Oncol. 2004; 22(18): 3751–3757, doi: 10.1200/jco.2004.03.029, indexed in Pubmed: 15365071.
24. Yuda S, Hayashi T, Yasui K, et al. Pericardial effusion and multiple organ involvement are independent predictors of mortality in patients with systemic light chain amyloidosis. Intern Med. 2015; 54(15): 1833–1840, doi: 10.2169/internalmedicine.54.3500, indexed in Pubmed: 26234222.
25. Kaya F, Arslan D, Vatansev H, et al. Growth-differentiation factor-15 and tissue doppler imaging in detection of anthracycline-induced cardiomyopathy during therapy of childhood cancers. J Pediatr Hematol Oncol. 2016; 38(3): e107–e112, doi: 10.1097/MPH.0000000000000491, indexed in Pubmed: 26907646.
26. Hromádka M, Seidlerová J, Suchý D, et al. Myocardial fibrosis detected by magnetic resonance in systemic sclerosis patients — relationship with biochemical and echocardiography parameters. Int J Cardiol. 2017; 249: 448–453, doi: 10.1016/j.ijcard.2017.08.072, indexed in Pubmed: 28935460.
27. Echeverría LE, Rojas LZ, Gómez-Ochoa SA, et al. Cardiovascular biomarkers as predictors of adverse outcomes in chronic Chagas cardiomyopathy. PLoS One. 2021; 16(10): e0258622, doi: 10.1371/journal.pone.0258622, indexed in Pubmed: 34710112.
28. Garcia-Pavia P, Rapezzi C, Adler Y, et al. Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases. Eur Heart J. 2021; 42(16): 1554–1568, doi: 10.1093/eurheartj/ehab072, indexed in Pubmed: 33825853.
29. Kittleson MM, Ruberg FL, Ambardekar AV, et al. 2023 ACC expert consensus decision pathway on comprehensive multidisciplinary care for the patient with cardiac amyloidosis: a report of the American College of Cardiology solution set oversight committee. J Am Coll Cardiol. 2023; 81(11): 1076–1126, doi: 10.1016/j.jacc.2022.11.022, indexed in Pubmed: 36697326.
30. Briasoulis A, Bampatsias D, Papamichail A, et al. Invasive and non-invasive diagnostic pathways in the diagnosis of cardiac amyloidosis. J Cardiovasc Dev Dis. 2023; 10(6): 256, doi: 10.3390/jcdd10060256, indexed in Pubmed: 37367421.

Identifying associations between the social network index, its components, and the prevalence of cardiovascular diseases in Polish adults. Results of the cross-sectional WOBASZ II study

Aleksandra M Piwońska[1]*, Jerzy Piwoński[1]*, Alicja Cicha-Mikołajczyk[1], Magdalena Kozela[2], Andrzej Pająk[2], Witold Śmigielski[1], Magdalena Kwaśniewska[3], Tomasz Zdrojewski[4], Andrzej Tykarski[5], Krystyna Kozakiewicz[6], Wojciech Drygas[1]

[1]Department of Epidemiology, Cardiovascular Disease Prevention, and Health Promotion, National Institute of Cardiology, Warszawa, Poland
[2]Department of Epidemiology and Population Studies, Institute of Public Health, Jagiellonian University Medical College, Kraków, Poland
[3]Department of Preventive Medicine, Medical University of Lodz, Łódź, Poland
[4]Department of Preventive Medicine and Education, Medical University of Gdansk, Gdańsk, Poland
[5]Department of Hypertension, Angiology and Internal Medicine, Poznan University of Medical Sciences, Poznań, Poland
[6]Division of Cardiology and Structural Heart Diseases, Medical University of Silesia, Katowice, Poland
*Both authors equally contributed to the study

Editorial
by Rutledge et al.

Correspondence to:
Aleksandra Piwońska, MD, PhD, Department of Epidemiology, Cardiovascular Disease Prevention and Health Promotion, National Institute of Cardiology, Alpejska 42, 04–628 Warszawa, Poland, phone: +48 22 812 55 86, e-mail: apiwonska@ikard.pl

DOI: 10.33963/v.kp.98066

Received:
August 1, 2023

Accepted:
October 31, 2023

Early publication date:
November 13, 2023

ABSTRACT

Background: Psychosocial risk factors are important determinants of cardiovascular diseases (CVDs): people involved in positive relationships live longer than those with low social support (SS).

Aims: Our study aimed to evaluate the association between SS, components of the social network, and CVDs.

Methods: A cross-sectional population-based survey WOBASZ II conducted in the years 2013–2014 included a sample of 6043 individuals, aged 20 and over, who completed the Berkman-Syme questionnaire to assess SS using the social network index (SNI).

Results: Higher percentage of low SS was observed in women (52.15%) compared to men (45.4%) (P <0.001). People with a low SNI had a worse CVD risk factor profile. None of the analyzed social contacts (with children, relatives, or friends), regardless of how satisfactory they were, was associated with CVDs in men. In women, satisfying contact with children or relatives appeared to be associated with better cardiovascular health. Furthermore, active participation in organized social activity increased the chance of arrhythmia in both sexes: 1.50 (1.04–2.15); P = 0.029 in men; 1.47 (1.11–1.95); P = 0.007 in women. Although a low SNI was associated with analyzed CVDs in the univariate analysis, it was not confirmed in the fully adjusted model.

Conclusions: More women had low SS compared to men. People with low SS had a worse CVD risk factor profile. There was a significant independent relationship between different components of the SNI, such as social contacts and CVDs in women and active participation in organized social activity and arrhythmia in both sexes.

Key words: Berkman-Syme questionnaire, cardiovascular diseases, cross-sectional study, Polish population, social support

WHAT'S NEW?

The main novelty of our study was that we not only analyzed the social support (SS) index as a whole but also particular components of the social network index (SNI), taking into account their quality. We showed worse cardiovascular disease (CVD) risk factor profile in individuals with a low SNI and found that social contact (with children, relatives, or friends), its quality, and the number of sources of social ties (none or 1, 2, and 3) were associated with cardiovascular health, but only in women. In turn, active participation in organized social activity increased the chance of arrhythmia in both sexes and, additionally, CVDs in women. The results of our study let us draw attention to the issue of SS as it is known that persons receiving higher support have better physical and psychological health, better lifestyle, and greater medication adherence.

INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of morbidity and mortality, responsible for most social costs, deterioration in quality of life, and shortening of life expectancy [1]. It is well known that people involved in positive relationships live longer than those with low social support (SS) [2]. This is especially true for people with low SS, low socioeconomic status, or depression. The simplest definition of SS was proposed by Sarason: social support means assistance available to the individual in a difficult or stressful situation [3]. Lack of social support affects people negatively [4]. Some psychological factors that lead to chronic physiological stress, such as low SS or depression, are considered determinants of cardiovascular health because they can cause chronic systemic inflammation and increase the frequency of potentially negative behaviors that lead to the formation of new or increased intensity of current risk factors [5, 6]. In turn, a high level of SS has a positive impact on health behavior as well as on compliance with physician recommendations.

Although the overall beneficial effect of SS has been consistently reported in most studies, components of SS in different populations may not have the same effect. Different forms, sources, and types of SS can be critical in protecting various communities. In post-transformation Poland, after profound social and economic changes, the level of social support is similar to that of Western European countries [7] although it has recently decreased [8]. Furthermore, it is impossible to ignore the effect of the COVID-19 pandemic. Because of restrictions during the pandemic, the frequency of social face-to-face contact and its quality has changed, which influenced social well-being. Also, new forms of contact were created, e.g. online SS (home working, home education), which had existed before the pandemic but have increased during it, and some of them have remained since the COVID-19 pandemic ended.

This study aimed to evaluate the association between social support in general, as well as different components of the social network and CVDs, taking into account the quality of social contacts.

METHODS

Research design and participants

The methods of the National Multicenter Health Examination Survey (Polish acronym WOBASZ II) were previously published [9]. In summary, the study was carried out in 2013–2014 in a sample of the Polish population, aged 20 and over. The random selection of participants stratified according to sex, administrative units, and type of urbanization was carried out using the electronic database of national individual personal identification numbers (PESEL) with a response rate of 46.5%. The study was accepted by the Field Bioethics Committee (no. 1344/12). Before data collection, all respondents signed an informed consent for both questionnaires, physical examination, and blood tests. Finally, 6043 individuals (2710 men and 3333 women) were examined who completed the Berkman-Syme questionnaire [10].

Data assessment

The study protocol involved conducting a face-to-face questionnaire, physical examination, and laboratory tests. For the present analysis, we identified people who suffered: from ischemic heart disease (IHD), arrhythmia, and cardiovascular diseases (CVDs) based on self-reported data. Individuals with IHD had a medical history of diagnosis or hospitalization for acute coronary syndrome including myocardial infarction (MI), percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), a history of MI, or a diagnosis of IHD without hospitalization. Persons with arrhythmia had a medical history of diagnosis or hospitalization for arrhythmia, including atrial fibrillation and other heart rhythm disturbances, or an implanted pacemaker/cardioverter-defibrillator. Hypertensive people were defined as those with arterial blood pressure ≥140/90 mm Hg (mean taken from the 2nd and 3rd blood pressure measurements made during the survey) and/or those reporting use of antihypertensive medication. Subjects with a self-reported medical history of diabetes or with a fasting blood glucose level ≥7.0 mmol/l or on hypoglycemic treatment were considered diabetic. Obesity was diagnosed as a body mass index (BMI) ≥30 kg/m^2. The current smoker was a person who regularly smokes at least one cigarette a day, a former smoker was a person who had smoked in the past, stopped smoking, and did not smoke at the time of the survey; and a non-smoker was a person who had never smoked cigarettes.

Assessment of social support

Social support was evaluated according to the "social network scale" by Berkman-Syme [10]. The Berkman-Syme

questionnaire, composed of 31 questions on marital status, contacts with children, friends, and relatives, and active participation in organized social activities, was used to assess SS in the examined population. The respondents' answers received codes or points, and suitable code tables were used to calculate the social network index (SNI) to identify low, medium, high, and very high SS in the examined persons. For our analysis, the last two subgroups were combined into one "high" SS group. The method applied in the study was in agreement with the WHO MONICA Psychosocial Optional Study (MOPSY) guidelines [11]. Additionally, we analyzed different components of the SNI, e.g., contacts with at least 1 child, at least 1 relative, or at least 1 friend, together with their quality (combined none or unsatisfactory contact vs. satisfactory contact, according to subjective assessment) and also participation in at least 1 organization: social, political, sports, charity organizations and unions (combined no or passive vs. very or moderately active participation). Furthermore, we assigned participants to 3 groups, according to the number of sources of satisfactory social contacts (children, relatives, friends; at least 1 satisfactory contact) — none or 1 source, 2 sources (i.e., children & relatives, children & friends, relatives & friends), or 3 sources.

Statistical analysis

The study population was divided into three groups according to the SNI (low, moderate, high). All analyses were performed separately in men and women. Quantitative and qualitative variables were presented as median (IQR — interquartile range) and number (percentage), respectively. The Kruskal-Wallis or Mann-Whitney tests were used for comparison of continuous traits and the χ^2 test for categorical attributes. The prevalence of SNI components was adjusted for age and presented as means with a 95% confidence interval (95% CI). Logistic regression models were applied first to investigate the associations between the level of SNI or its components and risk factors, and, second, between them and CVDs, IHD, and arrhythmia. The multivariable models were adjusted for socio-demographic and CVD risk factors and comorbidity. The results of logistic regression were presented as odds ratios (OR) with 95% CI. Statistical analyses were performed with SAS version 9.4 (SAS, Cary, NC, US). A *P*-value <0.05 was considered statistically significant.

RESULTS

The characteristics of the study participants by sex and SS level are shown in Table 1. In general, men were younger than women (median [IQR] age, 49.0 [35.0–61.0] years vs. 51.0 [37.0–62.0] years; $P = 0.005$). Both men and women differed significantly in all analyzed parameters except for the prevalence of obesity and CVDs. Furthermore, compared to women, men were more often smokers and were more frequently diagnosed with hypertension, diabetes, and IHD. On the other hand, women were better educated, less likely to be single, more likely to be widows, and they were more often diagnosed with arrhythmia and low SS. Both men and women differed in age between SNI groups. Median age decreased with higher SNI. Additionally, significant disparities were observed in the prevalence of the analyzed risk factors/comorbidities between SNI groups, with the highest prevalence in people with a low SNI (Table 1).

Taking into account the relationship between the prevalence of CVDs, IHD, and arrhythmia and the quality of social contacts with children, relatives, or friends, we found that, regardless of participants' age, none of these three types of social relationships, no matter how satisfactory they were, was associated with CVDs in men. However, women who reported satisfactory contacts with at least one child or one relative had a significantly lower prevalence of CVDs, IHD, or arrhythmia (Table 2). Furthermore, the prevalence of CVDs, IHD, and arrhythmia in women decreased significantly with more sources of satisfactory social contact, while active participation in organized social activities was associated with a higher prevalence of arrhythmia in both men and women (Table 2).

The frequency of satisfactory contacts with children, relatives, or friends increased with a higher SS both in men and women. In general, slightly more women than men reported satisfactory social contacts, except for the high SNI group, where there were no differences between men and women. Additionally, women reported more often support from three sources of social contacts, regardless of the level of the SNI. Men and women did not differ in their active participation in organized social activities. More than 70.0% of men and women with a high SNI actively participated in organized social activities, compared to none in the low SNI group (Table 3).

Although raw data on study population characteristics showed that there were significant differences in the prevalence of CVD risk factors (smoking, hypertension, diabetes mellitus [DM], and obesity) between the SNI groups, with the highest frequency in the lowest SNI group, in regression models adjusted for age and education, a significant association was found only between smoking and a low SNI in men and between hypertension and a low SNI in women (Table 4, Model 1). In the SNI component-based model (marital status, number of sources of satisfactory social ties, and active participation in organized social activity) adjusted for age and education, we found more associations between SNI components and risk factors. Married status was associated with less smoking in both sexes and more prevalent obesity in men. In turn, having two sources of satisfactory social contacts (compared to none or just one source) was associated with lower chance of hypertension in men, while active participation in organized social activities was associated with lower chance of DM in men and lower odds of hypertension and smoking in women (Table 4, Model 2).

In the univariate regression analysis (Table 5, Model 1), it was found that a low or moderate SNI (compared to a high SNI level) was associated with much higher odds of

Table 1. Participants characteristics. The WOBASZ II Study (n = 6043)

	Men					Women					$P_{M vs. W}$
	Total	Social network index			*P*-value	Total	Social network index			*P*-value	
		Low	Moderate	High			Low	Moderate	High		
N (%)	2710 (44.9)	1229 (45.4)	944 (34.8)	537 (19.8)	–	3333 (55.1)	1738 (52.1)	1136 (34.1)	459 (13.8)	–	–
Age, years, median (IQR)	49 (35–61)	55 (42–65)	48 (36–59)	34 (25–48)	<0.001	51 (37–62)	55 (41–65)	47 (35–58)	39 (26–53)	<0.001	0.005
Education											
Primary, n (%)	388 (14.3)	263 (21.4)	95 (10.1)	30 (5.6)	<0.001	605 (18.2)	453 (26.1)	137 (12.1)	15 (3.3)	<0.001	<0.001
Vocational, n (%)	842 (31.1)	433 (35.2)	301 (31.9)	108 (20.1)		607 (18.2)	377 (21.7)	190 (16.8)	40 (8.7)		
Secondary, n (%)	962 (35.5)	376 (30.6)	349 (37.1)	237 (44.1)		1251 (37.6)	637 (36.7)	437 (38.5)	177 (38.6)		
High, n (%)	516 (19.1)	157 (12.8)	197 (20.9)	162 (30.2)		865 (26.0)	268 (15.5)	370 (32.6)	227 (49.4)		
Marital status											
Married/cohabited, n (%)	1892 (69.8)	978 (79.6)	686 (72.7)	228 (42.5)	<0.001	2152 (64.6)	1186 (68.2)	776 (68.3)	190 (41.4)	<0.001	<0.001
Single, n (%)	591 (21.8)	117 (9.5)	184 (19.5)	290 (54.0)		446 (13.4)	67 (3.9)	154 (13.6)	225 (49.0)		
Divorced/separated, n (%)	126 (4.7)	72 (5.9)	42 (4.4)	12 (2.2)		225 (6.7)	119 (6.8)	88 (7.7)	18 (3.9)		
Widowed, n (%)	101 (3.7)	62 (5.0)	32 (3.4)	7 (1.3)		510 (15.3)	366 (21.1)	118 (10.4)	26 (5.7)		
Risk factors & comorbidities											
Smoking status											
Current smoker, n (%)	784 (29.0)	379 (30.9)	255 (27.1)	150 (28.1)	<0.001	642 (19.3)	355 (20.4)	211 (18.6)	76 (16.6)	0.08	<0.001
Former smoker, n (%)	914 (33.8)	463 (37.7)	312 (33.2)	139 (26.0)		623 (18.7)	334 (19.2)	216 (19.0)	73 (15.9)		
Non-smoker, n (%)	1004 (37.2)	385 (31.4)	374 (39.7)	245 (45.9)		2066 (62.0)	1049 (60.4)	708 (62.4)	309 (67.5)		
Comorbidity											
Hypertension, n (%)	1318 (49.3)	676 (55.6)	458 (49.4)	184 (34.7)	<0.001	1361 (41.3)	868 (50.4)	387 (34.6)	106 (23.3)	<0.001	<0.001
Diabetes, n (%)	299 (11.4)	182 (15.2)	85 (9.4)	32 (6.2)	<0.001	291 (9.1)	206 (12.3)	71 (6.5)	14 (3.1)	<0.001	0.003
Obesity, n (%)	658 (25.5)	313 (26.9)	241 (26.7)	104 (20.1)	0.008	848 (26.9)	497 (30.3)	276 (26.0)	75 (16.9)	<0.001	0.20
Cardiovascular health status											
Cardiovascular disease, n (%)	519 (19.4)	291 (24.1)	168 (18.1)	60 (11.3)	<0.001	677 (20.7)	398 (23.4)	214 (19.2)	65 (14.4)	<0.001	0.21
Ischemic heart disease, n (%)	299 (11.1)	168 (13.8)	101 (10.8)	30 (5.6)	<0.001	277 (8.4)	182 (10.6)	73 (6.5)	22 (4.8)	<0.001	<0.001
Arrhythmia, n (%)	239 (9.0)	130 (10.8)	77 (8.3)	32 (6.0)	0.004	393 (12.1)	211 (12.5)	144 (12.9)	38 (8.4)	0.035	<0.001
Atrial fibrillation, n (%)	116 (4.3)	61 (5.0)	40 (4.3)	15 (2.8)	0.11	160 (4.9)	101 (5.9)	48 (4.3)	11 (2.4)	0.005	0.34
Other heart rhythm disturbances, n (%)	185 (6.9)	101 (8.4)	57 (6.1)	27 (5.1)	0.022	294 (9.0)	148 (8.7)	116 (10.3)	30 (6.6)	0.053	0.004

P-value — for comparisons between social network index levels; P_{MvsW} — for comparisons between sexes; obesity — body mass index ≥30 kg/m^2

Abbreviation: IQR, interquartile range

CVDs, IHD, or arrhythmia in both sexes (with a higher OR in men), but in the fully adjusted model (Table 5, Model 2) no significant associations were observed between the SNI and CVDs, IHD, or arrhythmia.

Active participation in organized social activities in the univariate analysis (Table 6, Model 1A) was significantly associated with CVDs and IHD in men and only with IHD in women but was not observed in the fully adjusted model. The number of sources of satisfactory social contact did not matter in men in the context of the analyzed diseases, but, in women, having at least two sources of satisfactory social contact was associated with 40%–50% lower chance of CVDs and arrhythmia, compared to those with none or one source of social bonds (Table 6, Model 1B). In the fully adjusted model (Table 6, Model 2), active participation in organized social activities was associated with higher chance of arrhythmia in both sexes and CVDs in women. We included the results of further in-depth analyses regarding arrhythmia in Supplementary material (*Tables S1* and *S2*). No significant association was found between the number of sources of satisfactory social contact in men, but in women having more than two sources of satisfactory social contact was related to lower chance of CVDs and arrhythmia, compared to having none or just one source. Marital status was not related to any of the analyzed diseases.

Based on our analysis, it is worth noting that risk factors/comorbidities turned out to be more strongly related to cardiovascular health status than social ties.

DISCUSSION

Cardiovascular diseases are the leading cause of mortality in people under 65 years of age and are a primary health, social, and economic problem in Poland. The number of CVD

Table 2. Relationship between prevalence of CVD, IHD, and arrhythmia and satisfaction with different components of the social network by sex (data adjusted for age). The WOBASZ II Study (n = 6043)

Organized social activity	Men		*P*-value	Women		*P*-value
	Active participation[a]			Active participation[a]		
	No	Yes		No	Yes	
N (%)	2012 (74.4)	693 (25.6)	–	2625 (78.9)	702 (21.1)	–
CVD, % (95% CI)	19.1 (17.5–20.7)	20.4 (17.6-23.1)	0.43	20.2 (18.8-21.7)	22.6 (19.7-25.4)	0.15
IHD, % (95% CI)	10.9 (9.6–12.2)	11.7 (9.4–13.9)	0.56	8.6 (7.6–9.6)	7.6 (5.6–9.5)	0.35
Arrhythmia, % (95% CI)	8.3 (7.1–9.5)	10.8 (8.7–12.9)	0.047	11.3 (10.1–12.6)	14.6 (12.2–17.0)	0.017
Social contact with child/children[b]	**Social contact**		***P*-value**	**Social contact**		***P*-value**
	None or unsatisfactory	Satisfactory		None or unsatisfactory	Satisfactory	
N (%)	71 (3.6)	1908 (96.4)	–	43 (1.5)	2732 (98.5)	–
CVD, % (95% CI)	23.6 (14.5–32.7)	22.7 (20.9–24.4)	0.84	36.4 (24.5–48.3)	22.5 (21.0–24.0)	0.023
IHD, % (95% CI)	14.3 (6.9–21.8)	13.2 (11.7–14.6)	0.77	18.7 (10.4–27.0)	9.2 (8.2–10.3)	0.027
Arrhythmia, % (95% CI)	16.8 (9.8–23.8)	10.2 (8.8–11.5)	0.07	21.0 (11.0–31.0)	12.8 (11.5–14.0)	0.11
Social contacts with at least 1 relative	**None or unsatisfactory**	**Satisfactory**	***P*-value**	**None or unsatisfactory**	**Satisfactory**	***P*-value**
N (%)	217 (8.1)	2480 (91.9)	–	198 (6.0)	3123 (94.0)	–
CVD, % (95% CI)	19.6 (14.7–24.5)	19.4 (18.0–20.9)	0.94	27.1 (21.7–32.4)	20.4 (19.1–21.7)	0.018
IHD, % (95% CI)	11.7 (7.8–15.7)	11.1 (9.9–12.2)	0.76	8.3 (4.6–12.0)	8.5 (7.5–9.4)	0.95
Arrhythmia, % (95% CI)	9.7 (6.0–13.4)	8.8 (7.7–9.9)	0.67	19.4 (14.9–23.9)	11.6 (10.5–12.8)	0.001
Social contacts with at least 1 friend	**None or unsatisfactory**	**Satisfactory**	***P*-value**	**None or unsatisfactory**	**Satisfactory**	***P*-value**
N (%)	383 (14.2)	2314 (85.8)	–	440 (13.2)	2885 (86.8)	–
CVD, % (95% CI)	18.5 (14.8–22.2)	19.7 (18.2–21.2)	0.55	21.7 (18.1–25.3)	20.6 (19.2–22.0)	0.56
IHD, % (95% CI)	10.8 (7.8–13.8)	11.2 (10.0–12.4)	0.82	9.3 (6.9–11.8)	8.3 (7.3–9.2)	0.43
Arrhythmia, % (95% CI)	8.7 (5.9–11.6)	9.0 (7.9–10.2)	0.86	12.0 (8.9–15.0)	12.1 (10.9–13.2)	0.95
	Number of sources of social contacts		***P*-value**	**Number of sources of social contacts**		***P*-value**
	0 or 1	2	3		0 or 1	2	3	
N (%)	190 (7.2)	912 (34.6)	1531 (58.2)	–	126 (3.9)	877 (27.0)	2241 (69.1)	–
CVD, % (95% CI)	18.1 (12.9–23.3)	21.6 (19.2–24.0)	18.3 (16.4–20.1)	0.09	31.2 (24.5–37.8)	21.7 (19.1–24.2)	19.7 (18.1–21.3)	0.003
IHD, % (95% CI)	11.3 (7.0–15.5)	12.7 (10.7–14.7)	10.2 (8.7–11.7)	0.16	11.6 (6.9–16.2)	10.5 (8.8–12.3)	7.4 (6.3–8.5)	0.005
Arrhythmia, % (95% CI)	9.5 (5.6–13.5)	9.6 (7.8–11.5)	8.3 (6.9–9.7)	0.51	20.1 (14.4–25.7)	12.4 (10.3–14.5)	11.3 (10.0–12.7)	0.011

[a]Active participation in at least 1 organization; [b]Only for people who declared having a child/children

Abbreviations: CVD, cardiovascular disease; CI, confidence interval; IHD, ischemic heart disease

Table 3. Distribution of satisfaction with social contacts, number of sources of social contacts, and organized social activity by the social network index and sex. The WOBASZ II Study (n = 6043)

	Social Network Index								
	Low			Moderate			High		
	Men	Women	*P*-value	Men	Women	*P*-value	Men	Women	*P*-value
N (%)	1229 (45.4)	1738 (52.1)	<0.001	944 (34.8)	1136 (34.1)	0.54	537 (19.8)	459 (13.8)	<0.001
Marital status									
Married	978 (79.6)	1186 (68.2)	<0.001	686 (72.7)	776 (68.3)	0.030	228 (42.5)	190 (41.4)	0.73
Satisfaction with contacts with at least									
1 friend, n (%)	911 (74.6)	1351 (78.0)	0.030	878 (93.5)	1079 (95.1)	0.12	525 (97.8)	455 (99.1)	0.09
1 relative, n (%)	1072 (87.9)	1584 (91.7)	<0.001	882 (93.7)	1090 (96.0)	0.017	526 (98.1)	449 (98.0)	0.91
1 child, n (%)	984 (95.5)	1551 (98.1)	<0.001	690 (97.7)	944 (98.9)	0.048	234 (96.3)	237 (98.7)	0.08
Number of sources of social contacts									
0–1, n (%)	132 (11.1)	88 (5.3)	<0.001	44 (4.8)	29 (2.6)	0.009	14 (2.7)	9 (2.0)	0.50
2, n (%)	369 (31.2)	452 (27.0)	0.015	262 (28.3)	219 (19.5)	<0.001	281 (53.7)	206 (46.0)	0.016
3, n (%)	683 (57.7)	1134 (67.7)	<0.001	620 (66.9)	874 (77.9)	<0.001	228 (43.6)	233 (52.0)	0.009
Organized social activities									
Active participation[a], n (%)	0 (0.0)	0 (0.0)	-	317 (33.6)	369 (32.5)	0.62	376 (70.2)	333 (72.6)	0.40

[a]Active participation in at least 1 organization

Table 4. Impact of the social network index level, sources of social contacts, and organized social activities on selected CVD risk factors in men and women. The WOBASZ II Study (n = 6043)

Sex	Model	Predictor	Cardiovascular risk factor			
			Smoking	Hypertension	Diabetes	Obesity
			OR (95% CI); *P*-value	OR (95% CI); *P*-value	OR (95% CI); *P*-value	OR (95% CI); *P*-value
Men	**Model 1**	**Age**	0.97 (0.97–0.98); <0.001	1.06 (1.06–1.07); <0.001	1.06 (1.05–1.07); <0.001	1.02 (1.02–1.03); <0.001
		Education				
		Primary	4.35 (3.07–6.16); <0.001	0.95 (0.68–1.31); 0.75	1.70 (0.998–2.90); 0.051	0.91 (0.64–1.31); 0.62
		Vocational	3.84 (2.88–5.13); <0.001	1.25 (0.97–1.61); 0.09	1.43 (0.88–2.34); 0.15	1.29 (0.97–1.71); 0.08
		Secondary	2.33 (1.76–3.08); <0.001	1.14 (0.89–1.46); 0.29	1.66 (1.02–2.71); 0.040	1.41 (1.07–1.85); 0.014
		SNI level				
		Low	1.35 (1.05–1.74); 0.020	0.97 (0.76–1.25); 0.83	1.05 (0.68–1.61); 0.83	1.05 (0.80–1.38); 0.72
		Moderate	1.07 (0.83–1.38); 0.60	1.09 (0.85–1.39); 0.51	0.90 (0.58–1.40); 0.64	1.17 (0.89–1.53); 0.26
	Model 2	**Age**	0.98 (0.97–0.99); <0.001	1.06 (1.05–1.07); <0.001	1.06 (1.05–1.07); <0.001	1.02 (1.01–1.02); <0.001
		Education				
		Primary	3.93 (2.74–5.64); <0.001	1.03 (0.73–1.44); 0.88	1.57 (0.89–2.75); 0.12	1.16 (0.80–1.70); 0.44
		Vocational	3.92 (2.91–5.28); <0.001	1.36 (1.04–1.77); 0.023	1.33 (0.80–2.23); 0.28	1.42 (1.05–1.91); 0.023
		Secondary	2.28 (1.71–3.03); <0.001	1.23 (0.96–1.58); 0.11	1.66 (0.999–2.76); 0.050	1.56 (1.17–2.07); 0.002
		Marital status				
		Married	0.78 (0.63–0.97); 0.028	0.87 (0.70–1.09); 0.23	0.91 (0.66–1.26); 0.57	2.15 (1.66–2.78); <0.001
		Number of sources of social contacts				
		3	0.79 (0.55–1.11); 0.17	0.82 (0.57–1.17); 0.27	0.96 (0.59–1.56); 0.86	1.38 (0.90–2.10); 0.14
		2	0.89 (0.63–1.26); 0.51	0.62 (0.43–0.89); 0.010	0.81 (0.49–1.36); 0.42	1.26 (0.81–1.95); 0.30
		Organized social activity				
		Active participation[a]	0.87 (0.70–1.07); 0.19	1.21 (0.98–1.48); 0.07	0.65 (0.45–0.94); 0.022	1.16 (0.93–1.44); 0.19
Women	**Model 1**	**Age**	0.98 (0.98–0.99); <0.001	1.09 (1.08–1.10); <0.001	1.07 (1.05–1.08); <0.001	1.04 (1.03–1.04); <0.001
		Education				
		Primary	2.09 (1.48–2.95); <0.001	1.43 (1.05–1.95); 0.023	2.25 (1.29–3.92); 0.004	1.88 (1.38–2.56); <0.001
		Vocational	2.85 (2.13–3.80); <0.001	1.84 (1.41–2.41); <0.001	2.22 (1.29–3.82); 0.004	1.81 (1.37–2.39); <0.001
		Secondary	2.34 (1.82–3.01); <0.001	1.23 (0.97–1.56); 0.08	1.51 (0.90–2.53); 0.12	1.46 (1.14–1.87); 0.003
		SNI level				
		Low	1.26 (0.94–1.69); 0.12	1.37 (1.03–1.82); 0.033	1.58 (0.88–2.84); 0.12	1.13 (0.84–1.51); 0.43
		Moderate	1.12 (0.83–1.50); 0.46	1.14 (0.84–1.53); 0.40	1.35 (0.74–2.48); 0.33	1.28 (0.95–1.72); 0.10
	Model 2	**Age**	0.98 (0.98–0.99); <0.001	1.09 (1.08–1.10); <0.001	1.06 (1.05–1.08); <0.001	1.04 (1.03–1.04); <0.001
		Education				
		Primary	1.99 (1.40–2.84); <0.001	1.43 (1.05–1.97); 0.025	2.50 (1.39–4.46); 0.002	1.87 (1.37–2.56); <0.001
		Vocational	2.81 (2.10–3.76); <0.001	1.86 (1.41–2.44); <0.001	2.59 (1.47–4.55); <0.001	1.75 (1.31–2.32); <0.001
		Secondary	2.24 (1.73–2.89); <0.001	1.21 (0.95–1.54); 0.12	1.60 (0.93–2.76); 0.09	1.39 (1.08–1.79); 0.001
		Marital status				
		Married	0.76 (0.63–0.93); 0.007	0.98 (0.81–1.19); 0.87	0.83 (0.63–1.11); 0.21	1.11 (0.93–1.34); 0.26
		Number of sources of social contacts				
		3	1.50 (0.90–2.50); 0.12	0.70 (0.43–1.14); 0.15	0.71 (0.40–1.26); 0.24	1.08 (0.69–1.68); 0.75
		2	1.28 (0.75–2.16); 0.36	0.81 (0.49–1.35); 0.42	0.64 (0.35–1.17); 0.15	0.97 (0.61–1.54); 0.89
		Organized social activities				
		Active participation[a]	0.75 (0.59–0.96); 0.021	0.76 (0.61–0.94); 0.011	0.80 (0.54–1.17); 0.24	0.86 (0.69–1.07); 0.16

Reference: high SNI, high education level, unmarried, 0–1 sources of social contacts, none or passive participation in organized social activities

[a]Active participation in at least 1 organization

Abbreviations: OR, odds ratio; SNI, social network index; other — see Table 2

deaths was decreasing in Poland from 1991, but due to the COVID-19 pandemic, this positive trend of declining CVD mortality was reversed with a 17% excess in CVD deaths in 2020 [12]. Poland still belongs to countries with high cardiovascular risk, with standardized rates of CVD deaths higher by about 40% compared to the European average [13].

Psychosocial risk factors such as low SS, social isolation, stress, and depression were shown to play an important role in CVD pathogenesis and the risk of cardiovascular death. In the Framingham Heart Study, a low SNI score was associated with 62% higher all-cause mortality compared to the highest SNI group [14]. Deficiencies in social relationships are associated with increased risk of developing coronary heart disease and stroke [15]. Undoubtedly, social support, its changes and the way of its provision during the COVID-19 pandemic played a particularly important role, which requires further research.

Researchers in the Australian questionnaire substudy (ASPREE Longitudinal Study of Older People — ALSOP), conducted in more than 11 000 individuals aged 70 and over, suggest that social isolation and low SS should be considered in future CVD risk prediction models [16]. Data from the Multi-Ethnic Study of Atherosclerosis (MESA), which examined CVD risk factors, showed that emotional

Table 5. Impact of SNI level on CVD, IHD, and arrhythmia in men and women (logistic regression analysis). The WOBASZ II Study (n = 6043)

Sex	Model	Predictor	Cardiovascular disease	Ischemic heart disease	Arrhythmia
			OR (95% CI); *P*-value	OR (95% CI); *P*-value	OR (95% CI); *P*-value
Men	Model 1	SNI level			
		Low	2.49 (1.85–3.36); <0.001	2.68 (1.79–4.01); <0.001	1.89 (1.26–2.82); 0.002
		Moderate	1.74 (1.27–2.38); <0.001	2.04 (1.33–3.11); 0.001	1.41 (0.92–2.16); 0.11
	Model 2	Age	1.08 (1.07–1.09); <0.001	1.08 (1.06–1.09); <0.001	1.06 (1.04–1.07); <0.001
		Education			
		Primary	0.82 (0.52–1.31); 0.41	1.32 (0.73–2.37); 0.36	1.04 (0.57–1.89); 0.90
		Vocational	0.94 (0.63–1.39); 0.74	1.54 (0.90–2.62); 0.11	0.97 (0.57–1.66); 0.91
		Secondary	1.19 (0.81–1.76); 0.37	1.47 (0.86–2.49); 0.16	1.48 (0.88–2.46); 0.14
		Current smoker	0.67 (0.51–0.89); 0.005	0.65 (0.45–0.92); 0.016	0.59 (0.40–0.88); 0.010
		Hypertension	1.69 (1.30–2.20); <0.001	1.60 (1.15–2.22); 0.005	2.08 (1.44–2.98); <0.001
		Diabetes	1.81 (1.34–2.45); <0.001	1.73 (1.23–2.42); 0.002	1.61 (1.11–2.34); 0.012
		Obesity	1.09 (0.85–1.41); 0.49	1.21 (0.90–1.64); 0.21	0.95 (0.68–1.33); 0.77
		SNI level			
		Low	0.85 (0.58–1.24); 0.38	0.79 (0.49–1.27); 0.32	0.75 (0.46–1.21); 0.23
		Moderate	0.97 (0.66–1.42); 0.85	1.02 (0.63–1.66); 0.92	0.90 (0.55–1.45); 0.66
Women	Model 1	SNI level			
		Low	1.82 (1.37–2.43); <0.001	2.34 (1.49–3.69); <0.001	1.55 (1.08–2.23); 0.017
		Moderate	1.42 (1.05–1.92); 0.024	1.37 (0.84–2.24); 0.21	1.61 (1.11–2.35); 0.013
	Model 2	Age	1.06 (1.05–1.07); <0.001	1.09 (1.07–1.10); <0.001	1.04 (1.03–1.05); <0.001
		Education			
		Primary	1.02 (0.71–1.46); 0.91	2.01 (1.06–3.80); 0.033	0.70 (0.46–1.05); 0.09
		Vocational	0.91 (0.64–1.28); 0.58	1.60 (0.83–3.08); 0.16	0.68 (0.45–1.01); 0.06
		Secondary	0.95 (0.71–1.28); 0.73	1.57 (0.86–2.88); 0.14	0.78 (0.56–1.09); 0.15
		Current smoker	1.07 (0.83–1.38); 0.59	0.86 (0.56–1.34); 0.51	1.07 (0.79–1.45); 0.66
		Hypertension	1.31 (1.04–1.64); 0.020	2.15 (1.49–3.09); <0.001	1.27 (0.97–1.67); 0.08
		Diabetes	1.21 (0.90–1.62); 0.21	1.17 (0.82–1.68); 0.38	1.23 (0.88–1.72); 0.23
		Obesity	1.56 (1.26–1.92); <0.001	1.71 (1.28–2.29); <0.001	1.39 (1.09–1.79); 0.009
		SNI level			
		Low	0.76 (0.54–1.07); 0.11	0.61 (0.35–1.05); 0.07	0.87 (0.58–1.31); 0.51
		Moderate	0.93 (0.66–1.31); 0.67	0.70 (0.40–1.24); 0.22	1.22 (0.81–1.82); 0.34

Reference: high SNI, high education level, currently nonsmoker, lack of hypertension, lack of diabetes, body mass index <30 kg/m^2

Model 1 — univariate analysis; Model 2 — multivariable analysis

Abbreviations: see Tables 2 and 4

SS played a protective role against severe CVDs (confirmed CHD death, confirmed or likely MI, resuscitated cardiac arrest, other atherosclerotic CVD death, or fatal or nonfatal stroke) [17].

As psychosocial risk factors influence health, they are worth considering in research studies to examine the scale of the problem both in the general population and in the population of people with high cardiovascular risk.

Social support can be obtained from relatives, friends, organizations, health care professionals, and even through the Internet, and it is a complex form of mutual interactions of its components (i.e., marital status, social contact with children, relatives or friends, and active participation in organizations), so its effect on health depends on the type of support and on who gives this support. Personal relationships and family support can be based on emotional support, also support in providing information about health promotion, preparing healthy food or accompanying during physical activities, so the role of social relationships in sustaining good health should be underlined [18]. The role of support groups (family and friends) in the preventive cardiology programs for high-risk individuals was underlined in the EUROACTION project [19]. Therefore, our study evaluated associations not only between SS as a whole index but also between particular components of SNI and CVDs in Polish adults based on the results of the population-based cross-sectional survey. In men, except for active participation in organized social activities, the type of social contact (with children, relatives, or friends) or the number of sources of social contact did not play a role in maintaining cardiovascular health. In women, satisfactory contact with children and relatives and support from more than one source of social contact were associated with better cardiovascular health. This is consistent with some findings from the Polish HAPIEE cohort, in which the associations between psychosocial risk factors and CVD incidence were much stronger in women than in men [20]. The number of social connections in women is not always associated with higher SS because women's involvement in many different social roles may be related to increased stress and overwork [21]. However, we did not confirm this relationship because more sources of satisfactory interpersonal contacts were independently associated with better CHS in women.

Table 6. Impact of SNI components on CVD, IHD, and arrhythmia in men and women (logistic regression analysis). The WOBASZ II Study (n = 6043)

Sex	Model	Predictor	Cardiovascular disease OR (95% CI); *P*-value	Ischemic heart disease OR (95% CI); *P*-value	Arrhythmia OR (95% CI); *P*-value
Men	Model 1A	Organized social activity			
		Active participation[a]	0.76 (0.61–0.96); 0.020	0.74 (0.55–0.99); 0.043	1.02 (0.75–1.38); 0.91
	Model 1B	Number of sources of social contacts			
		3	1.16 (0.79–1.70); 0.46	1.03 (0.65–1.64); 0.89	0.96 (0.58–1.59); 0.87
		2	0.77 (0.51–1.15); 0.20	0.67 (0.41–1.10); 0.11	0.67 (0.39–1.15); 0.14
	Model 2	Age	1.08 (1.07–1.09); <0.001	1.08 (1.06–1.09); <0.001	1.05 (1.04–1.07); <0.001
		Education			
		Primary	0.77 (0.48–1.25); 0.29	1.22 (0.66–2.24); 0.53	0.99 (0.53–1.85); 0.98
		Vocational	0.91 (0.61–1.38); 0.67	1.55 (0.89–2.68); 0.12	0.96 (0.55–1.67); 0.89
		Secondary	1.12 (0.75–1.67); 0.58	1.39 (0.80–2.40); 0.24	1.41 (0.84–2.37); 0.20
		Current smoker	0.66 (0.50–0.88); 0.005	0.63 (0.44–0.91); 0.013	0.57 (0.38–0.86); 0.008
		Hypertension	1.78 (1.36–2.33); <0.001	1.62 (1.16–2.26); 0.004	2.22 (1.53–3.22); <0.001
		Diabetes	1.92 (1.41–2.61); <0.001	1.75 (1.24–2.47); 0.002	1.66 (1.14–2.44); 0.009
		Obesity	1.10 (0.85–1.43); 0.49	1.23 (0.90–1.68); 0.19	0.98 (0.70–1.38); 0.92
		Organized social activites			
		Active participation*	1.12 (0.84–1.50); 0.45	1.22 (0.85–1.74); 0.28	1.50 (1.04–2.15); 0.029
		Number of sources of social contacts			
		3	1.19 (0.73–1.93); 0.49	1.03 (0.59–1.79); 0.91	0.98 (0.54–1.78); 0.95
		2	1.45 (0.87–2.41); 0.15	1.16 (0.65–2.09); 0.61	1.09 (0.58–2.04); 0.78
		Marital status			
		Married	0.95 (0.70–1.28); 0.72	0.98 (0.68–1.40); 0.90	0.80 (0.55–1.17); 0.25
Women	Model 1A	Organized social activity			
		Active participation[a]	1.00 (0.82–1.24); 0.97	0.70 (0.50–0.97); 0.033	1.22 (0.95–1.56); 0.12
	Model 1B	Number of sources of social contacts			
		3	0.55 (0.37–0.82); 0.003	0.65 (0.37–1.14); 0.13	0.53 (0.33–0.83); 0.006
		2	0.44 (0.29–0.66); <0.001	0.60 (0.33–1.09); 0.09	0.45 (0.27–0.73); 0.001
	Model 2	Age	1.06 (1.05–1.07); <0.001	1.09 (1.07–1.10); <0.001	1.04 (1.03–1.05); <0.001
		Education			
		Primary	1.07 (0.74–1.55); 0.72	2.14 (1.11–4.12); 0.022	0.72 (0.47–1.10); 0.13
		Vocational	0.95 (0.67–1.35); 0.78	1.61 (0.82–3.13); 0.16	0.72 (0.48–1.08); 0.11
		Secondary	0.99 (0.73–1.33); 0.92	1.61 (0.87–2.98); 0.13	0.82 (0.59–1.16); 0.26
		Current smoker	1.10 (0.85–1.42); 0.48	0.91 (0.59–1.41); 0.67	1.12 (0.83–1.53); 0.46
		Hypertension	1.35 (1.07–1.70); 0.011	2.12 (1.47–3.06); <0.001	1.31 (0.99–1.73); 0.06
		Diabetes	1.21 (0.89–1.64); 0.22	1.16 (0.80–1.67); 0.43	1.23 (0.87–1.74); 0.25
		Obesity	1.52 (1.23–1.88); <0.001	1.62 (1.21–2.19); 0.001	1.39 (1.08–1.79); 0.011
		Organized social activity			
		Active participation[a]	1.42 (1.11–1.82); 0.005	1.29 (0.87–1.91); 0.20	1.47 (1.11–1.95); 0.007
		Number of sources of social contacts			
		3	0.55 (0.34–0.89); 0.015	1.04 (0.53–2.05); 0.90	0.49 (0.30–0.82); 0.006
		2	0.52 (0.31–0.87); 0.012	1.03 (0.51–2.08); 0.95	0.50 (0.29–0.85); 0.011
		Marital status			
		Married	1.06 (0.86–1.32); 0.57	1.15 (0.84–1.58); 0.38	1.02 (0.79–1.31); 0.90

Reference: high SNI, high education level, unmarried, 0–1 sources of social contacts, none or passive participation in organized social activities, currently nonsmoker, lack of hypertension, lack of diabetes, body mass index <30 kg/m^2

Model 1A and Model 1B — univariate analysis; Model 2 — multivariable analysis

[a]Active participation in at least 1 organization

Abbreviations: see Table 2 and 4

In general, there is a difference between men and women in SS use. Men use support less often than women to deal with life experiences [22] although their health benefits from SS were the same or even greater than women's benefits. There are at least two probable reasons for that: first, men believe they do not need any help from others, and second, the traditional perception of gender roles, which emphasizes independence and low emotional disclosure in men, does not let them ask for help (this can be seen as a weakness). So, for men, the use of support is associated, to a greater extent than in women, with weighing costs (decreased sense of self-control and self-efficacy) and benefits (feeling better, more calm) [23].

Notable is the contribution of organized social activities in the SNI. They can be perceived as the fourth source of satisfying contacts, especially in people who have few or no sources of social ties, and in this sense, we tried to explain its protective impact in the univariate analysis. However,

we suppose that with the full and/or excessive involvement of the individual in social activities, the protective role of this component ends and it becomes an additional burden and/or workload, which is visible in the multivariable analysis in the case of arrhythmia (in both sexes). The observed association requires more detailed research, and we plan to do so in our future work. In the Framingham Heart Study, the results of the follow-up analysis on associations between the SNI and the incidence and mortality due to atrial fibrillation showed that among the components of SNI, only active participation in organized social activities was associated with a higher incidence of atrial fibrillation (HR, 1.35 [1.16–1.57]; $P = 0.001$) [14]. This is partly consistent with our results (we found a higher prevalence of arrhythmia in people who actively participated in organized social activities); however, our study was not observational.

In line with the results of the European Social Survey that indicated a relationship between education and social support and suggested the need to consider socioeconomic factors in research on health effects of social support [24], we included in our models the level of education. In contrast to our predictions, in a fully adjusted model, no significant and independent association between the SNI (as a whole index) and cardiovascular health was found. The sociodemographic risk factors (age, education) and risk factors/comorbidities (smoking, hypertension, DM, and obesity) were found to be more strongly associated with cardiovascular health compared to social ties.

People who receive more support are known to have better physical and psychological health, better quality of life [25, 26], greater sense of self-worth [27], better lifestyle, and increased compliance with medications and rehabilitation. On the contrary, lack of support is a barrier to adherence to a healthy lifestyle, as we showed in our previous study WOBASZ (2003–2005), where low SS was associated with unhealthy lifestyle [28].

Low SS was very prevalent in the Polish population, in 2013–2014 almost half of adult Poles had low SS (with predominance in women) compared to 31.0% of men and 39.0% of women in WOBASZ [28]. Individuals with low SS were older and characterized by a worse risk factor profile (higher prevalence of obesity, smoking, hypertension) and worse cardiovascular health (more cases of CVDs, IHD, and arrhythmia). The prevalence of classical risk factors in low SS individuals was even higher than the Polish population average [29].

Given that the prevalence of low SS has increased significantly since 2003–2005 (from 31.0% to 45.4%% in men, and from 39.0% to 52.2% in women), and probably has grown even more during the COVID-19 pandemic (this requires investigations), it is important to consider it as a CVD risk factor and also as a factor that plays an important role in CVDs prevention. Although data analyzed in our study were collected 10 years ago, the results allowed us to elucidate the importance of social contact and its associations with CVDs. We demonstrated that even if support measured by the SNI does not seem to matter, its components such as satisfactory social contacts and the number of social ties play an important role in relation to CVDs. Probably these associations persist, even if the social support mechanisms have changed. Last but not least, we are convinced that our data will be interesting for readers and will be used in future comparative analyses.

Limitations

A major limitation is the cross-sectional nature of the WOBASZ II study, which allowed us to analyze the associations, but not the cause-and-effect relationship between SNI and CVDs. Furthermore, the WOBASZ II study was an epidemiological survey, made on more than 6000 individuals, so according to the specificity of epidemiological studies, especially those made on thousands of participants, nearly all data including medical history are self-reported and based on questionnaires (without clinical verification). An additional limitation is the response rate of slightly less than 50% [9], which follows trends toward lower response rates in European studies.

CONCLUSIONS

The results of our study showed a higher prevalence of low SS (presented as a low SNI) in women compared to men. Participants with low SS had a worse cardiovascular disease risk factor profile. Low SS was associated with CVDs, IHD, and arrhythmia in both sexes only in a univariate analysis. None of the analyzed social contacts (with children, relatives, or friends), no matter how satisfactory they were, was associated with cardiovascular health in men. However, in women, satisfactory contact with children or relatives appeared to be associated with a lower prevalence of CVDs or arrhythmia. Active participation in organized social activities was associated with higher chance of arrhythmia in both sexes, regardless of other risk factors/comorbidities and age. However last finding should be interpreted with caution due to self-reported data on arrhythmia (without clinical verification of diagnosis), so it requires further investigations.

Supplementary material

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

Article information

Conflict of interest: None declared.

Funding: WOBASZ II was financed from the resources of the Polish Ministry of Health within the framework of the National Programme of Prevention and Treatment of Cardiovascular Diseases POLKARD (2010–2012) — Task: Analyses and epidemiology: "Monitoring of the epidemiological situation in Poland in the field of cardiovascular diseases" (no. 5/8/1/2012/101/945; to GB).

REFERENCES

1. World Health Organization (WHO). Fact sheets: Cardiovascular diseases (CVDs). 2020. www.who.int/en/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds) (accessed: July 25, 2023).
2. Ford ES, Ahluwalia IB, Galuska DA. Social relationships and cardiovascular disease risk factors: findings from the third national health and nutrition examination survey. Prev Med. 2000; 30(2): 83–92, doi: 10.1006/pmed.1999.0606, indexed in Pubmed: 10656835.
3. Sarason I, Levine H, Basham R, et al. Assessing social support: The Social Support Questionnaire. J Pers Soc Psychol. 1983; 44: 127–139, doi: 10.1037/0022-3514.44.1.127.
4. Rico-Uribe LA, Caballero FF, Olaya B, et al. Loneliness, social networks, and health: a cross-sectional study in three countries. PLoS One. 2016; 11(1): e0145264, doi: 10.1371/journal.pone.0145264, indexed in Pubmed: 26761205.
5. Dar T, Radfar A, Abohashem S, et al. Psychosocial stress and cardiovascular disease. Curr Treat Options Cardiovasc Med. 2019; 21(5): 23, doi: 10.1007/s11936-019-0724-5, indexed in Pubmed: 31028483.
6. Roncella A. Psychosocial risk factors and ischemic heart disease: a new perspective. Rev Recent Clin Trials. 2019; 14(2): 80–85, doi: 10.2174/1574887114666190301141628, indexed in Pubmed: 30836925.
7. WHO Health for all database. Availability of social support. https://gateway.euro.who.int/en/indicators/hfa_621-0600-availability-of-social-support/visualizations/#id=27318&tab=table (accessed: September 20, 2023).
8. Zhou J, Havens KL, Starnes CP, et al. Changes in social support of pregnant and postnatal mothers during the COVID-19 pandemic. Midwifery. 2021; 103: 103162, doi: 10.1016/j.midw.2021.103162, indexed in Pubmed: 34649034.
9. Drygas W, Niklas AA, Piwońska A, et al. Multi-centre national population health examination survey (WOBASZ II study): assumptions, methods, and implementation. Kardiol Pol. 2016; 74(7): 681–690, doi: 10.5603/KP.a2015.0235, indexed in Pubmed: 26620680.
10. Berkman LF, Syme SL. Social networks, host resistance, and mortality: a nine-year follow-up study of Alameda county residents. Am J Epidemiol. 1979; 109(2): 186–204, doi: 10.1093/oxfordjournals.aje.a112674, indexed in Pubmed: 425958.
11. World Health Organization. MONICA Psychosocial Optional Study Manual: Suggested Measurement Instruments Copenhagen: WHO Regional Office for Europe, 1989.
12. Information of deaths in Poland in 2020 [article in Polish]. Ministry of Health 2021. www.gov.pl/web/zdrowie/raport-o-zgonach-w polsce-w 2020-r (accessed: September 20, 2023).
13. Wojtyniak B, Goryński P. Health situation of the Polish population and its determinants. National Institute of Public Health [text in Polish]. Warszawa, 2020.
14. Kornej J, Ko D, Lin H, et al. The association between social network index, atrial fibrillation, and mortality in the Framingham Heart Study. Sci Rep. 2022; 12(1): 3958, doi: 10.1038/s41598-022-07850-9, indexed in Pubmed: 35273243.
15. Valtorta NK, Kanaan M, Gilbody S, et al. Loneliness and social isolation as risk factors for coronary heart disease and stroke: systematic review and meta-analysis of longitudinal observational studies. Heart. 2016; 102(13): 1009–1016, doi: 10.1136/heartjnl-2015-308790, indexed in Pubmed: 27091846.
16. Freak-Poli R, Ryan J, Neumann JT, et al. Social isolation, social support and loneliness as predictors of cardiovascular disease incidence and mortality. BMC Geriatr. 2021; 21(1): 711, doi: 10.1186/s12877-021-02602-2, indexed in Pubmed: 34922471.
17. Riahi SM, Yousefi A, Saeedi F, et al. Associations of emotional social support, depressive symptoms, chronic stress, and anxiety with hard cardiovascular disease events in the United States: the multi-ethnic study of atherosclerosis (MESA). BMC Cardiovasc Disord. 2023; 23(1): 236, doi: 10.1186/s12872-023-03195-x, indexed in Pubmed: 37142978.
18. Berkman LF. The role of social relations in health promotion. Psychosom Med. 1995; 57(3): 245–254, doi: 10.1097/00006842-199505000-00006, indexed in Pubmed: 7652125.
19. Wood DA. EUROACTION: A European Society of Cardiology demonstration project in preventive cardiology: A cluster randomised controlled trial of a multi-disciplinary preventive cardiology programme for coronary patients, asymptomatic high risk individuals and their families. Summary of design, methodology and outcomes. Eur Heart J. 2004; 6(Suppl J): J3–J15, doi: 10.1093/eurheartj/6.suppl_j.j3.
20. Kozela M, Doryńska A, Bobak M, et al. Accumulation of psychosocial risk factors and incidence of cardiovascular disease: a prospective observation of the Polish HAPIEE cohort. Kardiol Pol. 2019; 77(5): 535–540, doi: 10.33963/KP.14814, indexed in Pubmed: 31066730.
21. Orth-Gomér K, Wamala SP, Horsten M, et al. Marital stress worsens prognosis in women with coronary heart disease: The Stockholm Female Coronary Risk Study. JAMA. 2000; 284(23): 3008–3014, doi: 10.1001/jama.284.23.3008, indexed in Pubmed: 11122587.
22. Taylor SE, Klein LC, Lewis BP, et al. Biobehavioral responses to stress in females: tend-and-befriend, not fight-or-flight. Psychol Rev. 2000; 107(3): 411–429, doi: 10.1037/0033-295x.107.3.411, indexed in Pubmed: 10941275.
23. Larsen BA. Psychological mechanisms of gender differences in social support use under stress. US San Diego Electronic Theses and Dissertations. https://escholarship.org/uc/item/1p66v767 (accessed: September 8, 2023).
24. von dem Knesebeck O, Geyer S. Emotional support, education and self-rated health in 22 European countries. BMC Public Health. 2007; 7: 272, doi: 10.1186/1471-2458-7-272, indexed in Pubmed: 17908313.
25. Shahin W, Kennedy GA, Stupans I. The association between social support and medication adherence in patients with hypertension: A systematic review. Pharm Pract (Granada). 2021; 19(2): 2300, doi: 10.18549/PharmPract.2021.2.2300, indexed in Pubmed: 34221197.
26. Luna E, Ruiz M, Malyutina S, et al. The prospective association between frequency of contact with friends and relatives and quality of life in older adults from Central and Eastern Europe. Soc Psychiatry Psychiatr Epidemiol. 2020; 55(8): 1001–1010, doi: 10.1007/s00127-020-01834-8, indexed in Pubmed: 32040668.
27. Thomas PA, Liu H, Umberson D. Family relationships and well-being. Innov Aging. 2017; 1(3): igx025, doi: 10.1093/geroni/igx025, indexed in Pubmed: 29795792.
28. Piwoński J, Piwońska A, Sygnowska E. Is level of social support associated with health behaviours modifying cardiovascular risk? Results of the WOBASZ study. Kardiol Pol. 2012; 70(8): 803–809, indexed in Pubmed: 22933212.
29. Pająk A, Jankowski P, Zdrojewski T. The burden of cardiovascular disease risk factors: A current problem. Kardiol Pol. 2022; 80(1): 5–15, doi: 10.33963/KP.a2022.0018, indexed in Pubmed: 35137945.

Prognosis for patients with apical hypertrophic cardiomyopathy: A multicenter cohort study based on propensity score matching

Huihui Ma[1, 2*], Yongmei Zhou[1, 2*], Ye He[3], Chaoping Yu[4], Qian Liao[1, 2], Hutao Xi[1, 2, 5], Rong Luo[6], Mingjiang Liu[1, 2], Jianhong Tao[1, 2], Tianhu Liu[4*], Xiaoping Li[1, 2]

[1]Department of Cardiology, Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu, Sichuan, China
[2]Chinese Academy of Sciences Sichuan Translational Medicine Research Hospital, Chengdu, China
[3]Visual Computing and Virtual Reality Key Laboratory of Sichuan Province, Sichuan Normal University, Chengdu, Sichuan, China
[4]Department of Cardiology, Pidu District People's Hospital, Chengdu, Sichuan, China
[5]Southwest Medical University, Luzhou, Sichuan, China
[6]Institute of Geriatric Cardiovascular Disease, Chengdu Medical College, Chengdu, Sichuan, China
*These authors contributed equally to this work.

Correspondence to:
Xiaoping Li, PhD,
Sichuan Provincial People's Hospital,
Section 32, 1st Ring Road West,
Qingyang District,
610072 Chengdu, Sichuan, China,
phone: +86 28 873 94 344,
e-mail: lixiaoping0119@163.com

DOI: 10.33963/v.kp.98355

Received:
June 26, 2023

Accepted:
November 29, 2023

Early publication date:
December 11, 2023

ABSTRACT

Background: Apical hypertrophic cardiomyopathy (AHCM) is a subtype of HCM, and few studies on the prognosis in AHCM are available.

Aims: This study aimed to explore the clinical prognosis for AHCM and non-AHCM patients through clinical data based on propensity score matching (PSM) in a large cohort of Chinese HCM patients.

Methods: The cohort study included 2268 HCM patients, 226 AHCM and 2042 non-AHCM patients from 13 tertiary hospitals, who were treated between 1996 and 2021. Fifteen demographic and clinical variables of 226 AHCM patients and 2042 non-AHCM patients were matched using 1:2 PSM. A Cox proportional hazard regression model was constructed to assess the effect of AHCM on mortality.

Results: During a median follow-up of 5.1 (2.4–8.4) years, 353 (15.6%) of the 2268 HCM patients died, of whom 205 died due to cardiovascular mortality/cardiac transplantation and 94 experienced sudden cardiac death (SCD). In the matched cohort, the ACHM patients had lower rates of all-cause mortality ($P = 0.003$), cardiovascular mortality/cardiac transplantation ($P = 0.03$), and SCD ($P = 0.02$) than the non-AHCM patients. Furthermore, the Cox proportional hazard regression model showed that AHCM was an independent prognostic predictor of all-cause HCM mortality ($P = 0.004$) and a univariable prognostic predictor of cardiovascular mortality/cardiac transplantation ($P = 0.03$) and for SCD ($P = 0.03$). However, AHCM was not significant in multivariable Cox regression models in relation to cardiovascular mortality/cardiac transplantation and SCD.

Conclusion: AHCM had a favorable prognosis both before and after matching, with lower all-cause mortality, cardiovascular mortality/cardiac transplantation, and SCD than non-AHCM.

Key words: apical hypertrophic cardiomyopathy, all-cause mortality, cardiovascular mortality/cardiac transplantation, propensity score matching, sudden cardiac death

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most common hereditary cardiomyopathy and usually manifests as thickening of the left ventricular wall without secondary causes and left ventricular dilatation [1]. Notably, apical hypertrophic cardiomyopathy (AHCM) is a specific type of primary HCM that was first reported in Japan by Sakamoto et al. in 1976 [2]. Myocardial hypertrophy in AHCM is mainly limited to the apex of the left ventricular papillary muscle, usually without left ventricular outflow tract (LVOT) dynamic obstruction and an LVOT gradient [3–4]. Moreover, AHCM is the most common HCM in East Asian populations, accounting for 25% of all

WHAT'S NEW?

Propensity score matching can address the imbalance of confounders in observational studies. This study aimed to explore the clinical prognosis in apical hypertrophic cardiomyopathy (AHCM) and non-AHCM patients through clinical data based on propensity score matching. We showed that AHCM had a favorable prognosis both before and after matching, with lower all-cause mortality, cardiovascular mortality/cardiac transplantation, and sudden cardiac death than non-AHCM.

the cases of HCM in the Asian population and 1%–10% of the HCM cases in non-Asian populations [5].

HCM patients may experience palpitations, shortness of breath, chest tightness, and chest pain, as well as symptoms of cardiac dysfunction [1]. Nevertheless, AHCM patients may be more likely to have fewer clinical signs or symptoms [3]. The typical clinical features of AHCM are giant negative T waves (GNTs) on electrocardiogram (ECG) and "spade-like" changes on echocardiography [2, 3]. Many studies have confirmed the favorable prognosis in AHCM [5–9]. However, recent studies have questioned this [4, 10], as fatal arrhythmias and even sudden cardiac death (SCD) have also been reported in AHCM patients [11–14].

Propensity score matching is a statistical technique introduced in 1983 and provides a method for effectively adjusting for confounding variables that are known and measured in observational data [15]. Studies on AHCM prognosis are not completely consistent, and there are few studies on the prognostic value of AHCM in HCM patients. Therefore, this study aimed to evaluate AHCM prognosis as well as the effect of AHCM on HCM mortality based on propensity score matching.

METHODS

Study population

We conducted a multicenter cohort study on 2268 HCM patients, 226 with AHCM and 2042 with non-AHCM, who were hospitalized at 13 tertiary hospitals from 1996 to 2021. In addition, we performed propensity score matching for AHCM and non-AHCM with a 1:2 ratio. Ultimately, 226 AHCM patients and 452 non-AHCM patients were enrolled after matching. Patients with cardiac or systemic disease capable of producing similar magnitudes of hypertrophy, such as cardiac amyloidosis, Fabry disease, Noonan syndrome, and amyloidosis cardiomyopathy etc., were excluded.

Diagnostic criteria and definitions

HCM is defined as a wall thickness of left ventricular myocardium ≥15 mm in one or more left segments. It can be measured by any imaging technique (echocardiography, cardiac magnetic resonance imaging [CMR], or computed tomography [CT]), rather than explained by loading conditions alone [16, 17]. Patients with familial HCM or a family history of SCD in first-degree relatives with a smaller degree of wall thickness (13–14) can be diagnosed with HCM [16].

The diagnostic criteria for AHCM include a left ventricular apex (below the insertion of papillary muscles) ≥15 mm as shown by a two-dimensional echocardiogram or CMR. However, since the apex is the thinnest part of the left ventricle, a lower threshold (13–14 mm) can be used to diagnose AHCM when clinical manifestations and other imaging features (electrocardiography, family history, genotyping, CMR imaging, echocardiography, *etc.*) favor AHCM diagnosis [16–18].

Follow-up and endpoint

The follow-up began in October 2011, and the last follow-up was completed in August 2022. The primary endpoint of the study was all-cause mortality, and the secondary endpoints were cardiovascular mortality/cardiac transplantation and SCD. Cardiovascular mortality was defined as stroke, cerebral infarction, heart failure (HF), and appropriate implantable cardioverter-defibrillator (ICD) discharges. SCD was an unexpected death that occurred in the absence of or within 1 hour from symptom onset in patients who had previously experienced a relatively stable or uneventful course [19]. Ventricular arrhythmias were defined as frequent ventricular premature beats and ventricular tachycardia detected by a 24-hour Holter electrocardiogram. Non-sustained ventricular tachycardia was also indicated by a 24-hour Holter electrocardiogram. Data on the occurrence of all-cause mortality, cardiovascular mortality/cardiac transplantation, and SCD during follow-up were collected by reviewing medical records (outpatient center attendance and hospitalization), performing telephone interviews, and reviewing survival status records through the National Police Stations. Patients who were lost within 6 months of discharge were regarded as lost to follow-up. The study conformed to the principles of the Declaration of Helsinki and was approved by the Ethics Commission of Sichuan Provincial People's Hospital.

Statistical analysis

Continuous variables were described as medians with interquartile ranges (IQR), and differences between the two groups were analyzed by the Mann–Whitney U test. The Shapiro–Wilk test was used to define the normal distribution. Categorical variables were expressed as proportions, and differences between groups were analyzed by the Pearson χ^2 test. A logit model was performed based on 28 baseline variables, and variables with a $P \leq 0.15$ were then entered into propensity score matching (e.g., age,

sex, syncope, family history of SCD, ventricular arrhythmias, QRS duration, QTc duration, QT duration, PR duration, right bundle branch block [RBBB], left ventricular [LV] diameter, left atrial [LA] diameter, left ventricular ejection fraction [LVEF], Log N-terminal pro-B-type natriuretic peptide [NT-proBNP], creatinine). Propensity score matching was performed using a 1:2 ratio in R using the MatchIt package with nearest-neighbor matching to adjust for potential confounding in the comparison between the AHCM and non-AHCM groups. Cumulative survival estimates were calculated according to the Kaplan–Meier method, and differences were assessed by the log-rank test. A stepwise variable selection procedure for Cox's proportional hazard model was performed to identify the factors independently associated with mortality by R packages My.stepwise. Hazard ratios (HRs), 95% confidence intervals (CIs), and *P* values were provided. The survival curve was obtained based on the R packages survival. Analysis was performed with R Version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria), with *P*-values <0.05 considered statistically significant.

RESULTS

Baseline characteristics

Table 1 summarizes the baseline clinical characteristics of the unmatched and matched cohorts. In the unmatched cohort, a total of 2268 patients met the initial inclusion criteria, of whom 1435 (63.3%) were males and 833 females (36.7%), with a median age of 56 (46–66) years. Compared to the non-AHCM patients, the AHCM patients had a more infrequent history of syncope and familial HCM, lower incidence of ventricular arrhythmias and ventricular tachycardia, shorter QRS and QTc duration, smaller LA diameter, smaller interventricular septum (IVS) thickness and maximal LV wall thickness, and a lower circulating Log (NT-proBNP) level. The matched cohort analysis showed that 24 baseline variables were not significantly different between the two groups except for IVS thickness, maximal LV wall thickness, beta-blockers, and Ca^{2+} antagonists.

Follow-up results of the unmatched cohort

Before matching, the median follow-up time was 5.1 (2.4–8.4) years. Meanwhile, there were 18 (8.0%) patients and 335 (16.4%) patients in all-cause mortality in the AHCM group and non-AHCM group, respectively. Nine (4.0%) cardiovascular deaths occurred in the AHCM group, and 196 (9.6%) occurred in the non-AHCM group. SCD occurred in 3 (1.3%)ACHM patients and 91 (4.5%) patients with non-AHCM. The Kaplan-Meier curves for the unmatched cohort of AHCM and non-AHCM patients are shown in Figure 1. There were significant differences between AHCM and non-AHCM in relation to all-cause mortality (*P* <0.001), cardiovascular mortality/cardiac transplantation (*P* <0.001), and SCD (*P* = 0.009).

Outcome of propensity score matching analysis

Primary endpoint: All-cause mortality

The Kaplan–Meier curves for all-cause mortality in the AHCM and non-AHCM patients after matching are shown in Figure 2A. Notably, all-cause mortality was lower in AHCM patients (*P* = 0.003). The Cox proportional hazard model for all-cause mortality in the unmatched and matched cohorts is shown in Table 2. According to the Cox proportional hazard regression model, AHCM (HR, 0.461; 95% CI, 0.271–0.784; *P* = 0.004), age (HR, 1.040; 95% CI, 1.022–1.059; *P* <0.001), LVEF (HR, 0.976; 95% CI, 0.953–0.999; *P* = 0.04), and Log (NT-proBNP) (HR, 7.181; 95% CI, 3.767–13.687; *P* <0.001) were independent prognostic predictors of all-cause mortality in the matched cohort.

Secondary endpoint: Cardiovascular mortality/ /cardiac transplantation and SCD

The Kaplan–Meier curves for cardiovascular mortality/ /cardiac transplantation after matching are shown in Figure 2B. The AHCM patients had lower cardiovascular mortality/cardiac transplantation (*P* = 0.03) than the non-AHCM patients. Meanwhile, Cox regression analysis showed that AHCM was a univariable predictor of cardiovascular mortality/cardiac transplantation (HR, 0.448; 95% CI, 0.214–0.935; *P* = 0.03), which was not confirmed after adjusting for other clinical predictors in the multivariable analysis (HR, 0.506; 95% CI, 0.239–1.069; *P* = 0.07). In the matched cohort (Table 3), male sex (HR, 0.485; 95% CI, 0.260–0.904; *P* = 0.02), ventricular arrhythmias (HR, 2.318; 95% CI, 1.064–5.052; *P* = 0.03), QTc duration (HR, 1.007; 95% CI, 1.002–1.013; *P* = 0.01), and Log (NT-proBNP) (HR, 10.114; 95% CI, 4.085–25.045; *P* <0.001) were independent prognostic predictors of cardiovascular mortality/cardiac transplantation.

Likewise, after matching, the AHCM patients had a lower rate of SCD (*P* = 0.020) (Figure 2C). The Cox proportional hazard regression model is shown in Table 4. Left bundle branch block (HR, 8.654; 95% CI, 1.665–44.993; *P* = 0.01), diastolic blood pressure (HR, 0.955; 95% CI, 0.920–0.992; *P* = 0.02), LV diameter (HR, 1.067; 95% CI, 1.014–1.123; *P* = 0.01), Log (NT-proBNP) (HR, 5.142; 95% CI, 1.030–25.670; *P* = 0.046), IVS thickness (HR, 1.126; 95% CI, 1.035–1.226; *P* = 0.006), and Ca^{2+} antagonists (HR, 0.313; 95% CI, 0.102–0.962; *P* = 0.04) were independent prognostic predictors of SCD. AHCM was a univariable predictor (HR, 0.262; 95% CI, 0.077–0.885; *P* = 0.03) but not significant in multivariable Cox regression models for SCD.

Subgroup analysis

To better investigate the effect of AHCM on HCM mortality, we generated forest plots showing the differences in the subgroups. In the all-cause mortality group (Figure 3A), AHCM was a protective predictor in the subgroups of males, with New York Heart Association (NYHA) class I–II, age ≤60 years, LV diameter ≤50 mm, LVEF >55%, and Log

Table 1. Baseline characteristics of the unmatched and the propensity score matched cohort

Variables	Unmatched cohort (n = 2268)				Matched cohort (n = 678)		
	Non-AHCM (n = 2042)	AHCM (n = 226)	*P*-value	%missing	Non-AHCM (n = 452)	AHCM (n = 226)	*P*-value
Follow-up time, year, median (Q1–Q3)	4.9 (2.4–8.3)	7.1 (3.8–10.0)	<0.001	0	5.3 (2.7–8.7)	7.0 (2.8–10.0)	0.02
Age, years, median (Q1–Q3)	55 (45–65)	59 (48–66)	0.097	0	56 (47–67)	57 (49–66)	0.63
Sex, male, n (%)	1262 (61.8)	173 (76.5)	0.001	0	338 (74.8)	173 (76.5)	0.68
NYHA I-II class, n (%)	1242 (60.9)	140 (61.9)	0.80	0	300 (66.4)	140 (61.9)	0.29
DBP, mm Hg, median (Q1–Q3)	75 (68–82)	80 (70–80)	0.11	0.04	79 (70–86)	80 (70–80)	0.53
Syncope, n (%)	283 (13.9)	18 (8.0)	0.02	0	36 (8.0)	18 (8.0)	1.000
FHCM, n (%)	186 (9.1)	7 (3.1)	0.003	0	23 (5.1)	7 (3.1)	0.32
Family history of SCD, n (%)	33 (1.6)	2 (0.9)	0.57	0	5 (1.1)	2 (0.9)	1.000
Electrocardiograph							
QRS, ms, median (Q1–Q3)	100 (88–119)	96 (83–108)	<0.001	12.52	95 (84–107)	98 (84–107)	0.37
QT, ms, median (Q1–Q3)	420 (389–450)	426 (390–449)	0.47	12.92	418 (389–440)	420 (398–445)	0.09
QTc, ms, median (Q1–Q3)	449 (427–478)	443 (418–469)	0.01	13.89	447 (422–460)	447 (424–464)	0.65
PR, ms, median (Q1–Q3)	164 (150–190)	162 (151–184)	0.47	20.28	169 (149–178)	166 (151–180)	0.86
Atrial fibrillation, n (%)	370 (18.1)	38 (16.8)	0.69	0	60 (13.3)	38 (16.8)	0.26
LBBB, n (%)	68 (3.3)	4 (1.8)	0.29	0	6 (1.3)	4 (1.8)	0.91
RBBB, n (%)	103 (5.0)	10 (4.4)	0.81	0	19 (4.2)	10 (4.4)	1.000
Ventricular arrhythmias, n (%)	368 (18.0)	25 (11.1)	0.01	0	43 (9.5)	25 (11.1)	0.62
VT, n (%)	216 (10.6)	13 (5.8)	0.03	0	25 (5.5)	13 (5.8)	1.000
NSVT, n (%)	140 (7.0)	10 (4.8)	0.28	3.22	12 (2.7)	10 (4.4)	0.32
Echocardiography							
LV diameter, mm, median (Q1–Q3)	43 (40–47)	47 (44–51)	<0.001	8.11	46 (43–49)	47 (44–50)	0.09
LA diameter, mm, median (Q1–Q3)	39 (35–44)	37 (34–42)	<0.001	7.41	38 (34–42)	38 (34–41)	0.998
RA, n (%)	121 (6.6)	13 (6.6)	1.000	10.89	20 (4.4)	13 (5.8)	0.57
RV diameter, mm, median (Q1–Q3)	20 (18-22)	21 (19-22)	<0.001	12.83	20 (18–22)	20 (19–22)	0.06
LVEF, %, median (Q1–Q3)	68 (62–73)	66 (61–71)	0.71	9.08	66 (63–72)	66 (63–70)	0.54
IVS, mm, median (Q1–Q3)	19 (15–22)	12 (10–15)	<0.001	6.70	17 (14–19)	13 (10–17)	<0.001
Maximal wall thickness, mm, median (Q1–Q3)	19 (17–23)	16 (14–20)	<0.001	5.56	18 (16–20)	17 (14–20)	<0.001
LVOT obstruction, n (%)	975 (47.7)	30 (13.3)	<0.001	0	168 (37.2)	30 (13.3)	<0.001
Laboratory investigations							
Log (NT-proBNP), fmol/l, median (Q1–Q3)	3.1 (2.8–3.4)	2.9 (2.7–3.1)	<0.001	28.09	3.1 (2.8–3.1)	3.0 (2.8–3.1)	0.43
Creatinine, µmol/l, median (Q1–Q3)	76.9 (64.6–91.2)	77.9 (69.3–91.0)	0.37	5.91	79.3 (66.7–88.7)	79.5 (70.8–89.4)	0.45
Medicine at baseline							
Beta-blocker, n (%)	1578 (77.5)	188 (83.6)	0.04	0.26	342 (75.7)	189 (83.6)	0.02
Ca^{2+} antagonists, n (%)	451 (22.2)	77 (34.2)	<0.001	0.67	112 (24.8)	77 (34.1)	0.01
Aspirin, n (%)	829 (40.7)	168 (74.7)	<0.001	0.26	221 (48.9)	168 (74.3)	<0.001
Warfarin, n (%)	208 (10.2)	22 (9.8)	0.93	0.26	36 (8.0)	22 (9.7)	0.53
Cordarone, n (%)	120 (5.9)	9 (4.0)	0.31	0.26	21 (4.6)	9 (4.0)	0.84
Endpoints							
All-cause mortality, n (%)	335 (16.4)	18 (8.0)	0.001	0	64 (14.2)	18 (8.0)	0.03
Cardiovascular mortality/cardiac transplantation, n (%)	196 (9.6)	9 (4.0)	0.008	0	34 (7.5)	9 (4.0)	0.11
SCD, n (%)	91 (4.5)	3 (1.3)	0.04	0	19 (4.2)	3 (1.3)	0.08

Data are presented as number (percentage) or median (Q1–Q3)

Abbreviations: AHCM, apical hypertrophic cardiomyopathy; DBP, diastolic blood pressure; FHCM, familial hypertrophic cardiomyopathy; IVS, interventricular septum; LA, left atrial; LBBB, left bundle branch block; LV, left ventricular; LVEF, left ventricular ejection fraction; NSVT, non-sustained ventricular tachycardia; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RBBB, right bundle branch block; RV, right ventricular; VT, ventricular tachycardia

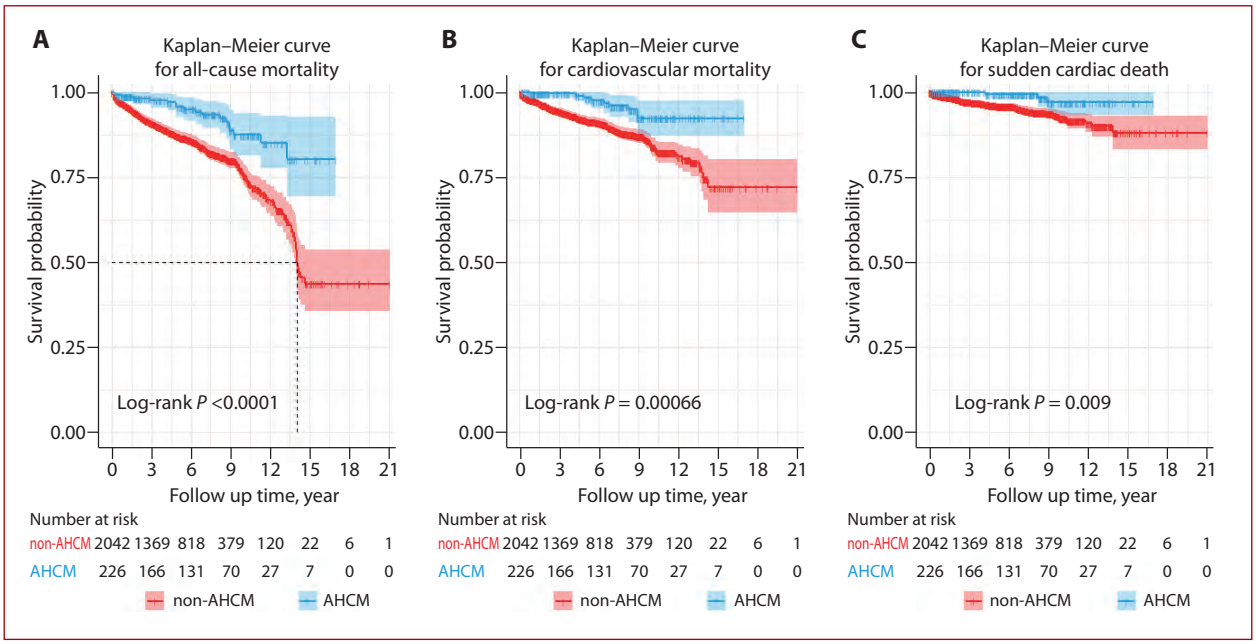


Figure 1. Kaplan–Meier curves for the unmatched cohort. **A.** All-cause mortality. **B.** Cardiovascular mortality/cardiac transplantation. **C.** Sudden cardiac death

Abbreviations: see — Table 1

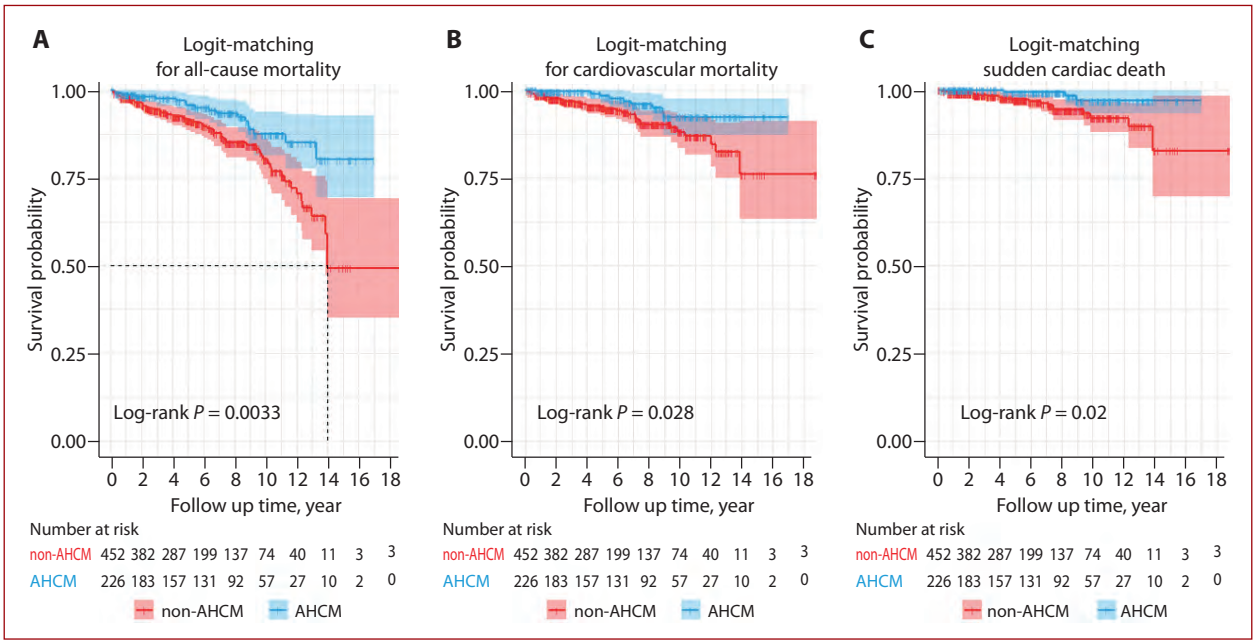


Figure 2. Kaplan–Meier curves for the matched cohort. **A.** All-cause mortality. **B.** Cardiovascular mortality/cardiac transplantation. **C.** Sudden cardiac death

Abbreviations: see — Table 1

Table 2. Multivariable Cox regression for primary all-cause mortality of the unmatched and the propensity score matched cohort

Variables	Unmatched cohort			Matched cohort		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
AHCM	0.608	0.323–1.147	0.13	0.461	0.271–0.784	0.004
Age	1.032	1.020–1.044	<0.001	1.040	1.022–1.059	<0.001
Ventricular arrhythmias	0.878	0.487–1.585	0.67	1.672	0.888–3.146	0.11
RA	0.571	0.299–1.089	0.09	0.224	0.030–1.688	0.15
LVEF	0.965	0.952–0.978	<0.001	0.976	0.953–0.999	0.04
Log (NT-proBNP)	3.658	2.581–5.184	<0.001	7.181	3.767–13.687	<0.001
NSVT	2.534	0.995–6.456	0.051	—	—	—
Atrial fibrillation	1.220	0.850–1.752	0.28	—	—	—
DBP	0.986	0.974–0.997	0.02	—	—	—
QT	0.995	0.992–0.998	<0.001	—	—	—
LV diameter	1.003	0.978–1.029	0.80	—	—	—
Betablocker	0.593	0.417–0.842	0.003	—	—	—
Concordance		0.797			0.730	

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

Table 3. Multivariable Cox regression for cardiovascular mortality/cardiac transplantation of the unmatched and the propensity score matched cohort

Variables	Unmatched cohort			Matched cohort		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
AHCM	0.506	0.218–1.178	0.11	0.506	0.239–1.069	0.07
Male	1.015	0.685–1.505	0.94	0.485	0.260–0.904	0.02
Ventricular arrhythmias	0.991	0.522–1.882	0.98	2.318	1.064–5.052	0.03
Ca2+ antagonists	1.132	0.728–1.760	0.58	0.536	0.254–1.131	0.10
Log (NT-pro-BNP)	3.168	2.091–4.799	<0.001	10.114	4.085–25.045	<0.001
LVEF	0.956	0.939–0.973	<0.001	—	—	—
Creatinine	1.002	1.000–1.004	0.03	—	—	—
QTc	—	—	—	1.007	1.002–1.013	0.01
Concordance		0.789			0.753	

Abbreviations: see Tables 1 and 2

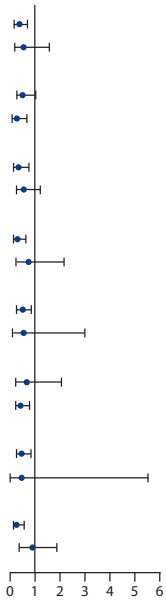
Table 4. Multivariable Cox regression for sudden cardiac death of the unmatched and the propensity score matched cohort

Variables	Unmatched cohort			Matched cohort		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
AHCM	0.189	0.025–1.403	0.10	—	—	—
DBP	0.982	0.960–1.004	0.11	0.955	0.920–0.992	0.02
QT	0.999	0.988–1.009	0.79	1.008	0.998–1.018	0.12
LV diameter	1.057	1.014–1.102	0.01	1.067	1.014–1.123	0.01
RV diameter	0.703	0.229–2.162	0.54	0.876	0.755–1.016	0.08
Log (NT-pro-BNP)	3.042	1.054–6.152	0.002	5.142	1.030–25.670	0.046
Ventricular arrhythmias	—	—	—	2.467	0.885–6.881	0.08
LBBB	—	—	—	8.654	1.665–44.993	0.01
IVS	—	—	—	1.126	1.035–1.226	0.006
Ca^{2+} antagonists	—	—	—	0.313	0.102–0.962	0.04
Concordance		0.769			0.816	

Abbreviations: see Tables 1 and 2

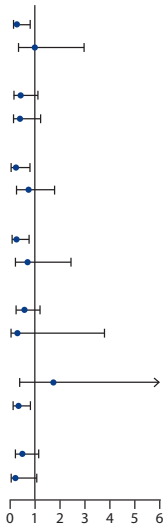
A **Hazard ratio for all-cause mortality**

Group	non-AHCM	AHCM	Adjusted HR (95% CI)	Adjusted *P*-value
Sex				
Male	338 (511)	173 (511)	0.369 (0.196, 0.698)	0.002
Female	114 (167)	53 (167)	0.554 (0.193, 1.586)	0.27
Age				
Age >60	174 (270)	96 (270)	0.514 (0.257, 1.028)	0.06
Age ≤60	278 (408)	130 (408)	0.259 (0.098, 0.679)	0.006
NYHA class				
I–II	300 (440)	140 (440)	0.347 (0.162, 0.740)	0.006
III–IV	152 (238)	86 (238)	0.565 (0.259, 1.230)	0.15
AF				
No	392 (580)	188 (580)	0.306 (0.153, 0.610)	0.001
Yes	60 (98)	38 (98)	0.751 (0.260, 2.169)	0.6
Ventricular arrhythmias				
No	409 (610)	201 (610)	0.500 (0.283, 0.883)	0.02
Yes	43 (68)	25 (68)	0.528 (0.092, 3.023)	0.47
LV diameter				
LV diameter >50	93 (149)	56 (149)	0.670 (0.220, 2.040)	0.48
LV diameter ≤50	359 (529)	170 (529)	0.428 (0.229, 0.799)	0.008
LVEF				
LVEF >55%	421 (641)	220 (641)	0.456 (0.253, 0.820)	0.009
LVEF ≤55%	31 (37)	6 (37)	0.447 (0.036, 5.554)	0.53
Log(NT-proBNP)				
Log(NT-proBNP) >3	249 (361)	112 (361)	0.278 (0.133, 0.583)	0.001
Log(NT-proBNP) ≤3	203 (317)	114 (317)	0.847 (0.377, 1.903)	0.69



B **Hazard ratio for cardiovascular mortality**

Group	non-AHCM	AHCM	Adjusted HR (95% CI)	Adjusted *P*-value
Sex				
Male	338 (511)	173 (511)	0.267 (0.090, 0.791)	0.02
Female	114 (167)	53 (167)	0.935 (0.296, 2.956)	0.91
Age				
Age >60	174 (270)	96 (270)	0.403 (0.145, 1.116)	0.08
Age ≤60	278 (408)	130 (408)	0.347 (0.099, 1.216)	0.098
NYHA class				
I–II	300 (440)	140 (440)	0.181 (0.041, 0.802)	0.02
III–IV	152 (238)	86 (238)	0.709 (0.285, 1.767)	0.46
AF				
No	392 (580)	188 (580)	0.248 (0.084, 0.729)	0.01
Yes	60 (98)	38 (98)	0.669 (0.185, 2.413)	0.54
Ventricular arrhythmias				
No	409 (610)	201 (610)	0.533 (0.238, 1.190)	0.13
Yes	43 (68)	25 (68)	0.283 (0.021, 3.758)	0.34
LV diameter				
LV diameter >50	93 (149)	56 (149)	1.691 (0.406, 7.033)	0.47
LV diameter ≤50	359 (529)	170 (529)	0.296 (0.113, 0.777)	0.01
Log(NT-proBNP)				
Log(NT-proBNP) >3	249 (361)	112 (361)	0.481 (0.202, 1.150)	0.01
Log(NT-proBNP) ≤3	203 (317)	114 (317)	0.193 (0.035, 1.059)	0.06



C **Hazard ratio for SCD**

Group	non-AHCM	AHCM	Adjusted HR (95% CI)	Adjusted *P*-value
Sex				
Male	338 (511)	173 (511)	0.226 (0.051, 1.009)	0.05
Female	114 (167)	53 (167)	0.460 (0.027, 7.986)	0.59
Age				
Age >60	174 (270)	96 (270)	0.092 (0.010, 0.831)	0.03
Age ≤60	278 (408)	130 (408)	0.324 (0.068, 1.551)	0.16
AF				
No	392 (580)	188 (580)	0.238 (0.053, 1.070)	0.06
Yes	60 (98)	38 (98)	0.117 (0.006, 2.227)	0.15
Ventricular arrhythmias				
No	409 (610)	201 (610)	0.241 (0.054, 1.067)	0.06
Yes	43 (68)	25 (68)	0.283 (0.053, 12.631)	0.89
LV diameter				
LV diameter >50	93 (149)	56 (149)	0.914 (0.154, 5.419)	0.92
LV diameter ≤50	359 (529)	170 (529)	0.108 (0.014, 0.835)	0.03
Log(NT-proBNP)				
Log(NT-proBNP) >3	249 (361)	112 (361)	0.257 (0.057, 1.164)	0.08
Log(NT-proBNP) ≤3	203 (317)	114 (317)	0.302 (0.034, 2.654)	0.28

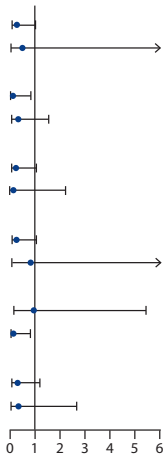


Figure 3. Forest plots of subgroup analyses.
A. All-cause mortality.
B. Cardiovascular mortality/cardiac transplantation.
C. Sudden cardiac death.
The forest plots showing the difference of AHCM on the prognosis of HCM in different populations and different outcomes

Abbreviations: SCD, sudden cardiac death; other — see Tables 1 and 2

(NT-proBNP) >3. In the cardiovascular mortality/cardiac transplantation group, AHCM was also a protective predictor in the subgroups of male patients, with NYHA class I-II, LV diameter≤50 mm (Figure 3b), and, additionally, in the SCD subgroups aged > 60 years and with LV diameter ≤50 mm (Figure 3c).

DISCUSSION

To the best of our knowledge, this is one of the largest cohort studies of HCM in China. In our study, both in the matched and unmatched cohorts, we found that AHCM patients had a favorable prognosis, with lower all-cause mortality, cardiovascular mortality/cardiac transplantation, and SCD. According to the Cox proportional hazard regression model, AHCM was an independent prognostic predictor of all-cause mortality and an univariable prognostic predictor of cardiovascular mortality/cardiac transplantation and SCD in HCM. However, AHCM was not significant in multivariable Cox regression models for cardiovascular mortality/cardiac transplantation and SCD. Eventually, the subgroup analysis showed that in each subgroup AHCM was consistently a protective predictor of all-cause mortality, cardiovascular mortality/cardiac transplantation, and SCD.

Generally, the incidence of AHCM is relatively low, which is 3%–25% of HCM [3, 4, 20]. In our study, AHCM patients accounted for 10% of all HCM patients, which was similar to Western countries (1%–11%) but lower than reported in Japan (13%–25%) [3, 4, 21]. Compared with classical HCM, AHCM is more sporadic, with lower frequency of sarcomere mutations, more atrial fibrillation (AF), and different risk factors for SCD [20, 22, 23]. There are no strong specific recommendations to guide AHCM diagnosis, family screening, and patient risk stratification [19]. In our study, similar to previous results, AHCM patients had less familial HCM. AF, which was the most frequent morbid event in AHCM compared with other arrhythmias, was not significantly different in AHCM and non-AHCM. Additionally, ventricular arrhythmias and ventricular tachycardia were rarer in AHCM, which may be the reason for better AHCM prognosis in our study. Previous studies have also reported that malignant ventricular arrhythmias and mortality are associated with apical aneurysms in AHCM patients in Western countries, compared with a 2% incidence of apical aneurysms in HCM patients and a 13%–15% incidence of apical aneurysms in AHCM patients [24–26]. In our study, apical ventricular aneurysm was present in only a few patients, which may be another reason for the favorable prognosis in AHCM. Moreover, the extent of myocardial hypertrophy is also an important prognostic factor in AHCM patients [10, 20, 27]. In this study, both IVS thickness and maximal LV wall thickness of AHCM were smaller than those of non-AHCM, and left ventricular outflow tract obstruction was less common, which may also contribute to the favorable prognosis in AHCM.

In our study, the Cox proportional hazard regression model showed that AHCM was an independent prognostic predictor of all-cause mortality and an univariable protective predictor of cardiovascular mortality/cardiac transplantation and SCD in HCM. To better investigate the effect of AHCM on the prognosis in HCM, we performed a subgroup analysis, and the results suggested that AHCM was invariably a protective predictor of all-cause mortality in the following subgroups: males, NYHA class I–II, age ≤60 years, LV diameter ≤50 mm, LVEF >55%, and Log (NT-proBNP) >3. In the case of cardiovascular mortality/cardiac transplantation, AHCM was also a protective predictor of SCD in these subgroups: male, NYHA class I–II, and LV diameter ≤50 mm subgroups, as well as in the age >60 years and LV diameter ≤50 mm.

Regarding long-term AHCM prognosis, most research has shown that AHCM usually has a favorable prognosis [4–10]. A meta-analysis showed that annual mortality in AHCM was lower than that in non-AHCM patients (0.81% to 1.55%) [28, 29]. Furthermore, Eriksson et al., in their retrospective study of 105 North American ACHM patients followed up for 15 years found that there were no SCD and that cardiovascular mortality was 1.9% [5]. Kim et al. [30] used the inverse probability of treatment weighted method and the propensity score matching method to compare the long-term outcomes of all-cause and cardiac mortality rates between AHCM and asymmetric HCM [30], and the results showed that the all-cause mortality rates of AHCM and asymmetric HCM were similar. However, AHCM had lower cardiovascular mortality [30]. Zadok et al. [28] evaluated the risk of SCD in AHCM patients based on the HCM Risk-SCD 5-year prediction model, and the results showed that AHCM had a lower 5-year SCD risk [28].

In our study, the annual all-cause mortality rates of AHCM and non-AHCM were 0.1% and 2.6%, respectively. The annual rate of cardiovascular mortality/cardiac transplantation in AHCM was 0.07%, and that in non-AHCM was 1.5%. For SCD, annual mortality in AHCM was 0.02% and non-AHCM was 0.7%. The Kaplan–Meier curves showed that AHCM had lower all-cause mortality, cardiovascular mortality/cardiac transplantation, and SCD both before and after matching. However, Moon et al. [4] and Klarich et al. [10] reported that AHCM prognosis was not as favorable as previously reported. Meanwhile, recent data have shown that the annual cardiovascular mortality rate in AHCM is 0.5% to 4%, approaching that of classic HCM [17]. Notably, an earlier study reported that one-third of AHCM patients in Western countries may develop adverse clinical events and potentially life-threatening complications such as myocardial infarction, ventricular arrhythmias, and stroke [5, 24]. Similarly, ACHM patients in our study still experienced ventricular arrhythmias and SCD, but there were fewer patients than those with non-AHCM. Altogether, combining the results of all studies, most of these studies concluded that ACHM patients had a favorable prognosis

compared with other forms of HCM, but not for all AHCM patients [4, 10, 31]. Therefore, it is necessary to consider and manage ACHM patients clinically.

Current management of HCM focuses on symptom relief, risk stratification, prevention of sudden cardiac death, and family screening [32, 33]. Medical therapy for apical HCM patients is similar to that for typical HCM patients [3, 16]. Currently, mavacamten, a first-class, selective, and reversible β-myosin allosteric inhibitor, which can inhibit the binding of myosin and actin and reduce the number of actin-myosin cross-bridges, has been shown to improve NYHA class, health status, cardiac biomarkers, and cardiac structure of patients [33, 34], but mainly for obstructive HCM. However, ACHM patients are less likely to have LVOT obstruction. Therefore, better clinical treatment of AHCM is expected.

In this cohort study, there were numerous covariate imbalances, and the number of patients in the AHCM group was significantly different from that in the non-AHCM group before matching. This can make the accuracy of unmatched cohort results questionable. Therefore, to adjust for potential confounding bias in the clinical features of AHCM and non-AHCM patients, we used 1:2 propensity score matching. Our results showed that the AHCM prognosis was favorable both before and after matching, which was consistent with most previous studies. Given the diversity of prognoses in AHCM in different studies, its role in HCM risk stratification should not be disregarded. Furthermore, the incidence of AHCM is low, and the lack of risk predictors and guidelines makes it a clinical challenge to predict which patients are at risk for adverse events. Therefore, more and larger studies are required to explore the prognosis in AHCM and reach a consensus or issue guidelines.

Study limitations

There are some limitations to this study. First, this is a multicenter cohort study with patients from 13 tertiary centers, so there may be some heterogeneity among the different hospitals. Second, genetic testing of patients was not performed in our study, so differences in gene mutations between AHCM and non-AHCM could not be investigated. Third, LGE is closely related to the prognosis in cardiomyopathy, but there were too many missing data in this study, making it impossible to compare LGE outcomes between the two groups in this study. Fourth, depending on the pattern of hypertrophy, AHCM has been described as "pure AHCM" and "mixed AHCM", but in our study, we did not distinguish between them. Finally, the medications were only recorded during the in-hospital treatment of the patients, and no follow-up data were recorded, which we did not further analyze in our study.

CONCLUSION

Patients with AHCM have a favorable prognosis, with lower all-cause mortality, cardiovascular mortality/cardiac transplantation, and SCD both before and after matching. Furthermore, AHCM was an independent prognostic predictor of all-cause mortality and an univariable prognostic predictor of cardiovascular mortality/ cardiac transplantation and SCD in HCM patients.

Article information

Acknowledgements: The authors would like to thank the following hospitals for the multicenter data: the First Affiliated Hospital of Chengdu Medical; the Second Affiliated Hospital of Chengdu Medical College & Nuclear Industry 416 Hospital; the Third Affiliated Hospital of Chengdu Medical & Pidu District People's Hospital; the Mianyang Central Hospital; the Sichuan Mianyang 404 Hospital; the Third People's Hospital of Chengdu; the Hospital of Chengdu University of TCM &TCM Hospital of Sichuan Province; the Xichang People's Hospital; the First Affiliated Hospital of Chongqing Medical University; the Second Affiliated Hospital of Chongqing Medical University; the Affiliated Hospital of Southwest Medical University and others.

Conflict of interest: None declared.

Funding: This work was supported by National Natural Science Foundation of China (No. 32171182). Zhong Nanshan Medical Foundation of Guangdong Province (No. ZNSA-2020017). Natural Science Foundation of Sichuan Province (No. 2022NSFSC0538).

REFERENCES

1. Antunes M, Scudeler TL. Hypertrophic cardiomyopathy. Int J Cardiol Heart Vasc. 2020; 27: 100503, doi: 10.1016/j.ijcha.2020.100503, indexed in Pubmed: 32309534.
2. Sakamoto T, Tei C, Murayama M, et al. Giant T wave inversion as a manifestation of asymmetrical apical hypertrophy (AAH) of the left ventricle. Echocardiographic and ultrasono-cardiotomographic study. Jpn Heart J. 1976; 17(5): 611–629, doi: 10.1536/ihj.17.611, indexed in Pubmed: 136532.
3. Paluszkiewicz J, Krasinska B, Milting H, et al. Apical hypertrophic cardiomyopathy: diagnosis, medical and surgical treatment. Kardiochir Torakochirurgia Pol. 2018; 15(4): 246–253, doi: 10.5114/kitp.2018.80922, indexed in Pubmed: 30647749.
4. Moon J, Shim CY, Ha JW, et al. Clinical and echocardiographic predictors of outcomes in patients with apical hypertrophic cardiomyopathy. Am J Cardiol. 2011; 108(11): 1614–1619, doi: 10.1016/j.amjcard.2011.07.024, indexed in Pubmed: 21890076.
5. Eriksson MJ, Sonnenberg B, Woo A, et al. Long-term outcome in patients with apical hypertrophic cardiomyopathy. J Am Coll Cardiol. 2002; 39(4): 638–645, doi: 10.1016/s0735-1097(01)01778-8, indexed in Pubmed: 11849863.
6. Kitaoka H, Doi Y, Casey SA, et al. Comparison of prevalence of apical hypertrophic cardiomyopathy in Japan and the United States. Am J Cardiol. 2003; 92(10): 1183–1186, doi: 10.1016/j.amjcard.2003.07.027, indexed in Pubmed: 14609593.
7. An S, Fan C, Yan L, et al. Comparison of Long-Term Outcome between Apical and Asymmetric Septal Hypertrophic Cardiomyopathy. Cardiology. 2017; 136(2): 108–114, doi: 10.1159/000448239, indexed in Pubmed: 27595481.
8. Yan L, Wang Z, Xu Z, et al. Two hundred eight patients with apical hypertrophic cardiomyopathy in China: clinical feature, prognosis, and comparison of pure and mixed forms. Clin Cardiol. 2012; 35(2): 101–106, doi: 10.1002/clc.20995, indexed in Pubmed: 22125122.
9. Lee CH, Liu PY, Lin LJ, et al. Clinical features and outcome of patients with apical hypertrophic cardiomyopathy in Taiwan. Cardiology. 2006; 106(1): 29–35, doi: 10.1159/000092590, indexed in Pubmed: 16612066.

10. Klarich KW, Attenhofer Jost CH, Binder J, et al. Risk of death in long-term follow-up of patients with apical hypertrophic cardiomyopathy. Am J Cardiol. 2013; 111(12): 1784–1791, doi: 10.1016/j.amjcard.2013.02.040, indexed in Pubmed: 23540548.
11. Okishige K, Sasano T, Yano K, et al. Serious arrhythmias in patients with apical hypertrophic cardiomyopathy. Intern Med. 2001; 40(5): 396–402, doi: 10.2169/internalmedicine.40.396, indexed in Pubmed: 11393409.
12. Wilson P, Marks A, Rastegar H, et al. Apical hypertrophic cardiomyopathy presenting with sustained monomorphic ventricular tachycardia and electrocardiographic changes simulating coronary artery disease and left ventricular aneurysm. Clin Cardiol. 1990; 13(12): 885–887, doi: 10.1002/clc.4960131213, indexed in Pubmed: 2282734.
13. Partanen J, Kupari M, Heikkilä J, et al. Left ventricular aneurysm associated with apical hypertrophic cardiomyopathy. Clin Cardiol. 1991; 14(11): 936–939, doi: 10.1002/clc.4960141115, indexed in Pubmed: 1764832.
14. Cubukçu AA, Scott PJ, Williams GJ. Apical hypertrophic cardiomyopathy presenting as acute subendocardial myocardial infarction. Int J Cardiol. 1993; 38(3): 329–332, doi: 10.1016/0167-5273(93)90254-e, indexed in Pubmed: 8463017.
15. Badhiwala JH, Karmur BS, Wilson JR. Propensity score matching: a powerful tool for analyzing observational nonrandomized data. Clin Spine Surg. 2021; 34(1): 22–24, doi: 10.1097/BSD.0000000000001055, indexed in Pubmed: 32804684.
16. Elliott PM, Anastasakis A, Borger MA, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J. 2014; 35(39): 2733–2779, doi: 10.1093/eurheartj/ehu284, indexed in Pubmed: 25173338.
17. Hughes RK, Knott KD, Malcolmson J, et al. Apical hypertrophic cardiomyopathy: the variant less known. J Am Heart Assoc. 2020; 9(5): e015294, doi: 10.1161/JAHA.119.015294, indexed in Pubmed: 32106746.
18. Jan MF, Todaro MC, Oreto L, et al. Apical hypertrophic cardiomyopathy: Present status. Int J Cardiol. 2016; 222: 745–759, doi: 10.1016/j.ijcard.2016.07.154, indexed in Pubmed: 27521551.
19. Minami Y, Kajimoto K, Terajima Y, et al. Clinical implications of midventricular obstruction in patients with hypertrophic cardiomyopathy. J Am Coll Cardiol. 2011; 57(23): 2346–2355, doi: 10.1016/j.jacc.2011.02.033, indexed in Pubmed: 21636036.
20. Patel H, Ko Ko NL, Kumar S, et al. "Acing" the hidden spade: review of diagnosis, follow-up, prognosis, and various associations of apical variant hypertrophic cardiomyopathy. Cureus. 2019; 11(1): e3979, doi: 10.7759/cureus.3979, indexed in Pubmed: 30967979.
21. Ho HH, Lee KLF, Lau CP, et al. Clinical characteristics of and long-term outcome in Chinese patients with hypertrophic cardiomyopathy. Am J Med. 2004; 116(1): 19–23, doi: 10.1016/j.amjmed.2003.09.020, indexed in Pubmed: 14706661.
22. Gruner C, Care M, Siminovitch K, et al. Sarcomere protein gene mutations in patients with apical hypertrophic cardiomyopathy. Circ Cardiovasc Genet. 2011; 4(3): 288–295, doi: 10.1161/CIRCGENETICS.110.958835, indexed in Pubmed: 21511876.
23. Klarich KW, Attenhofer Jost CH, Binder J, et al. Risk of death in long-term follow-up of patients with apical hypertrophic cardiomyopathy. Am J Cardiol. 2013; 111(12): 1784–1791, doi: 10.1016/j.amjcard.2013.02.040, indexed in Pubmed: 23540548.
24. Chen CC, Lei MH, Hsu YC, et al. Apical hypertrophic cardiomyopathy: correlations between echocardiographic parameters, angiographic left ventricular morphology, and clinical outcomes. Clin Cardiol. 2011; 34(4): 233–238, doi: 10.1002/clc.20874, indexed in Pubmed: 21400548.
25. Rowin EJ, Maron BJ, Haas TS, et al. Hypertrophic cardiomyopathy with left ventricular apical aneurysm: implications for risk stratification and management. J Am Coll Cardiol. 2017; 69(7): 761–773, doi: 10.1016/j.jacc.2016.11.063, indexed in Pubmed: 28209216.
26. Moro E, D'Angelo G, Nicolosi GL, et al. Long-term evaluation of patients with apical hypertrophic cardiomyopathy. Correlation between quantitative echocardiographic assessment of apical hypertrophy and clinical-electrocardiographic findings. Eur Heart J. 1995; 16(2): 210–217, doi: 10.1093/oxfordjournals.eurheartj.a060887, indexed in Pubmed: 7744093.
27. Huang G, Fadl SA, Sukhotski S, et al. Apical variant hypertrophic cardiomyopathy "multimodality imaging evaluation". Int J Cardiovasc Imaging. 2020; 36(3): 553–561, doi: 10.1007/s10554-019-01739-x, indexed in Pubmed: 31853820.
28. Zadok O, Hasdai D, Witberg G, et al. Calculated risk for sudden cardiac death in patients with apical versus nonobstructive nonapical hypertrophic cardiomyopathy. Am J Cardiol. 2018; 122(9): 1551–1556, doi: 10.1016/j.amjcard.2018.07.014, indexed in Pubmed: 30197054.
29. Pelliccia F, Pasceri V, Limongelli G, et al. Working Group on Cardiomyopathies and Pericardial Diseases of the Italian Society of Cardiology. Long-term outcome of nonobstructive versus obstructive hypertrophic cardiomyopathy: A systematic review and meta-analysis. Int J Cardiol. 2017; 243: 379–384, doi: 10.1016/j.ijcard.2017.06.071, indexed in Pubmed: 28747036.
30. Kim SH, Kim SO, Han S, et al. Long-term comparison of apical versus asymmetric hypertrophic cardiomyopathy. Int Heart J. 2013; 54(4): 207–211, doi: 10.1536/ihj.54.207, indexed in Pubmed: 23924932.
31. Yang K, Song YY, Chen XY, et al. Apical hypertrophic cardiomyopathy with left ventricular apical aneurysm: prevalence, cardiac magnetic resonance characteristics, and prognosis. Eur Heart J Cardiovasc Imaging. 2020; 21(12): 1341–1350, doi: 10.1093/ehjci/jeaa246, indexed in Pubmed: 32888301.
32. Pysz P, Rajtar-Salwa R, Smolka G, et al. Mavacamten — a new disease-specific option for pharmacological treatment of symptomatic patients with hypertrophic cardiomyopathy. Kardiol Pol. 2021; 79(9): 949–954, doi: 10.33963/KP.a2021.0064, indexed in Pubmed: 34268723.
33. Ismayl M, Abbasi MA, Marar R, et al. Mavacamten treatment for hypertrophic cardiomyopathy: a systematic review and meta-analysis of randomized controlled trials. Curr Probl Cardiol. 2023; 48(1): 101429, doi: 10.1016/j.cpcardiol.2022.101429, indexed in Pubmed: 36167226.
34. Tian Z, Li L, Li X, et al. Effect of mavacamten on Chinese patients with symptomatic obstructive hypertrophic cardiomyopathy: The EXPLORER-CN randomized clinical trial. JAMA Cardiol. 2023; 8(10): 957–965, doi: 10.1001/jamacardio.2023.3030, indexed in Pubmed: 37639259.

Hemodynamic effects of larger volume intra-aortic balloon pump during high-risk percutaneous coronary interventions

Aleksander Zeliaś[1,2], Wojciech Zajdel[3], Krzysztof Malinowski[4,5], Jolanta Geremek[3], Tomasz Tokarek[2,6], Dariusz Dudek[5], Krzysztof Żmudka[3]

[1]The Faculty of Medicine and Health Sciences, University of Applied Sciences in Nowy Sacz, Nowy Sącz, Poland
[2]Center for Invasive Cardiology, Electrotherapy and Angiology Intercard, Nowy Sącz, Poland
[3]Clinic of Interventional Cardiology, John Paul II Hospital, Kraków, Poland
[4]Department of Bioinformatics and Telemedicine, Faculty of Medicine, Jagiellonian University Medical College, Kraków, Poland
[5]Center for Digital Medicine and Robotics, Jagiellonian University Medical College, Kraków, Poland
[6]Center for Innovative Medical Education, Jagiellonian University Medical College, Kraków, Poland

Correspondence to:
Aleksander Zeliaś, MD, PhD, Center for Invasive Cardiology, Electrotherapy and Angiology Intercard, Kilińskiego 68, 33–300 Nowy Sącz, Poland, phone +48 18 540 02 00, e-mail: a.zelias@intercard.net.pl

DOI: 10.33963/v.kp.98410

Received:
May 28, 2023

Accepted:
December 5, 2023

Early publication date:
December 20, 2023

ABSTRACT

Background: Percutaneous coronary intervention in high-risk patients (HRPCI) is associated with increased risk of complications. Mechanical circulatory support devices, including intra-aortic balloon pump (IABP) may bridge patient safely throughout the procedure.

Aim: We aimed to describe hemodynamic effects of larger (MEGA) compared to standard (STRD) volume IABP or no balloon control group (CTRL) during HRPCI.

Methods: In this single-center, open-label randomized controlled trial HRPCI were randomly assigned to three groups according to planned hemodynamic support: MEGA, STDR and CTRL in a 1:1:1 scheme. Screening failure patients formed registry (REG). We analyzed data from pulmonary artery catheter especially cardiac output and cardiac power output (CPO) with Fick method and pulmonary artery wedge pressure (PCWP), as well as left ventricle systolic pressure (LVSP) with PIGTAIL catheter. We also calculated endocardial viability ratio (EVR) and analyzed pressure tracings from the IABP console. We compared baseline and on-support values. Final hemodynamic analysis was done on per-treatment basis, including REG patients.

Results: A total of 47 patients were analyzed (16 MEGA, 10 STRD and 21 CTRL). Compared to CTRL we found significant increase from baseline to on-support value for cardiac output and CPO in the MEGA, but not in the STRD group. The change in EVR (increase) and in LVSP (decrease) was significant equally in MEGA and STRD vs. CTRL group, but PCWP did not change significantly for both balloons vs. CTRL. Diastolic augmented pressure with IABP was higher in MEGA than STRD and was positively correlated with systolic unloading.

Conclusions: We observed more favorable hemodynamic effects of larger compared to standard volume balloon.

Key words: complex high-risk and indicated patients, high-risk percutaneous coronary intervention, intra-aortic balloon pump, pulmonary artery catheter, right heart catheterization

INTRODUCTION

Percutaneous coronary intervention (PCI) in patients with many well-known clinical, anatomical, and procedural risk factors, so called complex high-risk and indicated patients (CHIP) is associated with higher risk of complications [1, 2]. Percutaneous mechanical circulatory support devices (MCS) are often used to decease this risk — the strategy named "protected PCI" [3]. However, randomized data do not show clear benefit of this practice, so guidelines give only a weak indication for it use [4, 5]. Of the 3 widely available systems, the intraaortic balloon pump (IABP) is the least potent, but at the same time less invasive and cheaper than hemodynamically more effective but larger devices, like percutaneous axial flow pump (AFP) Impella (2.5/CP) or even

WHAT'S NEW?

Percutaneous coronary intervention in high-risk patients is frequently protected with mechanical circulatory support. Despite increasing use of more powerful devices, like Impella, the proof for their superiority in reduction of hard clinical endpoints is lacking. Our detailed assessment of data from right and left heart catheterization and arterial pressure tracings, including index of oxygen delivery and consumption (endocardial viability ratio) during high-risk coronary intervention demonstrate that intraaortic balloon of higher volume may have more favorable hemodynamic profile than standard balloon and hence might be a cheaper alternative to more potent but expensive devices for this indication.

more aggressive extracorporeal membrane oxygenator [6]. Currently the Impella pump is being increasingly used for high-risk PCI (HRPCI) [7], but due to high cost, poor availability, and complications rate, IABP is not completely abandoned by many operators worldwide. The larger volume type balloon was not well studied so far and theoretically may have more favorable hemodynamic profile than standard one.

In our previous work we were able to show that it might be more effective in reducing hemodynamic instability during HRPCI without effect on major adverse cardiovascular events (MACE) and safety endpoints compared to standard balloon or no-balloon control group [8]. Now, we aimed to describe in detail the effects of larger volume balloon by analyzing the additional hemodynamic data obtained during that study by right (RHC) and left heart catheterization (LHC).

METHODS

The hemodynamic data for the present analysis come from an already published study from a large academic tertiary center [8]. Study methodology was presented in detail previously, so they need only to be briefly mentioned. We included patients if they were rejected from coronary artery bypass grafting by Heart Team because of advanced age or many comorbidities and had left ventricular ejection fraction (EF) equal of less than 35% with significant unprotected left main stenosis, multivessel or last remaining vessel disease. The main exclusions were: 1) acute coronary syndrome of less than 48 hours before PCI; 2) cardiogenic shock; 3) acute stoke or 4) contraindications to IABP placement e.g., due to severe peripheral arterial disease (PAD) or 5) contraindications to dual antiplatelet therapy.

Our study was prospective and randomized. Eligible patients were randomized in 1:1:1 ratio using multiple permuted blocks utilizing online tool to one of the three study groups: 1) PCI without any MCS (CTRL); 2) PCI with a standard volume IABP (STRD): 40 cc >162 cm and 34 cc <162 cm; 3) PCI with a larger volume IABP (MEGA): 50 cc >162 cm and 40 cc <162 cm. Screening failure patients were assigned to registry (REG). Before PCI, RHC with pulmonary artery catheter (PAC) and LHC with PIGTAIL catheter were done. During PCI invasive, uninterrupted blood pressure tracing was taken from independent (usually radial) arterial catheter. From PAC standard hemodynamic values were obtained including cardiac output (CO) and index (CI) by the Fick principle, cardiac power output (CPO), which was calculated as mean arterial pressure (mm Hg) times CO (l/min) divided by 451 to express value in (W), as well as pulmonary artery wedge pressure (PCWP), stroke volume (SV) and mixed venous oxygen saturation (SvO_2). LHC was done to access left ventricular systolic (LVSP) and end-diastolic pressures (LVEDP), contractility (product od pressure and time – dP/dt) and endocardial viability ratio (EVR), which is an indirect measure of the balance between oxygen supply and demand of the left ventricle [9]. To calculate EVR the area between diastolic aortic and LVEDP (diastolic pressure time index) is divided by the area under LVSP (tension time index TTI), which is illustrated in Figure 1.

We also analyzed data from IABP console set in 1:2 mode (Figure 2). On the aortic pressure curve, it can be seen, among others, augmented diastolic pressure (D) when balloon inflates and systolic unloading (B–F) i.e., the drop of systolic pressure after balloon deflation.

All interventions were done by two experienced operators aiming at achieving complete revascularization based on viability testing and optimal angiographic result implanting 2nd generation drug eluting stents (DES) and using rotational atherectomy and intravascular ultrasound as needed. Procedural success was defined as combined: residual stenosis of less than 30%, TIMI 3 flow, and no major complications. Patient received periprocedural pharmacotherapy and general care according to existing guidelines. The protocol was approved by the Jagiellonian University Ethics Committee (decision number 122.6110.63.2016) and was done in accordance with Declaration of Helsinki. Signed, written, informed consent was obtained from every patient.

Statistical analysis

We used all available data obtained from the whole cohort of patients included in the study and categorized according to final hemodynamic support implemented (per-treatment analysis). Categorical variables were presented as counts and percentages, and continuous variables were presented as mean with standard deviation or median with the first and the third quartile as appropriate. Normality was assessed using the Shapiro–Wilk test. Equality of variances was tested using the Levene test. Comparisons of continuous variables were preformed using analysis of variance

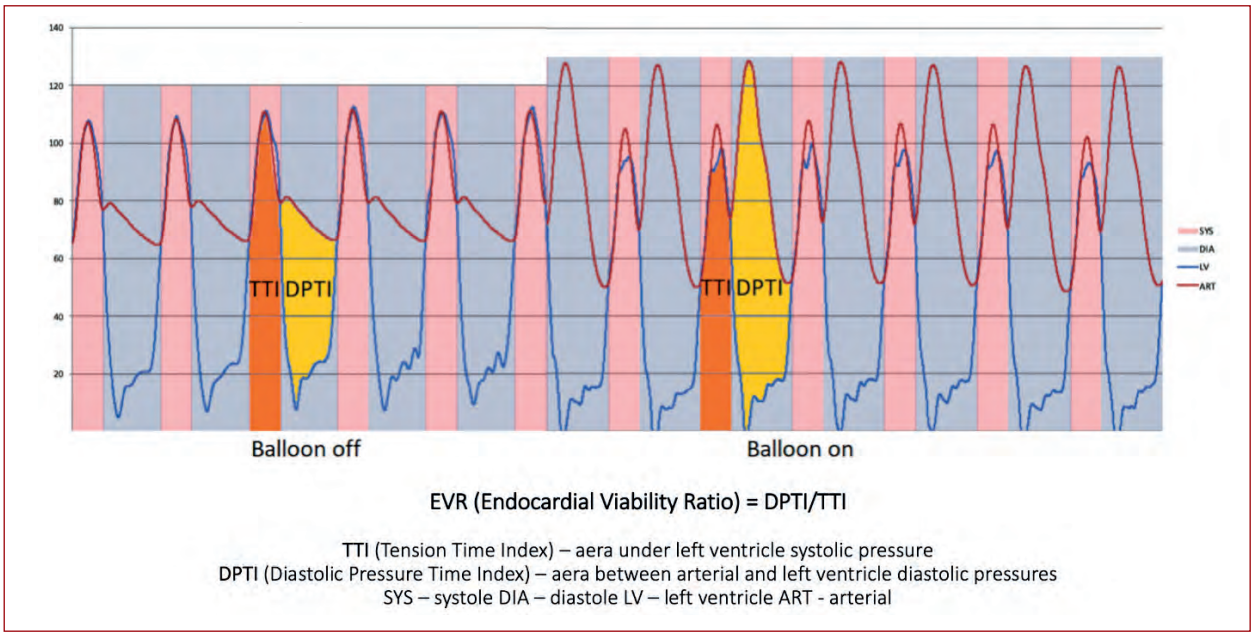


Figure 1. Calculation of EVR — in this example EVR was 0.76 off- vs. 1.71 on-support

Parameters of IABP support (1:2 mode)

Unassisted diastolic pressure (A)	mmHg
Unassisted systolic pressure (B)	mmHg
Dicrotic notch pressure (C)	mmHg
Augmented diastolic pressure (D)	mmHg
Assisted end-diastolic pressure (E)	mmHg
Assisted systolic pressure (F)	mmHg
Systolic unloading (B-F)	mmHg
Diastolic augmentation (D-A)	mmHg
Diastolic unloading (A-E)	mmHg
Deflation pressure (D-E)	mmHg

Print from the console with marked measurement points

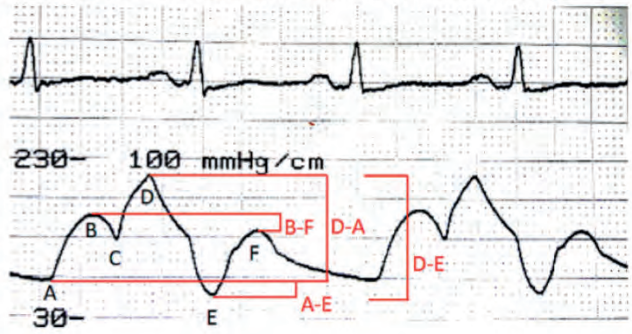


Figure 2. Hemodynamic parameters taken from the IABP console (1:2 setting)

or Kruskal–Wallis test as appropriate. *Post hoc* analysis, if necessary, was performed using Tukey's HSD or the Steel-Dwass test, as appropriate. Pearson's or Spearman's correlation coefficients were calculated, as appropriate, based on the normality of the data. Fisher's exact test or the χ^2 test were used to compare distributions of nominal variables.

Paired analysis was performed using the mixed effect models. For each analyzed variable, a mixed effect model was created with time point of measurement as well as group as fixed effects and patient ID as a random effect — which allows for the correlation between two measurements for the same patient to be taken into account. Then comparisons of patient-wise differences between time-points across groups were performed.

All tests were two-sided, and P <0.05 was assumed to indicate statistical significance. All data management and analysis activities were performed using JMP 14.2 (2019, SAS Institute Inc., Cary, NC, US) and R 3.5.3 (R Core Team [2019]).

RESULTS

In the study period we were able to screen 47 patients, 36 of which were randomized: 13 in MEGA, 14 in STDR and 9 in CTRL group. 4 patients in STDR group and 1 patient in MEGA group did not receive IABP because of severely angulated and/or calcified femoral/iliac arteries precluded device placement. 11 patients were screening failures but were treated according to the study protocol (4 of them received IABP of larger volume) and formed a REG. Ultimately, for the present study, we included all patients, randomized and from the registry and performed per-treatment analysis. Final cohort was composed of 47 subjects: 21 in CTR, 10 in STD and 16 in MEGA group, as is illustrated in a study flow chart — Supplementary material, *Figure S1*.

There were no significant baseline differences between the groups except for more frequent incidence of PAD in CTRL. The risk profile of the patients was very high with a mean EF of 32%, median Syntax Score of 38 points, median Euroscore II mortality risk of 6%, and median

Table 1. Clinical, demographic, echocardiographic, angiographic and procedural data

Variable	MEGA	STRD	CTRL	Total	*P*-value
N (%)	16 (34)	10 (21)	21 (45)	47 (100)	0.81
Demographic data:					
Age, years, mean (SD)	71.4 (8.4)	71.3 (11.5)	71.7 (10.1)	71.5 (9.7)	0.99
Male sex, n (%)	13 (81.3)	8 (80.0)	18 (85.7)	39 (82.9)	0.90
ACS, n (%)	11 (68.8)	3 (30.0)	8 (38.1)	22 (46.8)	0.08
Clinical symptoms:					
CCS class 3/4, n (%)	10 (62.5)	7 (70.0)	10 (47.6)	27 (57.5)	0.56
NYHA class 3/4, n (%)	11 (68.8)	8 (80.0)	14 (66.7)	33 (70.2)	0.16
Medical history:					
Hypertension, n (%)	16 (100.0)	10 (100.0)	20 (95.2)	46 (97.9)	0.44
Diabetes, n (%)	7 (43.8)	6 (60.0)	10 (47.6)	23 (48.9)	0.71
Smoking, n (%)	8 (53.3)	8 (80.0)	16 (76.2)	32 (69.6)	0.25
Previous MI, n (%)	8 (50.0)	6 (60.0)	13 (61.9)	27 (57.5)	0.76
Previous PCI, n (%)	5 (31.3)	4 (40.0)	7 (33.3)	16 (34.0)	0.90
Previous CABG, n (%)	2 (12.5)	1 (10.0)	2 (9.5)	5 (10.6)	0.96
Previous stroke, n (%)	2 (12.5)	0 (0.0)	6 (28.6)	8 (17.0)	0.11
Heart failure, n (%)	10 (62.5)	6 (60.0)	16 (76.2)	32 (68.1)	0.57
Atrial fibrillation, n (%)	5 (31.3)	5 (50.0)	6 (28.6)	16 (34.0)	0.48
Dyslipidemia, n (%)	13 (81.3)	6 (60.0)	15 (71.4)	34 (72.3)	0.54
CKD, n (%)	7 (43.8)	1 (10.0)	5 (23.8)	13 (27.7)	0.15
PAD, n (%)	6 (37.5)	0 (0.0)	11 (52.4)	17 (36.1)	0.004*
Echo examination:					
EF, %, mean (SD)	33 (9)	29 (11)	33 (13)	32 (11)	0.67
Significant MR, n (%)	8 (50.0)	4 (40.0)	8 (38.1)	20 (42.6)	0.78
Risk scales:					
Syntax score, median (Q1–Q3)	36.5 (29.1–49.6)	38.5 (29.6–43.0)	36.3 (27.8–45.5)	38.0 (29.0–44.5)	0.45
EuroScore II, median (Q1–Q3)	8 (4–14)	6 (2–8)	5 (4–15)	6 (3–12)	0.72
BCIS-1 JS, median (Q1–Q3)	12.0 (9.0–12.0)	12.0 (10.0–12.0)	12.0 (8.0–12.0)	12.0 (8.0–12.0)	0.24
Angiographic data:					
Left main stenosis, n (%)	11 (68.8)	6 (60.00)	15 (71.43)	32 (68.09)	0.82
CTO, n (%)	12 (75.0)	9 (90.00)	17 (80.95)	38 (80.85)	0.64
PCI ≥2 vessels, n (%)	13 (81.3)	7 (70.00)	17 (80.95)	37 (78.72)	0.76
Radiation, mGy, median (Q1–Q3)	1819 (1295–3200)	1628 (1360–3603)	2067 (1566–3072)	1947 (1331–3173)	0.93
Contrast volume, ml, mean (SD)	317 (89)	310 (94)	295 (71)	305 (81)	0.88
No. of stents, median (Q1–Q3)	2.0 (1.0–3.0)	2.0 (1.0–2.3)	2.0 (1.5–2.5)	2.0 (1.0–3.0)	0.82
Rotablation, n (%)	2 (12.5)	3 (30.0)	5 (23.8)	10 (21.3)	0.53
IVUS usage, n (%)	3 (18.8)	5 (50.0)	5 (23.8)	13 (27.7)	0.21
PCI success, n (%)	11 (68.8)	8 (80.0)	16 (76.2)	35 (74.5)	0.07

Data are presented as numbers (n) and percentages (%), mean and standard deviation (SD) or median and interquartile range (IQR: Q1–Q3)
**Post-hoc* analysis: MEGA vs. CTR $P = 0.87$; MEGA vs. STD $P = 0.012$; STD vs. CTR $P = 0.11$

Abbreviations: ACS, acute coronary syndrome; BCIS JS, British Cardiovascular Intervention Society Jeopardy Score; CABG, coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; CKD, chronic kidney disease; CTO, chronic total occlusion; IVUS, intravascular ultrasound; MI, myocardial infarction; MR, mitral regurgitation; NYHA, New York Heart Association, PAD, peripheral arterial disease; PCI, percutaneous coronary intervention

BCIS-1 Jeopardy Score of 12.0. The overall success rate of PCI was 74.5%. The clinical data are presented in Table 1.

The results of hemodynamic measurements before and post-IABP placement (or after 15 min from baseline in CTRL) obtained from PAC and LHC are shown in Table 2. There was significant difference in LVSP (MEGA 112 vs. STRD 113 vs. CTRL 145 mm Hg; $P < 0.01$) and EVR values (1.97 vs. 1.68 vs. 0.82, respectively; $P < 0.01$) on-support between the groups. dP/dt value was also close to reach statistical significance. All other parameters did not differ, although CO, CI and CPO were numerically higher in MEGA than STRD or CTRL group.

Then, using paired analysis-mixed effect models, we assessed device specific change (i.e., the difference between first and second measurement) for all analyzed hemodynamic parameters. We observed significant increase of on-support CO, CI, SV, CPO, and SvO_2, as well as a decrease of dP/dt in respect to CTRL in the MEGA, but not in the STRD group. The change in EVR (increase) and in LVSP (decrease) was significant both in MEGA and STRD vs. CTRL group, but at the same time, PCWP did not changed significantly vs. CTRL either in MEGA or in STRD. Results are shown in Figure 3.

Finally, we compared balloon function parameters from the IABP console (as shown in Figure 2). We found that diastolic augmented pressure (D) was significantly greater in MEGA vs. STRD group (170.1 vs. 139.5 mm Hg; $P = 0.02$). Moreover, there was a trend towards higher di-

Table 2. The results of hemodynamic measurements before and post-IABP placement

VARIABLE	time	MEGA	STRD	CTRL	*P*-value
LVSP, mm Hg	1st	135 (29)	126 (30)	135 (28)	0.75
	2nd	113 (22)	112 (23)	145 (26)	0.003
dP/dt, mm Hg × s^{-1}	1st	1292 (426)	1079 (389)	1302 (485)	0.48
	2nd	1166 (429)	991 (418)	1389 (464)	0.09
EVR	1st	0.81 (0.16)	0.88 (0.16)	0.86 (0.16)	0.75
	2nd	1.97 (0.39)	1.68 (0.28)	0.82 (0.14)	<0.001
MAP, mm Hg	1st	88 (16)	82 (8)	85 (15)	0.53
	2nd	93 (17)	89 (10)	88 (16)	0.88
PCWP, mm Hg	1st	15.7 (9.5)	15.8 (7.6)	14.0 (4.7)	0.88
	2nd	11.9 (7.7)	11.9 (6.2)	11.7 (4.7)	0.97
MPAP, mm Hg	1st	27.6 (16.4)	24.1 (7.4)	25.6 (8.8)	0.93
	2nd	22.5 (12.5)	22.2 (7.2)	22.9 (10.1)	0.97
HR, min^{-1}	1st	74 (8)	69 (15)	72 (13)	0.31
	2nd	71 (8)	70 (19)	67 (10)	0.55
SV, ml	1st	57 (15)	63 (19)	59 (24)	0.75
	2nd	64 (12)	65 (21)	61 (18)	0.72
CO, l/min	1st	4.17 (1.04)	4.07 (0.59)	4.04 (1.4)	0.77
	2nd	4.52 (0.84)	4.24 (0.59)	3.98 (1.02)	0.17
CI, l/min/m^2	1st	2.25 (0.58)	2.11 (0.23)	2.18 (0.67)	0.73
	2nd	2.44 (0.48)	2.22 (0.36)	2.13 (0.46)	0.20
CPO, W	1st	0.82 (0.26)	0.74 (0.12)	0.80 (0.36)	0.91
	2nd	0.94 (0.27)	0.83 (0.16)	0.79 (0.29)	0.32
SvO_2, %	1st	61 (11)	63 (7)	62 (12)	0.99
	2nd	64 (8.0)	64 (8)	63 (11)	0.91

Data are presented as a mean and standard deviation (SD)
Time: 1st — baseline, 2nd — after IABP placement (MEGA or STRD) or after 15 min in CTRL

Abbreviations: CI, cardiac index; CO, cardiac output; CPO, cardiac power output; dP/dt, pressure time product; EVR, endocardial viability ratio; HR, heart rate; LHC, left heart catheterization; LVSP, left ventricle systolic pressure; MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure; PAC, pulmonary artery catheter; PCWP, pulmonary artery wedge pressure; SV, stroke volume; SvO_2, mixed venous oxygen saturation

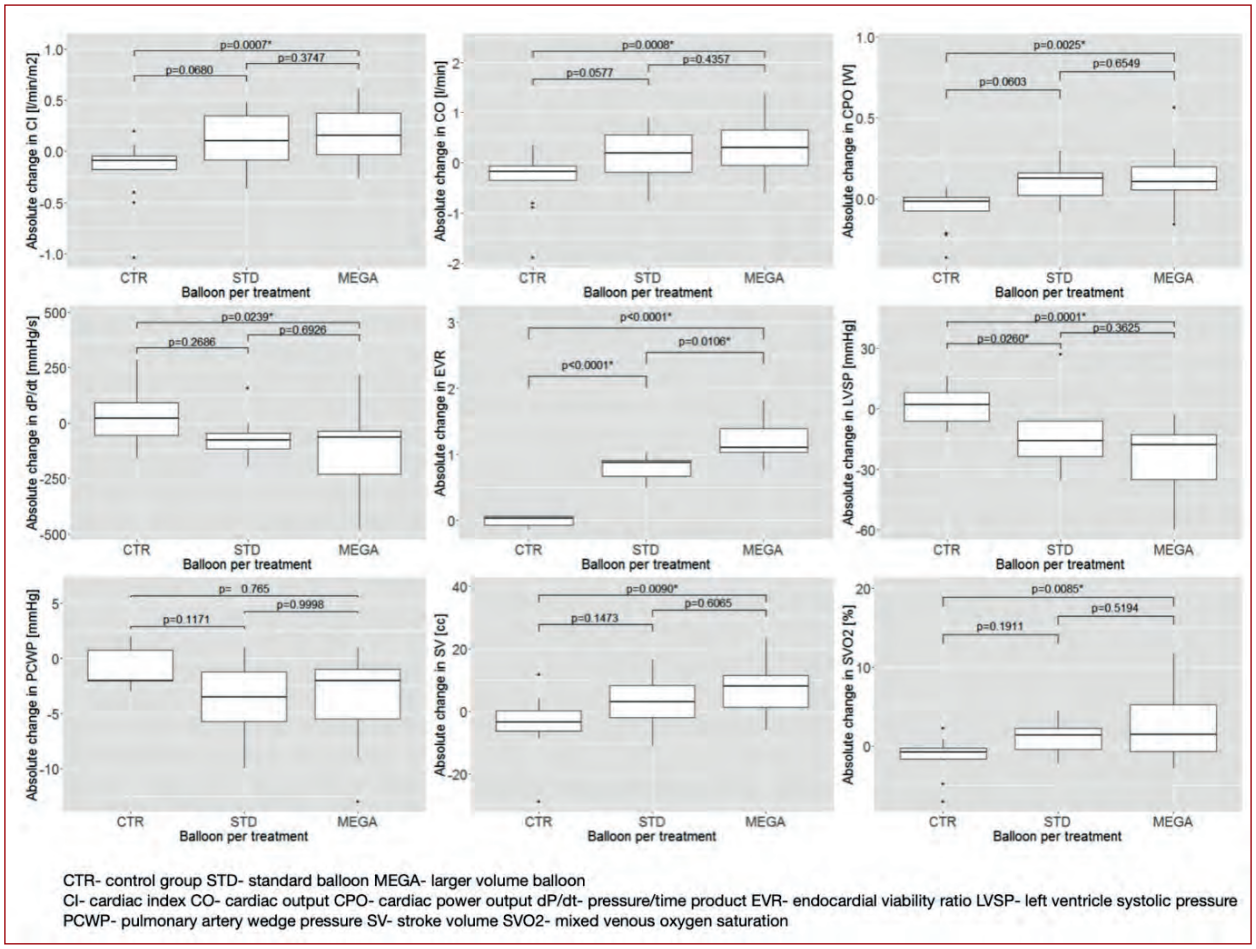


Figure 3. Device-specific change (on-support vs. off-support) of hemodynamic parameters

Table 3. The comparison of balloon function parameters between MEGA and STDR

VARIABLE, mm Hg	MEGA	STRD	*P*-value
Unassisted diastolic pressure (A)	67.14 (11.2)	62.9 (9.89)	0.35
Unassisted systolic pressure (B)	132.50 (26.94)	127.00 (27.94)	0.63
Dicrotic notch pressure (C)	105.60 (24.50)	98.60 (21.44)	0.47
Augmented diastolic pressure (D)	170.07 (36.40)	139.50 (21.16)	0.02
Assisted end-diastolic pressure (E)	56.47 (14.00)	55.90 (14.23)	0.92
Assisted systolic pressure (F)	117.53 (24.61)	113.50 (21.82)	0.68
Systolic unloading (B–F)	17.50 (8.23)	13.50 (10.22)	0.30
Diastolic augmentation (D–A)	97.21 (28.54)	76.60 (21.07)	0.07
Diastolic unloading (A–E)	8.50 (5.49)	7.00 (6.27)	0.54
Deflation pressure (D–E)	113.60 (43.98)	83.60 (24.52)	0.06

Data are presented as a mean and standard deviation (SD); units of pressure are mm Hg

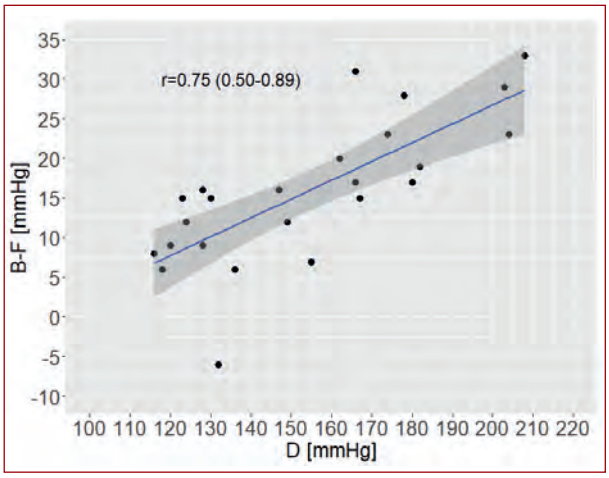


Figure 4. Correlation between diastolic augmented pressure (D) and systolic unloading (B–F)

astolic augmentation (D–A) and deflation pressure (D–E) in MEGA vs. STRD group, which may also indicate clinically significant difference (Table 3).

Additionally, we found significant positive correlation ($r = 0.75$; $P \leq 0.001$) between augmented diastolic pressure (D) with the systolic unloading (B–F), i.e., the higher was augmentation pressure the greater was drop in aortic (and left ventricular — not shown) systolic pressure — Figure 4.

There was no difference in hospital and 1-year follow up in MACE between the groups, as well as in the rate of major and minor bleeding according to Academic Research Consortium (BARC), vascular access site complication or acute renal failure — Supplementary material, *Table S1*. The causes of major bleeds in decreasing order of frequency were: large hematoma at vascular access site (7), bleeding around vascular catheter without hematoma formation (2), significant hemoglobin drop without obvious cause (2), gastrointestinal bleeding (1), coronary artery perforation with tamponade (1), alveolar hemorrhage (1) and vascular surgical intervention (1).

DISCUSSION

In our study we presented in-depth analysis of invasive hemodynamics obtained during HRPCI with or without IABP support. We found that, although majority of on-support values were not different between the groups (except for higher EVR and lower LVSP with both IABP), the change of these parameters from off- to on-support varied significantly, i.e., the measured change in CO, CI, CPO, SV, SvO_2 and dP/dt was statistically significant vs CTRL in MEGA, but not in the STRD group. Both balloons were effective in reducing LVSP and increasing EVR, but none in reducing PCWP. This implies that even very small (10 cc) additional volume of an intra-aortic balloon may have clinically meaningful effect. In fact, we have already demonstrated that IABP of larger volume type implanted electively before HRPCI was able to reduce composite hemodynamic endpoint during the procedure (although in hospital and follow-up MACE were not different) [8]. Moreover, additional analyses of pressure tracings form IABP console, demonstrated that MEGA balloon provide higher diastolic augmentation pressure than STDR one, which in turn, was significantly correlated with greater systolic unloading, meaning less workload for an already severely stressed left ventricle. Likewise, EVR was also numerically higher with the larger vs. standard balloon, which may additionally imply more favorable oxygen supply-demand ratio of the MEGA type.

In a small study done by Kapur et al. [10] the authors were also able to demonstrate better hemodynamic profile of higher volume balloon, with greater augmented diastolic blood pressure, greater systolic unloading (which were both linearly correlated), and (contrary to our results) a larger reduction of PCWP of 50 cc balloon in comparison to 40 cc in both HRPCI and shock patients. 50 cc balloon recipients had also greater (and statistically significant) increase in CO and CI [10].

On the other hand, our study showed only modest increase in CO associated with counter-pulsation, e.g., for MEGA it was on average 0.4 l/min, and for STDR just around 0.2 l/min, and no reduction of PCWP. This confirms that IABP is a very weak hemodynamic support device, and it cannot adequately support the patient if serious complications might develop during HRPCI. Accordingly, the only randomized clinical trial (BCIS-1) that tested elective IABP use for HRPCI (but only of standard volume type) did not show any benefit in terms of MACE [11], but interestingly in the

long-term follow-up there was a reduction in mortality [12]. For this reason, nowadays, more potent devices like AFP Impella are being increasingly used for CHIP patients [13–15] and are preferred by various expert consensus statements [16]. In fact, randomized [17] and observational [18] data show greater hemodynamic effect of AFP vs. IABP, but at the same time they failed to show a reduction of hard clinical endpoints. On the contrary, there is some evidence from recent large registries that use of Impella was associated with increased mortality and morbidity, including bleeding, vascular access site and neurologic complications [19, 20].

The recent work from Polish authors compared retrospectively Impella (n = 28) and IABP (n = 22) use during HRPCI. Patients qualified for Impella support had lower EF and were younger despite having similar Euroscore II. Study demonstrated similar MACE and mortality rate during median 224 days of follow-up. On the contrary the major bleeding events and vascular complications were observed more often in the AFP group probably as a consequence of larger bore access side, different modes of vascular closure and higher dose of anticoagulants [21].

Therefore, it should be emphasized that hemodynamic support *per se* is not the primary goal of MCS therapy in the setting of HRPCI. To improve the prognosis, it is necessary to achieve complete and optimal revascularization and the device should provide just enough support for the completion of the complex procedure without hemodynamic compromise that might jeopardize the final result. At the same time, the risk associated with support device should not exceed the possible benefits. Finally, the cost and complexity of given strategy must be considered.

Accordingly, there is some evidence from retrospective studies that contemporary high-risk patients may be effectively treated with PCI without any support device with a very high procedural success and low MACE rate [22]. The authors state that, contrary to current recommendations and practice, HRPCI without any MCS usage is feasible and safe in most of CHIP patients. So, lacking conclusive results from randomized trials, the strategy of unprotected HRPCI must also be considered.

We would also like to stress the importance of hemodynamic monitoring using PAC. RHC is being increasingly advocated during MCS support, esp. in the field of cardiogenic shock [23, 24]. The valuable data that can be derived from RHC could help in choosing the device that best suits the needs of the given patient. Surprisingly often, stable HRPCI patients despite low EF, may have relatively well-preserved SV, CO and CI and a low PCWP, possibly allowing for a standby/bail-out only MCS therapy. On the contrary, in the more acute setting, like acute coronary syndrome or CS, these physiologic parameters may be much more disturbed, necessitating up-front (before PCI) implantation of the support device.

Additionally, it is worth to mention that the art of managing IABP nowadays may be rather lost among interventional cardiologists. To guarantee optimal hemodynamic support it is important to observe diastolic augmentation and systolic unloading on the IABP control panel and arterial pressure tracing after device placement.

Study limitation

Our study has several limitations. It was designed as a randomized study, but due to slow recruitment process (single-center study) we were able to randomize only 36 patients in 18 months. Moreover, we observed some cross-over because of inability to insert IABP when tortuous or calcified femoral and iliac vessels were discovered during the procedure. Additionally, several patients did not meet inclusion criteria, but still were treated according to the study protocol and were included in final per-treatment analysis. Therefore, our results should be considered as exploratory and hypothesis-generating. Nonetheless, the baseline values were well balanced between the groups, except for more frequent occurrence of PAD in CTRL.

CONCLUSION

Our in-depth physiologic analysis adds important new data on hemodynamic effect on higher volume intra-aortic balloon showing that it may have more favorable hemodynamic profile than standard volume IABP and hence might be considered as a possible cheaper alternative for some CHIP patients.

Supplementary material

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

Article information

Conflict of interest: None declared.

Funding: None.

REFERENCES

1. Chieffo A, Burzotta F, Pappalardo F, et al. Clinical expert consensus document on the use of percutaneous left ventricular assist support devices during complex high-risk indicated PCI: Italian Society of Interventional Cardiology Working Group Endorsed by Spanish and Portuguese Interventional Cardiology Societies. Int J Cardiol. 2019; 293: 84–90, doi: 10.1016/j.ijcard.2019.05.065, indexed in Pubmed: 31174920.
2. Kirtane AJ, Doshi D, Leon MB, et al. Treatment of higher-risk patients with an indication for revascularization. Circulation. 2016; 134(5): 422–431, doi: 10.1161/circulationaha.116.022061.
3. Bass TA. High-risk percutaneous coronary interventions in modern day clinical practice: current concepts and challenges. Circ Cardiovasc Interv. 2015; 8(12): e003405, doi: 10.1161/CIRCINTERVENTIONS.115.003405, indexed in Pubmed: 26628592.
4. Chieffo A, Dudek D, Hassager C, et al. Joint EAPCI/ACVC expert consensus document on percutaneous ventricular assist devices. EuroIntervention. 2021; 17(4): e274–e286, doi: 10.4244/EIJY21M05_01, indexed in Pubmed: 34057071.

5. Tycińska A, Grygier M, Biegus J, et al. Mechanical circulatory support. An expert opinion of the Association of Intensive Cardiac Care and the Association of Cardiovascular Interventions of the Polish Cardiac Society. Kardiol Pol. 2021; 79(12): 1399–1410, doi: 10.33963/KP.a2021.0169, indexed in Pubmed: 34861044.
6. Atkinson TM, Ohman EM, O'Neill WW, et al. A practical approach to mechanical circulatory support in patients undergoing percutaneous coronary intervention: an interventional perspective. JACC Cardiovasc Interv. 2016; 9(9): 871–883, doi: 10.1016/j.jcin.2016.02.046, indexed in Pubmed: 27151604.
7. Chieffo A, Ancona MB, Burzotta F, et al. Collaborators. Observational multicentre registry of patients treated with IMPella mechanical circulatory support device in ITaly: the IMP-IT registry. EuroIntervention. 2020; 15(15): e1343–e1350, doi: 10.4244/EIJ-D-19-00428, indexed in Pubmed: 31422925.
8. Zeliaś A, Zajdel W, Malinowski K, et al. Circulatory support with larger volume intra-aortic balloon pump vs. standard volume or no-balloon pump during high-risk percutaneous coronary interventions. A randomised study. Postepy Kardiol Interwencyjnej. 2020; 16(1): 30–40, doi: 10.5114/aic.2020.93910, indexed in Pubmed: 32368234.
9. Philips PA, Bregman D. Intraoperative application of intraaortic balloon counterpulsation determined by clinical monitoring of the endocardial viability ratio. Ann Thorac Surg. 1977; 23: 45–51, doi: 10.1016/s0003-4975(10)64068-4, indexed in Pubmed: 831644.
10. Kapur NK, Paruchuri V, Majithia A, et al. Hemodynamic effects of standard versus larger-capacity intraaortic balloon counterpulsation pumps. J Invasive Cardiol. 2015; 27(4): 182–188, indexed in Pubmed: 25840400.
11. Perera D, Stables R, Clayton T, et al. Elective intra-aortic balloon counterpulsation during high-risk percutaneous coronary intervention: a randomized controlled trial. JAMA. 2010; 304(8): 867–874, doi: 10.1001/jama.2010.1190, indexed in Pubmed: 20736470.
12. Perera D, Stables R, Clayton T, et al. Long-term mortality data from the balloon pump-assisted coronary intervention study (BCIS-1): a randomized, controlled trial of elective balloon counterpulsation during high-risk percutaneous coronary intervention. Circulation. 2013; 127(2): 207–212, doi: 10.1161/CIRCULATIONAHA.112.132209, indexed in Pubmed: 23224207.
13. Khera R, Cram P, Vaughan-Sarrazin M, et al. Use of mechanical circulatory support in percutaneous coronary intervention in the United States. Am J Cardiol. 2016; 117(1): 10–16, doi: 10.1016/j.amjcard.2015.10.005, indexed in Pubmed: 26547292.
14. Cohen MG, Matthews R, Maini B, et al. Percutaneous left ventricular assist device for high-risk percutaneous coronary interventions: Real-world versus clinical trial experience. Am Heart J. 2015; 170(5): 872–879, doi: 10.1016/j.ahj.2015.08.009, indexed in Pubmed: 26542494.
15. Chieffo A, Ancona MB, Burzotta F, et al. Observational multicentre registry of patients treated with IMPella mechanical circulatory support device in ITaly: the IMP-IT registry. EuroIntervention. 2020; 15(15): e1343–e1350, doi: 10.4244/EIJ-D-19-00428, indexed in Pubmed: 31422925.
16. Burzotta F, Trani C, Doshi SN, et al. Impella ventricular support in clinical practice: Collaborative viewpoint from a European expert user group. Int J Cardiol. 2015; 201: 684–691, doi: 10.1016/j.ijcard.2015.07.065, indexed in Pubmed: 26363632.
17. O'Neill WW, Kleiman NS, Moses J, et al. A prospective, randomized clinical trial of hemodynamic support with Impella 2.5 versus intra-aortic balloon pump in patients undergoing high-risk percutaneous coronary intervention: the PROTECT II study. Circulation. 2012; 126(14): 1717–1727, doi: 10.1161/CIRCULATIONAHA.112.098194, indexed in Pubmed: 22935569.
18. Azzalini L, Johal GS, Baber U, et al. Outcomes of Impella-supported high-risk nonemergent percutaneous coronary intervention in a large single-center registry. Catheter Cardiovasc Interv. 2021; 97(1): E26–E33, doi: 10.1002/ccd.28931, indexed in Pubmed: 32333721.
19. Amin AP, Spertus JA, Curtis JP, et al. The evolving landscape of impella use in the United States among patients undergoing percutaneous coronary intervention with mechanical circulatory support. Circulation. 2020; 141(4): 273–284, doi: 10.1161/CIRCULATIONAHA.119.044007, indexed in Pubmed: 31735078.
20. Kuno T, Takagi H, Ando T, et al. Safety and efficacy of mechanical circulatory support with Impella or intra-aortic balloon pump for high-risk percutaneous coronary intervention and/or cardiogenic shock: Insights from a network meta-analysis of randomized trials. Catheter Cardiovasc Interv. 2021; 97(5): E636–E645, doi: 10.1002/ccd.29236, indexed in Pubmed: 32894797.
21. Januszek R, Pawlik A, Rzeszutko Ł, et al. Clinical outcomes in patients undergoing complex, high-risk percutaneous coronary intervention and haemodynamic support with intra-aortic balloon versus Impella pump: Real-life single-centre preliminary results. Kardiol Pol. 2022; 80(12): 1224–1231, doi: 10.33963/KP.a2022.0203, indexed in Pubmed: 36047958.
22. Khalid N, Rogers T, Torguson R, et al. Feasibility and safety of high-risk percutaneous coronary intervention without mechanical circulatory support. Circ Cardiovasc Interv. 2021; 14(6): e009960, doi: 10.1161/CIRCINTERVENTIONS.120.009960, indexed in Pubmed: 34092089.
23. Saxena A, Garan AR, Kapur NK, et al. Value of hemodynamic monitoring in patients with cardiogenic shock undergoing mechanical circulatory support. Circulation. 2020; 141(14): 1184–1197, doi: 10.1161/CIRCULATIONAHA.119.043080, indexed in Pubmed: 32250695.
24. Chow JY, Vadakken ME, Whitlock RP, et al. Pulmonary artery catheterization in patients with cardiogenic shock: a systematic review and meta-analysis. Can J Anaesth. 2021; 68(11): 1611–1629, doi: 10.1007/s12630-021-02083-2, indexed in Pubmed: 34405356.

Prediction of major adverse cardiac events in patients with multivessel coronary artery disease with an interpretable classification tree model based on coronary computed tomography angiography

Daria Kaczmarek, Oliwia Matuszewska-Brycht, Mateusz Kobierecki, Milena Jakuszczonek, Jan Krekora, Jarosław Drożdż

2nd Department of Cardiology, Medical University of Lodz, Łódź, Poland

Correspondence to:
Daria Kaczmarek, MD,
2nd Department of Cardiology,
Medical University of Lodz,
Pomorska 251, 92–213 Łódź,
Poland,
phone: +48 42 201 43 16,
e-mail: dariaa.jedrzejewska@gmail.com

DOI: 10.33963/v.kp.98352

Received:
August 17, 2023

Accepted:
November 29, 2023

Early publication date:
December 21, 2023

INTRODUCTION

Cardiovascular diseases (CVD), the prevailing cause of death, contribute to almost one-third of all deaths around the world [1]. In 2030 CVD would cause more than 23 million deaths worldwide [2]. Patients with multivessel coronary artery disease (MVD) are particularly important due to their increased risk of acute coronary syndrome and sudden cardiac death [3]. According to our knowledge, currently there is no simple predictive model determining the occurrence of a major adverse cardiac event (MACE; cardiac death, myocardial infarction or unstable angina, stroke) during one year of follow-up in patients with MVD diagnosed by coronary computed tomography angiography (CCTA). Therefore, the aim of the study was to create a simple algorithm for the population of MVD patients that enables the risk estimation of MACE based solely on CCTA.

METHODS

Study population

We conducted a two-stage study in order to develop and test our model. In the first stage, 106 participants were enrolled after a hospitalization in the Cardiology Department of the Central Clinical Hospital in Lodz during the period 2020–2021. All the patients had MVD confirmed by invasive coronary angiography (ICA) after CCTA. Eligible patients were ≥18 years old, diagnosed with stable coronary artery disease (CAD) according to the European Society of Cardiology (ESC) guidelines [4]. Exclusion criteria were defined as permanent atrial fibrillation, acute coronary syndrome or stroke within the last 3 months.

In the second stage our model was validated using test external data to assess its reliability. For this purpose we collected another 52 CCTA records from patients admitted to the same department in 2022. The inclusion and exclusion criteria were the same. The only analyzed diagnostic method was CCTA. During follow-up, the specialist Heart Team classified patients into an appropriate treatment option of revascularization or conservative treatment taking into account patients' overall clinical condition and preferences as well as the ESC Guidelines.

The study complied with the Declaration of Helsinki and was approved by the local medical ethics committee. All the patients provided written informed consent prior to their participation in the study.

Analyzed parameters

All data collected from 106 patients was tested for correlation with the occurrence of MACE during one-year follow-up. A direct interview with each study participant or their family and medical data from one-year follow-up were the basis for the analysis. Survival data were based on the status in the central register of citizens.

CCTA was conducted on an outpatient basis in various computed tomography laboratories in the city of Lodz using iodine contrast agent and different at least 64-slice resolution CT scanners. Significant stenosis of the coronary artery was defined by the CCTA

described as significant, critical, severe or >70% narrowing of the coronary artery lumen. Coronary artery calcium score was also measured in each CT scan.

ICA examinations were performed by one hemodynamic team. Significant stenosis of the coronary artery in ICA was defined as >50% narrowing in the left main (LM) coronary artery and >70% narrowing in the rest of the epicardial arteries [5]. ICA was performed ≤6 months after the CCTA on the same patient.

Prediction algorithm

After the first study stage a classification tree model was generated using the Classification and Regression Tree Algorithm based on the CT variables. Gini split criterion was used. Our dataset was evaluated using 5-fold cross-validation to assess the optimal tree depth. We revealed that the optimal depth of the tree is two (mean accuracy: 88% for the training dataset; 85% for the test dataset; Supplementary material, *Figure S1*). With increasing tree depth, the training dataset accuracy rose, however, the evaluated dataset accuracy declined, as an example of data overfitting.

Statistical analysis

The classification tree performance was assessed using the test cohort collected in the second stage of the study. Receiver operating characteristic (ROC) curve was also calculated. Demographic and laboratory data were analyzed as follows. The normality of continuous variable distribution was assessed using the Shapiro–Wilk test along with the evaluation of histograms. Numerical variables were presented using the mean with SD or median with interquartile range (IQR), qualitative variables were presented as numbers with an appropriate percentage. *P*-value <0.05 was considered statistically significant. Univariate logistic regression was applied to further compare the influence of factors on the risk of MACE. The results of the logistic regression are presented as odds ratio (OR) with a 95% confidence interval (95% CI). All calculations were carried out in Python 3.11 with the Scikit-learn 1.2.2 package for constructing the classification tree.

RESULTS AND DISCUSSION

Figure 1A illustrates the algorithm that was created using the cohort of the first study stage. The parameter with the greatest significance in the MACE classification was the presence of LM significant stenosis. The second parameter with slightly lower significance was the presence of left anterior descending artery (LAD) significant stenosis.

The assessment of the second study stage cohort using the same classification tree demonstrated an accuracy of 84.5%, with a sensitivity of 80.0% and specificity of 86.5%, confirming that our algorithm exhibits a similar effectiveness on the external data. The confusion matrix in our second stage cohort is presented in Figure 1B.

Therefore, we propose a classification tree model which is simple to interpret (Figure 1C). The model is based solely on the LM significant stenosis as the first algorithm step, and the LAD significant stenosis as the second algorithm step. Despite its simplicity, the model accuracy was 87.7%, with sensitivity 71.4% and specificity 91.7% on our training data with the area under the receiver operating characteristic curve: 0.86 (95% CI, 0.80–0.92).

The first study group was predominantly male (n = 69.8%). The average age of the study population was 69.42 (8.28) years, and the mean body mass index: 27.91 (4.44) kg/m^2. Chronic heart failure, chronic kidney disease and diabetes mellitus type 2 were diagnosed in 52.8%, 18.9% and 35.8% of the group, respectively. The detailed characteristics are presented in Supplementary material, *Tables S1* and *S2*.

Other features that influence the risk of MACE in patients with MVD, in addition to the CCTA stenosis described above, are as folows: presence of heart failure (odds ratio [OR], 3.6; 95% CI, 1.20–10.71; $P = 0.02$), elevated creatinine level (OR, 2.81; 95% CI, 1.23–6.37; $P = 0.01$), elevated N-terminal pro-B-type natriuretic peptide level (OR, 1.77; 95% CI, 1.13–2.76; $P = 0.01$), elevated troponin level (OR, 4.52; 95% CI, 1.81–11.28; $P = 0.001$), history of COVID-19 infection (OR, 3.37; 95% CI, 1.04–10.90; $P = 0.04$) and the history of myocardial infarction (OR, 6.85; 95% CI, 2.12–22.13; $P = 0.001$). The detailed characteristics are presented in Supplementary material, *Table S3*.

Stenosis of the LM is a significant cause of stenocardia in patients with CAD [6]. Based on many current studies that prove the LM stenosis to be an independent indicator of an increased morbidity and mortality among patients with CAD [7, 8], the algorithm we developed may be an efficient tool for predicting the risk of MACE in patients with MVD.

CCTA is gaining in importance. According to the study by Rudziński et al. [9] which evaluated the long-term efficacy and safety of CCTA vs. ICA as the first-line imaging test in stable patients with a high clinical probability of obstructive CAD, no significant differences were found between both methods in MACE occurrence or long-term safety.

Study limitations

The study was conducted as a single-center retrospective study with a relatively small group of participants. All of these factors may lead to an increased risk of selection bias and accidental findings in relation to the factors correlating with the study endpoint.

CONCLUSIONS

Summarizing, we created the classification tree to predict the risk of MACE in patients with MVD in one-year observation. If confirmed on a larger sample size, these findings may provide an interpretable tool for the risk stratification of MACE using only CCTA results. In our study the significant stenosis of the LM and the LAD are the most statistically significant factors associated with a one-year risk of MACE in patients with MVD.

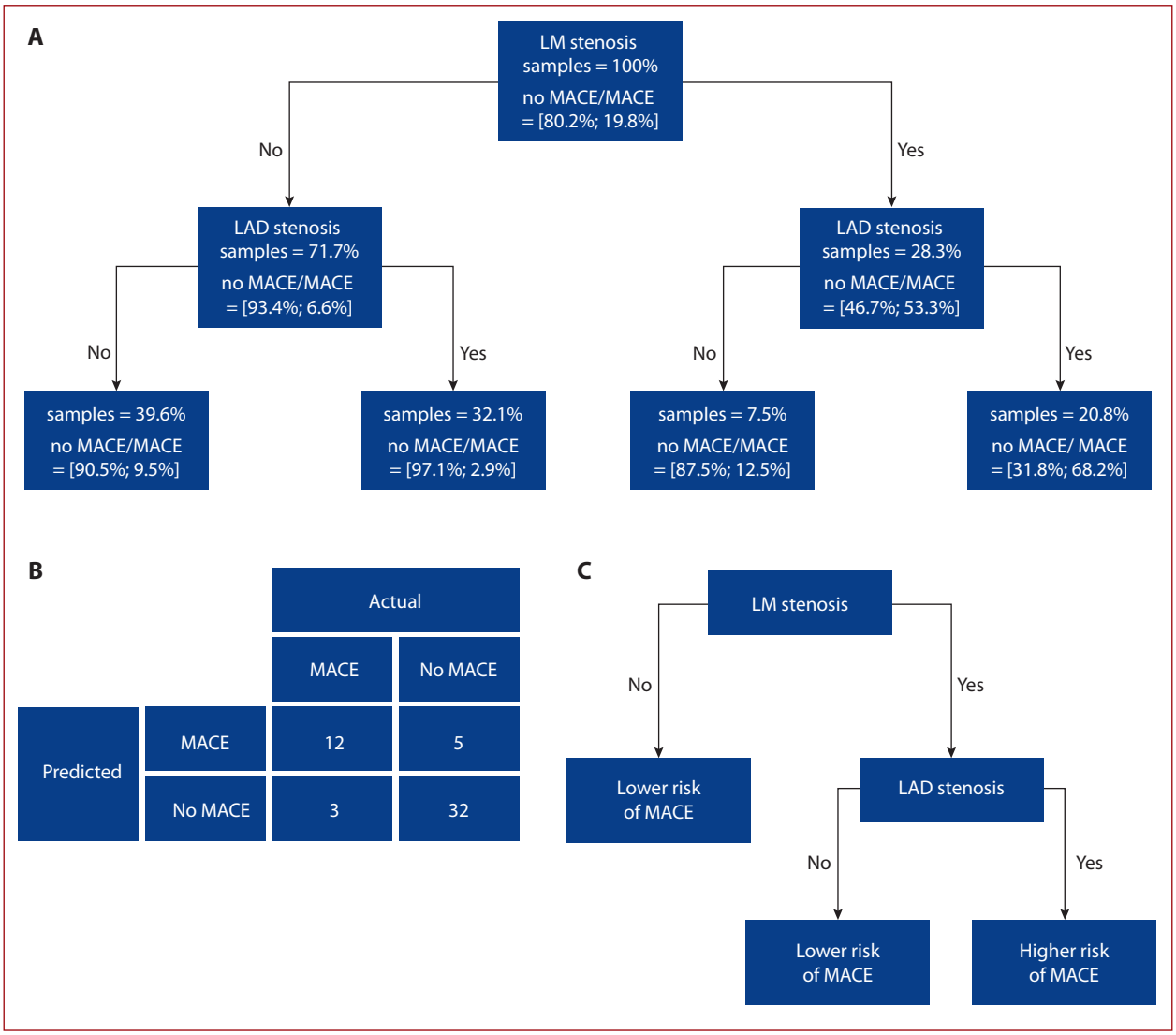


Figure 1. A. The major adverse cardiac event (MACE) classification algorithm on the basis of the cohort of the first study stage. **B.** The confusion matrix in the cohort of the second study stage. **C.** The classification tree model for prediction of MACE in patients with multivessel coronary artery disease (MVD) in one-year observation

Supplementary material

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

Article information

Conflict of interest: None declared.

Funding: None.

REFERENCES

1. GBD 2016 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017; 390(10100): 1151–1210, doi: 10.1016/S0140-6736(17)32152-9, indexed in Pubmed: 28919116.
2. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012; 380(9859): 2095–2128, doi: 10.1016/S0140-6736(12)61728-0, indexed in Pubmed: 23245604.
3. Brar SS, Syros G, Dangas G. Multivessel disease: percutaneous coronary intervention for classic coronary artery bypass grafting indications. Angiology. 2008; 59(Suppl 2): 83S–88S, doi: 10.1177/0003319708318862, indexed in Pubmed: 18544582.
4. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2020; 41(3): 407–477, doi: 10.1093/eurheartj/ehz425, indexed in Pubmed: 31504439.
5. Neglia D, Rovai D, Caselli C, et al. Detection of significant coronary artery disease by noninvasive anatomical and functional imaging. Circ Cardiovasc Imaging. 2015; 8(3): e002179, doi: 10.1161/CIRCIMAGING.114.002179, indexed in Pubmed: 25711274.
6. Sciagrà R, Tebbe U, Vogt A, et al. Occlusion of the common trunk of the left coronary artery. Physiopathological features and clinical findings [article in Italian]. G Ital Cardiol. 1986; 16(6): 516–521, indexed in Pubmed: 2944789.

7. Takaro T, Pifarre R, Fish R. Veterans Administration Cooperative Study of medical versus surgical treatment for stable angina — progress report. Section 3. Left main coronary artery disease. Prog Cardiovasc Dis. 1985; 28(3): 229–234, doi: 10.1016/0033-0620(85)90018-0, indexed in Pubmed: 3903867.
8. Eagle KA, Guyton RA, Davidoff R, et al. ACC/AHA guidelines for coronary artery bypass graft surgery: executive summary and recommendations: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1991 guidelines for coronary artery bypass graft surgery). Circulation. 1999; 100(13): 1464–1480, doi: 10.1161/01.cir.100.13.1464, indexed in Pubmed: 10500052.
9. Rudziński PN, Kruk M, Demkow M, et al. Efficacy and safety of coronary computed tomography angiography in patients with a high clinical likelihood of obstructive coronary artery disease. Kardiol Pol. 2022; 80(1): 56–63, doi: 10.33963/KP.a2021.0185, indexed in Pubmed: 34923618.

Valvular expression of factor XI correlates with valve calcification and aortic stenosis severity

Magdalena Kopytek[1, 2], Janusz Konstanty-Kalandyk[3, 4], Michał Ząbczyk[1, 2], Anetta Undas[1, 2], Joanna Natorska[1, 2]

[1]Thromboembolic Disorders Department, Institute of Cardiology, Jagiellonian University Medical College, Kraków, Poland
[2]Krakow Centre for Medical Research and Technologies, St. John Paul II Hospital, Kraków, Poland
[3]Department of Cardiovascular Surgery and Transplantology, Institute of Cardiology, St. John Paul II Hospital, Kraków, Poland
[4]Institute of Cardiology, Jagiellonian University Medical College, Kraków, Poland

Correspondence to:
Joanna Natorska, PhD, Institute of Cardiology, Jagiellonian University Medical College, 80 Prądnicka, 31–202 Kraków, Poland, phone: + 48 12 614 21 08, fax: +48 12 614 21 20, e-mail: j.natorska@szpitaljp2.krakow.pl

DOI: 10.33963/v.kp.97723

Received:
September 4, 2023

Accepted:
October 5, 2023

Early publication date:
October 19, 2023

INTRODUCTION

Aortic stenosis (AS) is a progressive disease with a pathogenesis similar to atherosclerosis [1]. AS progression is associated with aortic valve orifice and leaflet mobility reduction, and there is no available pharmacological treatment to prevent or at least retard disease progression [1]. Currently, the only therapeutic options for AS are surgical aortic valve replacement or transcatheter aortic valve implantation [2, 3]. Associated activation of both coagulation and inflammation leading to valvular calcification has been shown in AS [4, 5]. Growing evidence indicates a contribution of factor XI (FXI) to thrombosis [6] and atherogenesis [7]. However, the role of the intrinsic pathway of coagulation, especially FXI expression, in AS progression has not been studied. FXI plays an important role in blood coagulation and its activation to FXIa is mediated by activated FXII (FXIIa), through the feedback activation by tissue factor (TF)/thrombin, or *via* autoactivation [8]. FXIa converts FIX to its active form, but its activation is also catalyzed by the FVIIa-TF complex [8]. Kossmann et al. [9] demonstrated that FXI inhibition in mice, beyond antithrombotic effects, protects *also* against vascular inflammation, namely reactive oxygen species formation, leukocyte infiltration, and fibrotic remodeling. Importantly, FXIa inhibitors and antibodies to FXI reduced atherogenesis and inflammation in mice [10]. Here we investigated whether FXI is present within stenotic leaflets in severe AS patients and if its expression correlates with disease severity.

METHODS

We enrolled 20 patients between April 2022 and June 2023 with symptomatic severe AS. All patients underwent first-time elective surgical aortic valve replacement at the Department of Cardiovascular Surgery and Transplantology, John Paul II Hospital, Kraków, Poland. Data on demographics, medical history, and current treatment were collected using a standardized questionnaire. Severe AS was defined as mean transvalvular pressure gradient (PG_{mean}) ≥40 mm Hg, peak transvalvular velocity (V_{max}) ≥4.0 m/s, and aortic valve area (AVA) ≤1 cm^2 on transthoracic echocardiography [11]. Arterial hypertension, hypercholesterolemia, and atherosclerosis were diagnosed as previously described [12]. The exclusion criteria for AS patients included atherosclerotic vascular disease requiring revascularization, acute infection including infective endocarditis, rheumatic AS, diabetes mellitus, advanced chronic kidney disease, need for concomitant valvular surgery (e.g., mitral valve repair), percutaneous coronary intervention, recent (<3 months) acute coronary syndrome or cerebrovascular episode, diagnosed malignancy, and pregnancy. Angiographically documented coronary artery stenosis greater than 20% of the diameter was the exclusion criterion to avoid any influence of nonobstructive atherosclerosis [12, 13].

The ethics committee approved the study (8/KBL/OIL/2019 and 53/KBL/OIL/2022), and all participants provided their written informed consent in accordance with the Declaration of Helsinki.

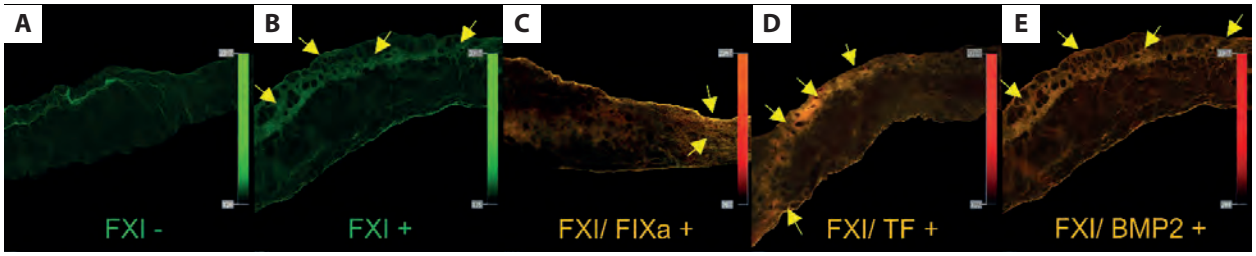


Figure 1. Valvular factor (F)XI expression together with active FIX(a), tissue factor (TF), and bone morphogenetic protein 2 (BMP2). Representative microphotographs of **A**. Valvular expression of (FXI) in control leaflets and **B**. Stenotic leaflets. **C**–**E**. Colocalization (orange) of FXI (green) and active FIX(a) (FIXa), TF, or bone morphogenetic protein 2 (BMP2) (red) within stenotic leaflets. Red arrowheads indicate the aortic side of the leaflet; yellow arrowheads indicate the immunopositive areas. Scale bar 200 µm, original magnification 4×

Fasting venous blood was drawn before aortic valve replacement. Citrated blood (9:1 of 0.106 M sodium citrate) was centrifuged at 2500 g for 20 minutes at 20°C, while blood drawn into serum tubes was centrifuged at 1600 g for 10 minutes at 4°C. Routine laboratory assays were used to determine glucose, creatinine, lipid profile, C-reactive protein, and fibrinogen.

Aortic valves were collected during open heart surgery, embedded in Cryomatrix (Thermo Scientific, Kalamazoo, MN, US), and sectioned into 5 µm slices with a Leica CM1520 cryostat. Five control valves were obtained at autopsy from apparently healthy individuals of similar age.

Activation of FXI was assessed indirectly by double staining of FXI with active FIX (FIXa) or TF. Immunostaining was conducted according to the previously described protocol [12] using primary antibodies against FXI (Santa Cruz Biotechnology, Dallas, TX, US), FIXa (Antibodies-online, Aachen, Germany), TF (Abcam, Cambridge, UK), and bone morphogenetic protein 2 (BMP2; Abcam). The corresponding secondary antibodies conjugated with AlexaFluor 488 or 594 (Abcam) were applied. A negative IgG isotype control was performed routinely. Olympus BX43 microscope (Tokyo, Japan) was used to analyze the images. The percentage of immunopositive areas was calculated as previously described [12, 13], and 15 serial step sections were analyzed per valve by two independent observers blinded for the sample origin.

Statistical analysis

All statistics were performed using STATISTICA software (Version 13.3, TIBCO Software, Palo Alto, CA, US). Categorical variables were presented as numbers and percentages, while continuous variables were expressed as means and standard deviations (SD) or medians and quartiles Q1–Q3. Normality was analyzed by the Shapiro-Wilk test. Associations between variables were calculated using Pearson or Spearman correlation coefficients, as appropriate. A *P*-value of <0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Baseline characteristics of AS patients are shown in Table S1 (Supplementary material, *Table S1*). *In loco* analysis revealed valvular expression of FXI within all studied stenotic valves, but not within control ones (Figure 1A and B). The mean (SD) FXI-immunopositive valve area constituted 21.5 (1.4)% of the total leaflet area, while means (SD) for FIXa and TF were 17.2 (2.5)% and 26.5 (5.1)%, respectively. The mean (SD) BMP2-positive area was 23.9 (4.1)%. The expression of studied proteins was observed at the aortic side of the stenotic leaflets and presented a condensed pattern of fluorescence. Interestingly, the expression of FXI co-expressed with FIXa in 66%, suggesting local activation of the intrinsic pathway as well as in 71% with TF, the major component of the extrinsic coagulation pathway (Figure 1C and D). Moreover, FXI co-expressed with BMP2 in 83% (Figure 1E), which supports our previous finding that coagulation activation is involved in leaflet calcification [4, 5, 12, 14]. Importantly, valvular amounts of FXI correlated with disease severity reflected by V_{max} (r = 0.54; *P* = 0.01), both transvalvular pressure gradients (PG_{mean} r = 0.49; *P* = 0.03; PG_{max} r = 0.53; *P* = 0.02), and AVA (r = –0.53; *P* = 0.02) (Supplementary material, *Figure S1*). Valvular expression of FIXa correlated with AVA (r = –0.49; *P* = 0.03) and V_{max} (r = 0.44; *P* = 0.049) but not transvalvular pressure gradients (both *P* >0.05).

To the best of our knowledge, this report provides the first evidence that the intrinsic coagulation pathway is activated within stenotic aortic valves. A strong co-expression of FXI with FIXa, TF, and BMP2 highlights the involvement of both coagulation pathways in valve calcification. Coagulation activation within stenotic valves is implicated in both valvular inflammation and calcification *via* the nuclear transcription factor kappa B (NF-κB) pathway [12]. Since the current study showed that abundant FXI valvular expression was associated with disease severity, it is tempting to speculate that FXIa inhibitors, such as asundexian or milvexian [15] might not only attenuate coagulation activation but also inflammatory response and thus retard AS progression. Importantly, phase II clinical trials showed that FXIa inhibitors prevent stroke and systemic embolism in patients with atrial fibrillation without increasing bleeding risk compared to non-vitamin K antagonist oral anticoagulants [15]. Therefore, FXIa inhibition might offer a novel strategy for preventing AS development and/or progression, at least in patients with an indication for anticoagulant therapy. Moreover, taking into account FXI

contribution to inflammation in atherosclerosis, targeting FXI might influence the cross-talk between coagulation and inflammation, resulting in retardation of aortic valve leaflets calcification. Clinical relevance of our findings requires further studies.

Supplementary material

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

Article information

Conflict of interest: None declared.

Funding: This work was supported by the Polish National Science Centre (UMO-2018/29/B/NZ5/02629 to JN and UMO-2021/41/N/NZ5/03323 to MK).

REFERENCES

1. Yutzey KE, Demer LL, Body SC, et al. Calcific aortic valve disease: a consensus summary from the Alliance of Investigators on Calcific Aortic Valve Disease. Arterioscler Thromb Vasc Biol. 2014; 34(11): 2387–2393, doi: 10.1161/ATVBAHA.114.302523, indexed in Pubmed: 25189570.
2. Dąbrowski M, Parma R, Huczek Z, et al. The Polish Interventional Cardiology TAVI Survey (PICTS): 10 years of transcatheter aortic valve implantation in Poland. The landscape after the first stage of the Valve for Life Initiative. Pol Arch Intern Med. 2021; 131(5): 413–420, doi: 10.20452/pamw.15887, indexed in Pubmed: 33739780.
3. Marzec K, Jaworska-Wilczyńska M, Kowalik I, et al. Comparison of long-term outcomes and risk factors of aortic stenosis treatment in patients undergoing transcatheter aortic valve implantation and surgical aortic valve replacement. Kardiol Pol. 2022; 80(7-8): 792–798, doi: 10.33963/KP.a2022.0122, indexed in Pubmed: 35521716.
4. Natorska J, Marek G, Hlawaty M, et al. Evidence for tissue factor expression in aortic valves in patients with aortic stenosis. Pol Arch Med Wewn. 2009; 119(10): 636–643, indexed in Pubmed: 19847139.
5. Kapusta P, Wypasek E, Natorska J, et al. Factor XIII expression within aortic valves and its plasma activity in patients with aortic stenosis: association with severity of disease. Thromb Haemost. 2012; 108(6): 1172–1179, doi: 10.1160/TH12-07-0455, indexed in Pubmed: 23052999.
6. Tucker EI, Marzec UM, White TC, et al. Prevention of vascular graft occlusion and thrombus-associated thrombin generation by inhibition of factor XI. Blood. 2009; 113(4): 936–944, doi: 10.1182/blood-2008-06-163675, indexed in Pubmed: 18945968.
7. Shnerb Ganor R, Harats D, Schiby G, et al. Factor XI deficiency protects against atherogenesis in apolipoprotein E/factor XI double knockout mice. Arterioscler Thromb Vasc Biol. 2016; 36(3): 475–481, doi: 10.1161/ATVBAHA.115.306954, indexed in Pubmed: 26800563.
8. He R, Chen D, He S. Factor XI: hemostasis, thrombosis, and antithrombosis. Thromb Res. 2012; 129(5): 541–550, doi: 10.1016/j.thromres.2011.11.051, indexed in Pubmed: 22197449.
9. Kossmann S, Lagrange J, Jäckel S, et al. Platelet-localized FXI promotes a vascular coagulation-inflammatory circuit in arterial hypertension. Sci Transl Med. 2017; 9(375): eaah4923, doi: 10.1126/scitranslmed.aah4923, indexed in Pubmed: 28148841.
10. Ngo ATP, Jordan KR, Mueller PA, et al. Pharmacological targeting of coagulation factor XI mitigates the development of experimental atherosclerosis in low-density lipoprotein receptor-deficient mice. J Thromb Haemost. 2021; 19(4): 1001–1017, doi: 10.1111/jth.15236, indexed in Pubmed: 33421301.
11. Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2022; 43(7): 561–632, doi: 10.1093/eurheartj/ehab395, indexed in Pubmed: 34453165.
12. Kopytek M, Mazur P, Ząbczyk M, et al. Diabetes concomitant to aortic stenosis is associated with increased expression of NF-κB and more pronounced valve calcification. Diabetologia. 2021; 64(11): 2562–2574, doi: 10.1007/s00125-021-05545-w, indexed in Pubmed: 34494136.
13. Kopytek M, Ząbczyk M, Mazur P, et al. Oxidized phospholipids associated with lipoprotein(a) contribute to hypofibrinolysis in severe aortic stenosis. Pol Arch Intern Med. 2022; 132(11): 16372, doi: 10.20452/pamw.16372, indexed in Pubmed: 36384266.
14. Natorska J. Diabetes mellitus as a risk factor for aortic stenosis: from new mechanisms to clinical implications. Kardiol Pol. 2021; 79(10): 1060–1067, doi: 10.33963/KP.a2021.0137, indexed in Pubmed: 34643267.
15. Santagata D, Donadini MP, Ageno W. Factor XI inhibitors for the prevention of cardiovascular disease: A new therapeutic approach on the horizon? Blood Rev. 2023: 101119, doi: 10.1016/j.blre.2023.101119, indexed in Pubmed: 37580207.

Reevaluation of indications for permanent pacemaker implantation after cardioneuroablation

Antoni Wileczek[1, 9], Edyta Stodolkiewicz-Nowarska[2], Agnieszka Reichert[3], Anna Kustron[9], Janusz Sledz[9], Wojciech Biernikiewicz[4], Bartłomiej Orlik[5], Michał Lipka[5], Andrzej Kutarski[6], Dagmara Hering[7], Magdalena Zając[8], Sebastian Stec[1, 2, 9]

[1]Division of Electrophysiology, Cardioneuroablation, Catheter Ablation and Cardiac Stimulation, Subcarpathian Center for Cardiovascular Intervention, Sanok, Poland
[2]CardioMedicum Medical Center, Institute of Cardiovascular Science, Kraków, Poland
[3]Sabamed Medical Center, Rzeszów, Poland
[4]Department of Cardiology, Specialistic Hospital, Sanok, Poland
[5]5th Department of Invasive Cardiology and Angiology, American Heart of Poland, Mielec, Poland
[6]Department of Cardiology, Medical University of Lublin, Poland,
[7]Department of Hypertension and Diabetology, Medical University of Gdansk, Gdańsk, Poland
[8]Department of Special Pedagogy and Speech Therapy, Faculty of Pedagogy, Kazimierz Wielki University, Bydgoszcz, Poland
[9]ELMEDICA, EP-Network, Skarżysko-Kamienna, Poland

Correspondence to:
Antoni Wileczek, MD,
Division of Electrophysiology,
Cardioneuroablation,
Catheter Ablation and Cardiac Stimulation,
Subcarpathian Center for Cardiovascular Intervention,
800-lecia 26,
38–500 Sanok, Poland,
phone: +48 663 517 874,
e-mail: antoniwileczek@gmail.com

DOI: 10.33963/v.kp. 97828

Received:
May 9, 2023

Accepted:
October 13, 2023

Early publication date:
October 20, 2023

INTRODUCTION

Cardioneuroablation (CNA) was shown to effectively treat functional bradycardia without the need for permanent pacemaker (PPM) implantation in a wide spectrum of bradyarrhythmias including sinus node dysfunction (SND), tachycardia-bradycardia syndrome, atrioventricular blocks (AVBs), cardioinhibitory or mixed vasovagal syncope (VVS), and cardioinhibitory carotid sinus syndrome or hypersensitivity. Pacemaker implantation is associated with costs, complications, and restrictions on daily activities [1–4]. However, although CNA is associated with a favorable risk-to-benefit ratio, low complication rates, and targeted modulation of cardiac autonomic innervation, currently, it is not recommended by guidelines [5, 6]. According to class I/IIa/IIb indications for PPM therapy, CNA has to be canceled or postponed in eligible patients following shared decision-making and informed consent [7]. We aimed to reassess indications for PPM implantation and discontinuation of PPM therapy after CNA in patients referred for an electrophysiological study and extracardiac vagal nerve stimulation (ECVS).

METHODS

Data were collected from the Rare-a-CaREgistry, a Polish prospective and retrospective multicenter ablation registry (2017–present) involving 10 centers (listed in Supplementary material, *Table S1*). Patients were recruited in the years 2017–2022. This study was planned to asses secondary outcomes, involving consecutive patients qualified for cardioneuroablation. Patients with various cardiovascular abnormalities were recruited, including structural heart disease, previous cardiac surgery, supraventricular or ventricular arrhythmia, prolonged corrected sinus node recovery time (>525 ms), previous ablation procedures, or PPM implantation. Patient demographics are presented in Supplementary material, *Table S2*. The management of patients before and after CNA encompassed comprehensive consultations, state-of-the-art cardiovascular autonomic testing, atropine tests, and electrographic (ECG) monitoring. Shared decision-making was used to explain possible treatment options and to provide patient-centered therapy in order to ascertain that the patient fulfilled indications for PPM therapy according to the European Society of Cardiology (ESC) guidelines and was aware that CNA was used as an alternative and experimental technique.

All patients had bradycardia-related symptoms documented by ECG. Patients were referred for CNA following a positive atropine test, defined as an increase in heart rate in sinus rhythm by at least 30% within 10 min-

utes after intravenous atropine administration at a dose of 0.02–0.04 mg/kg (maximum, 2 mg). Following atropine administration, patients were monitored for 30 minutes.

The primary endpoint of CNA was the resolution of ECVS-induced sinus arrest and AVB during proximal coronary sinus pacing. Anatomically guided biatrial and binodal CNA was performed, with fluoroscopic and ultrasonographic guidance for ECVS [8]. CNA was performed using three-dimensional electroanatomic systems (EnSite Velocity/Precision Mapping Systems, Abbott, US), as reported previously [8–10]. Six GPs were targeted: superior septal GP (left and right), inferior septal GP (left and right), vena cava superior/aortic root GP, and left superior GP. In patients with previous severe syncope, with high-risk professions, and with PPMs, reassessment with an electrophysiological study and ECVS was recommended before the decision to discontinue pacing and perform transvenous lead extraction was made [10]. In the subgroup of tachycardia-bradycardia with indications for PPM therapy, 26 of 100 (26%) patients underwent CNA and pulmonary vein isolation.

The study was approved by an appropriate institutional review board (Rare-a-CaREgistry, Rzeszow University, 6.04.2017; No. 5/4/2017), and written informed consent was obtained from all patients.

Statistical analysis

Numerical data were expressed by means with standard deviation. Categorical data were presented as absolute numbers with percentages. Variables before and after CNA were compared using McNemar's χ^2 and exact McNemar's χ^2 tests. Statistica v. 13 (Statsoft, Poland) was used for analysis. Statistical significance of the test was assumed at $P < 0.05$.

RESULTS AND DISCUSSION

Cardioneuroablation was performed in 195 consecutive adult patients (mean age 55.6 [14.3] years; women, 107 [54%]) (Figure 1). Of the 195 patients, 17 (8.2%) previously underwent PPM implantation.

As per the ESC guidelines [6], 100 of the 178 patients (56.1%) had *de novo* indications for PPM therapy before CNA: SND was reported in 88 patients (45%); AVB in 21 (10%); tachycardia-bradycardia syndrome in 26 (13%); cardioinhibitory VVS in 41 (21%); and cardioinhibitory carotid sinus syndrome or carotid sinus hypersensitivity in 3 patients (1.5%). Complex indications (≥2) were reported in 45 patients (23%). In 78 patients, the indication for CNA was symptomatic bradycardia, which is not a class I, IIa, and IIb indication for PPM therapy. According to the 2021 ESC guidelines, pacing therapy is not recommended in patients with cardioinhibitory vasovagal reflex diagnosed during the head-up tilt test and aged below 40 years. Therefore, such patients were not considered candidates for PPM therapy in our study. Several patients did not fulfill the criteria for severe recurrent syncopal episodes.

Indications for *de novo* PPM therapy were present in 32 of the 86 patients (37%) aged 60 years or older. During follow-up (mean, 23.7 [10.3] months) after successful CNA procedures (226 procedures in 195 patients; mean, 1.1 [0.2] procedures), no deaths were reported, and only 10 of the 195 patients (5%) experienced recurrent syncopal episodes. Of the 10 patients, 8 were diagnosed with orthostatic/vasodepressive syncope with a clear prodromal phase. Despite positive atropine tests before the procedure and CNA, 4 of the 100 patients (4%) with indications for pacing before CNA still demonstrated those indications at follow-up due to an intrinsic substrate. Finally, 6 of the 178 patients (3.4%) met *de novo* criteria for pacing after CNA ($P < 0.01$). These criteria included coexisting functional and structural bradycardia (n = 3), recurrent bradycardia after CNA with syncope and presyncope and refusal to undergo the second CNA procedure (n = 2), and late development of severe sinus chronotropic incompetence (n = 1) after successful CNA for prolonged functional AVB with syncope. Of the 195 patients, 7 (3.5%) developed major complications associated with CNA, including cardiac tamponade (2 patients), pericarditis (2 patients), pericardial effusion (1 patient), femoral aneurysm (1 patient), and pneumothorax, also in 1 patient. All complications were treated non-surgically and had no late consequences.

The discontinuation of PPM therapy and transvenous lead extraction after CNA were recommended and performed in 14 of the 17 patients (82.3%) with previous PPM implantation ($P < 0.01$). At the last follow-up visit, patients were asked about recurrence of bradycardia symptoms, and indications for bradycardia treatment were reconsidered. Of the 186 patients without PPM after CNA, 81% gave consent to another CNA procedure instead of PPM implantation and 10% accepted the management strategy of the physician's choice. In 4 of 100 patients after cardioneuroablation, PPM therapy was continued or initiated (Supplementary material, Table S2).

In our study, 56.1% of patients referred for CNA had *de novo* indications for permanent pacing. At middle-term follow-up, the number of patients with indications for pacing significantly decreased. Our findings suggest that CNA is an effective therapeutic approach in a wide range of patients with functional bradycardia. However, if needed, coexisting intrinsic and extrinsic substrates should be considered for further assessment and permanent pacing. Complex bradyarrhythmic substrates before and after CNA require ongoing comprehensive management including multidisciplinary consultations, cardiovascular autonomic testing, ECG monitoring, and shared decision-making. There is currently no clearly defined strategy in European or American guidelines for the management of SND/AVB secondary to persistent and/or paroxysmal vagal tone hyperactivity [5, 6, 11]. The superiority of CNA in patients with cardioinhibitory or mixed VVS was confirmed only in the ROMAN-1 study

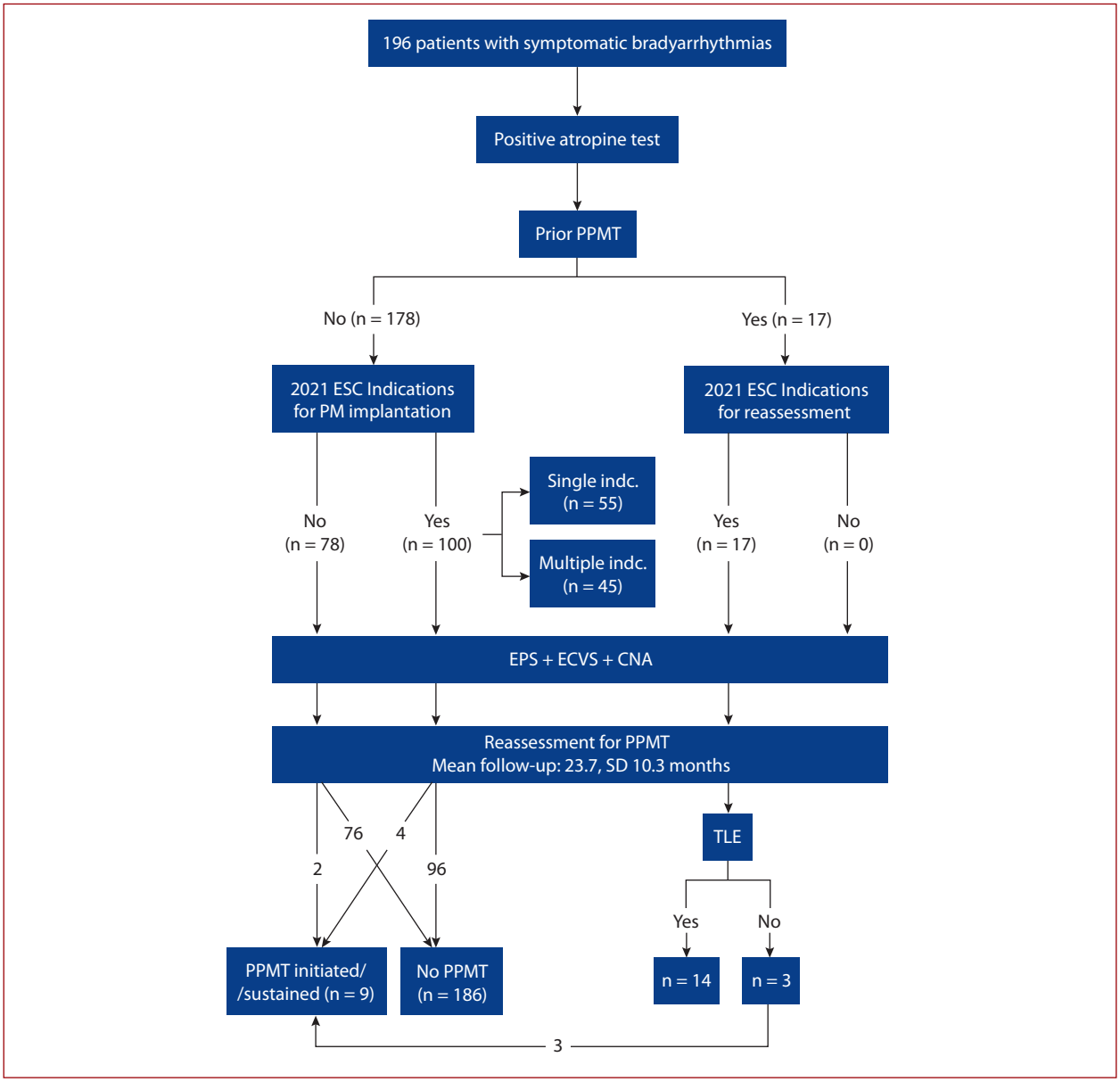


Figure 1. Flowchart of the study

Abbreviations: CNA, cardioneuroablation; ECVS, extracardiac vagal nerve stimulation; EPS, electrophysiological study; ESC, European Society of Cardiology; PM, pacemaker; PPMT, permanent pacemaker therapy; SD, standard deviation; TLE, transvenous lead extraction

although without a direct comparison with permanent pacing in patients older than 40 years [3].

CONCLUSIONS

More than 50% of patients referred for CNA had indications for permanent pacing (half of them had complex indications). While some patients may require permanent pacing due to failed can, coexisting, or *de novo* complex structural bradyarrhythmia, in pure functional bradycardia patients, CNA may be an alternative to permanent pacing as the first-line treatment option. This allows postponement or cancellation of permanent pacing in the majority of patients with suspected functional bradyarrhythmia. Based on these findings, ongoing comprehensive monitoring is required in patients with functional bradyarrhythmia to introduce patient-centered therapy and management strategies based on shared decision-making. Randomized controlled trials are warranted to validate indications for CNA and PPM therapy in this population.

Supplementary material

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

Article information

Conflict of interest: SS is the author of several patents in the field of cardiology and cardiac surgery and a shareholder in Medicine S.A. No specific product of any company was used or investigated in this trial. All other authors declare that they have no conflicts of interest.

Funding: None.

REFERENCES

1. Pachon JC, Pachon EI, Pachon JC, et al. „Cardioneuroablation" — new treatment for neurocardiogenic syncope, functional AV block and sinus dysfunction using catheter RF-ablation. Europace. 2005; 7(1): 1–13, doi: 10.1016/j.eupc.2004.10.003, indexed in Pubmed: 15670960.
2. Pachon JC, Pachon EI, Cunha Pachon MZ, et al. Catheter ablation of severe neurally meditated reflex (neurocardiogenic or vasovagal) syncope: cardioneuroablation long-term results. Europace. 2011; 13(9): 1231–1242, doi: 10.1093/europace/eur163, indexed in Pubmed: 21712276.
3. Piotrowski R, Baran J, Sikorska A, et al. Cardioneuroablation for reflex syncope: efficacy and effects on autonomic cardiac regulation — a prospective randomized trial. JACC Clin Electrophysiol. 2023; 9(1): 85–95, doi: 10.1016/j.jacep.2022.08.011, indexed in Pubmed: 36114133.
4. Aksu T, Gopinathannair R, Bozyel S, et al. Catheter ablation of atrioventricular block: from diagnosis to selection of proper treatment. JACC Case Rep. 2020; 2(11): 1793–1801, doi: 10.1016/j.jaccas.2020.07.050, indexed in Pubmed: 34317058.
5. Brignole M, Moya A, de La, et al. 2018 ESC Guidelines for the diagnosis and management of syncope. Eur Heart J. 2018; 39(21): 1883–1948, doi: 10.1093/eurheartj/ehy037, indexed in Pubmed: 29562304.
6. Glikson M, Nielsen JC, Kronborg MB, et al. 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. Europace. 2022; 24(1): 71–164, doi: 10.1093/europace/euab232, indexed in Pubmed: 34455427.
7. Chung MK, Fagerlin A, Wang PJ, et al. Shared decision making in cardiac electrophysiology procedures and arrhythmia management. Circ Arrhythm Electrophysiol. 2021; 14(12): e007958, doi: 10.1161/CIRCEP.121.007958, indexed in Pubmed: 34865518.
8. Wileczek A, Polewczyk A, Kluk M, et al. Ultrasound-guided imaging for vagus nerve stimulation to facilitate cardioneuroablation for the treatment of functional advanced atrioventricular block. Indian Pacing Electrophysiol J. 2021; 21(6): 403–406, doi: 10.1016/j.ipej.2021.06.008, indexed in Pubmed: 34186197.
9. Stec S, Jankowska-Polańska B, Jagielski D, et al. Rationale and design of SAN.OK randomized clinical trial and registry: Comparison of the effects of evidence-based pacemaker therapy and cardioneuroablation in sinus node dysfunction. Cardiol J. 2022; 29(6): 1031–1036, doi: 10.5603/CJ.a2022.0103, indexed in Pubmed: 36385604.
10. Reichert A, Wileczek A, Stec S. Cardioneuroablation for the effective treatment of recurrent vasovagal syncope to restore driving abilities. Kardiol Pol. 2022; 80(11): 1158–1160, doi: 10.33963/KP.a2022.0189, indexed in Pubmed: 35946179.
11. Brignole M, Aksu T, Calò L, et al. Clinical controversy: methodology and indications of cardioneuroablation for reflex syncope. Europace. 2023; 25(5), doi: 10.1093/europace/euad033, indexed in Pubmed: 37021351.

Medical therapy in heart failure before and after left ventricular assist device implantation

Rafał Dąbrowski, Edyta Smolis-Bąk, Ilona Kowalik, Jarosław Szymański, Krzysztof Kuśmierski, Jarosław Kuriata, Krzysztof Jaworski, Tomasz Chwyczko, Przemysław Leszek, Tomasz Zieliński, Ryszard Piotrowicz, Piotr Kołsut

National Institute of Cardiology, Warszawa, Poland

Correspondence to:
Rafał Dąbrowski, MD, PhD, Department of Coronary Artery Disease and Cardiac Rehabilitation, National Institute of Cardiology, Alpejska 42, 04–628 Warszawa, Poland,
phone: +48 343 44 09,
e-mail: rdabrowski45@gmail.com, rdabrowski@ikard.pl

DOI: 10.33963/v.kp.98042

Received:
July 11, 2023

Accepted:
October 30, 2023

Early publication date:
November 14, 2023

INTRODUCTION

Since their introduction in 2000, left ventricular assist devices (LVADs) have become an important treatment option for patients with heart failure with reduced ejection fraction (HFrEF). However, after LVAD implantation as a bridge to candidacy, recovery, transplantation, or destination therapy, patients require continuation of optimal medical therapy (OMT) [1]. So far, expert positions on heart failure (HF) permanent medical therapy have not focused on patients with LVADs [1–4].

The study aimed to compare medical therapy in patients before and after (at discharge) LVAD implantation.

METHODS

We included in this prospective single-center study all consecutive patients who were undergoing rehabilitation after LVAD implantation (Jan 1, 2019–Dec 31, 2021) at the Department of Coronary Artery Disease and Cardiac Rehabilitation, National Institute of Cardiology, Warsaw. Patients had implanted HeartMate3 and HVAD™ Systems (till June 3, 2021). Demographic, clinical characteristics, and medical therapy of HF were analyzed before and on discharge from the hospital. The analyzed data were obtained on an ongoing basis from hospital medical records. The study was supported by the State Committee for Scientific Research (STRATEGMED2/266798/15/NCBIR/2015). Bioethical Committee approval was issued on April 2, 2019 (IK-NPIA-0021-55/1784/2019).

Statistical analysis

In the statistical analysis, the results of continuous variables were presented in the forms of arithmetic means and standard deviations (normal distributions) or medians and quartiles (skewed distributions). Qualitative variables were reported as counts and percentages. McNemar's test (binary variables) or symmetry tests (nominal variables with 3 categories) were used to compare the significance of differences in treatment changes before and after the procedure. Two-sided testing was applied, and a P <0.05 was considered statistically significant. The analysis was performed using the SAS 9.4 statistical package (SAS Institute, NC, US).

RESULTS AND DISCUSSION

The study included 55 men with HFrEF, New York Heart Association class IV, after LVAD implantation. The mean age was 55.5 (10.7) years; left ventricular ejection fraction was 15.8 (4.6)%. The median length of hospital stay was 31 (24–43) days. Medical history included coronary artery disease: 31 patients (56.4%), valvular heart disease: 8 (14.5%), ventricular tachycardia/fibrillation: 37 (67.3%), atrial fibrillation: 35 (63.6%), cardiac resynchronization therapy: 11 (20%), implantable cardioverter-defibrillator: 50 (90.9%), stroke: 11 (20%), peripheral artery disease: 11 (20%), arterial hypertension: 34 (68%), diabetes: 21 (38.2%). Median creatinine concentration was 1.23 (0.94–1.97) mg/dl (Supplementary material, *Table S1*).

There were no changes before and after LVAD implantation in (1) use of beta-blockers (BB) –53 patients (96.4%) used them before LVAD implantation vs. 54 (98.2%) after the procedure (P = 0.56), (2) use of mineralocorticoid receptor antagonists (MRA): 53 patients (96.4%) vs. 50 (90.9%); P = 0.08,

Table 1. Medical therapy before and after LVAD implantation (n = 55)

	Before implantation	After implantation	*P*-value McNemar test	Drug withdrawal after implantation[a]	Drug initiation[b]
Beta-blockers	53 (96.4)	54 (98.2)	1.00	1 (1.9)	2 (3.7)
MRA	53 (96.4)	50 (90.9)	0.25	3 (5.7)	0 (0)
ACEI	33 (60.0)	16 (29.1)	<0.001	17 (51.5)	0 (0)
ARB	16 (29.1)	33 (60.0)	<0.001	2 (12.5)	19 (57.6)
VKA	30 (54.5)	48 (87.3)	<0.001	4 (13.3)	22 (45.8)
ASA	27 (49.1)	49 (89.1)	<0.001	2 (7.4)	24 (49.0)
Clopidogrel	1 (1.8)	1 (1.8)	1.00	1 (100)	1 (100)
Heparin	8 (14.5)	6 (10.9)	0.59	8 (100)	6 (100)
Loop diuretics					
0 (none)	3 (5.4)	9 (16.3)	0.09	9 (17.3)	3 (6.5)
1 (one)	27 (49.1)	31 (56.4)			
2 (two)	25 (45.5)	15 (27.3)			
Thiazide diuretics	11 (20.0)	0 (0)	0.004	11 (100)	0 (0)
Valsartan/sacubitril	4 (7.3)	2 (3.6)	0.50	2 (50.0)	0 (0)
SGLT-2i	1 (1.8)	2 (3.6)	1.00	0 (0)	1 (50.0)
Digoxin	9 (16.4)	8 (14.5)	0.80	8 (88.9)	7 (87.5)
Ivabradine	7 (12.7)	5 (9.1)	0.69	4 (57.1)	2 (40.0)
Amiodarone	17 (30.9)	7 (12.7)	0.012	13 (76.5)	3 (42.9)
Propafenone	1 (1.8)	1 (1.8)	1.00	1 (100)	1 (100)
Mexiletine	3 (5.4)	2 (3.6)	1.00	2 (66.7)	1 (50.0)
Sildenafil	11 (20.0)	18 (32.7)	0.13	7 (63.6)	14 (77.8)
Thyroxine	7 (12.7)	10 (18.2)	0.25	0 (0)	3 (30.0)
Metformin	10 (18.2)	9 (16.4)	1.00	3 (30.0)	2 (22.2)
Insulin	2 (3.6)	2 (3.6)	1.00	0 (0)	0 (0)
Allopurinol	30 (54.5)	38 (69.1)	0.045	4 (13.3)	12 (31.6)
Iron	8 (14.5)	9 (16.4)	0.80	7 (87.5)	8 (88.9)
Antidepressants	7 (12.7)	18 (32.7)	0.012	4 (57.1)	15 (83.3)
IPP	33 (60.0)	48 (87.3)	0.002	4 (12.1)	19 (39.6)

Data are presented as numbers (percentage). [a]Percentages in relation to the number of patients taking a given drug before implantation. [b]Percentages relative to the number of patients taking a given drug after implantation

Abbreviations: ACEI, angiotensin-converting enzyme *inhibitors;* ARB, angiotensin receptors blockers; ASA, acetylsalicylic acid; MRA, mineralocorticoid receptor antagonists; PPI, proton-pump inhibitors; SGLT-2i, sodium-glucose cotransporter 2 inhibitors; VKA, vitamin K antagonists

(3) loop diuretics, 1 or 2: 52 patients (94.6%) vs. 46 (83.7%); $P = 0.09$ — with tendency to reduce, (4) digoxin: 9 patients (16.4%) vs. 8 (14.5%); $P = 0.80$. The number of patients treated with sacubitril/valsartan was low: 4 (7.3%) before vs. 2 (3.6%) after the procedure; $P = 0.16$. There was a reduction in using (1) angiotensin-converting enzyme inhibitors (ACEI): 33 patients (60.0%) before vs. 16 (29.1%) after the procedure; $P < 0.001$, (2) thiazide diuretics: 11 patients (20%) before vs. 0 (0%) after the procedure; $P = 0.004$, and (3) amiodarone: 17 patients (30.9%) before vs. 7 (12.7%) after the procedure; $P = 0.012$.

At discharge, there was, however, an increase in the use of (1) angiotensin receptor blockers (ARB): 16 patients (29.1%) vs. 33 (60.0%); $P < 0.001$, (2) allopurinol 30 (54.5%) vs. 38 (69.1%); $P = 0.045$, and (3) proton-pump inhibitors: 33 (60%) vs. 48 (87.3%); $P = 0.002$. The number of patients receiving vitamin K antagonists increased: 30 (54.5%) vs. 48 (87.3%); $P < 0.001$, so did the number of patients taking aspirin: 27 (49.1%) vs. 49 (89.1); $P < 0.001$, due to implanted devices (Table 1). No adverse events that would cause withdrawal from any drug have been observed. There were no deaths during hospitalization.

The new findings of the current report are that HF optimal treatment in accordance with the guidelines, which includes the basic drug groups: BB, ACEI/ARB, MRA, and loop diuretics despite LVAD implantation was continued and ACEI usage was reduced in favor of the ARB, probably due to better tolerance. Continuation of treatment with loop diuretics despite improvement of left ventricular hemodynamic parameters may be surprising, but 56% of patients had chronic kidney disease (mean eGFR 49.1 ml/min, standard deviation 16). According to the 2019 European Association for Cardio-Thoracic Surgery Expert Consensus on long-term mechanical circulatory support, many patients still suffer from volume overload after LVAD implantation and require diuretic therapies [5]. During the study period, sodium-glucose cotransporter 2 inhibitors were not routinely used due to their limited availability and publication of the guidelines for their use only in the final phase of the study [2]. Despite a lack of well-controlled data, there are potential benefits of HFrEF OMT in LVAD patients to improve, among others, pulmonary circulation conditions, right ventricular support, and to reduce atrial and ventricular arrhythmias. Compared to other published retrospective studies, in our study the percentage of patients treated in the same way as before LVAD implantation was significantly higher. There were no significant differences in the treatment modes before

and after the procedure except for more frequent use of ARB and a reduction in the use of thiazide diuretics and amiodarone. Continued use of BB is important to reduce the risk of arrhythmia and control blood pressure. The reduced use of ACEI in favor of the ARB was probably due to better ARB tolerance and the growing use of valsartan in combination with sacubitril [3]. Continuation of MRA treatment is important in terms of inhibiting fibrosis, further remodeling of heart chambers, and reducing arrhythmias. Due to LVAD implantation, all patients received optimal anticoagulation (10.9% temporarily on heparin) and antiplatelet therapy.

The actual guidelines for the treatment of HF do not refer directly to the further medical treatment of LVAD patients in general because there have been no prospective studies on medical therapy in this group of patients so far [3, 4]. Continuing medical treatment in patients with cardiomyopathy of non-ischemic etiology has a key role in restoring the function of the cardiac muscle (class I C recommendation) [5]. HF medications (ACEI/ARB, BB, MRA, loop diuretics) should be considered during mechanical circulatory support (class IIa C recommendation) [5]. However, considering numerous comorbidities, such as cardiac arrhythmias, chronic kidney disease, liver failure, and others, OMT may be limited [6]. Treatment limitations may also result from improvement of the patient's hemodynamic status and prevention of excessive hypotension.

An analysis of 5840 LVAD recipients demonstrated that the use of ACEI/ARB was 53%, BB: 72%, loop diuretics: 66%, and MRA: only 34.4% at 6 months post implantation. Use of OMT (ACEI/ARB, MRA, BB) was higher for those implanted in more recent years [7]. Continued treatment for HF after surgery may improve the prognosis of LVAD patients. In a report of 12 144 durable-LVAD recipients, those receiving any neurohormonal blockade with either ACEI/ARB, BB, or MRA had significantly improved survival at 4 years postimplantation compared to those on no therapy (respectively: 56.0%; 95% confidence interval [CI], 54.5%–57.5% vs. 43.9%; 95% CI, 40.5%–47.7%). Patients on all three therapies had the lowest hazard of death compared to other groups (HR, 0.34; 95% CI, 0.28–0.41). Also, quality of life and functional status were improved with neurohormonal blockade [8]. According to some authors, the role of optimal treatment (LBA, ACEI/ARB, MRA, sacubitril/valsartan, sodium-glucose cotransporter 2 inhibitors, diuretics) in LVAD patients is not fully established [9]. Although, the 2023 International Society for Heart and Lung Transplantation Guidelines finally recommend neurohormonal blockade and the treatment of hypertension after LVAD implantation with ACEI, ARB, ARB-neprilysin inhibitors, BB, and MRA (class I B recommendation [10]), which confirms our results.

CONCLUSIONS

Left ventricular assist device implantations do not significantly change modes of medical therapy in HF, including drugs that improve prognosis. Interestingly, the use of ACEI has been significantly reduced in favor of the ARB probably due to better tolerance. This observation requires further studies.

Supplementary material

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

Article information

Conflict of interest: None declared.

Funding: None.

REFERENCES

1. Tycińska A, Grygier M, Biegus J, et al. Mechanical circulatory support. An expert opinion of the Association of Intensive Cardiac Care and the Association of Cardiovascular Interventions of the Polish Cardiac Society. Kardiol Pol. 2021; 79(12): 1399–1410, doi: 10.33963/KP.a2021.0169, indexed in Pubmed: 34861044.
2. Rosano GMC, Moura B, Metra M, et al. Patient profiling in heart failure for tailoring medical therapy. A consensus document of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2021; 23(6): 872–881, doi: 10.1002/ejhf.2206, indexed in Pubmed: 33932268.
3. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur J Heart Fail. 2021; 42(36): 3599–3726, doi: 10.1093/eurheartj/ehab368, indexed in Pubmed: 34447992.
4. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022; 145(18): e895–e1032, doi: 10.1161/CIR.0000000000001063, indexed in Pubmed: 35363499.
5. Potapov EV, Antonides C, Crespo-Leiro MG, et al. 2019 EACTS Expert Consensus on long-term mechanical circulatory support. Eur J Cardiothorac Surg. 2019; 56(2): 230–270, doi: 10.1093/ejcts/ezz098, indexed in Pubmed: 31100109.
6. Correale M, Paolillo S, Mercurio V, et al. Non-cardiovascular comorbidities in heart failure patients and their impact on prognosis. Kardiol Pol. 2021; 79(5): 493–502, doi: 10.33963/KP.15934, indexed in Pubmed: 34125921.
7. Khazanie P, Hammill BG, Patel CB, et al. Use of heart failure medical therapies among patients with left ventricular assist devices: insights from INTERMACS. J Card Fail. 2016; 22(9): 672–679, doi: 10.1016/j.cardfail.2016.02.004, indexed in Pubmed: 26892975.
8. McCullough M, Caraballo C, Ravindra NG, et al. Neurohormonal blockade and clinical outcomes in patients with heart failure supported by left ventricular assist devices. JAMA Cardiol. 2020; 5(2): 175–182, doi: 10.1001/jamacardio.2019.4965, indexed in Pubmed: 31738366.
9. Hollis IB, Doligalski CT, Jennings DJ. Pharmacotherapy for durable left ventricular assist devices. Pharmacotherapy. 2021; 41(1): 14–27, doi: 10.1002/phar.2491, indexed in Pubmed: 33278842.
10. Saeed D, Feldman D, Banayosy AEl, et al. The 2023 International Society for Heart and Lung Transplantation Guidelines for mechanical circulatory support: A 10-year update. J Heart Lung Transplant. 2023; 42(7): e1–e222, doi: 10.1016/j.healun.2022.12.004, indexed in Pubmed: 37245143.

Elevated lipoprotein(a) in the middle-aged Polish population: Preliminary data on the genetic background

Małgorzata Konieczyńska[1, 2*], Karol Nowak[2, 3*], Joanna Pudło[2], Monika Zasada[2], Magdalena Tlałka[2], Ewa Wypasek[2, 4], Jarosław Zalewski[2, 3], Maciej Polak[5], Anetta Undas[1, 2]

[1]Department of Thromboembolic Disorders, Institute of Cardiology, Jagiellonian University Medical College, Kraków, Poland
[2]The John Paul II Hospital, Kraków, Poland
[3]Department of Coronary Disease and Heart Failure, Institute of Cardiology, Jagiellonian University Medical College, Kraków, Poland
[4]Faculty of Medicine and Health Sciences, Andrzej Frycz Modrzewski Krakow University, Kraków, Poland
[5]Department of Epidemiology and Population Studies, Jagiellonian University Medical College, Kraków, Poland
*Both authors equally contributed to the study.

Correspondence to:
Małgorzata Konieczyńska, MD, PhD, Department of Thromboembolic Disorders, Institute of Cardiology, Jagiellonian University Medical College, Prądnicka 80, 31–202 Kraków, Poland.
phone: +48 12 614 30 04,
e-mail: malgorzata.konieczynska@uj.edu.pl

DOI: 10.33963/v.kp.97660

Received:
September 12, 2023

Accepted:
September 19, 2023

Early publication date:
October 9, 2023

INTRODUCTION

Elevated lipoprotein(a) (Lp[a]), a low-density lipoprotein (LDL)-like lipoprotein containing apolipoprotein (a) homologous to plasminogen, with the molecular weight ranging from 300 to 800 kDa due to a variety of apolipoprotein (a) isoforms, is a well-established genetically determined risk factor for cardiovascular disease (CVD), including coronary artery disease (CAD), myocardial infarction (MI), stroke, and peripheral arterial disease (PAD) [1, 2]. The current guidelines recommend that Lp(a) measurement once in a lifetime should be included in a comprehensive CVD risk evaluation and suggest a global risk underestimation at high or very high Lp(a) concentrations [1, 2]. Little is known about Lp(a) levels in the Polish population except for a small sample (n = 200) from the EUROASPIRE V survey, in which the prevalence of Lp(a) >50 mg/dl was 22.5% in patients without diagnosed CVD but with known risk factors [3].

Given ongoing trials on novel agents substantially reducing Lp(a) by 80% [2], we decided to assess the prevalence of elevated Lp(a) concentration in a middle-aged Polish population and its association with other CVD risk factors.

METHODS

We enrolled consecutive subjects participating in the "Malopolska coronary artery disease prophylactic program for people older than 40 years" from May 2022 to October 2022. The exclusion criteria were age <40 or >65 years, documented CAD or PAD, and a history of MI, stroke, or transient ischemic attack. The study was approved by the local Ethical Committee (OIL/KBL33/2022).

Data about baseline anthropometric and clinical characteristics, previous medical history, lifestyle, and family history of premature CVD were collected. The 10-year risk of the first CVD event was assessed with the Systematic Coronary Risk Evaluation 2 (SCORE2) algorithm. Dyslipidemia was defined as total cholesterol (TC) ≥190 mg/dl, or LDL cholesterol (LDL-C) ≥115 mg/dl, or triglycerides ≥150 mg/dl or statin use. Serum Lp(a) was determined using immunoturbidimetry (Roche Diagnostics, Mannheim, Germany). Elevated Lp(a) was defined as values >50 mg/dl [2]. Lp(a) >100 mg/dl was defined as a very high-risk group [2]. In that case, analysis of the *LPA* gene variant: c.5673A>G (p.Ile1891Met, used nomenclature: p.Ile4399Met, rs3798220), reported as associated with elevated plasma Lp(a) levels [4], was performed with a TaqMan SNP assay (Applied Biosystems, ThermoFisher Scientific, Foster City, CA, US) on the QuantStudio Dx Real-Time PCT Instrument (ThermoFisher Scientific).

Statistical analysis

Statistical analysis was performed with SPSS Statistics software (Version 28.0.1.0, IBM Corp., Armonk, NY, US). Continuous variables were expressed as medians (interquartile range) and categorical variables as numbers (percentage). Normal distribution was assessed

Table 1. Characteristics of the study population according to lipoprotein (a) concentration

	Lipoprotein (a), mg/dl			*P*-value
	<50	50–100	>100	
	n = 656 (82.0%)	n = 101 (12.6%)	n = 43 (5.4%)	
Age, years	49 (44–52)	47 (44–52)	52 (43–56)	0.20
Males	222 (33.8)	31 (30.7)	5 (11.6)[a]	0.001
BMI, kg/m^2	26.4 (24.0–29.8)	27.1 (24.2–31.3)	27.3 (23.9–30.4)	0.41
Current smoking	210 (32.0)	38 (37.6)	14 (32.6)	0.53
Hypertension	167 (25.5)	16 (15.8)	13 (30.2)	0.07
Diabetes mellitus	34 (5.2)	5 (5.0)	2 (4.7)	0.98
Dyslipidemia,	179 (27.3)	28 (27.7)	20 (46.5)[a]	0.025
Family history of premature CVD	282 (43.0)	39 (38.6)	19 (44.2)	0.69
SCORE2	2.40 (1.2–4.0)	2.25 (1.1–4.2)	2.35 (1.1–4.0)	0.97
Fasting glucose, mmol/l	5.2 (4.9–5.5)	5.2 (4.9–5.5)	5.2 (5.0–5.5)	0.80
CRP, mg/l	1.1 (0.6–2.3)	1.2 (0.6–3.0)	1.7 (0.7–3.5)	0.08
Total cholesterol, mmol/l	5.06 (4.52–5.67)	5.22 (4.73–5.82)	5.54 (5.19–6.02)[a]	0.004
LDL-cholesterol, mmol/l	3.23 (2.66–3.74)	3.39 (2.81–3.99)	3.56 (3.11–4.00)[a]	0.015
HDL-cholesterol, mmol/l	1.53 (1.28–1.82)	1.53 (1.27–1.85)	1.64 (1.36–1.99)	0.14
Triglycerides, mmol/l	1.12 (0.83–1.64)	1.16 (0.89–1.51)	1.08 (0.83–1.31)	0.54
Fibrinogen, g/l	2.84 (2.54–3.10)	2.83 (2.52–3.07)	3.10 (2.81–3.46)[a, b]	<0.001

Values are shown as number (percentage) or median (interquartile range) as appropriate
[a]*P* <0.05 between <50 mg/dl and >100 mg/dl. [b]*P* <0.05 between 50–100 mg/dl and >100 mg/dl

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; CRP, C-reactive protein, HDL, high-density lipoprotein; LDL, low-density lipoprotein; SCORE2, Systematic Coronary Risk Evaluation 2

using the Shapiro-Wilk test. Differences among the three groups were compared using the ANOVA test with the post-hoc Bonferroni correction when normally distributed or the Kruskal-Wallis test for multiple comparisons of non-normally distributed variables. Categorical variables were analyzed with the chi-square test or Fisher's exact test with a post-hoc z-test for comparison of column proportions with the Bonferroni correction. Associations between nonparametric variables were assessed by the Spearman rank correlation coefficient. All independent variables associated (P <0.2) with Lp(a) in a univariate model and simultaneously not correlated with other independent variables were included in the multivariate linear regression analysis to determine independent predictors of Lp(a) levels. A two-sided P <0.05 was considered statistically significant.

RESULTS AND DISCUSSION

We studied 800 individuals aged 49 (44–53) years (68% women), including 17.8% with Lp(a) >50 mg/dl with a higher proportion of females in this subgroup (Table 1). The prevalence of Lp(a) >50 mg/dl was 18.4% in Germany, which is almost identical to our population while in Finland or Greece, it was 6.0% [5, 6]. Our result is slightly lower than in the study by Ratajczak et al. [3], which evaluated CVD risk factors in subjects aged 18–80 (median, 52 [43–60]) years, while we assessed younger subjects. However, we did not observe a significant correlation between Lp(a) and age in contrast to a previous study in the general population, in which Lp(a) increased slightly with age [2].

Individuals with Lp(a) >100 mg/dl (maximum 237 mg/dl) were more often female and had dyslipidemia compared with those with Lp(a) <50 mg/dl (n = 682, 82.0%). Moreover, TC, LDL-C, and fibrinogen levels were 7.16% (P = 0.008), 9.54% (P = 0.047), and 9.15% (P <0.001), respectively, higher in the Lp(a) >100 mg/dl group compared with < 50 mg/dl. We did not observe any intergroup differences in the prevalence of a family history of premature CVD and the 10-year CVD risk (Table 1).

In multivariable analysis, after adjustment for age, Lp(a) levels were independently associated with female sex, LDL-C, and fibrinogen (Supplementary material, *Table S1*). The associations of Lp(a) with these variables have been reported previously [2, 7]. Higher Lp(a) in women is largely explained by an increase in Lp(a) in the peri- and post-menopausal period, which corresponds to elevated CVD risk in that still undertreated population [2, 8]. We observed higher Lp(a) levels in women aged >52 years as compared to the remainder (10.1 [3.9–45.0] vs. 7.0 [2.9–33.2] mg/dl; P = 0.034). Although the expression, synthesis, and metabolism of Lp(a) and LDL-C are independent, a weak positive correlation of their levels (in the current study, r = 0.11, P = 0.002) has been reported previously [9]. Statin use cannot reduce Lp(a) concentrations, whereas PCSK9 inhibitors lower Lp(a) by 15%–30% [2, 10]. Statins were used by 15.3% (n = 122) participants without any effect on Lp(a), as expected.

A positive association between fibrinogen and Lp(a) in our study (r = 0.135; P <0.001) is consistent with previous studies performed in the general population [7]. This association is of importance since fibrinogen is the key modulator of fibrin clot properties, and elevated Lp(a) has been associated with reduced clot permeability and susceptibility to lysis [11, 12].

Nine patients of 43 subjects with Lp(a) >100 mg/dl were genotyped, and in 4 (44.4%), the heterozygous *LPA* variant (c.5673A>G) was detected. The rs3798220 variant has been reported in 6.5% of apparently healthy Poles and 18.1% of patients with Lp(a) >75 mg/dl worldwide [13]. To our knowledge, this is the first report on genetic assessment of *LPA* variants in Poles with elevated Lp(a). Further research is needed to examine the genetic background of elevated Lp(a) in the Polish population.

Our study has limitations. Firstly, the size of the study population was limited, though it was the largest study sample in the Polish population. Secondly, clinical characteristics of the study participants were typical of screening programs; therefore, the findings could not be likely extrapolated to younger or older individuals as well as to those with CVD or the whole Polish population.

In conclusion, this study shows a relatively high (17.8%) prevalence of hyperlipoproteinemia(a) in a large Polish middle-aged population without evident CVD. In the upcoming era of new drugs with a potent Lp(a) lowering effect (e.g. pelacarsen) [2, 4], screening for elevated Lp(a) in high CVD-risk countries, including Poland [14], should be encouraged. Now, in individuals with high Lp(a), free of CVD, the management of modifiable risk factors as well as screening for high Lp(a) in families of the "index" subject should be implemented.

Supplementary material

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

Article information

Conflict of interest: None declared.

Funding: The study was supported by the Malopolska Voivodeship (no. 5/PS.IV/22). This article was supported by the science fund of the John Paul II Hospital, Cracow, Poland (FN13/2023 to MK).

REFERENCES

1. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021; 42(34): 3227–3337, doi: 10.1093/eurheartj/ehab484, indexed in Pubmed: 34458905.
2. Kronenberg F, Mora S, Stroes ESG, et al. Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement. Eur Heart J. 2022; 43(39): 3925–3946, doi: 10.1093/eurheartj/ehac361, indexed in Pubmed: 36036785.
3. Ratajczak J, Kubica A, Michalski P, et al. Determinants of lipid parameters in patients without diagnosed cardiovascular disease-results of the Polish arm of the EUROASPIRE V survey. J Clin Med. 2023; 12(7), doi: 10.3390/jcm12072738, indexed in Pubmed: 37048821.
4. Boffa MB, Koschinsky ML. Lipoprotein (a): truly a direct prothrombotic factor in cardiovascular disease? J Lipid Res. 2016; 57(5): 745–757, doi: 10.1194/jlr.R060582, indexed in Pubmed: 26647358.
5. van Buuren F, Horstkotte D, Knabbe C, et al. Incidence of elevated lipoprotein (a) levels in a large cohort of patients with cardiovascular disease. Clin Res Cardiol Suppl. 2017; 12(Suppl 1): 55–59, doi: 10.1007/s11789-017-0087-y, indexed in Pubmed: 28229283.
6. Raitakari O, Kivelä A, Pahkala K, et al. Long-term tracking and population characteristics of lipoprotein (a) in the Cardiovascular Risk in Young Finns Study. Atherosclerosis. 2022; 356: 18–27, doi: 10.1016/j.atherosclerosis.2022.07.009, indexed in Pubmed: 35961208.
7. Slunga L, Asplund K, Johnson O, et al. Lipoprotein(a) in a randomly selected 25-64 year old population: the Northern Sweden Monica Study. J Clin Epidemiol. 1993; 46: 617–624.
8. Duda-Pyszny D, Trzeciak P, Desperak P, et al. Comparison of clinical characteristics, in-hospital course, and 12-month prognosis in women and men with chronic coronary syndromes. Kardiol Pol. 2021; 79(4): 393–400, doi: 10.33963/KP.15749, indexed in Pubmed: 33463985.
9. Varvel S, McConnell JP, Tsimikas S. Prevalence of elevated Lp(a) mass levels and patient thresholds in 532 359 patients in the United States. Arterioscler Thromb Vasc Biol. 2016; 36(11): 2239–2245, doi: 10.1161/ATVBAHA.116.308011, indexed in Pubmed: 27659098.
10. Atar D, Langslet G, Tonstad S. Do we need new lipid-lowering agents in the era of PCSK9 inhibitors? Recent advances. Kardiol Pol. 2022; 80(7-8): 741–749, doi: 10.33963/KP.a2022.0117, indexed in Pubmed: 35521719.
11. Ząbczyk M, Ariëns RAS, Undas A. Fibrin clot properties in cardiovascular disease: from basic mechanisms to clinical practice. Cardiovasc Res. 2023; 119(1): 94–111, doi: 10.1093/cvr/cvad017, indexed in Pubmed: 36662542.
12. Kopytek M, Ząbczyk M, Mazur P, et al. Oxidized phospholipids associated with lipoprotein(a) contribute to hypofibrinolysis in severe aortic stenosis. Pol Arch Intern Med. 2022; 132(11), doi: 10.20452/pamw.16372, indexed in Pubmed: 36384266.
13. Karwatowska-Prokopczuk E, Clouet-Foraison N, Xia S, et al. Prevalence and influence of LPA gene variants and isoform size on the Lp(a)-lowering effect of pelacarsen. Atherosclerosis. 2021; 324: 102–108, doi: 10.1016/j.atherosclerosis.2021.03.036, indexed in Pubmed: 33872986.
14. Pająk A, Jankowski P, Zdrojewski T. The burden of cardiovascular disease risk factors: A current problem. Kardiol Pol. 2022; 80(1): 5–15, doi: 10.33963/KP.a2022.0018, indexed in Pubmed: 35137945.

Prevalence and severity of sinus tachycardia and arrhythmias by Holter monitoring in children with Duchenne muscular dystrophy

Magdalena Bazgier[1]*, Jarosław Meyer-Szary[1]*, Renata Tarnowska[1], Katarzyna Lisowska[1], Jolanta Wierzba[2], Joanna Kwiatkowska[1]

[1]Department of Pediatric Cardiology and Congenital Heart Defects, Medical University of Gdansk, Gdańsk, Poland
[2]Department of Pediatrics, Hematology and Oncology, Department of General Nursery, Medical University of Gdansk, Gdańsk, Poland
*Both authors equally contributed to the study.

Correspondence to:
Joanna Kwiatkowska, MD PhD, Department of Pediatric Cardiology and Congenital Heart Defects, Medical University of Gdansk, Dębinki 7, 80–211 Gdańsk, Poland,
phone: +48 58 349 28 70,
e-mail: joannak@gumed.edu.pl

DOI: 10.33963/v.kp.98326

Received:
June 21, 2023

Accepted:
November 27, 2023

Early publication date:
December 31, 2023

INTRODUCTION

Heart failure (HF) currently accounts for 30%–60% of deaths in Duchenne muscular dystrophy (DMD) patients [1, 2]. The development of dilated cardiomyopathy (DCM) is a slow but inevitable process, preceded by ongoing cardiac fibrosis as evidenced by late gadolinium enhancement (LGE) in cardiac magnetic resonance studies (CMR) [3, 4]. Arrhythmias evolve throughout patients' lives, with asymptomatic sinus tachycardia (ST) being one of the most common and early-occurring heart rhythm abnormalities of unknown prognostic value [5–7]. The assessment of the prevalence and severity of ST and arrhythmias in DMD patients of different age groups using Holter monitoring were the aim of our study.

METHODS

The data collected between year 2017–2019 (Supplementary material, *Figure S1*) were analyzed in a cross-sectional, single center prospective observational study. *Table S1* in supplementary material presents inclusion and exclusion criteria. The recordings were performed as a part of a routine, annual cardiological screening using Phillips Holter ECG system (Phillips DigiTrak XT) with the Zymed algorithm analyzer. The analysis included the assessment of heart rate (HR) variables, presence and severity of arrhythmias. The data published by Salameh et al. [8] based on the healthy population was used as reference and for calculations of the standardized values (z-scores) of the analyzed parameters. To characterize ST in detail, we developed sinus tachycardia severity scale (STSS) as shown in Supplementary material, *Table S2*.

Statistical analysis

The statistical analysis was performed using Wizard 2.0 (Evan Miller, Chicago, IL, US). Categorial data are given as counts and percentages and continuous data are presented as mean (standard deviation) or median (interquartile range) dependently on the distribution. The distribution was tested using the Shapiro–Wilk test. Standard statistical tests, including, χ^2, t-test, Pearson correlation test were used. Additionally simple linear and quadratic regressions were used dependently on best fit based on highest R^2 and multivariable models were analyzed. $P < 0.05$ was considered statistically significant.

The study was approved by the Institutional Bioethics Committee for Scientific Research.

RESULTS AND DISCUSSION

Two studies out of 72 collected Holter ECG recordings met the exclusion criteria being conducted in BB-treated patients. Eventually, 70 recordings in 70 caucasian patients including 2 girls, one recording each, were analyzed. Twenty-six (31.9%) recordings were done in patients taking angiotensin-converting-enzyme inhibitor (ACEi) and those patients were on average older (on-ACEi vs. no-ACEi: 11.5 [3.8] vs. 9.0 [3.9] years; $P < 0.001$). Most of the recordings (47, 67.1%) was done in patients taking steroids. There was no age-difference between steroid-treated and steroid-naive patients (10.1 [3.3] vs. 9.5 [4.8], respectively,

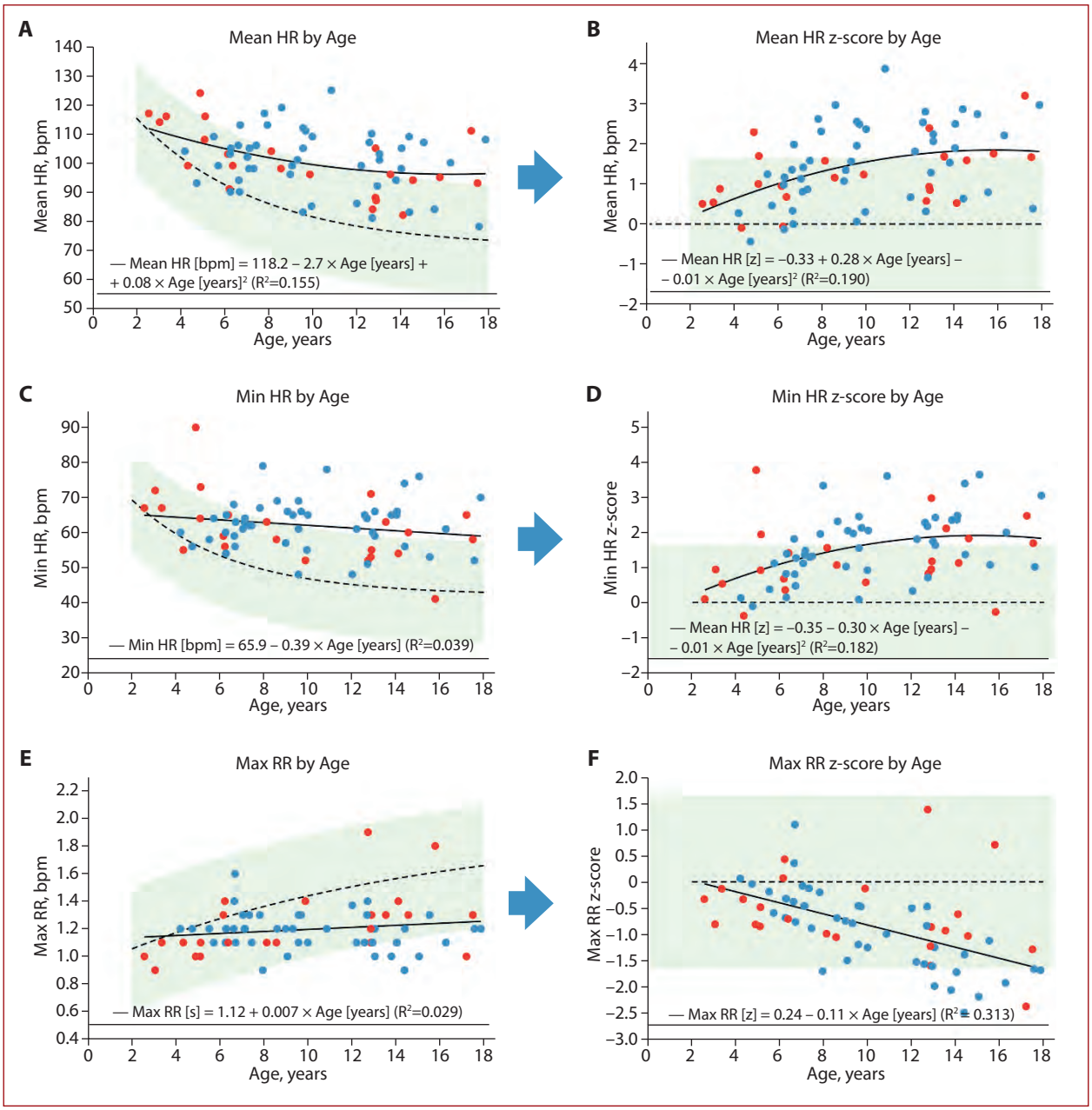


Figure 1. Age dependency of the studied parameters: **A.** Mean HR. **B.** Mean HR z-score. **C.** Minimum HR. **D.** Minimum HR z-score. **E.** Maximum RR. **F.** Maximum RR z-score *P*-value is for t-test for the comparison to the reference population [8]

Abbreviations: HR, heart rate; RR, RR distance

P = 0.51). Baseline and pharmacotherapy characteristics are presented in *Table S3* of the Supplementary material.

None of the analyzed parameters was dependent on total recording time (i.e., shorter recordings were not significantly biased). Mean HR was found to be statistically different from the reference healthy population, *P* <0.001 and inversely correlated with age (R^2 = 0.155; *P* <0.001) dropping at a rate slower than the reference population as shown in Figure 1A. For linear regression the drop was 0.95 bpm/year. The mean HR z-score used for assessment of the severity of ST revealed positive correlation with age (R^2 = 0.190; *P* <0.001), rising 0.09/year. A more detailed analysis of the time trend showed a nonlinear relation of these parameters to age best approximated by a quadratic equation with an inflection point around the age of 11 years as shown in Figure 1B. The age subgroup analysis showed that up to the age of 10 ST is becoming more severe and there is an annual increase of mean HR z-score of 0.20 while after the age of 12 years the mean HR z-score plateaus as 1.69 (0.88) with no significant rise thereafter. Consequently, ST was diagnosed in 27 (38.6%) cases overall in the analyzed sample. The ST prevalence was age-dependent (*P* = 0.02) — more common in older subgroups as shown in *Figure S2* and *S3A* (Supplementary material).

The minimum HR was higher and the maximum RR shorter than in the reference population (*P* <0.001 in both),

presenting no correlation with age ($P = 0.10$ and $P = 0.17$, respectively) as shown in Figure 1C and Figure 1E. Conversely, the minimum HR z-score was positively ($R^2 = 0.182$; $P < 0.001$, Figure 1D) and the maximum RR z-score was inversely correlated with age ($R^2 = 0.313$; $P < 0.001$, annual drop of –0.11, Figure 1F). Significant differences were present in age groups analysis of all the above-mentioned parameters as presented in *Figure S3B–C* in Supplementary material.

There was also no significant difference between ACEi-treated and ACEi-naive patients in Mean HR z-score ($P = 0.16$), minimum HR z-score ($P = 0.31$) and maximum RR z-score ($P = 0.22$) in multivariable model corrected for age.

No complex supraventricular or ventricular arrhythmias or higher degree block were found, thus none of the patients required starting antiarrhythmic treatment based on the analyzed recording. There was no correlation of SVPC and VPC prevalence with age ($P = 0.32$ and 0.140, respectively). The detailed Holter ECG recording results are summarized in *Table S4* of the Supplementary material.

Although the presence of ST is a well-known phenomenon in DMD, its reported prevalence ranges from 0 up to 50% dependently on the method (resting HR measurement vs. Holter monitoring), definition criteria, and cohort characteristics (age) [5, 9, 10]. While in the previous studies it was common to evaluate the prevalence of ST, its severity had not been assessed beforehand. In our study, based on the z-score calculation and analysis, we found that not only the prevalence, but also the severity of ST increases with age up to the age of about 12 years when it reaches its plateau. The exact reasons and pathomechanism behind this finding are uncertain. Previously suggested compensatory reaction to heart failure is improbable as most of the DMD patients in the younger age groups will still have preserved cardiac contractile function while in the older groups, where contractile disfunction onsets, the degree of ST (by Mean HR z-score) is stationary [4, 5, 10]. Alternatively, an autonomous disfunction was a suggested explanation but currently there is not enough scientific evidence to support this hypothesis [10]. Despite Thomas et al. [5] suggested link between elevated heart rate and DMD-CM development, ST's prognostic value remains uncertain.

In the reports available the prevalence and severity of both supraventricular and ventricular arrhythmias varies significantly with prevalence of VPC ranging from 14% to 58% [6, 7, 11]. In the presented study, the prevalence of ventricular arrhythmias was lower than in the study by Villa et al. [7]. Similarly to this study, we found supraventricular arrhythmias more prevalent, which is discrepant from the report by Chiang et al. [6], where ventricular arrhythmias, including nsVT were frequently diagnosed. As the age of 17 or more was found to be associated with the development of SVT/VT, the younger age of the population described in our study might explain this discrepancy. On the other hand, the deterioration of left ventricular systolic function is a predictor of significant Holter ECG findings also in younger patients [6, 7]. Contrary to other muscular dystrophies, e.g. Emery-Dreifuss muscular dystrophy, atrial fibrillation and atrioventricular blocks are rare in DMD [12]. The link between presence of fibrosis based on CMR LGE assessment and life-threatening arrhythmias regardless of contractile function, together with high incidence of fibrosis in DMD patients, poses another potential risk factor in this group of patients [3, 4, 13].

Supplementary material

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

Article information

Conflict of interest: None declared.

Funding: None.

REFERENCES

1. Eagle M, Baudouin SV, Chandler C, et al. Survival in Duchenne muscular dystrophy: improvements in life expectancy since 1967 and the impact of home nocturnal ventilation. Neuromuscul Disord. 2002; 12(10): 926–929, doi: 10.1016/s0960-8966(02)00140-2, indexed in Pubmed: 12467747.
2. Wittlieb-Weber CA, Knecht KR, Villa CR, et al. Risk factors for cardiac and non-cardiac causes of death in males with duchenne muscular dystrophy. Pediatr Cardiol. 2020; 41(4): 764–771, doi: 10.1007/s00246-020-02309-y, indexed in Pubmed: 32016582.
3. Silva MC, Meira ZM, Gurgel Giannetti J, et al. Myocardial delayed enhancement by magnetic resonance imaging in patients with muscular dystrophy. J Am Coll Cardiol. 2007; 49(18): 1874–1879, doi: 10.1016/j.jacc.2006.10.078, indexed in Pubmed: 17481447.
4. Kwiatkowska J, Meyer-Szary J, Bazgier M, et al. Left ventricular volumes and function affected by myocardial fibrosis in patients with Duchenne and Becker muscular dystrophies: a preliminary magnetic resonance study. Kardiol Pol. 2020; 78(4): 331–334, doi: 10.33963/KP.15223, indexed in Pubmed: 32125292.
5. Thomas TO, Morgan TM, Burnette WB, et al. Correlation of heart rate and cardiac dysfunction in Duchenne muscular dystrophy. Pediatr Cardiol. 2012; 33(7): 1175–1179, doi: 10.1007/s00246-012-0281-0, indexed in Pubmed: 22434508.
6. Chiang DY, Allen HD, Kim JJ, et al. Relation of cardiac dysfunction to rhythm abnormalities in patients with duchenne or becker muscular dystrophies. Am J Cardiol. 2016; 117(8): 1349–1354, doi: 10.1016/j.amjcard.2016.01.031, indexed in Pubmed: 26952271.
7. Villa CR, Czosek RJ, Ahmed H, et al. Ambulatory monitoring and arrhythmic outcomes in pediatric and adolescent patients with Duchenne muscular dystrophy. J Am Heart Assoc. 2015; 5(1): e002620, doi: 10.1161/JAHA.115.002620, indexed in Pubmed: 26722125.
8. Salameh A, Gebauer RA, Grollmuss O, et al. Normal limits for heart rate as established using 24-hour ambulatory electrocardiography in children and adolescents. Cardiol Young. 2008; 18(5): 467–472, doi: 10.1017/S1047951108002539, indexed in Pubmed: 18634710.
9. James J, Kinnett K, Wang Yu, et al. Electrocardiographic abnormalities in very young Duchenne muscular dystrophy patients precede the onset of cardiac dysfunction. Neuromuscul Disord. 2011; 21(7): 462–467, doi: 10.1016/j.nmd.2011.04.005, indexed in Pubmed: 21571532.
10. Thomas TO, Jefferies JL, Lorts A, et al. Autonomic dysfunction: a driving force for myocardial fibrosis in young Duchenne muscular dystrophy patients? Pediatr Cardiol. 2015; 36(3): 561–568, doi: 10.1007/s00246-014-1050-z, indexed in Pubmed: 25399404.

11. Perloff JK. Cardiac rhythm and conduction in Duchenne's muscular dystrophy: a prospective study of 20 patients. J Am Coll Cardiol. 1984; 3(5): 1263–1268, doi: 10.1016/s0735-1097(84)80186-2, indexed in Pubmed: 6707378.
12. Marchel M, Madej-Pilarczyk A, Steckiewicz R, et al. Predictors of mortality and cardiovascular outcomes in Emery-Dreifuss muscular dystrophy in a long-term follow-up. Kardiol Pol. 2021; 79(12): 1335–1342, doi: 10.33963/KP.a2021.0159, indexed in Pubmed: 34783354.
13. Ganesan AN, Gunton J, Nucifora G, et al. Impact of Late Gadolinium Enhancement on mortality, sudden death and major adverse cardiovascular events in ischemic and nonischemic cardiomyopathy: A systematic review and meta-analysis. Int J Cardiol. 2018; 254: 230–237, doi: 10.1016/j.ijcard.2017.10.094, indexed in Pubmed: 29407096.

Successful pregnancy course and outcome in a patient with unusual coincidence of two structural heart defects: Ebstein anomaly and biventricular non-compaction cardiomyopathy — extremely rare, but there!

Janusz Kudlicki[1]*, Agnieszka Styczeń[1]*, Jacek Zawiślak[1], Klaudia Artykiewicz-Zawiślak[1], Andrzej Tomaszewski[1], Elżbieta Czekajska-Chehab[2], Tomasz Zapolski[1]*

[1]Department of Cardiology, Medical University of Lublin, Lublin, Poland
[2]Department of Medical Radiology, Medical University of Lublin, Lublin, Poland
*These authors equally contributed to the study.

Correspondence to:
Agnieszka Styczeń, MD, Department of Cardiology, Medical University of Lublin, Jaczewskiego 8, 20–954 Lublin, Poland,
phone: +48 696 554 194,
e-mail: styczen.agnieszka@gmail.com

DOI: 10.33963/v.kp.98283

Received:
October 23, 2023

Accepted:
November 21, 2023

Early publication date:
December 7, 2023

We present the case of a 26-year-old pregnant woman (GIPI, 30 hbd) with an Ebstein anomaly (EA) confirmed by two-dimensional transthoracic echocardiography (2D TTE). The patient was referred to the Cardiology Department because of dry cough, dyspnea at rest, and cardiac arrhythmias that had persisted since 27 hbd. On admission, the patient's general condition was average, and laboratory tests (high sensitivity troponin I, B-type natriuretic peptide) were normal. An electrocardiogram (ECG) showed sinus tachycardia, dextrogram, incomplete right bundle branch block, ST-segment elevation in lead V1, tall and peaked T waves in leads I, II, V2–V5; biphasic P waves in lead V1 (Figure 1A). A Holter ECG was performed, which recorded 4 non-sustained ventricular tachycardias (nsVTs) consisting of polymorphic evolutions (Figure 1B). 2D TTE showed displacement of the tricuspid valve (TV) leaflets by 21 mm with visible signs of the right ventricle (RV) atrialization and severe tricuspid regurgitation. Additionally, impaired left ventricular (LV) contractility (LV ejection fraction [LVEF] ~43%) and increased LV trabeculation were noted in the apical region, which was not visualized during previous TTEs (Figure 1C–D). Following the tests, extended-release metoprolol was added to therapy. During hospitalization, the fetus's well-being was also monitored — the correct fetal position and optimal flows in the umbilical artery.

Subsequently, in 36/37 hbd the patient delivered a live daughter (birth weight — 2280 g, Apgar 10 at 1 min) during a planned C-section. The early postpartum period was uneventful; no arrhythmias were observed. After postpartum discharge, a control Holter ECG was performed twice at home; in neither examination did nsVTs recur. Due to the inability to perform magnetic resonance, a cardiac tomography multiplanar reconstruction was then performed, confirming EA with an intraventricular displacement of the TV plane by approximately 50 mm; significant deepening of the LV free and inferior wall trabeculae and periapically in the RV were clearly visible. Global and regional contractility disorders of both ventricles were noted — LVEF ~29%, RVEF ~38%. (Figure 1E–F; Supplementary material, *Figure S1*). Due to significantly decreased LVEF, implantation of a cardioverter-defibrillator for primary prevention of sudden cardiac death was considered. The patient started treatment for heart failure with reduced LVEF according to the European Society of Cardiology guidelines consisting of a beta-blocker, angiotensin-receptor neprilysin inhibitor, and loop diuretic.

EA constitutes a rare congenital heart disease with varying degrees of downward displacement of the septal and posterior TV leaflets, triggering RV atrialization and dysfunction; the prevalence is 1:200 000 live births. [1] During pregnancy, the probability of right ventricular failure rises due to an increase in blood volume, cardiac output, and afterload. [2] The clinical picture of non-compaction cardiomyopathy varies, ranging

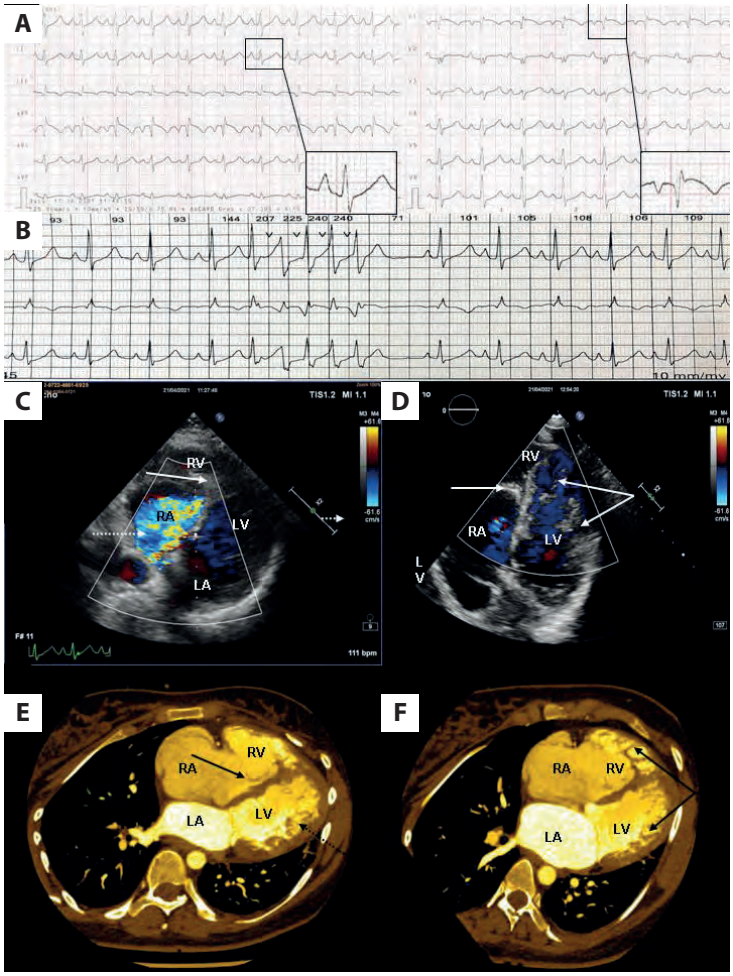


Figure 1. A. ECG on admission: sinus tachycardia 105/min, right axis deviation, IRBBB. ST-segment elevation in lead V1, tall and peaked P waves in leads I, II, and V2–V5 I; biphasic P waves in lead V1. **B.** Holter ECG: nsVT consisting of polymorphic evolutions. **C.** Echocardiography — 2D TTE SC: displacement of the septal leaflet of the tricuspid valve towards the RV (solid arrow) with visible signs of RV atrialization. **D.** Echocardiography — 2D TTE modified 4C: displacement of the septal leaflet of the tricuspid valve towards the RV (solid arrow) with visible signs of RV atrialization and increased LV trabeculation with blood turbulence in the intertrabecular lacunas on color Doppler in the LV apical region (double solid arrows). **E.** CT MPR 4C: displacement of the septal leaflet of the tricuspid valve towards the right ventricle (solid arrow) with visible signs of RV atrialization and increased left ventricular trabeculation in the LV apical area (dashed arrow). **F.** CT MPR 4C: visible increased ventricular trabeculation in both the RV and LV apical areas (double solid arrows)

Abbreviations: 2D TTE 4C, two-dimensional transthoracic echocardiography 4-chamber apical view; 2D TTE SC, two-dimensional transthoracic echocardiography subcostal view; CT MPR 4C, cardiac tomography multiplanar reconstruction 4-chamber view; CT MPR TV, cardiac tomography multiplanar reconstruction transverse view; ECG, electrocardiogram; IRBB, incomplete right bundle branch block; LA, left atrium; LV, left ventricle; nsVT, non-sustained ventricular tachycardia; RA, right atrium; RV, right ventricle

from asymptomaticity to dangerous manifestations, such as chronic heart failure, arrhythmias, thromboembolic episodes, and sudden cardiac death [3]. Non-compaction cardiomyopathy, a rare myocardial abnormality, sometimes coexists with Ebstein disease in approximately 5% of patients, significantly worsening the prognosis [4]. The described coexistence of these two very uncommon heart diseases can definitely be included in the casuistry. Despite medical advances, cardiovascular diseases are still the leading cause of non-obstetric maternal deaths during pregnancy (0.5%–4% in the West) [5].

Supplementary material

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

Article information

Conflict of interest: None declared.

Funding: None.

REFERENCES

1. Thareja SK, Frommelt MA, Lincoln J, et al. A systematic review of Ebstein's anomaly with left ventricular noncompaction. J Cardiovasc Dev Dis. 2022; 9(4): 115, doi: 10.3390/jcdd9040115, indexed in Pubmed: 35448091.
2. Katsuragi S, Kamiya C, Yamanaka K, et al. Risk factors for maternal and fetal outcome in pregnancy complicated by Ebstein anomaly. Am J Obstet Gynecol. 2013; 209(5): 452.e1–452.e6, doi: 10.1016/j.ajog.2013.07.005, indexed in Pubmed: 23860210.
3. Warchoł I, Książczyk M, Dębska-Kozłowska A, et al. Biventricular non-compaction cardiomyopathy: Rare disease and far rarer case. Kardiol Pol. 2022; 80(12): 1272–1273, doi: 10.33963/KP.a2022.0208, indexed in Pubmed: 36082796.
4. Kumor M, Lipczyńska M, Biernacka EK, et al. Cardiac arrest and ventricular arrhythmia in adults with Ebstein anomaly and left ventricular non-compaction. J Cardiol. 2018; 71(5): 484–487, doi: 10.1016/j.jjcc.2017.11.012, indexed in Pubmed: 29305187.
5. Bardhi E, Faralli I, Deroma M, et al. Non-compaction cardiomyopathy in pregnancy: a case report of spongy myocardium in both mother and foetus and systematic review of literature. J Matern Fetal Neonatal Med. 2021; 34(17): 2910–2917, doi: 10.1080/14767058.2019.1671337, indexed in Pubmed: 31570025.

Danon disease: Rare cause of cardiomyopathy

Julia Dzierla, Weronika Pelczar-Płachta, Filip Baszkowski, Waldemar Bobkowski

Department of Pediatric Cardiology, University of Medical Sciences, Poznań, Poland

Correspondence to:
Weronika Pelczar-Płachta, MD, Department of Pediatric Cardiology, University of Medical Sciences, Szpitalna 27/33, 60–572 Poznań, Poland,
phone: +48 618491370
e-mail: weronika.pelczarplachta@gmail.com

DOI: 10.33963/v.kp.97064

Received:
July 19, 2023

Accepted:
August 17, 2023

Early publication date:
August 24, 2023

Danon disease is the only X-linked dominant storage disease and is one of the few glycogenoses concerning cardiac muscle. It is caused by a mutation that impairs autophagocytosis and accumulates glycogen in cells [1, 2]. Symptoms manifest earlier and more severely in men, very often in adolescence [2]. Cardiomyopathy often coexists with myopathy and mental retardation [1].

A 9-year-old male patient with palpitations was admitted to the Department of Pediatric Cardiology due to suspected paroxysmal tachyarrhythmia. In the patient's family history, there was a grandmother's heart transplantation (HTx) due to unknown cardiomyopathy, which had been performed 23 years earlier. Laboratory tests showed elevated levels of N-terminal pro-B-type natriuretic peptide (8396 pg/ml [reference range <83 pg/ml]), hs-TnI (257.5 ng/l [reference range <52 ng/l]), and creatine kinase (CK of 563 U/l [reference range <137 U/l]). Electrocardiogram was indicative of left ventricular hypertrophy: the Sokolow-Lyon index was78 mm (norm 37 mm), inverted T wave in V5-V6, and shortened PR were 100 ms, prolonged QRS was 140 ms, with characteristic slurring in II, aVF, and V2–V6 suggestive of ventricular pre-excitation.

The latest data showed that in Danon disease these ECG features may occur in the absence of an additional conduction pathway and they can mimic Wolff-Parkinson-White syndrome; therefore, an invasive electrophysiological procedure was not performed [4]. Twenty-four-hour Holter monitoring showed 17 episodes of supraventricular tachycardia (max. 170/min; up to 23 consecutive heartbeats). Transthoracic echocardiography revealed features of left ventricular hypertrophy and overload (Figure 1A, 1B). Cardiac magnetic resonance imaging (MRI) showed myocardial fibrosis. Hypertrophic cardiomyopathy was diagnosed, and antiarrhythmic treatment was initiated (metoprolol succinate ER 2 mg/kg *per os*). During the following hospitalization, a full diagnostic panel was performed. Congenital metabolic diseases (including Pompe disease) were excluded, and Gas chromatography–mass spectrometry urine and tandem mass spectrometry blood tests were correct. A genetic test was performed and confirmed a pathogenic mutation in the LAMP-2(Xq24) gene [1, 3]. The presence of this mutation confirmed Danon disease. In addition, the genetic test revealed the same gene mutation in the patient's two-year-old brother despite a lack of symptoms.

During the next few months, subsequent hospital admissions due to progressing heart failure occurred. Ultrasonography showed fluid accumulation in the pleural and peritoneal cavity. Moreover, a single episode of atrial fibrillation was observed with signs of clinical deterioration. The patient underwent electrical cardioversion (Figure 1C) with 50J, and sinus rhythm was restored. However, severe hypotension occurred, and the patient was transferred to the Intensive Care Department, where he was treated with constant infusion of dopamine and dobutamine. Due to inadequate SVT control and disqualification from ablation, treatment was changed to HTx. Cardiac catheterization before HTx showed characteristics of glycogen storage disease i.e. post- and pre-capillary pulmonary hypertension (mPAP: 42 mm Hg, PCWP: 19 mm Hg, PVR: 6.4 WU, PVRI: 8.8 WU/m^2) with negative vasoreactivity testing with epoprostenol (12 ng/kg/min +100% oxygen), with a significant decrease in pulmonary resistance (<3 WU) and increased PCPW (mPAP: 39 mm

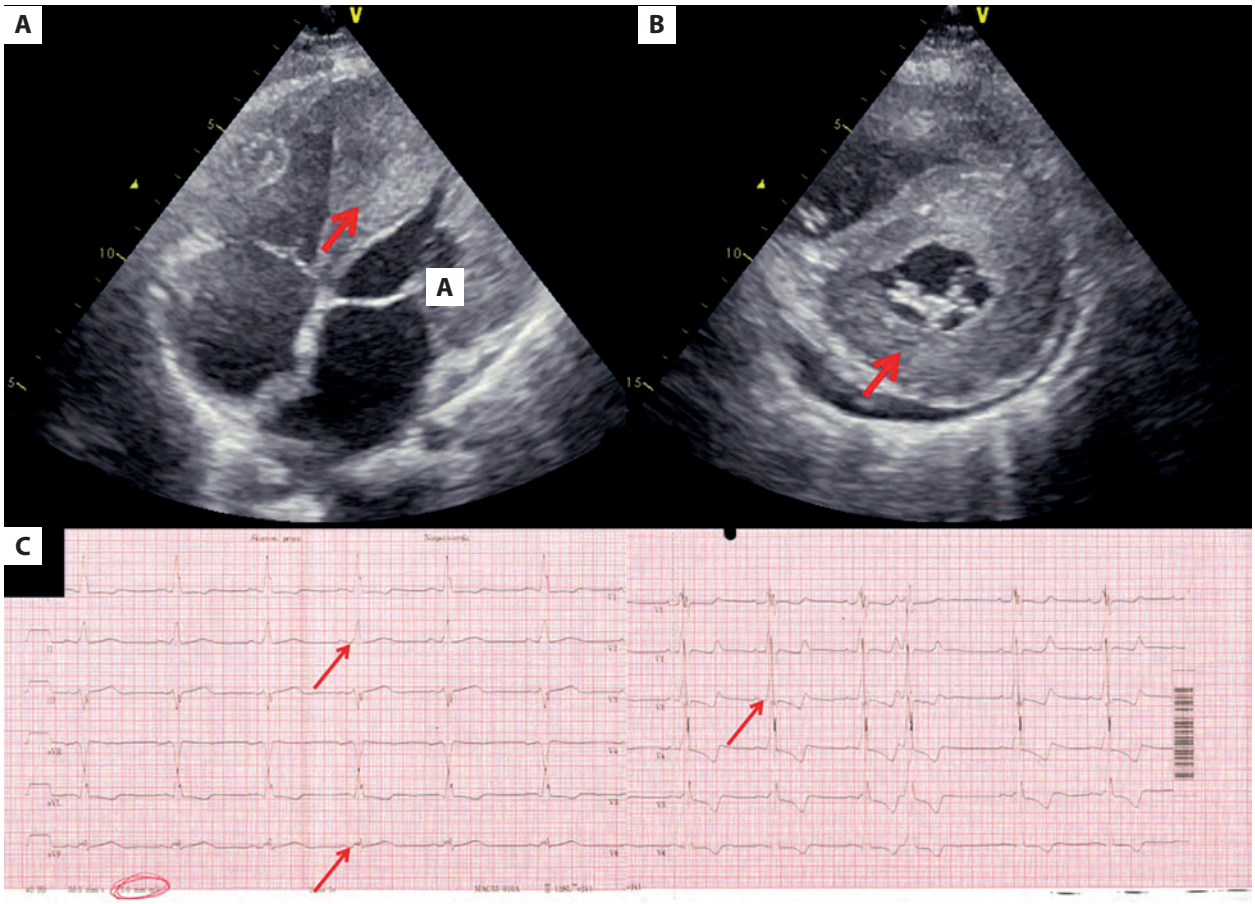


Figure 1. A. Echocardiography — apical four-chamber view: left ventricular hypertrophy: 3.3/1.9 cm, asymmetric hypertrophy of intraventricular septum (red arrow): 2.6 cm (Z score: 21.67), and left ventricular ejection fraction: 78%. **B.** Echocardiography — parasternal short axis — mitral valve: hypertrophy of the left ventricular posterior wall (red arrow): 2.1 cm (Z score: 11.08), presence of trace amounts of fluid. **C.** 12-lead electrocardiogram with signs of left ventricular hypertrophy and characteristic slurring of the upstroke of the QRS complex in II, aVF, V2–V6 (red arrows) mimicking ventricular pre-excitation

Hg, PCWP: 27 mm Hg, PVR: 2.86 WU, PVRI: 3.94 WU/m^2) [5]. Rapid progression of cardiomyopathy resulted in urgent qualification for HTx. Multicenter cooperation enabled efficient transfer to a transplant center, and transplantation was performed seven months after the diagnosis of Danon disease. The surgery was successful, but one month later, severe Ebstein–Barr virus infection caused the patient's death.

Article information

Conflict of interest: None declared.

Funding: None.

REFERENCES

1. D'souza RS, Levandowski C, Slavov D, et al. Danon disease: clinical features, evaluation, and management. Circ Heart Fail. 2014; 7(5): 843–849, doi: 10.1161/CIRCHEARTFAILURE.114.001105, indexed in Pubmed: 25228319.
2. Boucek D, Jirikowic J, Taylor M. Natural history of Danon disease. Genet Med. 2011; 13(6): 563–568, doi: 10.1097/GIM.0b013e31820ad795, indexed in Pubmed: 21415759.
3. Zhai Y, Miao J, Peng Y, et al. Clinical features of Danon disease and insights gained from LAMP-2 deficiency models. Trends Cardiovasc Med. 2023; 33(2): 81–89, doi: 10.1016/j.tcm.2021.10.012, indexed in Pubmed: 34737089.
4. Konrad T, Sonnenschein S, Schmidt FP, et al. Cardiac arrhythmias in patients with Danon disease. Europace. 2017; 19(7): 1204–1210, doi: 10.1093/europace/euw215, indexed in Pubmed: 27742774.
5. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2022; 43(38): 3618–3731, doi: 10.1093/eurheartj/ehac237, indexed in Pubmed: 36017548.

Melanoma metastasis of the heart: Case report of an atypical metastatic location

Mateusz Sajdok[1, 2*], Michał Kawa[3*], Marcin Miszczyk[4], Anna Błach[5, 6], Olgierd Chrabański[6–8], Tomasz Soral[1, 2], Adam Śmietana[3], Daniel Stadnik[3, 9], Paulina Musik[3], Jolanta Biernat[1], Marek Deja[10, 11], Krzysztof S Gołba[1, 2]

[1]Department of Electrocardiology, Upper Silesian Heart Center, Medical University of Silesia, Katowice, Poland
[2]Department of Electrocardiology and Heart Failure, Medical University of Silesia, Katowice, Poland
[3]Student's Scientific Society, Department of Electrocardiology and Heart Failure, Medical University of Silesia, Katowice, Poland
[4]3rd Radiotherapy and Chemotherapy Department, Maria Skłodowska-Curie National Research Institute of Oncology, Gliwice, Poland
[5]Department of Cardiology and Structural Heart Diseases, Medical University of Silesia, Katowice, Poland
[6]Department of Nuclear Medicine, Voxel Diagnostic Center, Katowice, Poland
[7]Department of Radiodiagnostics, Interventional Radiology and Nuclear Medicine, Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland
[8]Department of Nuclear Medicine and Endocrine Oncology, Maria Skodowska-Curie National Research Institute of Oncology, Gliwice Branch, Gliwice, Poland
[9]Department of Pneumonology, Upper Silesian Medical Center, Medical University of Silesia, Katowice, Poland
[10]Department of Cardiac Surgery, Upper Silesian Heart Center, Medical University of Silesia, Katowice, Poland
[11]Department of Cardiac Surgery, Medical University of Silesia, Katowice, Poland
*Both authors equally contributed to the study.

Correspondence to:
Mateusz Sajdok, MD, Department of Electrocardiology, Upper Silesian Heart Center, Ziołowa 45/47, 40–635, Katowice, Poland,
phone: +48 32 359 88 93,
e-mail: msajdok@gcm.pl

DOI: 10.33963/v.kp.97945

Received:
August 5, 2023

Accepted:
October 23, 2023

Early publication date:
December 19, 2023

Melanoma is an aggressive skin cancer that most commonly metastasizes to the lymph nodes, brain, and lungs. Due to its increasing incidence, it is projected to become the second most common malignancy in the United States by 2040 [1]. In recent years, the median survival of patients with melanoma has increased substantially due to improved treatment methods [2] and earlier, more accessible diagnosis [3].

We present the case of a 47-year-old female patient with a 7-year history of melanoma and a recent metastasis to the right atrium of the heart (RA). The primary cancer, a small skin lesion on the back of her thigh (Figure 1A), was excised in 2015. Histopathology confirmed melanoma (BRAF "–"). Between 2019 and 2022, the patient was diagnosed with skin, central nervous system (CNS), and pelvic lymph node metastases. The patient received pelvic lymphadenectomy and nivolumab monotherapy. In addition, CNS metastases were treated with seven separate courses of CyberKnife stereotactic radiosurgery for 4 years.

In September 2021, a PET scan showed increased glucose metabolism in the RA. Magnetic resonance imaging (MRI) confirmed a 15 × 16 × 18 mm tumor. The differential diagnosis included a thrombus and metastatic tumor, and anticoagulant therapy (low-molecular-weight heparin in therapeutical dose) was introduced. One year later, MRI showed a twofold increase in the tumor size (27.5 × 36 × 39.5 mm) and infiltration of the atrial wall and right coronary artery. A subsequent PET scan indicated a very high glucose metabolism (SUVmax — 20.4) (Figure 1B; Supplementary material, *Figures S1, S2*). A biopsy of the tumor and the AngioVac technique [4] were not performed due to concerns about intraprocedural rupture of the infiltrated RA wall. The patient reported only mild fatigue, and no rhythm abnormalities were observed. Echocardiography initially showed no flow obstruction into the right heart (Supplementary material, *Videos S1, S2, S3*). The multidisciplinary team consisting of an oncologist, cardiologist, cardiac surgeon, and radiation oncologist decided to continue the previous immunotherapy and postpone surgery due to the patient's high procedural risk and oligosymptomatic state.

Contrast-enhanced computed tomography (CT) was performed six weeks later to plan further treatment. Despite a significant increase in tumor size (37 × 41 × 44 mm) (Figure 1C–D) and an additional pedunculated, mobile mass in the LV (9 × 5 mm), combined immunotherapy (ipilimumab + nivolumab)

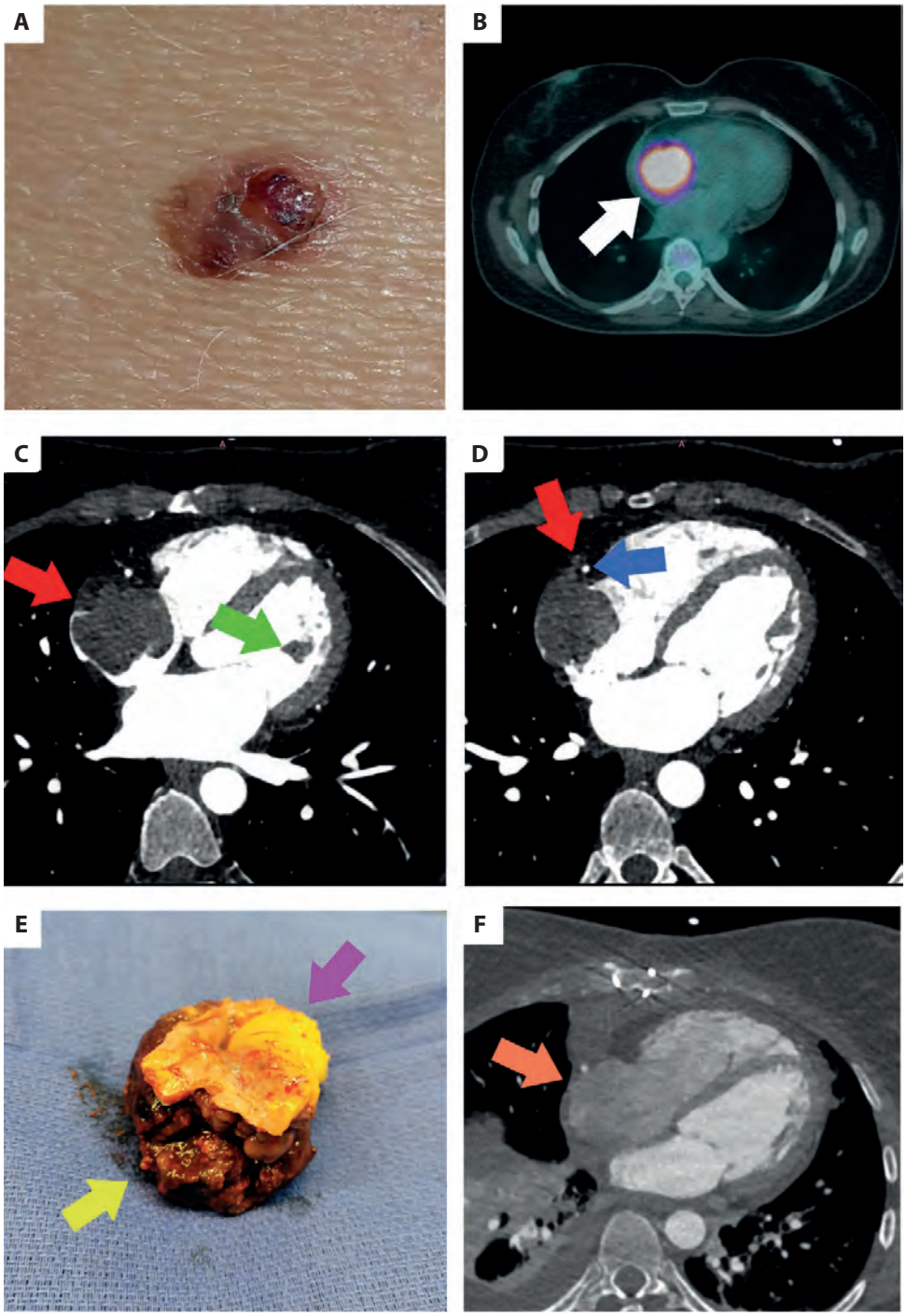


Figure 1. A. Initial skin lesion, excised surgically in 2015. **B.** 18F-FDG PET-CT scan (05.2023) with increased glucose metabolism in the right atrium (white arrow). **C.** and **D.** Contrast-enhanced CT of the heart. Red arrow points at the right atrium wall infiltration, the blue arrow points at the right coronary artery infiltration, green arrow points at the pedunculated, mobile LV mass (9 × 5 mm). **E.** Tumor after excision: tumor mass — yellow arrow, atrial wall — purple arrow. **F.** CT one week after surgery (orange arrow — RA)

Abbreviations: 18F-FDG PET-CT, positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose integrated with computed tomography; CT, computed tomography; LV, left ventricle; RA, right atrium

was initiated. Radiotherapy was considered; however, due to the massive RA wall infiltration seen on cardiac CT, it was considered impossible to safely deliver sufficient RT dose considering the risk of atrial wall perforation. Given the gradually increasing fatigue and progressing RA obstruction observed on echocardiography (Supplementary material, *Videos S4, S5*), a radical surgical resection was performed (Figure 1E–F; Supplementary material, *Video S6*). A histopathological examination confirmed metastatic melanoma with inflammatory cell infiltration and necrosis inside the tumor. At a four-week follow-up, the patient presented with a significant reduction in fatigue

without surgical complications. An echocardiographic study showed moderate tricuspid regurgitation with normal ejection fraction and matched postoperative CT and echocardiography regarding the RA.

Considering the prolonged survival enabled by advanced systemic therapies [2] and advances in imaging techniques [3], the incidence of atypical-location metastases will probably increase, including cardiac metastases of melanoma that qualify for surgical intervention [5]. This change in the metastatic landscape calls for development of effective, standardized treatment for these patients.

Supplementary material

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

Article information

Conflict of interest: None declared.

Funding: None.

REFERENCES

1. Rahib L, Wehner MR, Matrisian LM, et al. Estimated projection of US cancer incidence and death to 2040. JAMA Netw Open. 2021; 4(4): e214708, doi: 10.1001/jamanetworkopen.2021.4708, indexed in Pubmed: 33825840.
2. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med. 2017; 377(14): 1345–1356, doi: 10.1056/NEJMoa1709684, indexed in Pubmed: 28889792.
3. Zitzelsberger T, Eigentler TK, Krumm P, et al. Imaging characteristics of cardiac metastases in patients with malignant melanoma. Cancer Imaging. 2017; 17(1): 19, doi: 10.1186/s40644-017-0122-8, indexed in Pubmed: 28666473.
4. Puślecki M, Stefaniak S, Katarzyński S, et al. AngioVac: The first in Poland percutaneous solid thrombus aspiration from the right atrium. Kardiol Pol. 2022; 80(1): 103–104, doi: 10.33963/KP.a2021.0128, indexed in Pubmed: 34643258.
5. Noel A, Toquet C, Dewilde J. Prolonged survival after surgery for cardiac metastasis from malignant melanoma. J Cardiol Cases. 2014; 10(4): 150–152, doi: 10.1016/j.jccase.2014.06.012, indexed in Pubmed: 30534229.

Misleading transition: How His-bundle pacing imitated left bundle branch pacing

Maciej Fularz[1], Przemysław Mitkowski[2]

[1]Department of Cardiology, University of Zielona Gora, Zielona Góra, Poland
[2]1st Department of Cardiology, Poznan University of Medical Sciences, Poznań, Poland

Correspondence to:
Maciej Fularz, MD,
Department of Cardiology,
University of Zielona Gora,
Zyty 28, 65–046 Zielona Góra,
Poland,
phone: +48 68 32 96 381,
e-mail: m.fularz@cm.uz.zgora.pl

DOI: 10.33963/v.kp.98208

Received:
July 19, 2023

Accepted:
November 12, 2023

Early publication date:
December 7, 2023

Transitions of the paced QRS complex are pivotal in confirming conduction system pacing. Non-selective capture is usually observed at higher pacing output. A decrease in pulse amplitude could lead to selective capture of either the myocardium or conduction system. Identifying this phenomenon in most cases of His-bundle pacing (HBP) is relatively simple. Selective HBP usually provides QRS complexes identical to the intrinsic rhythm. Myocardial-only capture in the para-Hisian site produces broader QRS with left bundle branch block morphology. Appropriate diagnosis of transitions in left bundle branch pacing (LBBP) may be more challenging as differences between distinct modalities could be subtle. Jastrzębski et al. [1] provided useful criteria. During transition to selective LBBP, the V6–V1 interpeak interval increases due to loss of myocardial capture and, in consequence, more delayed right ventricle activation, while R-wave peak time in lead V6 remains unchanged. During transition to myocardial capture, R-wave peak time in lead V6 increases because left ventricle activation is less rapid. An isoelectric interval may also be useful as it occurs during selective HBP and selective LBBP [2].

An 84-year-old female patient with permanent atrial fibrillation and bradycardia was qualified for implantation of a single-chamber pacemaker. The intrinsic QRS complex was narrow. The lead was positioned in the basal septum to perform LBBP. An intraprocedural transition of paced QRS complex was demonstrated and identified as a transition from non-selective to selective LBBP (Figure 1A). Echocardiography confirmed that the lead was deployed deep in the basal septum (Figure 1B). The bipolar electrical parameters on the day after implantation were: R-wave 2.8–4.0 mV, pacing threshold 0.5 V × 0.4 ms, and impedance 552 ohms. Postprocedural chest radiograms are shown in Supplementary material, *Figure S1*. During a follow-up outpatient visit, a gradual output decrease test was performed. Surprisingly, an additional transition was found. In the first step, non-selective capture transformed to selective HBP and after a further decrease in pulse amplitude, selective HBP with right bundle branch block (RBBB) occurred (Figure 1C).

Transition to selective HBP was absent during the procedure probably due to temporarily equal capture thresholds of the myocardium and right bundle branch fibers. In consequence, a direct transition from non-selective capture to QRS complex with RBBB pattern occurred, and it was initially diagnosed as selective LBBP. Later demonstration of transition to selective HBP during the control visit revealed that the paced QRS complex with RBBB morphology was actually selective HBP with RBBB. Reachability of this type of capture could be explained by the longitudinal dissociation of His-bundle [3, 4]. According to this theory, fibers predestined to form right and left bundle branches are isolated from each other within His-bundle. Hence, their capture thresholds may differ, and selective recruitment of left bundle branch fibers inside His-bundle is achievable. The final diagnosis of HBP was also supported by a potential to QRS complex interval of 40 ms (Figure 1D) and relatively low R-wave sensing.

The three main lessons learned from the presented case are (1) His-bundle can be captured in deep septum [5], which may result in terminal R-wave during non-selective capture

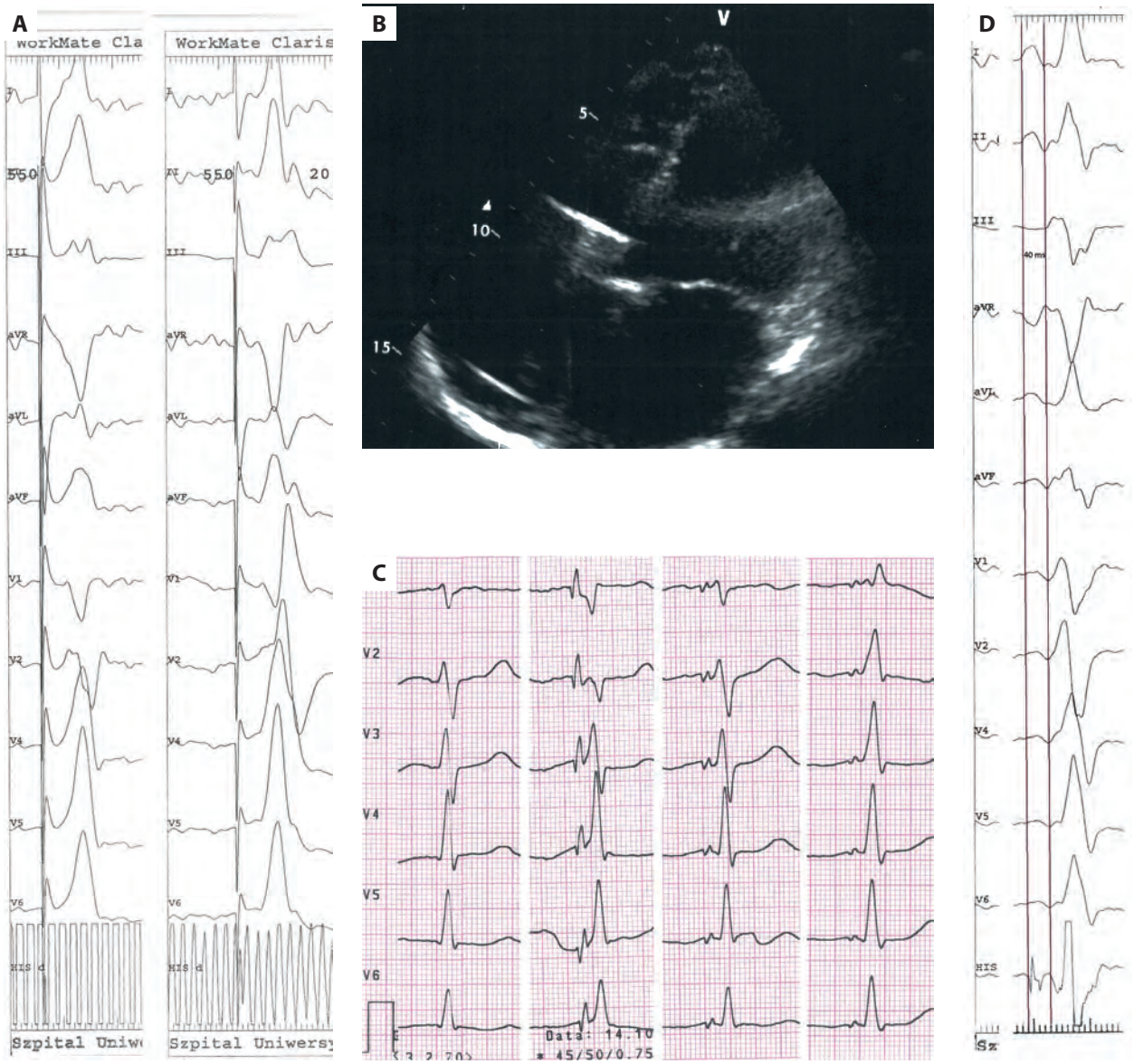


Figure 1. A. Intraprocedural transition initially diagnosed as transition to selective left bundle branch capture. Note the manifestation of the right bundle branch block pattern (terminal R-wave in lead V1, terminal S-wave in lead I) and the presence of an isoelectric interval after the pacing spike (most visible in leads V4–V6) during selective capture, while R-wave peak time in lead V6 was constant at 80 ms. **B.** Echocardiographic image shows the deep position of the lead in the basal interventricular septum. **C.** Native QRS complex (first on the left) and transitions of paced QRS morphology from non-selective capture with tiny terminal R-wave (second from the left, output 2 V × 0.4 ms) to selective His-bundle pacing (third from the left, output 0.75 V × 0.4 ms) and finally to selective His-bundle capture with right bundle branch block (fourth from the left, output 0.5 V × 0.4 ms) during the gradual decrease of pulse amplitude (precordial leads are shown, sweep speed 50 mm/s). The second and the fourth QRS complexes correspond with the paced QRS complexes presented in panel A. **D.** Intraprocedural recording of conduction system potential (at the bottom)

due to a left-sided myocardial component, resembling non-selective LBBP; (2) Left bundle branch fibers may be selectively captured inside the distal His-bundle, which may imitate selective LBBP; (3) Some transitions may not be demonstrable due to temporarily equal capture thresholds of two structures and may appear later.

Supplementary material

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

Article information

Conflict of interest: None declared.

Funding: None.

REFERENCES

1. Jastrzębski M, Burri H, Kiełbasa G, et al. The V6-V1 interpeak interval: a novel criterion for the diagnosis of left bundle branch capture. Europace. 2022; 24(1): 40–47, doi: 10.1093/europace/euab164, indexed in Pubmed: 34255038.
2. Wu H, Jiang L, Shen J. Recording an isoelectric interval as an endpoint of left bundle branch pacing with continuous paced intracardiac electrogram monitoring. Kardiol Pol. 2022; 80(6): 664–671, doi: 10.33963/KP.a2022.0094, indexed in Pubmed: 35380007.
3. Jastrzebski M, Kukla P, Czarnecka D. His bundle capture proximal to the site of bundle branch block: A novel pitfall of the para-Hisian pacing maneuver. HeartRhythm Case Rep. 2018; 4(1): 22–25, doi: 10.1016/j.hrcr.2017.09.002, indexed in Pubmed: 29379721.
4. Teng AE, Massoud L, Ajijola OA. Physiological mechanisms of QRS narrowing in bundle branch block patients undergoing permanent His bundle pacing. J Electrocardiol. 2016; 49(5): 644–648, doi: 10.1016/j.jelectrocard.2016.07.013, indexed in Pubmed: 27485351.
5. Vijayaraman P. Deep septal, distal His bundle pacing for cardiac resynchronization therapy. HeartRhythm Case Rep. 2020; 6(10): 791–793, doi: 10.1016/j.hrcr.2020.07.024, indexed in Pubmed: 33101957.

Unroofed coronary sinus: A case vignette emphasizing the role of three-dimensional transesophageal echocardiogram

Mehmet Rasih Sonsoz, Duygu Inan

Department of Cardiology, Basaksehir Cam & Sakura City Hospital, Istanbul, Turkey

Correspondence to:
Mehmet Rasih Sonsoz, MD, Department of Cardiology, Basaksehir Cam & Sakura City Hospital,
Basaksehir Olimpiyat Boulevard, 34480, Istanbul, Turkey,
phone: +90 212 909 60 00 / 213 11,
e-mail: mrsonsoz@gmail.com

DOI: 10.33963/v.kp.98404

Received:
October 10, 2023

Accepted:
December 4, 2023

Early publication date:
December 7, 2023

A 42-year-old man was admitted to our outpatient cardiac center for chronic exertional dyspnea. His medical history was unremarkable. Cardiovascular examination revealed a 2/6 systolic murmur at the lower left sternal border. An electrocardiogram showed normal sinus rhythm. A transthoracic echocardiogram showed normal biventricular systolic functions, mild tricuspid regurgitation, mildly enlarged right atrium (area: 21.4 cm^2) and right ventricle (basal diameter: 4.5 cm). Contrast echocardiography from the right antecubital vein showed a right-to-left transition of bubbles in the first three cycles (Figure 1A–B; Supplementary material, *Video S1*). Transesophageal echocardiography demonstrated marked turbulent flow in the right atrium from the coronary sinus (CS). There was a defect on the roof of the CS in the left atrium (1.5 × 0.7 cm) (Figure 1C–D; Supplementary material, *Videos S2–S6*). The patient was referred for surgical repair.

This case illustrates the challenging aspects of defining the dilatation of the right

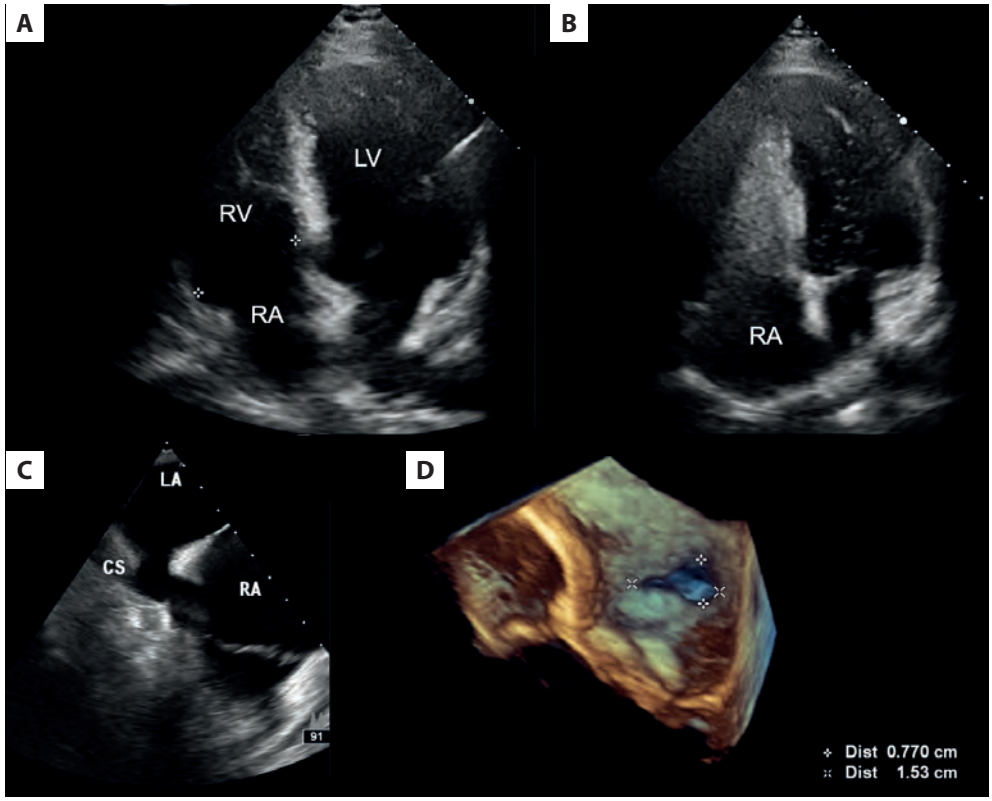


Figure 1. A. Apical four-chamber view demonstrates the mildly dilated right heart chambers. **B.** Contrast echocardiography from the right antecubital vein showed a right-to-left transition of bubbles in the first three cycles. **C.** Transesophageal echocardiography revealed a defect between the left atrium and the coronary sinus. **D.** Three-dimensional echocardiography provided visualization of the pear-shaped defect

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

heart chambers. Meticulous examination of the interatrial septum is crucial in finding a left-to-right shunt when the right ventricle is dilated. Unroofed coronary sinus is a rare congenital cardiac anomaly, characterized by a partially deficient or completely absent wall of the CS within the left atrium leading to a left-to-right shunt [1]. Because it can accompany a secundum atrial septal defect, it is crucial to fully delineate the anatomy before percutaneous intervention [2]. Computed tomography scans may not visualize the exact dimensions of the opening of the unroofed coronary sinus but additional abnormalities (i.e., persistent left superior vena cava or partial pulmonary venous return abnormality) can be delineated in detail [3]. Classically, patients with large unroofed coronary sinus are surgically corrected although a transcatheter therapeutic approach to the coronary sinus could be feasible [3–5]. Our Heart Team decided on the surgical correction due to the local expertise on congenital heart disease. The thorough assessment of the interatrial septum *via* a three-dimensional echocardiogram had a pivotal role in the diagnosis and management of the patient.

Supplementary material

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

Article information

Conflict of interest: None declared.

Funding: None.

REFERENCES

1. Silvestry FE, Cohen MS, Armsby LB, et al. Guidelines for the echocardiographic assessment of atrial septum and patent foramen ovale: from the American Society of Echocardiography and Society for Cardiac Angiography and Interventions. J Am Soc Echocardiogr. 2015; 28(8): 910–958, doi: 10.1016/j.echo.2015.05.015, indexed in Pubmed: 26239900.
2. Karavelioglu Y, Cagli K, Yetim M, et al. Missed unroofed coronary sinus. Echocardiography. 2019; 36(3): 613–614, doi: 10.1111/echo.14274, indexed in Pubmed: 30735270.
3. Cinteză EE, Filip C, Duică G, et al. Unroofed coronary sinus: update on diagnosis and treatment. Rom J Morphol Embryol. 2019; 60(1): 33–40, indexed in Pubmed: 31263825.
4. Wang JK, Chen SJ, Hsu JY, et al. Midterm follow-up results of transcatheter treatment in patients with unroofed coronary sinus. Catheter Cardiovasc Interv. 2014; 83(2): 243–249, doi: 10.1002/ccd.25185, indexed in Pubmed: 24038929.
5. Konigstein M. Coronary sinus Reducer: An adjunctive tool for the treatment of patients with chronic total occlusion of the right coronary artery. Kardiol Pol. 2022; 80(1): 1–2, doi: 10.33963/KP.a2022.0001, indexed in Pubmed: 34981825.

Atrial pacemaker implantation in an adult patient with Fontan circulation and chronotropic insufficiency

Krzysztof Boczar[1], Andrzej Ząbek[1, 2], Lidia Tomkiewicz-Pająk[2, 3], Mateusz Ulman[1], Jacek Lelakowski[1, 2]

[1]Department of Electrocardiology, The John Paul II Hospital, Kraków, Poland
[2]Institute of Cardiology, Jagiellonian University Medical College, Kraków, Poland
[3]John Paul II Hospital, The Adult Congenital Heart Disease Centre at the Jagiellonian University Medical College, Kraków, Poland

Correspondence to:
Krzysztof Boczar MD, PhD, Department of Electrocardiology, The John Paul II Hospital, Prądnicka 80, 31–202 Kraków, Poland,
phone: + 48 12 614 22 77,
e-mail: krzysiek.boczar@gmail.com

DOI: 10.33963/v.kp.98423

Received:
October 20, 2023

Accepted:
December 6, 2023

Early publication date:
December 21, 2023

A 22-year-old female with congenital heart disease was referred to our hospital with recurrent syncope and symptoms of worsening exercise tolerance. She had been born with right ventricular hypoplasia, an atrial septal defect, and a ventricular septal defect. The patient had undergone pulmonary artery banding, hemi-Fontan operation at one year of age, and fenestrated Fontan completion two years later.

Electrocardiographic (ECG) monitoring showed episodes of sinus bradycardia with normal atrioventricular conduction (Figure 1A). A spiroergometric test revealed an insufficient chronotropic response with the presence of severe dizziness, hypotension, and pre-syncope during exercise [1]. Considering the experience of our center in implanting pacemakers in patients with Fontan circulation, a collective decision was made to qualify the patient for an intravascular pacemaker [2]. Contrary to a previously described case, due to the lack of atrioventricular conduction disturbances, a plan was set to perform an intraprocedural assessment of fast atrioventricular conduction to exclude any distal conduction disturbances in

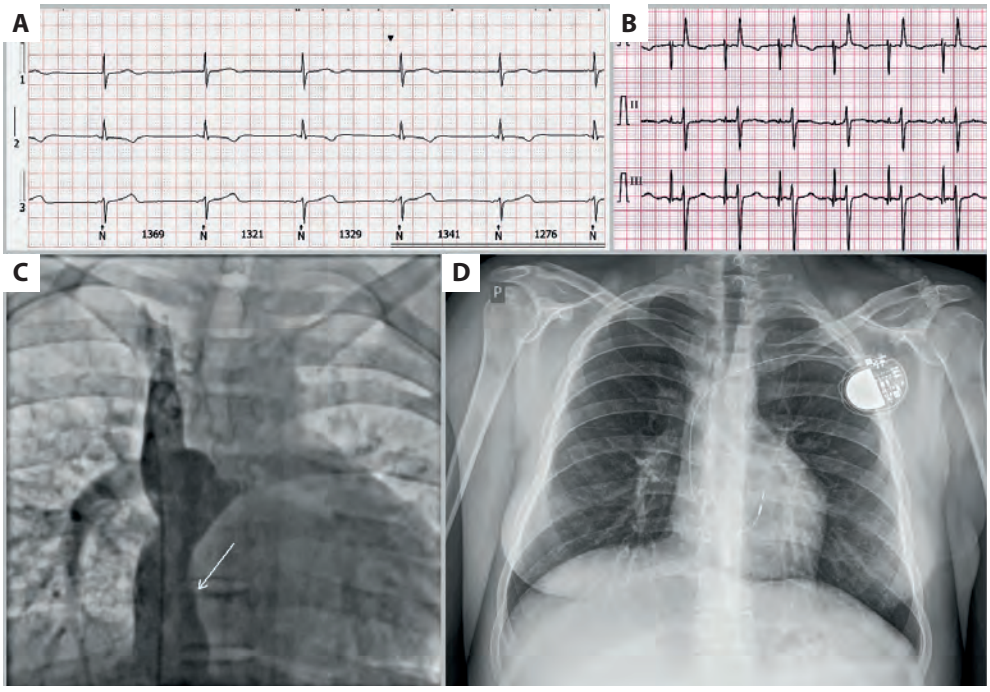


Figure 1. A. Electrocardiogram (ECG) monitoring with episodes of sinus bradycardia with normal atrioventricular conduction. **B.** ECG registration showing AAI pacing. **C.** Fluoroscopy of heart catheterization with detailed hemodynamic and angiographic evaluation of Fontan circulation. The arrow indicates fenestration between the Fontan circulation and the atrium. **D.** The chest radiograph after the procedure, showing the correct position of the atrial pacing lead

the His–Purkinje system. The aim was to avoid implantation of a ventricular pacing lead, which reduces the complexity of the procedure and minimizes the risk of complications associated with the implantation of a dual-chamber pacing system.

Pre-procedural planning included heart catheterization with detailed hemodynamic and angiographic evaluation (Figure 1C) and ECG-gated cardiac contrast-enhanced computed tomography. Pacemaker implantation was carried out under light analgosedation in a hybrid operating room. Venous access was gained by puncture of the left subclavian vein. Fenestration in the Fontan baffle was cannulated with the Medtronic Attain Command™ delivery system (Medtronic, Minneapolis, MN, US). The lumenless Medtronic SelectSecure™ 3830 lead was placed in the right atrium via the Medtronic C315HIS Delivery Catheter. We obtained the correct sensing and pacing parameters. Atrial pacing test showed normal atrioventricular conduction up to 150 heartbeats per minute well tolerated by the patient.

The procedure and postoperative period were uneventful. A chest radiograph showed the correct position of the atrial lead (Figure 1D). Pacing parameters were excellent, and appropriate pacemaker function was confirmed on ECG monitoring (Figure 1B). Echocardiography showed no intracardiac thrombi or pericardial effusion. Treatment with warfarin was introduced for thromboembolic prevention [3]. The pacing program was set to AAIR 60/min. At the 3-month follow-up visit, the patient reported an improvement in exercise tolerance, resolution of dizziness, and pre-syncope symptoms. Echocardiography showed normal blood flow through the fenestration tunnel with no intracardiac thrombi or pericardial effusion. The spiroergometric test showed improvement in exercise tolerance, without previously observed symptoms of severe dizziness, hypotension, and pre-syncope. Pacing parameters remained within the normal range (sensing: >5.6 mV, impedance: 405 oms, and pacing threshold: 1 V/0.4 ms). The percentage of atrial pacing was 72%. There were no arrhythmic events recorded in the pacemaker's memory.

Our moderate experience shows that transvenous pacemaker implantation can successfully and safely restore chronotropic competence in patients with hemi-Fontan circulation with subsequent fenestration. However, we still need large, prospective, and multicenter studies to objectively assess the effectiveness and safety of this pacing method in this group of patients.

Article information

Conflict of interest: None declared.

Funding: None.

REFERENCES

1. Okólska M, Skubera M, Matusik P, et al. Chronotropic incompetence causes multiple organ complications in adults after the Fontan procedure. Kardiol Pol. 2021; 79(4): 410–417, doi: 10.33963/KP.15853, indexed in Pubmed: 33687864.
2. Boczar K, Ząbek A, Tomkiewicz-Pająk L, et al. Atrioventricular sequential pacemaker implantation in an adult patient with a Fontan circulation. Kardiol Pol. 2022; 80(4): 497–498, doi: 10.33963/KP.a2022.0069, indexed in Pubmed: 35258093.
3. Umamaheshwar KL, Singh AS, Sivakumar K. Endocardial transvenous pacing in patients with surgically palliated univentricular hearts: A review on different techniques, problems and management. Indian Pacing Electrophysiol J. 2019; 19(1): 15–22, doi: 10.1016/j.ipej.2018.11.013, indexed in Pubmed: 30508590.

Catheter-directed therapy for treatment of acute pulmonary embolism in a teenage patient: The role of close cooperation between the Pulmonary Embolism Response Team and pediatric physicians

Jakub Stępniewski[1–3], Wojciech Magoń[1–3], Marcin Waligóra[1–3], Kamil Jonas[1–3], Łukasz Wilczek[2], Beata Zauska-Pitak[4], Sebastian Góreczny[4], Grzegorz Kopeć[1, 2]

[1]Pulmonary Circulation Centre, Institute od Cardiology, Jagiellonian University Medical College, Kraków, Poland
[2]Department of Cardiac and Vascular Diseases, John Paul II Hospital, Kraków, Poland
[3]Department of Medical Education, Jagiellonian University Medical College, Kraków, Poland
[4]Department of Pediatric Cardiology, University Children's Hospital, Jagiellonian University Medical College, Kraków, Poland

Correspondence to:
Grzegorz Kopeć MD, PhD, Department of Cardiac and Vascular Diseases, John Paul II Hospital, Prądnicka 80, 31–202 Kraków, Poland,
phone: +48 500 099 734,
fax: +48 12 614 33 32,
e-mail: grzegorzkrakow1@gmail.com

DOI: 10.33963/v.kp.97954

Received:
March 29, 2023

Accepted:
October 24, 2023

Early publication date:
November 15, 2023

Acute pulmonary embolism (PE) occurs relatively rarely in adolescence. According to the 2018 American Society of Hematology guidelines, pulmonary arteries (PA) reperfusion treatment should be considered in children when hemodynamic compromise is present despite anticoagulation [1]. Catheter-directed therapies (CDT) have emerged as valuable reperfusion modalities [2, 3]; however, evidence of their utility in the pediatric population is scarce. Pulmonary Embolism Response Teams (PERT) have been created to support decision-making in severe and complex PE scenarios [4, 5].

We report a case of a 16-year-old girl referred to our PERT from a pediatric cardiology department due to intermediate-high-risk PE. She had a history of combined (etonogestrel and ethinylestradiol) oral contraceptives and antipsychotic use. Her symptoms occurred suddenly with syncope, dyspnea, and chest discomfort. Once computed angiotomography showed bilateral, proximal PA emboli, intravenous unfractionated heparin was started and continued at our tertiary pediatric cardiology and intensive care unit. Despite anticoagulation with activated partial thromboplastin time maintained between 46–70 s, symptoms and signs of cardiorespiratory compromise persisted over 24 hours. Her systolic blood pressure was 95 mm Hg, and her heart rate (HR) was 120/min. She required an oxygen supply of 4 l/min to maintain arterial oxygen saturation ($SatO_2$) over 90%. Echocardiography revealed persistent dilation and impairment of the right ventricle (RV). No signs of chronic pulmonary hypertension were present. Troponin levels rose from 0.02 to 0.064 ng/ml (reference range <0.014 ng/ml) and the N-terminal pro-B-type natriuretic peptide from 2224 to 4480 pg/ml (reference range <206 pg/ml).

As no significant improvement could be observed, the PERT considered her condition potentially life-threatening and decided to pursue CDT in an off-label fashion for the pediatric population. After receiving her and her parents' informed consent, urgent percutaneous embolectomy with the Penumbra Lightning 12 system was performed, which evacuated a substantial thrombus and improved the mean PA pressure (mPAP) measured invasively from 34 to 32 mm Hg and the cardiac index (CI) from 1.48 to 1.58 l/min/m^2. To optimize the effect of embolectomy, we decided to supplement it with bilateral low-dose-local-thrombolysis with a cumulative alteplase dose of 20 mg delivered over 10 hours. The rationale for such an approach stemmed from reported significant distress experienced by the patient (chest discomfort) during manipulations with the embolectomy catheter, which precluded complete thrombus removal and achievement of intended clinical and hemodynamic efficacy. This strategy resulted in a further mPAP reduction to 21 mm Hg, CI increase to

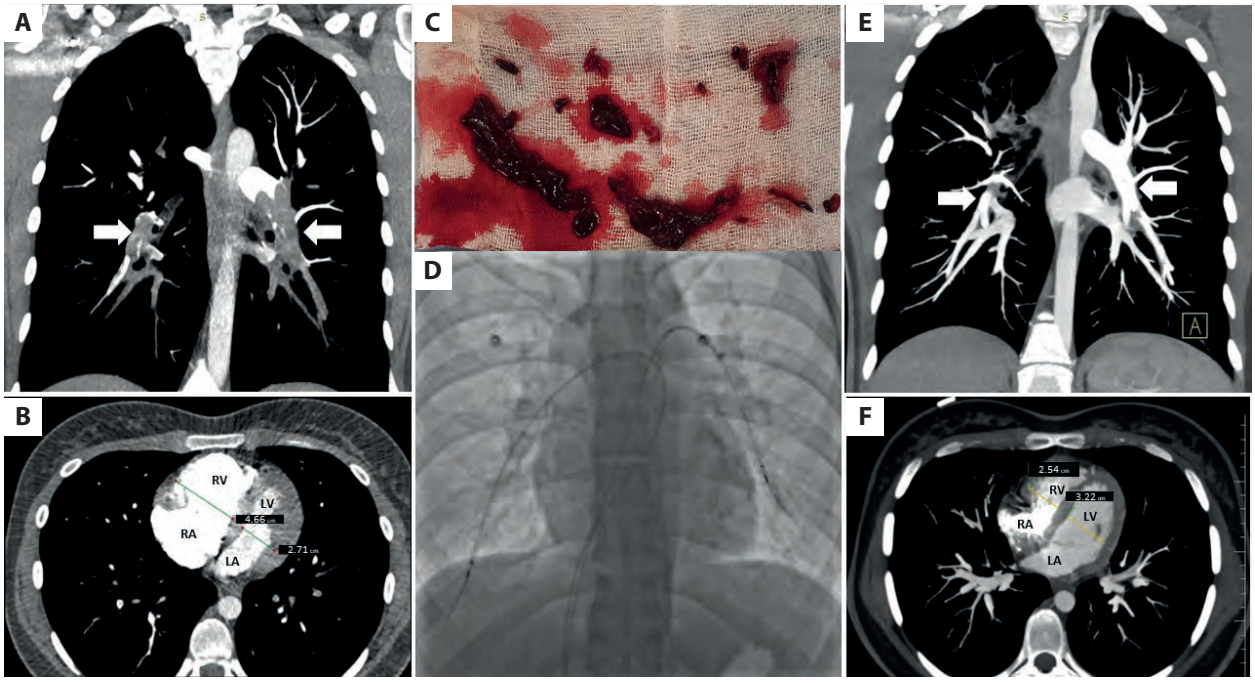


Figure 1. A. Angio CT of a 16-year-old girl with sudden syncope, dyspnea, and chest discomfort confirming the diagnosis of pulmonary embolism with massive proximal clots in both PAs (arrows). **B.** Angio CT showing dilation of the RV and the RV-to-LV ratio of 1.7; no thickening of the RV wall is present. **C.** Clots evacuated from PAs with the PENUMBRA Lightning 12 system during catheter-directed embolectomy procedure based on the Pulmonary Embolism Response Team's decision as no significant clinical improvement could be reached despite therapeutic anticoagulation, which led to a mPAP reduction from 34 to 32 mm Hg and CI improvement from 1.48 to 1.58 l/min/m^2 as assessed by right heart catheterization. **D.** Fluoroscopy showing infusion catheters placed within remaining clots in both PAs for low-dose catheter-directed thrombolysis, with a total dose of 20 mg delivered during 10 hours and resulting in a further mPAP reduction to 21 mm Hg and CI increase to 2.38 l/min/m^2. **E.** Angio CT presenting treatment results with a reduction of clot burden in both PAs (arrows) and improvement in the RV/LV ratio to 0.78 (**F**)

Abbreviations: Angio CT, computed angiotomography; CI, cardiac index; LA, left atrium; LV, left ventricle; mPAP, mean pulmonary artery pressure; PA, pulmonary artery; RA, right atrium; RV, right ventricle

2.38 l/min/m^2, improvement in symptoms and vital signs, and reduction in N-terminal pro-B-type natriuretic peptide levels to 1608 pg/ml.

The patient was ambulated the next day and transferred back to the pediatric cardiology clinic. Rivaroxaban was started on the 1st post-procedural day. Her subsequent hospital stay was uneventful, and she was discharged home without exercise limitation.

This case showed that CDT use in a teenage girl was safe and resulted in a rapid clinical improvement. It was, to the best of our knowledge, the first successful use of the PENUMBRA Lightning 12 system in a pediatric patient. Promoting partnerships between pediatric physicians and PERTs may bring benefit to PE management in this population.

Article information

Conflict of interest: None declared.

Funding: This article was supported by the science fund of the Saint John Paul II Hospital, Kraków, Poland (no. FN/17/2020 to JS)

REFERENCES

1. Monagle P, Cuello CA, Augustine C, et al. American Society of Hematology 2018 Guidelines for management of venous thromboembolism: treatment of pediatric venous thromboembolism. Blood Adv. 2018; 2(22): 3292–3316, doi: 10.1182/bloodadvances.2018024786, indexed in Pubmed: 30482766.
2. Stępniewski J, Kopeć G, Musiałek P, et al. Hemodynamic effects of ultrasound-assisted, catheter-directed, very low-dose, short-time duration thrombolysis in acute intermediate-high risk pulmonary embolism (from the EKOS-PL study). Am J Cardiol. 2021; 141: 133–139, doi: 10.1016/j.amjcard.2020.11.004, indexed in Pubmed: 33220318.
3. Stępniewski J, Magoń W, Podolec P, et al. The PENUMBRA Lightning 12 system for treatment of acute intermediate-high pulmonary embolism. Initial experience in Pulmonary Circulation Center Krakow, Poland. Postepy Kardiol Interwencyjnej. 2022; 18(3): 314–316, doi: 10.5114/aic.2022.120974, indexed in Pubmed: 36751285.
4. Araszkiewicz A, Kurzyna M, Kopeć G, et al. Pulmonary embolism response team: A multidisciplinary approach to pulmonary embolism treatment. Polish PERT Initiative Report. Kardiol Pol. 2021; 79(12): 1311–1319, doi: 10.33963/KP.a2021.0130, indexed in Pubmed: 34643260.
5. Kopeć G, Araszkiewicz A, Kurzyna M, et al. Role of catheter-directed therapies in the treatment of acute pulmonary embolism. Expert opinion of the Polish PERT Initiative, Working Group on Pulmonary Circulation, Association of Cardiovascular Interventions, and Association of Intensive Cardiac Care of the Polish Cardiac Society. Kardiol Pol. 2023; 81(4): 423–440, doi: 10.33963/KP.a2023.0075, indexed in Pubmed: 36951599.

Septal branch in heart failure: Significant implications of an insignificant branch

Marin Pavlov[1, 2], Irzal Hadžibegović[1], Nikola Pavlović[1], Šime Manola[1]

[1]Department of Cardiology, Dubrava University Hospital, Zagreb, Croatia
[2]University North, Koprivnica, Croatia

Correspondence to:
Marin Pavlov, MD, PhD, Department of Cardiology, Dubrava University Hospital, Avenija Gojka Šuška 6, 10000 Zagreb, Croatia, phone: +38 59 923 602 86, e-mail: mpavlov@kbd.hr

DOI: 10.33963/KP.a2023.0169

Received:
June 19, 2023

Accepted:
July 30, 2023

Early publication date:
August 4, 2023

A 71-year-old male with a history of stroke and diabetes was admitted for left-sided heart failure and non-ST-segment elevation myocardial infarction. Echocardiography revealed a dilated left ventricle with reduced ejection fraction (20%), inferobasal and apical scar, and anteroseptal akinesia with preserved myocardial wall thickness. Later was confirmed on a single-photon emission computed tomography. Coronary angiography showed chronic total occlusion of the right coronary artery, subocclusive non-calcified stenosis of the ostial/proximal and mid segments of the left anterior descending (LAD) artery and significant circumflex artery (Cx) stenosis (Figure 1). The Heart Team opted for percutaneous coronary intervention (PCI) with the PulseCath iVAC 2L support. This was achieved through the left femoral approach while PCI was performed through right femoral access. Following predilaton, the Cx was stented with an Orsiro 2.75/26 mm (Biotronik) drug-eluting stent (DES). Subsequently, after predilation, the 2.75/26 mm (Biotronik) DES and Ultimaster 3.0/30 mm (Terumo) DES were implanted in the left main and the LAD, followed by the proximal optimization technique (POT)/ /kissing/POT sequence. A good result was achieved at the left main and LAD level; however, occlusion of a strong first septal branch (SB) occurred. The newly developed right bundle branch block progressed to a complete atrioventricular (AV) block, requiring temporary transvenous electrostimulation.

Negotiating the SB proved to be challenging but was eventually achieved with a Fielder XTA (Asahi) wire over the Sasuke dual lumen microcatheter (Asahi). Recanalization was achieved with semi-compliant 1.5/10 mm balloon dilatation, which was immediately followed by resolution of conduction abnormalities. The POT proximal to the SB led to SB occlusion, but the procedure was finished after additional SB balloon dilatation (Supplementary material, *Video S1*). The further course was uneventful.

During LAD PCI, SBs are usually neglected [1]. Preferable take-off angle, large collateral network, and small calibers render SB intervention unnecessary. Nevertheless, clinically silent and structurally insignificant SB occlusions do occur [2]. Conversely, experiences from alcohol septal ablation of the first SB suggest that as many as 9%–20% of patients need pacemaker implantation due to a new heart block [2]. This is because both the right bundle branch and the left anterior fascicle of the heart conduction system are supplied exclusively by the first SB [3]. In 2019, Nojima et al. [3] reported a case with a complete AV block developing 3 days following LAD PCI, which resulted in occlusion of the first SB. In a literature review, the authors found only 8 similar cases, rendering such events reasonably rare. Similarly, the SB was reopened with 1.5 mm semi-compliant balloon dilatation over a polymer jacket wire; wiring was achieved with a microcatheter. Negotiation of the SB proved much more challenging in our case. In such a scenario, a double-lumen catheter may provide a crucial aid in achieving optimal angulation for the secondary wire.

Preserving both adequate AV conduction and avoiding a complete bundle branch block in our patient were of vital interest to "do no harm". Otherwise, resynchronization therapy would have to be considered. This was avoided by successful recanalization of

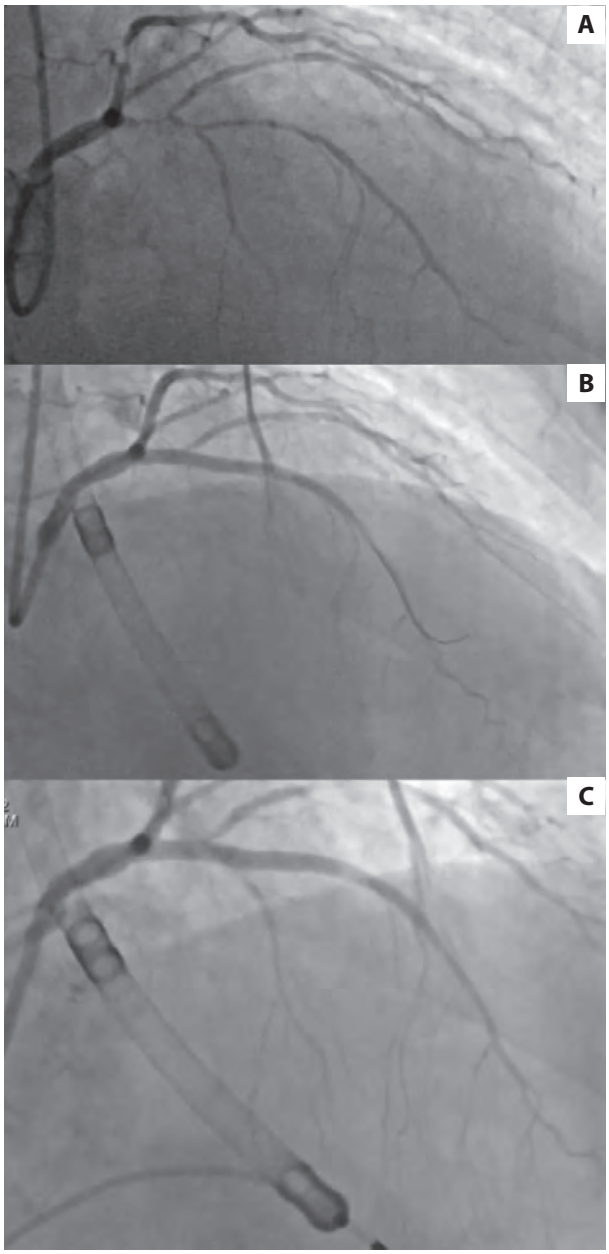


Figure 1. Right anterior oblique view of the left main and left anterior descending coronary arteries. **A**. Initial finding. **B.** After stent delivery; optimal results at the level of the left main and proximal left anterior descending artery; however, occlusion of the septal branch occurred. **C.** After septal branch recanalization

the presumably "insignificant" LAD branch. Strategies to prevent SB occlusion during LAD PCI in heart failure patients should be implemented.

Supplementary material

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

Article information

Conflict of interest: None declared.

Funding: None.

REFERENCES

1. Dorfman TA, Resar JR. Thrombotic occlusion of a large septal perforator presenting as ST-segment elevation in V1-V2 and treated with aspiration thrombectomy: a brief review of the literature. J Invasive Cardiol. 2011; 23(1): E255–E259, indexed in Pubmed: 21183777.
2. Gao F, Khalid U. Inadvertent septal ablation during percutaneous coronary intervention. Cureus. 2021; 13(11): e19227, doi: 10.7759/cureus.19227, indexed in Pubmed: 34877205.
3. Zimetbaum PJ, Josephson ME. Use of the electrocardiogram in acute myocardial infarction. N Engl J Med. 2003; 348(10): 933–940, doi: 10.1056/NEJMra022700, indexed in Pubmed: 12621138.
4. Nojima Y, Ihara M, Adachi H, et al. Rescue percutaneous coronary intervention for a lethal "jailed" septal perforator branch to resolve delayed complete atrioventricular block. Int Heart J. 2019; 60(2): 457–461, doi: 10.1536/ihj.18-280, indexed in Pubmed: 30799381.

Revascularization technique with use of lithotripsy of intracranial calcified critical stenosis of the internal carotid artery

Paweł Latacz[1], Krzysztof Kwiecień[1], Marian Simka[2]

[1]Department of Vascular Surgery and Angiology, Brothers of Mercy St. John of God Hospital, Kraków, Poland
[2]Department of Anatomy, University of Opole, Opole, Poland

Correspondence to:
Paweł Latacz MD, PhD,
Department of Vascular Surgery and Angiology,
Brothers of Mercy St. John of God Hospital,
Trynitarska 11, 31–061 Kraków, Poland,
phone: +48 12 379 71 28,
e-mail: pawlat@me.com

DOI: 10.33963/v.kp.97960

Received:
August 29, 2023

Accepted:
October 24, 2023

Early publication date:
November 2, 2023

Intravascular lithotripsy (IL) is increasingly becoming a useful method for endovascular management of calcified plaques in different arterial territories (coronary, renal, mesenteric, extremity, and extracranial carotid arteries), especially, if such stenoses cannot be addressed using cutting balloons or transcatheter atherectomy devices [1–4]. This case report demonstrates a successful application of IL of a highly calcified lesion in the cavernous (C4) segment of the right internal carotid artery (ICA) in a 62-year-old symptomatic female patient presenting with transient ischemic attack and a 2-month history of right-hemisphere stroke. Computed tomography angiography (CTA) revealed 60% stenosis in the brachiocephalic trunk, 30% stenosis in the cervical (C1) segment, and a critically stenosed calcified cavernous (C4) segment of the right ICA. Since standard management of this lesion was associated with high risk of unsuccessful revascularization, which, in turn, could result in complete occlusion and life-threatening stroke, we decided to address it using IL.

The overall endovascular strategy was explained to the patient, and she gave informed consent. Catheter angiography demonstrated good inflow to the left cerebral hemisphere but no collateral inflow to the right side. On the right side, our findings were in line with CTA (Figure 1A). Firstly, a guidewire was navigated into the M1 segment of the middle cerebral artery. The stenosis in the C4 segment of ICA was predilated using balloons under the pressure of 8–16 atm. Such a pressure, which was much higher in comparison with standard angioplasty for intracranial lesions, was used because the target lesion was highly calcified. Then, we introduced a 3.5/12 mm Shockwave C^2 (Shockwave Medical, Santa Clara, CA, US) intravascular lithotripsy catheter (Figure 1B). At the level of calcified plaque, we inflated a balloon of this system under the pressure of 2–4 atm. and performed 2, then 4, and again 4 applications of sonic energy; then the lesion was dilated with the balloon under the pressure of 6–12 atm. Since the stenosis was recoiling (Figure 1C), we advanced an aspiration catheter up to the lesion, and through this catheter implanted a 3.5/12 mm Xience Sierra drug-eluting stent (Abbott, Chicago, IL, US) (Figure 1D). This stent is characterized by a higher radial force than typical stents used to address intracranial lesions. Still, there was a considerable risk of recoil, which could not be reopened if a standard radial force stent was used. Besides, this stent has a low profile, which facilitated its navigation to the intracranial part of the ICA. The final angiographic result of the procedure was good (residual stenosis <10%) with correct inflow to the arteries of the right hemisphere (Figure 1E). The postprocedural course (6 months) was uneventful. CTA performed 8 weeks after the procedure did not show re-stenosis (Figure 1F).

Although the procedure was successful, it should be noted that the first two applications of sonic energy were poorly tolerated by the patient; she experienced extremely high noise during lithotripsy. Therefore, further applications were performed under analgosedation. We demonstrated that intravascular lithotripsy of a highly calcified critical stenosis in the intracranial part of the ICA is feasible. However, for the time being, the safety profile of such procedures remains uncertain.

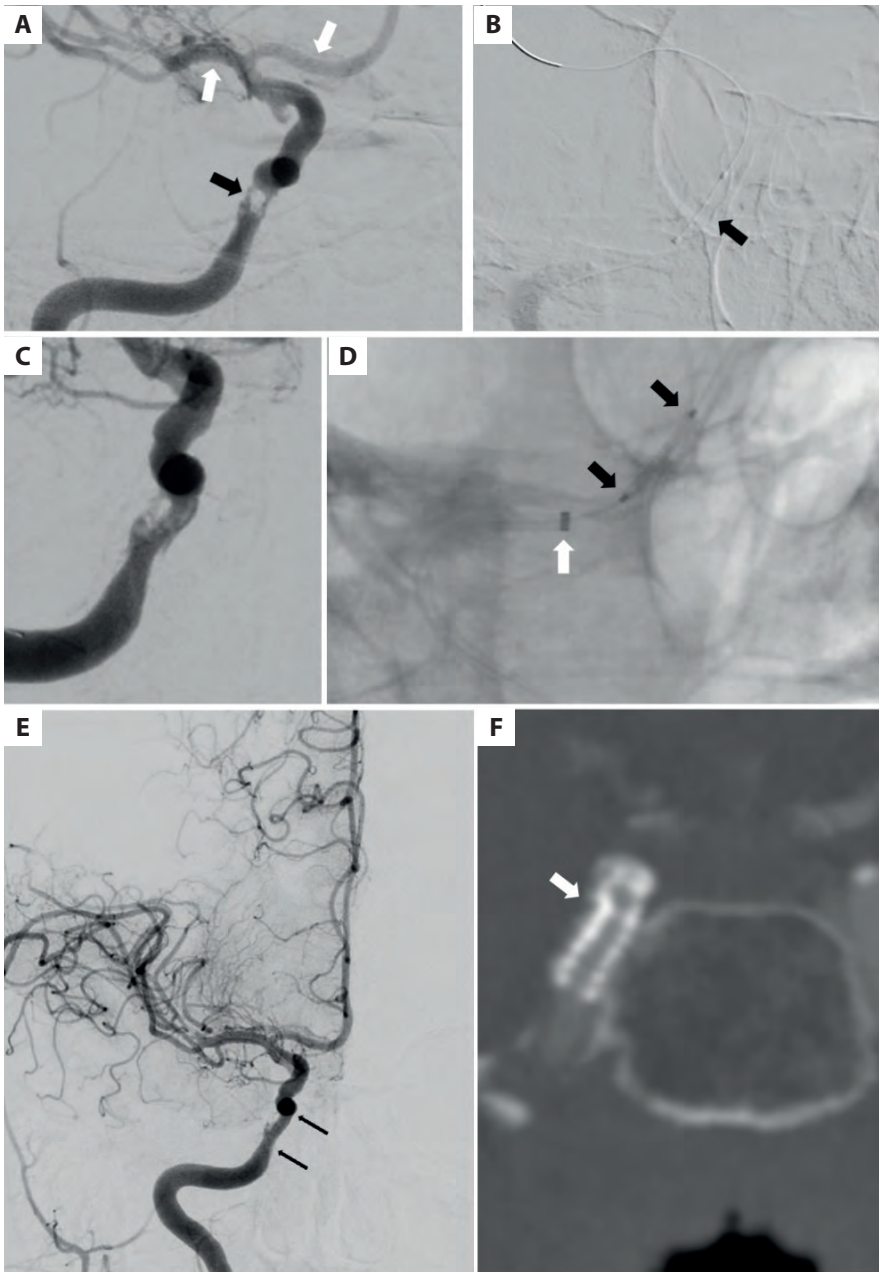


Figure 1. A. Angiography of the right internal carotid artery, critical calcified stenosis in the cavernous (C4) segment (black arrow); white arrows point to the middle and anterior cerebral arteries. **B.** Lithotripsy balloon at the level of the target lesion, black arrows show proximal and distal markers of the device. **C.** Control angiography after 5 minutes; recoil with visible dissection. **D.** Stent prepared for implantation, white arrow points to the end of aspiration catheter, black arrows point to the stent markers. **E.** Control angiography in the anteroposterior view after stent implantation; good result with minor residual stenosis and good inflow to the right anterior and middle cerebral arteries, yet without communication to the left cerebral hemisphere; arrows show implanted stent. **F.** Control computed tomography angiography, patent stent with minor residual stenosis and good inflow to the arteries of the right cerebral hemisphere

Article information

Conflict of interest: None declared.

Funding: None.

REFERENCES

1. Case BC, Yerasi C, Forrestal BJ, et al. Intravascular lithotripsy facilitated percutaneous endovascular intervention of the aortic arch: a single-center experience. Cardiovasc Revasc Med. 2020; 21(8): 1006–1015, doi: 10.1016/j.carrev.2020.04.029, indexed in Pubmed: 32386683.
2. Kang K, Wilson J. Intravascular lithotripsy of underexpanded and recoiled freshly implanted internal carotid stents. Cardiovasc Revasc Med. 2022; 40S: 200–204, doi: 10.1016/j.carrev.2022.02.003, indexed in Pubmed: 35232665.
3. Giannopoulos S, Speziale F, Vadalà G, et al. Intravascular lithotripsy for treatment of calcified lesions during carotid artery stenting. J Endovasc Ther. 2021; 28(1): 93–99, doi: 10.1177/1526602820954244, indexed in Pubmed: 32869718.
4. Misztal M, Trystuła M, Konieczyńska M, et al. Intravascular lithotripsy with peripheral Shockwave catheter — a breakthrough in calcified carotid artery stenosis treatment. Postepy Kardiol Interwencyjnej. 2020; 16(4): 491–494, doi: 10.5114/aic.2020.101778, indexed in Pubmed: 33598026.

Coumadin ridge: An echocardiographic trap

Bartłomiej Włochacz[1, 2], Agnieszka Jurek[1], Piotr Łyżwa[1], Marta Mielniczuk[1], Beata Uziębło-Życzkowska[1], Artur Maliborski[3], Paweł Krzesiński[1]

[1]Department of Cardiology and Internal Medicine, Military Institute of Medicine, National Research Institute, Warszawa, Poland
[2]Department of Anesthesia and Intensive Care, Military Institute of Medicine, National Research Institute, Hospital in Legionowo, Poland
[3]Medical Imaging Laboratory, Military Institute of Medicine, National Research Institute, Warszawa, Poland

Correspondence to:
Bartłomiej Włochacz, MD, Department of Anesthesia and Intensive Care, Military Institute of Medicine, National Research Institute, Hospital in Legionowo, Zegrzyńska 8, 05–119 Legionowo, Poland,
phone: +48 26 181 63 72,
e-mail: bwlochacz@wim.mil.pl

DOI: 10.33963/v.kp.96688

Received:
May 25, 2023

Accepted:
July 26, 2023

Early publication date:
August 10, 2023

A 63-year-old male, with no history of chronic conditions, was admitted to the Department of Cardiology for myocardial infarction. The patient reported chest discomfort. Physical examination revealed no significant abnormalities; the heart rate was regular at 62/min and blood pressure was 154/95 mm Hg. Electrocardiography showed anterior and inferior wall ischemia. We performed invasive coronary angiography and primary percutaneous coronary intervention on the left anterior descending artery followed by staged percutaneous coronary intervention on the circumflex artery on the next day. Laboratory test results showed elevated troponin T levels. Bedside echocardiography revealed segmental myocardial systolic dysfunction with reduced ejection fraction (Biplane Simpson method 35%), with no significant valvular disease. There was a longitudinal structure within the left atrium (Figure 1A). Echocardiography was then repeated in the echocardiography laboratory and showed the presence of an additional structure located at the lateral wall of the left atrium, adjacent to the left atrial appendage (LAA) and the left superior pulmonary vein. The motion of this structure was consistent with the cardiac cycle, and its echogenicity was comparable to that of heart tissues (Figure 1B and 1C). This finding prompted a tentative diagnosis of a prominent coumadin ridge. Transesophageal echocardiography (TEE) showed a structure, which resembled a cotton swab, with a narrow proximal part and a bulbous distal part (Figure 1D). Cardiac magnetic resonance imaging (cMRI) showed a structure in a four-chamber view, which was not visible in any other sequences and showed no contrast enhancement (Figure 1E). This structure was then assumed to be a prominent coumadin ridge; therefore, no further investigations were performed, nor was any anticoagulant treatment initiated.

A coumadin ridge is an anatomic variant, which is an embryological remnant, detected in the left atrium between the left superior pulmonary vein and the LAA. Being aware of the existence of this structure may be crucial for differential diagnosis of any focal lesions found in the left atrium and planning of percutaneous transcatheter interventions, such as ablation or LAA closure. Coumadin ridges show inter-individual variability, and their estimated prevalence is 60% on gross postmortem examinations [1]. The ridge tissue fold contains the ligament of Marshall, an autonomic nerve bundle and a small atrial or sinoatrial-node artery. The vestigial ridge is usually invisible on echocardiography; however, if prominent, the structure may be misdiagnosed [2]. On TEE, its shape resembles that of a cotton swab ("Q-tip sign") [3]. Computed tomography or cMRI can be useful in differential diagnosis [4].

Utmost caution should be exercised every time a coumadin ridge-like focal lesion in the left atrium is diagnosed since myxomas, fibromas, and thrombi may be also found in the same location [5]. On TEE, a coumadin ridge interferes with good imaging of the LAA, which should be imaged omitting the structure, preferably "above" the entrance to the LAA, moving the structure to the side. Coumadin ridges may also impede the flow of blood in the LAA and may be associated with thromboembolic complications, which requires further study. Imaging study results should be interpreted in the clinical context, with the thromboembolic risk and possible

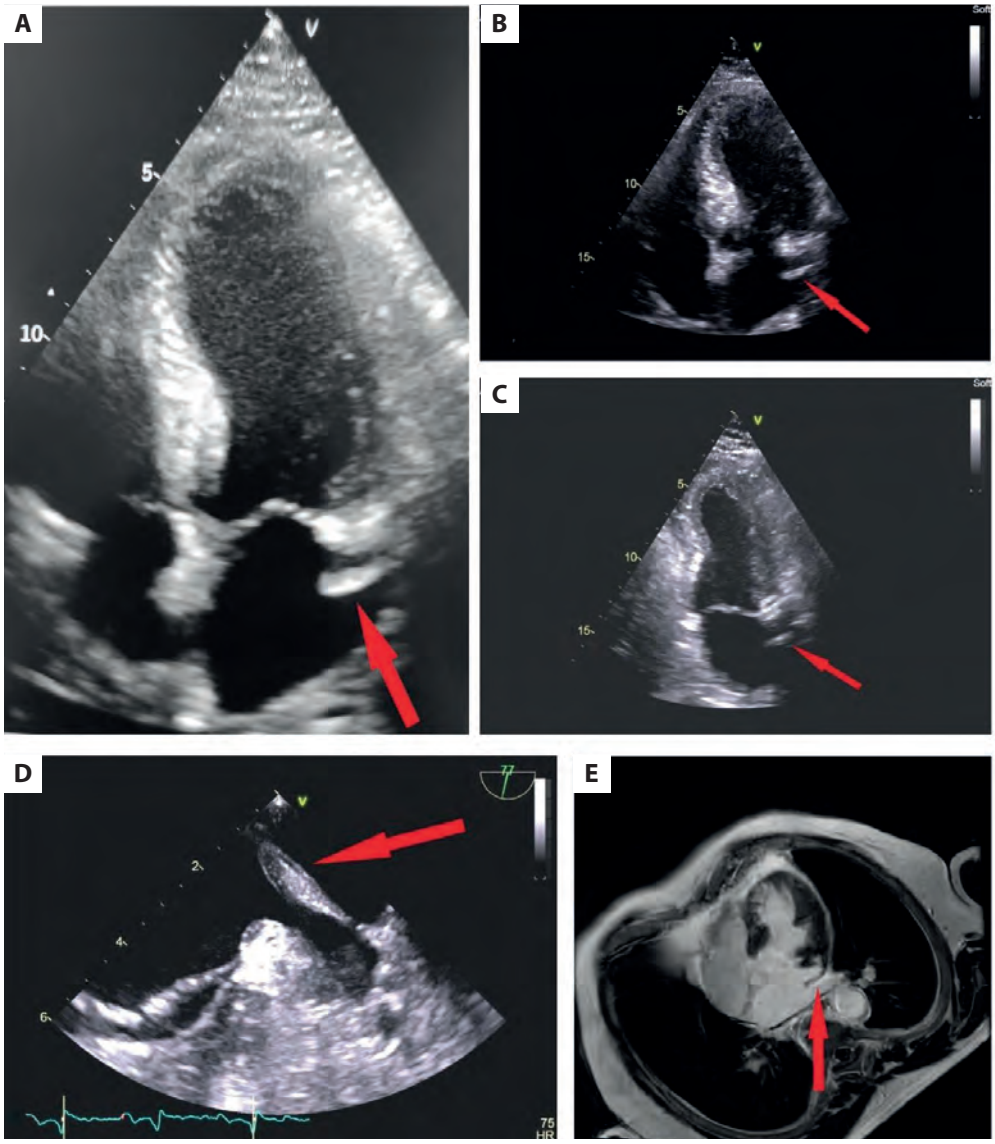


Figure 1. A. A focal lesion in the left atrium measuring 19 × 5 mm (apical four-chamber view) first noticed on bedside transthoracic echocardiography in a cardiac intensive care unit patient (red arrow). **B.** The coumadin ridge-like focal lesion in the left atrium (apical four-chamber view) visualized on repeat transthoracic echocardiography performed in the local echocardiography laboratory (red arrow). **C.** The coumadin ridge-like focal lesion in the left atrium (two-chamber view) visualized on repeat transthoracic echocardiography performed in the local echocardiography laboratory (red arrow). **D.** The location and structure of the coumadin ridge-like lesion measuring approximately 28 mm on transesophageal echocardiography (modified bi-commissural view) (red arrow). **E.** The coumadin ridge-like lesion in the left atrium on cardiac magnetic resonance imaging (red arrow)

cancer history taken into consideration. In the presented case, TEE and cMRI were used to determine the nature of the lesion.

Being aware of the presence of anatomic variants within the left atrium, along with their structure and location, is indispensable to avoid initiating unnecessary therapeutic interventions and expanding the scope of diagnostic investigations.

Article information

Conflict of interest: The authors of this article declare no financial or personal ties to any individuals or organizations.

Funding: None.

REFERENCES

1. Piątek-Koziej K, Hołda J, Tyrak K, et al. Anatomy of the left atrial ridge (coumadin ridge) and possible clinical implications for cardiovascular imaging and invasive procedures. J Cardiovasc Electrophysiol. 2020; 31(1): 220–226, doi: 10.1111/jce.14307, indexed in Pubmed: 31808228.
2. Lodhi AM, Nguyen T, Bianco C, et al. Coumadin ridge: An incidental finding of a left atrial pseudotumor on transthoracic echocardiography. World J Clin Cases. 2015; 3(9): 831–834, doi: 10.12998/wjcc.v3.i9.831, indexed in Pubmed: 26380830.
3. Agostini F, Click RL. More than just the "Q-tip sign". J Am Soc Echocardiogr. 2001; 14(8): 832–833, doi: 10.1067/mje.2001.110373, indexed in Pubmed: 11490333.
4. Gupta S, Plein S, Greenwood JP. The coumadin ridge: An important example of a left atrial pseudotumour demonstrated by cardiovascular magnetic resonance imaging. J Radiol Case Rep. 2009; 3(9): 1–5, doi: 10.3941/jrcr.v3i9.210, indexed in Pubmed: 22470681.
5. Suzuki R, Morimoto K, Itou Y, et al. Resection of a myxoma originating from the coumadin ridge with superior transseptal approach: Report of a case [article in Japanese]. Kyobu Geka. 2021; 74(8): 611–614, indexed in Pubmed: 34334604.

The sixtieth anniversary of the first pacemaker implantation in Poland

Alicja Dąbrowska-Kugacka, Ewa Lewicka

Department of Cardiology and Electrotherapy, Medical University of Gdansk, Gdańsk, Poland

Correspondence to:
Prof. Alicja Dąbrowska-Kugacka, MD, PhD,
Department of Cardiology and Electrotherapy,
Medical University of Gdansk,
Smoluchowskiego 17,
80–214 Gdańsk, Poland,
e-mail: alicja.dabrowska-kugacka@gumed.edu.pl

DOI: 10.33963/v.kp. 98513

Received:
November 30, 2023

Accepted:
December 8, 2023

Early publication date:
December 12, 2023

September 12, 1963 is a very important date in the history of cardiac electrotherapy in Poland. This is the day when the first cardiac pacemaker in Poland was implanted. The procedure was performed by a surgeon Professor Zdzisław Kieturakis (Figure 1), in cooperation with cardiologists: Prof. Jakub Penson, Prof. Konstanty Leonowicz and Dr. Wojciech Kozłowski (Figure 2) from the 3rd Department of Internal Diseases, Medical University of Gdansk, directed by Prof. Mieczysław Gamski (Figure 3). On November 23, 2023, the 60th anniversary of this event was celebrated and it took place in the so-called hospital on Łąkowa Street in Gdańsk, where the first historic operation took place (Figures 4–6). Arche Hotel Uphagen House is currently located at this place, however, it has been renovated preserving all historical details of the previously operated hospital, and at every step the interior design reminds of the great history of this location. One of the special guests of the event was Prof. Grażyna Świątecka — the first, long-term Head of the 2nd Department of Heart Diseases of the Medical University of Gdansk, which was separated from the 3rd Department of Internal Diseases in 1992 at the hospital in Łąkowa Street. In 2004 the headquarters of the 2nd Department of Heart Diseases moved to Dębinki Street in Gdańsk, and the clinic changed its name to the currently in force — the 2nd Department of Cardiology and Cardiac Electrotherapy. Professor Grażyna Świątecka, awarded the Saint Wojciech's Medal (honorary award of the Gdansk City Council) and the White Eagle Order, was to celebrate her 90th birthday a few days later. During the anniversary evening, at the Arche Hotel Uphagen House, a memorial site for former cardiologists was ceremonially opened, old photographs of distinguished doctors were hung on the walls, including those showing Dr. Wojciech Kozłowski and of course Prof. Grażyna Świątecka and her team from the 2nd Department of Heart Diseases of the Medical University of Gdansk. A showcase has appeared which will be a mini-museum of our clinic. Old pacemakers, and cardioverter-defibrillators (ICD), as well as a blood pressure monitor, and a needle for lumbar puncture of the famous Professor Mieczysław Gamski, former head of the 3rd Department of Internal Diseases are presented on the display. During the ceremony Professor Grażyna Świątecka recalled important events from the history of the clinic. She recalled the creation in October 1994 of the first Polish magazine devoted to the field of cardiac electrotherapy, the quarterly "Electrophysiology and Pacing of the Heart". In 1999, the magazine changed its name to "Folia Cardiologica", and in 2006,

Figure 1. Professor Zdzisław Kieturakis

Figure 2. Doctor Wojciech Kozłowski

Figure 3. Professor Mieczysław Gamski

Figures 4 and 5. Guests at the ceremony of 60th anniversary of the first pacemaker implantation (photo by Sylwia Mierzewska)

Figure 6. Professor Grażyna Świątecka, Professor Ludmiła Daniłowicz-Szymanowicz, Professor Ewa Lewicka during the anniversary (photo by Sylwia Mierzewska)

the editor-in-chief Grażyna Świątecka was replaced by Prof. Wojciech Zaręba from Rochester (US). In 2007, the journal changed its name to "Cardiology Journal", which became an international title, published only in English. In this historic hospital, in 1999 under the supervision of Prof. Świątecka, the first Polish recommendations on heart pacing were developed. During the ceremony an archival film was presented showing how pacemakers were implanted in the early 1970s. Additionally, an old pacemaker with "fixed ventricular rate" from the years 70^{s} was presented to the audience — nowadays it is shown to medical students during classes. It is unusual: transparent, you can see the entire amazing structure, it looks as if its elements were embedded in amber. A work of medical art! Over time, it will also return to the mini-museum in Arche Hotel Uphagen House. It is also worth mentioning that the hotel is now situated on Zdzislaw Kieturakis Street. The first pacemaker in the world constructed by the engineer Rune Elmquist was implanted on October 12, 1958 by Dr. Ake Senning from Sweden. Already 5 years later, this innovative method appeared in Poland, and at that time it was a really serious, complicated procedure that required a thoracotomy and exposing the heart — because the pacing electrodes were sewn directly onto the heart. It was undoubtedly a milestone in the development of cardiology! It is worth emphasizing that it all started in Gdansk, thanks to the daughter of the first patient who worked in Polish Ocean Lines and had tight connections with Sweden. The indication to implant the pacemaker was 3rd degree atrioventricular block with epizodes of asystole. The next year after implantation the pacemaker had to be replaced 3 times due to battery depletion. Warsaw introduced pacemakers' implantations 3 years later. Prof. Grażyna Świątecka greatly promoted cardiac electrotherapy. In the years 1992–1998 she chaired the board of Cardiac Pacing and Clinical Electrophysiology Section of the Polish Society

Figure 7. Doctor Mieczysław Mirowski

of Cardiology. During her presidency, a lot of events worth mentioning happened in this field. In July 1995, the first implantation of an ICD with a transvenous electrode in Poland was performed at Łąkowa hospital. The method of terminating dangerous ventricular arrhythmias by ICD was introduced by a Polish Jew, Mieczysław Mirowski (Figure 7), who was a student of the Gdańsk *Alma Mater* for a year in 1946. Then he immigrated to Israel, France,

Figure 8. Professor Andrzej Lubiński and Doctor Rajmund Wilczek

and finally to the United States of America and, as a doctor, began working on the construction of a small device that, when implanted in humans, could interrupt, for example, ventricular fibrillation. In 1980, the first ICD in the world was implanted in the United States. In Poland it was done 6 years later in Katowice by Prof. Maria Trusz-Gluza and Prof. Włodzimierz Kargul in the 1st Cardiological Department led by Prof. Leszek Giec, and again it was an open-heart procedure. Doctors from Gdańsk (Prof. Andrzej Lubiński and Dr. Rajmund Wilczek, Figure 8) were the first in Poland to implant an ICD with a transvenously inserted electrode. This special evening recalled many important events from the history of cardiac electrotherapy in Poland.

Article information

Conflict of interest: None declared.

Funding: None.

Management of myocardial infarction complicated by cardiogenic shock: Expert opinion of the Association of Intensive Cardiac Care and Association of Cardiovascular Interventions of the Polish Society of Cardiology

Przemysław Trzeciak[1], Janina Stępińska[2], Robert Gil[3], Michał Hawranek[1], Klaudiusz Nadolny[4, 5], Agnieszka Tycińska[6], Stanisław Bartuś[7], Marek Gierlotka[8], Marta Kałużna-Oleksy[9], Robert Zymliński[10], Marek Grygier[9], Wojciech Wojakowski[11], Mariusz Gąsior[1]

Reviewers: Jacek Kubica[12], Wiktor Kuliczkowski[13]

[1]3rd Department of Cardiology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia in Katowice, Silesian Center for Heart Diseases, Zabrze, Poland
[2]Department of Medical Communication, School of Public Health, Centre of Postgraduate Medical Education, Warszawa, Poland
[3]Department of Cardiology, Ministry of Interior and Administration National Medical Institute, Warszawa, Poland
[4]Department of Emergency Medical Service, Faculty of Medicine, Silesian Academy in Katowice, Katowice, Poland
[5]Regional Ambulance Service in Sosnowiec, Sosnowiec, Poland
[6]Department of Cardiology, Medical University of Bialystok, Białystok, Poland
[7]2nd Department of Cardiology, Institute of Cardiology, Jagiellonian University Medical College, Kraków, Poland
[8]Department of Cardiology, University Hospital, Institute of Medical Sciences, University of Opole, Opole, Poland
[9]1st Department of Cardiology, Poznań University of Medical Sciences, Poznań, Poland
[10]Institute of Cardiac Diseases, Wroclaw Medical University, Wrocław, Poland
[11]Department of Cardiology and Structural Heart Diseases, Medical University of Silesia in Katowice, Poland
[12]Department of Cardiology and Internal Medicine, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun, Bydgoszcz, Poland
[13]Department of Heart Diseases, Wroclaw Medical University, Wrocław, Poland

Correspondence to:
Przemysław Trzeciak, MD, PhD, 3rd Department of Cardiology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia in Katowice, Silesian Center for Heart Disease, Skłodowskiej-Curie 9, 41–800 Zabrze, Poland, phone: +48 32 373 34 81, e-mail: przemyslaw.t@wp.pl

DOI: 10.33963/v.kp.97817

Received:
September 8, 2023

Accepted:
October 10, 2023

Early publication date:
October 12, 2023

ABSTRACT

Despite significant advances in interventional cardiology and mechanical circulatory support (MCS) techniques, outcomes for patients with myocardial infarction (MI) complicated by cardiogenic shock (CS) remain suboptimal.

This expert consensus aims to provide information on the current management of patients with MI complicated by CS in Poland and to propose solutions, including systemic ones, for all stages of care. The document uses data from the Polish PL-ACS Registry of Acute Coronary Syndromes, which includes records of more than 820 000 hospital admissions.

We describe the role of medical rescue teams, highlighting the necessity to expand their range of competencies at the level of prehospital care. We emphasize the importance of treating the underlying cause of CS and direct patient transfer to centers capable of performing percutaneous coronary interventions. We present current recommendations of scientific societies on MCS use. We underline the role of the Cardiac Shock Team in the management of patients with MI complicated by CS. Such teams should comprise an interventional cardiologist, a cardiothoracic surgeon, and an intensive care physician. Patients should be transferred to highly specialized CS centers, following the example of so-called Cardiac Shock Care Centers described in some other countries. We propose criteria for the operation of such centers Other important aspects discussed in the document include the role of rehabilitation, multidisciplinary care, and long-term follow-up of treatment outcomes. The document was developed in cooperation with experts from different scientific societies in Poland, which illustrates the importance of interdisciplinary care in this patient population.

Key words: acute myocardial infarction, Cardiac Shock Care Center, Cardiac Shock Team, cardiogenic shock, intensive care, interventional treatment, mechanical circulatory support, prehospital care

INTRODUCTION

According to the definition of the European Society of Cardiology (ESC), cardiogenic shock (CS) is a life-threatening condition stemming from primary cardiac dysfunction, which results in low cardiac output leading to organ hypoperfusion and multiorgan failure [1]. Hemodynamically, CS is characterized by increased left ventricular end-diastolic pressure and wedge pressure, low systolic blood pressure despite adequate hydration, and low cardiac output. Based on clinical examination, CS patients are characterized as "wet and cold". The use of inotropes and vasopressors, mechanical circulatory support (MCS), and/or renal replacement therapy in CS patients may lead to an increase in systolic blood pressure to ≥90 mm Hg, but this does not necessarily result in the resolution of CS.

In more than 80% of cases, CS is caused by myocardial infarction (MI) with left and/or right ventricular failure. In an American study assessing approximately 4.3 million hospital admissions due to ST-segment elevation myocardial infarction (STEMI) in the years 2000–2017, CS was reported in 8.5% of patients [2]. Although CS is more often diagnosed in patients with STEMI, it also occurs in about 4% of individuals with non-STEMI (NSTEMI) [3] and in patients with out-of-hospital cardiac arrest.

The less common causes of CS include mechanical complications of MI: ventricular septal defect (4%), left ventricular free wall rupture (2%), or acute mitral regurgitation (7%) [4]. Apart from MI, CS may be also caused by acute decompensated heart failure, heart valve disease, myocarditis, acute pulmonary embolism, aortic dissection, postpartum cardiomyopathy, arrhythmia, or takotsubo syndrome [5].

Classification of cardiogenic shock

In clinical practice, CS is diagnosed on the basis of clinical criteria such as persistent hypotension unresponsive to fluid therapy with concomitant signs of organ hypoperfusion such as low urinary output and/or cognitive disturbances. An additional sign is increased blood lactate level. The reference range for serum lactate levels is <2.0 mmol/l. In the 9-point CardShock risk score proposed by Harjola et al. [6], a serum lactate level of 2.0–4.0 mmol/l scores 1 point, while a level of more than 4.0 mmol/l scores 2 points.

In the SHOCK study (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock), the hemodynamic criteria for CS diagnosis included the cardiac index of ≤2.2 l/min/m^2 and pulmonary capillary wedge pressure of ≥15 mm Hg [7].

In the most recent guidelines of the Society for Cardiovascular Angiography and Interventions, the authors distinguished 5 stages of CS [8]. The classification is presented in Table 1.

This expert consensus aimed to provide information on the management of patients with MI complicated by CS in current clinical practice in Poland and to suggest solutions, including systemic ones, for all stages of care. For this consensus, we used the database of the State Medical Rescue (Państwowe Ratownictwo Medyczne [PRM]) and the Polish PL-ACS Registry of Acute Coronary Syndromes (Ogólnopolski Rejestr Ostrych Zespołów Wieńcowych). The PL-ACS Registry contains data on almost 820 000 hospital admissions (as of the end of 2022). The prevalence rates of CS in patients with STEMI and NSTEMI were assessed on the basis of PL-ACS Registry data for the years 2004–2019 (Figure 1).

PREHOSPITAL CARE

A prompt diagnosis and emergency medical treatment are among the most important steps in CS management. In the prehospital setting, these are provided mainly by medical rescue teams (MRTs). In Poland, MRTs operate within the framework of PRM. To monitor and optimize Polish emergency medical services, a command support system was developed, known as SWD PRM (System Wspomagania Dowodzenia Państwowego Ratownictwa Medycznego). SWD PRM is a central information and communication technology system that collects data on the diagnostic, medical, and transport activities of all MRTs. This allows assessment of the number and quality of emergency medical service activities performed by MRT members [9]. In an analysis of SWD PRM data, Nadolny et al. [10] reported that

Table 1. Classification of CS based on the Society for Cardiovascular Angiography and Interventions guidelines [8]

A	A hemodynamically stable patient without signs or symptoms of CS but at risk of its development (i.e., large myocardial infarction, decompensated heart failure). **At risk**
B	A patient with clinical evidence of hemodynamic instability (including hypotension, tachycardia, and hemodynamic abnormalities) without hypoperfusion. **Beginning CS**
C	A patient with clinical signs and symptoms of hypoperfusion who initially requires pharmacological or mechanical support. Hypotension is typically present. **Classic CS**
D	A patient with clinical evidence of shock but worsening or not improving despite escalation of therapy. **Deteriorating CS**
E	Circulatory collapse, cardiopulmonary resuscitation, and/or ECMO. A patient with refractory shock or actual/impending circulatory collapse. **Extremis CS**

Abbreviations: CS, cardiogenic shock; ECMO, extracorporeal membrane oxygenation

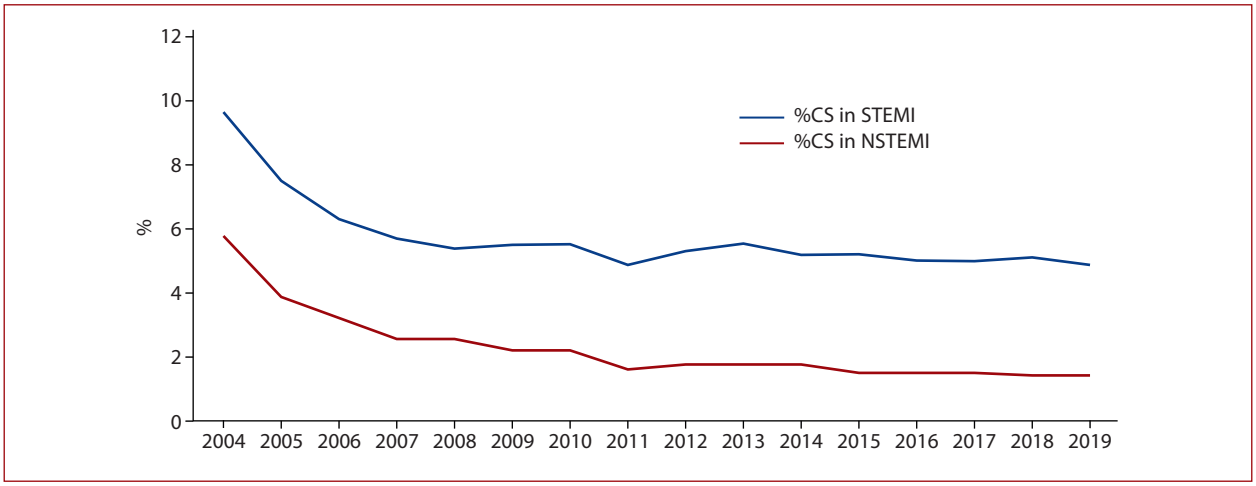


Figure 1. Rates of CS in patients with NSTEMI and STEMI; data from the PL-ACS registry for the years 2004–2019

systolic blood pressure lower than 90 mm Hg (ie, CS stage A-C) was recorded in 10.2% of almost 17 000 emergency ambulance calls to patients with STEMI.

The diagnosis should be established within 10 minutes after the first contact of the medical team with the patient. Delays in diagnosis are one of the quality-of-care indicators and a significant prognostic factor in patients with STEMI, including those with CS [11, 12]. The authors of the ESC guidelines on the management of patients with STEMI recommend that medical teams transfer these patients to a center capable of performing percutaneous coronary intervention (PCI) and that they bypass non-PCI centers (class of recommendation I, level of evidence C) [11]. This applies also to the Polish setting. The patient transfer should be preceded by a prehospital transmission of the electrocardiogram (ECG). In Poland, prehospital ECG transmission was performed in 37.5% of STEMI patients in 2018 based on SWD PRM data [10]. Although there are more than 160 catheterization laboratories that provide treatment for MI patients, not all of them are equipped with a system that can receive ECG transmissions. The key element of prehospital management is the ECG transmission and a rapid patient transfer to a reference center. A study based on the PL-ACS registry showed that transferring STEMI patients directly to a PCI-capable center was associated with a reduction in 12-month mortality rates [13].

So far, it has not been determined which cardiac centers should receive patients with CS. According to the scientific statement of the American Heart Association, CS patients may be transported directly to so-called "cardiac shock centers" providing the highest level of specialty care. Patients with confirmed STEMI can be also transferred to PCI-capable hospitals. If hemodynamic instability and CS persist, CS teams should be ready to receive such patients at their centers [5].

In our opinion, efforts should be made to ensure that all patients with MI complicated by CS are transferred directly to centers providing the highest level of specialty care such as the CS centers in the United States. The criteria for the operation of such centers in Poland are discussed below. Transfer to CS centers should be provided not only to the highest-risk CS patients (stages D and E). Patients with CS stages A-C also might derive the greatest benefits from such an approach because aggressive treatment strategies may prevent disease progression. Another argument for the direct transport of patients to CS centers is the limited availability of fully equipped ambulances that can secure the transfer of CS patients between hospitals. Until the network of CS centers is developed in Poland, patients should be transferred to PCI centers with on-site cardiothoracic surgery capabilities. If such a center is not within a reachable distance, transfer to the nearest interventional cardiology center should be considered. The decision on where to transfer the CS patient should be made after the MRT transmits the ECG recordings and consults the patient with a cardiologist from the center of the highest reference level.

Prehospital care involves the establishment of CS diagnosis and the initiation of treatment. Treatment provided by the MRT in Poland differs depending on whether it is a basic ambulance service (ambulance without an emergency physician on board) or a specialist ambulance service (with an emergency physician on board). Inotropes and vasopressors are the key players in the pharmacological treatment of CS. In the Polish setting, MRTs have access to the following medications: epinephrine, norepinephrine, dopamine, and dobutamine. In line with the ESC guidelines, norepinephrine can be considered in patients with hypotension [1]. According to Polish regulations, epinephrine is the only medication that can be administered by a paramedic, including a nurse paramedic, without the physician's order. The basic MRT ambulance is equipped with an infusion pump [14].

The current range of competencies should be changed to ensure that the members of basic MRTs can administer inotropes and vasopressors that are part of the ambulance

equipment (e.g. after they consult the case with the physician from the receiving hospital). Basic MRTs should be also authorized to perform a wider range of interventions (e.g., endotracheal intubation). According to current regulations, a paramedic can perform endotracheal intubation only in patients with sudden cardiac arrest [15].

In the prehospital setting, MI patients usually receive dual antiplatelet therapy with acetylsalicylic acid and $P2Y_{12}$ inhibitors. However, data on the efficacy and safety of $P2Y_{12}$ inhibitors in the prehospital treatment of STEMI patients are still limited. In cases where the diagnosis of STEMI is uncertain, a $P2Y_{12}$ inhibitor should not be used until the diagnosis is confirmed [11]. The use of ticagrelor and prasugrel is limited to selected patient populations. Therefore, the decision on the use of these medications and the choice of the other antiplatelet drug should always be discussed with the physician from the receiving cardiac center. This is another argument for increasing the number of real-time ECG transmissions.

Areas for improvement in prehospital care

- Real-time ECG transmission systems available in all invasive cardiology centers providing care for MI patients.
- An increase in the number of real-time ECG transmissions, consultations, and direct patient transfers to referral centers.
- Establishing rules for patient transfer. Patients with MI complicated by CS should be transferred directly to centers of the highest reference level, following the example of CS centers in the United States. Until such centers are created in Poland, patients should be transferred to PCI centers with on-site cardiothoracic surgery facilities. If such a center is not within a reachable distance, a transfer to the nearest interventional cardiology center should be considered.
- Authorizing basic MRTs to administer inotropes/vasopressors and to perform endotracheal intubation.

IN-HOSPITAL CARE

The in-hospital management of patients with MI complicated by CS is a multistep process that depends mainly on the patient's clinical condition. Early diagnosis and triage are the most important management steps in the emergency department. The key element of therapy in the MI setting is the treatment of the underlying cause, that is, percutaneous coronary revascularization. In CS patients, it is important to consider possible mechanical complications of MI, because they significantly worsen prognosis and usually require treatment at highly specialized centers with cardiothoracic surgery facilities. All patients with MI complicated by CS are treated in intensive care units (ICUs). Some patients do not respond to pharmacological treatment, which necessitates the use of MCS. This section discusses the key elements of in-hospital care.

Emergency room setting

At the emergency department that receives a CS patient, prompt diagnostic workup should be done to confirm the diagnosis and to triage the patient to an appropriate category in terms of the type of management and the level of urgency. Patients with MI should undergo 12-lead ECG and echocardiography, among other examinations. If MI is confirmed as the cause of CS, patients in stages A and B should be directly transferred to the catheterization laboratory for PCI [16, 17]. Patients with CS stages C or D should be stabilized first using vasopressors and mechanical ventilation. However, this should not significantly delay reperfusion. Patients in severe condition (CS stage E) should be assessed to identify potential benefits of an aggressive treatment strategy and to define therapeutic goals [17–20].

Revascularization

The introduction of urgent percutaneous revascularization and its increasing availability over the years have significantly reduced early mortality rates in patients with MI complicated by CS from 70%–80% to 40%–50% [21]. This trend was reflected in the ESC guidelines. The ESC guidelines on the management of STEMI recommend emergency PCI in CS patients unless the anatomy of the infarct-related artery (IRA) is unsuitable for the intervention [11]. In Poland, the network of catheterization laboratories available 24 hours 7 days a week makes it possible to quickly perform emergency PCI. According to the PL-ACS registry, in recent years, almost 90% of patients were treated by PCI, with low rates of cardiothoracic surgery procedures (Figures 2 and 3).

A delay in revascularization is one of the strongest predictors of unfavorable prognosis [19, 22, 23]. The FITT-STEMI trial (Feedback Intervention and Treatment Times in ST-Elevation Myocardial Infarction) showed that in patients with STEMI complicated by CS, every 10-minute delay in providing treatment within 60–180 minutes after the first contact with the emergency medical services resulted in an additional 3.3 deaths per 100 patients undergoing PCI [23].

While there is no doubt as to the importance of revascularization of the IRA in CS patients, the need for revascularization of other stenosed arteries has been debated for many years. It is estimated that even up to 70%–80% of CS patients have multivessel coronary artery disease defined as coronary stenoses or occlusions in a vessel other than the IRA [24]. The 2017 ESC guidelines on the management of STEMI recommend PCI of non-IRA lesions during the index procedure in CS patients (class of recommendation IIa, level of evidence C) [11].

However, in 2018, the ESC and the European Association of Cardiothoracic Surgery developed new guidelines on myocardial revascularization, in which routine treatment of non-culprit lesions is no longer recommended during the primary PCI (class of recommendation III, level of evidence B) [25]. The change of recommendations was

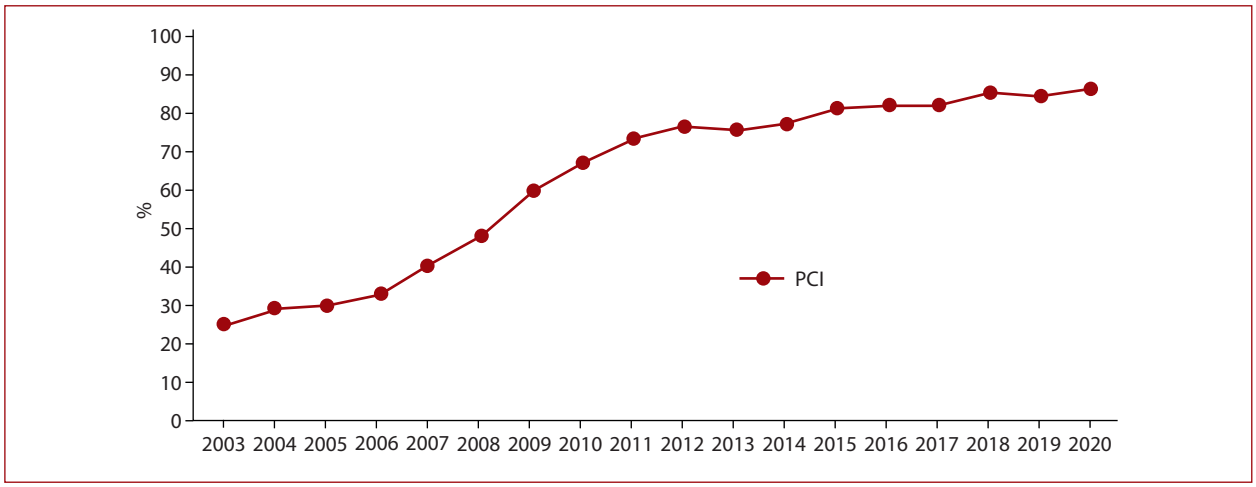


Figure 2. Rates of PCI in patients with MI complicated by CS data from the PL-ACS registry for the years 2003–2020

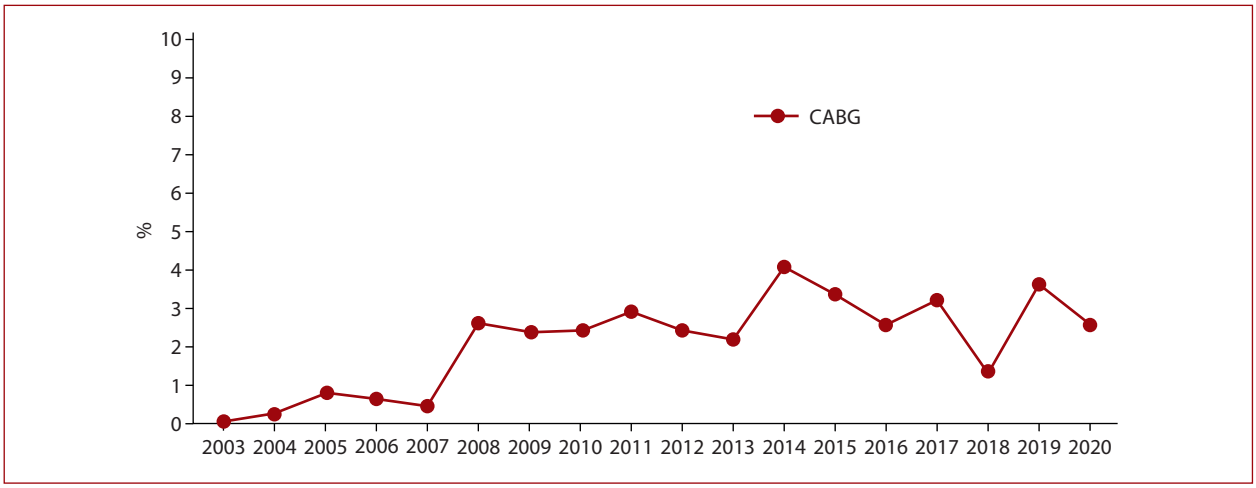


Figure 3. Rates of CABG in patients with MI complicated by CS ; data from the PL-ACS registry for the years 2003–2020

guided by the results of the randomized multicenter CULPRIT-SHOCK trial (Culprit Lesion Only PCI vs. Multivessel PCI in Cardiogenic Shock). The study showed a significantly lower incidence of the composite endpoint (death from any cause and/or renal replacement therapy at 30 days) in patients who underwent PCI of the culprit lesion only (45.9% vs. 55.4%; relative risk [RR], 0.83; 95% confidence interval [CI], 0.71–0.96; $P = 0.01$). This was caused mainly by a reduction in the rate of all-cause death (43.3% vs. 51.5%; $P = 0.03$) [26]. At 1-year follow-up, there were no differences in mortality rates, and the risk of rehospitalization and repeat revascularization was higher in the culprit-lesion-only PCI group. The highest mortality rates in CS patients are reported in the first 30 days. In the CULPRIT-SHOCK study, a relative reduction in the rate of death from any cause was 16% (RR, 0.84; 95% CI, 0.72–0.98) in the culprit-lesion PCI group. Between the 30 day and 1-year follow-up periods, the mortality rate was 6.6% and did not differ between the groups (RR, 1.08; 95% CI, 0.60–1.93) [26]. Therefore, long-term outcomes do not affect the recommendation to perform PCI of the IRA in CS patients.

The guidelines of cardiac societies usually recommend percutaneous revascularization [11, 25]. Coronary artery bypass grafting (CABG) is recommended mainly in patients in whom PCI failed or was not feasible because of unsuitable coronary anatomy. The rates of CABG in CS patients in randomized trials are usually below 5% [21, 27], which is in line with the rates of surgical revascularization reported in the PL-ACS registry (Figure 3).

Fibrinolysis

Thanks to the network of catheterization laboratories in Poland, fibrinolysis is used extremely rarely. The ESC guidelines recommend that CS patients undergo immediate PCI (class of recommendation I, level of evidence B), and fibrinolysis should be considered if primary PCI cannot be performed within 120 minutes from STEMI diagnosis and mechanical complications have been excluded (class of recommendation IIa, level of evidence C). Rescue PCI is indicated immediately in the case of failed fibrinolysis or if patients present with hemodynamic or electrical instability or worsening ischemia (class of recommendation I, level

of evidence A) [11]. In CS patients, the greatest benefits of fibrinolysis are observed within the first 2 hours from the onset of MI. After 3 hours from MI, these benefits are significantly reduced [28].

Mechanical complications of MI

In some patients, CS is caused by mechanical complications of MI that often require cardiac surgery. The reported rates of papillary muscle rupture, ventricular septal defect, and free wall rupture in STEMI patients are 0.05%–0.26%, 0.17%–0.21%, and 0.01%–0.52%, respectively [29, 30]. Conservative treatment of these complications is associated with poor prognosis. The guidelines of the American College of Cardiology Foundation/American Heart Association, and the ESC recommend early cardiac surgery in patients with hemodynamic instability. Mortality rates in these patients range from 20% to 87% and depend on the type of the complication [1, 31]. Owing to a limited number of studies on percutaneous interventions for ventricular septal defect and papillary muscle rupture, a decision on the treatment strategy should be made by the Heart Team or the CS team [32–34] and should be guided primarily by the center's experience.

Intensive care

The key factors that determine successful outcomes are adequate volume expansion, appropriate ventilation strategy, and prevention of bleeding complications and multiorgan failure. CS patients require hemodynamic monitoring at the ICU. Invasive hemodynamic monitoring with a Swan-Ganz catheter is helpful in CS patients and is indispensable in those with concomitant pulmonary edema [35]. Despite advances in technology, the use of noninvasive hemodynamic monitoring is still insufficient. In ICU patients, hourly diuresis should be assessed and ultrafiltration can be considered to reduce volume overload. In some centers, ultrafiltration seems to be underused or is started too late during treatment.

Pharmacological treatment in CS patients aims to improve perfusion of the key organs by increasing the cardiac output and arterial blood pressure. It is estimated that almost 90% of CS patients are administered inotropes and vasopressors [27]. These agents increase oxygen demand and cause vasoconstriction, which may impair microcirculation and increase cardiac afterload. Therefore, they should be used at the lowest possible doses and for the shortest possible time. Inotropes are used to increase cardiac output and blood pressure, improve peripheral perfusion, and help maintain the function of individual organs [36]. They can be considered in patients with systolic blood pressure lower than 90 mm Hg, with signs of hypoperfusion, who do not respond to standard treatment including fluid therapy (class of recommendation IIb, level of evidence C). Typically, dobutamine is used. In patients on chronic beta-blocker treatment, levosimendan can be considered because its inotropic action is independent of beta-adrenergic stimulation. In STEMI patients, phosphodiesterase III inhibitors are not recommended. In patients with acute left ventricular failure and hypoperfusion, norepinephrine is favored over dopamine (class of recommendation IIb, level of evidence B) [11].

In a randomized trial, De Backer et al. [37] compared dopamine with norepinephrine in a relatively small group of CS patients. Patients in the dopamine group showed higher rates of arrhythmia and no significant reduction in mortality [37]. Comparative studies with catecholamine in patients with MI complicated by CS are lacking [36, 38]. In a recent randomized study in patients with MI complicated by CS, no significant difference was noted between epinephrine and norepinephrine in terms of the effect on arterial pressure and cardiac index. However, patients receiving epinephrine showed a higher incidence of refractory CS (37% vs. 7%; $P = 0.008$), which led to premature termination of the study [36]. Mortality rates increase exponentially with an increase in catecholamines [39]. Instead of escalating inotrope doses, MCS should be considered.

Mechanical circulatory support

Over the past decade, early revascularization has become increasingly available, stent technology has vastly improved, and antiplatelet drugs have become even more effective. Despite this, no reduction in mortality in patients with MI and CS has been reported in Poland (Figure 4). According to the PL-ACS registry data for the past 15 years, patients are becoming increasingly older and more often have a history of MI, PCI, stroke, diabetes, peripheral vascular disease, and out-of-hospital cardiac arrest (Figure 5).

To improve prognosis, there have been increasing efforts to determine the role of MCS in this population of patients [40]. MCS is recommended in patients who cannot be stabilized with pharmacological treatment. Most often, it is used to unload the ventricle and improve organ perfusion. Data from randomized clinical trials on the efficacy and safety of different types of MCS are lacking. Moreover, there is generally no consensus as to when to refer the patient for MCS. According to the guidelines, the treatment starts with the use of catecholamines. In our opinion, it is necessary to apply a standard protocol for determining MCS eligibility. The Swan-Ganz catheter should be considered in all patients receiving MCS. The fulfillment of the criteria should be an indication for MCS, irrespective of the time since starting the pharmacological treatment. It is important that the same protocol is used across all centers. Previous experience shows that novel treatment methods are initiated too late, especially if there is limited access to these methods and there is only a small group of clinicians with sufficient training and expertise.

Intra-aortic balloon counterpulsation

Intra-aortic balloon pump (IABP) is the most well-established method of MCS. Over the years, cardiac societies

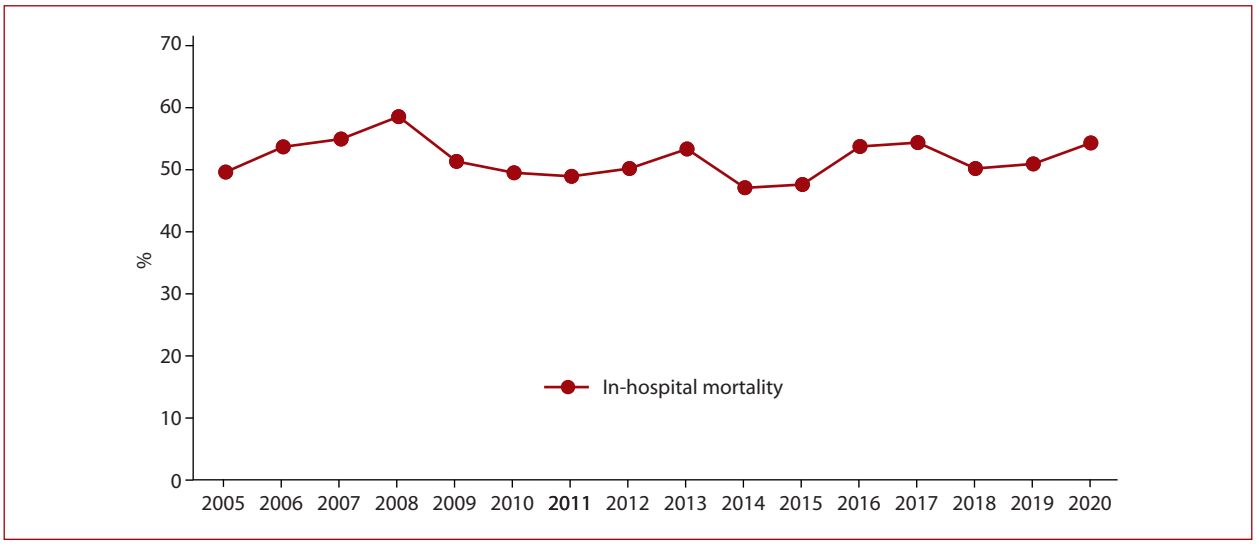


Figure 4. In-hospital mortality in patients patients with MI complicated by CS; data from the PL-ACS registry for the years 2003–2020

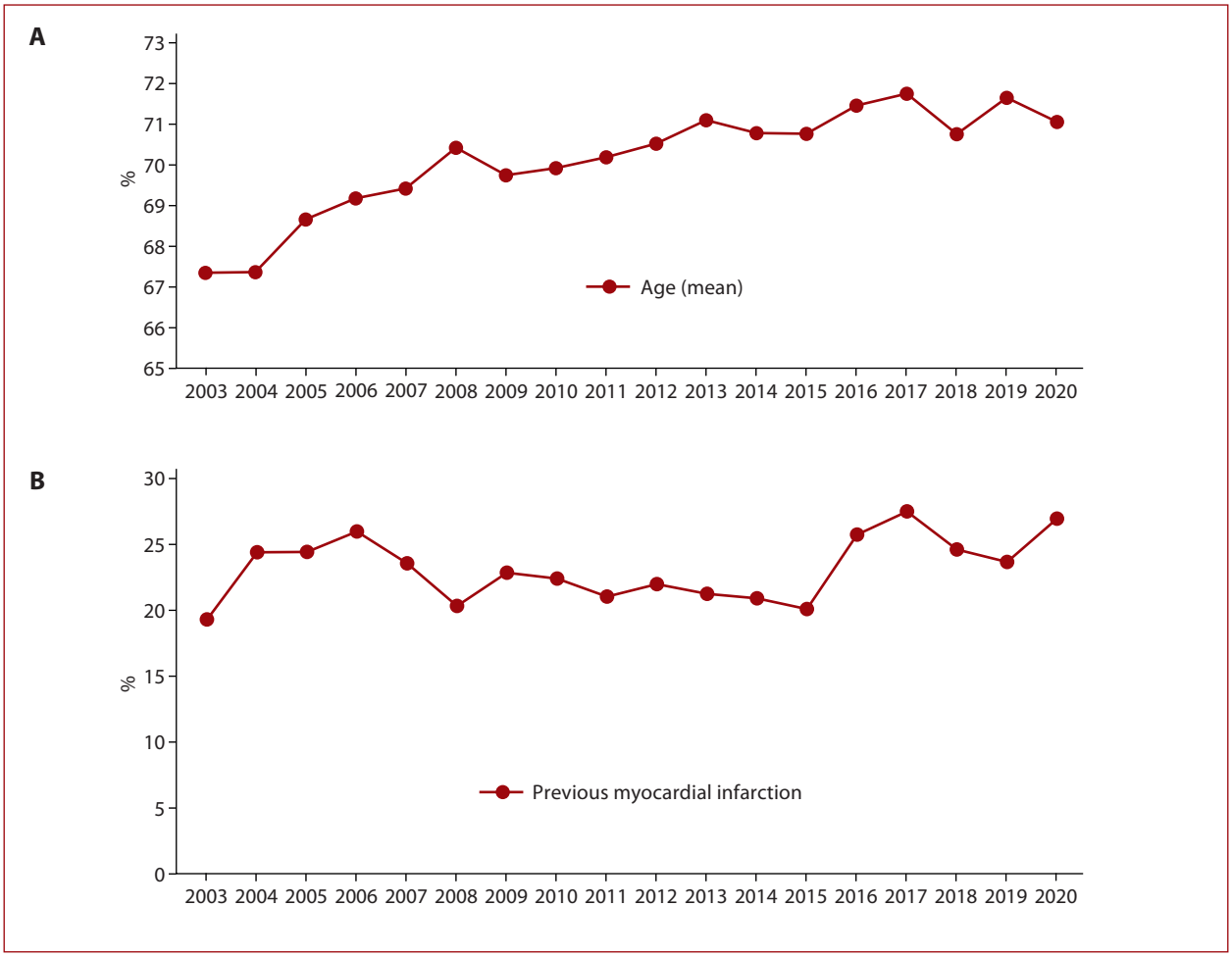


Figure 5. Characteristics of patients with MI complicated by CS; data from the PL-ACS registry for the years 2003-2020 **A**. Mean age. **B**. Rates of previous MI. **C**. Rates of previous PCI. **D**. Rates of previous stroke. **E**. Rates of diabetes. **F**. Rates of IABP use

Table 2. Recommendations on the use of the intra-aortic balloon pump in patients with cardiogenic shock based on the ESC guidelines on the management of heart failure, ST-segment elevation myocardial infarction, and revascularization

ESC guidelines	Recommendations	Class of recommendations	Level of evidence
Heart failure 2021 [1]	Routine use of IABP is not recommended in CS patients	III	B
STEMI 2017 [11]	Routine use of IABP is not recommended.	III	B
Myocardial revascularization 2018 [25]	Routine use of IABP is not recommended in patients with ACS complicated by CS	III	B

Abbreviations: ACS, acute coronary syndrome; IABP, intra-aortic balloon pump; STEMI, ST-segment elevation myocardial infarction; other — see Table 1

have changed their recommendations on IABP use, which affected the popularity of the device in clinical practice. IABP is the most accessible and frequently used MCS device in patients with MI complicated by CS (Figure 5F). In 2012, the results of the IABP-SHOCK II study (Intra-Aortic Balloon Pump in Cardiogenic SHOCK II) were published, reporting no significant differences in 30-day all-cause mortality between patients assigned to IABP vs. no IABP (41.3% vs. 39.7%; $P = 0.69$) [27]. The 6-year follow-up of the IABP-SHOCK II study showed that IABP had no effect on long-term outcomes in patients with MI complicated by CS No differences in mortality, recurrent MI, repeat revascularization or rehospitalization rates were shown between the IABP group and controls [41]. This led to an update of the 2017 ESC recommendations on the use of IABP in STEMI patients complicated by CS. According to the guidelines, IABP should be considered in patients with mechanical complications of MI: severe mitral regurgitation and ventricular septal rupture (class of recommendation IIa, level of evidence C) [11]. Recommendations on IABP use based on the most recent ESC guidelines on the management of heart failure, STEMI, and myocardial revascularization are presented in Table 2. Considering limited access to advanced MCS techniques, it seems justified to identify CS patients other than those with mechanical complications who also might benefit from IABP.

Impella, Impella RP

Following the results of the IABP-SHOCK II study and the changes in recommendations, the frequency of using IABP support has dropped significantly, both in Europe and in the United States [42]. At the same time, the popularity of other MCS devices has increased. This includes the Impella device (Abiomed, Danvers, MA, US), which is a microaxial flow pump that pulls blood from the left ventricle to the aorta.

The following Impella devices are currently available: Impella CP, Impella 5.0, and WK Impella 5.5. The last of these pumps is equipped with intelligent technology and can be also used in CS patients. Impella CP has been designed for use via the percutaneous femoral artery approach, while Impella 5.0 and 5.5 require a surgical approach. Impella CP, which was designed specifically for CS patients, comes with the SmartAssist heart pump, which allows for sustained peak flows of up to 4.3 l/min, repositioning without imaging, and hemodynamic monitoring.

The large diameter of Impella devices and the need for intensive anticoagulation regimens compromise the benefits conferred by the high level of circulatory support. Mechanical support with Impella pumps is associated with increased risk of vascular complications and major bleeding, which constitutes the main limitation of MCS [43]. Moreover, the IABP-SHOCK II subanalysis showed that some CS patients survive without the need for support (50%–60%) [41].

The remaining CS patients (40%–50%) constitute the most challenging population. These are both patients with severe CS, who cannot be rescued irrespective of the type of MCS, and patients in whom MCS can improve chances of survival. The identification of eligible patients who can gain the most benefit from MCS at minimal risk of complications remains challenging.

In addition to patient identification, it is important to develop management algorithms that would cover the whole spectrum of care. Currently, there are no data that could serve as the basis for developing precise recommendations on MCS use in patients with CS. According to the 2018 ESC guidelines on myocardial revascularization, MCS may be considered in selected patients with CS caused by acute coronary syndromes, depending on patient age, comorbidities, neurological function, and prospects for long-term prognosis and quality of life (class of recommendation IIb, level of evidence C) [25].

In line with the 2021 expert consensus of the European Association of Percutaneous Coronary Interventions/Association of Acute Cardiovascular Care (EAPCI/ACVC), microaxial flow pumps (including Impella) may be considered short-term therapy in CS stages C or D, in patients with a potentially reversible cause of CS, or in candidates for long-term left ventricular assist device support or heart transplant [44].

In clinical practice, microaxial flow pumps, such as Impella, may be considered in patients with CS caused mainly by acute left ventricular failure, who do not present with hypoxia and acute right ventricular failure. Caution is advised in patients with inferior wall and right ventricular MI complicated by CS.

Recently, the Impella RP device has been introduced to clinical practice. Impella RP is inserted via the femoral artery approach. It pumps blood directly from the inferior vena cava to the pulmonary artery. In line with current knowledge, Impella RP can be used in patients with right heart failure complicated by CS.

In selected patients with biventricular heart failure who do not require extracorporeal membrane oxygenation (ECMO), the use of simultaneous biventricular MCS support (Bipella) can be considered. However, data from clinical research are lacking [44]. In the Polish setting, the use of Impella devices is limited by high cost. The procedure is usually available only in selected university medical centers. There are no uniform recommendations that guide the selection of patients who should be treated with Impella pumps.

Veno-arterial extracorporeal membrane oxygenation

ECMO is a form of life support in which blood is pumped and oxygenated outside the body. It offers the highest level of mechanical support, accommodating a blood flow of up to 7 l/min. Moreover, by providing blood oxygenation, ECMO can be used in patients with cardiac and respiratory failure. Following the guideline update that led to the reduced IABP use, there was an increase in the use of ECMO in the CS setting. However, evidence from randomized clinical trials on the use of ECMO in CS patients is limited [45]. A meta-analysis of prospective and retrospective studies by Ouweneel et al. [46] demonstrated a 13% increase in 30-day survival in patients assigned to the veno-arterial ECMO (VA- ECMO) group. In the propensity-matched analysis, VA-ECMO showed a 33% higher survival rate compared with IABP (219 patients in each group) [46]. On the other hand, registry studies showed no significant improvement in survival despite the higher frequency of use [44].

In the ESC guidelines, recommendations for ECMO are similar to those for microaxial flow pumps (class of recommendation IIb, level of evidence C). There are no specific recommendations for the use of VA-ECMO. In clinical practice, VA-ECMO can be considered in patients after successful resuscitation, particularly in the presence of respiratory failure and/or right heart failure.

According to the EAPCI/ACVC consensus, VA-ECMO can be considered in patients with severe hemodynamic abnormalities, especially if they present with left heart failure and/or respiratory failure in the course of CS (stages C, D, or E). This applies particularly to patients with a reversible underlying cause of CS or to candidates for long-term left ventricular assist device support or heart transplant [44]. Thus, ECMO is not a therapeutic option that can be used in all patients with CS. In the Polish setting, the use of ECMO is additionally limited by the insufficient availability and lack of uniform recommendations for the identification of eligible CS patients.

The ECLS-SHOCK study in 217 patients with MI and CS, which was presented at the 2023 ESC Congress, failed to show that VA-ECMO improves 30-day outcomes. At 30 days, death from any cause occurred in 47.8% of patients in the VA-ECMO group and 49.0% of patients in the control group (RR, 0.98; 95% CI, 0.80–1.19; $P = 0.81$) [47]. Therefore, it cannot be ruled out that the reported outcomes will influence future recommendations on the use of VA-ECMO support.

Cardiac Shock Team and Cardiac Shock Care Centers

Considering high mortality rates, CS patients should be managed at centers providing the highest level of specialty care [5, 48–51]. It is increasingly suggested that CS patients should be treated by a multidisciplinary team referred to in the literature as the "cardiac shock team". The CS team should comprise an invasive cardiologist, an intensive care physician, a cardiac surgeon, and an advanced heart failure expert [47, 52–54]. A few studies reported that the management of CS patients by the CS team was associated with a reduction in 30-day mortality [52, 55].

Recent literature describes the benefits of creating CS centers, that is, referral centers dedicated to CS patients. A classification of centers providing CS treatment into Level I, II, and III centers has been proposed. Level III centers are local hospitals without a catheterization laboratory. These are hospitals to which patients are usually transported in the first place. In most cases, the CS patient should be promptly transferred from a non-PCI center to a center with a higher level of specialty care. Level II centers are PCI centers without advanced MCS capabilities. Finally, level I centers are CS centers with a catheterization laboratory and advanced MCS available 24 hours 7 days a week, and with on-site cardiothoracic surgery facilities. They can receive patients with cardiac arrest. The catheterization laboratory and CS teams are immediately alerted if a patient with CS has been admitted to the hospital or if their admission is planned. A prompt multidisciplinary consultation aims to facilitate decision-making on treatment, including MCS [46, 48, 49].

Currently, in Poland, most patients with MI complicated by CS are admitted to the nearest center with a catheterization laboratory available 24 hours 7 days a week. These are often centers with a limited availability of specialist personnel, especially during night duty. Moreover, these centers usually provide only IABP support. In our opinion, all patients with MI complicated by CS should be transported to the most highly specialized centers (CS centers) directly from the field, provided that the duration of transport does not result in a significant delay in the treatment of the underlying cause of CS. Until the network of CS centers is developed in Poland, patients should be treated at PCI-capable centers with on-site cardiothoracic surgery facilities. Such an approach to management increases the possibility of providing MCS and surgical treatment of the mechanical complications of MI. If such a center is not within a reachable distance and the transfer might delay treatment, transporting the patient to the nearest PCI-capable center should be considered.

Efforts should be made to set up CS centers capable of performing the whole range of interventional cardiology

and cardiac surgery procedures and with sufficient capacity to accommodate a large number of patients each year. Except for a catheterization laboratory and a highly specialized cardiology unit, these centers should also have cardiothoracic surgery and intensive care units as well as imaging facilities, including a computed tomography laboratory. This is particularly important for CS patients after out-of-hospital cardiac arrest. It is important that CS centers have access to MCS techniques described in this consensus and that patients are managed by CS teams comprising a cardiologist, an interventional cardiologist, an intensive care physician, a cardiothoracic surgeon, and a nurse with specialization in anesthesiology and intensive care. To ensure a quick patient transfer, helicopter landing areas should be constructed on the property of the hospital or within a short distance from the hospital. In Poland, helipads are available only in a few multispecialty hospitals and university centers. It seems that in the Polish setting, a single CS center should serve a population of 1–1.5 million inhabitants, after considering geographic and demographic factors. The development of a national treatment program for patients with MI complicated by CS and a network of CS centers should become a priority for the cardiac community in Poland.

The proposed algorithm for the management of patients with MI complicated by CS including prehospital and hospital care, is presented in Figure 6 (central illustration).

Figure 6. Algorithm for the management of patients with MI complicated by CS (central illustration)

Areas for improvement in the hospital setting

- A system for the in-hospital management of CS patients should be developed. The first step is to determine how many such centers are needed and to define the criteria for their operation. This applies to centers of all referral levels.
- All patients with MI complicated by CS should be managed by a multidisciplinary CS team.
- Patients should be treated at CS centers, that is, centers providing the highest level of specialty care and a full range of diagnostic and treatment procedures. Until CS centers are developed, patients should be preferably transferred to PCI-capable centers with on-site cardiothoracic surgery facilities.
- Considering limited access to advanced MCS, it is important to identify CS patients who might benefit from this type of support. At the same time, efforts should

be made to consistently increase the availability of MCS and to extend indications for their use in line with the recommendations of scientific societies. Education on the use of MCS is also important.
- Research on the benefits of various MCS techniques in CS patients should be conducted at centers of the highest reference level.

CARE AFTER HOSPITAL DISCHARGE

For a long time, the role of care after hospital discharge for improving outcomes in patients with MI complicated by CS has been underestimated. This refers particularly to cardiac rehabilitation. Data on the number of CS patients participating in a cardiac rehabilitation program after hospital discharge are lacking. A few years ago, a program for comprehensive care after MI (Kompleksowa Opieki nad Chorym po Zawale Serca [KOS Zawał]), was introduced in Poland. It not only provided access to rehabilitation but also to regular cardiac monitoring. However, it was estimated that fewer than 20% of patients with MI participate in the program, and there are no data on CS rates in this population. A rehabilitation program and multispecialty care should be provided to all patients after MI.

There are also no data on the long-term outcomes of patients with MI complicated by CS. To improve the effectiveness and quality of treatment, it is necessary to monitor the incidence of cardiovascular adverse events in long-term follow-up.

Areas for improvement in patient care after hospital discharge

- Patients with MI complicated by CS should be included in a rehabilitation program and multispecialty care.
- Long-term outcomes should be assessed, for example, by monitoring the rates of cardiovascular adverse events.

CONCLUSION

Despite significant advances in intensive care and an increase in the number of catheterization laboratories, MI complicated by CS is still associated with high mortality rates. Although novel MCS devices offer considerable promise, randomized clinical trials are needed to confirm their efficacy. The limited availability of highly specialized centers with access to advanced MCS techniques as well as the high cost of the MCS technology constitute additional barriers to the widespread use of MCS.

This consensus presents a number of organizational solutions for all stages of CS management. Several suggestions, such as establishing CS centers, require implementation of systemic solutions. To achieve these goals, an expert panel comprising specialists in CS treatment and policymakers should be convened.

Article information

Conflict of interest: None declared.

Funding: None.

REFERENCES

1. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021; 42(36): 3599–3726, doi: 10.1093/eurheartj/ehab368, indexed in Pubmed: 34447992.
2. Vallabhajosyula S, Dewaswala N, Sundaragiri PR, et al. Cardiogenic Shock Complicating ST-Segment Elevation Myocardial Infarction: An 18-Year Analysis of Temporal Trends, Epidemiology, Management, and Outcomes. Shock. 2022; 57(3): 360–369, doi: 10.1097/SHK.0000000000001895, indexed in Pubmed: 34864781.
3. Kolte D, Khera S, Dabhadkar KC, et al. Trends in coronary angiography, revascularization, and outcomes of cardiogenic shock complicating non-st-elevation myocardial infarction. Am J Cardiol. 2016; 117(1): 1–9, doi: 10.1016/j.amjcard.2015.10.006, indexed in Pubmed: 26541908.
4. Hochman JS, Buller CE, Sleeper LA, et al. Cardiogenic shock complicating acute myocardial infarction--etiologies, management and outcome: a report from the SHOCK Trial Registry. SHould we emergently revascularize Occluded Coronaries for cardiogenic shocK? J Am Coll Cardiol. 2000; 36(3 Suppl A): 1063–1070, doi: 10.1016/s0735-1097(00)00879-2, indexed in Pubmed: 10985706.
5. Diepen Sv, Katz J, Albert N, et al. Contemporary management of cardiogenic shock: a scientific statement from the American Heart Association. Circulation. 2017; 136(16), doi: 10.1161/cir.0000000000000525.
6. Pöss J, Köster J, Fuernau G, et al. Clinical picture and risk prediction of short-term mortality in cardiogenic shock. Eur J Heart Fail. 2015; 17(5): 501–509, doi: 10.1002/ejhf.260, indexed in Pubmed: 25820680.
7. Kohsaka S, Menon V, Iwata K, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. N Engl J Med. 1999; 341(9): 625–634, doi: 10.1056/NEJM199908263410901, indexed in Pubmed: 10460813.
8. Naidu SS, Baran DA, Jentzer JC, et al. SCAI SHOCK Stage Classification Expert Consensus Update: A Review and Incorporation of Validation Studies: This statement was endorsed by the American College of Cardiology (ACC), American College of Emergency Physicians (ACEP), American Heart Association (AHA), European Society of Cardiology (ESC) Association for Acute Cardiovascular Care (ACVC), International Society for Heart and Lung Transplantation (ISHLT), Society of Critical Care Medicine (SCCM), and Society of Thoracic Surgeons (STS) in December 2021. J Am Coll Cardiol. 2022; 79(9): 933–946, doi: 10.1016/j.jacc.2022.01.018, indexed in Pubmed: 35115207.
9. Nadolny K, Kozłowski R, Wardyn T. Command Support System of State Medical Rescue - the future of the medical rescue system in Poland [in Polish]. Ogólnopolski Przegląd Medyczny. 2017; 4: 61–67.
10. Nadolny K, Ładny JR, Gałązkowski R, et al. Medical emergency team interventions in patients with ST-segment elevation myocardial infarction in Poland in 2018. Kardiol Pol. 2020; 78(4): 292–299, doi: 10.33963/KP.15222, indexed in Pubmed: 32124868.
11. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018; 39(2): 119–177, doi: 10.1093/eurheartj/ehx393, indexed in Pubmed: 28886621.

12. Terkelsen CJ, Sørensen JT, Maeng M, et al. System delay and mortality among patients with STEMI treated with primary percutaneous coronary intervention. JAMA. 2010; 304(7): 763–771, doi: 10.1001/jama.2010.1139, indexed in Pubmed: 20716739.
13. Kawecki D, Gierlotka M, Morawiec B, et al. Direct admission versus interhospital transfer for primary percutaneous coronary intervention in st-segment elevation myocardial infarction. JACC Cardiovasc Interv. 2017; 10(5): 438–447, doi: 10.1016/j.jcin.2016.11.028, indexed in Pubmed: 28216215.
14. Ordinance of the Minister of Health of June 22, 2023 on emergency medical activities and health services other than emergency medical activities that may be provided by a paramedic. (Dz. U.2023 poz.1180. Available online: https://isap.sejm.gov.pl/isap.nsf/DocDetails.xsp?id=WDU20230001180.
15. Regulation of the Minister of Health of 28.02.2017 on the type and scope of preventive, diagnostic, therapeutic and rehabilitative services provided by a nurse or midwife independently without a physician's order. Dz. U. Poz. 497. Available online: https://isap.sejm.gov.pl/isap.nsf/DocDetails.xsp?id=wdu20170000497.
16. Lancellotti P, Price S, Edvardsen T, et al. The use of echocardiography in acute cardiovascular care: recommendations of the European Association of Cardiovascular Imaging and the Acute Cardiovascular Care Association. Eur Heart J Cardiovasc Imaging. 2015; 16(2): 119–146, doi: 10.1093/ehjci/jeu210, indexed in Pubmed: 25378470.
17. Tehrani BN, Truesdell AG, Psotka MA, et al. A standardized and comprehensive approach to the management of cardiogenic shock. JACC Heart Fail. 2020; 8(11): 879–891, doi: 10.1016/j.jchf.2020.09.005, indexed in Pubmed: 33121700.
18. van Diepen S, Hochman JS, Stebbins A, et al. Association between delays in mechanical ventilation initiation and mortality in patients with refractory cardiogenic shock. JAMA Cardiol. 2020; 5(8): 965–967, doi: 10.1001/jamacardio.2020.1274, indexed in Pubmed: 32432650.
19. Kochar A, Al-Khalidi HR, Hansen SM, et al. Delays in primary percutaneous coronary intervention in ST-segment elevation myocardial infarction patients presenting with cardiogenic shock. JACC Cardiovasc Interv. 2018; 11(18): 1824–1833, doi: 10.1016/j.jcin.2018.06.030, indexed in Pubmed: 30236355.
20. Rogers JG, Patel CB, Mentz RJ, et al. Palliative care in heart failure: the PAL-HF randomized, controlled clinical trial. J Am Coll Cardiol. 2017; 70(3): 331–341, doi: 10.1016/j.jacc.2017.05.030, indexed in Pubmed: 28705314.
21. Jeger RV, Radovanovic D, Hunziker PR, et al. Ten-year trends in the incidence and treatment of cardiogenic shock. Ann Intern Med. 2008; 149(9): 618–626, doi: 10.7326/0003-4819-149-9-200811040-00005, indexed in Pubmed: 18981487.
22. Hochman JS, Sleeper LA, Webb JG, et al. Cardiogenic shock complicating acute myocardial infarction-etiologies, management and outcome: a report from the SHOCK Trial Registry. SHould we emergently revascularize Occluded Coronaries for cardiogenic shocK? J Am Coll Cardiol. 2000; 36(3 Suppl A): 1063–1070, doi: 10.1016/s0735-1097(00)00879-2, indexed in Pubmed: 10985706.
23. Scholz KH, Maier SKG, Maier LS, et al. Impact of treatment delay on mortality in ST-segment elevation myocardial infarction (STEMI) patients presenting with and without haemodynamic instability: results from the German prospective, multicentre FITT-STEMI trial. Eur Heart J. 2018; 39(13): 1065–1074, doi: 10.1093/eurheartj/ehy004, indexed in Pubmed: 29452351.
24. Ohman EM, Zwischenberger BA, Thiele H, et al. Management of cardiogenic shock. Eur Heart J. 2015; 36(20): 1223–1230, doi: 10.1093/eurheartj/ehv051, indexed in Pubmed: 25732762.
25. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019; 40(2): 87–165, doi: 10.1093/eurheartj/ehy394, indexed in Pubmed: 30165437.
26. Thiele H, Akin I, Sandri M, et al. PCI strategies in patients with acute myocardial infarction and cardiogenic shock. N Engl J Med. 2017; 377(25): 2419–2432, doi: 10.1056/NEJMoa1710261, indexed in Pubmed: 29083953.
27. Thiele H, Zeymer U, Neumann FJ, et al. Intraaortic balloon support for myocardial infarction with cardiogenic shock. N Engl J Med. 2012; 367(14): 1287–1296, doi: 10.1056/NEJMoa1208410, indexed in Pubmed: 22920912.
28. Krittanawong C, Hahn J, Kayani W, et al. Fibrinolytic therapy in patients with acute ST-elevation myocardial infarction. Interv Cardiol Clin. 2021; 10(3): 381–390, doi: 10.1016/j.iccl.2021.03.011, indexed in Pubmed: 34053624.
29. Elbadawi A, Elgendy IY, Mahmoud K, et al. Temporal trends and outcomes of mechanical complications in patients with acute myocardial infarction. JACC Cardiovasc Interv. 2019; 12(18): 1825–1836, doi: 10.1016/j.jcin.2019.04.039, indexed in Pubmed: 31537282.
30. French JK, Hellkamp AS, Armstrong PW, et al. Mechanical complications after percutaneous coronary intervention in ST-elevation myocardial infarction (from APEX-AMI). Am J Cardiol. 2010; 105(1): 59–63, doi: 10.1016/j.amjcard.2009.08.653, indexed in Pubmed: 20102891.
31. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013; 127(4): e362–e425, doi: 10.1161/CIR.0b013e3182742cf6, indexed in Pubmed: 23247304.
32. Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J. 2014; 35(37): 2541–2619, doi: 10.1093/eurheartj/ehu278, indexed in Pubmed: 25173339.
33. Damluji AA, van Diepen S, Katz JN, et al. Mechanical complications of acute myocardial infarction: a scientific statement from the american heart association. Circulation. 2021; 144(2): e16–e35, doi: 10.1161/CIR.0000000000000985, indexed in Pubmed: 34126755.
34. Gong FF, Vaitenas I, Malaisrie SC, et al. Mechanical complications of acute myocardial infarction: a review. JAMA Cardiol. 2021; 6(3): 341–349, doi: 10.1001/jamacardio.2020.3690, indexed in Pubmed: 33295949.
35. Garan AR, Kanwar M, Thayer KL, et al. Complete hemodynamic profiling with pulmonary artery catheters in cardiogenic shock is associated with lower in-hospital mortality. JACC Heart Fail. 2020; 8(11): 903–913, doi: 10.1016/j.jchf.2020.08.012, indexed in Pubmed: 33121702.
36. Levy B, Clere-Jehl R, Legras A, et al. Epinephrine versus norepinephrine for Cardiogenic shock after acute myocardial infarction. J Am Coll Cardiol. 2018; 72(2): 173–182, doi: 10.1016/j.jacc.2018.04.051, indexed in Pubmed: 29976291.
37. De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med. 2010; 362(9): 779–789, doi: 10.1056/NEJMoa0907118, indexed in Pubmed: 20200382.
38. Levy B, Perez P, Perny J, et al. Comparison of norepinephrine-dobutamine to epinephrine for hemodynamics, lactate metabolism, and organ function variables in cardiogenic shock. A prospective, randomized pilot study. Crit Care Med. 2011; 39(3): 450–455, doi: 10.1097/CCM.0b013e3181ffe0eb, indexed in Pubmed: 21037469.
39. Basir MB, Schreiber TL, Grines CL, et al. Effect of early initiation of mechanical circulatory support on survival in cardiogenic shock. Am J Cardiol. 2017; 119(6): 845–851, doi: 10.1016/j.amjcard.2016.11.037, indexed in Pubmed: 28040188.
40. Tycińska A, Grygier M, Biegus J, et al. Mechanical circulatory support. An expert opinion of the Association of Intensive Cardiac Care and the Association of Cardiovascular Interventions of the Polish Cardiac Society. Kardiol Pol. 2021; 79(12): 1399–1410, doi: 10.33963/KP.a2021.0169, indexed in Pubmed: 34861044.
41. Thiele H, Zeymer U, Thelemann N, et al. Intraaortic Balloon Pump in Cardiogenic Shock Complicating Acute Myocardial Infarction: Long-Term 6-Year Outcome of the Randomized IABP-SHOCK II Trial. Circulation. 2019; 139(3): 395–403, doi: 10.1161/CIRCULATIONAHA.118.038201, indexed in Pubmed: 30586721.
42. Shah M, Patnaik S, Patel B, et al. Trends in mechanical circulatory support use and hospital mortality among patients with acute myocardial infarction and non-infarction related cardiogenic shock in the United States. Clin Res Cardiol. 2018; 107(4): 287–303, doi: 10.1007/s00392-017-1182-2, indexed in Pubmed: 29134345.
43. Thiele H, Jobs A, Ouweneel DM, et al. Percutaneous short-term active mechanical support devices in cardiogenic shock: a systematic review and collaborative meta-analysis of randomized trials. Eur Heart J. 2017; 38(47): 3523–3531, doi: 10.1093/eurheartj/ehx363, indexed in Pubmed: 29020341.

44. Chieffo A, Dudek D, Hassager C, et al. Joint EAPCI/ACVC expert consensus document on percutaneous ventricular assist devices. EuroIntervention. 2021; 17(4): e274–e286, doi: 10.4244/EIJY21M05_01, indexed in Pubmed: 34057071.
45. Ostadal P, Rokyta R, Karasek J, et al. Extracorporeal Membrane Oxygenation in the Therapy of Cardiogenic Shock: Results of the ECMO-CS Randomized Clinical Trial. Circulation. 2023; 147(6): 454–464, doi: 10.1161/CIRCULATIONAHA.122.062949, indexed in Pubmed: 36335478.
46. Ouweneel DM, Schotborgh JV, Limpens J, et al. Extracorporeal life support during cardiac arrest and cardiogenic shock: a systematic review and meta-analysis. Intensive Care Med. 2016; 42(12): 1922–1934, doi: 10.1007/s00134-016-4536-8, indexed in Pubmed: 27647331.
47. Thiele H, Zeymer U, Akin I, et al. Extracorporeal Life Support in Infarct-Related Cardiogenic Shock. N Engl J Med. 2023; 389(14): 1286–1297, doi: 10.1056/NEJMoa2307227, indexed in Pubmed: 37634145.
48. Rab T, Ratanapo S, Kern K, et al. Cardiac Shock Care Centers. JACC. 2018; 72(16): 1972–1980, doi: 10.1016/j.jacc.2018.07.074.
49. Patarroyo Aponte MM, Manrique C, Kar B. Systems of care in cardiogenic shock. Methodist Debakey Cardiovasc J. 2020; 16(1): 50–56, doi: 10.14797/mdcj-16-1-50, indexed in Pubmed: 32280418.
50. Alvarez Villela M, Clark R, William P, et al. Systems of care in cardiogenic shock. Front Cardiovasc Med. 2021; 8: 712594, doi: 10.3389/fcvm.2021.712594, indexed in Pubmed: 34616782.
51. Lu DY, Adelsheimer A, Chan K, et al. Impact of hospital transfer to hubs on outcomes of cardiogenic shock in the real world. Eur J Heart Fail. 2021; 23(11): 1927–1937, doi: 10.1002/ejhf.2263, indexed in Pubmed: 34114302.
52. Tehrani BN, Truesdell AG, Psotka MA, et al. A standardized and comprehensive approach to the management of cardiogenic shock. JACC Heart Fail. 2020; 8(11): 879–891, doi: 10.1016/j.jchf.2020.09.005, indexed in Pubmed: 33121700.
53. Tchantchaleishvili V, Hallinan W, Massey HT. Call for organized statewide networks for management of acute myocardial infarction-related cardiogenic shock. JAMA Surg. 2015; 150(11): 1025–1026, doi: 10.1001/jamasurg.2015.2412, indexed in Pubmed: 26375168.
54. Garan AR, Kirtane A, Takayama H. Redesigning care for patients with acute myocardial infarction complicated by cardiogenic shock: the "shock team". JAMA Surg. 2016; 151(7): 684–685, doi: 10.1001/jamasurg.2015.5514, indexed in Pubmed: 26865474.
55. Taleb I, Koliopoulou AG, Tandar A, et al. Shock team approach in refractory cardiogenic shock requiring short-term mechanical circulatory support: a proof of concept. Circulation. 2019; 140(1): 98–100, doi: 10.1161/CIRCULATIONAHA.119.040654, indexed in Pubmed: 31549877.

MULTIMEDIALNA PLATFORMA WIEDZY MEDYCZNEJ

tvmed

- **Ponad 5000 wyemitowanych nagrań**
- **Ponad 300 transmitowanych konferencji**
- **Ponad 2000 współpracujących z nami specjalistów**
- **Ponad 1600 godzin materiałów wideo**

Dostęp do najlepszej wiedzy medycznej w ramach jednej prostej opłaty. Warto skorzystać już dziś!

www.tvmed.pl

KARDIOLOGIA

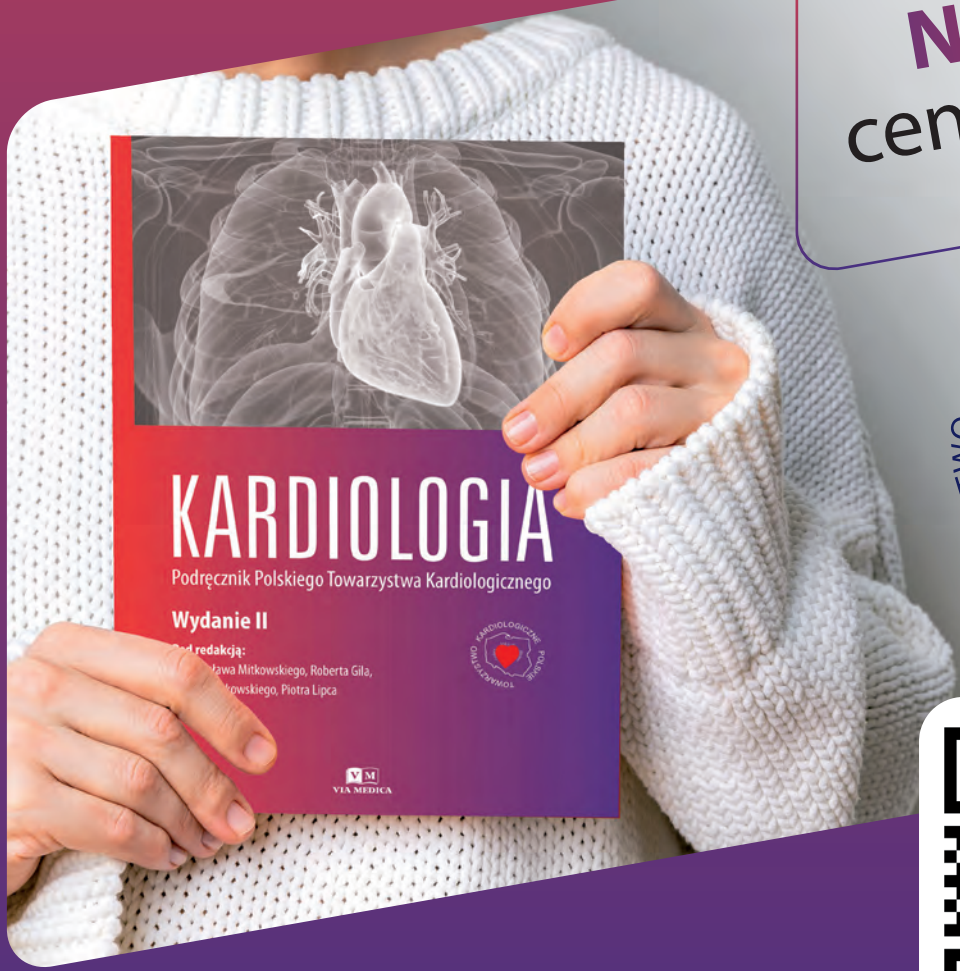
Podręcznik Polskiego Towarzystwa Kardiologicznego

Wydanie II

Pod redakcją:

Przemysława Mitkowskiego, Roberta Gila,
Adama Witkowskiego, Piotra Lipca

NOWOŚĆ
cena od 95,-



TOWARZYSTWO KARDIOLOGICZNE POLSKIE

VIA MEDICA

ikamed.pl
Internetowa księgarnia medyczna