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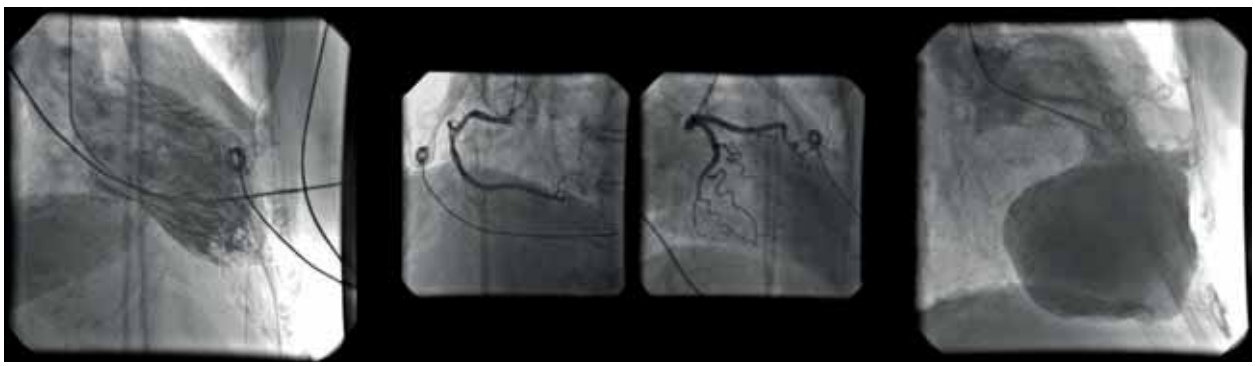

Giant apical pseudoaneurysm in the left ventricle as a late complication of Takotsubo syndrome, see p. 925

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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
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KARDIOLOGIA POLSKA
Polish Heart Journal

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SHORT COMMUNICATION

CLINICAL VIGNETTE

It is better to be young and healthy than the opposite

Roman Jaeschke

Department of Medicine and Department of Health Research Method, Evaluation and Impact
McMaster University, Hamilton, ON, Canada

Related article
by Szczeklik et al.

Correspondence to:
Roman Jaeschke, MD,
Department of Medicine and
Department of Health Research Method,
Evaluation and Impact,
McMaster University, 1280 Main Street West, Hamilton, ON, Canada,
phone: 905 525 9140,
e-mail: jaeschke@mcmaster.ca

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In the article presented in this issue of *Kardiologia Polska* (*Polish Heart Journal*) [1], its authors describe the incidence of major complications after abdominal aortic surgery, including myocardial injury after non-cardiac surgery (MINS), acute renal injury (AKI) and bleeding independently associated with mortality (BIMS). Such data may be useful to clinicians participating in preoperative assessment, those taking care of patients in the perioperative time, and those involved in the long-term care of those patients after surgery. Reading about those patients leads me to reflect on my place of work — an intensive care unit — where such patients frequently are admitted after surgery.

First, patients with indications for aortic surgery are all high-risk patients. Parts of the cardiovascular system usually do not get diseased in isolation from other parts — aortic disease is frequently associated with disease in the coronary, cranial, mesenteric, and peripheral circulation. As a group, those patients have a high prevalence of risk factors for complications: hypertension, diabetes, heart failure, previously diagnosed coronary artery disease (CAD), and, if not, in most cases undiagnosed CAD disease. Moreover, most are older (regardless of how we define it). The authors report one-month mortality among all those patients as 6.9% although it may well differ dramatically depending on circumstances, for example, ruptured aneurysm versus elective surgery.

The second issue, and the first surprise, is the frequency of those events: >40% in the case of MINS, >40% in the case of BIMS, and over 15% in the case of AKI. Admittedly, the criteria for finding them are lax — for example, a small increase in troponins or 6-hour urine output below 0.5 cc/kg/h or transfusion of 1 unit of packet red blood cells (pRBC, about 300 ml). No question that if we look for such events, there will be plenty of them.

The third issue is the prognostic significance of the occurrence of those events (MINS, BIMS, AKI). This is another surprise for most of us — having MINS diagnosed (vs. not) is associated with mortality of 12.4% vs. 2.6%; in the case of BIMS the corresponding numbers are 12.3% vs. 1.7% and for AKI 32.6% vs. 1.1%. These are likely eye-opening numbers.

The fourth and fifth issues are of utmost importance. To start, could we improve prognosis by preventing those events? We know the characteristics of those patients (older, with multiple comorbidities). We know at least some of the perioperative factors associated with them — for example, tachycardia, or depth and duration of hypotension — even mean blood pressure below 65 mm Hg and certainly below 55 mm Hg, and even for a few minutes [2, 3]. Could we prevent those events and their consequences? The answer is not clear, and, so far, a series of well-done randomized controlled trials have failed to confirm the usefulness of several interventions, including antiplatelet therapy (ASA), beta-blockers, clonidine, or even a strategy aimed at avoiding hypotension [4]. However, it seems that a strong focus on avoiding hypotension (dehydration, bleeding, excessive sedation) and tachycardia, even as a marker of ongoing problems (dehydration, pain, or not taking pre-op beta-blockers) in the postoperative time, will not hurt and may well help our patients. The importance of rapid recognition of intraoperative and postoperative bleeding

seems crucial. Speed of reaction to those events, as well as speed of reaction to renal dysfunction (usually related to hypovolemia or hypotension), is likely to play a role. All this requires system-wide ability to detect and appropriately react to the physiological phenomena (monitoring technology and presence of trained personnel to react to observations) [5].

The last issue is what to do once we detect those events. This is not entirely clear, and the course of action may depend not only on the nature and severity of complications but also on a host of other factors. Renal injury and the need for transfusion are likely consequences of a one-time event. The issue of troponin elevation in a person at high risk requires more in-depth considerations. There is reasonably compelling although non-conclusive observational evidence suggesting use of ASA and lipid-lowering therapy (statin) in MINS patients. Otherwise, the management (investigations and treatment) may range from "not much" to multi-pronged pharmacological treatment, either permanent or until further risk stratification is completed. Those investigations may vary in scope and intensity from regular stress tests (likely in patients considered very low risk due to lack of major cardiovascular risk factors and minor troponin elevation without ongoing or documented dynamic ECG changes), through echocardiogram checks to look for wall motion abnormalities, pharmacologic stress testing looking for ischemia and its extent, and non-invasive imaging tests (for example, computed tomography angiography), to regular coronary angiography investigations with PCI intervention if needed. What can be done will also depend on patients' values and preferences and the system's ability to "process" a large number of patients, hence there will be different thresholds for action in different geographic areas, further modified by patients' choices. In terms of treatments, attention to and control of modifiable risk factors (smoking, hypertension, hyperlipidemia, and diabetes) are crucial, with consideration given to the use of renin-angiotensin blockade (ACEi or ARB), beta-blockers, and, when indicated, SGLT-2 inhibitors.

In conclusion, from the perspective of an ICU clinician, the occurrence of complications is common and has significant prognostic implications. Once detected, complications should not be ignored but managed with an explicit plan of action, even if it includes 'only' referral for future risk assessment.

Article information

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REFERENCES

1. Studzińska D, Polok K, Chwała M, et al. The incidence of cardiovascular and other major complications after open abdominal aortic surgery. Kardiol Pol. 2023; 81(9) : 870–877, doi: 10.33963/KP.a2023.0153, indexed in Pubmed: 37401577.
2. Ruetzler K, Smilowitz NR, Berger JS, et al. Diagnosis and management of patients with myocardial injury after noncardiac surgery: a scientific statement from the American Heart Association. Circulation. 2021; 144(19): e287–e305, doi: 10.1161/CIR.0000000000001024, indexed in Pubmed: 34601955.
3. Salmasi V, Maheshwari K, Yang D, et al. Relationship between Intraoperative Hypotension, Defined by Either Reduction from Baseline or Absolute Thresholds, and Acute Kidney and Myocardial Injury after Noncardiac Surgery: A Retrospective Cohort Analysis. Anesthesiology. 2017; 126(1): 47–65, doi: 10.1097/ALN.0000000000001432, indexed in Pubmed: 27792044.
4. Marcucci M, Painter TW, Conen D, et al. Hypotension-Avoidance versus hypertension-avoidance strategies in noncardiac surgery: an international randomized controlled trial. Ann Intern Med. 2023; 176(5): 605–614, doi: 10.7326/M22-3157, indexed in Pubmed: 37094336.
5. Szczeklik W, Fronczek J, Górka J, et al. Attitudes of healthcare professionals towards the introduction of rapid response teams in Poland: a survey study after 6 months of a pilot program in 25 hospitals. Pol Arch Intern Med. 2019; 129(12): 949–955, doi: 10.20452/pamw.15092, indexed in Pubmed: 31808754.

Shockwave Intravascular Lithotripsy in all-comers with resistant *de novo* calcified coronary disease or stent underexpansion: Growing evidence

George Kassimis[1], Grigoris V Karamasis[2]

[1]2nd Department of Cardiology, Hippokration Hospital, Medical School, Aristotle University of Thessaloniki, Greece
[2]2nd Department of Cardiology, Attikon University Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece

Related article
by Rola et al.

Correspondence to:
George Kassimis MD, MSc, PhD, FESC, FRCP,
2nd Department of Cardiology, Hippokration Hospital, Medical School, Aristotle University of Thessaloniki,
49 Konstantinoupoleos road, 54642, Thessaloniki, Greece,
phone: +30 23 108 92 349,
e-mail: gksup@yahoo.gr

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Over the past few years, the number of percutaneous coronary interventions (PCI) performed in patients with severely calcified coronary artery disease (CAD) has significantly increased [1]. Heavily calcified lesions are challenging in terms of adequate lesion preparation, equipment delivery, and optimal stent deployment [2]. Several PCI adjunctive tools for plaque modification have been introduced to deal with severely calcified lesions safely and effectively [3].

Shockwave Intravascular Lithotripsy (S-IVL) has emerged as a novel therapy for the treatment of vascular calcification [2]. The Shockwave Medical Coronary IVL catheter (Santa Clara, CA, US) consists of a 0.014-inch guidewire-compatible balloon catheter with two lithotripsy emitters incorporated into the shaft of a 12-mm-long balloon [4]. The IVL catheter is delivered, inflated, and deflated as any other balloon. During brief and low-pressure balloon inflation, 10 IVL pulses are delivered creating acoustic shockwaves that spread circumferentially and transmurally with minimal effect on soft tissue while imparting compressive stress on calcified plaques [4]. Each balloon catheter can deliver up to 80 pulses or 120 with the latest generation Shockwave C^{2+} system with interval deflations to allow distal coronary perfusion [4].

The safety and efficacy of the S-IVL system have been supported by the company-sponsored single-arm prospective DISRUPT CAD studies (I, II, III, and IV) [5]. In a patient-level pooled analysis of these studies reporting results from 628 patients across 72 sites in 12 countries, the primary safety (i.e., absence of in-hospital major adverse cardiovascular events) and effectiveness (i.e., procedural success) endpoints were achieved in 92.7% and 92.4% of patients, respectively [5]. At 30 days, the rates of target lesion failure, cardiac death, and stent thrombosis were 7.2%, 0.5%, and 0.8%, respectively. Rates of post-IVL and final serious angiographic complications were 2.1% and 0.3%, with no IVL-associated perforations, abrupt closures, or episodes of no reflow [5].

In this issue of *Kardiologia Polska* (*Polish Heart Journal*), Rola et al. [6] present data from the Lower Silesia Shockwave Registry (LSSR). The registry includes 131 PCI cases where the S-IVL system was used between May 2019 and September 2022 in two high-volume Polish cardiac centers. S-IVL was used either for calcium modification in resistant calcified lesions before stent deployment (76% of recruited cases) or for stent optimization in significantly underexpanded previously implanted stents (25% of cases). The study evaluated procedural success and clinical outcomes in-hospital and in 6-month follow-up. Procedural success was met in 96% of cases, with 3 cases of device failure (i.e., S-IVL balloon rupture) without clinical consequences. Regarding clinical outcomes, in-hospital MACE was 4.6% and 7.9% at 6 months.

Several clinical and procedural aspects of the study are important and add to the existing literature. Firstly, 87% of the patients presented with acute coronary syndrome (ACS)

(8.4% ST-segment elevation myocardial infarction [STEMI] and 74% non-STEMI [NSTEMI]). ACS was essentially an exclusion criterion for the DISRUPT CAD studies. Nevertheless, ACS cases represent a significant part of PCI procedures in high-volume cardiac centers. Calcified culprit lesions are frequent in NSTEMI and STEMI patients undergoing urgent or emergency PCI and directly impact future target lesion failure [7, 8]. Having an easy, safe, and effective method for calcium modification is important, and the current study supports S-IVL use in this cohort.

In 1 of 4 cases in the LSS Registry, S-IVL was used to treat significant underexpansion of previously implanted stents. Although initially an "off-label" use, S-IVL for stent restenosis secondary to underexpansion became a popular strategy for this challenging clinical scenario with limited therapeutic options [9–11]. The LSSR data show that S-IVL is a relatively safe and effective approach when dealing with stent underexpansion.

The previous use of rotational or orbital atherectomy was not an exclusion criterion for the study, and 13.7% of the patients had atherectomy debulking before S-IVL use. The occasional complementary use of the 2 calcium-modifying modalities should be noted, a strategy that appeared to be safe and effective in a recently published report from the international multicenter Rota-Shock Registry [12]. Finally, the left main artery constituted 20.6% of the treated vessels in the study, adding to previous reports [13, 14] that supported S-IVL use to treat LM lesions (another exclusion criterion in the DISRUPT CAD studies).

The current study carries the inherent limitations of registry-based studies such as potential selection bias, retrospective data collection, and lack of a control group or adjudication for procedural and clinical endpoints. From a procedural perspective, the lack of universal post-dilation (applied in 77% of cases) and the relatively low use of intracoronary imaging for the specific cohort (23.7%) should be noted.

Nevertheless, the study by Rota et al. provides real-life data in a high-risk population supporting the use of S-IVL as an everyday tool for calcium modification. This kind of data are necessary for S-IVL to demonstrate its safety and efficacy outside the "sterile" environment of clinical studies where several exclusion criteria are applied. In conclusion, the Lower Silesia Shockwave Registry showed short- and long-term safety and efficacy for S-IVL in the treatment of resistant *de novo* calcified coronary disease and stent underexpansion. Still, the lack of comparative studies in the literature regarding S-IVL is striking. Studies comparing S-IVL with other calcium/plaque modifying techniques are needed. Furthermore, the high price of the device compared to alternative modalities, merits cost-effectiveness analysis and adequate reimbursement policies [15].

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REFERENCES

1. Barbato E, Gallinoro E, Abdel-Wahab M, et al. Management strategies for heavily calcified coronary stenoses: an EAPCI clinical consensus statement in collaboration with the EURO4C-PCR group. Eur Heart J. 2023 [Epub ahead of print], doi: 10.1093/eurheartj/ehad342, indexed in Pubmed: 37208199.
2. Kassimis G, Didagelos M, De Maria GL, et al. Shockwave Intravascular Lithotripsy for the Treatment of Severe Vascular Calcification. Angiology. 2020; 71(8): 677–688, doi: 10.1177/0003319720932455, indexed in Pubmed: 32567327.
3. Kassimis G, Raina T, Kontogiannis N, et al. How Should We Treat Heavily Calcified Coronary Artery Disease in Contemporary Practice? From Atherectomy to Intravascular Lithotripsy. Cardiovasc Revasc Med. 2019; 20(12): 1172–1183, doi: 10.1016/j.carrev.2019.01.010, indexed in Pubmed: 30711477.
4. Kereiakes DJ, Virmani R, Hokama JY, et al. Principles of Intravascular Lithotripsy for Calcific Plaque Modification. JACC Cardiovasc Interv. 2021; 14(12): 1275–1292, doi: 10.1016/j.jcin.2021.03.036, indexed in Pubmed: 34167671.
5. Kereiakes DJ, Di Mario C, Riley RF, et al. Intravascular Lithotripsy for Treatment of Calcified Coronary Lesions: Patient-Level Pooled Analysis of the Disrupt CAD Studies. JACC Cardiovasc Interv. 2021; 14(12): 1337–1348, doi: 10.1016/j.jcin.2021.04.015, indexed in Pubmed: 33939604.
6. Rola P, Furtan Ł, Włodarczak S, et al. Safety and efficacy of a novel calcified plaque modification device - Shockwave Intravascular Lithotripsy - in all-commers with Coronary Artery Disease: Mid-term outcomes. Kardiol Pol. 2023; 81(9): 878–885, doi: 10.33963/KP.a2023.0152, indexed in Pubmed: 37448216.
7. Généreux P, Madhavan MV, Mintz GS, et al. Ischemic outcomes after coronary intervention of calcified vessels in acute coronary syndromes. Pooled analysis from the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) and ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) TRIALS. J Am Coll Cardiol. 2014; 63(18): 1845–1854, doi: 10.1016/j.jacc.2014.01.034, indexed in Pubmed: 24561145.
8. Kurihara O, Takano M, Yamamoto E, et al. Calcified plaques in patients with acute coronary syndromes. JACC Cardiovasc Interv. 2019; 12(6): 531–540, doi: 10.1016/j.jcin.2018.12.013, indexed in Pubmed: 30898249.
9. Kassimis G, Didagelos M, Kouparanis A, et al. Intravascular ultrasound-guided coronary intravascular lithotripsy in the treatment of a severely under-expanded stent due to heavy underlying calcification. To re-stent or not? Kardiol Pol. 2020; 78(4): 346–347, doi: 10.33963/KP.15173, indexed in Pubmed: 32024806.
10. Tovar Forero MN, Sardella G, Salvi N, et al. Coronary lithotripsy for the treatment of underexpanded stents: the international & multicentre CRUNCH registry. EuroIntervention. 2022; 18(7): 574–581, doi: 10.4244/EIJ-D-21-00545, indexed in Pubmed: 35318955.
11. Honton B, Lipiecki J, Monségu J, et al. Mid-term outcome of de novo lesions vs. in stent restenosis treated by intravascular lithotripsy procedures: Insights from the French Shock Initiative. Int J Cardiol. 2022; 365: 106–111, doi: 10.1016/j.ijcard.2022.07.023, indexed in Pubmed: 35870637.

12. Sardella G, Stefanini G, Leone PP, et al. Coronary lithotripsy as elective or bail-out strategy after rotational atherectomy in the rota-shock registry. Am J Cardiol. 2023; 198: 1–8, doi: 10.1016/j.amjcard.2023.04.032, indexed in Pubmed: 37182254.
13. Salazar CH, Gonzalo N, Aksoy A, et al. Feasibility, safety, and efficacy of intravascular lithotripsy in severely calcified left main coronary stenosis. JACC Cardiovasc Interv. 2020; 13(14): 1727–1729, doi: 10.1016/j.jcin.2020.04.022, indexed in Pubmed: 32703602.
14. Cosgrove CS, Wilson SJ, Bogle R, et al. Intravascular lithotripsy for lesion preparation in patients with calcific distal left main disease. EuroIntervention. 2020; 16(1): 76–79, doi: 10.4244/EIJ-D-19-01052, indexed in Pubmed: 32224480.
15. Kassimis G, Ziakas A, Didagelos M, et al. Shockwave coronary intravascular lithotripsy system for heavily calcified de novo lesions and the need for a cost-effectiveness analysis. Cardiovasc Revasc Med. 2022; 37: 128–134, doi: 10.1016/j.carrev.2021.06.125, indexed in Pubmed: 34246610.

Tailoring guideline-directed medical therapy in heart failure with reduced ejection fraction: A practical guide

Agnieszka Kapłon-Cieślicka[1], Panagiotis Vardas[2, 3], Marcin Grabowski[1], Małgorzata Lelonek[4]

[1]1st Chair and Department of Cardiology, Medical University of Warsaw, Warszawa, Poland
[2]Heart Sector, Hygeia Hospitals Groups, Athens, Greece
[3]Department of Cardiology, Medical School, University of Crete, Heraclion, Greece
[4]Department of Noninvasive Cardiology, Medical University of Lodz, Łódź, Poland

Correspondence to:
Agnieszka Kapłon-Cieślicka, MD, PhD,
1st Chair and Department of Cardiology,
Medical University of Warsaw,
Clinical Central Hospital, MUW Clinical Center,
Banacha 1A,
02–097 Warszawa, Poland,
phone: +48 22 599 29 58,
e-mail: agnieszka.kaplon@gmail.com

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ABSTRACT

According to the 2021 European Society of Cardiology guidelines, the four pillars of medical therapy in heart failure with reduced ejection fraction (HFrEF) include sodium-glucose co-transporter-2 inhibitors, beta-blockers, mineralocorticoid receptor antagonists, and angiotensin-converting enzyme inhibitors or angiotensin receptor-neprilysin inhibitors. However, in clinical practice, concomitant use of all four drug groups in target doses is often limited by their intolerance or fear of potential complications. Herein, we present strategies to initiate or modify HFrEF therapy in frequent but challenging clinical scenarios (symptomatic hypotension, atrial fibrillation, kidney disease or worsening renal function, hyperkalemia) in a way that does not lead to unnecessary reduction or cessation of life-saving treatment.

Key words: atrial fibrillation, hyperkalemia, hypotension, therapy optimization, worsening kidney function

INTRODUCTION

The 2021 European Society of Cardiology (ESC) guidelines have changed the algorithm of pharmacotherapy in heart failure with reduced ejection fraction (HFrEF) [1]. Apart from introducing sodium-glucose co-transporter-2 inhibitors (SGLT2i) as the fourth pillar of guideline-directed medical therapy (GDMT) in HFrEF, they have switched from a clearly outlined stepwise approach (with angiotensin-converting enzyme inhibitors [ACEi] and beta-blockers initiated in step 1, and mineralocorticoid receptor antagonists [MRA] in step 2) to a more general recommendation to implement the "fantastic four" (ACEi/angiotensin receptor-neprilysin inhibitors [ARNI], beta-blockers, MRA, and SGLT2i) in every patient with HFrEF [1, 2]. This has triggered a considerable debate about whether those four drug groups should be initiated simultaneously or stepwise, given their effects on hemodynamics, renal function, and potassium levels [3, 4]. In HFrEF, atrial fibrillation (AF), symptomatic hypotension, kidney disease, and hyperkalemia are common problems, which may mandate a modification in GDMT [5]. However, HFrEF patients mustn't be denied life-prolonging medications simply due to fear of their adverse effects in the setting of comorbidities or complications. Recently, consensus documents of the Heart Failure Association of the ESC have addressed common problems encountered in patients with HFrEF [5, 6]. Still, non-HF specialists often have concerns regarding full GDMT implementation and feel overwhelmed by the abundance of additional medications that may be indicated in HFrEF.

This practical guide aims to help non-HF specialists (general practitioners, internal medicine specialists, cardiologists, geriatricians, pulmonologists, nephrologists, and other physicians taking care of HFrEF patients) to develop an individualized approach to HFrEF pharmacotherapy based on patient clinical profiling.

INITIATION OF GDMT IN HFREF: GENERAL STRATEGY AND SPECIFIC SITUATIONS

If feasible, simultaneous initiation of drugs from all four groups (ACEi/ARNI, beta-blockers,

MRA, and SGLT2i) is advisable [3]. In fact, simultaneous initiation with rapid up-titration of GDMT has proven safe and is superior to sequential introduction with slow, stepwise titration, shortening the time required to reach the target doses of disease-modifying drugs [7]. Given that the reduction in cardiovascular endpoints with GDMT occurs as early as 2–6 weeks after its initiation, delaying its introduction with the traditional stepwise approach seems unjustified [7–10]. Notably, ARNI may be considered as first-line therapy in ACEi-naïve HFrEF patients, and such a strategy with cautious stepwise ARNI up-titration was proven safe and effective [1, 11–13]. Importantly, the STRONG-HF trial has demonstrated that rapid up-titration of GDMT in patients with acute HF reduces the risk of all-cause death or HF readmission in post-discharge follow-up [14].

Symptomatic hypotension

Still, some patients will not tolerate simultaneous introduction and/or up-titration of all four GDMT drug groups. One of the main barriers, especially in advanced HFrEF or in older, fragile patients is symptomatic hypotension. The prevalence of hypotension in HF is reported in 10-15% of clinical trials; however, it is significantly higher in routine clinical practice [15]. In the WET-HF registry, in patients discharged after HFrEF decompensation, 35% had systolic blood pressure (BP) lower than 100 mm Hg, and the GDMT prescription rate in those patients was 63% [16]. ARNI should not be introduced if systolic blood pressure (BP) is lower than 100 mm Hg [5]. Symptomatic hypotension may also hinder initiation/up-titration of ACEi and beta-blockers, while SGLT2i and MRA have only a modest effect on BP [5]. Among MRA, eplerenone might be preferred in the setting of hypotension, given its lower antihypertensive potency compared to spironolactone [17, 18]. Within beta-blockers, bisoprolol or metoprolol CR/XL may be preferred in hypotensive patients over vasodilating beta-blockers, especially if the heart rate (HR) exceeds 70 bpm. In patients with sinus rhythm and HR over 70 bpm., ivabradine may be added if beta-blockers cannot be up-titrated due to symptomatic hypotension [5]. In contrast to sinus rhythm, there is no evidence for a prognostic benefit of beta-blockers in HFrEF with atrial fibrillation (AF), and HR of <70 bpm has been associated with unfavorable outcomes [19, 20]. Thus, in hypotensive HFrEF patients with AF, beta-blockers may be reduced or even discarded, with digoxin used for rate control if needed (maintaining a ventricular rate of >70 bpm) [5]. This approach may allow initiation and up-titration of ACEi/ARNI.

Chronic kidney disease

Another common problem in HFrEF is chronic kidney disease (CKD), which affects up to half of all HFrEF patients [21]. In CKD patients, a common concern is an anticipated, further decrease in estimated glomerular filtration rate (eGFR) and a rise in serum potassium after initiation of renin-angiotensin-aldosterone system inhibitors (RAASi). In the ESC HF Long-Term registry, serum potassium ≥5.0 mmol/l was present in 16%, and ≥5.5 mmol/l — in 3.5% of chronic HF patients [22]. In long-term follow-up, approximately one-quarter of HF patients develop hyperkalemia [23]. However, given that CKD is associated with a doubled risk of all-cause death in HFrEF (and thus constitutes a stronger prognostic factor than left ventricular ejection fraction), HFrEF patients with concomitant CKD are most likely to benefit from GDMT [24]. Furthermore, most of the HFrEF "fantastic four" (namely ACEi/ARNI and SGLT2i) exert not only cardioprotective but also nephroprotective actions [25-28]. Thus, while contraindications should, naturally, be followed (MRA contraindicated with eGFR of <30 ml/min/1.73 m^2, dapagliflozin — with eGFR of <25 ml/min/1.73 m^2, and empagliflozin — with eGFR of <20 ml/min/1.73 m^2), HFrEF patients with CKD should not be denied life-saving pharmacotherapy for HFrEF, and GDMT should be implemented and cautiously up-titrated in those patients [6]. Importantly, a drop in eGFR after introduction of RAASi and SGLT2i is not only acceptable (and with no need for RAASi dose reduction unless a rise in creatinine exceeds 50% from baseline) but actually indicative of a more potent nephroprotective effect, as it results from lowering the hydrostatic pressure in glomerulus due to predominant vasodilation of *vas efferens* with ACEi and SGLT2i [6]. Reduction of intraglomerular hypertension initially manifests itself as lower glomerular filtration but, over time, protects the kidneys from glomerular loss and, thus, reduces the slope of eGFR decline. In HF, this positive effect on eGFR slope is most evident with SGLT2i, strong with ARNI, and for ACEi and angiotensin receptor blockers — observed only in those with diabetes [6, 25–30].

Table 1 presents the recommended approaches to GDMT initiation in HFrEF patients, depending on clinical profiles.

ADJUSTING DIURETIC THERAPY IN HFREF

Although they are not disease-modifying drugs, diuretics are a mainstay of HF therapy. Diuretics are recommended in HFrEF patients with symptoms and/or signs of congestion to alleviate symptoms and reduce HF hospitalization admissions [1]. Diuretic therapy aims to achieve and maintain euvolemia with the lowest diuretic dose. Complete diuretic withdrawal is also a viable option in stable euvolemic HFrEF patients [31]. Achieving and maintaining euvolemia is important, not solely for improving symptom control and quality of life, but also for prognosis, and even residual congestion after HF decompensation was shown to be associated with adverse outcomes [31, 32].

Loop diuretics are the first-line treatment used for decongestion. In acute, congested HFrEF patients, they are given intravenously, and their efficacy should be monitored with systematic measurements of urine output and sodium excretion (urine spot analysis). Inadequate diuresis and/or sodium excretion dictates doubling the dose of a loop diuretic, repeated until the maximum dose has been

Table 1. Initiation of guideline-directed medical therapy in heart failure with reduced ejection fraction depending on the patient's clinical profile

Clinical profile of a HFrEF patient	ACEi / ARNI	BB	MRA	SGLT2i	Other agents
Sinus rhythm					
Sinus rhythm, normotension, normocardia, eGFR >60 ml/min/1.73 m^2, normokalemia	ACEi[1] → ARNI *or* ARNI[2]	BB[3]	MRA[4]	SGLT2i[5]	Loop diuretic[6] (if congested)
Sinus rhythm, SBP <100 mm Hg, HR >70 bpm, eGFR >60 ml/min/1.73 m^2, normokalemia	ACEi ARNI	BB (bisoprolol or metoprolol CR/XL may be preferred)	MRA (eplerenone may be preferred)	SGLT2i	Ivabradine Loop diuretic (if congested)
Sinus rhythm, SBP <100 mm Hg, HR <70 bpm, eGFR >60 ml/min/1.73 m^2, normokalemia	ACEi ARNI	BB	MRA (eplerenone may be preferred)	SGLT2i	Loop diuretic (if congested)
Atrial fibrillation					
Non-paroxysmal AF, normotension, eGFR >60 ml/min/1.73 m^2, normokalemia	ACEi → ARNI *or* ARNI	BB (for rate control)	MRA	SGLT2i	OAC[7] Digoxin (if needed for rate control) Loop diuretic (if congested)
Non-paroxysmal AF, SBP <100 mm Hg, eGFR >60 ml/min/1.73 m^2, normokalemia	ACEi ARNI	BB (can be discarded)	MRA (eplerenone may be preferred)	SGLT2i	OAC Digoxin (if needed for rate control) Loop diuretic (if congested)
Kidney disease and hyperkalemia					
Sinus rhythm, normotension, normocardia, eGFR 30–60 ml/min/1.73 m^2	ACEi → ARNI *or* ARNI	BB	MRA (initiate triple therapy with ACEi/ARNI + BB + SGLT2i → in 1–2 weeks if eGFR >30 ml/min/1.73 m^2 and K+ <5.0 mmol/l → add MRA)	SGLT2i	Loop diuretic (if congested)
Sinus rhythm, normotension, normocardia, eGFR 15–30 ml/min/1.73 m^2	ACEi ARNI[8]	BB	MRA	SGLT2i (empagliflozin when eGFR >20 ml/min/1.73m^2; dapagliflozin when eGFR >25 ml/min/1.73 m^2)	Loop diuretic (if congested)
Sinus rhythm, normotension, normocardia, eGFR <15 ml/min/1.73 m^2	ACEi ARNI	BB	MRA	SGLT2i	Hydralazine or isosorbide dinitrate (may be considered)
Sinus rhythm, normotension, normocardia, hyperkalemia	ACEi / ARNI (do not initiate if K+ >5.4 mmol/l)	BB	MRA (do not initiate if K+ >5.0 mmol/l)	SGLT2i	K$^+$ binders[9] Loop diuretic

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARNI, angiotensin receptor-neprilysin inhibitor; BB, beta-blocker; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose co-transporter-2 inhibitor; HR, heart rate; bpm, beats per minute; SBP, systolic blood pressure; AF, atrial fibrillation; eGFR, estimated glomerular filtration rate; OAC, oral anticoagulant; K+, potassium

[1] ACEi listed in the ESC guidelines and registered for use in HF: captopril, enalapril, lisinopril, ramipril, trandolapril; ACEi not listed in the ESC guidelines but registered for HF in Poland: benazepril, quinapril, cilazapril, perindopril; ACEi not registered for HF in Poland: imidapril, zofenopril (zofenopril is registered for use in acute myocardial infarction with or without HF). [2]Sacubitril/valsartan. [3]BB listed in the ESC guidelines and registered for use in HFrEF: bisoprolol, carvedilol, metoprolol succinate (CR/XL), nebivolol. [4]MRA listed in the ESC guidelines and registered for use in HFrEF: eplerenone, spironolactone. [5]SGLT2i listed in the ESC guidelines and registered for use in HFrEF: dapagliflozin, empagliflozin. [6]Loop diuretics registered for use in HFrEF in Poland: furosemide, torasemide. [7]Non-vitamin K antagonist oral anticoagulants (NOAC) should be preferred to vitamin K antagonists (VKA), except for patients with moderate-to-severe mitral stenosis or mechanical prosthesis; NOAC registered for AF in Poland: dabigatran, rivaroxaban, apixaban. [8] According to the ESC guidelines [1] and ESC consensus documents [2, 3], ARNI should not be used when eGFR is <30 ml/min/1.73 m^2; according to Summary of Product Characteristics sacubitril/valsartan may be cautiously used in a lower dose in patients with eGFR <30 ml/min/1.73 m^2 and is contraindicated in end-stage kidney disease. [9]Unavailable in Poland

Medication that should be initiated from the start in all patients, preferably simultaneously, at low doses but with subsequent timely up-titration to target doses or maximum doses tolerated by the patient (up-titration refers to ACEi/ARNI, BB, and MRA)

Medication that should not be used

Medication that should be initiated cautiously, possibly step by step rather than simultaneously, in very small doses with subsequent cautious up-titration to maximum doses tolerated by the patient (up-titration refers to ACEi/ARNI, BB, and MRA). Loop diuretics should be intiated only in congested patients and continued at a minimum dose required for euvolemia (or disontinued if not needed)

Medication that can be discontinued

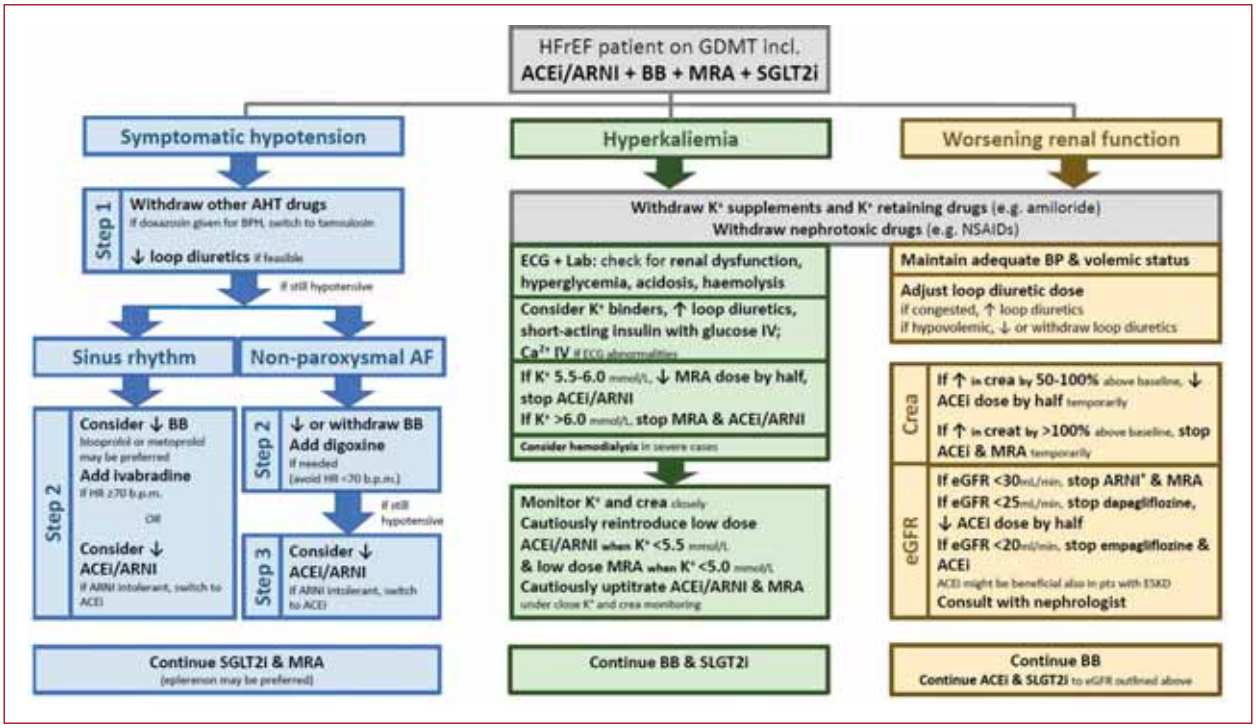

Figure 1. Modification of guideline-directed medical therapy in heart failure with reduced ejection fraction in specific clinical situations

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; AHT, antihypertensive; ARNI, angiotensin receptor-neprilysin inhibitor; bpm, beats per minute; BB, beta-blocker; BP, blood pressure; BPH, benign prostatic hyperplasia; Ca^{2+}, calcium; crea, creatinine; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; GDMT, guideline-directed medical therapy; HR, heart rate; HRrEF, heart failure with reduced ejection fraction; incl., including; K^+, potassium; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose co-transporter-2 inhibitor

*According to the ESC guidelines [1] and ESC consensus documents [2, 3], ARNI should not be used when eGFR is <30 ml/min/1.73 m^2; according to SmPC, sacubitril/valsartan may be cautiously used in a lower dose in patients with eGFR <30 ml/min/1.73 m^2, and is contraindicated in end-stage kidney disease

reached [1, 31, 33]. In refractory cases, a combination of loop diuretics with diuretic agents that block sodium reabsorption at different sites in the nephron, such as thiazides (distal convoluted tubule) or acetazolamide (proximal convoluted tubule), i.e. sequential nephron blockade, may help overcome diuretic resistance [1, 31]. Importantly, of disease-modifying drugs, not only MRA but also SGLT2i and ARNI possess diuretic properties and may enhance the diuretic effect of loop diuretics [31, 34, 35].

Modification of GDMT in HFrEF: Specific situations

Patients with chronic HFrEF experience not only HF exacerbations but also other problems (e.g. hypotension, worsening renal function, hyperkalemia, hypokalemia, hyponatremia), which may represent GDMT complications but can also result from disease progression (or, usually, the interplay between both) [5, 31, 36–38]. Irrespective of their etiology, these problems may require modification of HFrEF pharmacotherapy. Nonetheless, every effort should be made to maintain disease-modifying drugs, if possible, in adequate dosing. For example, hyperkalemia in HF was associated with discontinuation and lower doses of MRA during follow-up, and discontinuation of MRA due to hyperkalemia was associated with higher all-cause mortality in HFrEF [23].

Detailed algorithms for problem solving have been proposed in Figure 1. In each case, an attempt should be made to identify and treat the specific cause of deterioration. This includes a scrupulous assessment and, if needed, correction of the patient's volemic status. A decision to down-titrate disease-modifying drugs should always be preceded by a careful revision of current pharmacotherapy, and reduction or withdrawal of other agents (e.g. other antihypertensives or loop diuretics in patients with symptomatic hypotension, nephrotoxic drugs, and potassium supplements in those with worsening renal function and/or hyperkalemia, thiazide-type diuretics in those with hyponatremia) [36–38]. If disease-modifying drugs are reduced or temporarily withdrawn, an attempt to re-introduce or up-titrate them should be made as soon as the complication has resolved [5].

PRACTICAL CHECKLISTS TO OPTIMIZE GDMT IMPLEMENTATION IN CHALLENGING CLINICAL SCENARIOS

In HFrEF, cardiac and extracardiac comorbidities as well as complications arising in the course of the disease may impose therapy modification, which, in real-world practice, often results in underutilization of GDMT. Even more worrisome, a fear of potential complications (such as fear of

hypotension with concomitant use of ACEi/ARNI, MRA, and beta-blockers, or fear of worsening renal function and/or hyperkalemia with concomitant ACEi/ARNI and MRA use), even before they occur, often limits full implementation of GDMT. This is unjustified, given the long-term positive effect of HFrEF medications on left-ventricular remodeling and function (leading to increased cardiac output and less hypotension), nephroprotective actions of ACEi/ARNI and SGLT2i (leading to preservation of kidney function), and reduced risk for hyperkalemia with MRA when used in combination with ARNI or SGLT2i [25–31, 39–41].

Thus, despite evidence for prognosis improvement with GDMT, its implementation remains poor, and most HFrEF patients do not receive drugs from all recommended groups or do not reach their target doses [42–44]. Herein, we provide practical checklists to help non-HF specialists adjust pharmacotherapy in some common clinical situations in a way that would prevent any unnecessary down-titration or cessation of life-saving HFrEF medications (*Checklists 1–3*). Notably, different clinical scenarios require different strategies, and handling of the same problem (e.g. hypotension) may differ depending on patient comorbidities (e.g. atrial fibrillation; see *Checklists 1 and 2*). Furthermore, patients' clinical and laboratory status changes over time, which should lead to appropriate adjustment of hitherto therapy. For example, a patient's kidney function may deteriorate (requiring therapy modification) but also improve under treatment (enabling introduction of previously contraindicated agents or drug up-titration; see *Checklist 3*). One of the key factors determining therapy modification in different

Checklist 1. Heart failure with reduced ejection fraction (HFrEF) and sinus rhythm

HFrEF + sinus rhythm	
☐ ACEi/ARNI ☐ Beta-blockers ☐ MRA ☐ SGLT2i	To improve prognosis
Problem-solving: symptomatic hypotension	
STEP 1	☐ Withdraw other antihypertensives ☐ Consider reduction or withdrawal of loop diuretics (in hypo- or euvolemic patients)*
If still hypotensive	
STEP 2	☐ Continue SGLT2i and MRA • Consider switching from spironolactone to eplerenone ☐ Consider dose reduction of ACEi/ARNI or beta-blocker but refrain from withdrawal if possible • Consider switching beta-blocker to bisoprolol or metoprolol CR/XL • Consider switching from ARNI to ACEi

*Assessment of volemia/congestion should include: clinical assessment (weight change, presence of pulmonary congestion, peripheral edema, hepatomegaly, pleural effusion, ascites, and signs of increased jugular venous pressure) and laboratory testing (natriuretic peptides concentrations and their changes, echocardiography with estimation of left ventricular filling pressures, assessment of the inferior vena cava, and assessment of congestion on chest X-ray and/or lung ultrasound) [31, 44, 45].

Checklist 2. Heart failure with reduced ejection fraction (HFrEF) and non-paroxysmal atrial fibrillation (AF)

HFrEF + non-paroxysmal AF	
☐ OAC ☐ ACEi/ARNI ☐ MRA ☐ SGLT2i	To improve prognosis
☐ Beta-blocker ☐ Digoxin	For HR control
Problem-solving: symptomatic hypotension	
STEP 1	☐ Withdraw other antihypertensives ☐ Consider reduction or withdrawal of loop diuretics (in hypo- or euvolemic patients)*
If still hypotensive	
STEP 2	☐ Continue SGLT2i and MRA • Consider switching from spironolactone to eplerenone ☐ Consider dose reduction or withdrawal of a beta-blocker • Use digoxin (with or without a beta-blocker) for HR control • Keep HR >70 b.p.m • If still on beta-blocker, switch to bisoprolol or metoprolol CR/XL ☐ Continue ACEi/ARNI
If still hypotensive	
STEP 3	☐ Consider dose reduction of ACEi/ARNI but refrain from withdrawal if possible • Consider switching from ARNI to ACEi

*Assessment of volemia/congestion should include: clinical assessment (weight change, presence of pulmonary congestion, peripheral edema, hepatomegaly, pleural effusion, ascites, and signs of increased jugular venous pressure) and laboratory testing (natriuretic peptides concentrations and their changes, echocardiography with estimation of left ventricular filling pressures and assessment of the inferior vena cava, and assessment of congestion on chest X-ray and/or lung ultrasound) [31, 44, 45].

Checklist 3. Heart failure with reduced ejection fraction (HFrEF) and renal dysfunction

HFrEF + chronic kidney disease (CKD)			
☐ ACEi/ARNI ☐ SGLT2i		of HFrEF and CKD (cardio- and nephro-protection)	To improve prognosis
☐ MRA ☐ Beta-blocker		of HFrEF (cardio-protection)	
Problem-solving: GDMT in HFrEF with CKD			
eGFR, ml/min/1.73 m²	**Drugs to be initiated/continued**	**Drugs to be discontinued**	
>30	☐ ACEi/ARNI ☐ MRA ☐ Beta-blocker ☐ SGLT2i		
25–30	☐ ACEi (low dose) ☐ Beta-blocker ☐ SGLT2i	☐ ARNI* ☐ MRA	
20–25	☐ ACEi (low dose) ☐ Beta-blocker ☐ Empagliflozin	☐ ARNI* ☐ MRA ☐ Dapagliflozin	
<20	☐ Beta-blocker	☐ ARNI* ☐ MRA ☐ SGLT2i	
	☐ ACEi (low dose) may be beneficial in end-stage CKD (especially if on dialysis) – consult with a nephrologist		
Problem-solving: worsening renal function (WRF) in HFrEF			
STEP 1 **General measures**	☐ Identify WRF cause (pre-renal, renal, post-renal) and treat it ☐ Withdraw nephrotoxic drugs (e.g. NSAIDs) ☐ Withdraw K+ supplements and K+ retaining drugs (e.g. amiloride) ☐ Monitor serum creatinine, urea/BUN, electrolytes and urine output ☐ Assess BP, congestion, and volume status • If congested, intensify diuretic treatment** • If hypovolemic, withdraw loop diuretics**		
STEP 2 **GDMT modification**	**Increase in serum creatinine from baseline**	**Serum creatinine, mg/dl**	**eGFR, ml/min/1.73 m²**	**GDMT modification**
	<50%	<3.0	>25 (<10% decrease from baseline)	NO
	50%–100%	3.0–3.5	20–25	Temporarily reduce ACEi/ARB dose by half
	>100%	>3.5	<20	Stop RAASi

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARNI, angiotensin receptor-neprilysin inhibitor; bpm, beats per minute; BUN, blood urea nitrogen; BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GDMT, guideline-directed medical therapy; HR, heart rate; HFrEF, heart failure with reduced ejection fraction; K+, potassium; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose co-transporter-2 inhibitor; OAC, oral anticoagulant; WRF, worsening renal function; NSAID, non-steroidal anti-inflammatory drugs; RAASi, renin-angiotensin-aldosterone system inhibitors

*According to the ESC guidelines [1] and ESC consensus documents [2, 3], ARNI should not be used when eGFR is <30 ml/min/1.73 m²; according to SmPC, sacubitril/valsartan may be cautiously used in a lower dose in patients with eGFR <30 ml/min/1.73 m² and is contraindicated in end-stage kidney disease. **Assessment of volemia/congestion should include: clinical assessment (weight change, presence of pulmonary congestion, peripheral edema, hepatomegaly, pleural effusion, ascites, and signs of increased jugular venous pressure) and laboratory testing (natriuretic peptides concentrations and their changes, echocardiography with estimation of left ventricular filling pressures and assessment of the inferior vena cava, and assessment of congestion on chest X-ray and/or lung ultrasound) [26, 39, 40]

clinical scenarios is assessment of the patient's volemic status and signs of congestion [31, 45, 46].

Clinical case 1: Ambulatory HFrEF patient with chronic kidney disease

A 68-year-old man was referred to an ambulatory HF center due to newly diagnosed HFrEF (on transthoracic echocardiogram: EF 33%, regional contractile abnormalities suggestive of ischemic HF etiology). He reported moderate limitation in physical activity (New York Heart Association [NYHA], class II) in the previous few months and denied any chest pain. He was a smoker, with untreated hypercholesterolemia and a history of posttraumatic left nephrectomy 20 years earlier. On physical examination, there were no signs of congestion and BP was 135/80 mm Hg. Electrocardiogram showed sinus rhythm of 80 bpm, and a QS complex in leads V2–V3. Laboratory tests showed a creatinine level of 1.48 mg/dl with eGFR of 47 ml/min/1.73 m², potassium of 4.4 mmol/l, NT-proBNP of 2100 pg/ml, and low-density lipoprotein (LDL) cholesterol of 136 mg/dl.

Given reduced eGFR, triple HFrEF therapy was initiated, including metoprolol CR 25 mg once daily (o.d.), empagliflozin 10 mg o.d., and sacubitril/valsartan 24/26 mg twice daily (b.i.d). Furthermore, due to suspected ischemic etiology, antiplatelet and statin treatment was initiated, and elective coronary angiography was scheduled.

Two weeks later, the patient came for ambulatory control. He reported improved exercise tolerance. His BP was 128/75 mm Hg and HR — 75 bpm. In laboratory tests, creatinine increased to 1.67 mg/dl (with eGFR of

41 ml/min/1.73 m^2), and potassium to 4.7 mmol/l. Given that the increase in creatinine was below 50%, and eGFR remained above 30 ml/min with potassium below 5.0 mmol/l, eplerenone 25 mg o.d. was initiated. Metoprolol CR dose was increased to 50 mg o.d.

On the subsequent control, 2 weeks later, creatinine was 1.71 mg/dl (with eGFR of 40 ml/min/1.73 m^2) and potassium was 4.9 mmol/l. Metoprolol CR and sacubitril/valsartan were further up-titrated (to 100 mg o.d. and 49/51 mg b.i.d., respectively).

Further 3 weeks later, the patient was in the New York Heart Association class I/II, with BP of 115/70 mm Hg and HR of 70 bpm, and had a creatinine level of 1.65 mg/dl and potassium level of 4.8 mmol/l, which allowed up-titration of eplerenone to the maximum dose of 50 mg o.d.; metoprolol CR dose was also increased. On the subsequent visit, 3 weeks later, sacubitril/valsartan was up-titrated to the maximum dose of 97/103 mg b.i.d.

Comment: This case demonstrates initiation of a triple HFrEF therapy in a patient with a baseline eGFR of 30–60 ml/min /1.73 m^2, followed by a timely introduction of an MRA, and subsequent up-titration of all HFrEF medication to target doses within 10 weeks from his initial presentation.

Clinical case 2: Hospitalized HFrEF patient with atrial fibrillation, hypotension, and worsening renal function

A 77-year-old woman with a long-standing history of dilative cardiomyopathy (EF 27%, left ventricular diastolic diameter of 62 mm) and paroxysmal AF (after 2 procedures of pulmonary vein isolation in the past, with a left atrial volume index of 61 ml/m^2) was admitted to hospital for HF decompensation. She reported increasing dyspnea and edema one month before hospitalization. Her previous HFrEF treatment consisted of carvedilol 25 mg b.i.d., ramipril 5 mg b.i.d., spironolactone 25 mg o.d., and dapagliflozin 10 mg o.d. She was also on chronic oral anticoagulation with apixaban. Her last known creatinine level before hospitalization was 1.1 mg/dl (eGFR, 48 ml/min/1.73 m^2). On admission, she was in AF with a ventricular rate of approximately 120 bpm and had BP of 100/55 mm Hg (without signs of hypoperfusion), with signs of both pulmonary and peripheral congestion (ankle edema, jugular vein distention). Her creatinine was 1.7 mg/dl, eGFR 29 ml/min/1.73 m^2, and potassium 5.8 mmol/l.

Attempted electrical cardioversion was unsuccessful. Carvedilol and spironolactone were stopped, ramipril dose was reduced, and digoxin was introduced together with intravenous furosemide treatment. This led to significant decongestion (improvement in symptoms and signs, weight reduction of 6 kg over 3 days), a reduction in creatinine (to 1.2 mg/dl) and potassium level (to 4.8 mmol/l), and a reduction in ventricular rate (to 100 bpm). The treatment was switched to oral furosemide. Bisoprolol was introduced (initially 2.5 mg o.d., later up-titrated to 5 mg o.d. to maintain a ventricular rate of approximately 80 bpm). Eplerenone (25 mg o.d.) was introduced, and ramipril was carefully up-titrated to 5 mg b.i.d. The patient's BP remained low (95/60 mm Hg, although without symptomatic hypotension) which precluded switching from ramipril to ARNI. The patient was discharged on day 7, in good general condition, with symptoms in NYHA class II, no signs of residual congestion, and with permanent AF. On discharge, she received bisoprolol 5 mg o.d. and digoxin 0.1 mg o.d. for rate control within AF, ramipril 5 mg b.i.d, eplerenone 50 mg o.d., dapagliflozine 10 mg o.d. and furosemide 40 mg o.d.

Comment: This case demonstrates HFrEF decompensation (possibly due to rapid ventricular rate within AF) with hypotension and worsening renal function. An increase in creatinine of >50% demanded a reduction in ACE inhibitor dose and temporary cessation of MRA. However, after decongestion with loop diuretics, kidney function was restored enabling up-titration of an ACE inhibitor and re-introduction of MRA (eplerenone was chosen due to its smaller hypotensive effect). Due to hypotension in this decompensated HFrEF patient, the beta-blocker (carvedilol) was temporarily stopped and subsequently exchanged for another (bisoprolol), with a smaller relative impact on BP and a greater impact on HR. Given that the patient remained hypotensive and in AF, up-titration of a beta-blocker was not deemed a priority, instead, digoxin was introduced for rate control. SGLT2i was maintained throughout hospitalization.

CONCLUSIONS

Patients with HFrEF remain under the care of many non-HF specialists, thus, this article aimed to provide practical guidance including checklists on initiation of HFrEF therapy and its modification in challenging clinical situations. Optimal HFrEF treatment should be based on the four pillars of GDMT (ACEi/ARNI, beta-blockers, MRA, and SGLT2i) and also utilize other therapies, depending on the patient's clinical profile, to provide the maximum benefit for each patient. Appropriate drug choice and titration enable effective HFrEF treatment even in complex clinical scenarios.

Article information

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REFERENCES

1. McDonagh T, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur J Heart Fail. 2022; 24(1): 4–131, doi: 10.1002/ejhf.2333.
2. Ponikowski P, Voors A, Anker S, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur J Heart Fai. 2016; 18(8): 891–975, doi: 10.1002/ejhf.592.
3. Straw S, McGinlay M, Witte KK. Four pillars of heart failure: contemporary pharmacological therapy for heart failure with reduced ejection fraction. Open Heart. 2021; 8(1), doi: 10.1136/openhrt-2021-001585, indexed in Pubmed: 33653703.
4. McMurray JJV, Packer M. How should we sequence the treatments for heart failure and a reduced ejection fraction? A redefinition of evidence-based medicine. Circulation. 2021; 143(9): 875–877, doi: 10.1161/CIRCULATIONAHA.120.052926, indexed in Pubmed: 33378214.
5. 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.
6. Mullens W, Martens P, Testani JM, et al. Renal effects of guideline-directed medical therapies in heart failure: a consensus document from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2022; 24(4): 603–619, doi: 10.1002/ejhf.2471, indexed in Pubmed: 35239201.
7. Brownell NK, Ziaeian B, Fonarow GC. The Gap to Fill: Rationale for Rapid Initiation and Optimal Titration of Comprehensive Disease-modifying Medical Therapy for Heart Failure with Reduced Ejection Fraction. Card Fail Rev. 2021; 7: e18, doi: 10.15420/cfr.2021.18, indexed in Pubmed: 34950508.
8. McMurray JJV, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014; 371(11): 993–1004, doi: 10.1056/NEJMoa1409077, indexed in Pubmed: 25176015.
9. Packer M, Anker SD, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med. 2020; 383(15): 1413–1424.
10. McMurray JJV, Solomon SD, Inzucchi SE, et al. DAPA-HF Trial Committees and Investigators. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019; 381(21): 1995–2008.
11. Senni M, McMurray JJV, Wachter R, et al. Initiating sacubitril/valsartan (LCZ696) in heart failure: results of TITRATION, a double-blind, randomized comparison of two uptitration regimens. Eur J Heart Fail. 2016; 18(9): 1193–1202, doi: 10.1002/ejhf.548, indexed in Pubmed: 27170530.
12. DeVore AD, Braunwald E, Morrow DA, et al. Angiotensin-Neprilysin inhibition in acute decompensated heart failure. N Engl J Med. 2019; 380(6): 539–548, doi: 10.1056/NEJMoa1812851, indexed in Pubmed: 30415601.
13. Witte KK, Wachter R, Senni M, et al. Rationale and design of TRANSITION: a randomized trial of pre-discharge vs. post-discharge initiation of sacubitril/valsartan. ESC Heart Fail. 2018; 5(2): 327–336, doi: 10.1002/ehf2.12246, indexed in Pubmed: 29239515.
14. Mebazaa A, Davison B, Chioncel O, et al. Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised, trial. Lancet. 2022; 400(10367): 1938–1952, doi: 10.1016/S0140-6736(22)02076-1, indexed in Pubmed: 36356631.
15. Cautela J, Tartiere JM, Cohen-Solal A, et al. Management of low blood pressure in ambulatory heart failure with reduced ejection fraction patients. Eur J Heart Fail. 2020; 22(8): 1357–1365, doi: 10.1002/ejhf.1835, indexed in Pubmed: 32353213.
16. Izumi K, Kohno T, Goda A, et al. Low blood pressure and guideline-directed medical therapy in patients with heart failure with reduced ejection fraction. Int J Cardiol. 2023; 370: 255–262, doi: 10.1016/j.ijcard.2022.10.129, indexed in Pubmed: 36270494.
17. Weinberger MH, Roniker B, Krause SL, et al. Eplerenone, a selective aldosterone blocker, in mild-to-moderate hypertension. Am J Hypertens. 2002; 15(8): 709–716, doi: 10.1016/s0895-7061(02)02957-6, indexed in Pubmed: 12160194.
18. Struthers A, Krum H, Williams GH. A comparison of the aldosterone-blocking agents eplerenone and spironolactone. Clin Cardiol. 2008; 31(4): 153–158, doi: 10.1002/clc.20324, indexed in Pubmed: 18404673.
19. Kotecha D, Holmes J, Krum H, et al. Efficacy of β blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. Lancet. 2014; 384(9961): 2235–2243, doi: 10.1016/S0140-6736(14)61373-8, indexed in Pubmed: 25193873.
20. Cleland JGF, Bunting KV, Flather MD, et al. Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials. Eur Heart J. 2018; 39(1): 26–35, doi: 10.1093/eurheartj/ehx564, indexed in Pubmed: 29040525.
21. Mullens W, Damman K, Testani JM, et al. Evaluation of kidney function throughout the heart failure trajectory - a position statement from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2020; 22(4): 584–603, doi: 10.1002/ejhf.1697, indexed in Pubmed: 31908120.
22. Rossignol P, Lainscak M, Crespo-Leiro MG, et al. Unravelling the interplay between hyperkalaemia, renin-angiotensin-aldosterone inhibitor use and clinical outcomes. Data from 9222 chronic heart failure patients of the ESC-HFA-EORP Heart Failure Long-Term Registry. Eur J Heart Fail. 2020; 22(8): 1378–1389, doi: 10.1002/ejhf.1793, indexed in Pubmed: 32243669.
23. Martens P, Kooij J, Maessen L, et al. The importance of developing hyperkalaemia in heart failure during long-term follow-up. Acta Cardiol. 2021; 76(6): 589–597, doi: 10.1080/00015385.2020.1748346, indexed in Pubmed: 32264757.
24. Damman K, Valente MAE, Voors AA, et al. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. Eur Heart J. 2014; 35(7): 455–469, doi: 10.1093/eurheartj/eht386, indexed in Pubmed: 24164864.
25. Heerspink H, Stefánsson B, Correa-Rotter R, et al. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2020; 383(15): 1436–1446, doi: 10.1056/nejmoa2024816.
26. Packer M, Butler J, Zannad F, et al. Empagliflozin and major renal outcomes in heart failure. N Engl J Med. 2021; 385(16): 1531–1533, doi: 10.1056/NEJMc2112411, indexed in Pubmed: 34449179.
27. Damman K, Gori M, Claggett B, et al. Renal effects and associated outcomes during angiotensin-neprilysin inhibition in heart failure. JACC Heart Fail. 2018; 6(6): 489–498, doi: 10.1016/j.jchf.2018.02.004, indexed in Pubmed: 29655829.
28. Spannella F, Giulietti F, Filipponi A, et al. Effect of sacubitril/valsartan on renal function: a systematic review and meta-analysis of randomized controlled trials. ESC Heart Fail. 2020; 7(6): 3487–3496, doi: 10.1002/ehf2.13002, indexed in Pubmed: 32960491.
29. Jhund PS, Solomon SD, Docherty KF, et al. Efficacy of dapagliflozin on renal function and outcomes in patients with heart failure with reduced ejection fraction: results of DAPA-HF. Circulation. 2021; 143(4): 298–309, doi: 10.1161/CIRCULATIONAHA.120.050391, indexed in Pubmed: 33040613.
30. Zannad F, Ferreira JP, Pocock SJ, et al. Cardiac and kidney benefits of empagliflozin in heart failure across the spectrum of kidney function: insights from EMPEROR-reduced. Circulation. 2021; 143(4): 310–321, doi: 10.1161/CIRCULATIONAHA.120.051685, indexed in Pubmed: 33095032.
31. Mullens W, Damman K, Mullens W, et al. The use of diuretics in heart failure with congestion - a position statement from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2019; 21(2): 137–155, doi: 10.1002/ejhf.1369, indexed in Pubmed: 30600580.
32. Rubio-Gracia J, Demissei BG, Ter Maaten JM, et al. Prevalence, predictors and clinical outcome of residual congestion in acute decompensated heart failure. Int J Cardiol. 2018; 258: 185–191, doi: 10.1016/j.ijcard.2018.01.067, indexed in Pubmed: 29544928.
33. Verbrugge FH. Utility of urine biomarkers and electrolytes for the management of heart failure. Curr Heart Fail Rep. 2019; 16(6): 240–249, doi: 10.1007/s11897-019-00444-z, indexed in Pubmed: 31741232.
34. Vardeny O, Claggett B, Kachadourian J, et al. Reduced loop diuretic use in patients taking sacubitril/valsartan compared with enalapril: the PARA-

DIGM-HF trial. Eur J Heart Fail. 2019; 21(3): 337–341, doi: 10.1002/ejhf.1402, indexed in Pubmed: 30741494.
35. Boorsma EM, Beusekamp JC, Ter Maaten JM, et al. Effects of empagliflozin on renal sodium and glucose handling in patients with acute heart failure. Eur J Heart Fail. 2021; 23(1): 68–78, doi: 10.1002/ejhf.2066, indexed in Pubmed: 33251643.
36. Kapłon-Cieślicka A, Soloveva A, Mareev Y, et al. Hyponatraemia in heart failure: time for new solutions? Heart. 2022; 108(15): 1179–1185, doi: 10.1136/heartjnl-2021-320277, indexed in Pubmed: 34903584.
37. Schefold JC, Filippatos G, Hasenfuss G, et al. Heart failure and kidney dysfunction: epidemiology, mechanisms and management. Nat Rev Nephrol. 2016; 12(10): 610–623, doi: 10.1038/nrneph.2016.113, indexed in Pubmed: 27573728.
38. Sarwar CMS, Papadimitriou L, Pitt B, et al. Hyperkalemia in heart failure. J Am Coll Cardiol. 2016; 68(14): 1575–1589, doi: 10.1016/j.jacc.2016.06.060, indexed in Pubmed: 27687200.
39. Lelonek M, Grabowski M, Kasprzak JD, et al. An expert opinion of the Heart Failure Association of the Polish Cardiac Society on the 2021 European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic heart failure: Heart failure guidelines from a national perspective. Kardiol Pol. 2022; 80(2): 239–246, doi: 10.33963/KP.a2022.0021, indexed in Pubmed: 35076082.
40. Ferreira JP, Zannad F, Pocock SJ, et al. Interplay of mineralocorticoid receptor antagonists and empagliflozin in heart failure: emperor-reduced. J Am Coll Cardiol. 2021; 77(11): 1397–1407, doi: 10.1016/j.jacc.2021.01.044, indexed in Pubmed: 33736821.
41. Shen Li, Kristensen SL, Bengtsson O, et al. Dapagliflozin in HFrEF Patients Treated With Mineralocorticoid Receptor Antagonists: An Analysis of DAPA-HF. JACC Heart Fail. 2021; 9(4): 254–264, doi: 10.1016/j.jchf.2020.11.009, indexed in Pubmed: 33549554.
42. Kapłon-Cieślicka A, Benson L, Chioncel O, et al. A comprehensive characterization of acute heart failure with preserved versus mildly reduced versus reduced ejection fraction - insights from the ESC-HFA EORP Heart Failure Long-Term Registry. Eur J Heart Fail. 2022; 24(2): 335–350, doi: 10.1002/ejhf.2408, indexed in Pubmed: 34962044.
43. Savarese G, Bodegard J, Norhammar A, et al. Heart failure drug titration, discontinuation, mortality and heart failure hospitalization risk: a multinational observational study (US, UK and Sweden). Eur J Heart Fail. 2021; 23(9): 1499–1511, doi: 10.1002/ejhf.2271.
44. Gorczyca-Głowacka I, Mastalerz-Migas A, Lelonek M. Real-life implementation of guidelines for heart failure with reduced ejection fraction management. Kardiol Pol. 2023; 81(9): 919–921, doi: 10.33963/KP.a2023.0144, indexed in Pubmed: 37401578.
45. Kapłon-Cieślicka A, Lund LH. Do we need a definition of acute heart failure with preserved ejection fraction? Ann Med. 2021; 53(1): 1470–1475, doi: 10.1080/07853890.2021.1968028, indexed in Pubmed: 34431429.
46. Hollenberg SM, Warner Stevenson L, Ahmad T, et al. 2019 ACC Expert Consensus Decision Pathway on Risk Assessment, Management, and Clinical Trajectory of Patients Hospitalized With Heart Failure: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2019; 74(15): 1966–2011, doi: 10.1016/j.jacc.2019.08.001, indexed in Pubmed: 31526538.

Infections of cardiac implantable electronic devices: Epidemiology, mechanisms, and preventive measures

Vassil Traykov[1], Krasimir Dzhinsov[2, 3], Paweł T Matusik[4, 5]

[1]Department of Invasive Electrophysiology, Clinic of Cardiology, Acibadem City Clinic University Hospital Tokuda, Sofia, Bulgaria
[2]Interventional Electrophysiology and Cardiac Pacing Unit, Interventional Cardiology Department, University Hospital "Sveti Georgi" — Plovdiv, Bulgaria
[3]Research Institute, Medical University — Plovdiv, Bulgaria
[4]Department of Electrocardiology, Institute of Cardiology, Faculty of Medicine, Jagiellonian University Medical College, Kraków, Poland
[5]Department of Electrocardiology, The John Paul II Hospital, Kraków, Poland

Correspondence to:
Vassil Traykov, MD, PhD, Clinic of Cardiology, Acibadem City Clinic Tokuda Hospital Sofia, Bulgaria, phone: +35 98 79 430 365, e-mail: vtraykov@yahoo.com

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ABSTRACT

Cardiac implantable electronic device (CIED) infections represent a complication associated with high morbidity and mortality. Despite enormous efforts to prevent them, the rates of infections continue to rise out of proportion to the reported increase in CIED implantation rates. Following extensive research of various prevention strategies and new technologies, several organizations have issued recommendations and consensus papers covering this topic. Our narrative review aims to provide a summary of the existing preventive strategies put forward by the European Heart Rhythm Association consensus and European Society of Cardiology guidelines and introduce the most recent developments in the field, including optimized surgical site management and appropriate periprocedural antithrombotic drug use. It also provides an overview of epidemiology, mechanisms, risk factors, and risk stratification approaches. It focuses on the pre-, intra-, and postprocedural actions that should be taken to mitigate CIED infection risks. Future directions in the prevention of CIED infections have also been addressed.

Key words: cardiac implantable electronic device, defibrillator, epidemiology, pacemaker, infection, prevention, risk

INTRODUCTION

Following the first reports on cardiac pacemakers published in the late 1950s and the subsequent development of implantable cardioverter-defibrillators (ICD) in the 1980s, cardiac implantable electronic devices (CIEDs) have become the standard of care in managing cardiac rhythm and conduction disturbances. Published data show a constant increase in the numbers and complexity of CIED implantations worldwide [1]. This growth has been accompanied by an increasing rate of complications, especially with the wider introduction of cardiac resynchronization therapy pacemakers (CRT-P) and defibrillators (CRT-D) [2]. The rate of CIED infections has been shown to increase out of proportion to the reported rise in device implantation [1, 3]. The possible causes are the increasing CIED complexity, comorbidities, and longer life expectancy. On the other hand, CIED infections represent an essential factor for increased morbidity and mortality among CIED recipients [4]. From an economic perspective, CIED infection management puts a significant financial burden on healthcare systems due to additional treatment, prolonged hospital stays, and reinterventions [5–7].

Despite various preventive strategies to reduce CIED complications [8], reports show significant differences in their implementation [9]. Meticulous antisepsis and preoperative antibiotic prophylaxis are highly effective and recommended by various consensus papers and guidelines [8, 10]. New technologies, including subcutaneous ICDs and leadless pacemakers, also aid in the reduction in CIED infections. However, these apply only to selected patients. The role of antibiotic-eluting envelopes (AEEs) for effective CIED infection prevention has been demonstrated by randomized studies [11].

Moreover, advances in diagnostics, including use of procalcitonin in the recognition of device pocket infection, have been done recently [12].

This narrative review presents an overview of the epidemiology and mechanisms of CIED infections as well as the existing and developing strategies to prevent them. It highlights the strategies for risk stratification and focuses on the value of preprocedural, intraprocedural, and postprocedural measures and actions to prevent CIED infections.

EPIDEMIOLOGY, ETIOLOGY, AND MECHANISMS OF CIED INFECTIONS

Infections related to the CIED develop at a rate ranging from 1 to 7% depending on the type and complexity of the implantation [2, 6, 11, 13]. Previously reported data demonstrated a significant rise in the infection rates over time from 1.45% to 3.41%, with the highest increase for CRT-P/D devices [1]. Real-life data on infection rates contrast with results from randomized studies, which report much lower infection rates in the range of 0.6%–1.3% [4, 11, 13–15]. This could result, at least in part, from predominant participation of high-volume centers in randomized studies. The infection rate is highest early after the procedure (in the first 3 months) [16]. Infections are well-known to be associated with increased morbidity and mortality, especially in the case of systemic and delayed (3–12 months) localized infections [4, 16, 17]. This trend is preserved even after lead extraction (complete CIED removal) [4] and successful infection eradication [17].

CIED infections develop via two major mechanisms. The most common is local hardware (leads and pulse generator) contamination [18]. The introduction of normal skin flora might occur in the surgical wound during the implantation or later with the development of erosion. Contamination of the pocket leads to bacterial growth and subsequent (mostly early) pocket infection [11, 19, 20]. Later in its course, the infection may spread along the leads and eventually cause secondary systemic infection resulting in device-related endocarditis. In the second mechanism, remote infectious foci (e.g., from contaminated vascular catheters, surgical site infection, septic thrombophlebitis, etc.) causing bacteremia might result in direct lead seeding, which later may progress to systemic infection, while the device pocket remains unaffected.

Device infections are caused mainly by Gram-positive bacteria (70%–90% of the isolates). Some of them are normally non-pathogenic. These are usually coagulase-negative staphylococci (mainly *Staphylococcus epidermidis*). *Staphylococcus aureus* is also a commonly isolated microorganism responsible for pocket infection (especially in early cases) and also the most common isolate in bacteremia [21–26]. Almost half of all staphylococcal CIED infections have been reported to be caused by methicillin-resistant staphylococci [21]. Gram-negative bacteria are isolated in about 9% of the cases, while fungi are rare [25]. No causative microorganism is identified in about a third of the patients [11].

RISK ASSESSMENT

Any preventive measure shows the highest benefit when directed to the population at the highest risk. Identifying risk factors and risk stratification play a central role in determining the CIED recipients for whom more aggressive preventive measures should be taken to reduce the infection rate.

Factors associated with higher CIED infection risk can be modifiable, with specific interventions addressing them able to mitigate the risk, or non-modifiable, determining persistently elevated risk of infection. Apart from that, risk factors can be grouped into patient-related, procedure-

Table 1. Major risk factors for cardiac implantable electronic device infections

Risk factors	Odds ratio
Patient-related factors	
End-stage renal disease	8.73
Prior CIED infection	7.84
Fever before implantation	4.27
Immunosuppression	3.44
Renal failure (eGFR <30 ml/min/1.73 m^2)[a]	1.45[a]–3.02
COPD	2.95
NYHA class ≥II	2.47
Skin disorder	2.46
Immunocompromised (therapy or disease-suppressing resistance to infection)	2.28[a]
Malignancy	2.23
Diabetes mellitus	2.08
Heparin bridging	1.87
Congestive heart failure	1.65
Oral anticoagulation	1.59
Device-related factors	
Epicardial leads	8.09
Abdominal pocket	4.01
CRT	2.73[a]
Two or more leads	2.02
ICD	1.77[a]
Dual chamber device	1.45
Procedure-related factors	
Reintervention <30 days	16.29
Procedure duration >1 hour	13.96
Hematoma	4.95-11.3[b]
Revision or upgrade	4.01[a]–6.46
Lead repositioning	6.37
Replacement	4.93
Two or more prior procedures	3.43[a]
Inexperienced operator	2.85
Temporary pacing	2.31
Single prior procedure	1.51[a] (P = 0.058)[a]

Abbreviations: CIED, cardiac implantable electronic device; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; h, hour; ICD, implantable cardioverter-defibrillator

[a, b]Data come from randomized controlled trials

Figures taken from previously published non-randomized data by Polyzos et al. [27], Sławek-Szmyt et al. [28], and from randomized data by Birnie et al.[a] [29] and Tarakji et al.[b] [32]

-related, and device-related [8]. The magnitude of different risk factors is presented in Table 1.

Patient-related risk factors

Some comorbidities are well-established risk factors. End-stage renal disease and renal insufficiency or failure are consistently reported as one of the most important risk factors [14, 27, 28]. Other conditions such as immunosuppression, chronic obstructive pulmonary disease (COPD), congestive heart failure, valvular heart disease (esp. prior valvular surgery), systemic autoimmune disorders, malignancy, diabetes, and skin disorders also carry a significant risk of CIED infection [15, 27–29]. Although often non-modifiable as risk factors, optimal management of these conditions (e.g., control of diabetes) has been shown to lower infection risk [30].

Younger age has been identified as a risk factor in the randomized Prevention of Arrhythmia Device Infection Trial (PADIT) population and by a recent large observational study [15, 29]. While a consistent explanation for this finding is lacking, the qualities of subcutaneous tissue at a younger age might predispose to more traumatization during implantation (esp. pocket creation) and subsequent higher predisposition to infection [31]. Conversely, a smaller observational study including only 1000 ICD and CRT recipients demonstrated a significantly higher risk of CIED infection (odds ratio [OR], 5.93; 95% confidence interval [CI], 1.77–19.84) in patients older than 75 years [28]. This might be due to the inclusion of more frail and morbid patients in this series.

Fever before implantation is another well-established and major modifiable risk factor for CIED infection (OR, 5.34; 95% CI,1.002–28.43) [8]. The administration of certain medications, such as corticosteroids and antithrombotic drugs, also represents a potentially modifiable patient-related risk factor. According to a recent analysis of randomized data, a history of atrial arrhythmia and the number of previous procedures were also associated with increased infection risk after secondary procedures [32]. In the same study, some geographical regions (outside North America and Europe) and lower body mass index were also associated with increased risk.

Device-related factors

Device-related factors mainly include system size and complexity. Implantation of complex systems, presence of at least two leads, and implantation of high-power devices are associated with increased infection risk [8, 27, 33–35] (Table 1). A sizeable real-life registry from Denmark reported significantly increased infection risk in patients with complex devices — ICD (HR, 1.26, 95% CI, 1.09–1.47), CRT-P (HR, 1.68; 95% CI, 1.67–2.11), and CRT-D systems (HR, 2.22; 95% CI, 1.83–2.70) as compared to conventional antibradycardia devices [35]. Another, more recent analysis of data from the same registry reported that complex systems (CRT-P and CRT-D) are associated with increased risk for both pocket and systemic CIED infections, while ICD implantation portended a higher risk of systemic infection compared to implantation of antibradycardia pacemakers [15]. In the PADIT study population, implantation of CRT and ICD, as well as secondary procedures, were all associated with increased risk for CIED infection in a full prediction model (OR, 2.73; 95% CI, 1.72–4.31; OR, 1.77; 95% CI, 1.09–2.87 and OR, 4.01; 95% CI, 2.62–6.13, for CRT, ICD, and secondary procedures, respectively) [14]. Similar findings were reported in the WRAP-IT dataset as well [32].

Procedure-related risk factors

Previously published observational and randomized studies demonstrated that early reintervention (within 30 days) and lengthy procedure duration (> 1 hour) were associated with the highest risk of CIED infections [8, 27, 32–34]. Procedure duration is mainly affected by procedure complexity, patients' anatomy, and operator skills and experience.

Postprocedural hematoma is another well-established risk factor that has been widely studied. The randomized BRUISE CONTROL INFECTION study, including 659 patients with CIED infection, demonstrated that the development of hematoma was associated with more than 7-fold increased risk of infection (hazard ratio [HR], 7.7; 95% CI, 2.9–20.5) within one-year follow-up [33]. Another recent analysis based on the WRAP-IT population (n = 6800 participants) demonstrated an 11-fold increase in CIED infection risk (HR, 11.3; 95% CI, 5.5–23.2) in the patients developing clinically significant hematoma [34].

Risk scores

Risk score systems for preprocedural risk assessment represent an essential tool for better risk stratification of low- and high-risk patients. They can not only facilitate clinical decision-making and patient counseling but also help healthcare systems and decision-makers be prepared for the scale of these severe complications. Mittal et al. [36] were among the first to develop a risk scoring system that included 7 clinical variables and 0 to 25 points (a higher number signifying higher risk). The infection risk increased significantly from the low-risk group (score 0-7, 1% infection rate) to the medium-risk group (score 8–14, 3.4% infection rate), and the high-risk group (score ≥15, 11.1% infection rate). Shariff et al. [37] also proposed a risk score including ten clinical and procedural variables. In a retrospective study, in patients who underwent *de novo* CIED implantation, Shariff score ≥4 was associated with more than three-fold increased risk of CIED infection — RR 3.20 (1.29–12.59) [38]. Another risk score designed by Kolek et al. included several clinical variables also known to be associated with CIED infection risk [39, 40]. The only risk score developed based on a dataset of a randomized trial is the PADIT risk score system [29]. It identified five independent predictors: Prior procedure(s) (P, 1 = 1 point, at least 2 = 4 points), Age (A, 60–69 years = 1 point, <60 years = 2 points), Depressed estimated glomerular

filtration rate (D, <30 ml/min = 1 point), Immunocompromised (I, 3 points), and Type of procedure (T, ICD = 2 points, CRT = 4 points, revision or upgrade = 5 points). The score, ranging from 0 to 15 points, was used to group patients into low (<1%, 0 to 4 points), intermediate (1%–3%, 5 to 6 points), and high (>3%, ≥7 points) risk groups with hospitalization rates due to CIED infection of 0.51%, 1.42%, and 3.41%, respectively. The PADIT risk score was validated externally in a large dataset of 54 042 procedures where each unit increase in the PADIT risk score was associated with a 28% increase in the infection risk [41]. Following PADIT risk score development, Boriani et al. [42] developed the RI-AIAC infection score based on registry data with 2675 patients. The RI-AIAC score is a 5-point scoring system, and the authors have identified several major clinical characteristics associated with increased CIED infection risk (especially type of procedure and diabetes). Interestingly, a score created to assess the risk of bleeding complications in CIED recipients — the PACE DRAP score — has also been shown to be helpful in CIED infection risk stratification [28]. It is important to note that none of these risk scores are entirely exhaustive. For instance, the most widely used PADIT risk score does not include important risk factors such as prior CIED infection, some comorbidities (e.g. malignancy), and concomitant antithrombotic therapy. Real-life studies have shown that previous CIED infection remains an important risk factor despite adjustment for the PADIT risk score [41].

PREVENTION STRATEGIES

Infections associated with CIEDs represent a significant challenge for healthcare providers and systems. Therefore, prevention is essential to reduce their incidence and diminish mortality and morbidity associated with them. In the case of CIED infection, preventive strategies include multiple measures at different time points during the management of these patients – before, during, and immediately after the implantation [8].

PREPROCEDURAL MEASURES

Patient selection and preprocedural patient-related factors

Careful patient selection and procedure timing are essential in CIED infection prevention. The risk-benefit ratio should always be considered individually before the procedure, with strict adherence to the recommendations [10]. For instance, a significant proportion (up to 50%) of patients might not need reimplantation of a new device following extraction for CIED infection [43-45]. Cardioneuroablation, as a new treatment modality for vasovagal syncope, is also likely to make implantation in some patients obsolete [46]. Careful consideration of temporal variation in the risk and postponing an implantation/reimplantation procedure to gain time to implement preventive measures play a central role in the decision-making process [47].

Preprocedural fever is a factor that necessitates postponing the procedure. As suggested by the available data, a reasonable afebrile period before undertaking the implantation procedure is at least 24 hours [48]. Isolated leucocytosis, without other clinical symptoms and signs (bacteremia, elevated inflammatory biomarkers) of ongoing infection, has not been associated with CIED infections and should not delay implantation [49]. Optimizing treatment and better control of comorbidities (e.g., better glycemic control in diabetic patients) is very important to minimize the risk of CIED infections.

Some studies have demonstrated the benefit of identifying *S. aureus* carriers by nasal swabs and subsequent decolonization with topical mupirocin and chlorhexidine skin wash to reduce healthcare-associated *S. aureus* infections [50]. Whether this strategy would prove beneficial in reducing CIED-related infections has not been specifically studied.

Implantation of temporary pacing leads should be avoided to reduce the risk of CIED infection. Alternative solutions, such as considering transcutaneous pacing in the most severe cases or administering medications to increase heart rate, should be sought and implemented. When needed, temporary transvenous pacing is better carried out via jugular/subclavian access rather than groin access, as this may be associated with lower infection risk. If possible, removing all central venous lines should be considered before CIED surgery [27]. In the case when vascular access was via a subclavian vein, the CIED should be implanted on the contralateral side. If that is not possible or feasible, it is always advisable to postpone the implantation after removing the central venous line.

If hair removal at the procedural site is needed, this should be done using electric clippers with a disposable head (not razors) [51]. Preprocedural skin wash with an antimicrobial agent is not routinely recommended due to diverging data from studies on other types of surgery and not specifically CIED implantation [8].

Antithrombotic therapy

Patients undergoing CIED implantation frequently need concomitant antiplatelet or anticoagulant therapy. As shown above, postoperative hematoma is a decisive risk factor for CIED infection; therefore, every effort should be made to minimize the risk of hematoma formation. One widely implemented strategy is uninterrupted vitamin K antagonist (VKA) therapy during implantation [52]. The Bridge or Continue Coumadin for Device Surgery Randomized Controlled Trial (BRUISE-CONTROL) demonstrated that uninterrupted VKA therapy, as compared to heparin bridging, resulted in fewer clinically significant device-pocket hematomas as compared to a strategy involving perioperative VKA interruption and bridging with heparin in patients with high thromboembolic risk (including patients after mechanical heart valve replacement) 3.5 vs. 16% (RR, 0.19; 95% CI, 0.10–0.36) [53]. The ran-

domized BRUISE CONTROL-2 study found no difference in the clinically significant device pocket hematoma incidence with continued direct oral anticoagulants (DOAC) therapy vs. DOAC interruption in patients with atrial fibrillation and CHA_2DS_2-VASc score ≥2 [54]. A combined analysis of these two trials also demonstrated similar bleeding and pocket hematoma outcomes between interrupted or continued DOAC therapy vs. uninterrupted VKA (OR, 0.86; 95% CI, 0.38–1.96) [55]. In patients with low thromboembolic risk, temporary withholding of oral anticoagulation for the implantation is a well-established strategy [8].

Concomitant single or dual antiplatelet therapy increases bleeding risk in CIED recipients [56, 57]. Analyses of randomized studies demonstrated that a clinically significant hematoma develops in 9.8% of the patients on concomitant antiplatelet therapy versus 4.3% in those without, corresponding to a doubling of the risk (OR, 1.97; 95% CI, 1.20–3.21) [55]. Therefore, recent guidelines and consensus documents recommend discontinuing antiplatelet therapy (especially $P2Y_{12}$ inhibitors) for at least 5 days before the procedure, if possible [8, 10]. In patients on dual antiplatelet therapy following percutaneous coronary intervention (PCI), discontinuation of one of the antiplatelet agents (usually $P2Y_{12}$ inhibitor) for 3–7 days before the procedure is recommended based on thromboembolic and bleeding risk [10].

Antibiotic prophylaxis

Previous studies have demonstrated a significant and considerable reduction in the incidence of CIED infection with preprocedural intravenous antibiotic prophylaxis [58, 59]. In the randomized trial of de Oliveira et al., preprocedural administration of 1 g cefazolin was associated with a significant reduction in infection rates as compared to placebo (0.63% vs. 3.28%; RR, 0.19; $P = 0.016$) [59]. Current guidelines recommend such a strategy as the standard of care [8, 10]. Antibiotics should protect against *S. aureus* as the most common causative organism in acute infections. Randomized trials have used flucloxacillin (1–2 g) and first-generation cephalosporins — e.g., cefazolin (1–2 g) [14, 59]. In cases of allergy to beta-lactams, the recommended choice is vancomycin (15 mg/kg) [8]. Antibiotics against methicillin-resistant *S. aureus* (MRSA) are not used routinely and could be considered based on local MRSA prevalence and patient risk. Antibiotic administration should be completed within one hour before the skin incision to ensure adequate antibiotic tissue levels.

Alternative systems and approaches in high-risk patients

The development of technology has brought in leadless pacemakers and subcutaneous ICD as an alternative to conventional transvenous systems. As these devices have no or only minimal intravascular components, they are expected to be associated with lower risk of infection. The absence of a pocket in leadless pacemakers eliminates the risk of CIED pocket infection although hematogenous seeding might still be possible. Extensive observational studies report a significantly lower infection rate with this new technology, but results from randomized studies are lacking [60]. Leadless pacemakers may also be associated with reduced risk of infection in patients after transvenous lead extraction [61]. High costs and lack of reimbursement are among the factors limiting their use in clinical practice. However, when considering total costs for the management of patients with recurrent CIED infections, leadless pacemaker implantation seems to be financially justified, at least in some healthcare systems [62].

Subcutaneous ICDs (S-ICD) are a viable option for patients requiring protection from ventricular tachyarrhythmias and have no pacing or CRT indication. Results from the EFFORTLESS S-ICD registry showed that at five years of follow-up, the overall infection rate in S-ICD recipients was 2.4% with an erosion rate of 1.7% [63]. A recent secondary analysis of the PRAETORIAN trial demonstrated a significantly lower rate of systemic infections in S-ICD recipients than those receiving a transvenous ICD (0% vs. 1.2%) [64].

Implanting an epicardial system may also provide a solution in selected high-risk patients, particularly those in whom preserving venous access is crucial [65].

Other preprocedural measures

An appropriate environment in the operating room/catheterization laboratory where CIED implantations are carried out is essential. These facilities should meet all the standards applicable for other surgical procedures involving implants [8, 66]. The staff at the implantation facility should be trained to follow strict sterile techniques.

Procedure times should be minimized as the duration of the implantation is a well-established risk factor for CIED infection. Long procedures (>60 minutes) are associated with infectious complications [27]. Extensive real-life data have demonstrated that, compared to procedure durations up to 30 minutes, the risk of infections is 2.4-fold higher in procedures longer than 120 minutes [35]. Many factors have an impact on procedure duration. Among those are lack of appropriate staff training [67], certification of operators [68], and patient volume [69]. These are all organizational issues that should be best addressed before starting any activity i.e., before performing any procedures. However, procedural difficulties associated with patient-related factors, e.g. anatomical/structural abnormalities/changes or bleeding, also play a role in procedural duration.

SURGICAL TECHNIQUE AND INTRAPROCEDURAL FACTORS

Surgical preparation

Results from randomized trials demonstrated that skin antisepsis with a 2% alcoholic chlorhexidine solution was associated with a lower incidence of surgical site infections as compared to povidone-iodine (alcoholic or aqueous

solution) [70]. It is also associated with a lower infection rate with intravascular catheter insertion [71]. Despite the lack of randomized data on CIED implantation, the use of alcoholic chlorhexidine is recommended [8]. To provide sufficient time for the antiseptic to exert its effect and to minimize fire hazards when using electrocautery, it should be left to dry completely before the incision is made. Many operators use iodophor-impregnated incisive drapes, but there are no data showing that they reduce infection rates [9].

Surgical technique

Good surgical techniques including minimizing operative tissue damage, meticulous hemostasis, and appropriate wound closure, are crucial elements in infection prevention during the CIED implantation procedure.

Gloves change

Many operators change their gloves initially during prepping and/or later before handling the device. This is usually done by removing the outer pair of gloves with double-gloving or re-scrubbing. Observational studies have shown a high rate of glove contamination during the implantation before handling the device [72]. As significant, randomized studies in the field are lacking, the practice of glove change has been recommended based on expert consensus. The use of non-powdered gloves is preferable because glove powder has been demonstrated to facilitate infection [73].

Hemostasis and prevention of hematoma

Adequate hemostasis is key in the prevention of hematoma formation. Minimizing trauma by respecting tissue architecture and ensuring good wound closure is extremely important. Electrocautery is widely implemented in most centers, but the use of a plasma electron avalanche knife has been shown to be associated with a reduced incidence of hematoma compared to electrocautery in high-risk patients [74]. Some observational studies advocate for the use of hemostatic agents such as tranexamic acid [75]. However, results are controversial, and therefore this strategy cannot be recommended as a standard practice until larger-scale studies demonstrate its unequivocal benefit and safety. Routine addition of epinephrine to the local anesthetic during the procedure is discouraged as one small randomized single-center study demonstrated a higher incidence of hematoma formation with this strategy [76]. Capsulectomy entails the removal of the fibrous capsule formed around the device during secondary procedures. The rationale behind this practice is that the fibrous capsule has been known to facilitate bacterial colonization and subsequent infection. A randomized study demonstrated that routine capsulectomy during secondary procedures results in more hemorrhagic complications (6.1% vs. 0.8%; $P = 0.03$) with no effect on the incidence of pocket infection (1.5% vs. 4.7%; $P = 0.13$) [77]. Therefore, performing capsulectomy on a routine basis is discouraged.

Pocket irrigation and local instillation of antibiotics and antiseptics

The PADIT trial demonstrated no difference in the infection rate with the application of incremental antibiotic strategy, including antibiotic pocket wash before skin closure along with postoperative cephalexin or cephadroxil as compared to preprocedural cefazolin infusion only [14]. The recent Randomized Stand-Alone Use of the Antimicrobial Envelope in High-Risk Cardiac Device Patients (ENVELOPE) trial showed no difference in infection rates in high-risk patients receiving chlorhexidine skin preparation, preprocedural antibiotics, and an AEE (control arm) compared to adding an antibiotic pocket wash and a 3-day course of postoperative antibiotics to the initial treatment [13]. Observational studies do not support performing routine povidone-iodine pocket irrigation to reduce infection rates [78]. Based on these data, local instillation with antibiotics or antiseptic solutions is not recommended [8]. However, gentamicin-impregnated collagen sponge use was associated with reduced CIED infections in a recent 10-year analysis with propensity score matching [79]. In all cases, vigorous pocket irrigation with saline should be done to remove debris and potential contaminants from the pocket during the implantation.

Antibiotic eluting envelopes

In their early versions, AEEs consisted of non-absorbable polypropylene mesh, but this design was associated with significant pocket fibrosis and was therefore abandoned. An antibacterial mesh envelope has been designed and marketed (TYRX™; Medtronic, Inc. Monmouth Junction, NJ, US). It is made of a synthetic mesh of glycolide, caprolactone, and trimethylene carbonate absorbed in the body over nine weeks. The mesh is coated with an absorbable polyacrylate polymer releasing minocycline and rifampin in the tissues over seven days. This antibiotic combination has been shown to have additive effects on resistant bacteria such as MRSA [80] and covers the whole spectrum of Staphylococcus spp. (81), as well as other species [82].

The randomized WRAP-IT trial assessed AEE benefits in patients undergoing device implantations. It included 6983 patients with high infection risk randomized to AEE vs. standard of care [82]. Major infections occurred in 0.7% of patients receiving TYRX™ vs. 1.2% in controls (HR, 0.60; 95% CI, 0.36–0.98) [11]. The positive outcome was entirely driven by the lower rate of pocket infections, which comprised 75% of all major events — 0.4% vs. 1% in the control group (HR, 0.39; 95% CI, 0.21–0.72). The benefit of AEE was sustained during long-term follow-up [83]. A meta-analysis summarizing a major observational and randomized trials and a recent real-world study demonstrated similar findings [84, 85]. Further analyses of the WRAP-IT population showed a more than 11-fold higher risk of major CIED infection in patients with pocket hematoma and without the AEE [34]. In patients who received the AEE and later developed pocket hematoma, the risk was 82% lower (HR, 0.18; 95% CI,

0.04–0.85), and the infection rate was comparable to those without hematoma. A significant limitation of the study was the exclusion of patients at very high risk (e.g., those with pocket intervention in the previous 365 days, patients on dialysis, on chronic immunosuppressive therapy, or those with previous CIED infection within 12 months), which probably explains the lower than expected infection rate. The cost-effectiveness of this device, especially in high-risk patients, has been demonstrated in many healthcare systems [86–89].

Another available absorbable CIED envelope is made of a decellularized and non-crosslinked extracellular matrix produced from porcine intestinal submucosa [90]. This envelope does not possess antibiotic-eluting properties *per se* but can be impregnated with gentamycin before implantation [90, 91]. Before recommending this envelope for routine clinical use, results from ongoing randomized trials are awaited.

Wound closure

Adequate wound closure is of paramount importance to prevent pocket infections. Closure in layers has been shown to reduce the risk of dehiscence [92]. Various suture materials, staples, or adhesives may be used for wound closure. However, it is extremely important to ensure timely (within 7–14 days) removal of non-absorbable suture material. No firm data have demonstrated the impact of suture material on the infection risk, but consensus documents recommend the use of non-braided monofilament sutures for skin closure as they may be less prone to bacterial adhesion [8]. With absorbable sutures, care should be taken to avoid a "stitch abscess", especially at the pole of the wound where the knot is located.

POSTPROCEDURAL MEASURES

Postprocedural antibiotic therapy

Postoperative antibiotic therapy is not recommended based on the results of the large PADIT trial. The trial tested the benefit of incremental perioperative antibiotic therapy to reduce CIED infections in a cluster cross-over design. In 19 603 patients (of whom 12 842 were high risk), the authors did not find a significant reduction in infections in the patients treated with an incremental regimen consisting of preprocedural cefazolin plus vancomycin, bacitracin pocket wash, and postoperative 2-day administration of oral cephalexin (OR, 0.77; 95% CI, 0.56–1.05) [14]. However, incremental antibiotic use compared to standard care was associated with a trend toward a 23% reduction in hospitalization for infection. This finding was not significant, at least in part due to the low infection rate during only 1-year follow-up in the PADIT trial [29]. Similarly, the recent ENVELOPE trial did not find an additional benefit of antibiotic pocket wash and a 3-day postoperative antibiotic course in addition to standard care and an AEE in high-risk CIED patients [13]. These results should be interpreted in light of the low incidence of CIED infections with peri- and post-operative antibiotic use (course of 5 days) in the long-term follow-up [93].

Wound care

Mechanical compression devices have also been designed to be applied after wound closure. Some of these devices have demonstrated benefit in reducing postoperative hematoma [94–96]. Pressure dressings may be used for 24 hours although their efficacy has not been demonstrated. In any case, a sterile dressing should be left on the wound for 2–10 days, and patients should be given instructions for wound care, i.e., changing the dressing only if impregnated with blood or wound secretions and not soaking the wound until completely healed [8].

Reintervention

Some procedure-related complications (lead dislodgement, hematoma, etc.) may require reintervention. Proper timing is crucial in these cases as the infection risk of repeat procedures is time-dependent and very high in early reinterventions [27, 48]. As shown by the Prospective Evaluation of Pacemaker Lead Endocarditis (PEOPLE) study, reinterventions before hospital discharge are associated with 15-fold increased risk of CIED infection [48]. Apart from taking all the measures to avoid the need for repeat procedures (meticulous hemostasis, good lead fixation, etc.), careful consideration of the risks and benefits of early reintervention is extremely important.

The most important risk factors and major risk reduction strategies are summarized in Figure 1.

FUTURE DIRECTIONS

There are several gaps in evidence related to CIED infection prevention that require further study to answer important questions in the field. More studies on nasal and/or skin treatment of bacterial decolonization to prevent CIED infections would be valuable, especially in high-risk patients. Randomized studies on skin preparation before CIED placement and use of adhesive incise drapes are eagerly awaited. Studies on the use of antiseptic/antimicrobial solutions (e.g. taurolidine) for pocket and hardware wash are ongoing (NCT05576194), but large, randomized trials are needed. Investigations onto different approaches expected to increase guideline-driven care for patients with CIED infections are ongoing (NCT05471973).

CONCLUSION

As a result of increasing device complexity and more prevalent comorbidities in patients undergoing CIED placement, the incidence of CIED infections has grown significantly. They are associated with high morbidity and mortality, as well as high healthcare costs for hospital stay, diagnostics, medical therapy, and interventional (or surgical) procedures. Therefore, identifying risk factors is crucial for implementing structured prevention meas-

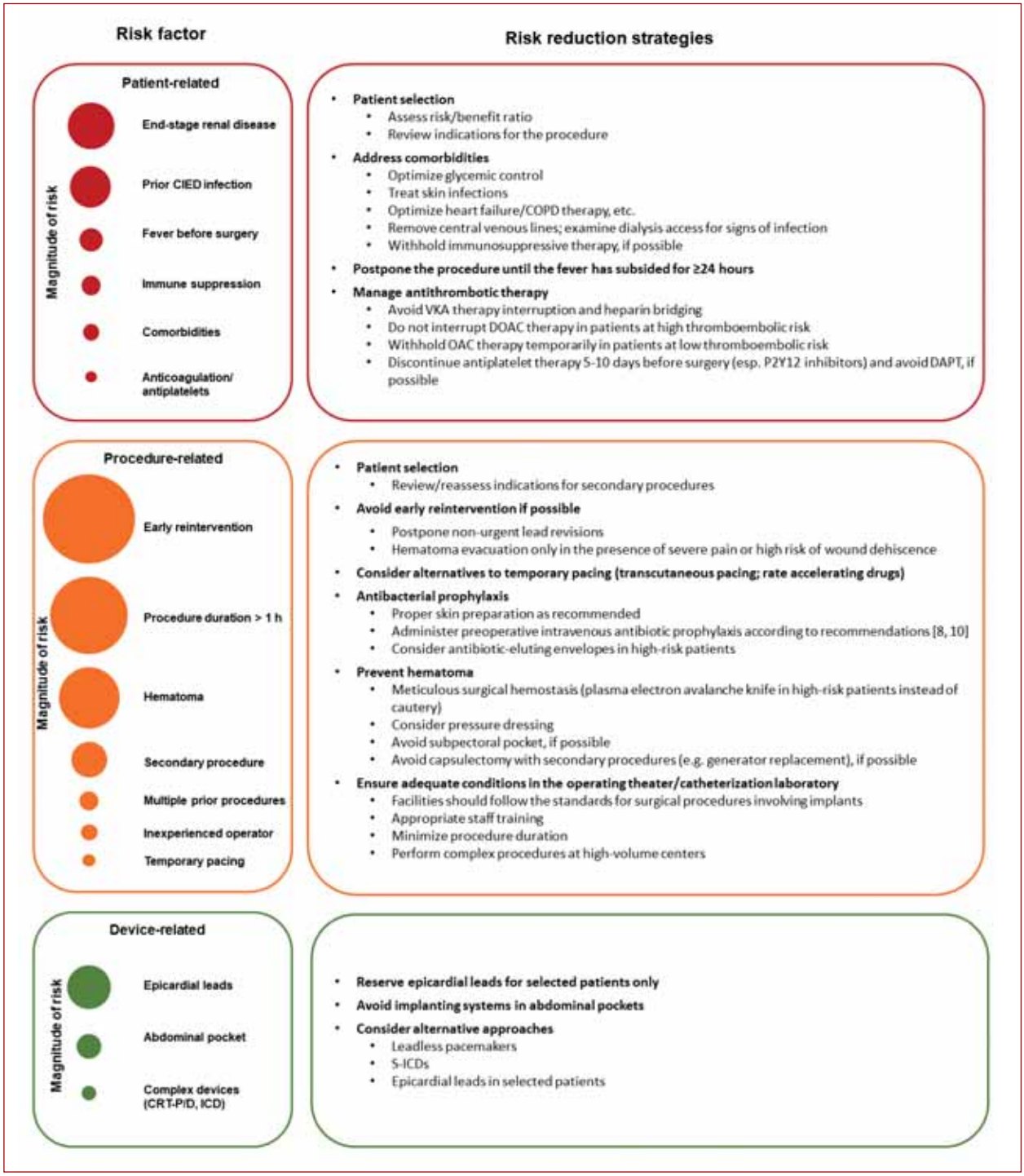

Figure 1. The most important risk factors of cardiovascular implantable electronic device infections along with the corresponding strategies to mitigate that risk. Colored circles reflect the magnitude of risk based on the results presented in Table 1

ures and actions at the preprocedural, intraprocedural, and postprocedural levels, which could bring about a meaningful reduction in CIED infection incidence. These actions should target patients and procedures but also should be directed to the environment in the operating room, staff training, and institutional measures. Importantly, studying and incorporating new methods and technologies such as AEEs, leadless pacemakers, and S-ICDs is another action to be taken for more effective prevention of CIED infections.

Article information

Conflict of interest: VT declares receiving speaker fees and other honoraria from Boehringer Ingelheim, Astra Zeneca, Berlin Menarini, Abbott, Novartis, Bayer, Merck, Pfizer, and Biotronik. KD declares receiving speaker fees from Sandoz, Servier, Boehringer Ingelheim, Astra Zeneca, Berlin-Chemie/Menarini, Novartis, Bayer, Pfizer, and Medtronic. PTM received speech honorarium from Boehringer Ingelheim, Polish Cardiac Society 2018 Scientific Grant in cooperation with Berlin-Chemie/Menarini (sponsor of the grant: Berlin-Chemie/Menarini Poland LLC) and participated in educational activities which were supported by CIED manufacturers as well as Polpharma. None of the declared potential conflicts of interest are related to the current work.

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REFERENCES

1. Joy PS, Kumar G, Poole JE, et al. Cardiac implantable electronic device infections: Who is at greatest risk? Heart Rhythm. 2017; 14(6): 839–845, doi: 10.1016/j.hrthm.2017.03.019, indexed in Pubmed: 28315744.
2. Greenspon AJ, Patel JD, Lau E, et al. 16-year trends in the infection burden for pacemakers and implantable cardioverter-defibrillators in the United States 1993 to 2008. J Am Coll Cardiol. 2011; 58(10): 1001–1006, doi: 10.1016/j.jacc.2011.04.033, indexed in Pubmed: 21867833.
3. Voigt A, Shalaby A, Saba S. Rising rates of cardiac rhythm management device infections in the United States: 1996 through 2003. J Am Coll Cardiol. 2006; 48(3): 590–591, doi: 10.1016/j.jacc.2006.05.016, indexed in Pubmed: 16875991.
4. Lee DH, Gracely EJ, Aleem SY, et al. Differences of mortality rates between pocket and nonpocket cardiovascular implantable electronic device infections. Pacing Clin Electrophysiol. 2015; 38(12): 1456–1463, doi: 10.1111/pace.12748, indexed in Pubmed: 26351247.
5. Sridhar AR, Lavu M, Yarlagadda V, et al. Cardiac implantable electronic device-related infection and extraction trends in the U.S. Pacing Clin Electrophysiol. 2017; 40(3): 286–293, doi: 10.1111/pace.13009, indexed in Pubmed: 28084622.
6. Clémenty N, Carion PL, Léotoing Lde, et al. Infections and associated costs following cardiovascular implantable electronic device implantations: a nationwide cohort study. Europace. 2018; 20(12): 1974–1980, doi: 10.1093/europace/eux387, indexed in Pubmed: 29672690.
7. Romanek J, Farkowski M, Bukowski H, et al. The cost of CIED infectious complications treatment in Poland from the perspective of Polish hospitals. Kardiol Pol. 2022; 80(9): 919–925, doi: 10.33963/KP.a2022.0144, indexed in Pubmed: 35698969.
8. Blomström-Lundqvist C, Traykov V, Erba PA, et al. European Heart Rhythm Association (EHRA) international consensus document on how to prevent, diagnose, and treat cardiac implantable electronic device infections-endorsed by the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS), the Latin American Heart Rhythm Society (LAHRS), International Society for Cardiovascular Infectious Diseases (ISCVID) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Europace. 2020; 22(4): 515–549, doi: 10.1093/europace/euz246, indexed in Pubmed: 31702000.
9. Traykov V, Bongiorni MG, Boriani G, et al. Clinical practice and implementation of guidelines for the prevention, diagnosis and management of cardiac implantable electronic device infections: results of a worldwide survey under the auspices of the European Heart Rhythm Association. Europace. 2019; 21(8): 1270–1279, doi: 10.1093/europace/euz137, indexed in Pubmed: 31209483.
10. Glikson M, Nielsen JC, Kronborg MB, et al. 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. Eur Heart J. 2021; 42(35): 3427–3520, doi: 10.1093/eurheartj/ehab364, indexed in Pubmed: 34455430.
11. Tarakji KG, Mittal S, Kennergren C, et al. Antibacterial Envelope to Prevent Cardiac Implantable Device Infection. N Engl J Med. 2019; 380(20): 1895–1905, doi: 10.1056/NEJMoa1901111, indexed in Pubmed: 30883056.
12. Knoll K, O'Connor M, Chouchane A, et al. A prospective case-control validation of procalcitonin as a biomarker diagnosing pacemaker and implantable cardioverter-defibrillator pocket infection. Kardiol Pol. 2022; 80(7-8): 782–791, doi: 10.33963/KP.a2022.0124, indexed in Pubmed: 35521718.
13. Ellis CR, Greenspon AJ, Andriulli JA, et al. Randomized trial of stand-alone use of the antimicrobial envelope in high-risk cardiac device patients. Circ Arrhythm Electrophysiol. 2023; 16(5): e011740, doi: 10.1161/CIRCEP.122.011740, indexed in Pubmed: 36960716.
14. Krahn AD, Longtin Y, Philippon F, et al. Prevention of arrhythmia device infection trial: the PADIT trial. J Am Coll Cardiol. 2018; 72(24): 3098–3109, doi: 10.1016/j.jacc.2018.09.068, indexed in Pubmed: 30545448.
15. Olsen T, Jørgensen OD, Nielsen JC, et al. Risk factors for cardiac implantable electronic device infections: a nationwide Danish study. Eur Heart J. 2022; 43(47): 4946–4956, doi: 10.1093/eurheartj/ehac576, indexed in Pubmed: 36263789.
16. Han HC, Wang J, Birnie DH, et al. Association of the timing and extent of cardiac implantable electronic device infections with mortality. JAMA Cardiol. 2023; 8(5): 484–491, doi: 10.1001/jamacardio.2023.0467, indexed in Pubmed: 37017943.
17. Rizwan Sohail M, Henrikson CA, Jo Braid-Forbes M, et al. Increased long-term mortality in patients with cardiovascular implantable electronic device infections. Pacing Clin Electrophysiol. 2015; 38(2): 231–239, doi: 10.1111/pace.12518, indexed in Pubmed: 25243484.
18. Da Costa A, Lelièvre H, Kirkorian G, et al. Role of the preaxillary flora in pacemaker infections: a prospective study. Circulation. 1998; 97(18): 1791–1795, doi: 10.1161/01.cir.97.18.1791, indexed in Pubmed: 9603533.
19. Uslan DZ, Sohail MR, St Sauver JL, et al. Permanent pacemaker and implantable cardioverter defibrillator infection: a population-based study. Arch Intern Med. 2007; 167(7): 669–675, doi: 10.1001/archinte.167.7.669, indexed in Pubmed: 17420425.
20. Polewczyk A, Jacheć W, Polewczyk M, et al. Early, delayed and late cardiac implantable electronic device infections: do the timing of onset and pathogens matter? J Clin Med. 2022; 11(14), doi: 10.3390/jcm11143929, indexed in Pubmed: 35887692.
21. Hussein AA, Baghdy Y, Wazni OM, et al. Microbiology of Cardiac Implantable Electronic Device Infections. JACC Clin Electrophysiol. 2016; 2(4): 498–505, doi: 10.1016/j.jacep.2016.01.019, indexed in Pubmed: 29759872.
22. Bongiorni MG, Tascini C, Tagliaferri E, et al. Microbiology of cardiac implantable electronic device infections. Europace. 2012; 14(9): 1334–1339, doi: 10.1093/europace/eus044, indexed in Pubmed: 22399202.
23. Wang R, Li X, Wang Qi, et al. Microbiological characteristics and clinical features of cardiac implantable electronic device infections at a tertiary hospital in China. Front Microbiol. 2017; 8: 360, doi: 10.3389/fmicb.2017.00360, indexed in Pubmed: 28321212.
24. Sandoe JAT, Barlow G, Chambers JB, et al. Guidelines for the diagnosis, prevention and management of implantable cardiac electronic device infection. Report of a joint Working Party project on behalf of the British Society for Antimicrobial Chemotherapy (BSAC, host organization), British Heart Rhythm Society (BHRS), British Cardiovascular Society (BCS), British Heart Valve Society (BHVS) and British Society for Echocardiography (BSE). J Antimicrob Chemother. 2015; 70(2): 325–359, doi: 10.1093/jac/dku383, indexed in Pubmed: 25355810.
25. Sohail MR, Uslan DZ, Khan AH, et al. Management and outcome of permanent pacemaker and implantable cardioverter-defibrillator infections. J Am Coll Cardiol. 2007; 49(18): 1851–1859, doi: 10.1016/j.jacc.2007.01.072, indexed in Pubmed: 17481444.
26. Longtin Y, Gervais P, Birnie DH, et al. Impact of choice of prophylaxis on the microbiology of cardiac implantable electronic device infections: insights from the prevention of arrhythmia device infection trial (PADIT). Open Forum Infect Dis. 2021; 8(11): ofab513, doi: 10.1093/ofid/ofab513, indexed in Pubmed: 34859113.
27. Polyzos KA, Konstantelias AA, Falagas ME. Risk factors for cardiac implantable electronic device infection: a systematic review and meta-analysis. Europace. 2015; 17(5): 767–777, doi: 10.1093/europace/euv053, indexed in Pubmed: 25926473.
28. Sławek-Szmyt S, Araszkiewicz A, Grygier M, et al. Predictors of Long-Term Infections After Cardiac Implantable Electronic Device Surgery - Utility of Novel PADIT and PACE DRAP Scores. Circ J. 2020; 84(10): 1754–1763, doi: 10.1253/circj.CJ-20-0305, indexed in Pubmed: 32893235.
29. Birnie DH, Wang J, Alings M, et al. Risk factors for infections involving cardiac implanted electronic devices. J Am Coll Cardiol. 2019; 74(23): 2845–2854, doi: 10.1016/j.jacc.2019.09.060, indexed in Pubmed: 31806127.
30. de Vries FEE, Gans SL, Solomkin JS, et al. Meta-analysis of lower perioperative blood glucose target levels for reduction of surgical-site infection.

Br J Surg. 2017; 104(2): e95–e9e105, doi: 10.1002/bjs.10424, indexed in Pubmed: 27901264.
31. Mahtani K, Maclean E, Schilling RJ. Prevention and Management of Cardiac Implantable Electronic Device Infections: State-of-the-Art and Future Directions. Heart Lung Circ. 2022; 31(11): 1482–1492, doi: 10.1016/j.hlc.2022.06.690, indexed in Pubmed: 35989213.
32. Tarakji KG, Krahn AD, Poole JE, et al. Risk Factors for CIED Infection After Secondary Procedures: Insights From the WRAP-IT Trial. JACC Clin Electrophysiol. 2022; 8(1): 101–111, doi: 10.1016/j.jacep.2021.08.009, indexed in Pubmed: 34600848.
33. Essebag V, Verma A, Healey JS, et al. Clinically significant pocket hematoma increases long-term risk of device infection: BRUISE CONTROL INFECTION study. J Am Coll Cardiol. 2016; 67(11): 1300–1308, doi: 10.1016/j.jacc.2016.01.009, indexed in Pubmed: 26988951.
34. Tarakji KG, Korantzopoulos P, Philippon F, et al. Infectious consequences of hematoma from cardiac implantable electronic device procedures and the role of the antibiotic envelope: A WRAP-IT trial analysis. Heart Rhythm. 2021; 18(12): 2080–2086, doi: 10.1016/j.hrthm.2021.07.011, indexed in Pubmed: 34280568.
35. Olsen T, Jørgensen OD, Nielsen JC, et al. Incidence of device-related infection in 97 750 patients: clinical data from the complete Danish device-cohort (1982-2018). Eur Heart J. 2019; 40(23): 1862–1869, doi: 10.1093/eurheartj/ehz316, indexed in Pubmed: 31155647.
36. Mittal S, Shaw RE, Michel K, et al. Cardiac implantable electronic device infections: incidence, risk factors, and the effect of the AigisRx antibacterial envelope. Heart Rhythm. 2014; 11(4): 595–601, doi: 10.1016/j.hrthm.2013.12.013, indexed in Pubmed: 24333543.
37. Shariff N, Eby E, Adelstein E, et al. Health and economic outcomes associated with use of an antimicrobial envelope as a standard of care for cardiac implantable electronic device implantation. J Cardiovasc Electrophysiol. 2015; 26(7): 783–789, doi: 10.1111/jce.12684, indexed in Pubmed: 25845917.
38. Balla C, Brieda A, Righetto A, et al. Predictors of infection after "de novo" cardiac electronic device implantation. Eur J Intern Med. 2020; 77: 73–78, doi: 10.1016/j.ejim.2020.02.030, indexed in Pubmed: 32127301.
39. Kolek MJ, Dresen WF, Wells QS, et al. Use of an antibacterial envelope is associated with reduced cardiac implantable electronic device infections in high-risk patients. Pacing Clin Electrophysiol. 2013; 36(3): 354–361, doi: 10.1111/pace.12063, indexed in Pubmed: 23252988.
40. Kolek MJ, Patel NJ, Clair WK, et al. Efficacy of a bio-absorbable antibacterial envelope to prevent cardiac implantable electronic device infections in high-risk subjects. J Cardiovasc Electrophysiol. 2015; 26(10): 1111–1116, doi: 10.1111/jce.12768, indexed in Pubmed: 26222980.
41. Ahmed FZ, Blomström-Lundqvist C, Bloom H, et al. Use of healthcare claims to validate the Prevention of Arrhythmia Device Infection Trial cardiac implantable electronic device infection risk score. Europace. 2021; 23(9): 1446–1455, doi: 10.1093/europace/euab028, indexed in Pubmed: 33755136.
42. Boriani G, Proietti M, Bertini M, et al. Incidence and predictors of infections and all-cause death in patients with cardiac implantable electronic devices: the italian nationwide RI-AIAC registry. J Pers Med. 2022; 12(1), doi: 10.3390/jpm12010091, indexed in Pubmed: 35055406.
43. De Schouwer K, Vanhove R, Garweg C, et al. Re-implantation after extraction of a cardiac implantable electronic device. Acta Cardiol. 2020; 75(6): 505–513, doi: 10.1080/00015385.2019.1620997, indexed in Pubmed: 31145671.
44. Al-Hijji MA, Killu AM, Yousefian O, et al. Outcomes of lead extraction without subsequent device reimplantation. Europace. 2017; 19(9): 1527–1534, doi: 10.1093/europace/euw184, indexed in Pubmed: 27707785.
45. Döring M, Hienzsch L, Ebert M, et al. Extraction of infected cardiac implantable electronic devices and the need for subsequent re-implantation. Int J Cardiol. 2020; 309: 84–91, doi: 10.1016/j.ijcard.2019.12.044, indexed in Pubmed: 31973885.
46. 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.
47. Maille B, Koutbi L, Resseguier N, et al. Seasonal variations in cardiac implantable electronic device infections. Heart Vessels. 2019; 34(5): 824–831, doi: 10.1007/s00380-018-1292-4, indexed in Pubmed: 30415372.
48. Klug D, Balde M, Pavin D, et al. Risk factors related to infections of implanted pacemakers and cardioverter-defibrillators: results of a large prospective study. Circulation. 2007; 116(12): 1349–1355, doi: 10.1161/CIRCULATIONAHA.106.678664, indexed in Pubmed: 17724263.
49. Kumar DS, Tompkins CM, Veenhuyzen GD, et al. Significance of leukocytosis prior to cardiac device implantation. Pacing Clin Electrophysiol. 2018; 41(9): 1197–1200, doi: 10.1111/pace.13443, indexed in Pubmed: 29987911.
50. Bode LGM, Kluytmans JA, Wertheim HFL, et al. Preventing surgical-site infections in nasal carriers of Staphylococcus aureus. N Engl J Med. 2010; 362(1): 9–17, doi: 10.1056/NEJMoa0808939, indexed in Pubmed: 20054045.
51. Tanner J, Melen K, Tanner J, et al. Preoperative hair removal to reduce surgical site infection. Cochrane Database Syst Rev. 2011; 8(11): CD004122, doi: 10.1002/14651858.CD004122.pub4, indexed in Pubmed: 22071812.
52. Du L, Zhang Y, Wang W, et al. Perioperative anticoagulation management in patients on chronic oral anticoagulant therapy undergoing cardiac devices implantation: a meta-analysis. Pacing Clin Electrophysiol. 2014; 37(11): 1573–1586, doi: 10.1111/pace.12517, indexed in Pubmed: 25234639.
53. Birnie DH, Healey JS, Wells GA, et al. Pacemaker or defibrillator surgery without interruption of anticoagulation. N Engl J Med. 2013; 368(22): 2084–2093, doi: 10.1056/NEJMoa1302946, indexed in Pubmed: 23659733.
54. Birnie DH, Healey JS, Wells GA, et al. Continued vs. interrupted direct oral anticoagulants at the time of device surgery, in patients with moderate to high risk of arterial thrombo-embolic events (BRUISE CONTROL-2). Eur Heart J. 2018; 39(44): 3973–3979, doi: 10.1093/eurheartj/ehy413, indexed in Pubmed: 30462279.
55. Essebag V, Healey JS, Joza J, et al. Effect of direct oral anticoagulants, warfarin, and antiplatelet agents on risk of device pocket hematoma: combined analysis of BRUISE CONTROL 1 and 2. Circ Arrhythm Electrophysiol. 2019; 12(10): e007545, doi: 10.1161/CIRCEP.119.007545, indexed in Pubmed: 31610718.
56. Fensman SK, Grove EL, Johansen JB, et al. Predictors of pocket hematoma after cardiac implantable electronic device surgery: A nationwide cohort study. J Arrhythm. 2022; 38(5): 748–755, doi: 10.1002/joa3.12769, indexed in Pubmed: 36237873.
57. Kutinsky IB, Jarandilla R, Jewett M, et al. Risk of hematoma complications after device implant in the clopidogrel era. Circ Arrhythm Electrophysiol. 2010; 3(4): 312–318, doi: 10.1161/CIRCEP.109.917625, indexed in Pubmed: 20558847.
58. Da Costa A, Kirkorian G, Cucherat M, et al. Antibiotic prophylaxis for permanent pacemaker implantation: a meta-analysis. Circulation. 1998; 97(18): 1796–1801, doi: 10.1161/01.cir.97.18.1796, indexed in Pubmed: 9603534.
59. de Oliveira JC, Martinelli M, Nishioka SA, et al. Efficacy of antibiotic prophylaxis before the implantation of pacemakers and cardioverter-defibrillators: results of a large, prospective, randomized, double-blinded, placebo-controlled trial. Circ Arrhythm Electrophysiol. 2009; 2(1): 29–34, doi: 10.1161/CIRCEP.108.795906, indexed in Pubmed: 19808441.
60. Crossley GH, Piccini JP, Longacre C, et al. Leadless versus transvenous single-chamber ventricular pacemakers: 3 year follow-up of the Micra CED study. J Cardiovasc Electrophysiol. 2023; 34(4): 1015–1023, doi: 10.1111/jce.15863, indexed in Pubmed: 36807378.
61. El-Chami MF, Johansen JB, Zaidi A, et al. Leadless pacemaker implant in patients with pre-existing infections: Results from the Micra postapproval registry. J Cardiovasc Electrophysiol. 2019; 30(4): 569–574, doi: 10.1111/jce.13851, indexed in Pubmed: 30661279.
62. Syska P, Farkowski MM, Raulinajtys-Grzybek M, et al. How to decrease the cost of pacemaker infection treatment by adopting seemingly costly innovation? A budget impact analysis of a leadless pacemaker implantation. Kardiol Pol. 2022; 80(12): 1260–1262, doi: 10.33963/KP.a2022.0284, indexed in Pubmed: 36573599.
63. Boersma L, Barr C, Knops R, et al. Implant and Midterm Outcomes of the Subcutaneous Implantable Cardioverter-Defibrillator Registry: The EFFORTLESS Study. J Am Coll Cardiol. 2017; 70(7): 830–841, doi: 10.1016/j.jacc.2017.06.040, indexed in Pubmed: 28797351.
64. Knops RE, Pepplinkhuizen S, Delnoy PP, et al. Device-related complications in subcutaneous versus transvenous ICD: a secondary analysis of the PRAETORIAN trial. Eur Heart J. 2022; 43(47): 4872–4883, doi: 10.1093/eurheartj/ehac496, indexed in Pubmed: 36030464.

65. Asif A, Carrillo R, Garisto JD, et al. Epicardial cardiac rhythm devices for dialysis patients: minimizing the risk of infection and preserving central veins. Semin Dial. 2012; 25(1): 88–94, doi: 10.1111/j.1525-139X.2010.00757.x, indexed in Pubmed: 20807391.
66. Haines DE, Beheiry S, Akar JG, et al. Heart Rythm Society expert consensus statement on electrophysiology laboratory standards: process, protocols, equipment, personnel, and safety. Heart Rhythm. 2014; 11(8): e9–51, doi: 10.1016/j.hrthm.2014.03.042, indexed in Pubmed: 24814989.
67. Al-Khatib SM, Greiner MA, Peterson ED, et al. Patient and implanting physician factors associated with mortality and complications after implantable cardioverter-defibrillator implantation, 2002-2005. Circ Arrhythm Electrophysiol. 2008; 1(4): 240–249, doi: 10.1161/CIRCEP.108.777888, indexed in Pubmed: 19169382.
68. Curtis JP, Luebbert JJ, Wang Y, et al. Association of physician certification and outcomes among patients receiving an implantable cardioverter-defibrillator. JAMA. 2009; 301(16): 1661–1670, doi: 10.1001/jama.2009.547, indexed in Pubmed: 19383957.
69. Lin YS, Hung SP, Chen PR, et al. Risk factors influencing complications of cardiac implantable electronic device implantation: infection, pneumothorax and heart perforation: a nationwide population-based cohort study. Medicine (Baltimore). 2014; 93(27): e213, doi: 10.1097/MD.0000000000000213, indexed in Pubmed: 25501080.
70. Darouiche RO, Wall MJ, Itani KMF, et al. Chlorhexidine-Alcohol versus povidone-iodine for surgical-site antisepsis. N Engl J Med. 2010; 362(1): 18–26, doi: 10.1056/NEJMoa0810988, indexed in Pubmed: 20054046.
71. Mimoz O, Lucet JC, Kerforne T, et al. Skin antisepsis with chlorhexidine-alcohol versus povidone iodine-alcohol, with and without skin scrubbing, for prevention of intravascular-catheter-related infection (CLEAN): an open-label, multicentre, randomised, controlled, two-by-two factorial trial. Lancet. 2015; 386(10008): 2069–2077, doi: 10.1016/S0140-6736(15)00244-5, indexed in Pubmed: 26388532.
72. Kozon I, Riahi S, Lundbye-Christensen S, et al. Risk factors of cardiac device infection: Glove contamination during device procedures. Am J Infect Control. 2017; 45(8): 866–871, doi: 10.1016/j.ajic.2017.03.019, indexed in Pubmed: 28526307.
73. Suding P, Nguyen T, Gordon I, et al. Glove powder increases Staphylococcus aureus abscess rate in a rat model. Surg Infect (Larchmt). 2010; 11(2): 133–135, doi: 10.1089/sur.2008.055, indexed in Pubmed: 19622028.
74. Lind A, Ahsan M, Kaya E, et al. Early Pacemaker Implantation after Transcatheter Aortic Valve Replacement: Impact of PlasmaBlade™ for Prevention of Device-Associated Bleeding Complications. Medicina (Kaunas). 2021; 57(12), doi: 10.3390/medicina57121331, indexed in Pubmed: 34946276.
75. Beton O, Saricam E, Kaya H, et al. Bleeding complications during cardiac electronic device implantation in patients receiving antithrombotic therapy: is there any value of local tranexamic acid? BMC Cardiovasc Disord. 2016; 16: 73, doi: 10.1186/s12872-016-0251-1, indexed in Pubmed: 27105588.
76. Ilov N, Ilov N, Nechepurenko A, et al. Arguments to apply epinephrine for pocket hematoma reduction. The MAITRE study. J Atr Fibrillation. 2016; 9(1): 1391, doi: 10.4022/jafib.1391, indexed in Pubmed: 27909508.
77. Lakkireddy D, Pillarisetti J, Atkins D, et al. IMpact of pocKet rEvision on the rate of InfecTion and other CompLications in patients rEquiring pocket mAnipulation for generator replacement and/or lead replacement or revisioN (MAKE IT CLEAN): A prospective randomized study. Heart Rhythm. 2015; 12(5): 950–956, doi: 10.1016/j.hrthm.2015.01.035, indexed in Pubmed: 25625720.
78. Lakkireddy D, Valasareddi S, Ryschon K, et al. The impact of povidone-iodine pocket irrigation use on pacemaker and defibrillator infections. Pacing Clin Electrophysiol. 2005; 28(8): 789–794, doi: 10.1111/j.1540-8159.2005.00173.x, indexed in Pubmed: 16105006.
79. Matteucci A, Bonanni M, Massaro G, et al. Treatment with gentamicin-impregnated collagen sponges in reducing infection of implantable cardiac devices: 10-year analysis with propensity score matching. Rev Port Cardiol. 2023; 42(8): 711–717, doi: 10.1016/j.repc.2023.01.023, indexed in Pubmed: 37085085.
80. Bowker KE, Noel AR, Macgowan AP. Pharmacodynamics of minocycline against Staphylococcus aureus in an in vitro pharmacokinetic model. Antimicrob Agents Chemother. 2008; 52(12): 4370–4373, doi: 10.1128/AAC.00922-07, indexed in Pubmed: 18519719.
81. Gleva MJ, Poole JE. Prevention of cardiac implantable electronic device infections: update and evaluation of the potential role for capsulectomy or the antibiotic pouch. J Atr Fibrillation. 2017; 9(5): 1540, doi: 10.4022/jafib.1540, indexed in Pubmed: 29250274.
82. Tarakji KG, Krahn AD, Poole JE, et al. Worldwide randomized antibiotic envelope infection prevention trial (WRAP-IT). Am Heart J. 2016; 180(7): 12–21, doi: 10.1016/j.ahj.2016.06.010, indexed in Pubmed: 27659878.
83. Mittal S, Wilkoff BL, Kennergren C, et al. The World-wide Randomized Antibiotic Envelope Infection Prevention (WRAP-IT) trial: Long-term follow-up. Heart Rhythm. 2020; 17(7): 1115–1122, doi: 10.1016/j.hrthm.2020.02.011, indexed in Pubmed: 32087357.
84. Asbeutah AA, Salem MH, Asbeutah SA, et al. The role of an antibiotic envelope in the prevention of major cardiac implantable electronic device infections: A systematic review and meta-analysis. Medicine (Baltimore). 2020; 99(26): e20834, doi: 10.1097/MD.0000000000020834, indexed in Pubmed: 32590773.
85. Ziacchi M, Biffi M, Iacopino S, et al. REducing INFectiOns thRough Cardiac device Envelope: insight from real world data. The REINFORCE Project. Europace. 2023 [Epub ahead of print], doi: 10.1093/europace/euad224, indexed in Pubmed: 37490930.
86. Frausing MH, Johansen JB, Afonso D, et al. Cost-effectiveness of an antibacterial envelope for infection prevention in patients undergoing cardiac resynchronization therapy reoperations in Denmark. Europace. 2023; 25(6), doi: 10.1093/europace/euad159, indexed in Pubmed: 37345858.
87. Boriani G, Kennergren C, Tarakji KG, et al. Cost-Effectiveness analyses of an absorbable antibacterial envelope for use in patients at increased risk of cardiac implantable electronic device infection in Germany, Italy, and England. Value Health. 2021; 24(7): 930–938, doi: 10.1016/j.jval.2020.12.021, indexed in Pubmed: 34243836.
88. Kay G, Eby EL, Brown B, et al. Cost-effectiveness of TYRX absorbable antibacterial envelope for prevention of cardiovascular implantable electronic device infection. J Med Econ. 2018; 21(3): 294–300, doi: 10.1080/13696998.2017.1409227, indexed in Pubmed: 29171319.
89. Wilkoff BL, Boriani G, Mittal S, et al. Cost-Effectiveness of an antibacterial envelope for cardiac implantable electronic device infection prevention in the US healthcare system from the WRAP-IT trial. Circ Arrhythm Electrophysiol. 2020; 13(10): e008503, doi: 10.1161/CIRCEP.120.008503, indexed in Pubmed: 32915063.
90. Xiang K, Catanzaro JN, Elayi C, et al. Antibiotic-Eluting envelopes to prevent cardiac-implantable electronic device infection: past, present, and future. Cureus. 2021; 13(2): e13088, doi: 10.7759/cureus.13088, indexed in Pubmed: 33728111.
91. Deering TF, Catanzaro JN, Woodard DA. Physician antibiotic hydration preferences for biologic antibacterial envelopes during cardiac implantable device procedures. Front Cardiovasc Med. 2022; 9: 1006091, doi: 10.3389/fcvm.2022.1006091, indexed in Pubmed: 36620632.
92. Grubb BP, Welch M, Karabin B, et al. Initial experience with a technique for wound closure after cardiac device implantation designed to reduce infection and minimize tissue scar formation. Am J Ther. 2012; 19(2): 88–91, doi: 10.1097/MJT.0b013e3181ebd344, indexed in Pubmed: 20720483.
93. Senaratne JM, Wijesundera J, Chhetri U, et al. Reduced incidence of CIED infections with peri- and post-operative antibiotic use in CRT-P/D and ICD procedures. Medicine (Baltimore). 2022; 101(40): e30944, doi: 10.1097/MD.0000000000030944, indexed in Pubmed: 36221436.
94. Turagam MK, Nagarajan DV, Bartus K, et al. Use of a pocket compression device for the prevention and treatment of pocket hematoma after pacemaker and defibrillator implantation (STOP-HEMATOMA-I). J Interv Card Electrophysiol. 2017; 49(2): 197–204, doi: 10.1007/s10840-017-0235-9, indexed in Pubmed: 28413854.
95. Awada H, Geller JC, Brunelli M, et al. Pocket related complications following cardiac electronic device implantation in patients receiving anticoagulation and/or dual antiplatelet therapy: prospective evaluation of different preventive strategies. J Interv Card Electrophysiol. 2019; 54(3): 247–255, doi: 10.1007/s10840-018-0488-y, indexed in Pubmed: 30460588.
96. Fei YP, Wang L, Zhu CY, et al. Effect of a novel pocket compression device on hematomas following cardiac electronic device implantation in patients receiving direct oral anticoagulants. Front Cardiovasc Med. 2022; 9: 817453, doi: 10.3389/fcvm.2022.817453, indexed in Pubmed: 35282349.

The incidence of cardiovascular and other major complications after open abdominal aortic surgery

Dorota Studzińska[1, 2], Kamil Polok[2], Maciej Chwała[1], Marcin Zaczek[3], Wojciech Szczeklik[2]

[1]Department of Vascular Surgery and Angiology, St. John Grande Hospital, Kraków, Poland
[2]Center for Intensive Care and Perioperative Medicine, Jagiellonian University Medical College, Kraków, Poland
[3]Department of Internal Medicine, St. John Grande Hospital, Kraków, Poland

Editorial
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Correspondence to:
Wojciech Szczeklik, MD, PhD,
Jagiellonian University Medical College,
Centre for Intensive Care and Perioperative Medicine,
Wrocławska 1–3,
30–901 Kraków, Poland,
phone: +48 12 630 82 67,
e-mail: wojciech.szczeklik@uj.edu.pl

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ABSTRACT

Background: Abdominal aortic aneurysms (AAAs) and peripheral artery disease significantly increase the risk of perioperative complications.

Aim: The study aimed to determine the incidence of myocardial injury after noncardiac surgery (MINS), its association with 30-day mortality, as well as predictors of postoperative acute kidney injury (pAKI) and bleeding independently associated with mortality (BIMS) in patients undergoing open vascular surgeries involving the abdominal aorta.

Methods: We performed a retrospective cohort study using a sample of consecutive patients who underwent open abdominal aortic surgery due to infrarenal AAA and/or aortoiliac occlusive disease in a single tertiary center. In each patient, at least two postoperative troponin measurements were performed (on the first and second postoperative day). Creatinine and hemoglobin levels were measured preoperatively and at least twice postoperatively. The outcomes included MINS (primary outcome), pAKI, and BIMS (secondary outcomes). We assessed the associations between them and 30-day mortality and performed multivariable analysis to identify risk factors for these outcomes.

Results: The study group comprised 553 patients. The mean age was 67.6 years, and 82.5% of patients were male. The incidence of MINS, pAKI, and BIMS was 43.8%, 17.2%, and 45.8%, respectively. The 30-day mortality rate was higher in patients who developed MINS (12.0% vs. 2.3%; P <0.001), pAKI (32.6% vs. 1.1%; P <0.001), or BIMS (12.3% vs. 1.7%; P <0.001) compared to patients who did not develop these complications.

Conclusion: This study demonstrated that MINS, pAKI, and BIMS are common complications after open aortic surgeries, and they are related to a substantial increase in the 30-day mortality rate.

Key words: bleeding independently associated with mortality, myocardial injury after noncardiac surgery, open aortic surgery, postoperative acute kidney injury

INTRODUCTION

Abdominal aortic aneurysms (AAAs) and peripheral artery disease (PAD) significantly increase perioperative cardiovascular risk. This is largely attributed to the frequent coexistence of coronary artery disease and other cardiovascular diseases [1, 2]. Pathogenesis of AAA involves a degenerative process of the aortic wall caused by inflammation, structural defects in aorta matrix proteins, and overactive proteolysis leading to the destruction of collagen and elastin fibers [3]. Inflammation of the arterial wall is also an underlying process in the development of atherosclerosis [4]. Although there is a significant overlap of risk factors and prevalence of AAA with atherosclerosis, the etiology of most AAAs appears distinct from atherosclerosis [2].

Each year, several patients with AAA and PAD require vascular surgery, and they pose a particular challenge for clinicians involved in perioperative care. Open aneurysm repair

WHAT'S NEW?

This retrospective study includes exclusively patients undergoing open vascular surgery on the abdominal aorta in whom routine perioperative troponin, creatinine, and hemoglobin monitoring was performed. This approach adds novel information to the current knowledge by describing in detail the incidence of postoperative acute kidney injury and recently introduced perioperative outcomes such as myocardial injury after noncardiac surgery (MINS) and bleeding independently associated with mortality (BIMS). It demonstrates that they are common after open surgeries on the abdominal aorta and can be responsible for a substantial increase in the 30-day mortality rate. The awareness of their significance and knowledge about associated risk factors can facilitate identifying patients requiring particular vigilance in the perioperative period.

involves the replacement of the diseased aortic segment with a tube or bifurcated prosthetic graft [2]. PAD affecting the aortoiliac segment, especially with extensive lesions comprising the aorta up to the renal arteries and iliac arteries (aortoiliac occlusive disease), also may require open reconstruction e.g. aortobifemoral bypass surgery [1]. Recent studies suggested that patients undergoing vascular surgeries are at significantly elevated risk of postoperative myocardial injury and postoperative acute kidney injury (pAKI), which increase morbidity and long-term mortality [5–13].

Intraoperative blood loss and postoperative blood transfusion are common in vascular surgery and are associated with greatly increased risk of both 30-day adverse cardiovascular events and mortality [14, 15]. Bleeding independently associated with mortality (BIMS) is a recently introduced perioperative outcome with the definition based on robust data from a large prospective cohort study [16]. BIMS is associated with all-cause mortality within 30 days of noncardiac surgery and may account for approximately one-quarter of deaths occurring within 30 days of major noncardiac surgery [16].

Considering the clinical importance of postoperative myocardial injury, pAKI, and bleeding, we conducted this study to determine the incidence of these complications in the population of patients undergoing open vascular surgeries involving the abdominal aorta, their associations with 30-day mortality, and their predictors.

METHODS

Study design and population

We performed a retrospective cohort study using a sample of consecutive patients who underwent open abdominal aortic surgery from November 2010 to July 2017 in a tertiary vascular surgery center i.e. the Department of Vascular Surgery, St. John Grande Hospital, Kraków, Poland. Patients aged ≥45 years and undergoing open abdominal aortic surgery were considered eligible for the study. Study personnel extracted data from hospital charts and entered these data in the case report forms.

The study received approval from the Bioethics Committee of the Regional Chambers of Physicians in Kraków on December 27, 2016, before data were extracted. Individual patient consent was not obtained as it was not required by the local bioethics committee.

Study population

We included patients undergoing open aortic surgery (OAS) due to infrarenal AAA and/or PAD (i.e. aortoiliac occlusive disease). Patients were qualified for the surgery at the discretion of the attending physician according to the applicable guidelines (e.g. for AAA diameter ≥ 55 mm in men and ≥ 50 mm in women or the presence of symptoms for aortoiliac occlusive disease, the presence of symptoms such as short-distance intermittent claudication, ulceration, or necrosis) [17, 18]. Patients who died on the day of surgery and did not have postoperative troponin monitoring (n = 16) were excluded from the analysis. All patients were admitted to the Intensive Care Unit after surgery as per the standard of care in the participating center.

Perioperative monitoring of troponin, creatinine, and hemoglobin levels

In each patient (n = 553) at least two postoperative troponin (Tn) measurements were performed (on the first and second postoperative day). An electrocardiogram (ECG) was performed routinely in any case of Tn elevation as per the standard of care at the participating center. In a subgroup of 242 patients, Tn level was also measured preoperatively. Troponin monitoring was performed using high-sensitivity troponin T (hs-TnT, Roche, Basel, Switzerland) or ultra-sensitive Vidas troponin I (us-TnI, Biomerieux, Marcy-l'Étoile, France). Creatinine and hemoglobin levels were measured preoperatively and at least twice postoperatively. Diuresis (ml per hour) was routinely monitored for 2 postoperative days or longer if necessary.

The Revised Cardiac Risk Index (RCRI) score was calculated for all patients (i.e., one point for each of the following: history of ischemic heart disease, congestive heart failure, cerebrovascular disease, preoperative insulin therapy, preoperative serum creatinine concentration > 176.8 umol/l, and undergoing high-risk surgery) [19].

The American Society of Anesthesiologists (ASA) physical status score was calculated by the attending anesthesiologist according to the current guidelines [20].

Outcomes

The primary outcome of this study was myocardial injury after noncardiac surgery (MINS). Secondary outcomes were postoperative acute kidney injury (pAKI) and bleeding independently associated with mortality (BIMS).

MINS was defined as [9, 21, 22]:

- absolute postoperative hs-TnT ≥65 ng/l or postoperative 20–64 ng/l AND at least 5 ng/l increase compared to preoperative hs-TnT level (thresholds established in the Vascular Events In Noncardiac Surgery Patients Cohort Evaluation [VISION] study);
- postoperative us-TnI over the 99th percentile upper reference limit (≥19 ng/l) in patients who had no evidence of a non-ischemic etiology for the troponin elevation [7, 9, 21].

For patients with an elevated troponin level, study personnel looked for evidence of ischemic symptoms and/or ECG changes reported in the internist or cardiologist consultation or electronic health records from the day of myocardial injury diagnosis. The Fourth Universal Definition of Myocardial Infarction was used to diagnose myocardial infarction [23].

pAKI was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria [24]:

- Stage I: 1.5–1.9 times baseline or ≥0.3 mg/dl (≥26.5 µmol/l) increase in serum creatinine or urine output <0.5 ml/kg/h for 6–12 hours;
- Stage II: 2.0–2.9 times baseline in serum creatinine or urine output <0.5 ml/kg/h for ≥12 hours;
- Stage III: 3.0 times baseline or increase in serum creatinine to ≥4.0 mg/dl (≥353.6 µmol/l) or initiation of renal replacement therapy or anuria for ≥12 hours.

BIMS was defined as bleeding leading to postoperative hemoglobin <70 g/l, transfusion of ≥1 unit of red blood cells, or bleeding that was judged to be the cause of death [16].

The remaining outcomes included: 30-day mortality, in-hospital mortality, 30-day rehospitalization rate, in-hospital reoperation, gastrointestinal bleeding, requirement for transfusion, acute congestive heart failure, perioperative atrial fibrillation, stroke, nonfatal cardiac arrest, pneumonia, sepsis, pulmonary embolism, deep vein thrombosis, intestine ischemia, acute limb ischemia, and multiorgan failure. The detailed definitions of the remaining outcomes are presented in Supplementary material, *Table S1*.

Statistical analysis

The categorical variables were presented as counts and proportions and compared using the χ^2 test or Fischer's exact test. The continuous variables were presented as means (standard deviation, SD) or medians (interquartile ranges [IQR]). They were compared using the Mann-Whitney test or Student's t-test as appropriate. The differences in mortality were assessed using the log-rank test and visualized using the Kaplan-Meier curves. We performed multivariable analyses using logistic regression to evaluate the risk factors for MINS, pAKI, and BIMS. The model for MINS included age, sex, hypertension, coronary artery disease, chronic obstructive pulmonary disease (COPD), PAD, Lee's score, and duration of surgery. The model for pAKI additionally included preoperative estimated glomerular filtration rate (eGFR) according to the Modification of Diet in Renal Disease (MDRD) equation and intraoperative urine output per hour. The model for BIMS additionally included preoperative hemoglobin levels. This was a complete case analysis. All statistical analyses were performed using R, CRAN version 4.1.0 (packages: rms). A two-sided *P*-value < 0.05 was considered statistically significant.

RESULTS

Study population

This study included 553 patients undergoing open aortic surgery. The mean age was 67.6 (8.3) years, and males comprised 82.5% (456/553) of the study group. The median observation time was 30 days and ranged from 1 to 128 days. The majority of patients underwent open aneurysm repair with a tube prosthetic graft due to AAA (an aorta-aortic graft, 45.6%), aortobifemoral bypass surgery due to aortiiliac occlusive disease (20.6%), and simultaneous open aneurysm repair with aorto-biiliac bypass surgery (12.3%). Seven patients (1.3%) required suprarenal aortic clamping. Reimplantation of the mesenteric inferior artery to the prosthesis was performed in 5 patients (0.9%). Reimplantation of the accessory renal artery was performed in 2 patients (0.4%).

Baseline characteristics, laboratory results, and surgery characteristics in the total cohort and stratified by the incidence of MINS are presented in Table 1. Details on surgery and anesthesia type in the total cohort and stratified by the incidence of MINS are shown in Supplementary material, *Table S2*. Supplementary material, *Table S3* contains a comparison of baseline characteristics and complication rates stratified by the reason for surgery. Figure 1 demonstrates Kaplan-Meier curves comparing survival probability for patients who developed MINS, pAKI, and BIMS.

Myocardial injury after noncardiac surgery

Perioperative troponin monitoring was performed using hs-TnT in 411 patients (74.3%) and us-TnI in 142 patients (25.7%). MINS was diagnosed in 242 (43.8%) patients and occurred at a similar rate in patients undergoing surgery for AAA and PAD (43.2% vs. 45.6%; $P = 0.69$). The MINS incidence was higher among patients with hs-TnT monitoring compared to us-TnI (48.7% vs. 29.6%; $P < 0.001$). In patients with MINS, ischemic symptoms were present in 5.0% (12/242). Of 33 patients with MINS in whom echocardiography was performed, wall motion abnormalities were discovered in 14 patients (42.4%). Diagnostic criteria for myocardial infarction according to the Fourth Universal Definition of Myocardial Infarction were met in 16.1% of patients with MINS (39/242). The incidence of MINS was associated with a history of COPD (odds ratio [OR], 1.83; 95% confidence interval [CI], 1.24–2.70) and PAD (OR, 1.96; 95% CI, 1.33–2.90). Univariable analysis is summarized in Table 1 and multivariable analysis results are presented in Supplementary material, *Table S5*. Thirty-day mortality was

Table 1. Baseline characteristics, laboratory results, and surgery features

Feature	Total cohort (n = 553)	MINS (n = 242)	Non-MINS (n = 311)	*P*-value
Demographic and clinical characteristics				
Male sex, n (%)	456 (82.5)	196 (81.0)	260 (83.6)	0.49
Age, years, mean (SD)	67.6 (8.3)	68.38 (8.28)	66.95 (8.31)	0.045
Hypertension, n (%)	417 (75.5)	184 (76.3)	233 (74.9)	0.77
Coronary artery disease, n (%)	199 (36.1)	109 (45.2)	90 (28.9)	<0.001
High-risk coronary artery disease[a], n (%)	5 (0.9)	1 (0.4)	4 (1.3)	0.54
History of myocardial infarction, n (%)	103 (18.7)	58 (24.1)	45 (14.5)	0.006
History of cerebrovascular event, n (%)	41 (7.5)	21 (8.8)	20 (6.4)	0.37
Congestive heart failure, n (%)	41 (7.4)	21 (8.7)	20 (6.4)	0.40
Diabetes mellitus, n (%)	109 (19.7)	40 (16.5)	69 (22.2)	0.12
Chronic obstructive pulmonary disease, n (%)	167 (30.3)	92 (38.2)	75 (24.1)	0.001
Aortic stenosis, n (%)				0.16
None	531 (96.5)	227 (95.0)	304 (97.7)	
Mild	18 (3.3)	11 (4.6)	7 (2.3)	
Mechanical prosthesis	1 (0.2)	1 (0.4)	0 (0.0)	
Peripheral arterial disease, n (%)	340 (63.8)	174 (73.1)	166 (56.3)	<0.001
Chronic kidney disease requiring dialysis, n (%)	1 (0.2)	1 (0.4)	0 (0.0)	0.90
History of smoking (current or in the past), n (%)	469 (84.8)	197 (81.4)	272 (87.5)	0.07
Preoperative pharmacotherapy				
Acetylsalicylic acid, n (%)	392 (71.8)	159 (67.1)	233 (75.4)	0.04
Statin, n (%)	412 (75.5)	168 (70.9)	244 (79.0)	0.04
Angiotensin-converting-enzyme inhibitors, n (%)	284 (52.0)	129 (54.4)	155 (50.2)	0.37
Angiotensin receptor blockers, n (%)	43 (14.1)	9 (11.2)	34 (15.0)	0.51
Beta-blockers, n (%)	296 (54.1)	129 (54.4)	167 (53.9)	0.97
Non-dihydropyridine calcium channel blockers, n (%)	142 (26.0)	46 (19.4)	96 (31.1)	0.003
Dihydropyridine calcium channel blockers, n (%)	8 (1.5)	5 (2.1)	3 (1.0)	0.46
Diuretics, n (%)	174 (32.2)	74 (31.6)	100 (32.6)	0.89
Oral anticoagulants, n (%)	7 (1.3)	5 (2.1)	2 (0.6)	0.26
Low-molecular-weight heparin, n (%)	40 (7.4)	29 (12.4)	11 (3.6)	<0.001
Clopidogrel, n (%)	12 (2.2)	9 (3.8)	3 (1.0)	0.053
Fibrate, n (%)	11 (2.0)	4 (1.7)	7 (2.3)	0.87
Perioperative risk scores				
ASA score, n (%)				
2	140 (25.8)	50 (20.8)	90 (29.8)	<0.001
3	345 (63.7)	143 (59.6)	202 (66.9)	
4	49 (9.0)	39 (16.2)	10 (3.3)	
5	8 (1.5)	8 (3.3)	0 (0.0)	
The RCRI index, median (IQR)	1.0 (1.0–2.0)	2.00 (1.0–2.0)	1.0 (1.0–2.0)	<0.001
AAA characteristics				
AAA symptoms, n (%)				<0.001
Not symptomatic	342 (79.0)	133 (69.3)	209 (86.7)	
Symptomatic	56 (12.9)	27 (14.1)	29 (12.0)	
Ruptured	35 (8.1)	32 (16.7)	3 (1.2)	
AAA size based on CT scans, mm, median (IQR)	57.0 (52.0–65.0)	60.0 (53.0–70.0)	55.0 (52.0–61.0)	0.001
Laboratory results				
Baseline eGFR, ml/min/1.73 m^2, median (IQR)	85.3 (68.0–105.1)	79.3 (59.2–96.7)	89.1 (73.7–110.5)	<0.001
Baseline hemoglobin, g/dl, median (IQR)	14.5 (13.3–15.4)	14.2 (12.6–15.2)	14.7 (13.7–15.5)	<0.001
Surgery characteristics				
Emergent surgery, n (%)	88 (15.9)	54 (22.3)	34 (10.9)	<0.001
Surgery duration, min, median (IQR)	140 (115–180)	145 (115–175)	140 (115–180)	0.70
Intraoperative blood loss, ml, median (IQR)	700 (500–1000)	700 (500–1275)	700 (500–1000)	0.13
Intraoperative urine output, ml, median (IQR)	270 (150–440)	260 (150–455)	280 (150–440)	0.69

[a]Diagnosis ≤6 months before noncardiac surgery of myocardial infarction, acute coronary syndrome, Canadian Cardiovascular Society class III or IV angina
Abbreviations: AAA, abdominal aortic aneurysm; ASA, American Society of Anesthesiologists; CT, computed tomography; eGFR, estimated glomerular filtration rate; IQR, interquartile range; MINS, myocardial injury after noncardiac surgery; SD, standard deviation; RCRI, Revised Cardiac Risk Index

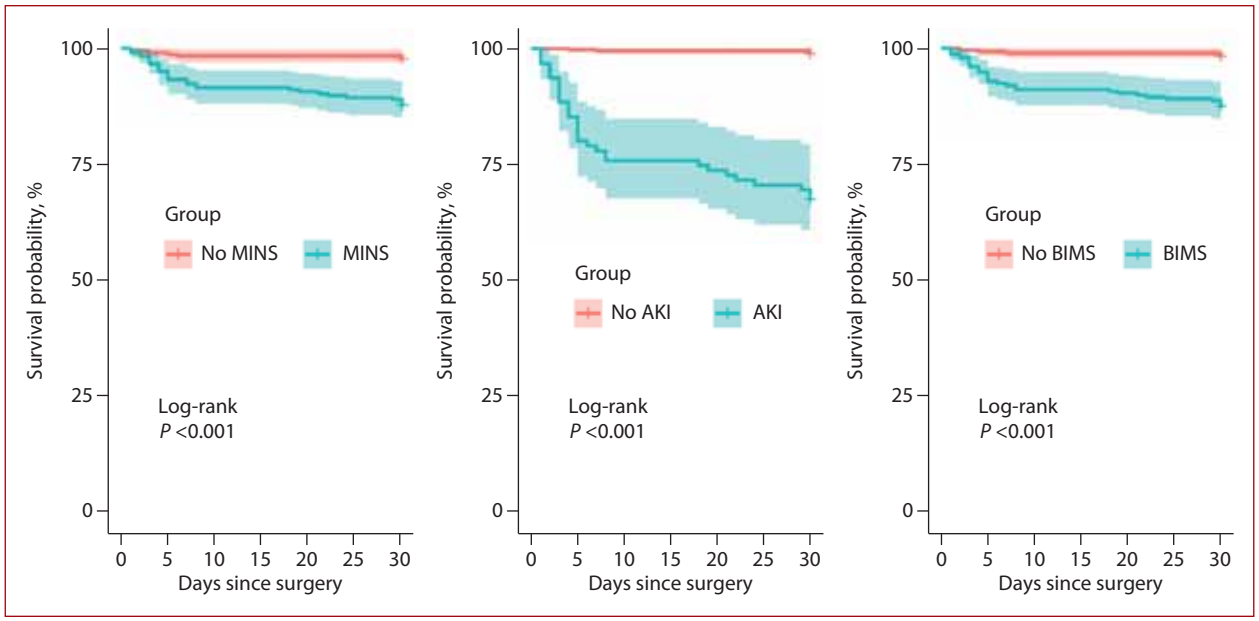

Figure 1. Kaplan-Meier curves comparing survival probability for patients who developed MINS, pAKI, and BIMS, respectively

Abbreviations: BIMS, bleeding independently associated with mortality; MINS, myocardial injury after noncardiac surgery; pAKI, postoperative acute kidney injury

higher in patients who developed MINS (12.0% vs. 2.3%; *P* <0.001).

Postoperative acute kidney injury

Postoperative acute kidney injury was diagnosed in 95 patients (17.2%), 20 of whom (21.1%) required postoperative continuous dialysis. According to the KDIGO criteria, pAKI was categorized as stage I in 54 patients (9.8%), stage II in 20 patients (3.6%), and stage III in 21 patients (3.8%). Patients undergoing surgery for AAA more often suffered from AKI (19.2% vs. 11.0%; *P* = 0.04) but not from pAKI requiring dialysis (3.6 vs. 3.7%; *P* = 1.0). There was no difference in the incidence of pAKI between patients who required suprarenal aortic clamping and the remaining patients (42.9% vs. 16.8%; *P* = 0.10). The risk of pAKI was associated with lower preoperative eGFR (OR, 0.97; 95% CI, 0.96–0.98 [per increase by 1 ml/min/1.73 m^2]) and longer surgery duration (OR, 1.92; 95% CI, 1.45–2.59 [per increase by 1 hour of surgery]). The univariable analysis is summarized in Supplementary material, *Table S4*, and multivariable analysis results are presented in Supplementary material, *Table S5*. Thirty-day mortality was higher in patients who developed pAKI (32.6% vs. 1.1%; *P* <0.001).

Bleeding independently associated with mortality (BIMS)

BIMS criteria were met by 253 patients (45.8%), among whom 197 (77.9%) required blood product transfusion. The BIMS incidence was similar in patients undergoing procedures for AAA and PAD (46.3 vs. 44.1%; *P* = 0.73). The risk of bleeding was associated with increasing age (OR, 1.05; 95% CI, 1.02–1.08), longer surgery duration (OR, 2.91; 95% CI, 2.21–3.92 [per increase by 1 hour of surgery]), and lower preoperative hemoglobin level (OR, 0.58; 95% CI, 0.50–0.67 [per increase by 1 g/dl of hemoglobin]). The univariable analysis is summarized in Supplementary material, *Table S4*, and multivariable analysis results are presented in Supplementary material, *Table S5*. Thitry-day mortality was higher in patients who developed BIMS (12.3% vs. 1.7%; *P* <0.001).

Other postoperative complications

Thirty-day mortality accounted for 6.5% (36/553) and hospital mortality was 6.9% (38/553). The most common postoperative complications were the need for reoperation (8.3%), pneumonia (7.8%), and postoperative atrial fibrillation (7.1%). All recorded postoperative complications and their incidence stratified by the coexistence of MINS are summarized in Table 2.

DISCUSSION

In this retrospective study aimed at assessment of perioperative complications, we demonstrated that MINS, pAKI, and BIMS are common after OAS and are associated with an increased 30-day mortality rate. Our results suggest that this population requires particular vigilance and an active approach toward the detection of postoperative complications.

Myocardial injury is a common complication in vascular surgery, often remains asymptomatic, and is associated with an almost 10-fold increase in short-term mortality [10, 25, 26].

In our study, in comparison to the data reported by Biccard et al. (a vascular surgery sub-analysis of the VISION study), the prevalence of MINS was higher (43.8% vs. 19.1%), with 95% of patients not presenting any symp-

Table 2. Summary of outcomes in the entire cohort and stratified by the incidence of MINS

Feature	Total cohort (n = 553)	MINS (n = 242)	Non-MINS (n = 311)	*P*-value
In-hospital death, n (%)	38 (6.9)	30 (12.4)	8 (2.6)	<0.001
30-day mortality, n (%)	36 (6.5)	29 (12.0)	7 (2.3)	<0.001
30-day rehospitalization, n (%)	5 (0.9)	2 (0.8)	3 (1.0)	1.00
Hospital LOS, days, median (IQR)	11.0 (9.0–15.0)	11.0 (9.0–16.0)	11.0 (9.0–14.0)	0.15
ICU LOS, days, median (IQR)	3.0 (2.0–3.0)	3.0 (2.0–4.0)	3.0 (2.0–3.0)	0.01
Myocardial infarction, n (%)	39 (7.1)	39 (16.1)	0 (0.0)	–
AKI, n (%)	95 (17.2)	67 (27.7)	28 (9.0)	<0.001
AKI requiring dialysis, n (%)	20 (3.6)	18 (7.5)	2 (0.6)	–
BIMS, n (%)	253 (45.8)	139 (57.4)	114 (36.7)	<0.001
Gastrointestinal tract bleeding, n (%)	5 (0.9)	3 (1.2)	2 (0.6)	–
Requirement for transfusion after surgery, n (%)	197 (35.6)	115 (47.5)	82 (26.4)	<0.001
Acute congestive heart failure, n (%)	17 (3.1)	13 (5.4)	4 (1.3)	0.01
Perioperative atrial fibrillation, n (%)	39 (7.1)	31 (12.8)	8 (2.6)	<0.001
Stroke, n (%)	2 (0.4)	0 (0.0)	2 (0.6)	0.59
Nonfatal cardiac arrest, n (%)	7 (1.3)	4 (1.7)	3 (1.0)	0.74
Pneumonia, n (%)	43 (7.8)	34 (14.0)	9 (2.9)	<0.001
Sepsis, n (%)	27 (4.9)	23 (9.5)	4 (1.3)	<0.001
Pulmonary embolism, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	–
Deep vein thrombosis, n (%)	1 (0.2)	1 (0.4)	0 (0.0)	–
Intestine ischemia, n (%)	7 (1.3)	5 (2.1)	2 (0.6)	0.27
Acute limb ischemia, n (%)	32 (5.8)	19 (7.9)	13 (4.2)	0.10
Multiorgan failure, n (%)	31 (5.6)	24 (9.9)	7 (2.3)	<0.001
In-hospital reoperation, n (%)	46 (8.3)	27 (11.2)	19 (6.1)	0.048

Abbreviations: AKI, acute kidney injury; BIMS, bleeding independently associated with mortality; ICU, intensive care unit; MINS, myocardial injury after noncardiac surgery; LOS, length of stay

toms of cardiac ischemia [10]. Markedly higher incidence of MINS in our cohort is probably related to the type of OAS procedures, which are some of the most complex procedures in vascular surgery encompassing clamping and cutting the aorta. Moreover, common prolongation of sedation in this population likely contributes to the high percentage of asymptomatic cases. Our study corroborates previously cited data indicating that MINS is associated with poorer short-term prognosis and higher rates of complication such as perioperative atrial fibrillation, pneumonia, sepsis, pAKI, and 30-day mortality.

Until now, the data on the prevalence of MINS in patients undergoing OAS have been scarce. A small cohort study of 31 patients who underwent open aortic repair due to AAA and had routine troponin I (TnI) measurements in the first 3 postoperative days revealed that 9 patients (29%) experienced significant elevation of TnI levels above the upper limit of normal [27]. In another small study including 38 patients who underwent OAS and had routine TnI measurement before surgery and in the first 3 postoperative days 31% of patients had increased levels of TnI postoperatively [28]. In our study, the incidence of myocardial injury was higher compared to those reports (43.8% vs. 29% and 31%). Moreover, the presented prevalence of myocardial infarction diagnosed according to the Fourth Universal Definition of Myocardial Infarction (16.1%) was higher than in some previous studies — i.e. 3.7% in a study by La Manach and al. and 4.2% in a study by Steely et al. [29, 30]. This difference is likely explained by the routine troponin monitoring using high-sensitivity assays in our study.

The available studies on major vascular surgeries demonstrated an association between preoperative renal dysfunction, prior stroke, prolonged surgery, surgical priority, requirement for red cell transfusion, and cardiovascular complications such as myocardial infarction, arrhythmias, pulmonary edema, and stroke [31, 32]. Our study extends the current knowledge by showing that COPD and PAD, but not age, sex, hypertension, coronary artery disease, duration of surgery, or RCRI, are related to increased risk of MINS in this population.

The reported incidence of pAKI within 30 days after OAS varies widely in available studies and ranges from 8.4 to 52.5%. This is very likely due to heterogeneity in definitions used in different studies [29, 31, 33, 34]. A recent report using the Acute Kidney Injury Network (AKIN) criteria for pAKI (analogous to the KDIGO definition), reported an incidence of 22.4% in patients who underwent OAS with an 8-fold increase in 30-day mortality [33]. Overall, the risk factors for pAKI in this study were intraoperative red blood cell transfusion and chronic kidney disease [33]. Another study in which pAKI was defined using the Aneurysm Renal Injury Score (ARISe), reported the incidence of pAKI equal to 26.3% in patients undergoing OAS and a higher mortality rate in patients who developed this complication (4.8% vs. 0.6%) [35]. According to this study, current smoking, hypertension, chronic kidney disease, and arrhythmias were predictors of pAKI. Our study confirms a high incidence of pAKI in patients undergoing OAS (17.2%) and its association with higher 30-day mortality (32.6% vs. 1.1%). We additionally showed that lower preoperative eGFR and

longer surgery duration were related to higher risk of pAKI. Interestingly, we did not confirm the previously described association between pAKI and intraoperative red blood cell transfusion. Finally, in both mentioned studies, analysis of pAKI predictors was performed on the whole study population without distinction regarding the type of surgery (open vs. endovascular) [33, 35].

Another crucial perioperative outcome with a multitude of definitions is bleeding. The most recent approach to define bleeding was the introduction of BIMS based on data from a prospective study of 16 079 patients aged ≥45 years having noncardiac surgery. Simultaneously an electronic risk calculator for BIMS was developed and internally validated [16]. The diagnostic criteria for BIMS were created based on their association with all-cause mortality within 30 days of noncardiac surgery. In our study, we showed that BIMS is a common complication after OAS affecting nearly every second patient, and it is associated with a substantial increase in the 30-day mortality rate (12.3% vs. 1.7% in the non-BIMS group). We identified age, longer surgery duration, and low preoperative hemoglobin level as predictors of BIMS. We believe there is an urgent need to standardize definitions of perioperative outcomes, particularly pAKI and bleeding. This will improve researchers' ability to reliably pool data from different reports to improve our understanding of incidence and risk factors of postoperative complications and their impact on short- and long-term mortality.

The main strength of our study is a relatively large and homogenous cohort of patients undergoing major open surgery involving the aorta. To our knowledge, this is the largest study describing the incidence of MINS, pAKI, and BIMS in this population encompassing routine measurement of appropriate markers. Such an approach enabled us to provide researchers and clinicians with precise estimates. From a practical point of view, preoperative evaluation of patients to identify risk factors for MINS, pAKI, and BIMS could allow the introduction of some interventions before the surgery recommended in the appropriate guidelines. These include e.g. temporarily withholding angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and aldosterone antagonists before surgery for pAKI prevention and correction of anemia for BIMS prevention [24, 36].

Our study also has several limitations. First, we did not perform routine troponin measurements before surgery in all patients (preoperative Tn level was available only in a subgroup of 242 patients). Thus, we could not exclude patients with chronic troponin elevation. However, available data suggest that elevated troponins before surgery account for only 13.8% of perioperative elevations [7, 10]. Second, the study carries limitations associated with its retrospective design e.g. lack of some potentially significant parameters (e.g. body mass index) prevented us from evaluating their association with postoperative complications. Third, due to the lack of troponin monitoring on the day of surgery, we had to exclude patients who died on the day of surgery and did not have postoperative troponin monitoring. Four, the recruitment period for this study ended five years before this analysis, and some clinical practices changed over that time. Fifth, this was a single-center study which limits the generalizability of the results due to the possible impact of the surgical approach typical for this center (e.g. lack of cell saver technique). Sixth, we did not gather precise data about preoperative electrocardiograms so we were unable to evaluate their association with postoperative complications in this cohort and thus validate some of our previous findings [37]. Finally, we were unable to perform a multivariable analysis of the association between mortality and outcomes of interest due to a relatively low 30-day mortality.

CONCLUSION

MINS, pAKI, and BIMS are common complications after OAS and are related to a substantial increase in the 30-day mortality rate. The majority of these events are asymptomatic and without systematic monitoring would likely go undetected. The awareness of their independent predictors can facilitate identifying high-risk patients susceptible to experiencing such complications.

Supplementary material

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

Article information

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REFERENCES

1. Aboyans V, Ricco JB, Bartelink MLEL, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). Eur Heart J. 2018; 39(9): 763–816, doi: 10.1093/eurheartj/ehx095, indexed in Pubmed: 28886620.
2. Wanhainen A, Verzini F, Van Herzeele I, et al. Editor's Choice - European Society for Vascular Surgery (ESVS) 2019 Clinical Practice Guidelines on the Management of Abdominal Aorto-iliac Artery Aneurysms. Eur J Vasc Endovasc Surg. 2019; 57(1): 8–93, doi: 10.1016/j.ejvs.2018.09.020, indexed in Pubmed: 30528142.
3. Norman PE, Powell JT. Site specificity of aneurysmal disease. Circulation. 2010; 121(4): 560–568, doi: 10.1161/CIRCULATIONAHA.109.880724, indexed in Pubmed: 20124136.
4. Libby P, Ridker P, Hansson G. Inflammation in atherosclerosis. J Am Coll Cardiol. 2009; 54(23): 2129–2138, doi: 10.1016/j.jacc.2009.09.009, indexed in Pubmed: 19942084.

5. Chertow GM, Burdick E, Honour M, et al. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. J Am Soc Nephrol. 2005; 16(11): 3365–3370, doi: 10.1681/ASN.2004090740, indexed in Pubmed: 16177006.
6. Kazmers A, Perkins AJ, Huber TS, et al. The impact of complications after vascular surgery in Veterans Affairs Medical Centers. J Surg Res. 1997; 67(1): 62–66, doi: 10.1006/jsre.1996.4946, indexed in Pubmed: 9070183.
7. Botto F, Alonso-Coello P, Chan MTV, et al. Myocardial injury after noncardiac surgery: a large, international, prospective cohort study establishing diagnostic criteria, characteristics, predictors, and 30-day outcomes. Anesthesiology. 2014; 120(3): 564–578, doi: 10.1097/ALN.0000000000000113, indexed in Pubmed: 24534856.
8. Puelacher C, Lurati Buse G, Seeberger D, et al. Perioperative myocardial injury after noncardiac surgery: incidence, mortality, and characterization. Circulation. 2018; 137(12): 1221–1232, doi: 10.1161/CIRCULATIONAHA.117.030114, indexed in Pubmed: 29203498.
9. Devereaux PJ, Chan MTV, Alonso-Coello P, et al. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. JAMA. 2012; 307(21): 2295–2304, doi: 10.1001/jama.2012.5502, indexed in Pubmed: 22706835.
10. Biccard BM, Scott DJ, Chan MTV, et al. Myocardial Injury after Noncardiac Surgery (MINS) in vascular surgical patients: a prospective observational cohort study. Ann Surg. 2018; 268(2): 357–363, doi: 10.1097/SLA.0000000000002290, indexed in Pubmed: 28486392.
11. Halvorsen S, Mehilli J, Cassese S, et al. 2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery. Eur Heart J. 2022; 43(39): 3826–3924, doi: 10.1093/eurheartj/ehac270, indexed in Pubmed: 36017553.
12. Legutko J, Wiewiórka Ł, Piątek J, et al. Transcatheter aortic valve implantation and hybrid coronary revascularization in a patient with severe aortic stenosis, complex coronary artery disease, and porcelain aorta. Kardiol Pol. 2021; 79(11): 1286–1287, doi: 10.33963/KP.a2021.0097, indexed in Pubmed: 34472073.
13. Głowacki J, Jackowska Z, Nożyński J, et al. Coral reef aorta involving the proximal part of the descending aorta. Kardiol Pol. 2019; 77(4): 486–487, doi: 10.33963/KP.14798, indexed in Pubmed: 31025656.
14. Bursi F, Barbieri A, Politi L, et al. Perioperative red blood cell transfusion and outcome in stable patients after elective major vascular surgery. Eur J Vasc Endovasc Surg. 2009; 37: 311–318, doi: 10.1016/j.ejvs.2008.12.002, indexed in Pubmed: 19111480.
15. Valentijn TM, Hoeks SE, Bakker EJ, et al. The impact of perioperative red blood cell transfusions on postoperative outcomes in vascular surgery patients. Ann Vasc Surg. 2015; 29: 511–519, doi: 10.1016/j.avsg.2014.08.021, indexed in Pubmed: 25462545.
16. Roshanov PS, Eikelboom JW, Sessler DI, et al. Bleeding impacting mortality after noncardiac surgery: a protocol to establish diagnostic criteria, estimate prognostic importance, and develop and validate a prediction guide in an international prospective cohort study. CMAJ Open. 2017; 5(3): E594–E603, doi: 10.9778/cmajo.20160106, indexed in Pubmed: 28943515.
17. Moll FL, Powell JT, Fraedrich G, et al. Management of abdominal aortic aneurysms clinical practice guidelines of the European society for vascular surgery. Eur J Vasc Endovasc Surg. 2011; 41 Suppl 1: S1–S58, doi: 10.1016/j.ejvs.2010.09.011, indexed in Pubmed: 21215940.
18. Tendera M, Aboyans V, Bartelink ML, et al. ESC Guidelines on the diagnosis and treatment of peripheral artery diseases: Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries: the Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC). Eur Heart J. 2011; 32(22): 2851–2906, doi: 10.1093/eurheartj/ehr211, indexed in Pubmed: 21873417.
19. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation. 1999; 100(10): 1043–1049, doi: 10.1161/01.cir.100.10.1043, indexed in Pubmed: 10477528.
20. ASA Physical Status Classification System, https://www.asahq.org/standards-and-guidelines/asa-physical-status-classification-system (accessed 12 January 2018).
21. Devereaux PJ, Biccard BM, Sigamani A, et al. Association of postoperative high-sensitivity troponin levels with myocardial injury and 30-day mortality among patients undergoing noncardiac surgery. JAMA. 2017; 317(16): 1642–1651, doi: 10.1001/jama.2017.4360, indexed in Pubmed: 28444280.
22. Devereaux PJ, Szczeklik W. Myocardial injury after non-cardiac surgery: diagnosis and management. Eur Heart J. 2020; 41(32): 3083–3091, doi: 10.1093/eurheartj/ehz301, indexed in Pubmed: 31095334.
23. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). J Am Coll Cardiol. 2018; 72(18): 2231–2264, doi: 10.1016/j.jacc.2018.08.1038, indexed in Pubmed: 30153967.
24. KDIGO Clinical Practice Guideline for Acute Kidney Injury, https://kdigo.org/guidelines/acute-kidney-injury/ (accessed 15 February 2021).
25. Landesberg G, Shatz V, Akopnik I, et al. Association of cardiac troponin, CK-MB, and postoperative myocardial ischemia with long-term survival after major vascular surgery. J Am Coll Cardiol. 2003; 42(9): 1547–1554, doi: 10.1016/j.jacc.2003.05.001, indexed in Pubmed: 14607436.
26. Górka J, Polok K, Fronczek J, et al. Myocardial injury is more common than deep venous thrombosis after vascular surgery and is associated with a high one year mortality risk. Eur J Vasc Endovasc Surg. 2018; 56(2): 264–270, doi: 10.1016/j.ejvs.2018.02.005, indexed in Pubmed: 29580830.
27. Andrews N, Jenkins J, Andrews G, et al. Using postoperative cardiac Troponin-I (cTi) levels to detect myocardial ischaemia in patients undergoing vascular surgery. Cardiovasc Surg. 2001; 9(3): 254–265, doi: 10.1016/s0967-2109(00)00139-3, indexed in Pubmed: 11336849.
28. Barbagallo M, Casati A, Spadini E, et al. Early increases in cardiac troponin levels after major vascular surgery is associated with an increased frequency of delayed cardiac complications. J Clin Anesth. 2006; 18(4): 280–285, doi: 10.1016/j.jclinane.2005.11.005, indexed in Pubmed: 16797430.
29. Le Manach Y, Ibanez Esteves C, Bertrand M, et al. Impact of preoperative statin therapy on adverse postoperative outcomes in patients undergoing vascular surgery. Anesthesiology. 2011; 114(1): 98–104, doi: 10.1097/ALN.0b013e31820254a6, indexed in Pubmed: 21178671.
30. Steely AM, Callas PW, Neal D, et al. Regional variation in postoperative myocardial infarction in patients undergoing vascular surgery in the United States. Ann Vasc Surg. 2017; 40: 63–73, doi: 10.1016/j.avsg.2016.07.099, indexed in Pubmed: 27908815.
31. Licker M, Christoph E, Cartier V, et al. Impact of anesthesia technique on the incidence of major complications after open aortic abdominal surgery: a cohort study. J Clin Anesth. 2013; 25(4): 296–308, doi: 10.1016/j.jclinane.2013.01.009, indexed in Pubmed: 23685100.
32. Sutzko DC, Andraska EA, Obi AT, et al. Risk factors associated with perioperative myocardial infarction in major open vascular surgery. Ann Vasc Surg. 2018; 47: 24–30, doi: 10.1016/j.avsg.2017.08.030, indexed in Pubmed: 28893702.
33. Bang JY, Lee JB, Yoon Y, et al. Acute kidney injury after infrarenal abdominal aortic aneurysm surgery: a comparison of AKIN and RIFLE criteria for risk prediction. Br J Anaesth. 2014; 113(6): 993–1000, doi: 10.1093/bja/aeu320, indexed in Pubmed: 25256546.
34. Filiberto AC, Ozrazgat-Baslanti T, Loftus TJ, et al. Optimizing predictive strategies for acute kidney injury after major vascular surgery. Surgery. 2021; 170(1): 298–303, doi: 10.1016/j.surg.2021.01.030, indexed in Pubmed: 33648766.
35. Castagno C, Varetto G, Quaglino S, et al. Acute kidney injury after open and endovascular elective repair for infrarenal abdominal aortic aneurysms. J Vasc Surg. 2016; 64(4): 928–933.e1, doi: 10.1016/j.jvs.2016.02.048, indexed in Pubmed: 27288101.
36. American Society of Anesthesiologists Task Force on Perioperative Blood Management. Practice guidelines for perioperative blood management: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Management. Anesthesiology. 2015; 122(2): 241–275, doi: 10.1097/ALN.0000000000000463, indexed in Pubmed: 25545654.
37. Studzińska D, Polok K, Rewerska B, et al. Prognostic value of preoperative electrocardiography in predicting myocardial injury after vascular surgery. Kardiol Pol. 2022; 80(5): 553–559, doi: 10.33963/KP.a2022.0085, indexed in Pubmed: 35344585.

Safety and efficacy of a novel calcified plaque modification technique — Shockwave Intravascular Lithotripsy — in patients with coronary artery disease: Mid-term outcomes

Piotr Rola[1, 2], Łukasz Furtan[2], Szymon Włodarczak[3], Mateusz Barycki[2], Michalina Kędzierska[4], Adrian Doroszko[5], Adrian Włodarczak[1, 3], Maciej Lesiak[6]

[1]Faculty of Health Sciences and Physical Culture, Witelon Collegium State University, Legnica, Poland
[2]Department of Cardiology, Provincial Specialized Hospital in Legnica, Legnica, Poland
[3]Department of Cardiology, The Copper Health Center, Lubin, Poland
[4]Faculty of Medicine, Wroclaw Medical University, Wrocław, Poland
[5]Department of Cardiology, Center for Heart Diseases, 4th Military Hospital, Faculty of Medicine, Wroclaw University of Science and Technology, Wrocław, Poland
[6]1st Department of Cardiology, Poznan University of Medical Sciences, Poznań, Poland

Editorial
by Kassimis et al.

Correspondence to:
Piotr Rola, MD, PhD,
Faculty of Health Sciences and Physical Culture,
Witelon Collegium State University,
Sejmowa 5A, 59–220 Legnica, Poland,
phone: + 48 76 721 14 43,
e-mail: piotr.rola@gmail.com

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ABSTRACT

Background: Coronary interventions in calcified lesions are associated with a higher rate of adverse clinical events. Initial aggressive plaque modification along with post-implantation optimization is pivotal for achieving a favorable outcome of percutaneous coronary intervention (PCI). Recently, the Shockwave C2 Intravascular Lithotripsy (S-IVL) System, a novel acoustic wave-based device designed to modify calcified plaque, has been introduced into clinical practice.

Aims: We evaluated the mid-term safety and efficiency of S-IVL in a cohort of 131 consecutive patients with severely calcified coronary lesions.

Methods: We retrospectively analyzed a total of 131 consecutive S-IVL PCI procedures. The study had two main inclusion criteria — the presence of a calcified resistant lesion (defined by inadequate non-compliant balloon catheter inflation) or a significantly underexpanded stent (more than 20% of reference diameter). The study had two primary endpoints — successful clinical outcome and safety concerns. Clinical success was defined as effective stent deployment or optimization of a previously underexpanded stent (with less than <20% in-stent residual stenosis). Safety outcomes were defined as periprocedural complications, such as device failure and major adverse cardiac and cerebrovascular events (MACCE). Clinical follow-up was performed at the end of hospitalization and 6 months after the index procedure.

Results: In-hospital MACCE was 4.6% with 1.5% target lesion revascularization (TLR) and one case of subacute fatal stent thrombosis. At 6-month follow-up, the MACCE rate was 7.9% with a concomitant TLR rate of 3.8%.

Conclusion: Our mid-term data confirm acceptable safety and efficacy of intravascular lithotripsy as a valuable strategy for lesion preparation and stent optimization in a cohort of 131 consecutive patients with severely calcified coronary lesions.

Key words: calcified lesions, lesion preparation, percutaneous coronary intervention, Shockwave Intravascular Lithotripsy, stent optimization

WHAT'S NEW?

Calcified lesions represent a challenging subset for percutaneous coronary intervention (PCI) with high risk of adverse events. Adequate lesion preparation and post-implantation stent optimization are crucial in achieving satisfactory long-term efficacy. This study is among the first to present real-life data from the Lower Silesia Shockwave Registry (LSSR), which aimed to evaluate the mid-term outcomes of PCI supported by a novel plaque modification method — Shockwave Intravascular Lithotripsy in a cohort of 131 consecutive patients. Our results confirm its feasibility and safety at 6-month follow-up in the high-risk population with advanced coronary artery disease.

INTRODUCTION

Despite undeniable improvement in percutaneous treatment of coronary artery disease resulting from the introduction of the second generation of drug-eluting stents, calcified coronary lesions are still a challenge for interventional cardiology. According to the literature, calcified plaque burden is increasing with age and the prevalence of renal insufficiency, hypertension, and diabetes [1]; it is an independent risk factor for future cardiovascular events [2]. Coronary interventions in calcified lesions are inextricably linked with a higher rate of periprocedural complications (including dissections, perforations, impairment of stent delivery, and deployment) and several long-term adverse events (such as stent failure, thrombosis, restenosis, and repeat revascularization) [3].

Aggressive plaque modification before stent implantation is part of contemporary practice and is crucial in avoiding unfavorable percutaneous coronary intervention (PCI) outcomes [4]. Numerous strategies aiming at appropriate preparation of calcified lesions have been implemented in the PCI armamentarium. Generally, the two main groups can be distinguished — first, balloon-depend technologies (semi-compliant, non-compliant, cutting, and scoring) and second, atheroablative devices (rotational, orbital, and laser) [5]. Although all listed devices can facilitate PCI in calcified lesions, the extent of calcium modification is limited and mainly focused on superficial plaque modification. Additionally, some device-associated periprocedural complications may unexpectedly occur in the course of the procedure.

Recently a novel technique dedicated to calcified plaque modification has been introduced into clinical practice — Shockwave C2 Intravascular Lithotripsy (S-IVL) (Shockwave Medical Inc, Santa Clara, CA, US). This balloon-based coronary system transforms electrical energy into mechanical (shock wave) leading to profound defragmentation of calcium nodules without affecting the vascular architecture [6]. Although initially small-sized studies confirmed the short-term safety and efficiency [7–11], the mid and long-term data are still missing. Since the subjects recruited to cardiac clinical trials are distinctly different from the "real-world" population of cardiac patients, an assessment of S-IVL in real-life registries seems to be extremely valuable.

METHODS

This study presents data from the Lower Silesia Shockwave Registry (LSSR) that includes all consecutive cases of PCI performed with the support of Shockwave Intravascular Lithotripsy from two cooperating cardiac centers. PCIs were performed between May 2019 and September 2022 in two high-volume centers from the Lower Silesia region of Poland.

All patients in the registry had a clinical indication for PCI, based on the current European Society of Cardiology (ESC) revascularization guidelines, if necessary, with the support of the local Heart Team. Patients enrolled in the study had to meet one of two main inclusion criteria: the presence of a highly calcified resistant lesion or a significantly underexpanded previously implanted stent (regardless of the time of implantation). The lesion was defined as resistant after unsuccessful high-pressure non-compliant (NC) balloon inflation (at least 20% of underexpansion, with at least 16 atm. [16]). The decision regarding initial lesion preparation was left at the operators' discretion and did not indicate a formal recruitment process. Patients meeting the inclusion criteria, who initially underwent advanced debulking procedures (orbital or rotational atherectomy), had also been recruited.

There were no angiographic exclusion criteria regarding lesion anatomy such as its length, tortuosity, severity, or prior stent placement. Operators, based on angiographic assessment, with additional support of intravascular imagining (IVUS/OCT) in the most challenging cases, determined the size of the S-IVL catheter and appropriate number of pulses for optimal vessel preparation or management of an underexpanded coronary stent.

The study had two primary endpoints — successful clinical outcome and safety concerns. Clinical success was defined as effective stent deployment or optimization of the previously not fully expanded stent (with less than <20% in-stent residual stenosis) [12] and the presence of TIMI 3 flow at the end of the procedure.

Safety outcomes were defined as periprocedural final serious angiographic complications (including perforation, abrupt closure, slow flow or no-reflow, unstable ventricular arrhythmias) and device failure (such as inability to cross the lesion, malfunction, or rapture). Also, adverse cardiac and cerebrovascular events (MACCE) were recorded. MAC-

CE involved death, myocardial infarction (MI), acute cerebrovascular events, and repeated revascularization of the target lesion (TLR)[13, 14]. Clinical follow-up was obtained by professional medical staff — personally or by telephone 6 months after the index procedure. On the initial visit (at the end of hospitalization), several data were collected regarding periprocedural characteristics, past medical history, basic laboratory tests at the time of admission, and pharmacotherapy at the time of discharge. The medical history was focused on the burden of cardiovascular disease (including coronary artery disease, hypertension, atrial fibrillation, chronic heart failure, presence of moderate/severe valvular heart disease, and history of stroke) and major cardiovascular risk factors defined according to the applicable definitions [15–17] and including diabetes mellitus and chronic kidney disease. On the first follow-up visit (6 months after the index procedure), data were collected on MACCE and any other revascularization procedures, involving stent thrombosis and restenosis [14]. This study was approved by the local ethics committee (Bioethical Committee at the Lower Silesian Chamber of Physicians — approval number 04/BOBD/2022). The study flowchart is presented in Figure 1.

Statistical analysis

Dependent on the normality of distribution (assessed by the Shapiro-Wilk test), the data were presented as means and standard deviations (SD), or medians and interquartile ranges (IQR). All calculations were made with the R language version 4.0.4

RESULTS

We retrospectively analyzed 131 consecutive S-IVL PCI procedures. Most of the cases were performed in the acute coronary syndrome (ACS) setting (87%) mainly non-ST-segment elevated myocardial infarction (NSTEMI) (74%). The ACS-based procedures (69.4%) were performed between May and September 2022. The study population

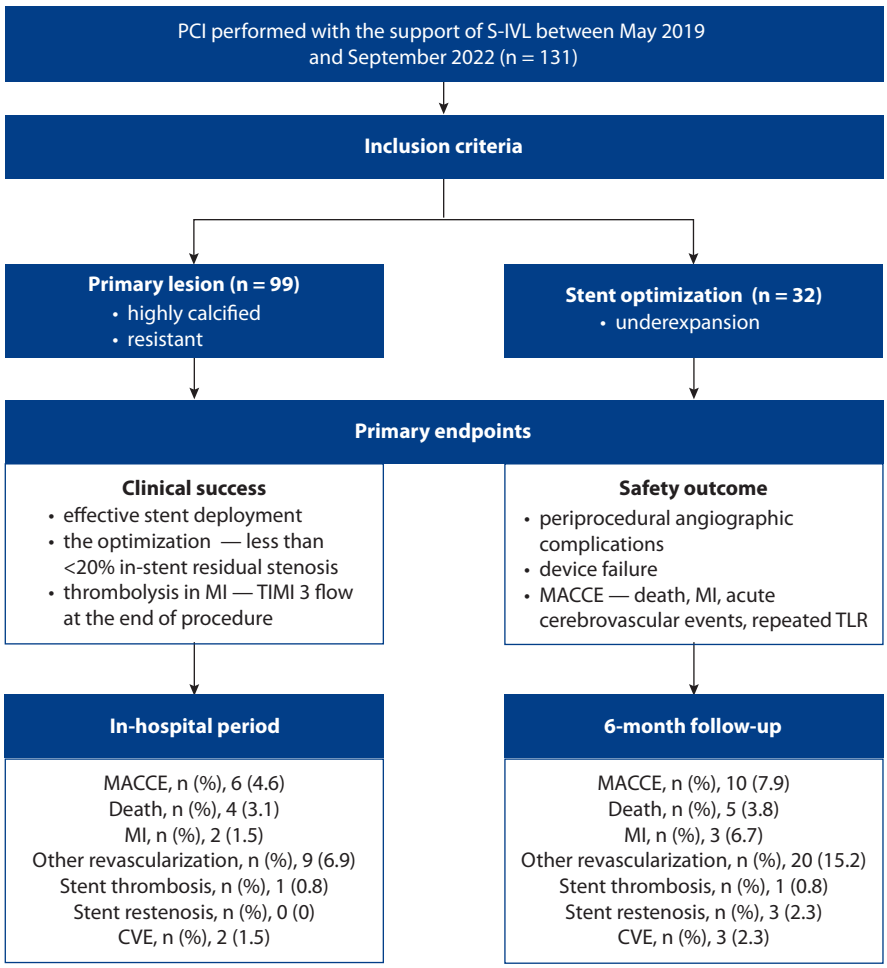

Figure 1. Study flowchart

Abbreviations: CVE, cerebrovascular episodes; MACCE, major adverse cardiac and cerebrovascular event; MI, myocardial infraction; PCI, percutaneous coronary intervention; S-IVL, Shockwave Intravascular Lithotripsy; TIMI, Thrombolysis in Myocardial Infarction; TLR, target lesion revascularization

Table 1. Study population baseline clinical characteristics

Shockwave intravascular	N = 131
Clinical features	
Age, mean (SD)	70.8 (7.5)
Sex, male, n (%)	92 (70.2)
Stable angina, n (%)	17 (13)
Unstable angina, n (%)	6 (4.6)
NSTEMI, n (%)	97 (74.0)
STEMI, n (%)	11 (8.4)
Diabetes mellitus, n (%)	75 (57.3)
Chronic heart failure, n (%)	64 (48.9)
Hypertension, n (%)	121 (92.4)
Hyperlipidemia, n (%)	127 (96.9)
Atrial fibrillation, n (%)	40 (30.5)
History of PCI, n (%)	68 (51.9)
History of MI, n (%)	63 (48.1)
History of CABG, n (%)	11 (8.4)
COPD, n (%)	13 (9.9)
History of stroke, n (%)	11 (8.4)
Moderate/severe valvular heart disease, n (%)	26 (19.8)
Chronic kidney disease, n (%)	31 (23.7)
LVEF, %, mean (SD)	48.2 (15.5)
Creatinine level, μmol/l, median (IQR)	82 (71–76.8)
Post-procedural pharmacotherapy	
Acetylsalicylic acid, n (%)	125 (95.4)
Clopidogrel, n (%)	78 (59.5)
Ticagrelor, n (%)	42 (32.1)
Prasugrel, n (%)	11 (8.4)
Statins, n (%)	125 (95.4)
NOAC/VKA, n (%)	37 (28.2)
ACEI/ARB, n (%)	115 (87.8)
β-blocker, n (%)	119 (90.8)
CCB, n (%)	42 (32.1)
Diuretic, n (%)	50 (38.1)
Oral antidiabetic, n (%)	64 (48.8)
Insulin, n (%)	22 (16.8)

Abbreviations: ACEI, angiotensin-converting-enzyme inhibitors; ARB, angiotensin receptor blockers; CABG, coronary artery bypass grafting; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; NOAC, non-vitamin K antagonist oral anticoagulants; NSTEMI, non-ST-segment elevation myocardial infraction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infraction; VKA, vitamin K antagonists; β-blocker, beta blocker

Table 2. Baseline procedural features of the study population

Shockwave intravascular	N = 131
Vessel treated	
LM, n (%)	27 (20.6)
LAD, n (%)	45 (34.3)
LCx, n (%)	18 (13.7)
RCA, n (%)	41 (31.2)
SYNTAX I score, median (IQR)	15.5 (9–25.7)
SYNTAX II PCI score, mean (SD)	37.5 (12.8)
SYNTAX II PCI four-year mortality, median (IQR)	18.2 (5.8–21.6)
SYNTAX II CABG score, mean (SD)	34.4 (10.2)
SYNTAX II CABG year mortality, median (IQR)	13.0 (6–15.4)
Primary lesion, n (%)	99 (75.6)
Stent underexpansion, n (%)	32 (24.4)
CTO lesions, n (%)	6 (4.6)
Post-atherectomy debulking, n (%)	18 (13.7)
Initial predilatation, n (%)	122 (93.1)
Predilatation pressure, atm, mean (SD)	19.5 (4.4)
Initial stenosis grade, %, mean (SD)	81.8 (11.7)
Final stenosis grade, %, mean (SD)	7.2 (13)
S-IVL diameter, mm, mean (SD)	3.22 (0.44)
S-IVL pulses, median (IQR)	50 (30-80)
Postdilatation, n (%)	101 (77.1)
Postdilatation pressure, atm, mean (SD)	19.3 (3.1)
Number of DES per procedure, mean (SD)	1.53 (0.4)
Total DES length per procedure, mm, median (IQR)	40.8 (26–66)
Number of DEB inflation, n (%)	21 (16)
Intravascular guidance, n (%)	31 (23.7)
Clinical success, n (%)	126 (96.1)
S-IVL perforations, n (%)	3 (2.3)
Radial access, n (%)	118 (90.0)
6 F guide catheter, n (%)	96 (73.2)
7 F or larger guide catheter, n (%)	35 (26.7)
Radiation dose, mGy, median (IQR)	1435.9 (663.3–1866.7)
Contrast volume, n (%), median (IQR)	230.2 (150–260.7)

Abbreviations: CABG, coronary artery bypass grafting; CTO, chronic total occlusion; Cx, circumflex artery; DEB, drug eluting balloon; DES, drug-eluting stent; LAD, left anterior descending; LM, left main; MACCE, major adverse cardiac and cerebrovascular event; PCI, percutaneous coronary intervention; RCA, right coronary artery; S-IVL, Shockwave Intravascular Lithotripsy

was dominated by male subjects (70.2%) at an average age of 70.8 years. The study cohort was characterized by a high prevalence of cardiovascular risk factors: hypercholesterolemia (96.7%), hypertension (92.4%), and diabetes mellitus (57.3%). Nearly one in two subjects had a history of myocardial infarction, and 60.3% underwent previous revascularization. The baseline clinical characteristics of the study cohort are presented in Table 1.

In terms of post-discharge pharmacotherapy, notably, a relatively large proportion of patients (59.5%) received clopidogrel as part of dual anti-platelet therapy (DAPT). The anatomical complexity of coronary artery disease (CAD) was relatively high, and the SYNTAX score I reached a median of 15.5 (9–25.7) with subsequent SYNTAX II — PCI score of 37.5 (12.8); estimated 4-year mortality reached 18.2%. The vast majority of PCI procedures were related to *de novo* lesions (75.6%), and the remaining 32 were concerned with significantly underexpanded stents. In 13.7% of all cases, S-IVL was used despite initial aggressive lesion preparation (orbital or rotational atherectomy). Clinical success criteria were met in 96.1% of cases. Notably, we noticed only 3 device failures (perforation of S-IVL catheter) without serious clinical consequences. The predominant vascular access point was the radial artery (90%). All procedural features are presented in Table 2.

During the hospitalization period, the MACCE rate was 4.6%. There were four deaths in the study cohort during this period. Most occurred in patients with advanced heart failure. The first fatality was a 71-year-old man with multiple comorbidities, coronary artery disease, with a history of MI previously treated with PCI, advanced heart failure with reduced ejection fraction, and implanted cardioverter-defibrillator (ICD), who was admitted because of cardiogenic shock in the course of STEMI.

He received PCI of the left anterior descending artery (LAD) (culprit lesion) and a few days later, due to symptoms of recurrent angina, we performed right coronary artery (RCA) PCI supported by S-IVL. The patient died several days later with symptoms of persistent cardiogenic shock despite implementing an intensive care protocol. The second death was observed in a 65-year-old man with a history of alcohol abuse and multiple organ dysfunction. He was admitted with NSTEMI and underwent PCI of the LAD supported by S-IVL. He was transferred to the Intensive Care Unit (ICU) directly after the procedure and died several days later from multiorgan dysfunction and clinical symptoms of stroke. The third case involved a 72-year-old woman with multiple comorbidities and advanced heart failure, who was admitted to the hospital with STEMI and pre-hospital arrest and treated with rescue PCI of the left main (LM). Approximately 24 hours later, the patient experienced another cardiac arrest. PCI of the RCA was performed, as the last possible revascularization procedure, with S-IVL support. The patient died several days later with symptoms of persistent cardiogenic shock. The last in-hospital death in our study was a 76-year-old woman with NSTEMI and advanced CAD. She underwent rescue PCI of the LM/LAD/Cx supported by S-IVL. Five days after PCI, ventricular fibrillation occurred, and control angiography revealed stent thrombosis, and, despite the second rescue PCI and prolonged resuscitation, the patient died. During this follow-up period, we also had an additional case of TLR in a 60-year-old man with NSTEMI and advanced highly calcified CAD. During the index procedure, the patient underwent rota-lithotripsy after unsuccessful initial lesion preparation with rotational atherectomy (presence of significant NC balloon underexpansion post-atherectomy). A few days later, the patient underwent additional PCI of the target lesion due to a symptomatic distal edge dissection. One elderly patient with high comorbidity was found to have suffered a stroke while hospitalized. However, it was not directly related to the periprocedural period.

At 6-month follow-up, MACCE was reported (7.9%) with a concomitant TLR rate of 3.8% (all undiscussed cases were related to in-stent restenosis; two of three were recurrent restenoses in underexpanded stents). Two additional deaths occurred. The first was an unexplained death 14 days after discharge in a patient with a high number of comorbidities and low left ventricular ejection fraction (LVEF of 25%) initially planned for implantation of a cardioverter-defibrillator (ICD) following 3-month optimal medical treatment of HF after complete revascularization. The second patient, who suffered from multiple comorbidities and advanced heart failure (LVEF, 15%–20%) with an ICD, died approximately 5 months after discharge. In this case, a second patient with newly diagnosed COVID-19 was admitted to the emergency department (ED) and died a few hours later with symptoms of acute cardiorespiratory failure. All the clinical follow-up data are summarized in Table 3.

Table 3. Clinical follow-up data of study cohort

Shockwave Intravascular N-131	
In-hospital period	
MACCE, n (%)	6 (4.6)
Death, n (%)	4 (3.1)
Myocardial infarction, n (%)	1 (0.8)
Target lesion revascularization, n (%)	2 (1.5)
Any other revascularization, n (%)	9 (6.9)
Stent thrombosis, n (%)	1 (0.8)
Stent restenosis, n (%)	0 (0)
Cerebrovascular episodes, n (%)	2 (1.5)
6-month follow-up	
MACCE, n (%)	10 (7.9)
Death, n (%)	6 (4.6)
Myocardial infarction, n (%)	3 (6.7)
Target lesion revascularization, n (%)	5 (3.8)
Any other revascularization, n (%)	20 (15.2)
Stent thrombosis, n (%)	1 (0.8)
Stent restenosis, n (%)	3 (2.3)
Cerebrovascular episodes, n (%)	3 (2.3)

Abbreviations: MACCE, major adverse cardiac and cerebrovascular event

DISCUSSION

Initially, the Shockwave C2 I-VL catheter was introduced into clinical practice in the field of peripheral interventions and has already undergone several clinical trials in various peripheral vascular beds [18]. Nevertheless, the history of S-IVL as a therapeutic tool in coronary artery disease is much shorter — S-IVL has been commercially available in Europe since 2018 and in the US and Japan since 2021. The scientific evidence for the efficacy of this technology in treating CAD is mainly based on small cohorts of patients who were recruited for the pre-market evaluation studies focused mainly on short-term outcomes and designed by the manufacturer [19, 20]. In this study, we present, as one of the first, "real-life" data from the Lower Silesia Shockwave Registry (LSSR), which evaluate the mid-term outcomes of S-ILV-assisted PCI in a cohort of 131 consecutive patients.

Coronary calcifications reduce vascular compliance, severely affecting both short- and long-term clinical outcomes in patients undergoing percutaneous revascularization [21]. Percutaneous interventions in calcified lesions are associated with increased periprocedural complications (dissection, perforation, MI) as well as suboptimal PCI outcomes, mainly concerning stent delivery and deployment, leading to malapposition, underexpansion, or stent fracture and potentially compromising drug adhesion and delivery [22]. This can lead to an increase in late adverse events such as restenosis, stent thrombosis, and the need for repeat revascularization [23]. Contemporary practice has evolved a variety of devices and strategies for treatment of coronary calcifications.

The well-established balloon-dependent methods (such as non-compliance, cutting, scoring) [24] together with the atherectomy devices (both, rotational and orbital) [25, 26] ensure that the success rate of the procedure can exceed 90%. A combination of the mentioned methods can result in an even higher success rate [27–31]. However, all of them have inherent limitations and may increase the risk of complications.

Intravascular lithotripsy (IVL) is a novel therapeutic strategy based on the use of acoustic pressure waves to treat calcium deposits in the vascular wall, similar to the method previously used in renal calculi. Lithotripsy emitters (source of acoustic pressure waves) are incorporated into the shaft of a balloon angioplasty catheter that delivers precisely localized acoustic pressure waves via a standard angioplasty wire. A unique property of S-IVL is the fact its action affects also deep calcium deposits in opposition to athero-ablation or the classical pressure-depend balloon methods mainly focused on superficial plaque modification. The recently published reports on the safety and efficacy of S-IVL are encouraging but have been concerned mainly with short-term outcomes of intravascular lithotripsy [7, 11, 31–34], with few data on longer-term follow-up [35].

In our real-world high-risk cohort (87% of patients with ACS), clinical success was even higher than that one presented in the pooled data from all Disturb trials (96.1% vs. 92.6%) [32]. Similar favorable results were observed in terms of in-hospital MACCE (4.6% vs. 6.5%), yet the in-hospital TLR rate was slightly higher than in the Disturb studies (1.5% vs. 0.3%). Interestingly, the high level of clinical success was maintained despite the high prevalence of patients with underexpansion of previously implanted stents (24.4%) and chronic total occlusion (4.6%), both well-known risk factors for adverse clinical outcomes [34, 36]. Especially in the case of patients in whom high-pressure dilatation of a non-compliant balloon failed to expand the stent, clinical success is generally lower [34, 37]. Currently, there are limited therapeutic options for refractory stent underexpansion [38]. Based on the data presented so far [39, 40], S-IVL appears to be a relatively safe and effective approach, which is related to its unique mechanism of action – an atraumatic balloon-based treatment that may help to avoid mechanical vascular trauma often observed with classic high-pressure balloon postdilatation. Another alternative to treat incomplete stent expansion is to perform debulking atherectomy. However, these challenging procedures are associated with high risk of acute complications [41, 42].

Notably, no in-hospital MACCE occurred despite the high anatomical complexity of treated lesions (SYNTAX Score 15.5 [9–25.7], total drug-eluting stent (DES) length per procedure 40.8 [26–66] mm). This might be partially related to the relatively common use of additional debulking methods (rotational or orbital atherectomy devices). Nevertheless, in our study cohort, S-IVL was used only in the setting of initial inadequate lesion preparation with an atherectomy device followed by NC balloon inflation. This suggests that the lesions treated with rota-lithotripsy were extremely challenging with deep calcium deposits. As a result, initial burr atheroablation most likely only pulverized superficial portions of calcified deposits without interacting with deep calcium [43]. The different mechanisms of S-IVL action, focusing on the disruption of the deep calcium plaque [6], allowed us to achieve adequate lesion preparation in this highly challenging cohort. This comprehensive approach has been previously reported [28–30, 44, 45]. Alternative approaches would be associated with an increase in burr size, which could seriously compromise the safety of this procedure [46].

The 6-month outcomes observed in our study are also encouraging: we noted a low number of TLR (3.8%), mainly related to the recurrent in-stent restenosis due to its previous underexpansion (3 of 5). This number of TLR is comparable to other alternative debulking methods — orbital atherectomy (1-year TLR, 4.7%) [47, 48], rotational atherectomy (9-month TLR 2, 11.7%) [49], or cutting/scoring balloon (9-month TLR 7%). Furthermore, if we excluded from our study cohort the patients who underwent the S-IVL procedure for post-stenting optimization, the TLR would decrease to 2%.

In our cohort study, we observed an encouraging safety profile (lack of vessel perforation or no-reflow phenomena), which may be related to a high number of low-size (6 F) (73.2%) radial access sites (90.0%), which has been shown to increase the safety of PCI procedures [50]. Additionally, during all analyzed PCI procedures, we observed only 3 cases of device failure (Shockwave catheter perforation) without any clinical consequences for the patient.

Our study has several limitations. First, it has a non-randomized retrospective study design lacking a control group. The second limitation is a relatively low number of intravascular imagining studies and a lack of external core lab analysis. Finally, heterogeneity, high number of stent optimization procedures, and additional use of an atherectomy device can complicate the analysis of study results.

CONCLUSIONS

The mid-term data from the Lower Silesia Shockwave Registry (LSSR) confirm the acceptable safety and efficacy of intravascular lithotripsy, which was a valuable strategy for lesion preparation and stent optimization in a cohort of 131 consecutive patients with severely calcified coronary lesions. Larger randomized trials are needed to evaluate fully this novel treatment modality. A head-to-head comparison with other advanced debulking techniques would be particularly valuable.

Article information

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REFERENCES

1. Grundy SM, Stone NJ. Coronary artery calcium: where do we stand after over 3 decades? Am J Med. 2021; 134(9): 1091–1095, doi: 10.1016/j.amjmed.2021.03.043, indexed in Pubmed: 34019857.
2. Jin HY, Weir-McCall JR, Leipsic JA, et al. The relationship between coronary calcification and the natural history of coronary artery disease. JACC Cardiovasc Imaging. 2021; 14(1): 233–242, doi: 10.1016/j.jcmg.2020.08.036, indexed in Pubmed: 33221216.
3. Fan LM, Tong D, Mintz GS, et al. Breaking the deadlock of calcified coronary artery lesions: A contemporary review. Catheter Cardiovasc Interv. 2021; 97(1): 108–120, doi: 10.1002/ccd.29221, indexed in Pubmed: 32865328.
4. Hemetsberger R, Abdelghani M, Toelg R, et al. Impact of coronary calcification on clinical outcomes after implantation of newer-generation drug-eluting stents. J Am Heart Assoc. 2021; 10(12): e019815, doi: 10.1161/JAHA.120.019815, indexed in Pubmed: 34056911.
5. Kassimis G, Raina T, Kontogiannis N, et al. How should we treat heavily calcified coronary artery disease in contemporary practice? From atherectomy to intravascular lithotripsy. Cardiovasc Revasc Med. 2019; 20(12): 1172–1183, doi: 10.1016/j.carrev.2019.01.010, indexed in Pubmed: 30711477.
6. Rola P, Włodarczak A, Barycki M, et al. Use of the shock wave therapy in basic research and clinical applications-from bench to bedsite. Biomedicines. 2022; 10(3), doi: 10.3390/biomedicines10030568, indexed in Pubmed: 35327369.
7. Rola P, Włodarczak A, Kulczycki JJ, et al. Feasibility of the intravascular lithotripsy in coronary artery disease. Short-term outcomes of the Lower-Silesia Shockwave Registry. Kardiol Pol. 2021; 79(10): 1133–1135, doi: 10.33963/KP.a2021.0093, indexed in Pubmed: 34415567.
8. Hill JM, Kereiakes DJ, Shlofmitz RA, et al. Intravascular lithotripsy for treatment of severely calcified coronary artery disease. J Am Coll Cardiol. 2020; 76(22): 2635–2646, doi: 10.1016/j.jacc.2020.09.603, indexed in Pubmed: 33069849.
9. Brinton TJ, Ali ZA, Hill JM, et al. Feasibility of shockwave coronary intravascular lithotripsy for the treatment of calcified coronary stenoses. Circulation. 2019; 139(6): 834–836, doi: 10.1161/CIRCULATIONAHA.118.036531, indexed in Pubmed: 30715944.
10. Rola P, Kulczycki JJ, Włodarczak A, et al. Intravascular lithotripsy as a novel treatment method for calcified unprotected left main diseases-comparison to rotational atherectomy-short-term outcomes. Int J Environ Res Public Health. 2022; 19(15), doi: 10.3390/ijerph19159011, indexed in Pubmed: 35897381.
11. Iwańczyk S, Włodarczak A, Hiczkiewicz J, et al. Feasibility of intravascular lithotripsy for calcific coronary lesions: A multi-institutional experience. Catheter Cardiovasc Interv. 2021; 98(4): E540–E547, doi: 10.1002/ccd.29792, indexed in Pubmed: 34051136.
12. Watanabe H, Morimoto T, Shiomi H, et al. Impact of angiographic residual stenosis on clinical outcomes after new-generation drug-eluting stents implantation: insights from a pooled analysis of the RESET and NEXT trials. J Am Heart Assoc. 2018; 7(13), doi: 10.1161/JAHA.118.008718, indexed in Pubmed: 29960987.
13. Thygesen K, Alpert J, Jaffe A, et al. Fourth universal definition of myocardial infarction (2018). Circulation. 2018; 138(20): e618–e651, doi: 10.1161/CIR.0000000000000617, indexed in Pubmed: 30571511.
14. Garcia-Garcia HM, McFadden EP, Farb A, et al. Standardized end point definitions for coronary intervention trials: the academic research consortium-2 consensus document. Eur Heart J. 2018; 39(23): 2192–2207, doi: 10.1093/eurheartj/ehy223, indexed in Pubmed: 29897428.
15. Levey AS, de Jong PE, Coresh J, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney Int. 2011; 80(1): 17–28, doi: 10.1038/ki.2010.483, indexed in Pubmed: 21150873.
16. López-Campos JL, Calle Rubio M, Izquierdo Alonso JL, et al. Forum COPD working group consensus on the diagnosis, treatment and follow-up of COPD. Arch Bronconeumol. 2021; 57(9): 596–599, doi: 10.1016/j.arbr.2021.06.007, indexed in Pubmed: 35702916.
17. ElSayed NA, Aleppo G, Aroda VR, et al. 2. Classification and diagnosis of diabetes: standards of care in diabetes-2023. Diabetes Care. 2023; 46(Suppl 1): S19–S40, doi: 10.2337/dc23-S002, indexed in Pubmed: 36507649.
18. Kereiakes DJ, Virmani R, Hokama JY, et al. Principles of intravascular lithotripsy for calcific plaque modification. JACC Cardiovasc Interv. 2021; 14(12): 1275–1292, doi: 10.1016/j.jcin.2021.03.036, indexed in Pubmed: 34167671.
19. Saito S, Yamazaki S, Takahashi A, et al. Intravascular lithotripsy for vessel preparation in severely calcified coronary arteries prior to stent placement: primary outcomes from the japanese disrupt CAD IV study. Circ J. 2021; 85(6): 826–833, doi: 10.1253/circj.CJ-20-1174, indexed in Pubmed: 33551398.
20. Blachutzik F, Honton B, Escaned J, et al. Safety and effectiveness of coronary intravascular lithotripsy in eccentric calcified coronary lesions: a patient-level pooled analysis from the Disrupt CAD I and CAD II Studies. Clin Res Cardiol. 2021; 110(2): 228–236, doi: 10.1007/s00392-020-01737-3, indexed in Pubmed: 32948882.
21. Copeland-Halperin RS, Baber U, Aquino M, et al. Prevalence, correlates, and impact of coronary calcification on adverse events following PCI with newer-generation DES: Findings from a large multiethnic registry. Catheter Cardiovasc Interv. 2018; 91(5): 859–866, doi: 10.1002/ccd.27204, indexed in Pubmed: 28722295.
22. Kobayashi Y, Okura H, Kume T, et al. Impact of target lesion coronary calcification on stent expansion. Circ J. 2014; 78(9): 2209–2214, doi: 10.1253/circj.cj-14-0108, indexed in Pubmed: 25017740.
23. Konigstein M, Madhavan MV, Ben-Yehuda O, et al. Incidence and predictors of target lesion failure in patients undergoing contemporary DES implantation-Individual patient data pooled analysis from 6 randomized controlled trials. Am Heart J. 2019; 213: 105–111, doi: 10.1016/j.ahj.2019.03.011, indexed in Pubmed: 31132582.
24. Rheude T, Rai H, Richardt G, et al. Super high-pressure balloon versus scoring balloon to prepare severely calcified coronary lesions: the ISAR-CALC randomised trial. EuroIntervention. 2021; 17(6): 481–488, doi: 10.4244/EIJ-D-20-01000, indexed in Pubmed: 33258774.
25. Bouisset F, Barbato E, Reczuch K, et al. Clinical outcomes of PCI with rotational atherectomy: the European multicentre Euro4C registry. EuroIntervention. 2020; 16(4): e305–e312, doi: 10.4244/EIJ-D-19-01129, indexed in Pubmed: 32250249.
26. Rola P, Furtan Ł, Włodarczak S, et al. Orbital atherectomy for treatment of calcified coronary artery lesions. First experiences in Poland: Short-term outcomes of the Lower-Silesia Orbital Atherectomy Registry (LOAR). Kardiol Pol. 2023; 81(2): 174–176, doi: 10.33963/KP.a2023.0003, indexed in Pubmed: 36594531.
27. Allali A, Toelg R, Abdel-Wahab M, et al. Combined rotational atherectomy and cutting balloon angioplasty prior to drug-eluting stent implantation in severely calcified coronary lesions: The PREPARE-CALC-COMBO study. Catheter Cardiovasc Interv. 2022; 100(6): 979–989, doi: 10.1002/ccd.30423, indexed in Pubmed: 36262074.
28. Włodarczak S, Rola P, Furtan Ł, et al. Orbital-Tripsy - orbital atherectomy facilitated by Shockwave Intravascular Lithotripsy: Novel bailout strategy in percutaneous coronary intervention in heavily calcified coronary lesions. Kardiol Pol. 2023; 81(3): 296–297, doi: 10.33963/KP.a2023.0005, indexed in Pubmed: 36573605.
29. Rola P, Furtan Ł, Włodarczak S, et al. Rota-Lithotripsy as a novel bail-out strategy for highly calcified coronary lesions in acute coronary syndrome. Biomedicines. 2022; 10(11), doi: 10.3390/biomedicines10112795, indexed in Pubmed: 36359315.
30. Włodarczak A, Kulczycki J, Furtan Ł, et al. Rotational atherectomy and intravascular lithotripsy: two methods versus a single lesion. Kardiol Pol. 2021; 79(6): 712–713, doi: 10.33963/KP.15962, indexed in Pubmed: 33890748.
31. Rola P, Włodarczak A, Kulczycki JJ, et al. Efficacy and safety of shockwave intravascular lithotripsy (S-IVL) in calcified unprotected left main percutaneous coronary intervention - short-term outcomes. Postepy Kardiol Interwencyjnej. 2021; 17(4): 344–348, doi: 10.5114/aic.2021.112524, indexed in Pubmed: 35126548.

32. Kereiakes DJ, Di Mario C, Riley RF, et al. Intravascular lithotripsy for treatment of calcified coronary lesions: patient-level pooled analysis of the disrupt CAD studies. JACC Cardiovasc Interv. 2021; 14(12): 1337–1348, doi: 10.1016/j.jcin.2021.04.015, indexed in Pubmed: 33939604.
33. Hill JM, Kereiakes DJ, Shlofmitz RA, et al. Intravascular lithotripsy for treatment of severely calcified coronary artery disease. J Am Coll Cardiol. 2020; 76(22): 2635–2646, doi: 10.1016/j.jacc.2020.09.603, indexed in Pubmed: 33069849.
34. Aksoy A, Salazar C, Becher MU, et al. Intravascular lithotripsy in calcified coronary lesions: a prospective, observational, multicenter registry. Circ Cardiovasc Interv. 2019; 12(11): e008154, doi: 10.1161/CIRCINTERVENTIONS.119.008154, indexed in Pubmed: 31707803.
35. Gibbs S, Wiens EJ, Minhas K. One-year outcomes in patients who underwent coronary intravascular shockwave lithotripsy for highly-calcified coronary lesions. Indian Heart J. 2022; 74(6): 524–526, doi: 10.1016/j.ihj.2022.10.001, indexed in Pubmed: 36220347.
36. Siudak Z, Bryniarski L, Malinowski KP, et al. Procedural outcomes in patients treated with percutaneous coronary interventions within chronic total occlusions stratified by gender. J Clin Med. 2022; 11(5), doi: 10.3390/jcm11051419, indexed in Pubmed: 35268510.
37. Ielasi A, Moscarella E, Testa L, et al. IntravaScular lithotripsy for the management of undilatable coronary stent: the SMILE registry. Cardiovasc Revasc Med. 2020; 21(12): 1555–1559, doi: 10.1016/j.carrev.2020.05.020, indexed in Pubmed: 32580881.
38. Shlofmitz E, Iantorno M, Waksman R. Restenosis of drug-eluting stents: a new classification system based on disease mechanism to guide treatment and state-of-the-art review. Circ Cardiovasc Interv. 2019; 12(8): e007023, doi: 10.1161/CIRCINTERVENTIONS.118.007023, indexed in Pubmed: 31345066.
39. Wańha W, Tomaniak M, Wańczura P, et al. Intravascular lithotripsy for the treatment of stent underexpansion: the multicenter IVL-DRAGON registry. J Clin Med. 2022; 11(7), doi: 10.3390/jcm11071779, indexed in Pubmed: 35407387.
40. Tovar Forero MN, Sardella G, Salvi N, et al. Coronary lithotripsy for the treatment of underexpanded stents: the international & multicentre CRUNCH registry. EuroIntervention. 2022; 18(7): 574–581, doi: 10.4244/EIJ-D-21-00545, indexed in Pubmed: 35318955.
41. Whiteside HL, Nagabandi A, Kapoor D. Safety and efficacy of stentablation with rotational atherectomy for the management of underexpanded and undilatable coronary stents. Cardiovasc Revasc Med. 2019; 20(11): 985–989, doi: 10.1016/j.carrev.2019.01.013, indexed in Pubmed: 30685339.
42. Neupane S, Basir M, Tan C, et al. Feasibility and safety of orbital atherectomy for the treatment of in-stent restenosis secondary to stent under-expansion. Catheter Cardiovasc Interv. 2021; 97(1): 2–7, doi: 10.1002/ccd.28675, indexed in Pubmed: 31985132.
43. Lee MS, Gordin JS, Stone GW, et al. Orbital and rotational atherectomy during percutaneous coronary intervention for coronary artery calcification. Catheter Cardiovasc Interv. 2018; 92(1): 61–67, doi: 10.1002/ccd.27339, indexed in Pubmed: 29045041.
44. Włodarczak A, Rola P, Barycki M, et al. Rota-Lithotripsy-A novel bail-out strategy for calcified coronary lesions in acute coronary syndrome. The first-in-man experience. J Clin Med. 2021; 10(9), doi: 10.3390/jcm10091872, indexed in Pubmed: 33925916.
45. Rola P, Włodarczak A, Barycki M, et al. "All hands on deck" - rota-lithotripsy - a combination of rotational atherectomy and intravascular lithotripsy (shockwave) with additional use of a Turnpike Gold microcatheter and guide extension as a novel approach for calcified lesions. Postepy Kardiol Interwencyjnej. 2021; 17(2): 214–217, doi: 10.5114/aic.2021.107503, indexed in Pubmed: 34400925.
46. Wańha W, Januszek R, Kołodziejczak M, et al. Procedural and 1-year outcomes following large vessel coronary artery perforation treated by covered stents implantation: Multicentre CRACK registry. PLoS One. 2021; 16(5): e0249698, doi: 10.1371/journal.pone.0249698, indexed in Pubmed: 33979357.
47. Généreux P, Lee AC, Kim CY, et al. Orbital atherectomy for treating de novo severely calcified coronary narrowing (1-year results from the pivotal ORBIT II trial). Am J Cardiol. 2015; 115(12): 1685–1690, doi: 10.1016/j.amjcard.2015.03.009, indexed in Pubmed: 25910525.
48. Kralisz P, Legutko J, Tajstra M, et al. Use of orbital atherectomy in coronary artery disease with severe calcification: A preliminary study. Kardiol Pol. 2023; 81(1): 61–63, doi: 10.33963/KP.a2022.0289, indexed in Pubmed: 36573609.
49. Fitzgerald S, Allali A, Toelg R, et al. Angiographic predictors of unplanned rotational atherectomy in complex calcified coronary artery disease: a pooled analysis from the randomised ROTAXUS and PREPARE-CALC trials. EuroIntervention. 2022; 17(18): 1506–1513, doi: 10.4244/EIJ-D-21-00612, indexed in Pubmed: 34609284.
50. Kolkailah AA, Alreshq RS, Muhammed AM, et al. Transradial versus transfemoral approach for diagnostic coronary angiography and percutaneous coronary intervention in people with coronary artery disease. Cochrane Database Syst Rev. 2018; 4(4): CD012318, doi: 10.1002/14651858.CD012318.pub2, indexed in Pubmed: 29665617.

Relationship between systemic inflammation indices and time of symptom onset in cardiac remodeling after first ST-segment elevation myocardial infarction

Ahmet Kivrak[1], Alp Yildirim[2]

[1]Department of Cardiology, Ankara Etlik City Hospital, Ankara, Turkey
[2]Department of Cardiology, Kirsehir Training and Research Hospital, Kirsehir, Turkey

Correspondence to:
Ahmet Kivrak, MD,
Department of Cardiology,
Ankara Etlik City Hospital, Varlik Neighborhood,
Halil Sezai Erkut 5, 06170, Ankara, Turkey,
phone: +90 312 797 0000,
e-mail: a.kivrak89@gmail.com

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ABSTRACT

Background: Circadian variations play a pivotal role in both leukocyte trafficking and inflammatory response. This may affect the course of cardiac healing after myocardial infarction (MI).

Aims: The present study investigated the relationship between the systemic immune inflammation (SII) index and the systemic inflammation response index (SIRI), two new inflammation indices integrating white blood cell subsets and platelets, and the time of onset of symptoms in left ventricular adverse remodeling (LVAR) after ST-segment elevation MI (STEMI).

Methods: In this retrospective study, we included 512 patients with first-time STEMI. The time of onset of symptoms was divided into 4 intervals: 06:00–11:59, 12:00–17:59, 18:00–23:59, and 00:00–05:59. The endpoint was LVAR, defined as an increase in left ventricular end-diastolic and end-systolic volume by ≥12% at 6 months.

Results: The time of onset of chest pain most often occurred between 06:00 and 11:59 AM. In this window of time, median SII and SIRI indices were higher than in other time intervals. An increased SIRI level (odds ratio [OR], 3.03; P <0.001), symptom onset in the morning hours (OR, 2.92; P = 0.03), and an increased Global Registry of Acute Coronary Events (GRACE) score (OR, 1.16; P <0.001) were determined as independent predictors of LVAR. The threshold value of the SIRI to discriminate between patients with and without LVAR was >2.5 (area under the curve [AUC], 0.84; P <0.001). The SIRI showed superior diagnostic performance compared to the SII index.

Conclusions: In STEMI patients, an increased SIRI was independently associated with LVAR. This was more pronounced between 06:00 and11:59 AM. Despite differences across circadian periods, the SIRI may be a potential screening tool for identifying LVAR patients at long-term risk of heart failure.

Key words: biomarker, cardiac remodeling, inflammation, myocardial infarction

INTRODUCTION

Acute myocardial infarction (MI) arises as a result of sudden occlusion of the coronary artery and results in necrotic tissue damage [1]. Cellular necrosis and degradation of the matrix cause rapid activation of the complement cascade, which is an important component of the immune-inflammatory response (IIR) [2]. Complement cascade activation allows leukocytes to infiltrate the infarct area to scavenge dead cells and matrix residues [3]. This inflammatory phase ends with repair pathways replacing dead cardiomyocytes with scar tissue. An excessive IIR can determine the extent of changes in ventricular size, shape, and function and can also play pathological roles, such as in the case of left ventricular (LV) adverse remodeling (LVAR) that can cause heart failure [4].

The circadian clock may play a prognostic role in the increased inflammatory response observed in the development of LVAR after acute MI. Epidemiological research has confirmed the association of acute MI development with a day/night pattern [5, 6]. Furthermore, studies have suggested that onset time in cases of acute MI independently predicts LV function, infarct size, and mortality rates [7, 8].

WHAT'S NEW?

This study provides new findings showing that the severity of inflammation, which plays an important role in cardiovascular events, is associated with circadian clock variations. In ST-segment elevation myocardial infarction (STEMI), increased systemic immune inflammation (SII) and response (SIRI) indices at presentation were independently associated with development of left ventricular adverse remodeling (LVAR) after STEMI. This association was more pronounced between 06:00 and 11:59 AM. Circadian clock variations may increase the severity of inflammation and thus contribute to the development of LVAR, which carries a long-term risk of heart failure.

The circadian clock can affect the infiltration of leukocytes into tissues [9, 10]. A population-based study of adults has shown that a blunted rest-activity rhythm is associated with an increase in leukocyte-based inflammatory indices [11]. Therefore, given the potential role of increased IIR in the development of LVAR after acute MI, we hypothesized that there might be an association between leukocyte-based inflammatory indices and the circadian clock. Among these indices, we evaluated the systemic immune inflammation (SII) index and systemic inflammation response index (SIRI), which have not yet been investigated in the context of LVAR but are claimed to have better prognostic roles in predicting cardiovascular events including acute MI [12–14]. The SII index, which is an indicator of inflammatory status, is calculated by platelet count × neutrophil count/lymphocyte count [15], while the SIRI, which is an indicator of the balance between the inflammatory response and immune status, is calculated by neutrophil count × monocyte count/lymphocyte count [16].

This study aimed to investigate the relationships between the SII index and SIRI and the time of onset of symptoms in the development of LVAR after acute MI.

METHODS

Patients diagnosed with first ST-segment elevation MI (STEMI) in a cardiac center between January 2018 and January 2020 were enrolled in this study. The study received the local ethics committee's approval (date: September 12, 2022, decision no. 146/19) and was conducted in compliance with the relevant ethical guidelines and the Declaration of Helsinki (2013 Brazilian revision). The local ethics committee waived the requirement for informed consent due to the retrospective nature of the research.

Study population

A total of 2182 STEMI patients undergoing primary percutaneous coronary intervention (pPCI) no later than 12 hours after the onset of chest pain were assessed retrospectively. STEMI in these patients was diagnosed according to the fourth universal definition of myocardial infarction [17], with management procedures following the latest guidelines of the European Society of Cardiology [18]. One thousand six hundred and seventy patients who were not diagnosed with STEMI upon applying those criteria were excluded. The following exclusion criteria were then also applied: a history of any systemic inflammatory or autoimmune diseases, history of myocardial infarction or heart failure, any mechanical complications (ventricular septal and/or free wall rupture, papillary muscle rupture, or cardiac tamponade), thyroid dysfunction, liver diseases, active hepatitis, malignancy, renal failure, history of anti-inflammatory or chronic corticosteroid drugs, sepsis, atrial fibrillation, elective or emergency coronary artery bypass grafting following an angiography procedure, major bleeding events, cardiogenic shock, requirement for an intra-aortic balloon pump, history of silent ischemia/infarct or right coronary artery occlusion, pregnancy or delivery in the last 90 days, lactation, and missing clinical data. After this exclusion process, 512 patients who had experienced STEMI for the first time were enrolled in this study.

Study protocol

The hospital's electronic information system and patient files were used to gather demographic and clinical data. Following the index event, echocardiographic evaluations were conducted for all patients at day 7 (baseline) and 6 months. Global Registry of Acute Cardiac Events (GRACE) risk scores were calculated using the official GRACE calculator (www.gracescore.org). Blood samples of all patients were taken on admission. We divided the 24 hours of the day into 4 intervals to evaluate the time of onset of symptoms, designating these windows of time as morning (06:00-11:59), daytime (12:00–17:59), evening (18:00–23:59), and nighttime hours (00:00–05:59).

Laboratory parameters

A Beckman Coulter LH 780 device (Mervue, Galway, Ireland) and Hitachi Modular P800 autoanalyzer (Roche Diagnostics Corp., Indianapolis, IN, US) were used to evaluate patients' venous blood samples. Levels of hemoglobin (photometrically), platelet count (impedance method), high sensitivity C-reactive protein (hs-CRP) (immunoturbidimetric method), albumin (bromocresol green method), triglycerides, and total cholesterol (enzymatic colorimetry), and high-density lipoprotein cholesterol (HDL-C) (homogeneous enzymatic colorimetry) were determined. The Friedewald formula was used to determine low-density lipoprotein cholesterol (LDL-C) [19]. The SII index and SIRI were respectively calculated as follows: SII = platelet count × neutrophil count/lymphocyte count

and SIRI = neutrophil count × monocyte count/lymphocyte count.

Echocardiographic evaluation

Echocardiographic data were obtained when patients underwent transthoracic echocardiographic evaluations with the Vivid 7 Dimension Cardiovascular Ultrasound System (General Electric Vingmed, Horten, Norway). All data were collected during hospital stays within 1 week following acute coronary syndrome destabilization in accordance with the relevant guidelines [20]. LV volumes were measured based on apical 4- and 2-chamber views, and the modified Simpson method was applied to calculate left ventricular ejection fraction (LVEF) as per the recommendations of the American Society of Echocardiography. Papillary muscles were excluded, and manual tracing began at the endocardial boundaries of the end-systolic and end-diastolic phases of the short-axis stack images, covering the left ventricle to the apex from the mitral annular line. LV stroke volume (SV) was obtained with the following formula: SV = LVEDV – LVESV, where LVEDV is the LV end-diastolic volume and LVESV is the LV end-systolic volume. For LVEF, the following formula was applied: EF = [(LVEDV – LVESV)/LVEDV] × 100.

LVAR was defined as a ≥12% increase in baseline LVEDV or LVESV at 6 months of follow-up [21].

Statistical analysis

All data were analyzed with IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, US). Numerical data determined to be normally distributed based on the results of Kolmogorov-Smirnov tests were given as mean (standard deviation [SD]) values while non-normally distributed variables were given as median (interquartile range [IQR]) values. For comparisons between groups, Student's t-test and Mann-Whitney U test were used in line with the normality of the considered distribution. Categorical variables were given as numbers and percentages, and inter-group comparisons were conducted with χ^2 and Fisher's exact tests. Spearman correlation analyses were applied to evaluate the relationships between numerical variables. Spearman correlation coefficients <0.10 were evaluated as negligible correlations, 0.10–0.39 as weak correlations, 0.40–0.69 as moderate correlations, 0.70–0.89 as strong correlations, and 0.90–1.00 as very strong correlations [22]. Changes in echocardiographic parameters were evaluated with paired-sample t-tests or Wilcoxon tests. The differences in these changes (Δ) between groups were evaluated by mixed-model repeated-measures analysis. Multivariable logistic regression analysis with the backward Wald method was subsequently performed to identify any possible independent predictors of LVAR. The receiver operating characteristic (ROC) curve analysis was applied to assess diagnostic performance. Threshold values were determined by the Youden index method. Comparison of the AUCs was performed with a nonparametric approach using the theory of generalized U-statistics to generate an estimated covariance matrix previously reported by DeLong et al. [23]. Significance was accepted at P <0.05 (*) for all statistical analyses.

RESULTS

The study population included 512 patients at a mean age of 55.8 (10.2) years, and these STEMI patients were mostly male. All patients received acetylsalicylic acid (ASA) plus ticagrelor, and they continued their current discharge treatment routinely for 6 months. Their basic characteristics are shown in Table 1. Patients' angiographic and echocardiographic findings are presented in Supplementary material, *Table S1*. The time of STEMI symptom onset was associated with circadian variations. The peak incidence of STEMI was seen in the morning hours, while the second highest frequency was observed at nighttime. At 6 months after STEMI, the number of patients who had developed LVAR was 25.4%. In the LVAR group, the rate of symptom onset in the morning hours, median SII index, and SIRI were higher compared to patients without LVAR (Table 1).

The median GRACE score was higher in the LVAR group compared to patients without LVAR, while other baseline echocardiographic parameters were similar between the groups (Supplementary material, *Table S1*). Baseline mean LVEF levels and median LV volumes were similar in the groups with and without LVAR. At 6 months after STEMI, median LV volumes increased, and mean LVEF levels decreased in the LVAR group (Supplementary material, *Table S2*).

Demographic and clinical findings did not differ significantly according to time of symptom onset. The median cardiac troponin, median SII index and SIRI were higher in patients who experienced symptom onset during the morning hours (Table 2). Mean door-to-balloon time and mean symptom-to-balloon time did not differ by time of symptom onset. The median GRACE score was higher in patients with symptom onset in the morning hours (Table 3).

For the considered circadian time windows, the median SII index and SIRI were higher in the LVAR group than in the group without LVAR (Figure 1). In the morning hours, there was a moderate positive correlation between the SII index and SIRI and the ΔLVEDV and ΔLVESV levels, while a moderate negative correlation was found with the ΔLVEF levels. In other time intervals, there was a weak correlation between the SII index and SIRI and the ΔLVEDV, ΔLVESV, and ΔLVEF levels (Supplementary material, *Table S3*).

Among the potential confounding factors associated with LVAR (Table 1 and Supplementary material, *Table S1*), time of onset of symptoms, cardiac troponin I, white blood counts, SII, SIRI, HDL-C, hs-CRP, and GRACE scores were included in the multivariable logistic regression model. The components of SII and SIRI were not included in the multivariable regression model because of their multicollinearity. An increased SIRI level, morning hours of symptom onset, and an increased GRACE score were

Table 1. Distribution of demographic and clinical findings by cardiac remodeling groups

Variables	All population n = 512	LVAR		*P*-value
		No n = 382	Yes n = 130	
Demographic findings				
Age, years	55.8 (10.2)	56.00 (9.3)	55.4 (8.3)	0.80
Male sex, n (%)	442 (88.0)	332 (86.9)	110 (84.6)	0.51
BMI, kg/m^2	27.5 (4.1)	27.6 (4.5)	27.2 (3.9)	0.34
Active smoking, n (%)	280 (54.7)	205 (53.7)	66 (57.7)	0.42
Hypertension, n (%)	240 (46.9)	180 (47.1)	60 (46.2)	0.86
Diabetes mellitus, n (%)	144 (28.1)	104 (27.2)	40 (30.8)	0.43
Clinical findings				
Symptoms, n (%)				
Chest pain	512 (100.0)	382 (100)	130 (100)	–
Shoulder or back pain	288 (56.3)	208 (54.5)	80 (61.5)	0.32
Arm pain	228 (44.5)	168 (44.0)	60 (46.2)	0.77
Dyspnea	192 (37.5)	132 (34.6)	60 (46.2)	0.10
Fatigue	320 (62.5)	230 (60.2)	90 (69.2)	0.24
Time of onset of symptoms, n (%)				
Morning hours	212 (41.4)	140 (36.6)	72 (55.4)	0.04[a]
Daytime hours	90 (17.6)	68 (17.8)	22 (16.9)	
Evening hours	70 (13.7)	56 (14.7)	14 (10.8)	
Night hours	140 (27.3)	118 (30.9)	22 (16.9)	
SBP, mm Hg	123.4 (17.9)	124 (17.5)	121.7 (18.9)	0.42
DBP, mm Hg	76.2 (12.3)	76.5 (11.9)	75.4 (13.4)	0.60
HR, bpm	76.8 (16.0)	76.1 (16.9)	78.6 (13.5)	0.30
LVEF, %	46.1 (10.1)	45.7 (9.3)	47.3 (11.5)	0.26
Laboratory findings				
cTn-I, ng/l	47 (39–59.6)	40.8 (32.5–50.9)	51 (40–58.3)	0.03[a]
Glucose, mg/dl	115 (96–149)	114.5 (96–146)	115 (97–163)	0.67
Hemoglobin, g/dl	14.1 (1.5)	14.1 (1.5)	14.0 (1.7)	0.21
WBC, ×10^9/l	11.6 (9.3–14.3)	10.6 (8.6–12.4)	12.2 (10.2–14.8)	0.03[a]
Neutrophils, ×10^9/l	7.5 (6.1–9.3)	7.2 (5.9–9.3)	8.4 (7.5–9.4)	<0.001[a]
Lymphocytes, ×10^9/l	2.4 (1.8–3.1)	2.5 (2–3.2)	2 (1.6–2.7)	<0.001[a]
Platelets, ×10^9/l	278.1 (69.5)	273.0 (68.0)	293.2 (72.3)	0.04[a]
Monocyte, ×10^9/l	0.7 (0.2)	0.7 (0.2)	0.8 (0.2)	<0.001[a]
SII	931 (658–1156)	858 (547–1023)	1257 (961–1523)	<0.001[a]
SIRI	2.2 (1.5–3.4)	1.9 (1–2.6)	3.5 (2.6–4.3)	<0.001[a]
Total cholesterol, mg/dl	199.0 (49.0)	198.1 (47.0)	201.4 (54.6)	0.64
HDL-cholesterol, mg/dl	42.2 (10.4)	43.5 (10.7)	38.1 (8.2)	<0.001[a]
LDL-cholesterol, mg/dl	137 (110–166)	137 (109–163)	140 (115–170)	0.52
Triglycerides, mg/dl	133 (100.5–184)	116 (90–183)	145 (116–190)	0.07
Creatinine, mg/dl	1.0 (0.2)	1.0 (0.2)	1.0 (0.2)	0.21
hs-CRP, mg/l	20.8 (13.5–28)	17.2 (10.7–24.8)	25.1 (19.7–32.7)	0.04[a]
Discharge therapy, n (%)				
Aspirin	512 (100.0)	382 (100.0)	130 (100.0)	1.00
Ticagrelor	512 (100.0)	382 (100.0)	130 (100.0)	1.00
ACEi/ARBs	500 (97.7)	372 (97.4)	128 (98.5)	0.98
Beta-blockers	492 (96.1)	366 (95.8)	126 (96.9)	0.97
Statins	504 (98.4)	376 (98.4)	128 (98.5)	0.99

Categorical variables were shown as number percentages. Numerical variables are mean (SD) or median (IQR)
[a]*P*-value <0.05 shows statistical significance

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; BMI, body mass index; cTn-I, cardiac troponin I; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HR, heart rate; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; LVAR, left ventricular adverse remodeling; SII, systemic immune inflammation index; SIRI, systemic inflammation response index; WBC, white blood counts

Table 2. Distribution of demographic and clinical findings by time of onset of symptoms groups

Variables	Morning hours n = 212	Daytime hours n = 90	Evening hours n = 70	Night hours n = 140	*P*-value
Demographic findings					
Age, years	54.7 (9.3)	54.1 (8.4)	54.3 (7.1)	53.0 (8.9)	0.44
Male sex, n (%)	180 (84.9)	79 (87.8)	60 (85.7)	125 (89.2)	0.73
BMI, kg/m^2	27.8 (3.6)	27.8 (5.1)	26.8 (6.5)	27.6 (2.8)	0.54
Active smoking, n (%)	114 (53.8)	48 (53.3)	36 (51.4)	82 (58.6)	0.77
Hypertension, n (%)	104 (49.1)	40 (44.4)	32 (45.7)	64 (45.7)	0.92
Diabetes mellitus, n (%)	58 (27.4)	26 (28.8)	20 (28.6)	40 (28.6)	0.79
Clinical findings					
Symptoms, n (%)					
Shoulder or back pain	102 (52.8)	56 (62.2)	38 (54.3)	82 (58.6)	0.71
Arm pain	90 (42.5)	36 (40.0)	34 (48.6)	68 (48.6)	0.74
Dyspnea	84 (39.6)	34 (37.8)	28 (40.0)	46 (32.9)	0.81
Fatigue	140 (66.0)	46 (51.1)	48 (68.6)	86 (61.4)	0.31
SBP, mm Hg	122.2 (17.3)	121.5 (15.2)	127.6 (21.9)	124.6 (18.7)	0.56
DBP, mm Hg	75.2 (12.6)	74.2 (10.0)	77.3 (13.8)	78.4 (12.3)	0.37
HR, beat per minute	77.1 (15.4)	75.5 (13.5)	78.6 (22.0)	76.2 (15.5)	0.85
Laboratory findings					
cTn-I, ng/l	55 (42.6–68.4)	38 (32–42)	36 (30–42)	47 (41–53)	0.004[a]
Glucose, mg/dl	128 (97–148)	120 (96–152)	114 (85–175)	116 (100–148)	0.69
Hemoglobin, g/dl	14.1 (1.6)	14.2 (1.7)	14.1 (1.4)	13.9 (1.5)	0.86
WBC, ×10^9/l	13.2 (10.2–14.9)	10.4 (8.4–12.3)	10.1 (8–12.1)	11.3 (8.6–13.2)	<0.001[a]
Neutrophils, ×10^9/l	8.6 (7.5–10.1)	6.5 (5.9–8.1)	6.1 (5.7–7)	7.3 (5.4–9.3)	<0.001[a]
Lymphocytes, ×10^9/l	2 (1.6–2.6)	2.8 (2.2–3.3)	2.6 (2.1–3)	2.8 (2.1–3.5)	<0.001[a]
Platelets, ×10^9/l	298.1 (68.2	264.1 (63.6	260.4 (58.5	270.2 (72.8)	<0.001[a]
Monocyte, ×10^9/l	0.8 (0.3)	0.7 (0.2)	0.7 (0.2)	0.7 (0.3)	<0.001[a]
SII	1213 (1008–1544)	759 (587–876)	547 (388–810)	796 (466–923)	<0.001[a]
SIRI	3.2 (2.0–4.1)	2.2 (1.5–2.5)	1.9 (0.9–2.2)	1.7 (0.9–2.3)	<0.001[a]
Total cholesterol, mg/dl	191.6 (49.4)	194.8 (43.1)	202.4 (47.1)	211.2 (51.3)	0.11
LDL-cholesterol, mg/dl	42.0 (9.8)	42.8 (10.7)	42.4 (9.4)	42.8 (11.5)	0.63
HDL-cholesterol, mg/dl	135 (96–157)	134 (105–166)	133.5 (125–163)	141 (128–179)	0.28
Triglycerides, mg/dl	120.5 (89–182.5)	125 (95.5–204)	164 (127–182)	162 (107–184)	0.12
Creatinine, mg/dl	1.0 (0.2)	1.0 (0.2)	1.0 (0.2)	1.0 (0.2)	0.66
hs-CRP, mg/l	24.6 (11.7–32.2)	19.3 (13–31.4)	20 (13.5–25.5)	19.4 (14.3–26)	0.80
Discharge therapy, n (%)					
ACEi/ARBs	208 (98.1)	88 (97.8)	66 (94.3)	138 (98.6)	0.57
Beta-blockers	204 (96.2)	90 (100.0)	68 (97.1)	130 (92.9)	0.30
Statins	208 (98.1)	88 (97.8)	70 (100.0)	138 (98.6)	0.99

Categorical variables were shown as number percentages. Numerical variables are mean (SD) or median (IQR)
[a]*P*-value <0.05 shows statistical significance. Bold characters show the difference between groups

Abbreviations: see Table 1

determined as independent predictors of LVAR. Accordingly, a 1% increase in the SIRI increased the risk of LVAR by 3.03-fold (odds ratio [OR], 3.03; *P* <0.001) (Table 4). The threshold value of the SIRI was found to be >2.5, with 78.5% sensitivity and 74.3% specificity. The threshold value of the SII index was found to be >1204.2, with 55.4% sensitivity and 87.4% specificity. The SIRI showed superior diagnostic performance compared to the SII index in predicting LVAR (Figure 2) (Supplementary material, *Table S4*).

DISCUSSION

To our knowledge, this is the first study in the literature to report the association between the SII index, SIRI, and the time of onset of symptoms in LVAR after STEMI. SII index and SIRI on admission were generally higher in patients who developed LVAR, but this difference was particularly pronounced in the morning hours between 06:00 and 11:59 AM. The SIRI was found to be an independent predictor of LVAR and showed superior diagnostic performance compared to the SII index.

Previous studies demonstrated that increased SII index and SIRI were important predictors of cardiovascular events [12–14]. Increased SII index and SIRI were related to increased risk of LVAR in patients experiencing STEMI for the first time. Immune system activation starting from the onset of acute MI allows neutrophils, as the first line of defense against inflammation, to gather in the ischemic zone to scavenge dead cell debris following this cardiac event [24]. Protein heteromers of neutrophil and platelet cells promote monocyte recruitment [25]. Moreover, neutrophils have the potential to modulate macrophages to the anti-inflammatory phenotype, while platelets can

Table 3. Distribution of angiographic and echocardiographic findings by time of onset of symptoms groups

Variables	Time of onset of symptoms				*P*-value
	Morning hours n = 212	Daytime hours n = 90	Evening hours n = 70	Night hours n = 140	
Angiographic findings					
Door-to-balloon time, min	43.2 (7.0)	44.1 (8.6)	41.5 (7.2)	42.6 (12.0)	0.39
Symptom-to-balloon time, min	310.2 (56.4)	307.2 (54.1)	237.8 (48.6)	306.2 (50.5)	0.41
GRACE score	142 (102–152)	118 (102–130)	112 (102–130)	128 (88–140)	0.02[a]
IRA, n (%)					
LAD	80 (37.7)	30 (33.3)	22 (31.4)	52 (37.1)	0.89
Cx	132 (62.3)	60 (66.7)	48 (68.6)	88 (62.9)	
Number of diseased vessels, n (%)					
1	144 (67.9)	74 (82.2)	46 (65.7)	102 (72.9)	0.27
≥2	68 (32.1)	16 (17.8)	24 (34.3)	38 (27.1)	
Pre-PCI TIMI flow, n (%)					
0	140 (66.0)	62 (68.9)	40 (57.1)	86 (61.4)	0.41
1	24 (11.3)	2 (2.2)	8 (11.4)	18 (12.9)	
2	18 (8.5)	8 (8.9)	10 (14.3)	22 (15.7)	
3	30 (14.2)	18 (20.0)	12 (17.1)	14 (10.0)	
Post-PCI TIMI flow >2, n (%)	200 (94.3)	86 (95.6)	70 (100.0)	132 (94.3)	0.60
Number of stents	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–2)	0.87
Echocardiographic findings					
Baseline					
LVEF, %	48.5 (9.1)	49.7 (9.9)	50.1 (7.3)	48.4 (9.8)	0.10
LVEDV, ml	150 (130–171)	142 (126–167)	140 (113–165)	146 (129–171)	0.13
LVESV, ml	74 (60–104)	70 (57–98)	72 (49–94)	74 (62–97)	0.11
Stroke volume, ml	70.0 (16.1)	69.7 (17.0)	70.8 (15.8)	70.2 (17.6)	0.99
6 months					
LVEF, %	48.3 (9.9)	51.2 (10.0)	54.2 (8.4)	49.6 (10)	0.01[a]
LVEDV, ml	154 (128–171)	140 (132–150)	138 (117–151)	143 (129–160)	0.04[a]
LVESV, ml	76 (55–95)	65 (54–82)	63 (50–72)	68 (53–99)	0.05[a]
Stroke volume, ml	73.7 (16.1)	75.9 (18.3)	74.8 (13.3)	73.3 (17.1)	0.84
LVAR, n (%)	72 (34.0)	22 (24.4)	14 (20.0)	22 (15.7)	0.04[a]

Categorical variables were shown as number percentages. Numerical variables are mean (SD) or median (IQR)
[a]*P*-value <0.05 shows statistical significance. Bold characters show the difference between groups

Abbreviations: Cx, circumflex artery; IRA, infarct-related artery; LAD, left anterior descending artery; LVAR, left ventricular adverse remodeling; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction

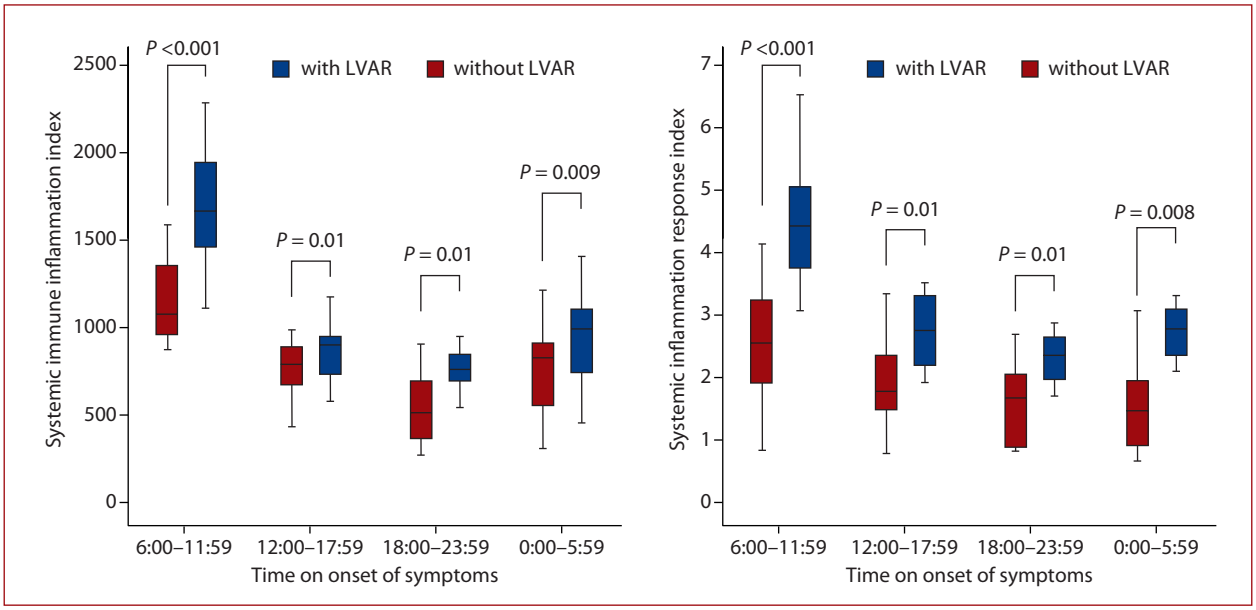

Figure 1. Box and whisker plots of SII and SIRI levels by time of onset of symptoms. Data are presented as median (interquartile range [IQR])

Table 4. Independent predictors of LVAR

Variables	Univariable regression				Multivariable regression			
	OR	95% CI		*P*-value	OR	95% CI		*P*-value
		Lower	Upper			Lower	Upper	
Time of onset of symptoms								
Morning hours	2.76	1.29	5.89	0.009[a]	2.92	1.32	6.10	0.03[a]
Daytime hours	1.74	0.68	4.43	0.25	1.89	0.75	4.80	0.32
Evening hours	1.34	0.47	3.83	0.58	1.45	0.53	4.04	0.62
Night hours	ref				ref			
cTn-I	1.08	1.01	1.16	0.03[a]	–	–	–	–
WBC	1.04	1.01	1.08	0.04[a]	–	–	–	–
Neutrophils	1.30	1.12	1.50	<0.001[a]	–	–	–	–
Lymphocytes	0.46	0.31	0.68	<0.001[a]	–	–	–	–
Platelets	1.04	1.01	1.08	0.04[a]	–	–	–	–
Monocyte	25.34	6.73	95.43	<0.001[a]	–	–	–	–
SII	1.02	1.01	1.03	<0.001[a]	–	–	–	–
SIRI	3.00	2.21	4.07	<0.001[a]	3.03	1.46	6.28	<0.001[a]
HDL	0.94	0.91	0.97	<0.001[a]	–	–	–	–
hs-CRP	1.04	1.01	1.08	0.04[a]	–	–	–	–
Grace score	1.14	1.05	1.23	0.003[a]	1.16	1.06	1.25	0.01[a]
						C-Statistics = 0.85; *P* <0.001[a]		

[a]*P*-value <0.05 shows statistical significance. The reference category (ref) for the time of onset of symptoms variable was "Night hours"

Abbreviations: CI, confidence interval; cTn-I, cardiac troponin I; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; OR, odds ratio; SII, systemic immune inflammation index; SIRI, systemic inflammation response index; WBC, white blood cell counts

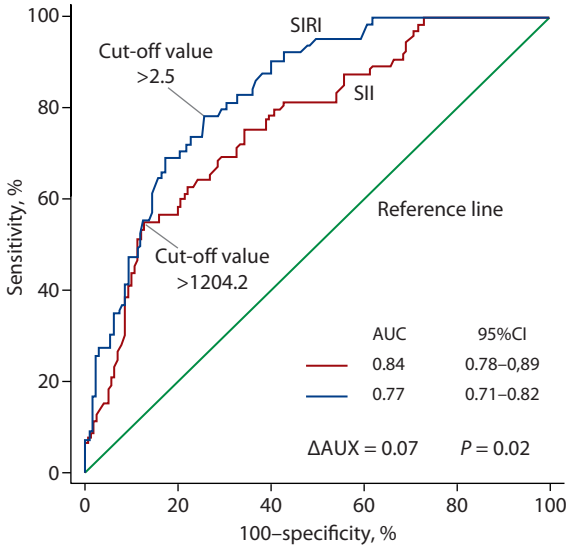

Figure 2. Diagnostic performance of SII and SIRI in predicting LVAR

Abbreviations: AUC, area under the curve; CI, confidence interval; SII, systemic immune inflammation index; SIRI, systemic inflammation response index

affect neutrophil functions [26]. This can release proteolytic enzymes and reactive oxygen species and cause an exacerbation of cardiac damage by damaging surviving myocytes [27]. This may also favor long-term tissue damage, resulting in poor wound healing due to exaggerated inflammation [28].

The relationships between LVAR and IIR indices are not surprising, as previous limited studies reported that increased values of the neutrophil count/lymphocyte count ratio (NLR) or leukocyte components were predictive of LVAR [29, 30]. The current findings both support and expand this literature. This study is the first to report the relationship between LVAR and SII and SIRI indices. The SII index and SIRI have been shown to be better prognostic markers as they contain all components of both the NLR and platelet count/lymphocyte count ratio [31, 32]. These inflammatory indices peaked between the morning hours of 06:00 and 11:59 AM. This suggests that the circadian clock may play a role in IIR and LVAR.

Some important mechanisms of the active phase of the circadian cycle may explain the potential role of IIR indices in the development of LVAR. In a healthy physiological state, circulating neutrophil and monocyte counts peak in the resting phase and are minimal in the active phase [33]. However, circadian variations in leukocyte trafficking due to MI-induced IIR are sensitive to acute inflammatory impulses from the first moment of the acute phase [34]. This sensitivity can result in higher infiltration of neutrophils and monocytes into the myocardium. In addition to this trafficking of neutrophils and monocytes, increased platelet aggregation in the morning phase may exacerbate inflammation [35]. This sequence of events may suggest that neutrophils, which play a role in the modulation of other subtypes of leukocytes, are more affected by the circadian clock, which can result in increasing inflammation or cardiac events. In the morning hours, excessive leukocyte activation may cause increased levels of reactive oxygen species and nitric oxide synthase activity, which play roles in the pathology of LVAR [36]. In nighttime hours, melatonin may play a role in the regulation of these factors [37].

Melatonin is known to influence the regulation of IIR responses, platelet aggregation, and leukocyte trafficking into damaged tissue [38]. Therefore, melatonin secreted in nighttime hours may cause both a more stable IIR and may protect cardiomyocytes from infarction. Administration of melatonin on admission in patients with early STEMI symptom onset was shown to result in reduced infarct size after pPCI [39].

In previous human studies, increased infarct size and mortality rate were associated with different circadian clocks [5–8]. The differences between studies may be due to patient selection. Previous studies included patients at elevated prognostic risk, such as those with a prior history of MI. When patients were evaluated in terms of the first incidence of STEMI, we found that the LVAR rate and IIR indices were higher in the morning hours. These findings are consistent with previous experimental studies that found that MI occurring in the active phase caused increased inflammation or infarct size and worse cardiac repair outcomes [9, 40]. Additionally, neutrophil modulation was shown to reduce infarct size and improve cardiac function [9]. In another MI study in a mouse model, the daily rhythm was randomized to a normal diurnal rhythm or disrupted environment for 5 days after MI. Disruption of the circadian rhythm caused further increases in cytokines, neutrophil and macrophage infiltration, and altered innate immune responses. As a result, poor cardiac healing and exacerbated LVAR were observed [41].

All patients received antiplatelet therapy in accordance with the guidelines [42]. Despite similar treatment protocols, patients with STEMI in the morning hours had elevated LV volumes at 6-month follow-up in the present study. In addition, there was a positive correlation between baseline IIR indices and change in LV volumes, and this relationship was more pronounced for the patients from the morning interval. These findings suggest that there may be a vicious circle between IIR indices, LV volumes, and the circadian clock in the development of LVAR.

Limitations of the study

The present study has some limitations. First, magnetic resonance imaging, the gold standard method in evaluating cardiac remodeling, could not be performed due to the retrospective nature of the study. Therefore, infarct size could not be measured. Second, complete blood counts at the time of admission to the hospital were evaluated but were not taken into account after the acute phase. In addition, cytokines or chemokines that may play a role in leukocyte trafficking were not analyzed. Evaluation of subtypes of leukocytes by flow cytometry analysis may be more revealing in the development of LVAR. Evaluations of these factors in future studies might further highlight the role of IIR indices varying throughout the circadian cycle in cases of LVAR.

CONCLUSIONS

In patients experiencing STEMI for the first time, an increased SIRI was independently associated with LVAR development. This relationship was more pronounced in the morning hours between 06:00 and 11:59 AM. Circadian variation in the onset of STEMI may play an important role in the severity of inflammation. Despite differences across the circadian periods, the SIRI may be a potential screening tool for identifying LVAR patients at long-term risk of heart failure.

Supplementary material

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

Article information

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REFERENCES

1. Yeap XY, Dehn S, Adelman J, et al. Quantitation of acute necrosis after experimental myocardial infarction. Methods Mol Biol. 2013; 1004: 115–133, doi: 10.1007/978-1-62703-383-1_9, indexed in Pubmed: 23733573.
2. Kologrivova I, Shtatolkina M, Suslova T, et al. Cells of the immune system in cardiac remodeling: main players in resolution of inflammation and repair after myocardial infarction. Front Immunol. 2021; 12: 664457, doi: 10.3389/fimmu.2021.664457, indexed in Pubmed: 33868315.
3. Frangogiannis NG. The immune system and the remodeling infarcted heart: cell biological insights and therapeutic opportunities. J Cardiovasc Pharmacol. 2014; 63(3): 185–195, doi: 10.1097/FJC.0000000000000003, indexed in Pubmed: 24072174.
4. Anzai A, Ko S, Fukuda K. Immune and inflammatory networks in myocardial infarction: current research and its potential implications for the clinic. Int J Mol Sci. 2022; 23(9), doi: 10.3390/ijms23095214, indexed in Pubmed: 35563605.
5. Kumar S, Kumar N, Kumar H, et al. Circadian variation in the onset of acute myocardial infarction in diabetics. J Ayub Med Coll Abbottabad. 2018; 30(1): 71–73, indexed in Pubmed: 29504334.
6. López Messa JB, Garmendia Leiza JR, Aguilar García MD, et al. Cardiovascular risk factors in the circadian rhythm of acute myocardial infarction [in Spanish]. Rev Esp Cardiol. 2004; 57(9): 850–858, indexed in Pubmed: 15373991.
7. Reiter R, Swingen C, Moore L, et al. Circadian dependence of infarct size and left ventricular function after ST elevation myocardial infarction. Circ Res. 2012; 110(1): 105–110, doi: 10.1161/CIRCRESAHA.111.254284, indexed in Pubmed: 22095727.
8. Seneviratna A, Lim GH, Devi A, et al. Circadian dependence of infarct size and acute heart failure in ST elevation myocardial infarction. PLoS One. 2015; 10(6): e0128526, doi: 10.1371/journal.pone.0128526, indexed in Pubmed: 26039059.
9. Schloss MJ, Horckmans M, Nitz K, et al. The time-of-day of myocardial infarction onset affects healing through oscillations in cardiac neutrophil recruitment. EMBO Mol Med. 2016; 8(8): 937–948, doi: 10.15252/emmm.201506083, indexed in Pubmed: 27226028.
10. Wang XL, Li L. Circadian clock regulates inflammation and the development of neurodegeneration. Front Cell Infect Microbiol. 2021; 11: 696554, doi: 10.3389/fcimb.2021.696554, indexed in Pubmed: 34595127.

11. Xu Y, Su S, McCall WV, et al. Blunted rest-activity rhythm is associated with increased white blood-cell-based inflammatory markers in adults: an analysis from NHANES 2011-2014. Chronobiol Int. 2022; 39(6): 895–902, doi: 10.1080/07420528.2022.2048663, indexed in Pubmed: 35260021.
12. Tosu AR, Kalyoncuoglu M, Biter Hİ, et al. Prognostic value of systemic immune-inflammation index for major adverse cardiac events and mortality in severe aortic stenosis patients after TAVI. Medicina (Kaunas). 2021; 57(6), doi: 10.3390/medicina57060588, indexed in Pubmed: 34201104.
13. Han K, Shi D, Yang L, et al. Prognostic value of systemic inflammatory response index in patients with acute coronary syndrome undergoing percutaneous coronary intervention. Ann Med. 2022; 54(1): 1667–1677, doi: 10.1080/07853890.2022.2083671, indexed in Pubmed: 35695557.
14. Doganay B, Celebi OO. Akut koroner sendromda akut stent trombozunun ve hastane içi mortalitenin yeni bir inflamasyon göstergesi: çoklu inflamasyon indeksi. JOMPAC. 2023; 4(2): 168–175, doi: 10.47582/jompac.1256573.
15. Hu Bo, Yang XR, Xu Y, et al. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. Clin Cancer Res. 2014; 20(23): 6212–6222, doi: 10.1158/1078-0432.CCR-14-0442, indexed in Pubmed: 25271081.
16. Qi Qi, Zhuang L, Shen Y, et al. A novel systemic inflammation response index (SIRI) for predicting the survival of patients with pancreatic cancer after chemotherapy. Cancer. 2016; 122(14): 2158–2167, doi: 10.1002/cncr.30057, indexed in Pubmed: 27152949.
17. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). Glob Heart. 2018; 13(4): 305–338, doi: 10.1016/j.gheart.2018.08.004, indexed in Pubmed: 30154043.
18. 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.
19. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972; 18(6): 499–502, indexed in Pubmed: 4337382.
20. 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.
21. Bulluck H, Go YY, Crimi G, et al. Defining left ventricular remodeling following acute ST-segment elevation myocardial infarction using cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2017; 19(1): 26, doi: 10.1186/s12968-017-0343-9, indexed in Pubmed: 28285594.
22. Schober P, Boer C, Schwarte LA. Correlation coefficients: appropriate use and interpretation. Anesth Analg. 2018; 126(5): 1763–1768, doi: 10.1213/ANE.0000000000002864, indexed in Pubmed: 29481436.
23. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics. 1988; 44(3): 837–845, indexed in Pubmed: 3203132.
24. Westman PC, Lipinski MJ, Luger D, et al. Inflammation as a driver of adverse left ventricular remodeling after acute myocardial infarction. J Am Coll Cardiol. 2016; 67(17): 2050–2060, doi: 10.1016/j.jacc.2016.01.073, indexed in Pubmed: 27126533.
25. Alard JE, Ortega-Gomez A, Wichapong K, et al. Recruitment of classical monocytes can be inhibited by disturbing heteromers of neutrophil HNP1 and platelet CCL5. Sci Transl Med. 2015; 7(317): 317ra196, doi: 10.1126/scitranslmed.aad5330, indexed in Pubmed: 26659570.
26. Ramirez GA, Manfredi AA, Maugeri N. Misunderstandings between platelets and neutrophils build in chronic inflammation. Front Immunol. 2019; 10: 2491, doi: 10.3389/fimmu.2019.02491, indexed in Pubmed: 31695699.
27. Peterson EA, Sun J, Wang J. Leukocyte-Mediated cardiac repair after myocardial infarction in non-regenerative vs. regenerative systems. J Cardiovasc Dev Dis. 2022; 9(2), doi: 10.3390/jcdd9020063, indexed in Pubmed: 35200716.
28. Nah DY, Rhee MY. The inflammatory response and cardiac repair after myocardial infarction. Korean Circ J. 2009; 39(10): 393–398, doi: 10.4070/kcj.2009.39.10.393, indexed in Pubmed: 19949583.
29. Börekçi A, Gür M, Türkoğlu C, et al. Neutrophil to lymphocyte ratio predicts left ventricular remodeling in patients with ST elevation myocardial infarction after primary percutaneous coronary intervention. Korean Circ J. 2016; 46(1): 15–22, doi: 10.4070/kcj.2016.46.1.15, indexed in Pubmed: 26798381.
30. Papageorgiou N, Falconer D, Ioannou A, et al. Full blood count as potential predictor of outcomes in patients undergoing cardiac resynchronization therapy. Sci Rep. 2019; 9(1): 13016, doi: 10.1038/s41598-019-49659-z, indexed in Pubmed: 31506584.
31. Chen JH, Zhai ET, Yuan YJ, et al. Systemic immune-inflammation index for predicting prognosis of colorectal cancer. World J Gastroenterol. 2017; 23(34): 6261–6272, doi: 10.3748/wjg.v23.i34.6261, indexed in Pubmed: 28974892.
32. Fu H, Zheng J, Cai J, et al. Systemic immune-inflammation index (SII) is useful to predict survival outcomes in patients after liver transplantation for hepatocellular carcinoma within Hangzhou criteria. Cell Physiol Biochem. 2018; 47(1): 293–301, doi: 10.1159/000489807, indexed in Pubmed: 29768257.
33. Pick R, He W, Chen CS, et al. Time-of-Day-Dependent trafficking and function of leukocyte subsets. Trends Immunol. 2019; 40(6): 524–537, doi: 10.1016/j.it.2019.03.010, indexed in Pubmed: 31109762.
34. Puhl SL, Steffens S. Neutrophils in Post-myocardial Infarction Inflammation: Damage vs. Resolution? Front Cardiovasc Med. 2019; 6: 25, doi: 10.3389/fcvm.2019.00025, indexed in Pubmed: 30937305.
35. Scheer FA, Michelson AD, Frelinger AL, et al. The human endogenous circadian system causes greatest platelet activation during the biological morning independent of behaviors. PLoS One. 2011; 6(9): e24549, doi: 10.1371/journal.pone.0024549, indexed in Pubmed: 21931750.
36. Han CY, Pichon TJ, Wang Xu, et al. Leukocyte activation primes fibrinogen for proteolysis by mitochondrial oxidative stress. Redox Biol. 2022; 51: 102263, doi: 10.1016/j.redox.2022.102263, indexed in Pubmed: 35158163.
37. Zhu Y, Gao H, Lu M, et al. Melatonin-Nitric oxide crosstalk and their roles in the redox network in plants. Int J Mol Sci. 2019; 20(24), doi: 10.3390/ijms20246200, indexed in Pubmed: 31818042.
38. Fu Z, Jiao Y, Wang J, et al. Cardioprotective role of melatonin in acute myocardial infarction. Front Physiol. 2020; 11: 366, doi: 10.3389/fphys.2020.00366, indexed in Pubmed: 32411013.
39. Dominguez-Rodriguez A, Abreu-Gonzalez P, de la Torre-Hernandez JM, et al. MARIA Investigators. Usefulness of early treatment with melatonin to reduce infarct size in patients with ST-segment elevation myocardial infarction receiving percutaneous coronary intervention (from the melatonin adjunct in the acute myocardial infarction treated with angioplasty trial). Am J Cardiol. 2017; 120(4): 522–526, doi: 10.1016/j.amjcard.2017.05.018, indexed in Pubmed: 28645475.
40. Durgan DJ, Pulinilkunnil T, Villegas-Montoya C, et al. Short communication: ischemia/reperfusion tolerance is time-of-day-dependent: mediation by the cardiomyocyte circadian clock. Circ Res. 2010; 106(3): 546–550, doi: 10.1161/CIRCRESAHA.109.209346, indexed in Pubmed: 20007913.
41. Alibhai FJ, Tsimakouridze EV, Chinnapareddy N, et al. Short-term disruption of diurnal rhythms after murine myocardial infarction adversely affects long-term myocardial structure and function. Circ Res. 2014; 114(11): 1713–1722, doi: 10.1161/CIRCRESAHA.114.302995, indexed in Pubmed: 24687134.
42. Hudzik B, Błachut A, Lesiak M, et al. Summary of the European Society of Cardiology guidelines on dual antiplatelet therapy in patients after percutaneous coronary interventions. Kardiol Pol. 2022; 80(10): 974–989, doi: 10.33963/KP.a2022.0198, indexed in Pubmed: 36036339.

Influence of sex on the functional assessment of myocardial ischemia

Barbara Zdzierak[1], Wojciech Zasada[1, 2], Agata Krawczyk-Ożóg[1, 3], Tomasz Rakowski[1, 4], Stanisław Bartuś[1, 4], Andrzej Surdacki[1, 4], Artur Dziewierz[1, 4]

[1]Clinical Department of Cardiology and Cardiovascular Interventions, University Hospital, Kraków, Poland
[2]KCRI, Kraków, Poland
[3]Department of Anatomy, HEART — Heart Embryology and Anatomy Research Team, Jagiellonian University Medical College, Kraków, Poland
[4]2nd Department of Cardiology, Institute of Cardiology, Jagiellonian University Medical College, Kraków, Poland

Correspondence to:
Artur Dziewierz, MD, PhD,
2nd Department of Cardiology,
Jagiellonian University Medical College,
Jakubowskiego 2,
30–688 Kraków, Poland,
phone: +48 12 400 2250,
e-mail: artur.dziewierz@uj.edu.pl

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ABSTRACT

Background: Fractional flow reserve (FFR) and non-hyperemic resting pressure ratios, such as instantaneous wave-free ratio (iFR) and resting full-cycle ratio (RFR), are recommended for evaluating the significance of angiographically intermediate coronary stenoses. Despite their usefulness, approximately 20% of assessed lesions exhibit discordance between FFR and iFR/RFR.

Aims: The role of sex in this discrepancy remains uncertain; thus, we aimed to investigate its impact on the discordance between FFR and iFR/RFR.

Methods: We reviewed 417 consecutive intermediate stenotic lesions from 381 patients, stratified by sex and assessed with both FFR and iFR/RFR. FFR ≤0.80 and iFR/RFR ≤0.89 were considered positive for ischemia.

Results: Of the 381 patients, 92 (24.1%) were women. Women were older, had a lower estimated glomerular filtration rate (eGFR), higher ejection fraction, and were more likely to have peripheral artery disease than men. Median FFR and iFR/RFR values were lower in men than in women (FFR 0.86 vs. 0.80; P <0.001; iFR 0.92 vs. 0.90; P = 0.049). However, overall discordance prevalence was similar for both sexes (20.6% vs. 15.1%; P = 0.22). In men, eGFR, insulin-treated diabetes mellitus, and arterial hypertension were predictors of positive FFR | negative iFR/RFR discordance, while eGFR, insulin-treated diabetes mellitus, atrial fibrillation, and chronic obstructive pulmonary disease were predictors of negative FFR | positive iFR/RFR discordance. No factors associated with either discordance were identified in women.

Conclusions: FFR and iFR/RFR results indicating significant ischemia were more common in men than women when assessing intermediate coronary stenoses. Nevertheless, sex did not predict discordant results.

Key words: borderline lesions; coronary artery disease; discordance; physiological assessment; sex

INTRODUCTION

Current guidelines recommend assessing the significance of intermediate coronary stenoses, defined as luminal narrowing with stenosis diameter of 50% to 90% on angiography, using invasive physiological methods (class I recommendation, level of evidence A) [1, 2]. Fractional flow reserve (FFR) remains the gold standard for detecting ischemia-inducing stenoses during maximum hyperemia, achieved through adenosine administration. Instantaneous wave-free ratio (iFR) and resting full-cycle ratio (RFR) are alternative invasive measurements for evaluating coronary stenosis significance without vasodilators [3, 4]. FFR and non-hyperemic methods (iFR/RFR) results are closely correlated [4–9]. However, a notable 20% discordance exists in identifying significant ischemia between FFR and iFR/RFR [4, 10–15]. Several clinical and anatomical factors have been suggested to contribute to this discordance, including diabetes mellitus, chronic kidney disease, valvular heart diseases, diastolic dysfunction, heart

WHAT'S NEW?

This study explores the impact of sex on invasive assessment of intermediate coronary stenoses using hyperemic (fractional flow reserve) and non-hyperemic (instantaneous wave-free ratio/resting full-cycle ratio) pressure ratios. As both non-hyperemic methods are considered equal, their results were combined. Results reveal that men have more significant ischemia than women, but sex is not a predictor of discordant results between hyperemic and non-hyperemic methods. Furthermore, we were able to discern specific predictors for positive fractional flow reserve | negative instantaneous wave-free ratio/resting full-cycle ratio discordance and negative fractional flow reserve | positive instantaneous wave-free ratio/resting full-cycle ratio discordance in men, while no such associated factors were found in women.

rate, and coronary artery stenosis severity and location [4, 16-18]. However, the role of sex in this discrepancy remains uncertain [4, 17]. Thus, we sought to investigate the impact of sex on the discordance between FFR and non-hyperemic methods (iFR/RFR) in patients undergoing invasive assessment of angiographically intermediate lesions.

METHODS

The main results of our study have been previously published [19]. Data were retrospectively collected for all consecutive patients hospitalized at the Clinical Department of Cardiology and Cardiovascular Interventions of the University Hospital in Kraków between January 2020 and December 2021, in whom invasive physiological assessment of the angiographically intermediate coronary lesions was performed, regardless of the method used. For this analysis, patients were stratified by sex.

All procedures were performed according to standard clinical methods via the radial or femoral approach, based on individual operator preferences. FFR and another non-hyperemic method were conducted, with either diagnostic or guiding catheters. FFR was measured during maximal hyperemia, achieved through an intracoronary bolus of adenosine ranging from 100-400 µg. The iFR or RFR was used for the non-hyperemic assessment depending on the operator's preferences and device availability. The mean value of three measurements was analyzed. As both methods are considered equal, iFR and RFR results were combined. Values of ≤0.89 for iFR/RFR and ≤0.80 for FFR were deemed positive for ischemia. In total, 599 vessels underwent FFR and/or iFR/RFR assessments, with both FFR and iFR/RFR measurements available for 417 vessels. Vessels assessed by FFR or iFR/RFR only (182) were excluded from the analysis (Figure 1). Lesions were classified into four groups based on iFR/RFR and FFR concordance ([FFR+|iFR/RFR+] and [FFR-|iFR/RFR-]) or discordance ([FFR-|iFR/RFR+/] and [FFR+|iFR/RFR-]). Additional analyses were conducted separately for lesions within the left anterior descending artery (LAD) and non-LAD arteries (diagonal branch, circumflex artery, marginal branch, right coronary artery). Lesions within the left main coronary artery were not evaluated in this study.

Ethics approval for this retrospective registry (no. 1072.6120.257.2022, November 16, 2022) was granted by

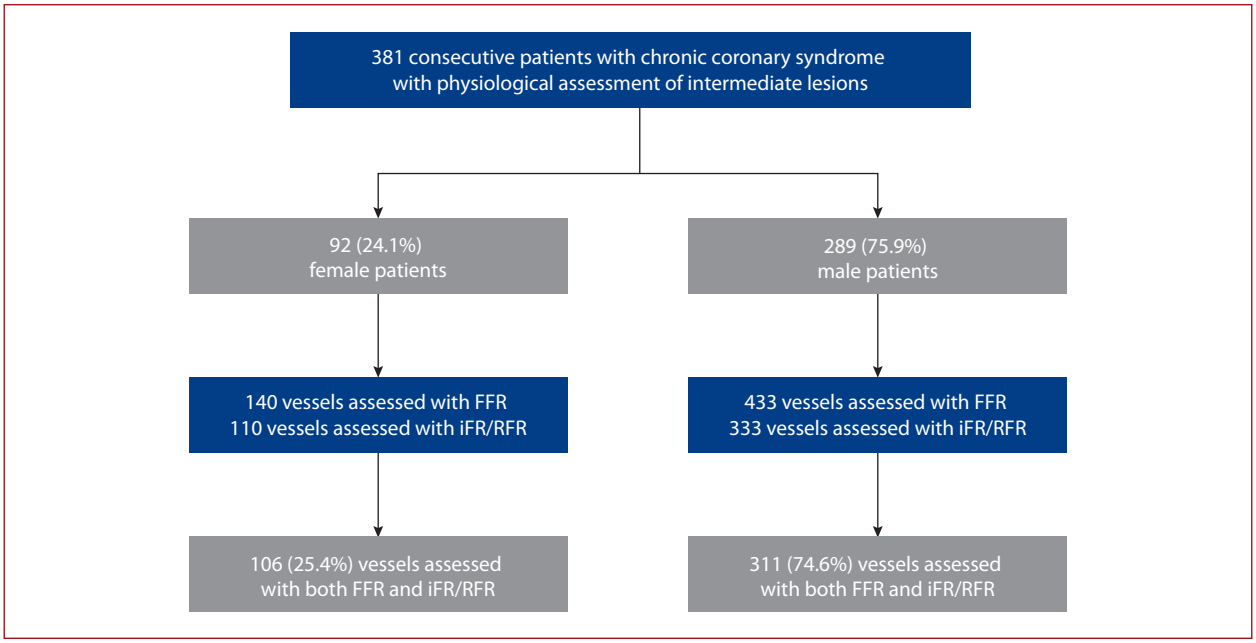

Figure 1. Patients and vessels allocation. Study groups marked with light grey color

Abbreviations: FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; RFR, resting full-cycle ratio

Table 1. Baseline clinical characteristic of study population

Variable	Sex		*P*-value
	Female 92 (24.1%)	Male 289 (75.9%)	
Age, years, mean (SD)	71.6 (9.6)	66.4 (10.1)	<0.001
Height, cm, median (IQR)	162.0 (158.0–165.0)	174.0 (170.0-178.0)	<0.001
Weight, kg, median (IQR)	78.0 (67.0–89.0)	85.0 (78.0-95.0)	<0.001
BMI, kg/m^2, median (IQR)	30.2 (24.9–33.4)	28.4 (25.7-31.2)	0.13
Diabetes mellitus, n (%)	39 (42.4)	115 (39.8)	0.66
Arterial hypertension, n (%)	83 (90.2)	248 (86.1)	0.31
Atrial fibrillation, n (%)	21 (23.1)	54 (18.7)	0.36
Previous MI, n (%)	36 (39.1)	142 (49.1)	0.09
Previous PCI, n (%)	42 (45.7)	154 (53.3)	0.20
Previous CABG, n (%)	7 (7.6)	46 (16.0)	0.38
PAD, n (%)	25 (16.3)	28 (12.3)	0.04
Current smoker, n (%)	34 (37.0)	156 (54.0)	0.005
COPD, n (%)	7 (7.6)	20 (6.9)	0.83
Previous stroke/TIA, n (%)	11 (12.0)	24 (8.3)	0.30
Dyslipidemia, n (%)	75 (81.5)	218 (75.4)	0.23
eGFR, ml/min/1.73 m^2, mean (SD)	70.9 (27.0)	78.2 (25.6)	0.02
HbA_{1c}, %, median (IQR)	6.7 (5.7–7.95)	6.8 (6.05-9.2)	0.24
LVEF, %, median (IQR)	55.0 (45.0–60.0)	50.0 (39.75-60.0)	0.02
Radial access, n (%)	79 (85.9)	234 (81.0)	0.29

Abbreviations: BMI, body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; SD, standard deviation; TIA, transient ischemic attack

the institutional ethical board of the Jagiellonian University Medical College.

Statistical analysis

Categorical variables were presented as numbers and percentages. Continuous variables were expressed as mean, standard deviation (SD), or median with interquartile range (IQR). Differences between groups were compared using Student's t-test for normally distributed variables and the Wilcoxon test for non-normally distributed continuous variables. Categorical variables were compared by Pearson's chi-squared test. Receiver operating characteristic (ROC) curves were created to assess the optimal cut-off values of FFR for predicting iFR/RFR ≤0.89 and iFR/RFR for predicting FFR ≤0.80. The optimal cut-off values were established by maximizing the Youden index. Univariable analyses based on logistic regression for FFR|iFR/RFR discordance predictors were presented. Two-sided *P*-values <0.05 were considered statistically significant. All calculations were performed with JMP®, Version 16.1.0 (SAS Institute Inc.).

RESULTS

Data were collected for 381 patients hospitalized at the Clinical Department of Cardiology and Cardiovascular Interventions of the University Hospital in Kraków between 2020 and 2021. A total of 599 vessels were assessed by FFR and/or iFR/RFR in these patients, with 92 (24.1%) of them being women (Figure 1). Women were older, had a lower estimated glomerular filtration rate (eGFR), higher ejection fraction, and were more likely to have peripheral artery disease than men (Table 1).

For further analysis, 417 vessels assessed with FFR and non-hyperemic methods (iFR or RFR) were selected. Among these, 106 vessels (25.4%) were assessed in women and 311 (74.6%) in men. The distribution of FFR and iFR/FFR values stratified by sex is shown in Figure 2. Overall, the median FFR and iFR/RFR were higher in women than men (FFR 0.86 vs. 0.80; *P* <0.001; iFR/RFR 0.92 vs. 0.90; *P* = 0.049), and men more frequently achieved positive results for both FFR and iFR/RFR (Table 2). In the analysis limited to lesions within LADs, women had higher FFR and iFR/RFR results than men, and results indicating significant ischemia were less common (Table 2). The prevalence of overall discordant results of FFR and iFR/RFR was similar between women and men (15.1% vs. 20.6%; *P* = 0.22). However, FFR-|iFR/RFR- concordant results were more common in women, while FFR+|iFR/RFR+ concordant results were more common in men (Figure 3). In men, eGFR, insulin-treated diabetes mellitus, and arterial hypertension were predictors of FFR+|iFR/RFR- discordance, and eGFR, insulin-treated diabetes mellitus, atrial fibrillation, and chronic obstructive pulmonary disease were predictors of FFR-|iFR/RFR+ discordance. No factors associated with either discordance were identified in women (Table 3).

ROC analysis confirmed the optimal cut-off point for FFR to identify patients with iFR/RFR ≤0.89 of 0.83 for women and 0.80 for men. Additionally, the optimal cut-off point for distinguishing groups with FFR ≤0.80 for iFR/RFR was 0.90 for women and 0.91 for men (Table 4).

Table 2. Results of vessel assessment in the study groups (per vessel)

Variable	Sex		*P*-value
	Female 106 (25.4%)	Male 311 (74.6%)	
Vessel assessed			
LAD, n (%)	65 (61.3)	184 (59.2)	0.70
non-LAD, n (%)	41 (38.7)	127 (40.8)	
All vessels			
FFR ≤0.80, n (%)	36 (34.0)	164 (52.7)	<0.001
FFR, median (IQR)	0.86 (0.77–0.90)	0.80 (0.75-0.86)	<0.001
iFR/RFR ≤0.89, n (%)	40 (37.7)	154 (49.5)	0.04
iFR/RFR, median (IQR)	0.92 (0.87–0.95)	0.90 (0.85-0.94)	0.049
LAD			
FFR ≤0.80, n (%)	26 (40.0)	123 (66.9)	0.001
FFR, median (IQR)	0.83 (0.77–0.88)	0.78 (0.73-0.83)	<0.001
iFR/RFR ≤0.89, n (%)	30 (46.2)	115 (62.5)	0.02
iFR/RFR, median (IQR)	0.90 (0.86–0.93)	0.88 (0.83-0.91)	0.02
Non-LAD			
FFR ≤0.80, n (%)	10 (24.4)	41 (32.3)	0.34
FFR, median (IQR)	0.89 (0.82–0.93)	0.84 (0.78-0.90)	0.03
iFR/RFR ≤0.89, n (%)	10 (24.4)	39 (30.7)	0.44
iFR/RFR, median (IQR)	0.94 (0.90–0.97)	0.93 (0.88-0.97)	0.69

Abbreviations: FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; IQR, interquartile range; LAD, left anterior descending artery; RFR, resting full-cycle ratio

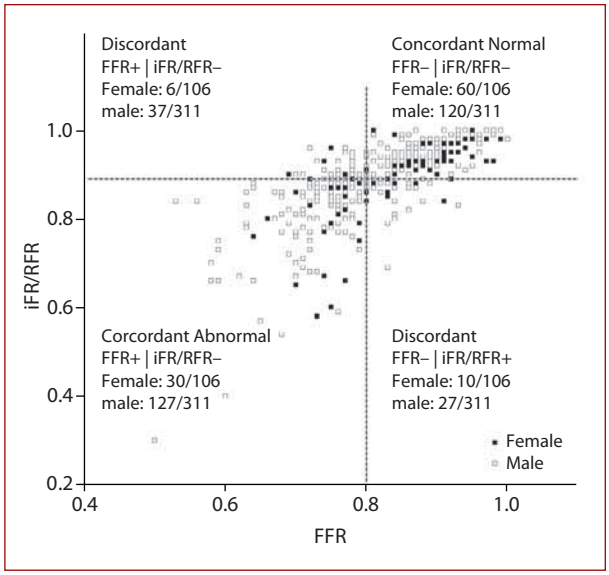

Figure 2. Fractional flow reserve and instantaneous wave-free ratio/resting full-cycle ratio results depending on sex

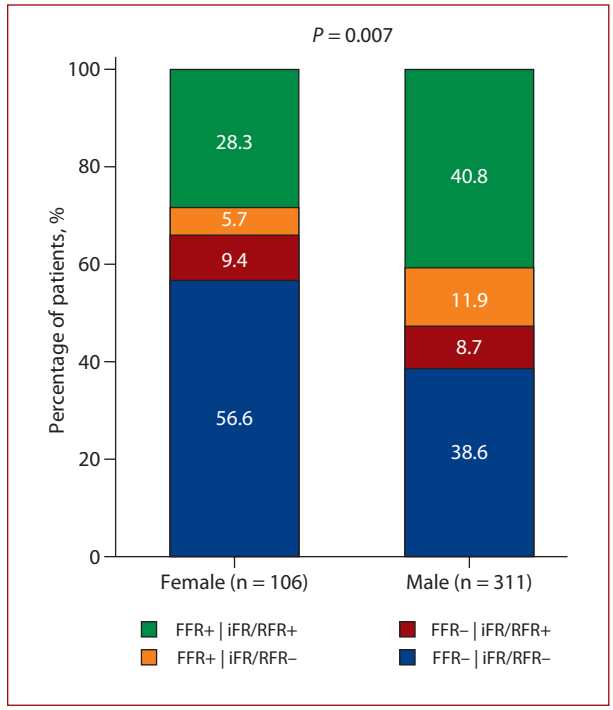

Figure 3. Frequency of different types of the discrepancy between fractional flow reserve and instantaneous wave-free ratio/resting full-cycle ratio stratified by sex

Abbreviations: FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; RFR, resting full-cycle ratio

DISCUSSION

We found that among assessed intermediate coronary stenoses, median FFR and iFR/RFR values were lower in men than in women. As a result, FFR and iFR/RFR values indicating significant ischemia were more common in men. However, sex was not identified as an independent predictor of FFR and iFR/RFR discordance.

Numerous randomized studies have shown that coronary revascularization guided by invasive measurements has better outcomes than revascularization guided by angiography alone [1, 3, 20]. Consequently, physiological testing of borderline coronary lesions with either hyperemic or non-hyperemic methods is recommended for identifying stenoses responsible for ischemia [1]. The iFR-SWEDEHEART [21] and DEFINE-FLAIR [22] studies confirmed the non-inferiority of iFR compared to FFR in assessing borderline coronary lesions, but the relative performance of these

Table 3. Univariable analysis for predictors of discordance between fractional flow reserve and instantaneous wave-free ratio/resting full-cycle ratio stratified by sex

Variables	*P*-value	Male crude OR (95% CI)	*P*-value	Female crude OR (95% CI)
Predictors of FFR+ | iFR/RFR- discordance				
eGFR per 1 ml/min/1.73 m^2	0.04	1.02 (1.01–1.03)	0.05	1.03 (0.99–1.06)
DM treatment (insulin vs. others)	0.02	0.20 (0.06–0.74)	–	–
Arterial hypertension (no vs. yes)	0.007	3.12 (1.37–7.08)	–	–
Predictors of FFR- | iFR/RFR+ discordance				
DM treatment (insulin vs. others)	0.047	5.14 (1.02–25.82)	0.07	5.83 (0.84–40.32)
AF (no vs. yes)	0.01	0.35 (0.15–0.80)	0.57	1.59 (0.32–7.96)
eGFR per 1 ml/min/1.73 m^2	0.02	0.98 (0.96–0.99)	0.95	1.00 (0.98–1.02)
COPD (no vs. yes)	0.002	0.20 (0.07–0.56)	0.97	1.05 (0.12–9.14)
Predictors of overall concordance				
AF (no vs. yes)	0.03	2.03 (1.07–3.85)	0.40	0.56 (0.15–2.13)

Abbreviations: AF, atrial fibrillation; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; IQR, interquartile range; OR, odds ratio; RFR, resting full-cycle ratio

Table 4. Receiver operating characteristic curves: classification accuracy of fractional flow reserve and instantaneous wave-free ratio/resting full-cycle ratio stratified by sex

	Optimal cut-off point	AUC (95% CI)	*P*-value
iFR/RFR to predict FFR ≤0.80			
Female	0.90	0.94 (0.88-0.98)	<0.001
Male	0.91	0.88 (0.84-0.91)	<0.001
FFR to predict iFR/RFR ≤0.89			
Female	0.83	0.90 (0.83-0.96)	<0.001
Male	0.80	0.88 (0.84-0.91)	<0.001

Abbreviations: AUC, the area under the curve; CI, confidence interval; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; RFR, resting full-cycle ratio

methods may be affected by sex [23, 24]. For instance, in DEFINE-FLAIR [25], the FFR-guided strategy was associated with a lower revascularization rate than the iFR-guided strategy in women, while this difference was not observed in men. Consistent with our study, FFR values were lower in men than women, and women had fewer functionally significant lesions [25]. However, iFR values were similar for both groups. Similarly, a study by Verdoia et al. evaluated 371 intermediate coronary stenoses in 325 patients undergoing coronary angiography and found that iFR values did not differ by sex [26]. In our study, iFR/RFR values were higher in women than men, but these differences were only marginally significant, possibly due to the inclusion of RFR-assessed patients.

Various factors might explain the higher FFR values in women than men, such as differences in myocardial masses, myocardial perfusion territories, vessel size, plaque structure, diastolic , and higher resting coronary blood flow in women [23, 24]. Additionally, women have higher resting coronary blood flow compared with men [27]. Thus, it may affect FFR measurement, which depends on net changes [3]. Microcirculatory disorders, more common in women, can also influence FFR values. A blunted coronary hyperemic response in patients with microvascular dysfunction could result in a smaller pressure gradient across a stenotic lesion and higher FFR values [16]. Women typically experience their first presentation of coronary artery disease about ten years later than men, often after menopause [24]. Older age is linked to a decrease in coronary flow reserve and an increase in microvascular resistance under hyperemia, which may lead to an underestimation of stenosis severity by FFR [28, 29]. Also, the absence of estrogens in postmenopausal women is thought to be related to the development and progression of microvascular dysfunction [30]. Female sex and older age are associated with the development of various comorbidities. In our study, women were more likely to have chronic kidney disease, resulting in lower eGFR observed in this group. Chronic kidney disease is associated with microcirculation damage and vessel calcifications; thus, the response to drugs inducing hyperemia may be falsified [16]. For instance, the FREAK study found a higher percentage of negative FFR values in patients with chronic kidney disease, suggesting a link between FFR results and creatinine levels [31]. Similarly, diabetes mellitus is often associated with diffuse vascular dysfunction in both large and micro-vessels [7, 18, 32–35]. Women have a longer life expectancy than men, so they are more likely to experience other age-related diseases, such as severe aortic stenosis [36]. Notably, in patients with severe aortic stenosis, FFR and iFR/RFR values may be affected by a falsely low aortic pressure due to the restricted orifice of the aortic valve [7, 16]. Furthermore, a reduced vasodilation ability in patients with severe aortic stenosis may result from myocardial hypertrophy, microvascular dysfunction, and elevated left ventricular end-diastolic pressure [16].

In previous research, we found discrepancies between FFR and iFR/RFR in 19.2% of assessed angiographically intermediate stenoses [19]. The present analysis revealed that sex was not associated with increased risk of discordant results. However, studies by Lee et al. [12], Arashi et al. [37], and Aoi et al. [38] identified female sex as an independent predictor of FFR+|iFR- discordance. Several clinical, angiographic, and hemodynamic factors can contribute to differences between FFR and iFR/RFR, including age, diabetes mellitus, chronic kidney disease, coronary artery stenosis location, atrial fibrillation, elevated left ventricular end-diastolic pressure, diastolic dysfunction, and microcirculation dysfunction [4, 10–14]. Microcirculation dysfunction is particularly prominent in women and is the strongest predictor [16]. For instance, Legutko et al. [39] found that microcirculation disorders were more prevalent in discrepant FFR/RFR vessels, independently of sex. In our study, both insulin-treated diabetes mellitus and eGFR were identified as predictors of FFR-|iFR/RFR+ discordance in men. As mentioned, diabetes mellitus and chronic kidney disease are associated with microcirculation dysfunction and more complex and diffused coronary disease and thus influence hyperemic response during FFR measurements. Our research suggests that not only the presence of diabetes mellitus but also its treatment and control may contribute to discrepancies. In addition, atrial fibrillation was a predictor of overall FFR vs. iFR/RFR discrepancy in men. A recent study highlighted increased beat-to-beat variability of individual iFR measurements in patients with atrial fibrillation, resulting in reduced reproducibility and increased lesion reclassification [40]. In contrast, FFR variability, reproducibility, and lesion reclassification were comparable between patients with atrial fibrillation and sinus rhythm. No predictors of discordance between FFR and iFR/RFR were identified in women, possibly due to a small sample size. In addition, microcirculatory dysfunction may be of particular importance in this subgroup.

The reliability of cut-off values of ≤0.80 for FFR and ≤0.89 for iFR/RFR indicating significant ischemia has been confirmed in numerous clinical studies [1, 3]. However, women tend to have higher FFR values at maximum hyperemia than men [23]. This discrepancy may be attributed to women's higher resting flow and more prevalent microcirculatory dysfunction. Previous studies on sex-related differences in FFR report an average difference of about 0.02 (0.01 to 0.04) between men and women [23, 25, 41]. Based on our study, an FFR cut-off of ≤0.83 seems reasonable for detecting ischemia-inducing lesions in women. On the other hand, in the DEFINE-FLAIR study [25], FFR-guided and iFR-guided strategies using standard cut-offs yielded similar clinical outcomes for both sexes. Clinicians should always take into account the influence of microcirculation dysfunction when interpreting FFR and iFR/RFR results [4, 16]. Notably, for women with borderline FFR values (0.80–0.83) and symptoms suggestive of ischemia, additional assessment of microvascular dysfunction using the index of myocardial resistance measurement should be strongly considered to guide treatment [23]. Microvascular disease is particularly concerning because it can contribute to adverse long-term cardiovascular outcomes even in the absence of significant coronary disease [42]. The suitability of applying a fixed FFR cut-off value for all patients is debatable and warrants further investigation.

Limitations

Our analysis is primarily limited by its small sample size and the imbalance between the number of women and men included. This may hinder assessment of the impact of comorbidities on FFR and iFR/RFR results in women. Additionally, the study did not include a noninvasive assessment of myocardial ischemia, which could have served as an additional reference technique. Furthermore, we did not have data on microcirculatory dysfunction, coronary flow reserve, concomitant valvular heart disease, or central venous pressure. We did not collect data on active and prior SARS-CoV-2 infections for this study, so their impact on FFR and iFR/RFR results was not evaluated. Lastly, the study did not provide quantitative coronary angiography analysis.

CONCLUSIONS

FFR and iFR/RFR results indicate that significant ischemia was more common in men than women when assessing intermediate coronary stenoses. Nevertheless, sex did not predict discordant results.

Article information

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REFERENCES

1. 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.
2. Siudak Z, Bartuś S, Hawranek M, et al. Interventional cardiology in Poland in 2021. Annual summary report of the Association of Cardiovascular Interventions of the Polish Cardiac Society (AISN PTK) and Jagiellonian University Medical College. Adv Cardiol Interv. 2022; 18(2): 87–89, doi: 10.5114/aic.2022.118523, indexed in Pubmed: 36051825.
3. Kogame N, Ono M, Kawashima H, et al. The impact of coronary physiology on contemporary clinical decision making. JACC Cardiovasc Interv. 2020; 13(14): 1617–1638, doi: 10.1016/j.jcin.2020.04.040, indexed in Pubmed: 32703589.
4. Michail M, Thakur U, Mehta O, et al. Non-hyperaemic pressure ratios to guide percutaneous coronary intervention. Open Heart. 2020; 7(2), doi: 10.1136/openhrt-2020-001308, indexed in Pubmed: 33004619.
5. Kumar G, Desai R, Gore A, et al. Real world validation of the nonhyperemic index of coronary artery stenosis severity-Resting full-cycle ratio-RE-VALIDATE. Catheter Cardiovasc Interv. 2020; 96(1): E53–E58, doi: 10.1002/ccd.28523, indexed in Pubmed: 31631521.

6. Kawase Y, Omori H, Tanigaki T, et al. In vivo validation of resting full-cycle ratio and diastolic pressure ratio: simultaneous measurement with instantaneous wave-free ratio. Cardiovasc Interv Ther. 2021; 36(1): 74–80, doi: 10.1007/s12928-020-00648-4, indexed in Pubmed: 32048184.
7. Dziewierz A, Rzeszutko Ł, Dudek D, et al. Impact of diabetes mellitus on the diagnostic performance of fractional flow reserve in patients with severe aortic stenosis. Kardiol Pol. 2022; 80(12): 1217–1223, doi: 10.33963/KP.a2022.0194, indexed in Pubmed: 35979641.
8. Berry C, van 't Veer M, Witt N, et al. VERIFY (VERification of Instantaneous Wave-Free Ratio and Fractional Flow Reserve for the Assessment of Coronary Artery Stenosis Severity in EverydaY Practice): a multicenter study in consecutive patients. J Am Coll Cardiol. 2013; 61(13): 1421–1427, doi: 10.1016/j.jacc.2012.09.065, indexed in Pubmed: 23395076.
9. Ziubryte G, Jarusevicius G. Fractional flow reserve, quantitative flow ratio, and instantaneous wave-free ratio: a comparison of the procedure-related dose of ionising radiation. Adv Cardiol Interv. 2021; 17(1): 33–38, doi: 10.5114/aic.2021.104765, indexed in Pubmed: 33868415.
10. Kobayashi Y, Johnson NP, Berry C, et al. The influence of lesion location on the diagnostic accuracy of adenosine-free coronary pressure wire measurements. JACC Cardiovasc Interv. 2016; 9(23): 2390–2399, doi: 10.1016/j.jcin.2016.08.041, indexed in Pubmed: 27838269.
11. Dérimay F, Johnson NP, Zimmermann FM, et al. Predictive factors of discordance between the instantaneous wave-free ratio and fractional flow reserve. Catheter Cardiovasc Interv. 2019; 94(3): 356–363, doi: 10.1002/ccd.28116, indexed in Pubmed: 30702186.
12. Lee JM, Rhee TM, Choi KiH, et al. Clinical outcome of lesions with discordant results among different invasive physiologic indices - resting distal coronary to aortic pressure ratio, resting full-cycle ratio, diastolic pressure ratio, instantaneous wave-free ratio, and fractional flow reserve. Circ J. 2019; 83(11): 2210–2221, doi: 10.1253/circj.CJ-19-0230, indexed in Pubmed: 31484836.
13. Lee JM, Shin ES, Nam CW, et al. Discrepancy between fractional flow reserve and instantaneous wave-free ratio: Clinical and angiographic characteristics. Int J Cardiol. 2017; 245: 63–68, doi: 10.1016/j.ijcard.2017.07.099, indexed in Pubmed: 28789845.
14. Lee SH, Choi KiH, Lee JM, et al. Physiologic characteristics and clinical outcomes of patients with discordance between FFR and iFR. JACC Cardiovasc Interv. 2019; 12(20): 2018–2031, doi: 10.1016/j.jcin.2019.06.044, indexed in Pubmed: 31563683.
15. Zasada W, Mikołajczyk F, Jędrychowska M, et al. Comparison of FFR, iFR, and QFR assessment in patients with severe aortic stenosis and coronary heart disease. Adv Cardiol Interv. 2022; 18(2): 118–121, doi: 10.5114/aic.2022.118527, indexed in Pubmed: 36051833.
16. Benenati S, De Maria GL, Scarsini R, et al. Invasive "in the cath-lab" assessment of myocardial ischemia in patients with coronary artery disease: When does the gold standard not apply? Cardiovasc Revasc Med. 2018; 19(3 Pt B): 362–372, doi: 10.1016/j.carrev.2018.01.005, indexed in Pubmed: 29429843.
17. Fogelson B, Tahir H, Livesay J, et al. Pathophysiological factors contributing to fractional flow reserve and instantaneous wave-free ratio discordance. Rev Cardiovasc Med. 2022; 23(2): 70, doi: 10.31083/j.rcm2302070, indexed in Pubmed: 35229561.
18. Rodríguez-Padial L, Moreu Burgos J, Barderas MG. Coronary flow reserve in degenerative aortic stenosis and diabetes mellitus: An intriguing question. Kardiol Pol. 2022; 80(12): 1187–1189, doi: 10.33963/KP.a2022.0256, indexed in Pubmed: 36621014.
19. Zdzierak B, Zasada W, Krawczyk-Ożóg A, et al. Comparison of fractional flow reserve with resting non-hyperemic indices in patients with coronary artery disease. J Cardiovasc Dev Dis. 2023; 10(2), doi: 10.3390/jcdd10020034, indexed in Pubmed: 36826530.
20. Berry C, McClure JD, Oldroyd KG. Meta-Analysis of death and myocardial infarction in the DEFINE-FLAIR and iFR-SWEDEHEART trials. Circulation. 2017; 136(24): 2389–2391, doi: 10.1161/CIRCULATIONAHA.117.030430, indexed in Pubmed: 28972006.
21. Montone RA, Minelli S, Aggarwal S, et al. Instantaneous wave-free ratio versus fractional flow reserve. N Engl J Med. 2017; 377(16): 1596–1597, doi: 10.1056/NEJMc1711333, indexed in Pubmed: 29045198.
22. Davies JE, Sen S, Dehbi HM, et al. Use of the instantaneous wave-free ratio or fractional flow reserve in PCI. N Engl J Med. 2017; 376(19): 1824–1834, doi: 10.1056/NEJMoa1700445, indexed in Pubmed: 28317458.
23. Tsao AL, Faxon DP. Fractional flow reserve: does sex matter? JACC Cardiovasc Interv. 2019; 12(20): 2047–2049, doi: 10.1016/j.jcin.2019.07.020, indexed in Pubmed: 31648765.
24. Lucà F, Abrignani MG, Parrini I, et al. Update on management of cardiovascular diseases in women. J Clin Med. 2022; 11(5), doi: 10.3390/jcm11051176, indexed in Pubmed: 35268267.
25. Kim CH, Koo BK, Dehbi HM, et al. Sex differences in instantaneous wave-free ratio or fractional flow reserve-guided revascularization strategy. JACC Cardiovasc Interv. 2019; 12(20): 2035–2046, doi: 10.1016/j.jcin.2019.06.035, indexed in Pubmed: 31648764.
26. Verdoia M, Nardin M, Viola O, et al. Impact of sex on the functional assessment of intermediate coronary lesions by instantaneous wave-free ratio. Cardiovasc Revasc Med. 2022; 37: 105–109, doi: 10.1016/j.carrev.2021.07.007, indexed in Pubmed: 34275742.
27. Kobayashi Y, Fearon WF, Honda Y, et al. Effect of sex differences on invasive measures of coronary microvascular dysfunction in patients with angina in the absence of obstructive coronary artery disease. JACC Cardiovasc Interv. 2015; 8(11): 1433–1441, doi: 10.1016/j.jcin.2015.03.045, indexed in Pubmed: 26404195.
28. Faria D, Mejia-Renteria H, Lee JM, et al. Age-related changes in the coronary microcirculation influencing the diagnostic performance of invasive pressure-based indices and long-term patient prognosis. Catheter Cardiovasc Interv. 2022; 100(7): 1195–1205, doi: 10.1002/ccd.30445, indexed in Pubmed: 36273417.
29. Kern MJ. Age and the cascade impact on coronary flow reserve (CFR) and discordance of fractional flow reserve and non-hyperemic pressure ratios (NHPR). Catheter Cardiovasc Interv. 2022; 100(7): 1206–1207, doi: 10.1002/ccd.30502, indexed in Pubmed: 36465005.
30. Tunc E, Eve AA, Madak-Erdogan Z. Coronary microvascular dysfunction and estrogen receptor signaling. Trends Endocrinol Metab. 2020; 31(3): 228–238, doi: 10.1016/j.tem.2019.11.001, indexed in Pubmed: 31787492.
31. Tebaldi M, Biscaglia S, Fineschi M, et al. Fractional flow reserve evaluation and chronic kidney disease: analysis from a multicenter italian registry (the FREAK study). Catheter Cardiovasc Interv. 2016; 88(4): 555–562, doi: 10.1002/ccd.26364, indexed in Pubmed: 26717890.
32. 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.
33. Dziewierz A, Zabojszcz M, Natorska J, et al. Dapagliflozin reduces plasma concentration of plasminogen activator inhibitor-1 in patients with heart failure with preserved ejection fraction and type 2 diabetes. Pol Arch Intern Med. 2022; 132(12), doi: 10.20452/pamw.16383, indexed in Pubmed: 36520466.
34. Fojt A, Kowalik R, Gierlotka M, et al. Three-year mortality after acute myocardial infarction in patients with different diabetic status. Pol Arch Intern Med. 2021; 131(11), doi: 10.20452/pamw.16095, indexed in Pubmed: 34581173.
35. Fojt AA, Kowalik RR, Gierlotka MM, et al. Impact of diabetes mellitus on outcomes in patients with myocardial infarction according to varying degrees of left ventricular systolic dysfunction. Kardiol Pol. 2022; 80(2): 172–181, doi: 10.33963/KP.a2022.0004, indexed in Pubmed: 34982833.
36. Setny M, Jankowski P, Kamiński K, et al. Secondary prevention of coronary heart disease in Poland: does sex matter? Results from the POLASPIRE survey. Pol Arch Intern Med. 2022; 132(3), doi: 10.20452/pamw.16179, indexed in Pubmed: 34935325.
37. Arashi H, Satomi N, Ishida I, et al. Hemodynamic and lesion characteristics associated with discordance between the instantaneous wave-free ratio and fractional flow reserve. J Interv Cardiol. 2019; 2019: 3765282, doi: 10.1155/2019/3765282, indexed in Pubmed: 31772528.
38. Aoi S, Toklu B, Misumida N, et al. Effect of sex difference on discordance between instantaneous wave-free ratio and fractional flow reserve. Cardiovasc Revasc Med. 2021; 24: 57–64, doi: 10.1016/j.carrev.2020.08.013, indexed in Pubmed: 32839130.
39. Legutko J, Niewiara L, Guzik B, et al. The impact of coronary microvascular dysfunction on the discordance between fractional flow reserve and resting full-cycle ratio in patients with chronic coronary syndromes. Front Cardiovasc Med. 2022; 9: 1003067, doi: 10.3389/fcvm.2022.1003067, indexed in Pubmed: 36277746.
40. Pintea Bentea G, Berdaoui B, Samyn S, et al. Reliability of fractional flow reserve and instantaneous wave-free ratio in assessing interme-

diate coronary stenosis in patients with atrial fibrillation. Am J Cardiol. 2022; 162: 105–110, doi: 10.1016/j.amjcard.2021.09.028, indexed in Pubmed: 34728064.
41. Shah SV, Zimmermann FM, Johnson NP, et al. Sex differences in adenosine-free coronary pressure indexes: a CONTRAST substudy. JACC Cardiovasc Interv. 2018; 11(15): 1454–1463, doi: 10.1016/j.jcin.2018.03.030, indexed in Pubmed: 30031722.
42. Taqueti VR, Hachamovitch R, Murthy VL, et al. Global coronary flow reserve is associated with adverse cardiovascular events independently of luminal angiographic severity and modifies the effect of early revascularization. Circulation. 2015; 131(1): 19–27, doi: 10.1161/CIRCULATIONAHA.114.011939, indexed in Pubmed: 25400060.

The impact of left circumflex coronary artery ostium stenosis on outcomes for patients after percutaneous coronary intervention for unprotected left main disease

Wojciech Jan Skorupski, Marta Kałużna-Oleksy, Przemysław Mitkowski, Aleksander Araszkiewicz, Włodzimierz Skorupski, Stefan Grajek, Małgorzata Pyda, Maciej Lesiak, Marek Grygier

Chair and 1st Department of Cardiology, Poznań University of Medical Sciences, Poznań, Poland

Correspondence to:
Wojciech Skorupski, MD,
1st Department of Cardiology,
Poznań University of Medical Sciences,
Długa 1/2, 61–848 Poznań, Poland,
phone: +48 61 854 92 22,
e-mail: wojtek.skorupski@wp.pl

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ABSTRACT

Background: The impact of left circumflex coronary artery (LCx) ostium atherosclerosis in left main coronary artery (LM) bifurcation disease is not well-known.

Aim: The study aimed to assess whether the involvement of LCx ostium carries prognostic implications in patients undergoing unprotected LM percutaneous coronary intervention (PCI).

Methods: Consecutive 564 patients with unprotected LM (ULMCA) disease who underwent LM PCI between January 2015 and February 2021, with at least 1 year of available follow-up were included in the study. The first group was composed of 145 patients with ULMCA disease with LCx ostium stenosis, and the second group consisted of 419 patients with ULMCA disease without LCx ostium stenosis.

Results: Patients in the group with ULMCA disease with LCx ostium stenosis were significantly older and had more comorbidities. The two-stent technique was used more often in the group with LCx ostium stenosis (62.8% vs. 14.6%; P <0.001). During 7-year follow-up, all-cause mortality did not differ significantly between groups with and without LCx ostium stenosis (P = 0.50). The use of one-stent or two-stent technique also did not impact mortality in patients with LCx ostial lesions (P = 0.75). Long-term mortality subanalysis for three groups of patients: (1) patients with LM plus LCx ostium stenosis; (2) LM plus left anterior descending artery (LAD) ostium stenosis; (3) LM plus LCx ostium plus LAD ostium stenosis also did not differ significantly (P = 0.63).

Conclusions: LCx ostium involvement in LM disease PCI is not associated with adverse long-term outcomes, which is highly beneficial for the Heart Team's decision-making process.

Key words: left circumflex coronary artery ostium, percutaneous coronary intervention, unprotected left main coronary artery

INTRODUCTION

Percutaneous coronary intervention (PCI) in left main coronary artery (LM) disease is widely used worldwide with documented favorable results in large studies. However, the impact of left circumflex coronary artery (LCx) ostium atherosclerosis in LM bifurcation disease is not well-known. Evidence from computed tomography angiography and fractional flow reserve (FFR) shows that the side branch supplies a smaller portion of the myocardium compared to the main branch and that a stenosis in the side branch is less likely to result in significant ischemia compared to a similar stenosis in the main artery [1]. Nevertheless, side branch occlusion is one of the most significant potential complications after LM stenting and may be a major reason why operators choose the two-stent technique [2]. Significant ostium stenosis of the side branch has also been reported to be a frequent source of side branch occlusion after stent implantation in the main vessel [3]. The European Bifurcation Club advocates use of the "jailing wire" technique which involves leaving a wire in the side branch while a stent

WHAT'S NEW?

The impact of left circumflex coronary artery (LCx) ostium atherosclerosis in left main coronary artery (LM) bifurcation disease is not well-known. This study aimed to evaluate whether the involvement of LCX ostium significantly influences outcomes of patients undergoing unprotected LM percutaneous coronary intervention (PCI). The main finding is that the LCX ostium involvement in LM disease PCI is not associated with long-term mortality, which is highly beneficial for the Heart Team's decision-making process. In patients with LM disease and LCx ostium stenosis, there is no significant difference in long-term mortality between groups operated on using one-stent or two-stent techniques. No significant differences in long-term mortality were observed regardless of the presence of coexisting lesions in the LCX ostium or left anterior descending artery ostium. A subgroup of patients without significant LCX ostium disease who underwent LCX stenting during LM PCI because of the plaque burden shift or carina shift presents favorable long-term outcomes.

is implanted in the main branch [4]. The study based on a small group showed that the patients with higher FFR in the jailed LCX had better long-term results than those with low FFR [5]. In terms of the one-stent technique in LM PCI, two mechanisms of acute luminal loss at the ostium of the left circumflex coronary artery have been suggested, i.e. carina shift and plaque shift [6–8]. Angioplasty in the area of huge atherosclerotic plaque around the bifurcation often results in plaque burden shifting to the coronary branch, sometimes causing subsequent occlusion [9]. However, recent articles demonstrated that the carina shift was the principal mechanism of ostial LCX lumen loss during LM PCI [10]. In the study performed by Kang et al., carina shift was associated with a narrow distal angle between the LAD and the LCX and a wide proximal angle between the LCX and the LM [10].

In this study, we aimed to assess whether the involvement of LCX ostium carries prognostic implications in patients undergoing unprotected LM PCI.

METHODS

Our study is part of a larger project concerning LM disease [11–13]. Currently, we analyzed all 564 patients with unprotected LM (ULMCA) disease PCI and with at least 1 year of available follow-up. Patients with significant LM stenosis (≥50% diameter) were prospectively enrolled in the study between January 2015 and February 2021 [14]. An ostial LCX lesion was defined as a lesion with at least 50% diameter stenosis by visual assessment and within 3 mm of the left main stem. Patients were divided into two groups: the first group was composed of 145 patients with unprotected LM disease with LCX ostium stenosis and the second group consisted of 419 patients with unprotected LM disease without LCX ostium stenosis. Established primary outcomes were in-hospital death, in-hospital myocardial infarction (MI), and long-term all-cause death (median [interquartile range (IQR)] follow-up was 1411 (IQR, 908 [max 2553] days). Survival analysis data were gathered by telephone contact or with the use of National Health Fund information. IVUS or OCT imaging were used in 202 (35.8%) patients and were not analyzed in great detail. The antiplatelet regimens were low-dose aspirin (75 mg daily) and clopidogrel (75 mg daily) for a minimum of 6 months after PCI, with the intention of 12 months of dual antiplatelet therapy. In patients without contraindications, a switch to ticagrelor or prasugrel was allowed.

Statistical analysis

All continuous variables were presented as medians (interquartile range [IQR]). Categorical variables were presented as numbers and percentages and were compared using the test for proportions or Fisher's exact test. The normality of the distribution of variables was assessed using the Shapiro-Wilk test. Differences between continuous variables were evaluated with a nonparametric Mann-Whitney test. The survival probability at follow-up was calculated using the Kaplan-Meier method. Log-rank tests were used to compare survival between different groups. *P*-values below 0.05 were considered significant. We used STATISTICA 13.7 (StatSoft, Inc., Tulsa, OK, US).

RESULTS

Patients in the group with ULMCA disease with LCX ostium stenosis were older (median [IQR], 69.0 [65.0–79.0] years vs. 68.0 [62.0–74.0] years; $P = 0.002$) (Table 1). In this group, comorbidities such as chronic kidney disease (44.8% vs. 28.6%; $P < 0.001$), diabetes (46.9% vs. 36.8%; $P = 0.03$), and previous stroke (13.1% vs. 7.9%; $P = 0.06$) were found more often. Naturally, the SYNTAX score was higher in the group with LCX ostium stenosis (28.0 [22.25–34.0] vs. 21 [14.0–28.0]; $P < 0.001$), also LM calcifications were found more often in this group (19.3% vs. 11.5%; $P = 0.02$). The number of implanted stents (2.0 [2.0–3.0] vs. 1.0 [1.0–2.0]; $P < 0.001$), total stent length (46.0 [36.0–64.0] vs. 33.0 [22.0–50.0]; $P < 0.001$), radiation time (19.5 [14.0–26.0] vs. 15.0 [11.0–21.0]; $P < 0.001$), and radiation dose (1436.5 [969–2151] vs. 1120.5 [706.5–1722.5]; $P < 0.001$) were higher in patients with LCX ostium lesions (Table 2). The two-stent technique was used more often in the group with LCX ostium stenosis (62.8% vs. 14.6%; $P < 0.001$). The trend toward more frequent use of crush techniques was observed in the group with LCX ostium involvement. Provisional stenting was performed more often in the group without LCX ostial disease. There were no differences between two study groups in terms of periprocedural complications, periprocedural mortality,

Table 1. Study population baseline characteristics

Variable	Patients with unprotected LM disease with LCX ostium stenosis (n = 145)	Patients with unprotected LM disease without LCX ostium stenosis (n = 419)	*P*-value
Age, year, median (IQR)	69.0 (65.0–79.0)	68.0 (62.0–74.0)	0.002
Sex, female, n (%)	38 (26.2)	104 (24.8)	0.74
Hypertension, n (%)	123 (84.8)	344 (82.1)	0.45
CKD, n (%)	65 (44.8)	120 (28.6)	<0.001
DM, n (%)	68 (46.9)	154 (36.8)	0.03
Stroke/TIA, n (%)	19 (13.1)	33 (7.9)	0.06
PVD, n (%)	27 (18.6)	61 (14.6)	0.25
AF, n (%)	26 (17.9)	58 (13.8)	0.23
Prior MI, n (%)	68 (46.9)	205 (48.9)	0.67
Stable angina, n (%)	76 (52.4)	239 (57.0)	0.33
Unstable angina, n (%)	35 (24.1)	119 (28.4)	0.32
NSTEMI, n (%)	28 (19.3)	55 (13.1)	0.07
STEMI, n (%)	6 (4.1)	15 (3.6)	0.76
Prior PCI LAD, n (%)	38 (26.2)	98 (23.4)	0.49
Prior PCI LCX, n (%)	27 (18.6)	66 (15.8)	0.42
Prior PCI RCA, n (%)	38 (26.2)	137 (32.7)	0.15
LVEDD, mm, median (IQR)	50.0 (47.0–56.0)	50.0 (46.0–55.0)	0.42
LVEF, %, median (IQR)	50.0 (45.0–60.0)	55.0 (45.0–60.0)	0.18
Coronary artery disease characteristics			
SYNTAX score, median (IQR)	28.0 (22.25–34.0)	21 (14.0–28.0)	<0.001
LM trifurcation, n (%)	23 (15.9)	50 (11.9)	0.22
LM calcification, n (%)	28 (19.3)	48 (11.5)	0.02
RCA recessive (a), n (%)	11 (7.6)	32 (7.6)	0.98
RCA with critical stenosis (b), n (%)	30 (20.7)	56 (13.4)	0.03
RCA total occlusion (c), n (%)	22 (15.2)	66 (15.8)	0.87
Lack of RCA support for LMCAD (a+b+c), n (%)	63 (43.4)	154 (36.8)	0.15

Abbreviations: AF, atrial fibrillation; DM, diabetes mellitus; CABG, coronary artery bypass graft; CAD, coronary artery disease; CKD, chronic kidney disease; LAD, left anterior descending; LCx, left circumflex; LM, left main; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PVD, peripheral vascular disease; PCI, percutaneous coronary intervention; RCA, right coronary artery; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischemic attack

Table 2. Left main percutaneous coronary intervention procedure characteristics

Variable	Patients with unprotected LM disease with LCX ostium stenosis (n = 145)	Patients with unprotected LM disease without LCX ostium stenosis (n = 419)	*P*-value
Number of stents, median (IQR)	2.0 (2.0–3.0)	1.0 (1.0–2.0)	< 0.001
Total length of implanted stents, mm, median (IQR)	46.0 (36.0–64.0)	33.0 (22.0–50.0)	< 0.001
Radiation time, min, median (IQR)	19.5 (14.0–26.0)	15.0 (11.0–21.0)	< 0.001
Radiation dose, mGy, median (IQR)	1436.5 (969–2151)	1120.5 (706.5–1722.5)	< 0.001
Contrast volume, ml, median (IQR)	250.0 (200–300)	227.5 (190–300)	0.13
Stenting LM bifurcation, n (%)	145 (100)	363 (86.6)[a]	–
One-stent technique, n (%)	54 (37.2)	310 (85.4)	< 0.001
Two-stents technique, n (%)	91 (62.8)	53 (14.6)	
Two-stents techniques	n = 91	n = 53	
Crush/DK-crush, n (%)	56 (61.5)	24 (45.3)	0.071
Cullote, n (%)	2 (2.2)	0 (0)	
T-stenting, n (%)	17 (18.7)	8 (15.1)	
Provisional stenting, n (%)	16 (17.6)	21 (39.6)	
IVUS/OCT, n (%)	36 (24.8)	166 (39.6)	0.001

[a]In this group, the percentages do not add up to 100% because not all patients underwent LM bifurcation percutaneous coronary intervention

Abbreviations: IVUS, intravascular ultrasound; LM, left main, DK-crush, double kissing crush technique; OCT, optical coherence tomography

and myocardial infarction type 4a. Median patient (IQR) follow-up was 1411 (908–2553) days. At 7-year follow-up, all-cause mortality between groups with and without LCX ostium stenosis did not differ ($P = 0.50$) (Figure 1). There was no difference in long-term all-cause mortality in patients with LCX ostial lesions who underwent procedures with either one-stent or two-stent technique ($P = 0.75$) (Figure 2). In our cohort, there were some patients without significant LCX ostium disease who underwent LCX stenting during LM PCI (13.4% of patients from the group without LCX ostium involvement) because of the plaque burden shift or carina shift; long-term results of these patients were satisfactory (Figure 3). Subanalysis for three groups of patients: (1) patients with LM plus LCX ostium

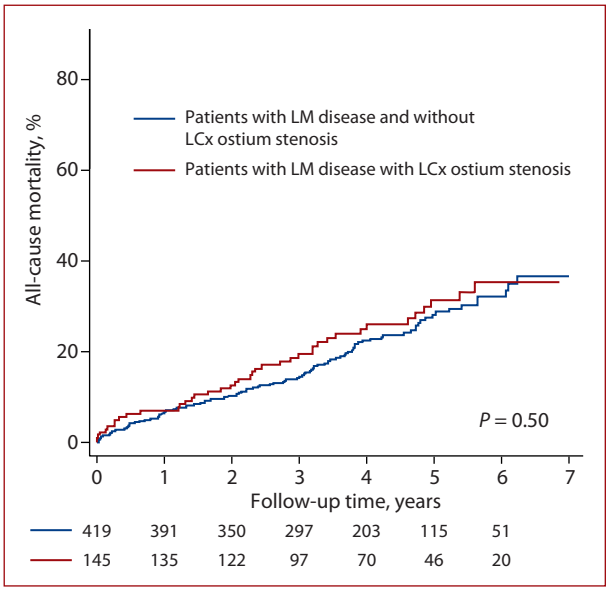

Figure 1. Kaplan-Meier analysis of all-cause mortality: patients with unprotected LM disease with LCx ostium stenosis vs. patients with unprotected LM disease without LCx ostium stenosis

Abbreviations: see Table 1

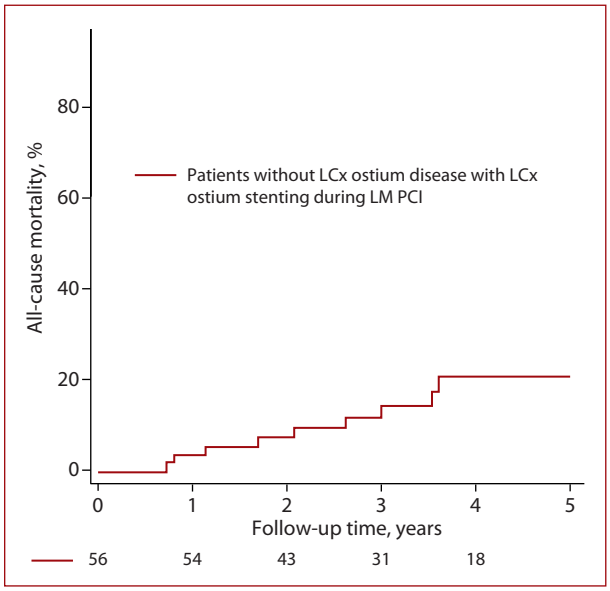

Figure 3. Kaplan-Meier analysis of all-cause mortality: patients without LCx ostium disease with LCx ostium stenting during LM PCI

Abbreviations: see Table 1

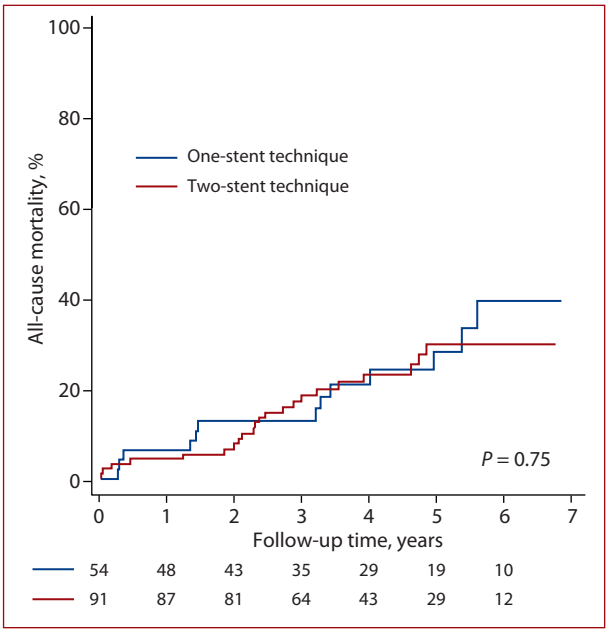

Figure 2. Kaplan-Meier analysis of all-cause mortality: one-stent vs. two-stent technique in patients with unprotected LM disease with LCx ostium stenosis

Abbreviations: see Table 1

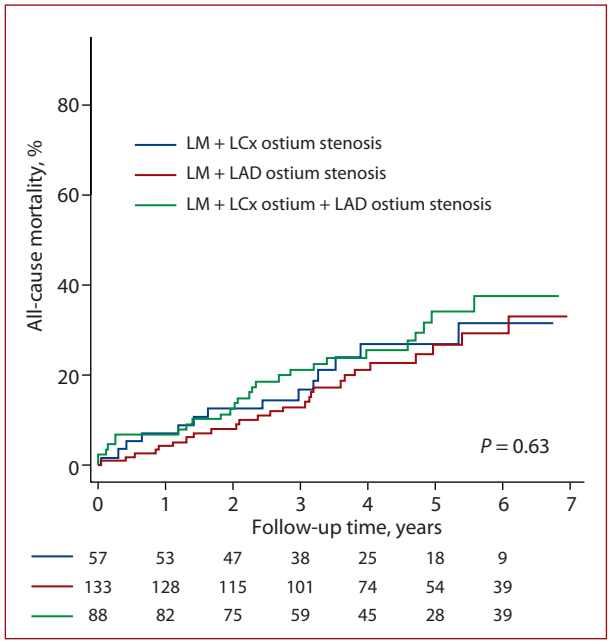

Figure 4. Kaplan-Meier analysis of all-cause mortality: LM + LCx ostium stenosis vs. LM + LAD ostium stenosis vs. LM + LCx ostium + LAD ostium stenosis

Abbreviations: see Table 1

stenosis, (2) LM plus LAD ostium stenosis, (3) LM plus LCX ostium plus LAD ostium stenosis was performed. Long-term mortality rates also did not differ in these groups ($P = 0.63$) (Figure 4).

DISCUSSION

The choice of stenting strategy in LM PCI is generally determined by the stenosis at the LCX ostium, atherosclerotic lesion length, and/or difficult coronary artery side branch access. These situations generally require initial use of two-stent strategies. Bailout stenting of a diseased coronary side branch can often be more demanding than opting for an up-front two-stent strategy. In other LM bifurcation cases, a provisional stenting strategy is usually chosen [15]. In the study performed by Park et al. [16], a group of patients with true bifurcation lesions had a significantly higher risk of major adverse cardiovascular events than those with non-true bifurcations (HR, 1.39; 95% CI, 1.08–1.80; $P = 0.01$); however, this study was not performed only on the LM disease population. Moreover, patients with Medina 1-0-1 had a lower

risk of cardiac death and MI than other patients with true bifurcation lesions [16]. Nevertheless, the LCX is not always last in the order of numbers in the Medina classification. In subanalysis from the EXCEL trial in 524 patients, both LM major side branches i.e. the LAD and LCX had ostial diameter stenosis ≥50% in 34.7% of cases [17]. In patients who underwent provisional stenting, a bailout stent was implanted in 28.6% of those with and 12.1% without both side branches ostium stenoses (P = 0.0005) [17]. Bailout stenting was performed in 1 in 6 cases in EXCEL, although it was needed more often when the major coronary side branch, usually the LCX, had ostium stenosis. In EXCEL, all-cause mortality rates were insignificantly lower in the group with LM bifurcation without involvement of both side branches ostia treated with the provisional approach vs. planned two-stent technique (6.1% vs. 13.0%; hazard ratio [HR], 0.46; 95% CI, 0.21–1.01). However, one- and two-stent techniques in LM disease, where both ostial coronary side branches were affected, resulted in comparable mortality rates [17]. In the EBC MAIN study, patients with true bifurcation of left main stem lesions who underwent PCI using the stepwise layered provisional method had fewer major cardiac incidents compared to planned dual stenting, although the difference was not statistically significant [18]. Therefore, the stepwise provisional approach should continue to be the preferred option for intervention in bifurcation of the distal left main stem [18].

Study limitations

One limitation of our study was the absence of a surgical group for comparison. Nevertheless, examining such a group alongside the coronary artery bypass grafting (CABG) group was not within the study's intended scope. Additionally, while the study was based on a prospective registry, not all clinical data were accessible. Thirdly, the follow-up did not include analysis of the antiplatelet regimen or duration of dual antiplatelet therapy (DAPT) after discharge. Lastly, intravascular imaging (IVUS or OCT) were not analyzed in great detail.

CONCLUSIONS

In this study, we evaluated whether the involvement of LCX ostium significantly influences the results in real-world patients undergoing unprotected LM PCI. As far as we know, this is the first study to assess this issue broadly. The main finding of the study is that the LCX ostium involvement in LM disease PCI is not associated with increased long-term mortality, which is highly beneficial for the Heart Team's decision-making process. Moreover, in patients with LM disease and LCX ostium stenosis, there was no significant difference in long-term mortality between groups operated on using one-stent or two-stent techniques. Also, there were no significant differences in long-term mortality regardless of coexisting LCX ostium or LAD ostium lesions. An interesting subgroup of patients without significant LCX ostium disease who underwent LCX stenting during LM PCI, because of the plaque burden shift or carina shift, also presented good long-term outcomes.

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REFERENCES

1. Kim HY, Doh JH, Lim HS, et al. Identification of coronary artery side branch supplying myocardial mass that may benefit from revascularization. JACC Cardiovasc Interv. 2017; 10(6): 571–581, doi: 10.1016/j.jcin.2016.11.033, indexed in Pubmed: 28259665.
2. Gwon HC, Song YB, Pan M. The story of plaque shift and carina shift. EuroIntervention. 2015; 11 Suppl V: V75–V77, doi: 10.4244/EIJV11SVA16, indexed in Pubmed: 25983177.
3. Fischman DL, Savage MP, Leon MB, et al. Fate of lesion-related side branches after coronary artery stenting. J Am Coll Cardiol. 1993; 22(6): 1641–1646, doi: 10.1016/0735-1097(93)90589-s, indexed in Pubmed: 8227832.
4. Banning AP, Lassen JF, Burzotta F, et al. Percutaneous coronary intervention for obstructive bifurcation lesions: the 14th consensus document from the European Bifurcation Club. EuroIntervention. 2019; 15(1): 90–98, doi: 10.4244/EIJ-D-19-00144, indexed in Pubmed: 31105066.
5. Lee CH, Choi SW, Hwang J, et al. 5-year outcomes according to FFR of left circumflex coronary artery after left main crossover stenting. JACC Cardiovasc Interv. 2019; 12(9): 847–855, doi: 10.1016/j.jcin.2019.02.037, indexed in Pubmed: 31072505.
6. Gil RJ, Vassilev D, Formuszewicz R, et al. The carina angle-new geometrical parameter associated with periprocedural side branch compromise and the long-term results in coronary bifurcation lesions with main vessel stenting only. J Interv Cardiol. 2009; 22(6): E1–E10, doi: 10.1111/j.1540-8183.2009.00492.x, indexed in Pubmed: 19702678.
7. Shimada Y, Courtney BK, Nakamura M, et al. Intravascular ultrasonic analysis of atherosclerotic vessel remodeling and plaque distribution of stenotic left anterior descending coronary arterial bifurcation lesions upstream and downstream of the side branch. Am J Cardiol. 2006; 98(2): 193–196, doi: 10.1016/j.amjcard.2006.01.073, indexed in Pubmed: 16828591.
8. Vassilev D, Gil R. Clinical verification of a theory for predicting side branch stenosis after main vessel stenting in coronary bifurcation lesions. J Interv Cardiol. 2008; 21(6): 493–503, doi: 10.1111/j.1540-8183.2008.00400.x, indexed in Pubmed: 18973506.
9. Nakamura S, Hall P, Maiello L, et al. Techniques for Palmaz-Schatz stent deployment in lesions with a large side branch. Cathet Cardiovasc Diagn. 1995; 34(4): 353–361, doi: 10.1002/ccd.1810340217, indexed in Pubmed: 7621549.
10. Kang SJ, Mintz G, Kim WJ, et al. Changes in left main bifurcation geometry after a single-stent crossover technique. Circ Cardiovasc Interv. 2011; 4(4): 355–361, doi: 10.1161/circinterventions.110.961045, indexed in Pubmed: 21712525.
11. Skorupski WJ, Grygier M, Araszkiewicz A, et al. The impact of right coronary artery support on outcomes of patients with unprotected left main disease undergoing percutaneous coronary intervention. Kardiol Pol. 2021; 79(6): 631–637, doi: 10.33963/KP.15972, indexed in Pubmed: 33909388.
12. Kałużna-Oleksy M, Skorupski WJ, Grygier M, et al. A personalized approach to percutaneous coronary interventions in the left main coronary artery-is the female gender associated with worse outcomes? J Pers Med. 2021; 11(6), doi: 10.3390/jpm11060581, indexed in Pubmed: 34203081.
13. Skorupski WJ, Kałużna-Oleksy M, Lesiak M, et al. Short- and long-term outcomes of left main coronary artery stenting in patients disqualified

from coronary artery bypass graft surgery. J Pers Med. 2022; 12(3), doi: 10.3390/jpm12030348, indexed in Pubmed: 35330348.
14. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. Considerations for the choice between coronary artery bypass grafting and percutaneous coronary intervention as revascularization strategies in major categories of patients with stable multivessel coronary artery disease: an accompanying article of the task force of the 2018 ESC/EACTS guidelines on myocardial revascularization. Eur Heart J. 2019; 40(2): 204–212, doi: 10.1093/eurheartj/ehy532, indexed in Pubmed: 30165435.
15. Collet C, Capodanno D, Onuma Y, et al. Left main coronary artery disease: pathophysiology, diagnosis, and treatment. Nat Rev Cardiol. 2018; 15(6): 321–331, doi: 10.1038/s41569-018-0001-4, indexed in Pubmed: 29599504.
16. Park TK, Park YH, Song YB, et al. Long-term clinical outcomes of true and non-true bifurcation lesions according to medina classification- results from the COBIS (Coronary Bifurcation Stent) II registry. Circ J. 2015; 79(9): 1954–1962, doi: 10.1253/circj.CJ-15-0264, indexed in Pubmed: 26134457.
17. Kandzari DE, Gershlick AH, Serruys PW, et al. Outcomes among patients undergoing distal left main percutaneous coronary intervention. Circ Cardiovasc Interv. 2018; 11(10): e007007, doi: 10.1161/CIRCINTERVENTIONS.118.007007, indexed in Pubmed: 30354633.
18. Hildick-Smith D, Egred M, Banning A, et al. The European bifurcation club Left Main Coronary Stent study: a randomized comparison of stepwise provisional vs. systematic dual stenting strategies (EBC MAIN). Eur Heart J. 2021; 42(37): 3829–3839, doi: 10.1093/eurheartj/ehab283, indexed in Pubmed: 34002215.

Outcomes of coronary revascularization vs. optimal medical therapy alone for ischemic left ventricular dysfunction: A meta-analysis of randomized controlled trials

Kamil Bujak[1, 2], Bartosz Hudzik[1], Łukasz Pyka[1], Michał Skrzypek[3], Salvatore Brugaletta[2], Manel Sabaté[2], Mateusz Tajstra[1], Jacek Legutko[4, 5], Wojciech Wojakowski[6], Mariusz Gąsior[1]

[1]3rd Department of Cardiology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland
[2]Hospital Clinic, Cardiovascular Clinic Institute, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Barcelona, Spain
[3]Department of Biostatistics, Faculty of Health Sciences in Bytom, Medical University of Silesia, Katowice, Poland
[4]Clinical Department of Interventional Cardiology, John Paul II Hospital, Kraków, Poland
[5]Department of Interventional Cardiology, Institute of Cardiology, Jagiellonian University Medical College, Kraków, Poland
[6]Department of Cardiology and Structural Heart Diseases, Medical University of Silesia, Katowice, Poland

Correspondence to:
Kamil Bujak, MD,
3rd Department of Cardiology,
Faculty of Medical Sciences in Zabrze,
Medical University of Silesia,
M Skłodowskiej-Curie 9, 41–800 Zabrze, Poland,
phone: +48 32 37 33 860,
e-mail: k.bujak@sccs.pl

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INTRODUCTION

Coronary artery disease (CAD) is the most frequent cause of heart failure with reduced ejection fraction worldwide. Observations that a large proportion of patients with ischemic heart failure have areas of dysfunctional-yet-viable myocardium have led to the hypothesis that coronary revascularization might improve left ventricular function and outcomes in this population [1].

Randomized controlled trials (RCTs) published in recent years did not demonstrate a significant superiority of routine coronary revascularization in patients with stable CAD over optimal medical therapy (OMT) [2]. However, patients with left ventricular systolic dysfunction (LVSD), who might potentially benefit the most from revascularization, were mainly excluded from these trials. Only a few RCTs compared coronary revascularization with OMT alone in patients with severe LVSD.

To the best of our knowledge, no meta-analysis has summarized the results of these trials. Therefore, we aimed to perform a meta-analysis comparing outcomes following coronary revascularization (both percutaneous and surgical) with OMT alone in patients with LVSD based on the latest available evidence from RCTs.

METHODS

This systematic review was prospectively registered in the PROSPERO (International Prospective Register of Systematic Reviews) database (CRD42022379549) and conformed to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [3].

PubMed and Scopus were systematically searched for original articles published in English before December 8, 2022. The search strategy is presented in Supplementary material, *Table S1*. Articles were eligible for inclusion in this meta-analysis if they presented results of RCTs comparing coronary revascularization (coronary bypass surgery [CABG] or percutaneous coronary intervention [PCI]) with OMT alone in patients with severe LVSD (left ventricular ejection fraction of 35% or less). If multiple reports from the same RCTs were available, papers presenting the longest follow-up were included in the meta-analysis.

The following data were extracted from eligible reports: clinical trial name, publication year, sample size, inclusion and exclusion criteria, mode of revascularization, data on the baseline and angiographic characteristics, event rates, and hazard ratios (HRs) with corresponding 95% confidence intervals (CI).

Subsequently, the included studies were assessed for bias using the Cochrane risk-of-bias tool for randomized trials version 2 (RoB 2). Any discrepancies between the two co-authors who independently searched for eligible papers, extracted data, and assessed data for bias were resolved by consensus.

The primary outcome of interest was cardiovascular death. Secondary outcomes included death from any cause and death from any cause or hospitalization for heart failure. All analyzed endpoints were defined according to the study protocols.

Statistical analysis

Random effects inverse variance meta-analysis was conducted based on estimates (i.e., log HR) and standard errors. Log HR and standard errors were calculated from HRs, and the corresponding 95% CI extracted from analyzed reports. If HRs and 95% CIs were unavailable, estimates and standard errors were calculated using reconstructed individual patient data from Kaplan-Meier survival curves using the freely available online tool: *IPDfromKM Shiny app* (https://www.trialdesign.org/one-page-shell.html#IPDfromKM). Heterogeneity was tested using Cochrane Q statistics. Publication bias was not assessed due to the small number of included studies. All statistical analyses were performed in *R* version 4.2.0 (R Core Team. R: A Language and Environment for Statistical Computing, https://www.r-project.org) with package *meta*. Relative treatment effects were presented as HR with 95% CI. A two-tailed *P*-value of <0.05 was considered significant.

RESULTS AND DISCUSSION

An electronic search revealed 4 762 records, and after removing duplicates, the titles and abstracts of 3 499 records were screened for eligibility. Nineteen records were selected for full-text assessment, and 3 RCTs that enrolled 2 050 patients followed up for a weighted mean of 7.3 years fulfilled the inclusion criteria of this meta-analysis [4–6]. The PRISMA flowchart is presented in Supplementary material, *Figure S1*, and details on the included studies are presented in Supplementary material, *Table S2*. The risk of bias was low in all included studies. The baseline characteristics of patients included in these trials are summarized in Supplementary material, *Table S3*.

Two of the three included reports provided data on the primary endpoint of cardiovascular death. Coronary revascularization was associated with reduced risk of primary endpoint compared to OMT alone (HR, 0.81; 95% CI, 0.70–0.94; *P* <0.01); (Figure 1A). There was also a trend toward a lower risk of death from any cause in patients who underwent revascularization (HR, 0.88; 95% CI, 0.78–1.01; *P* = 0.06); (Figure 1B). However, there was no difference between treatment strategies regarding the composite endpoint of death from any cause or hospitalization for heart failure (Figure 1C). Event rates according to study groups are presented in Supplementary material, *Table S4*. No significant statistical heterogeneity was identified regarding any of the analyzed outcomes.

The main finding of our meta-analysis is that coronary revascularization might be associated with improved survival, mainly driven by reduced cardiovascular mortality in patients with severe LVSD. This finding is in line with the data from observational studies, which were summarized in the recent meta-analysis [1]. However, some important limitations should be acknowledged. First, the results of only three RCTs comparing revascularization with OMT have been published to date. The STICHES trial, an extended follow-up study of the STICH trial, which had the most significant impact on the pooled estimates for all analyzed endpoints in this meta-analysis, evaluated only surgical revascularization. This trial demonstrated a reduced mortality rate in revascularized patients at ten years of follow-up. The REVIVED-BCIS2 trial, which compared OMT to PCI, demonstrated similar efficacy in terms of the primary endpoint of death from any cause or hospitalization for heart failure. Only the HEART trial studied both modes of revascularization in the invasive strategy arm but enrolled only 138 of the planned 800 patients because of the withdrawal of funding.

An open question remains whether the benefit of both modes of revascularization in patients with LVSD is similar. Contemporary RCTs have shown the superiority of CABG over PCI in patients with higher disease burden and lesion complexity, which is often the case in patients with ischemic heart failure [7]. However, patients with severe LVSD were underrepresented or excluded from these trials. Because severe LVSD and high comorbidity burden accompanying heart failure strongly increase perioperative risks, the results of these trials should not be translated to patients with severely impaired ventricular function. Unfortunately, no RCTs compared PCI against CABG in this population to date. The only available evidence comes from observational studies, which showed similar all-cause mortality in patients treated with PCI using drug-eluting stents in comparison to CABG [1].

Second, most of the analyzed patients in this meta-analysis were enrolled in the RCTs over a decade ago. Meanwhile, substantial progress in OMT was made. This might diminish the potential benefits from a revascularization strategy. On the other hand, the outcomes of patients treated invasively, mainly with PCI, improved as well, owing to broader utilization of newer generation stents and physiology- and imaging-guided revascularization [8].

Finally, considering the small number of included RCTs, statistical tools used in meta-analysis might be underpowered to assess between-study heterogeneity. For the same reason, we were unable to perform any meta-regression or subgroup analyses to identify the groups of patients who benefit the most from revascularization.

In conclusion, coronary revascularization in addition to OMT seems to be associated with reduced cardiovascular mortality in patients with severely impaired left ventricular

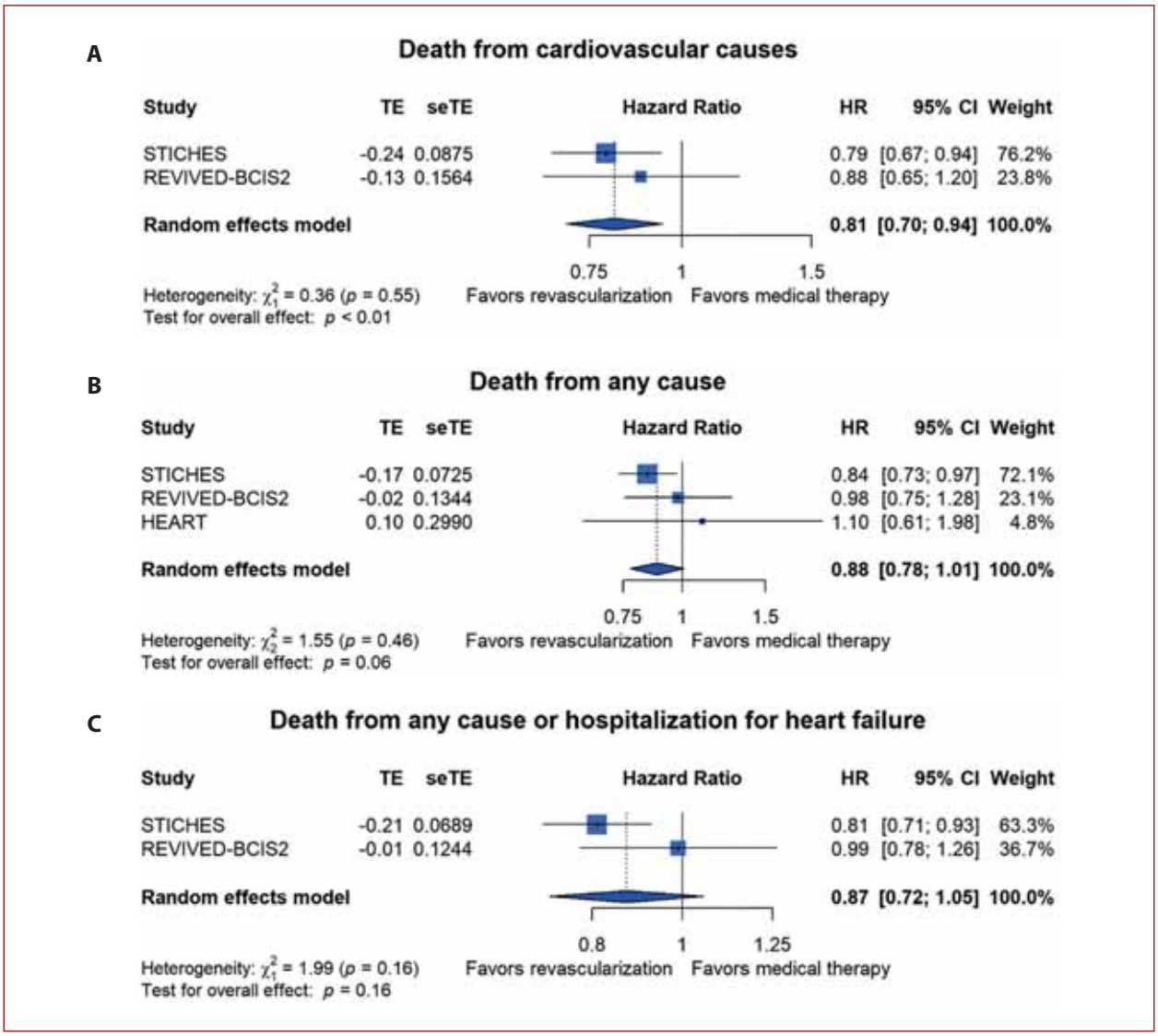

Figure 1. Forest plots presenting the meta-analysis results for primary (**A**) and secondary outcomes (**B, C**)

Abbreviations: CI, confidence interval; HEART, Heart Failure Revascularisation Trial; HR, hazard ratio; REVIVED-BCIS2, Revascularization for Ischemic Ventricular Dysfunction Trial; seTE, standard error of treatment estimate; STICHES, Surgical Treatment for Ischemic Heart Failure Extension Study; TE, estimate of treatment effect

function. However, whether this effect is independent of the mode of revascularization remains unclear.

Supplementary material

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

Article information

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REFERENCES

1. Yokoyama Y, Fukuhara S, Mori M, et al. Network meta-analysis of treatment strategies in patients with coronary artery disease and low left ventricular ejection fraction. J Card Surg. 2021; 36(10): 3834–3842, doi: 10.1111/jocs.15850, indexed in Pubmed: 34310729.
2. Nguyen DD, Spertus JA, Alexander KP, et al. Management of Coronary Disease in Patients with Advanced Kidney Disease. N Engl J Med. 2020; 382(17): 1608–1618, doi: 10.1056/NEJMoa1915925, indexed in Pubmed: 32227756.
3. Page MJ, McKenzie JE, Bossuyt PM, et al. Updating guidance for reporting systematic reviews: development of the PRISMA 2020 statement. J Clin Epidemiol. 2021; 134(3): 103–112, doi: 10.1016/j.jclinepi.2021.02.003, indexed in Pubmed: 33577987.
4. Perera D, Clayton T, O'Kane PD, et al. Percutaneous revascularization for ischemic left ventricular dysfunction. N Engl J Med. 2022; 387(15): 1351–1360, doi: 10.1056/NEJMoa2206606, indexed in Pubmed: 36027563.

5. Velazquez EJ, Lee KL, Jones RH, et al. Coronary-Artery bypass surgery in patients with ischemic cardiomyopathy. N Engl J Med. 2016; 374(16): 1511–1520, doi: 10.1056/NEJMoa1602001, indexed in Pubmed: 27040723.
6. Cleland JGF, Calvert M, Freemantle N, et al. The Heart Failure Revascularisation Trial (HEART). Eur J Heart Fail. 2011; 13(2): 227–233, doi: 10.1093/eurjhf/hfq230, indexed in Pubmed: 21156659.
7. Thuijs DJ, Davierwala P, Milojevic M, et al. Percutaneous coronary intervention versus coronary artery bypass grafting in patients with three-vessel or left main coronary artery disease: 10-year follow-up of the multicentre randomised controlled SYNTAX trial. Lancet. 2019; 394(10206): 1325–1334, doi: 10.1016/S0140-6736(19)31997-X, indexed in Pubmed: 31488373.
8. Banning AP, Serruys P, De Maria GL, et al. Five-year outcomes after state-of-the-art percutaneous coronary revascularization in patients with de novo three-vessel disease: final results of the SYNTAX II study. Eur Heart J. 2022; 43(13): 1307–1316, doi: 10.1093/eurheartj/ehab703, indexed in Pubmed: 34617993.

The efficacy and safety of predischarge initiation of angiotensin receptor/neprilysin inhibitor in patients with severe left ventricular dysfunction hospitalized for acute decompensated heart failure: Single-center experience

Marcin Książczyk, Małgorzata Lelonek

Department of Noninvasive Cardiology, Medical University of Lodz, Łódź, Poland

Correspondence to:
Marcin Książczyk, MD,
Department of Noninvasive Cardiology,
Medical University of Lodz,
Żeromskiego 113, 90–549 Łódź, Poland,
phone: +48 42 639 35 71,
e-mail:
marcin_ksiazczyk@interia.pl

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INTRODUCTION

Each episode of acute decompensated heart failure (ADHF) is related to a worsening of prognosis in patients with heart failure (HF) with reduced ejection fraction (HFrEF), which results from developing or progressing dysfunction of vital organs [1]. The period following ADHF and peridischarge days is called the early vulnerable phase. An initiation of optimal medical therapy (OMT) in this phase improves outcomes after ADHF [2]. Thus, the 2021 European Society of Cardiology guidelines highlight the need for OMT in patients with HFrEF and ADHF as soon as possible to reduce mortality and rehospitalization risk [3, 4]. TRANSITION was the first while PIONEEF-HF was the second randomized and multicentre trial to confirm that initiation of angiotensin receptor/neprilysin inhibitor (ARNI) after hemodynamic stabilization in patients with HFrEF and ADHF might be effective and safe [5, 6]. The results of those studies were fundamental in introducing ARNI in patients with HFrEF and ADHF [7].

Our study aimed to assess the efficacy and safety of predischarge initiation of ARNI in patients hospitalized for ADHF, especially in those with severe left ventricular (LV) dysfunction.

METHODS

We conducted a retrospective observational real-life single-center study that enrolled patients hospitalized and followed in the Department of Noninvasive Cardiology of the Medical University of Lodz between 2019 and 2021. The institutional review board approved the study (approval no. RNN/208/21/KE). The study enrolled 42 patients meeting the following inclusion criteria: (1) hospitalization for ADHF; (2) hemodynamic stability; (3) left ventricular ejection fraction (LVEF) ≤40%; (4) no prior therapy with ARNI. The exclusion criteria were: (1) age <18 years old; (2) estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2; (3) serum potassium >5.4 mmol/l; (4) history of angioedema or hypersensitivity to angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB); (5) history of heart transplant (HTx) or ventricular assist device (VAD); (6) significant aortic or mitral valve disease (except for functional mitral regurgitation) or other significant structural heart diseases; (7) postpartum cardiomyopathy; (8) severe pulmonary disease; (9) severe liver disease.

Patients enrolled in the study were receiving HFrEF therapy, including ACEI/ARB, beta-blockers, mineralocorticoid receptor antagonists (MRA), and, when indicated, diuretics and cardiac devices; 2 patients in the studied population were ACEI/ARB naïve.

All patients who achieved hemodynamic stability, defined as no need for intravenous diuretics or inotropes for ≥24 hours and systolic blood pressure (SBP) ≥100 mm Hg, received ARNI ≥12 hours before discharge. ARNI was initiated both for ACEI/ARB-naïve patients and those treated with ACEI/ARB. ACEI/ARB treatment was stopped before ARNI initiation. The starting dose and up-titration to the target dose or maximum tolerated one was as per label recommendations [8].

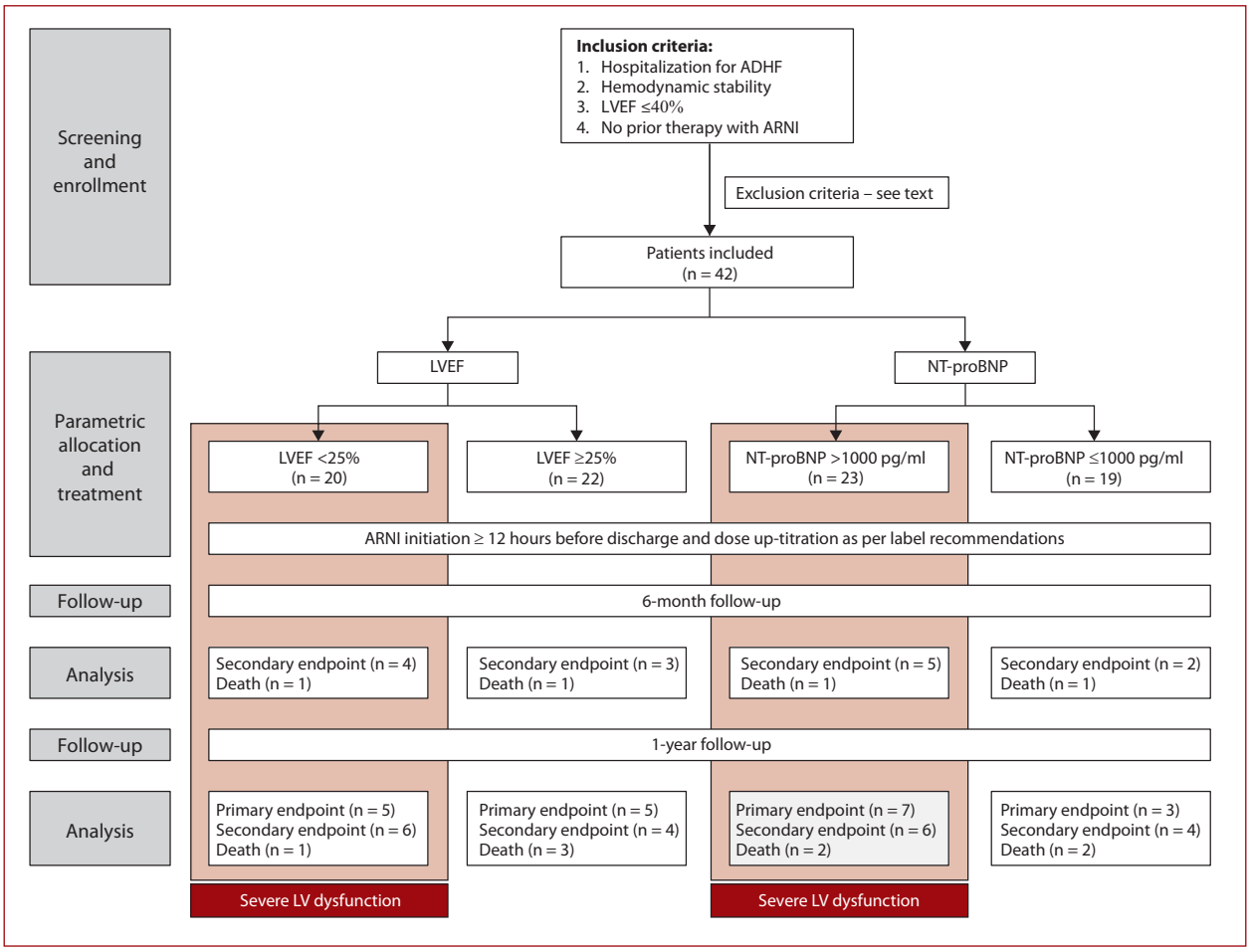

Figure 1. Study flowchart

Abbreviations: ADHF, acute decompensated heart failure; ARNI, angiotensin receptor/neprilysin inhibitor; LV, left ventricle; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide

At baseline, a complete history, selected lab tests, electrocardiogram, and transthoracic echocardiography were taken. Subjects were followed for 1 year with mandatory on-site visits at months 6 and 12 and mandatory phone calls or optional on-site visits at months 3 and 9 after discharge. Such events as hospitalization for HF (HHF), acute kidney injury (AKI), HTx, or death were monitored during follow-up. Mortality data were obtained both from a proxy if subjects were lost to follow-up or from the records if subjects died during index HHF.

We aimed to establish the efficacy and safety of predischarge ARNI initiation regarding LVEF and N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) values. The cut-off values for severe LV dysfunction were chosen as LVEF <25% [9] or NT-proBNP >1000 pg/ml [10]. Packer et al. [9] and Zile et al. [10] suggest that patients with LVEF <25% or NT-proBP >1000 pg/ml have a higher risk of HHF and death. The LVEF <25% and LVEF ≥25% groups and then the NT-proBNP >1000 pg/ml and ≤1000 pg/ml groups were compared.

The primary endpoint was composed of death or HHF within 1 year of follow-up. A secondary endpoint was composed of ≤50% of the target dose or drug discontinuation within 6 or 12 months of follow-up.

The baseline characteristics of the studied population were compared with the predischarge initiation group in the TRANSITION study.

The study flowchart is shown in Figure 1.

Statistical analysis

Baseline characteristics of participants were presented as means with standard devitions (SD) or medians with interquartile ranges depending on distribution for continuous variables or as numbers of subjects and percentages for categorical variables. Distribution of continuous variables was evaluated using the Shapiro-Wilk test. To compare differences between groups Student's, Welch's, U Mann-Whitney, χ^2, and Fischer's tests were used. A *P*-value <0.05 was deemed significant. All analyses were made using R statistical package version 4.0.2.

RESULTS AND DISCUSSION

A comparison of participant characteristics between groups at baseline regarding LVEF or NT-proBNP is presented in Supplementary material, *Table S1* and *S2*. Patients with LVEF <25% at baseline had a significantly more frequent history of 1-year HHF, higher Meta-Analysis Global Group in

Chronic Heart Failure (MAGGIC) score and 1-year mortality, NT-proBNP values, LV diameters/volumes, and lower tricuspid annular plane systolic excursion (TAPSE). Patients with NT-proBNP >1000 pg/ml at baseline had significantly more frequent history of 1-year HHF and recorded atrial fibrillation, higher MAGGIC score and 1-year mortality, proximal right ventricular diameter (RVD) and systolic pulmonary artery pressure (SPAP), lower SBP, diastolic blood pressures (DBP), LVEF and TAPSE.

In patients with severe LV dysfunction, we observed a lower frequency of target dose and a higher frequency of medium dose of ARNI achieved during the follow-up. Irrespective of LV dysfunction severity, at least 82% and 76% of all participants achieved the target dose at months 6 and 12, respectively. Interestingly, none of the participants was on dose 24/26 mg at follow-up points. It suggests that a well-tolerated dose of 24/26 mg allowed for its safe up-titration. ARNI dose reduction during the study (permanent or temporary) was observed more often in the group with severe LV dysfunction. The main reason for dose reduction was hypotension, which achieved significance in patients with NT-proBNP >1000 pg/ml ($P = 0.02$).

The frequency of all monitored events was similar irrespective of LVEF or NT-proBNP values, except for HHF. This was more frequent in patients with severe LV dysfunction.

The study endpoint occurrence rate was higher in patients with severe LV dysfunction (Supplementary material, *Tables S3–S4*).

Patients enrolled in the study were at high risk of death and/or HHF related to being in the vulnerable phase [2]. On the other hand, it is well known that use of all fundamental therapy drugs, including ARNI, in populations with severe LV dysfunction might be limited due to the tendency for lower blood pressure, especially after ADHF in the predischarge period [2-4].

A comparison of baseline characteristics between the predischarge initiation group in the TRANSITION study and the studied population is presented in Supplementary material, *Table S5*. The studied population was younger and had lower LVEF, higher New York Heart Association (NYHA) class and eGFR. What is more, in the studied population there were more cases of ischemic HF and higher percentage of HFrEF therapy, including ACEI/ARB, beta-blockers, MRA, diuretics, and cardiac devices. The comparison with the TRANSITION study seems reasonable because both studies involved the European population [5, 11].

Our study shows that ARNI is well tolerated in patients with severe LV dysfunction hospitalized for ADHF, and its initiation before discharge might be effective and safe.

Limitations

The study was carried out with a proportionate but relatively small group of patients during the 2019 coronavirus disease outbreak. Therefore, univariate or multivariate analyses were not feasible. The real-life and single-center protocol makes the study less reliable compared with randomized trials, i.e. the TRANSITION study. The study was conducted before flozins were established as a fundamental part of OMT in HF patients.

Supplementary material

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

Article information

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REFERENCES

1. Biegus J, Moayedi Y, Saldarriaga C, et al. Getting ahead of the game: in-hospital initiation of HFrEF therapies. Eur Heart J Suppl. 2022; 24(Suppl L): L38–L44, doi: 10.1093/eurheartjsupp/suac120, indexed in Pubmed: 36545227.
2. Gracia E, Singh P, Collins S, et al. The vulnerable phase of heart failure. Am J Ther. 2018; 25(4): e456–e464, doi: 10.1097/MJT.0000000000000794, indexed in Pubmed: 29985824.
3. Lelonek M, Grabowski M, Kasprzak JD, et al. An expert opinion of the Heart Failure Association of the Polish Cardiac Society on the 2021 European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic heart failure: Heart failure guidelines from a national perspective. Kardiol Pol. 2022; 80(2): 239–246, doi: 10.33963/KP.a2022.0021, indexed in Pubmed: 35076082.
4. McDonagh TA, Metra M, Adamo M, et al. ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021; 42: 3599–3726, doi: 10.1093/eurheartj/ehab368, indexed in Pubmed: 34447992.
5. Witte KK, Wachter R, Senni M, et al. Rationale and design of TRANSITION: a randomized trial of pre-discharge vs. post-discharge initiation of sacubitril/valsartan. ESC Heart Fail. 2018; 5(2): 327–336, doi: 10.1002/ehf2.12246, indexed in Pubmed: 29239515.
6. DeVore AD, Braunwald E, Morrow DA, et al. Angiotensin-Neprilysin inhibition in acute decompensated heart failure. N Engl J Med. 2019; 380(6): 539–548, doi: 10.1056/NEJMoa1812851, indexed in Pubmed: 30415601.
7. Seferovic PM, Ponikowski P, Anker SD, et al. Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2019; 21(10): 1169–1186, doi: 10.1002/ejhf.1531, indexed in Pubmed: 31129923.
8. Entresto, INN-sacubitril/valsartan. Summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/entresto-epar-product-information_en.pdf. First authorisation: 19 Nov 2015. Latest renewal: 25 Jun 2020. Accessed: 7 Mar 2023.
9. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med. 2001; 344(22): 1651–1658, doi: 10.1056/NEJM200105313442201, indexed in Pubmed: 11386263.
10. Zile MR, Claggett BL, Prescott MF, et al. Prognostic implications of changes in N-terminal pro-B-type natriuretic peptide in patients with heart failure. J Am Coll Cardiol. 2016; 68(22): 2425–2436, doi: 10.1016/j.jacc.2016.09.931, indexed in Pubmed: 27908347.
11. Straburzyńska-Migaj E, Dudek M, Kałużna-Oleksy M, et al. Comparison of the population of Polish patients participating in the TRANSITION study with the international population: a post-hoc analysis. Pol Arch Intern Med. 2023 [Epub ahead of print], doi: 10.20452/pamw.16410, indexed in Pubmed: 36633194.

Three varieties of sense-B-noise, a novel cause of inappropriate shocks in patients treated with a subcutaneous cardioverter-defibrillator

Szymon Budrejko, Maciej Kempa, Agnieszka Zienciuk–Krajka, Ludmiła Daniłowicz-Szymanowicz

Department of Cardiology and Electrotherapy, Faculty of Medicine, Medical University of Gdańsk, Gdańsk, Poland

Correspondence to:
Szymon Budrejko, MD, PhD, Department of Cardiology and Electrotherapy, Faculty of Medicine, Medical University of Gdańsk, Smoluchowskiego 17, 80–214, Gdańsk, Poland,
phone: +48 58 349 39 10,
e-mail: budrejko@gumed.edu.pl

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INTRODUCTION

The subcutaneous cardioverter-defibrillator (S-ICD), located outside the cardiovascular system, has been developed to provide primary or secondary protection against sudden cardiac death. That feature allows for a reduction in the rate of lead-related complications and infections, typical of transvenous systems. For that reason, S-ICD therapy expanded worldwide. It was adopted in Poland in 2014 [1] and is successfully used nowadays in selected patients not requiring cardiac pacing [2]. Nonetheless, a significant rate of inadequate shocks due to oversensing of T-waves, noise, and myopotentials remains an issue despite improvements in sensing algorithms.

Sensing and detection of the device rely on three electrical poles – two on the lead (distal sensing ring A and proximal sensing ring B) and the third on the can. Signals recorded between any two of them are called sensing vectors (primary [B to can], secondary [A to can], or alternate [A to B]). Recently, a novel clinical entity of inappropriate sensing has been identified in some of S-ICD recipients despite no apparent mechanical lead failure. It was named "sense-B-noise", as it is related to sensing vectors involving sensing ring B (primary or alternate). Clinical presentation is related to oversensing of noise in ECG signals, and inappropriate shocks delivered by the device. The phenomenon has been so far described in one series of six cases, where intermittent signal saturation, diminished QRS amplitudes, and disappearance of the artifacts after the inappropriate shock were deemed typical of that new entity [3]. Those characteristics may be important for differential diagnosis with other possible reasons for inappropriate shocks, such as, for example, electromagnetic interference (EMI).

METHODS

We present a series of three patients, who received S-ICD systems in our Department and who suffered from complications that were diagnosed as sense-B-noise during follow-up. Each of those three patients had a slightly different clinical picture of the same underlying problem.

RESULTS AND DISCUSSION

The first male patient with hypertrophic cardiomyopathy received an S-ICD in 2016 at the age of 39 for primary prevention of sudden cardiac death (SCD). Preoperative screening was positive for all three sensing vectors. The implanted system consisted of an A219 S-ICD device and 3401 lead (neither of them subject to any recall). The alternate sensing vector with 1x gain and Smart Pass filter on, as well as 210/230 bpm detection zones (conditional/non-conditional, respectively) were programmed. In 2018 he was admitted to a hospital in his residence area for inappropriate shocks (IAS) due to suspected noise. The first IAS occurred at an underground train station but the other three during transfer to the hospital; all of them without any symptoms suggestive of arrhythmia. The noise could not be reproduced with any maneuvers and was not consistent with EMI, and X-ray imaging did not reveal any lead failure. During surgical inspection, no abnormalities were found, so the system was explanted in one block (with the lead connected to the can), exchanged

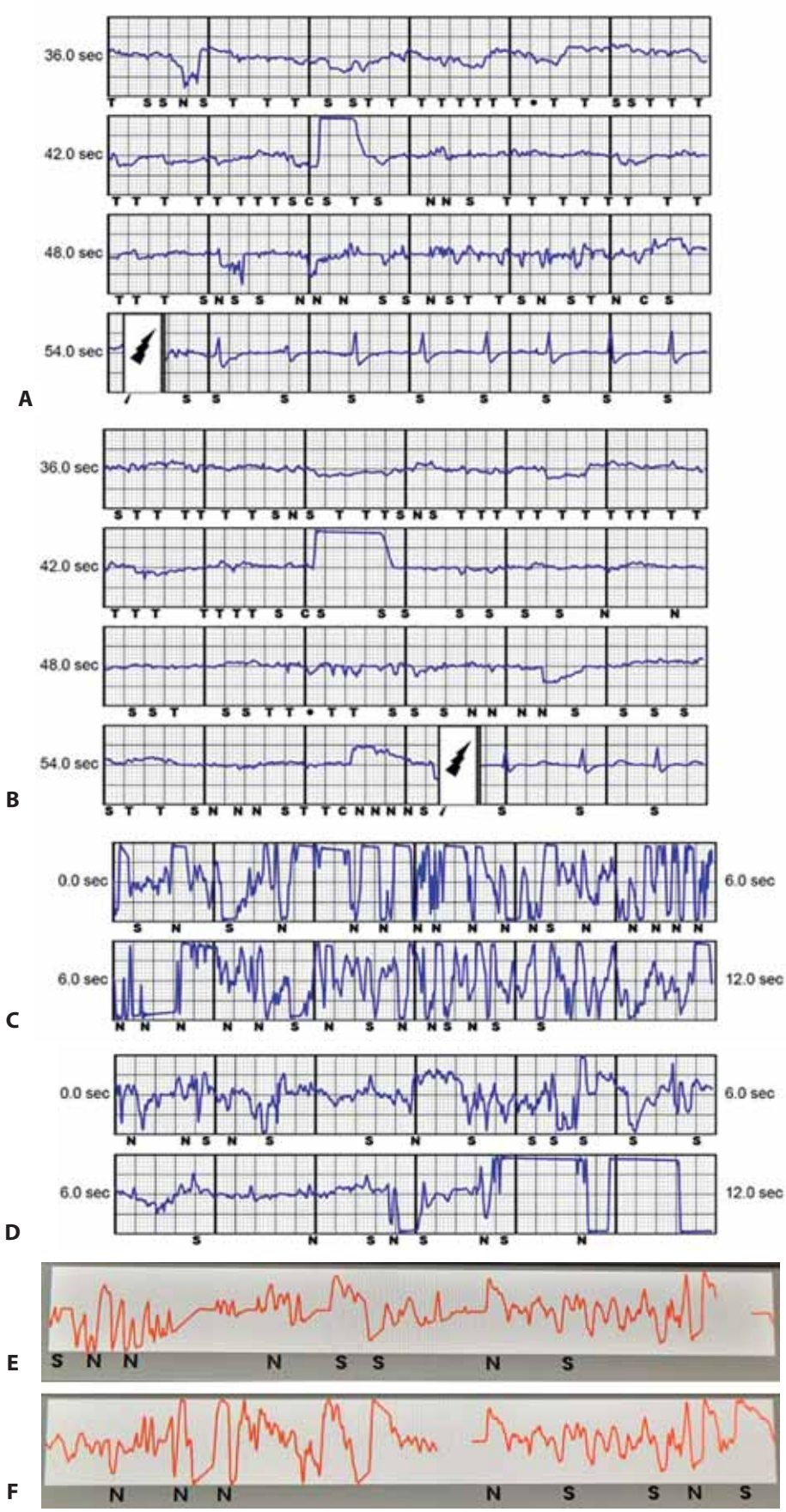

Figure 1. A, B. Two examples of inappropriate shocks due to noise oversensing in a patient with a subcutaneous implantable cardioverter-defibrillator (Patient 3, primary sensing vector). Note the noise itself, with a reduction of QRS amplitude, signal saturation, and normalization of signals immediately after shocks. **C, D.** Two examples of noise recorded as non-sustained episodes, without high-voltage therapy (Patient 2, alternate sensing vector). **E, F.** Similar noise observed during device interrogation and body position change from supine to sitting (Patient 3, alternate sensing vector)

for a new one, and the explanted system was sent to the manufacturer for investigation. No system failure was reported, the manufacturer proposed, as an explanation, sense-B-noise, and that diagnosis was finally accepted by our clinical team.

The second male patient with non-ischemic cardiomyopathy and left ventricular ejection fraction (LVEF) of 30% received an S-ICD for primary prevention in 2020 at the age of 40 (A219 device, 3401 lead, alternate sensing vector with 1× gain, Smart Pass on, 220/250 bpm detection zones). All three vectors were positive on screening. The lead was later subject to a recall, and the patient was included in the remote monitoring system. During follow-up, non-sustained episodes of noise were recorded by the device (Figure 1), all of them during the patient's normal life activity, with no suspected EMI. There was no apparent lead damage on X-ray imaging. The noise could not be reproduced with any provocative maneuvers. The manufacturer, similar to the first case, suggested sense-B-noise as the possible explanation and offered reprogramming to the secondary sensing vector as a solution. The patient refused to have the device reprogrammed and requested system replacement (being previously informed about the lead recall issue). His device was extracted in one block, and a new system was implanted during the same surgical procedure. Inspection of the explanted system by the manufacturer did not reveal any failure, and the sense-B-noise issue was again reported to us as the final diagnosis.

The third male patient received his S-ICD system in July 2022 for primary prevention (A219 device, 3501 lead, no recall, 210/230 bpm detection zones). He was 34 years old and suffered from heart failure due to left ventricular non-compaction. His LVEF was 10% at the moment of implantation despite optimal medical therapy. All three vectors were acceptable on pre-implant ECG screening, and the primary vector was automatically selected by the device (1× gain, Smart Pass on). The patient experienced 11 inappropriate shocks in December 2022, during normal activity at home, with no evidence of EMI. Oversensing of noise, with reduction of QRS amplitude, signal saturation, and normalization of signals immediately after shocks were found in recordings of the episodes at device interrogation (Figure 1). Those features are typical of sense-B-noise, so, on the basis of our previous experience, that was the initial diagnosis. But during interrogation of the device, the same noise could be seen in the live ECG window (alternate sensing vector active at that time), which was less indicative of sense-B-noise, but rather of lead failure. No apparent lead damage was found on the chest X-ray. The patient requested discontinuation of S-ICD therapy, his LVEF had improved to 45% by that time, and therefore the system was explanted and returned to the manufacturer for inspection. Thorough investigation did not reveal any electrical or mechanical failure of the lead or any other part of the system, so the sense-B-noise was eventually considered the most likely diagnosis reported back to us by the manufacturer.

Available data regarding that new clinical entity (the sense-B-noise issue) are scarce, and the manufacturer has not yet officially released any report on the evidence collected so far.

In the only available case series [3], patients had oversensing of noise and inappropriate shocks, which was also the case in our patients 1 and 3. What was different in our patient 3 is that the same noise could be observed during device interrogation although randomly (most likely during body position change). Our initial suspicion of lead failure was not confirmed either by X-ray or inspection of the explanted system by the manufacturer, and sense-B-noise was accepted as the final diagnosis. Conversely, patient 2 had non-sustained episodes of noise, without shocks, which has not been reported before. It is not known whether non-sustained episodes might foretell the sustained ones, with inappropriate shocks, or, in other words, if the sense-B-noise phenomenon might be progressive in the course of time.

The absence of mechanical lead failure in S-ICD recipients does not exclude noise oversensing. On the other hand, recorded noise is not always consistent with lead failure. Therefore, the sense-B-noise issue should be remembered and included in differential diagnosis in S-ICD patients presenting with inappropriate shocks. At the moment, there are no data on how to solve this problem, and any further guidance from the manufacturer is keenly awaited. As for now, we deemed the recommendation to reprogram the device into the secondary vector unsatisfactory. As long as we do not understand the nature of the phenomenon, we cannot accept any partial solution that does not offer absolute certainty that it will work.

Article information

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REFERENCES

1. Kaczmarek K, Zwoliński R, Bartczak K, et al. A subcutaneous implantable cardioverter-defibrillator - the first implantation in Poland. Kardiol Pol. 2015; 73(1): 62, doi: 10.5603/KP.2015.0010, indexed in Pubmed: 25625342.
2. Kempa M, Budrejko S, Tajstra M, et al. Subcutaneous implantable cardioverter-defibrillator therapy in Poland: Results of the Polish S-ICD Registry. Kardiol Pol. 2023; 81(5): 455–462, doi: 10.33963/KP.a2023.0046, indexed in Pubmed: 36871295.
3. Haeberlin A, Burri H, Schaer B, et al. Sense-B-noise: an enigmatic cause for inappropriate shocks in subcutaneous implantable cardioverter defibrillators. Europace. 2023; 25(2): 767–774, doi: 10.1093/europace/euac202, indexed in Pubmed: 36353759.

Real-life implementation of guidelines for heart failure management

Iwona Gorczyca-Głowacka[1], Agnieszka Mastalerz-Migas[2], Małgorzata Lelonek[3]

[1]Collegium Medicum, Jan Kochanowski University in Kielce, Kielce, Poland
[2]Department of Family Medicine, Wroclaw Medical University, Wrocław, Poland
[3]Department of Noninvasive Cardiology, Medical University of Lodz, Łódź, Poland

Correspondence to:
Iwona Gorczyca-Głowacka, MD, PhD,
Collegium Medicum, Jan Kochanowski University in Kielce,
IX Wieków Kielc 19A,
25–317 Kielce, Poland,
phone: +48 604 407 956,
e-mail:
iwona.gorczyca@interia.pl

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INTRODUCTION

In 2020 there were more than 740 000 patients with heart failure (HF) in Poland, and half of them suffered from heart failure with reduced ejection fraction (HFrEF) [1]. Four major therapeutic classes of drugs have been shown to reduce mortality in HFrEF patients: angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor-neprilysin inhibitors (ARNi), beta-blockers, mineralocorticoid receptor antagonists (MRA), and sodium-glucose cotransporter 2 inhibitors (SGLT2i) [2, 3]. The 2021 European Society of Cardiology (ESC) HF guidelines departed from the traditional approach to HF treatment and suggested that the four pillars of treatment should be prescribed to all HFrEF patients simultaneously [2]. More recently, in the American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA) guidelines, similar recommendation was included [3]. This study aimed to assess the implementation of the current guidelines in pharmacotherapy of HFrEF patients.

METHODS

This survey was an investigator-initiated survey initially designed and drafted by the Heart Failure Association of the Polish Cardiac Society. The survey was addressed to physicians caring for HFrEF patients, including cardiologists and physicians of other specialties. After validation, the survey was published on the website platform and shared via the group mailing list of the Heart Failure Association and Polish Society of Family Medicine. Physicians completed the online survey (Supplementary material, *Table S1*). The questions concerned their specialization, workplace characteristics, and pharmacotherapy used in HFrEF patients. Three main points for the proper implementation of the ESC guidelines have been identified:

- initiation of therapy with four classes of drugs (ACEi/ARNi, beta-blockers, MRA, SGLT2i),
- introduction of SGLT2i therapy in almost every patient,
- use of ARNi in almost every patient.

Statistical analysis

Pearson's χ^2 test of independence was used to compare the groups. *P*-values <0.05 were considered statistically significant. The calculations were done with the use of the STATISTICA PL 13.3 statistical package.

RESULTS AND DISCUSSION

The analysis was conducted in a group of 117 physicians, including 64 cardiologists (54.7%), 19 internal medicine physicians (16.2%), 30 general practice physicians (25.6%), and 4 physicians of other specializations (3.5%). It showed that in the study group, the following percentage of physicians implemented the studied elements of pharmacotherapy for HFrEF patients:

- initiation of therapy with four classes of drugs (ACEi/ARNi, beta-blockers, MRA, SGLT2i) — 64.1%,
- introduction of SGLT2i therapy in almost every patient — 53.8%;
- use of ARNi in almost every patient — 17.1% (Table 1).

In all groups, the majority were cardiologists, in the group of physicians choosing ARNi in almost every patient, cardiologists

Table 1. Comparison of respondent characteristics and HFrEF treatment between cardiologists and non-cardiologists

Characteristics	All n = 117	Cardiologists n = 64	Non-cardiologists n = 53	*P*-value
Number of patients with heart failure consulted per week				
<10	41 (35)	11 (17.2)	30 (56.6)	<0.0001
10–25	59 (50.4)	39 (60.9)	20 (37.7)	
26–50	13 (11.1)	11 (17.2)	2 (3.8)	
>50	4 (3.4)	3 (4.7)	1 (1.9)	
General principles of HFrEF treatment				
In accordance with post-hospital recommendations and aiming at dose optimization	24 (20.5)	5 (7.8)	19 (35.8)	<0.0001
In accordance with post-hospital recommendations and without aiming at dose optimization	9 (7.7)	2 (3.1)	7 (13.2)	
Initiating therapy with four classes of drugs	75 (64.1)	56 (87.5)	19 (35.8)	
No experience with new drugs	9 (7.7)	1 (1.6)	8 (15)	
Treatment of HFrEF in stable outpatients				
Without a change in current treatment	15 (12.8)	0 (0.0)	15 (28.3)	<0.0001
With changes in current treatment	82 (70.1)	54 (84.4)	28 (52.8)	
The decision to modify the treatment depends on test results	20 (17.1)	10 (15.6)	10 (18.9)	
General principles of SGLT2i therapy				
Used in almost every patient	63 (53.8)	47 (73.4)	16 (30.2)	<0.0001
More commonly used in patients with diabetes mellitus	26 (22.2)	5 (7.8)	21 (39.6)	
Used as a subsequent therapy after beta-blockers, ACEi/ARNi, MRA	20 (17.2)	9 (14.1)	11 (20.8)	
Used as a subsequent therapy after beta-blockers, ACEi/ARNi	8 (6.8)	3 (4.7)	5 (9.4)	
General rules for ARNi use				
Used in almost every patient	20 (17.1)	20 (31.2)	0 (0.0)	<0.0001
Used in fewer than one patient in three	76 (64.9)	30 (46.9)	46 (86.8)	
More commonly used in the outpatient center	2 (1.7)	2 (3.1)	0 (0.0)	
More commonly used in the hospital	19 (16.2)	12 (18.8)	7 (13.2)	
Reasons for non-use or infrequent use of ARNi				
Price barrier	65 (55.6)	28 (43.1)	37 (69.8)	0.0001
The need to monitor therapy	7 (6)	1 (1.6)	6 (11.3)	
Fear of discontinuing ACE-I for 36 hours	3 (2.6)	1 (1.6)	2 (3.8)	
Informing each patient about such therapy	42 (35.9)	34 (53.1)	8 (15.1)	

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARNi, angiotensin receptor-neprilysin inhibitor; HFrEF, heart failure with reduced ejection fraction; SGLT2i, sodium-glucose cotransporter 2 inhibitors`

accounted for as many as 95% of the respondents. The cardiologists worked more often in academic centers (39% vs. 11.3%, $P = 0.0005$) than non-cardiologists. Most cardiologists (82.8%) had consultations with more than 10 HFrEF patients per week compared to non-cardiologists (43.4%, $P < 0.0001$). Initiation of the therapy with four main classes of drugs (ACEi/ARNi, beta-blocker, MRA, SGLT2i) was declared by 87.5% of cardiologists and 35.8% of non-cardiologists ($P < 0.0001$). The use of SGLT2i in almost every HFrEF patient was reported by 73.4% of cardiologists and 30.2% of non-cardiologists ($P < 0.0001$). The use of ARNi in almost every patient was declared by 31.2% of cardiologists and by no non-cardiologists ($P < 0.0001$). A comparison of respondents' workplace and HFrEF management between cardiologists and non-cardiologists is presented in Supplementary material, *Table S1*.

The main findings of the survey are: (1) most physicians initiated HFrEF therapy with four major therapeutic classes; (2) new groups of drugs in HFrEF are implemented to varying degrees; (3) cardiologists implemented the ESC guidelines to a greater extent than non-cardiologists.

Treatment of HFrEF is an undeniable real success of modern medicine. There are treatments of confirmed effectiveness in HFrEF patients, including recently ACEI/ARNi, β-blockers, MRA, and SGLT2i, which reduce mortality and morbidity, and, therefore, are recommended as evidence-based treatments by the ESC and ACC/AHA/HFSA [2, 3]. Administering all four medications in appropriate doses may be a panacea for HFrEF patients; however, it has not been prevalent in everyday clinical practice because patients either receive doses that are lower than recommended, or they are undertreated by receiving too few groups of the drugs [4]. In the presented study, 64.1% of physicians declared prescribing all four groups of drugs in HFrEF patients, but we did not assess whether it was done synchronously or sequentially. In a study including 615 cardiologists, Fauvel et al. [5] showed that the number one drug prescribed for the sequential approach was ACEi/ARNi (74%), the second was beta-blockers (55%), MRA came as the third (52%), and SGLT2i (53%) was the fourth. Eighty-four percent of respondents perceived simultaneous administration of all four classes of medications as feasible during initial hospitalization, and 58% recognized dose optimization to be less important than introducing a new class [5]. In the presented study, we showed that new classes of drugs — ARNi and SGLT2i — are implemented in HFrEF patients with varying

frequency. SGLT2i added to ACEi/ARNi, beta-blocker, and MRA have been shown to reduce the risk of cardiovascular death and HF severity in HFrEF patients. However, 6% of the surveyed physicians had no experience with using SGLT2i in HFrEF patients. Treatment of chronic HFrEF patients with sacubitril/valsartan is safe and associated with significant clinical and objective improvement [6]. Taking into account the current state of knowledge, according to the opinion of experts from the Heart Failure Association of the Polish Cardiac Society, ARNi should be the preferred drug over ACEi/ARB in HFrEF patients [7]. This is confirmed by the recommendations contained in the latest 2022 AHA/ACC/HFSA guidelines. However, the widespread unavailability of the drug due to the lack of reimbursement is the greatest obstacle to initiating treatment with ARNi in HFrEF patients. In the presented study, only 17.1% of respondents prescribed ARNi in almost every HFrEF patient, and for 55.6% of physicians, the main barrier to introducing this therapy was its price. It is not surprising that the implementation of cardiac societies' guidelines is better in the group of cardiologists; however, training of non-cardiologists should be intensified because most HFrEF outpatients are treated by non-cardiologists.

We acknowledge several limitations. First, only HFrEF patients were included in the study, and no treatment intolerance or comorbidities were taken into account. Nevertheless, this complies with the previously proposed expert opinion strategy. Second, the presented study is a pilot study, hence the small number of respondents. Third, another limitation of the study is the incomplete participation of physicians invited to the study.

In conclusion, this survey is the first to provide real-life Polish data on the pharmacotherapy of HFrEF patients. Most physicians treating HFrEF patients adhere to two pillars of HFrEF treatment — they initiate therapy with four main classes of drugs and include SGLT2i in almost every patient. The use of pharmacotherapy in all patients with chronic cardiovascular diseases in accordance with the guidelines is not possible, if only because of contraindications to the use of given drugs. However, it is important to ensure that the guidelines are implemented in the largest possible number of patients. In addition, Polish doctors can use expert opinions of the Heart Failure Association of the Polish Cardiac Society, which facilitate guideline implementation [6–8].

Supplementary material

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

Article information

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REFERENCES

1. Maps of Health Needs. System and Implementation Analysis Database Platform. Epidemiology. Available online: https://basiw.mz.gov.pl/mapy-informacje/mapa-2022-2026/analizy/epidemiologia/. Accessed: January 03, 2023.
2. Sindone A, Doehner W, Manito N, et al. Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2019; 21(10): 1169–1186, doi: 10.1002/ejhf.1531, indexed in Pubmed: 31129923.
3. 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, doi: 10.1016/j.cardfail.2022.02.010, indexed in Pubmed: 35378257.
4. Shen Li, Jhund PS, Docherty KF, et al. Dementia-related adverse events in PARADIGM-HF and other trials in heart failure with reduced ejection fraction. Eur J Heart Fail. 2017; 19(1): 129–137, doi: 10.1002/ejhf.687, indexed in Pubmed: 27868321.
5. Fauvel C, Bonnet G, Mullens W, et al. Sequencing and titrating approach of therapy in heart failure with reduced ejection fraction following the 2021 European Society of Cardiology guidelines: an international cardiology survey. Eur J Heart Fail. 2023; 25(2): 213–222, doi: 10.1002/ejhf.2743, indexed in Pubmed: 36404398.
6. Lelonek M, Grabowski M, Kasprzak JD, et al. An expert opinion of the Heart Failure Association of the Polish Cardiac Society on the 2021 European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic heart failure: Heart failure guidelines from a national perspective. Kardiol Pol. 2022; 80(2): 239–246, doi: 10.33963/KP.a2022.0021, indexed in Pubmed: 35076082.
7. Lelonek M, Wiśniowska-Śmiałek S, Rubiś P, et al. Sacubitril/valsartan for heart failure with reduced ejection fraction: A first real-life observational study in Poland. Adv Clin Exp Med. 2021; 30(1): 67–75, doi: 10.17219/acem/128230, indexed in Pubmed: 33529509.
8. Nessler J, Siniarski A, Leszek P, et al. Expert opinion of the Heart Failure Working Group of the Polish Cardiac Society on the use of dapagliflozin in the treatment of heart failure with reduced ejection fraction. Kardiol Pol. 2021; 79(3): 363–370, doi: 10.33963/KP.15859, indexed in Pubmed: 33687868.

Two decades of follow-up of a 60-year-old cyanotic patient with an unoperated univentricular heart

Sonia Alicja Nartowicz, Agnieszka Bartczak-Rutkowska, Maciej Lesiak, Olga Trojnarska

1st Department of Cardiology, Poznan University of Medical Sciences, Poznań, Poland

Correspondence to:
Sonia Nartowicz, MD,
1st Department of Cardiology,
Poznan University of Medical Sciences,
Długa 1/2, 61–848 Poznań,
Poland,
phone: +48 61 854 91 46,
e-mail:
sonianartowicz@gmail.com

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Univentricular heart is a rare congenital heart malformation, and a life span of over 60 years is very unusual in this population [1]. A 60-year-old woman with this congenital heart defect due to non-restrictive ventricular septal defect (VSD) with consequent cyanosis (oxygen saturation = 75%), transposition of the great arteries (TGA), and pulmonary stenosis has been followed up for 20 years in our outpatient center. She was stable on her first visit. The examination revealed central cyanosis and a systolic murmur in the second left intercostal space and parasternal on the right side. On ECG, she had regular sinus rhythm, atrioventrivular (AV) block I, and right bundle branch block. Transthoracic echocardiography showed a heart with single ventricular physiology (82 mm) resulting from bidirectional VSD, ventricular wall — 13 mm, TGA with pulmonary trunk stenosis (max gradient 102 mm Hg), and its post-stenotic widening (Figure 1). The function of both ventricles was moderately impaired. Pulmonary function was preserved with no future of restriction in spirometry.

During the first 5 years of follow-up, the patient's condition was stable (New York Heart Association [NYHA] class II), and there were only single ventricular and supraventricular extrasystoles. The first severe clinical complication appeared in 2008, with a well rehabilitated ischemic stroke. Aspirin 75 mg/day was used. Subsequent hospitalization took place in 2019 due to worsening heart failure (HF) and pre-syncope, which resulted from significant posthemorrhagic anemia caused by massive epistaxis during home oxygen therapy, aggravated by thrombocytopenia. Aspirin was discontinued. I.e. a further incident leading to decompensation bleeding occurred after tooth extraction in 2020. In both cases, clinical improvement followed monitored HF treatment (low doses of diuretic, beta-blocker, aldosterone antagonist), blood transfusion, and iron supplementation. Two hospital admissions in 2022 were caused by HF exacerbation due to the deterioration of ventricular systolic function. Due to unsatisfactory improvement after diuretic treatment, levosimendan was added, making the patient's general condition better with decreased N-terminal prohormone of brain natriuretic peptide (NT-proBNP). The last hospitalization (2023) occurred because of aggravation of the hemodynamic conditions. Apart from diuretics, the patient required catecholamines and intravenous iron supply. The patient, treated with these preparations orally, remains in home therapy under our supervision, in serious but stable condition.

Unoperated univentricular patients reach adulthood only when there is a hemodynamic balance between two-way communication between the systemic and pulmonary circulation, which ensures sufficient oxygen supply within pulmonary stenosis and protects against severe pulmonary hypertension [2]. In our patient, over the years, inevitable complications have appeared due to leakage between the cavities (increasing pulmonary resistance, impaired ventricular function) and cyanosis, mainly in the form of thromboembolic complications, which are typical of these patients, due to an increase in blood viscosity resulting from chronic hypoxia [3]. The main management strategy is to provide medical care that will not disturb their fragile pathophysiological balance. It is important to use anticoagulants carefully and only in exceptional situations. Hemoglobin should be maintained at a higher level than the normal range, using iron supplementation for this purpose. Heart failure should be treated with

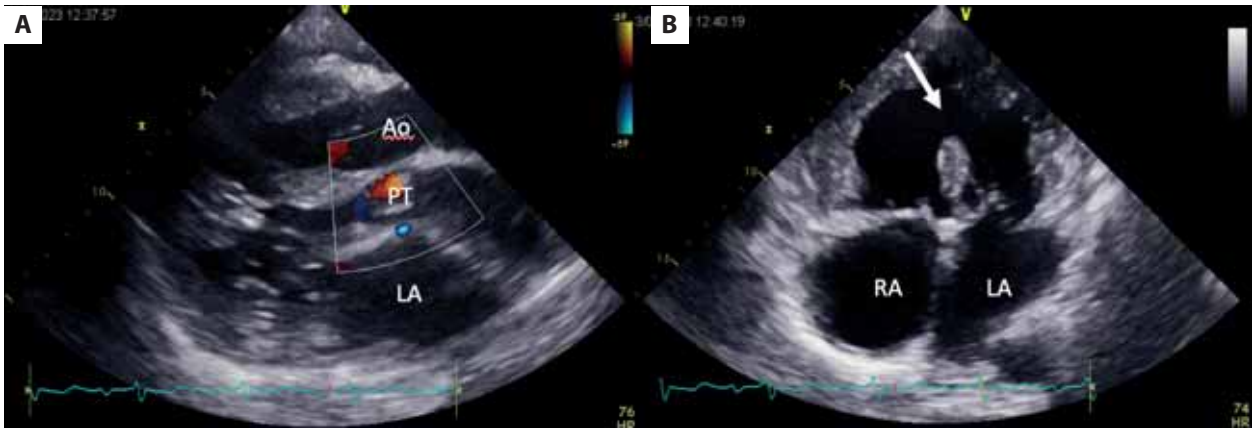

Figure 1. A. Echocardiography, parasternal long axis view. **B.** Echocardiography, four-chamber apical view; arrow indicates the ventricular septal defect

Abbreviations: Ao, aorta; LA, left atrium; PT, pulmonary trunk; RA, right atrium

all possible and available drugs. However, excessive reduction of preload (diuretics, angiotensin-converting enzyme inhibitors) and high doses of negative inotropes should be avoided [4]. These patients should have close contact with an adult congenital heart disease center [5].

Supplementary material

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Article information

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REFERENCES

1. Gesuete V, Fabi M, Bonvicini M. A 74-year-old unoperated univentricular heart: the oldest reported survival. Cardiol Young. 2016; 26(4): 805–807, doi: 10.1017/S1047951115001973, indexed in Pubmed: 26508431.
2. Rao PS. Diagnosis and management of cyanotic congenital heart disease: part I. Indian J Pediatr. 2009; 76(1): 57–70, doi: 10.1007/s12098-009-0030-4, indexed in Pubmed: 19391004.
3. Trojnarska O, Szczepaniak-Chichel L, Gabriel M, et al. Arterial stiffness and arterial function in adult cyanotic patients with congenital heart disease. J Cardiol. 2017; 70(1): 62–67, doi: 10.1016/j.jjcc.2016.09.003, indexed in Pubmed: 27756510.
4. Cordina RL, Celermajer DS. Chronic cyanosis and vascular function: implications for patients with cyanotic congenital heart disease. Cardiol Young. 2010; 20(3): 242–253, doi: 10.1017/S1047951110000466, indexed in Pubmed: 20416139.
5. Baumgartner H, De Backer J, Babu-Narayan SV, et al. 2020 ESC Guidelines for the management of adult congenital heart disease. Eur Heart J. 2021; 42(6): 563–645, doi: 10.1093/eurheartj/ehaa554, indexed in Pubmed: 32860028.

Giant apical pseudoaneurysm in the left ventricle as a late complication of Takotsubo syndrome: Not a benign course of the disease

Mislav Lozo[1, 2*], Lovel Giunio[1, 2*], Dino Miric[1, 2], Darija Bakovic[1, 2], Cristijan Bulat[3], Tonci Batinic[4], Anteo Bradaric[1, 2], Jaksa Zanchi[1, 2], Josip A Borovac[1, 2]

[1]Department of Cardiovascular Diseases, University Hospital of Split, Split, Croatia
[2]University of Split School of Medicine, Split, Croatia
[3]Department of Cardiac Surgery, University Hospital of Split, Split, Croatia
[4]Department of Radiology, University Hospital of Split, Split, Croatia
[*]Both authors equally contributed to the study

Correspondence to:
Josip A Borovac, MD, PhD, FHFA, Department of Cardiovascular Diseases, University Hospital of Split (KBC Split), Soltanska 1, 21 000 Split, Croatia, phone: +385 92 172 13 14, e-mail: jborovac@mefst.hr

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Left ventricular pseudoaneurysm (LVP) is a rare and life-threatening complication that is most often reported after myocardial infarction or cardiac surgery but can also occur after bacterial endocarditis, chest trauma, or myocardial tumor invasion [1, 2]. LVP develops when a zone of free-wall cardiac rupture is contained by the pericardium or scar tissue, without myocardial tissue involvement. Fatal rupture can be prevented by urgent surgical aneurysmectomy [3]. LVP patients treated with surgery have a mortality rate of 23%, while those treated medically die in 48% of cases [4]. To the best of our knowledge, LVP as a late complication of Takotsubo syndrome (TS) has not been described in the literature while Jaguszewski et al. reported on ventricular rupture as an early complication of TS thus confirming that this entity might not always have a benign course [5].

A 77-year-old female with a medical history of arterial hypertension, non-insulin-dependent type 2 diabetes mellitus, dyslipidemia, hypothyroidism, and rheumatoid arthritis presented with crushing substernal chest pain that started 5 hours earlier. Her ECG showed sinus tachycardia (104 bpm) and diffuse ST-segment elevations in the inferior and anteroseptal leads. She reported that the symptoms had started following an emotionally intense event (a large family reunion dinner). Cardioselective biomarkers were markedly high (high-sensitivity troponin I level of 4894 ng/l and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) level of 4221 pg/ml). A diagnosis of acute coronary syndrome was made, and an urgent invasive work-up was undertaken. We performed coronary angiography with left ventriculography that revealed the akinetic/dyskinetic midsegment and apical parts of the left ventricle (LV) accompanied by apical ballooning and hyperkinesis of the basal LV segments, consistent with TS diagnosis (Figure 1, Supplementary material, *Video S1*), with no obstructive coronary artery disease (Figure 1B). Furthermore, a transthoracic echocardiographic examination (TTE) showed the formation of an inferoapical mural thrombus (Figure 1C, far left) and reduced left ventricular ejection fraction (LVEF) of 42%. Thus, the patient was discharged with an oral anticoagulant in full therapeutic dose along with optimal medical therapy. Eight weeks later, the patient received a follow-up TTE that showed an increase in systolic function (LVEF, 53%) with complete resolution of the thrombus while the presence of a small inferoapical LV aneurysm was noted (Figure 1C, middle image).

Eight months after this first hospitalization, she presented again to the Emergency Department with worsening dyspnea upon minimal exertion, dry cough, and generalized weakness. Her NT-proBNP level was was 3041 pg/ml, and urgent TTE was performed. It showed a gigantic oval non-contractile structure connected to the LV via a narrow neck (Figure 1C, far right). LVEF was preserved

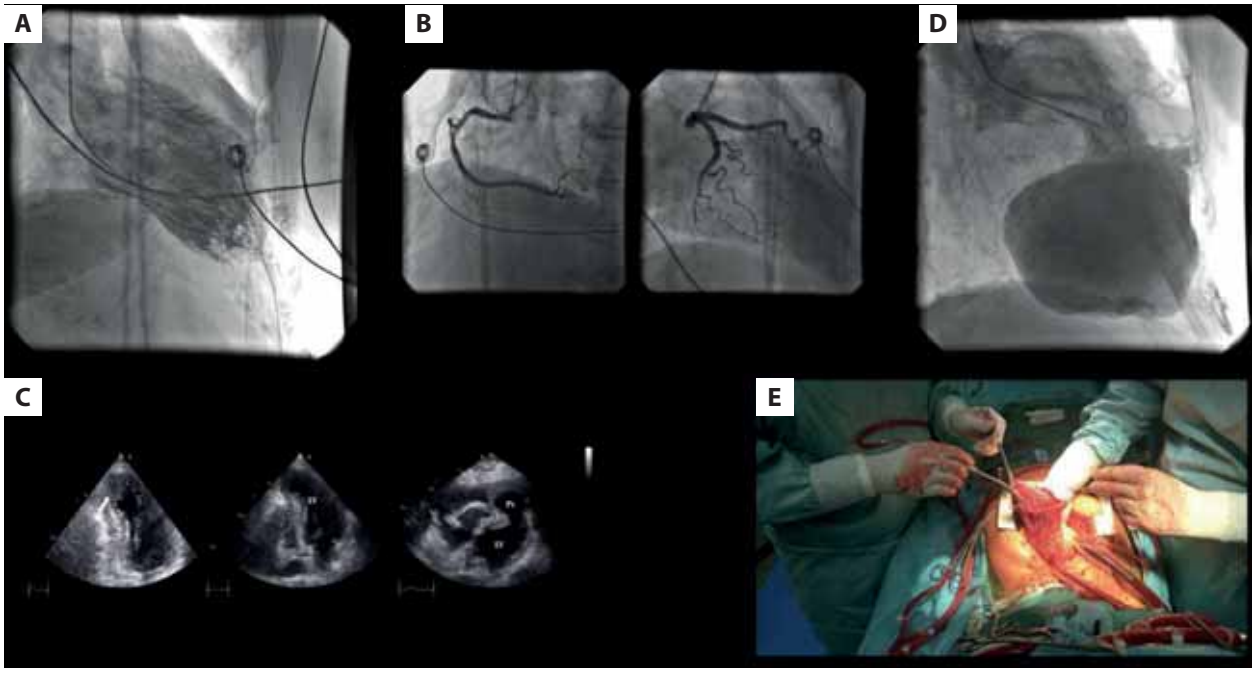

Figure 1. A. Left ventriculography performed during the first hospital admission showed apical ballooning with basal hypercontractility consistent with the diagnosis of Takotsubo syndrome as well as the presence of contrast filling defect in the inferoapical region indicating possible thrombus formation. **B.** Coronary angiography performed during the first hospital admission showed normal coronary anatomy without obstructive atherosclerotic disease. **C.** Images from transthoracic echocardiographic examination (TTE) performed during the first hospital admission showing a left ventricular (LV) thrombus (22 × 28 mm, white arrow) (the far left image) followed by complete dissolution of the thrombus 8 weeks later on follow-up TTE (middle image) and a huge oval non-contractile structure connected to LV via a narrow neck surrounded by the isoechogenic wall up to 17 mm of thickness visualized during the second hospitalization. **D.** Left ventriculography performed during the second hospitalization revealing an inferoapical pseudoaneurysm structure 72 × 65 mm in size, with a neck diameter measuring approximately 21 mm. **E.** Surgical resection of the pseudoaneurysm (aneurysmectomy) and closure of the LV by a double-layered pericardial patch performed by cardiac surgeons

(55%). Coronary angiography and left ventriculography were performed again — the coronary arteries were patent while ventriculography showed again the massive oval structure connected to LV via a narrow neck (Figure 1D, Supplementary material, *Video S2*). Cardiac magnetic resonance showed that the pseudoaneurysm wall consisted predominantly of a "sickle-like" mural thrombus up to 15 mm in size surrounded by a thin layer of visceral pericardium up to 2 mm, without perfusion, thus a diagnosis of giant LVP was made (Supplementary material, *Video S3*). Due to the high risk of spontaneous rupture, the patient was referred for urgent surgical aneurysmectomy that was performed by using a double-layer heterologous pericardial patch (Figure 1E). The patient was discharged six days after surgery and was followed up for one year.

Supplementary material

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REFERENCES

1. Caldeira A, Albuquerque D, Coelho M, et al. Left ventricular pseudoaneurysm: imagiologic and intraoperative images. Circ Cardiovasc Imaging. 2019; 12(12): e009500, doi: 10.1161/CIRCIMAGING.119.009500, indexed in Pubmed: 31766861.
2. Moreno R, Gordillo E, Zamorano J, et al. Long term outcome of patients with postinfarction left ventricular pseudoaneurysm. Heart. 2003; 89(10): 1144–1146, doi: 10.1136/heart.89.10.1144, indexed in Pubmed: 12975400.
3. Garcia-Guimaraes M, Velasco-Garcia-de-Sierra C, Estevez-Cid F, et al. Current role of cardiac imaging to guide surgical correction of a giant left ventricular pseudoaneurysm. Int J Cardiol. 2015; 198: 152–153, doi: 10.1016/j.ijcard.2015.06.129, indexed in Pubmed: 26186572.
4. Frances C, Romero A, Grady D. Left ventricular pseudoaneurysm. J Am Coll Cardiol. 1998; 32(3): 557–561, doi: 10.1016/s0735-1097(98)00290-3, indexed in Pubmed: 9741493.
5. Jaguszewski M, Fijalkowski M, Nowak R, et al. Ventricular rupture in Takotsubo cardiomyopathy. Eur Heart J. 2012; 33(8): 1027, doi: 10.1093/eurheartj/ehs054, indexed in Pubmed: 22416075.

A dislodged left atrial appendage occlusion device rescued with gastroenterological forceps

Catarina M Costa[1], Ricardo Alves Pinto[1], João C Silva[1], Paula G Dias[1], Carla M Sousa[2, 3], Filipe L Macedo[2, 3]

[1]Centro Hospitalar São João, Department of Cardiology, Porto, Portugal
[2]Centro Hospitalar São João, Cardiology Department, Porto, Portugal
[3]University of Porto, Faculty of Medicine, Porto, Portugal

Correspondence to:
Catarina M da Costa, MD, MS, Department of Cardiology, Alameda Prof. Hernâni Monteiro, 4200–319 Porto, Portugal, phone: +35 191 926 62 57, e-mail: catarinamarcosta@gmail.com

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A 67-year-old woman with atrial fibrillation and several hemorrhagic episodes was referred for percutaneous left atrial appendage occlusion (LAAO) [1]. We decided to perform LAAO with a Watchman FLXTM (Boston Scientific, Minneapolis, MN, US) under general anesthesia and with transesophageal echocardiogram (TOE) monitoring. In the cath lab, TOE showed a windsock-shaped left atrial appendage (LAA) with a landing zone of 20 × 23 mm, and fluoroscopy suggested an ostium size of 24 mm. Considering the borderline value in the sizing chart and anatomic characteristics, we opted for a 35-mm Watchman FLXTM (Figure 1A and B) [2].

After transseptal puncture, the device was deployed in the LAA fulfilling stability criteria (Figure 1C) [3]. However, immediately after releasing the device, it dislodged to the left atrium in a perpendicular position to the LAA, with significant peri and intra-device leaks (Figure 1D). Numerous percutaneous maneuvers to recapture were performed using the delivery catheter and two snares simultaneously, with no success (Supplementary material, *Video S1*).

An endomyocardial bioptome of 6 Fr × 105 cm was also used to open the LAAO. Although we managed to catch the top of the device, after several attempts it was obvious the gripping power was not enough to remove the device. Hence, we used RescueTM Alligator Long Grasping Forceps (Boston Scientific, Minneapolis, MN, US), mostly used in endoscopic procedures, which have higher grasping strength. These forceps were introduced within an 8.5 Fr × 71 cm Agilis NXT steerable introducer (Abbott Laboratories, Abbott Park, Chicago, IL, US) to orientate the forceps toward the device, and this succeeded in restraining it. To guarantee safe removal, a 20 Fr 65 cm GORE® DrySeal FlexIntroducer Sheath (Gore, Newark, DE, US), first manually given an archshape to orientate it toward the septum, softly approached the Watchman device, folding it into the sheath and pushing it outside (Figure 1E, Supplementary material, *Video S2*).

We emphasize that the procedure was performed under close TOE monitoring, with 3D echocardiography offering the most valuable guidance in this complex and risky retrieval, with success in the end. We concluded that the device had dislodged due to oversizing. Therefore, a 31-mm Watchman FLXTM was deployed, with complete sealing and no further complications (Figure 1F).

Supplementary material

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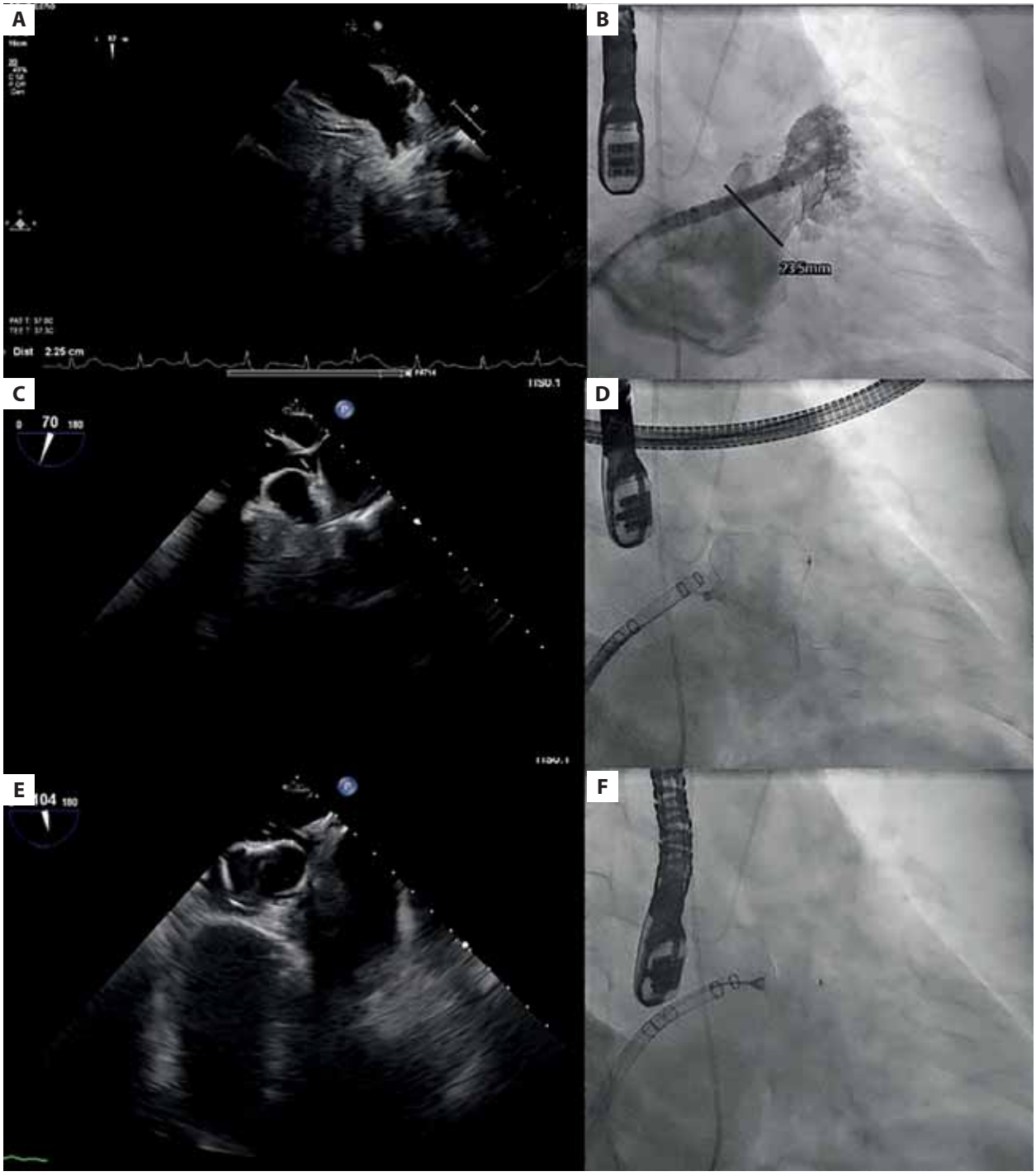

Figure 1. Pre-procedure measurements: (**A**) transesophageal echocardiogram (TEE) showed a landing zone of 20 × 23 mm while (**B**) fluoroscopy suggested a diameter of 24 mm. **C.** The 35-mm Watchman FLXTM device fulfilling the PASS (Position, Anchoring, Size, Seal) criteria on TEE. **D.** After releasing, the device moved to the left auricle in a perpendicular position to the left atrial appendage (TEE). **E.** Several attempts were made to remove the device, but only after using gastroenterological forceps, the device was captured and safely removed. **F.** A 31-mm Watchman FLXTM was deployed, with complete sealing and no further complications

REFERENCES

1. Collado FM, Lama von Buchwald CM, Anderson CK, et al. Left atrial appendage occlusion for stroke prevention in nonvalvular atrial fibrillation. J Am Heart Assoc. 2021; 10(21): e022274, doi: 10.1161/JAHA.121.022274, indexed in Pubmed: 34668395.
2. Grygier M, Olasińska-Wiśniewska A, Araszkiewicz A, et al. The Watchman FLX - a new device for left atrial appendage occlusion - design, potential benefits and first clinical experience. Postepy Kardiol Interwencyjnej. 2017; 13(1): 62–66, doi: 10.5114/aic.2017.66188, indexed in Pubmed: 28344619.
3. Kavinsky CJ, Kusumoto FM, Bavry AA, et al. SCAI/ACC/HRS institutional and operator requirements for left atrial appendage occlusion. Catheter Cardiovasc Interv. 2016; 87(3): 351–362, doi: 10.1002/ccd.26381, indexed in Pubmed: 26663263.

Vasculitis in acute cellular rejection early after heart transplantation

Zofia Lasocka[1], Rafał Pęksa[2], Jerzy Bellwon[1], Marcin Gruchała[1]

[1]1st Department of Cardiology, Medical University of Gdansk, Gdańsk, Poland
[2]Department of Pathomorphology, Medical University of Gdansk, Gdańsk, Poland

Correspondence to:
Zofia Lasocka, MD,
1st Department of Cardiology,
Medical University of Gdańsk,
Smoluchowskiego 17,
80–214 Gdańsk, Poland,
phone: +48 58 584 47 10,
e-mail:
zofia.lasocka@gumed.edu.pl

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We present a case of a 38-year-old male with cardiac graft rejection and concomitant vasculitis, admitted to our Department of Cardiology for protocol monitoring of graft rejection. The patient underwent heart transplantation 10 weeks earlier due to severe ischemic cardiomyopathy. The early postoperative period was complicated with primary graft dysfunction, diagnosed on the basis of the current guidelines. Due to low output syndrome and, consequently, kidney and liver failure, the patient required temporary venoarterial extracorporeal membrane oxygenation, renal replacement therapy, and albumin dialysis. First endomyocardial biopsies (EMBs) showed no signs of rejection.

On current admission, the patient reported exertional intolerance and dyspnea, NYHA (New York Heart Association) class II. Physical examination revealed no abnormalities. Blood tests demonstrated elevated B-type natriuretic peptide level — 253 pmol/l (normal <21 pmol/l), while troponin I was in the normal range — 0.023 µg/l (normal <0.036 µg/l). The immunosuppressive drugs taken by the patient included tacrolimus 4 mg b.i.d., mycophenolate mofetil 500 mg b.i.d., and prednisone 20 mg daily. Tacrolimus serum level was 15.5 µg/l, within the target range three months after heart transplantation.

On the electrocardiogram, regular sinus rhythm of 88 bpm, narrow QRS complexes, and no significant ST-T-wave changes were detected. A transthoracic echocardiogram revealed good systolic and diastolic function of the left ventricle and preserved right ventricular contractility, without any valvular defects.

Coronary angiography showed no significant stenosis in any of the epicardial arteries, while EMBs indicated infiltration of multiple inflammatory cells with myocyte injury, corresponding with acute cellular rejection (ACR) grade 2R. Additionally, lymphocyte infiltration was detected in the wall of intramyocardial arterial vessels, defined as vasculitis (Figure 1). The antibody-mediated rejection (AMR) was C4d-negative.

To treat the biopsy-proven graft rejection, a 3-day course of intravenous methylprednisolone 1000 mg/day was used. Then, oral prednisone at an increased dose of 1 mg/kg/day was introduced and then gradually reduced. The dosage of tacrolimus and mycophenolate mofetil did not change. After two weeks of enhanced immunosuppression, a repeat EMB revealed no evidence of lymphocyte infiltration in either myocardium or vessel walls (ACR grade 0R).

This is the first example of rejection-induced vasculitis in over 100 cardiac transplant recipients in our Heart Transplantation Center, successfully reversed with increased immunosuppression.

Vasculitis, defined as an inflammatory process affecting intramyocardial arteries up to capillaries, was demonstrated to be a negative predictor of both humoral and cellular rejection [1]. Moreover, the presence of this histological feature, despite the grade and type of rejection, carries a poor prognosis in terms of mortality and rejection persistence [2]. Although most described cases concerned mixed rejection (pathological AMR plus ACR) associated with the worst outcomes [3], vasculitis might also be observed in positive ACR without any sign of humoral rejection in the same EMBs, as presented in our case. This is especially worth noting as the frequency

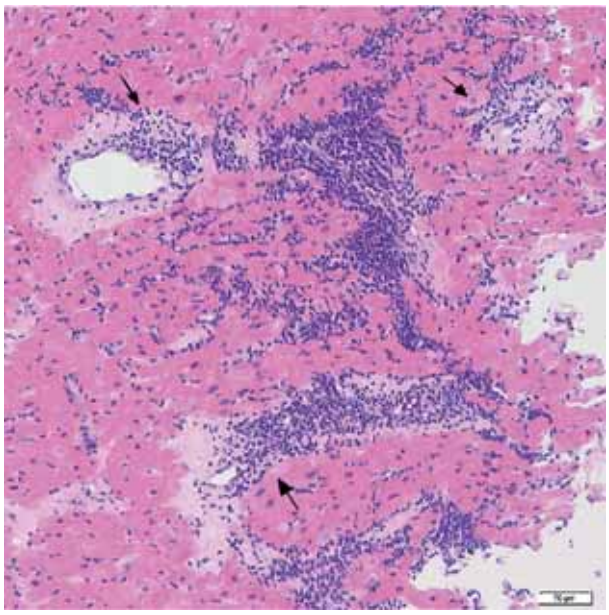

Figure 1. Interstitial, perivascular, and endocardial lymphocyte infiltration with prominent nucleoli associated with myocytolysis. Note the lymphocyte infiltration of the vascular walls (arrows). H&E, ×10

of ACR is approximately 45%, and both AMR and mixed rejection are detected in less than 5% of EMBs [4].

There are no specific guidelines concerning the management of heart transplant recipients with rejection-induced vascular damage. Only a few reports illustrated successful treatment of vasculitis with increased immunosuppression [5]. Our case corresponds with those outcomes, meaning that enhanced corticosteroid therapy should reverse lymphocyte infiltration in the myocardium and vessel wall.

Identification of cardiac recipients with rejection-induced vasculitis that need temporally enhanced immunosuppression is of great clinical importance to avoid further immunological aggression against the graft.

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REFERENCES

1. Fedrigo M, Romano A, Bottio T, et al. Vasculitis in post-heart transplant endomyocardial biopsy: possible relationship with mixed rejection, circulating donor specific antibodies and worse outcome. J Heart Lung Transplant. 2018; 37(4): S302, doi: 10.1016/j.healun.2018.01.767.
2. Cipullo R, Finger MA, Rossi Neto JM, et al. Vasculitides and eosinophils in endomyocardial biopsies as rejection predictors in heart transplantation. Arq Bras Cardiol. 2011; 97(2): 163–170, doi: 10.1590/s0066-782x2011005000069, indexed in Pubmed: 21655876.
3. Fedrigo M, Bottigliengo D, Romano A, et al. Clinical relevance of vasculitis in heart transplant. J Heart Lung Transplant. 2020; 39(4): S59–S60, doi: 10.1016/j.healun.2020.01.1252.
4. Fedrigo M, Bottigliengo D, Romano A, et al. Clinical relevance of vasculitis in mild form of rejections in heart transplant patients. J Pulm Med. 2021; 5: 1–6.
5. Ballester M, Obrador D, Carrió I, et al. Reversal of rejection-induced coronary vasculitis detected early after heart transplantation with increased immunosuppression. J Heart Transplant. 1989; 8(5): 413–417, indexed in Pubmed: 2795284.

Percutaneous left atrial appendage occlusion as a bridge to pulmonary vein isolation

Tomasz Podolecki[1, 2], Witold Streb[1, 2], Zbigniew Kalarus[1, 2]

[1]Department of Cardiology, Congenital Heart Diseases and Electrotherapy, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland
[2]Silesian Center for Heart Diseases in Zabrze, Zabrze, Poland

Correspondence to:
Tomasz Podolecki, MD, PhD, Department of Cardiology, Congenital Heart Diseases and Electrotherapy, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Silesian Centre for Heart Diseases in Zabrze, Curie-Skłodowskiej 9, 41–800 Zabrze, phone: +48 373 36 48, e-mail: tomekpod@interia.pl

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A 36-year-old woman was admitted to our center for persistent atrial fibrillation (AF) with New York Heart Association (NYHA) class II/III symptoms. The patient had a history of surgery for atrial septal defect type ostium secundum and mitral valve annuloplasty at the age of four and five, respectively. Echocardiography revealed severely reduced left ventricular ejection fraction (LVEF, 36%) with global hypokinesia and no significant valvular heart disease. Magnetic resonance imaging showed no signs of ischemic nor inflammatory cardiomyopathy, therefore, tachycardia-induced cardiomyopathy was diagnosed, and the patient was qualified for pulmonary vein isolation. However, transesophageal echocardiography (TEE) showed a massive thrombus located in the medial and distal part of the left atrial appendage (LAA) (Figure 1A). The strategy of rate control had to be chosen, as neither cardioversion nor cryoablation was permissible.

After four weeks, control TEE revealed a persistent LAA thrombus despite using the nonvitamin K antagonist oral anticoagulants (NOAC). The antithrombotic therapy was changed — NOAC was withdrawn and enoxaparin (1 mg per kg twice daily subcutaneously) with acetylsalicylic acid (75 mg/daily) were administered. Despite more aggressive antithrombotic treatment, the second control TEE, performed four weeks later, showed no thrombus resolution.

Given highly symptomatic AF and deterioration of heart failure symptoms to NYHA class III, the patient was qualified for left atrial appendage occlusion (LAAO) with a cerebral protection device to make possible cryoblation and electrical cardioversion. The procedure was performed using an Amplatzer Amulet 28 mm occluder with the SENTINEL cerebral protection system to minimize the risk of cerebral arterial embolization (Figure 1B). Despite neuroprotection, we also used the "no-touch technique", with no contrast injection and restriction on guidewire or catheter manipulation within LAA. We achieved complete occlusion of the LAA (Figures 1C and 1D), with no periprocedural complications. The patient was discharged in good clinical state one day after the procedure. Cryoablation with subsequent effective electrical cardioversion were performed 3 weeks later. Control echocardiography showed a significant increase in LVEF (LVEF, 50%).

The incidence of left atrial thrombus (LAT) in AF patients receiving oral anticoagulants varies from 1.6 to 8.0%, and over 90% of all thrombi are located within the LAA [1–3]. Thanks to more aggressive anticoagulation therapy, about 60% of thrombi might be resolved; however, such a strategy is burdened with significantly higher bleeding risk [1–3]. The presence of a LAT is associated with a significant increase in the risk of ischemic stroke and other thromboembolic complications, especially during electrical/pharmacological cardioversion and in procedures involving catheterization of the left atrium (LA). Therefore, both cardioversion and invasive procedures within LA are strongly contraindicated in the case of LAT presence [4]. However, a recent study demonstrated, that LAAO in the presence of LAT is feasible and quite safe, and the use of a cerebral protection device might reduce the risk of procedure-related thromboembolic events [5].

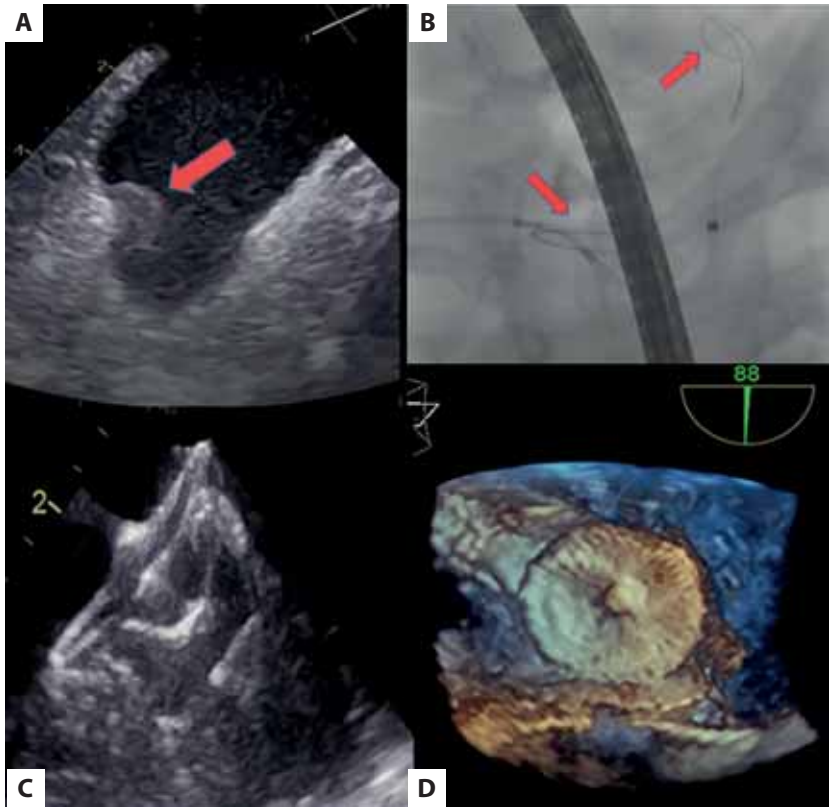

Figure 1. A. Visualization of the LAA thrombus on TEE. **B.** Sentinel cerebral protection system — arrows indicate the deployed device filters — fluoroscopy image. **C.** The LAA after closure with an Amplatzer Amulet occluder — TEE. **D.** The disc of Amplatzer Amulet occluder closing the LAA ostium — TEE 3D view

Abbreviations: LAA, left atrial appendage; TEE, transesophageal echocardiography

To the best of our knowledge, we have reported the first case of LAAO performed to facilitate cryoablation in a patient with persistent thrombus within the LAA.

Article information

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REFERENCES

1. Zhan Y, Joza J, Al Rawahi M, et al. Assessment and management of the left atrial appendage thrombus in patients with nonvalvular atrial fibrillation. Can J Cardiol. 2018; 34(3): 252–261, doi: 10.1016/j.cjca.2017.12.008, indexed in Pubmed: 29395705.
2. Frenkel D, D'Amato SA, Al-Kazaz M, et al. Prevalence of left atrial thrombus detection by transesophageal echocardiography: a comparison of continuous non-vitamin K antagonist oral anticoagulant versus warfarin therapy in patients undergoing catheter ablation for atrial fibrillation. JACC Clin Electrophysiol. 2016; 2(3): 295–303, doi: 10.1016/j.jacep.2016.01.004, indexed in Pubmed: 29766887.
3. Niku AD, Shiota T, Siegel RJ, et al. Prevalence and resolution of left atrial thrombus in patients with nonvalvular atrial fibrillation and flutter with oral anticoagulation. Am J Cardiol. 2019; 123(1): 63–68, doi: 10.1016/j.amjcard.2018.09.027, indexed in Pubmed: 30360887.
4. 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). Russian Journal of Cardiology. 2021; 26(9): 4701, doi: 10.15829/1560-4071-2021-4701.
5. Marroquin L, Tirado-Conte G, Pracoń R, et al. Management and outcomes of patients with left atrial appendage thrombus prior to percutaneous closure. Heart. 2022; 108(14): 1098–1106, doi: 10.1136/heartjnl-2021-319811, indexed in Pubmed: 34686564.

Aortic arch stent-graft implantation due to an endovascular leak as the fourth aortic intervention in a challenging patient

Jacek Kurnicki[1], Daniel Jarosz[1], Zbigniew Gałązka[1], Katarzyna Kurnicka[2]

[1]Department of General, Endocrine and Vascular Surgery, Medical University of Warsaw, Warszawa, Poland
[2]Department of Internal Medicine and Cardiology, Medical University of Warsaw, Warszawa, Poland

Correspondence to:
Katarzyna Kurnicka, MD, PhD, Department of Internal Medicine and Cardiology, Medical University of Warsaw, Lindleya 4, 02–005, Warszawa, Poland,
phone: +48 22 502 11 44,
e-mail: kkurnicka@yahoo.pl

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We present a 69-year-old female, former tobacco smoker, with hypertension, diabetes, and a history of aortic aneurysm, qualified for a novel procedure of branched aortic arch stent-graft implantation, as her fourth intervention on the aorta.

She underwent supra coronary ascending aorta replacement due to a large aneurysm (70 mm) and right lung upper lobe resection due to lung planocellular cancer four years earlier. After a year, a thoracoabdominal stent graft with visceral branches was implanted, followed by a thoracic stent graft below the left subclavian artery due to aortic aneurysm (Figure 1A).

Due to type IA endoleak, which occurred at the proximal end of the graft and resulted in persistent flow into the sac of the thoracic aneurysm (Figure 1B), the patient was qualified for another intervention involving implantation of a special stent graft with a branch to the brachiocephalic trunk.

Occlusion of the inflow towards the left common carotid artery and the left subclavian artery after implantation would have led to stroke and ischemia of the left upper limb; therefore, the patient underwent a carotid-carotid-subclavian bypass, one month before the procedure.

However, due to transient left-sided chest pain and exertional dyspnea, it was necessary to extend cardiac diagnostics. Fortunately, the resting electrocardiogram did not reveal ischemic changes, and troponin levels were not increased. Transthoracic echocardiography revealed proper function of the aortic valve, normal flow in the ascending aorta graft (Figure 1C, Supplementary material, *Video S1*) and aortic arch, and normal left ventricular ejection fraction (60%). Gated single-photon emission computed tomography with dipyridamole confirmed adequate coronary flow reserve.

Finally, a novel single-branched stent graft (Nexus) was safely implanted in the aortic arch and brachiocephalic trunk (Figure 1D), which eliminated the leak and protected the patient against further growth of the aneurysm (Figure 1E). The patient, with three implanted aortic stent grafts (Figure 1F) was discharged in good condition after 5 days.

The Nexus system is indicated for patients with aortic arch pathologies, including aneurysms, dissection, pseudoaneurysms, or penetrating ulcers. Planer et al. [1] described initial evaluation of the Nexus system in 28 patients. The thirty-day mortality rate was 7.1%, stroke rate was 3.6%, and one-year mortality was 10.7%, without device or aneurysm-related deaths.

In the described case, the Nexus system was used due to a type IA leak. Endovascular leaks are the most common complications after aortic stent-graft implantation, which may lead to the expansion of the aortic aneurysm or even to its rupture [2].

Surgery-related risk estimation indicates an approximately 30-day risk of cardiovascular death, myocardial infarction, and stroke [3]. Endovascular abdominal aortic aneurysm repair is an intermediate surgical risk intervention (1%–5%), while aortic arch interventions are procedures with a higher risk of complications, including stroke or aortic valve injury [4].

Our patient was challenging because of the history of previous ascending aorta surgery, two aortic stent-graft implantations, and a planned intervention on the aortic arch.

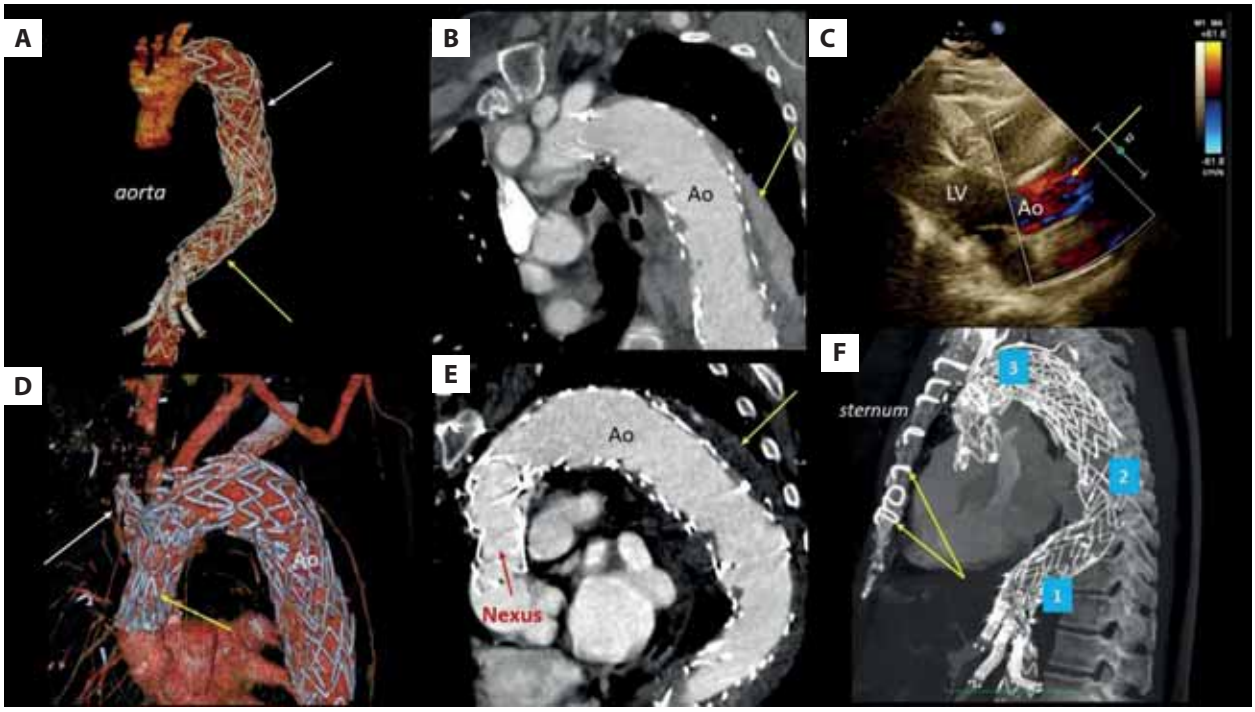

Figure 1. Computed tomography angiography and transthoracic echocardiography in a patient with a history of four procedures on the aorta. **A**. Computed tomography angiography of the aorta in 3D option: thoracic stent graft below the left subclavian artery (white arrow) and thoracoabdominal stent graft with visceral branches (yellow arrow). **B**. Computed tomography angiography: endovascular leak (arrow). **C**. Transthoracic echocardiography (color Doppler, long axis view): blood flow in the ascending aorta graft (arrow); see also Supplementary material, *Video S1*. **D**. Computed tomography angiography of the aorta in 3D option after the procedure: Nexus aortic arch stent graft (yellow arrows) and a branch to the brachiocephalic trunk (white arrow). **E**. Computed tomography angiography after the procedure: no endovascular leak (arrow). **F**. Computed tomography angiography: three aortic stent grafts in one patient (1–3); metal sutures on the sternum after cardiac surgery (arrows)

Abbreviations: Ao, aorta; LV, left ventricle

Biomarker measurements and noninvasive cardiac imaging were required because of transient unexplained symptoms in that high-risk patient [3]. O'Driscoll et al. [5] showed that echocardiographic indices obtained electively before surgery were more important in predicting outcomes than conventional risk factors in patients undergoing endovascular abdominal aneurysm repair.

It seems reasonable to assess individually all cardiologic patients before aortic endovascular interventions because they are often a challenge and require comprehensive evaluation.

Article information

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REFERENCES

1. Planer D, Elbaz-Greener G, Mangialardi N, et al. NEXUS Arch: A Multicenter Study Evaluating the Initial Experience With a Novel Aortic Arch Stent Graft System. Ann Surg. 2023; 277(2): e460–e466, doi: 10.1097/SLA.0000000000004843, indexed in Pubmed: 33714965.
2. Juraszek A, Czerny M, Rylski B. Thoracic endovascular aortic repair: Current evidence and challenges. Kardiol Pol. 2022; 80(5): 540–547, doi: 10.33963/KP.a2022.0093, indexed in Pubmed: 35380010.
3. Halvorsen S, Mehilli J, Cassese S, et al. 2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery. Eur Heart J. 2022; 43(39): 3826–3924, doi: 10.1093/eurheartj/ehac270, indexed in Pubmed: 36017553.
4. Shu C, Li J, Luo M, et al. Endovascular management of aortic arch diseases: current status and future trends. Cardiology Discovery. 2022; 2(4): 263–268, doi: 10.1097/cd9.0000000000000080.
5. O'Driscoll JM, Bahia SS, Gravina A, et al. Transthoracic echocardiography provides important long-term prognostic information in selected patients undergoing endovascular abdominal aortic repair. Circ Cardiovasc Imaging. 2016; 9(2): e003557, doi: 10.1161/CIRCIMAGING.115.003557, indexed in Pubmed: 26860969.

Rotablation-assisted percutaneous coronary intervention and deferred intravascular lithotripsy: Facilitated stenting in a young STEMI patient with familial hypercholesterolemia

George Kassimis[1–3], Konstantinos C Theodoropoulos[2], Matthaios Didagelos[2], Thomas Zegkos[2], Nikolaos Fragakis[1], Stavros Hadjimiltiades[3], Antonios Ziakas[2]

[1]2nd Department of Cardiology, Hippokration Hospital, Medical School, Aristotle University of Thessaloniki, Greece
[2]1st Department of Cardiology, AHEPA General Hospital, Aristotle University of Thessaloniki, Greece
[3]St. Luke's Hospital, Thessaloniki, Greece

Correspondence to:
George Kassimis MD, MSc, PhD, FESC, FRCP,
2nd Department of Cardiology, Hippokration Hospital, Medical School, Aristotle University of Thessaloniki, 49 Konstantinoupoleos Road, 54642, Thessaloniki, Greece,
phone: +30 23 108 92 349,
e-mail: gksup@yahoo.gr

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A 38-year-old male who was a current smoker with definite heterozygous familial hypercholesterolemia based on the Dutch Lipid Clinic diagnostic criteria (premature coronary artery disease and low-density lipoprotein (LDL) cholesterol, 330 mg/dl) [1] was admitted with anterior ST-segment elevation myocardial infarction (STEMI).

A coronary angiogram revealed a subacute occlusion of the proximal severely calcified left anterior descending (LAD) artery with TIMI 1 flow grade and further atheromatous disease at the mid and distal vessel (Supplementary material, *Figure S1* and *Videos S1* and *S2*).

Primary percutaneous coronary intervention (PPCI) of the LAD was performed by right-femoral artery access. Initial high-pressure (22 atm) pre-dilation with a non-compliant balloon (NCB) 2.5 × 15 mm Solarice (Medtronic, Santa Rosa, CA, US) was performed. Due to incomplete balloon expansion, inflations of a 3.0 × 10 mm Wolverine (Boston Scientific, Marlborough, MA, US) cutting balloon at nominal pressure were still unable to successfully "modify" the lesion (Figure 1A). Therefore, we performed two runs of rotational atherectomy (RA) with a Rotablator (Boston Scientific) burr size 1.5 mm, with RA speed set at 150 000 rotations/min, trying to minimize platelet activation and prevent slow flow (Figure 1B). Subsequently, high-pressure (22 atm) inflation of a 3.0 × 12 mm NCB Solarice (Medtronic) was performed, but despite lesion preparation with RA, a significant "dog-bone effect" was still observed (Figure 1C). TIMI 3 flow grade was achieved, with the presence of a mild non-flow limiting dissection at mid-vessel (Figure 1D, Supplementary material, *Video S3*), and stenting was deferred to avoid under-expansion in this emergency setting.

Hence, 3 months later, following healing of the LAD dissection (Figure 1E), we performed Shockwave Intravascular Lithotripsy (S-IVL) using a 3.5 × 12 mm catheter (Shockwave Medical, Inc.; Santa Clara, CA, US). After application of 40 ultrasonic pulses, full balloon expansion was obtained. A NCB 3.5 × 15 mm was successfully used, and a 3.5 × 38 mm drug-eluting stent Promus Premier (Boston Scientific) was implanted, followed by a Quantum Apex (Boston Scientific) 4.0 × 20 mm (20 atm) NCB post-dilation (Figure 1F). A good final angiographic result was achieved (Supplementary material, *Video S4*).

We described a successful staged implementation of a complex advanced plaque-modifying strategy (Primary Rota-CUT atherectomy and S-IVL deferred PCI) in a young STEMI patient. Similar combined treatment modalities have been described [2]. It is increasingly apparent that despite increasing the lumen size with RA and allowing catheter passage, there may still be extensive unaltered restrictive calcific plates within the intima and media, even after balloon dilation. This deeper calcium is not impacted by RA but can usually be modified by subsequent IVL. Intravascular imaging gives significant additional insights in addition to angiography into the distribution, concentricity, and severity of calcific disease. These data can then direct our initial therapeutic approach.

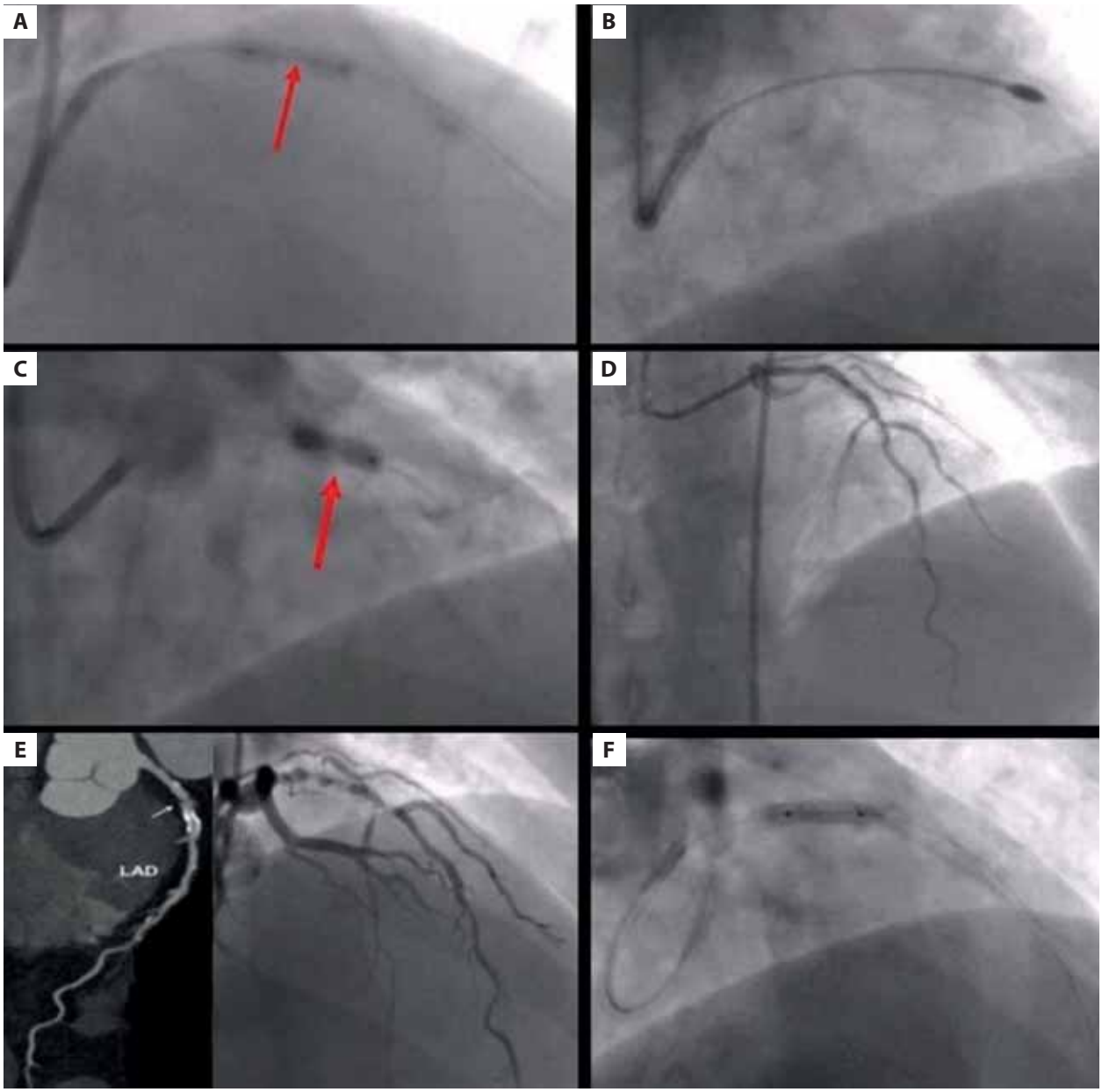

Figure 1. A. Pre-dilation with a cutting balloon still having a waist (red arrow). **B.** Successful RA. **C.** High-pressure (22 atm) inflation of an NCB post-RA was performed — a significant "dog-bone effect" was still observed (red arrow). **D.** Final angiographic result with TIMI 3 flow. Stenting was deferred while a mild non-flow limiting dissection can be noted just after a large diagonal branch.
E. CTCA (left panel) and angiographic PA cranial view (right panel) demonstrating distal LAD dissection healing (white arrow). **F.** Post-stent deployment dilatation with an NCB — there is no waist anymore

Abbreviations: CTCA, computed tomography coronary angiography; LAD, left anterior descending; NCB, non-compliant balloon; PA, postero-anterior; RA, rotational atherectomy

Moderate/severe calcification, present in approximately 30% of culprit lesions in acute coronary syndromes, adversely affects the safety/efficacy of primary PCI and suggests worse post-PCI outcomes [3]. Although RA is applied only in selected STEMI patients [4], IVL may mitigate adverse consequences of severe calcification [5]. The DISRUPT-CAD trials, however, have excluded patients with STEMI [6]. The safety of IVL in thrombus-laden lesions is unknown, and its "off-label" use in acute STEMI is not currently recommended till further data shed light on this high-risk scenario. However, IVL could be used in a staged fashion in STEMI patients to facilitate stenting at a time when there is less thrombus burden and myocardial electrical instability as in our case.

Supplementary material

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

Article information

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REFERENCES

1. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020; 41(1): 111–188, doi: 10.1093/eurheartj/ehz455, indexed in Pubmed: 31504418.
2. Kleczyński P, Zajdel W, Niewiara Ł, et al. Combined orbital atherectomy and intracoronary lithotripsy assisted by mechanical circulatory support in a patient with NSTEMI and last remaining vessel. Kardiol Pol. 2022 [Epub ahead of print], doi: 10.33963/KP.a2022.0269, indexed in Pubmed: 36446072.
3. Généreux P, Madhavan M, Mintz G, et al. Ischemic outcomes after coronary intervention of calcified vessels in acute coronary syndromes. J Am Coll Cardiol. 2014; 63(18): 1845–1854, doi: 10.1016/j.jacc.2014.01.034, indexed in Pubmed: 24561145.
4. Kassimis G, Theodoropoulos KC, Didagelos M, et al. Successful off-label use of rotational atherectomy in ST-segment elevation myocardial infarction: a case report. Cardiovasc Revasc Med. 2022; 40S: 272–275, doi: 10.1016/j.carrev.2021.11.014, indexed in Pubmed: 34801421.
5. Kassimis G, Ziakas A, Didagelos M, et al. Shockwave coronary intravascular lithotripsy system for heavily calcified de novo lesions and the need for a cost-effectiveness analysis. Cardiovasc Revasc Med. 2022; 37: 128–134, doi: 10.1016/j.carrev.2021.06.125, indexed in Pubmed: 34246610.
6. Karimi Galougahi K, Patel S, Shlofmitz RA, et al. Calcific plaque modification by acoustic shock waves: intravascular lithotripsy in coronary interventions. Circ Cardiovasc Interv. 2021; 14(1): e009354, doi: 10.1161/CIRCINTERVENTIONS.120.009354, indexed in Pubmed: 32907343.

Does a longer graft stent prevent cavity-spilling perforation?

Yeliz Guler[1], Bilal Boztosun[2]

[1]University of Health Sciences, Basaksehir Cam and Sakura City Hospital, Istanbul, Türkiye
[2]Department of Cardiology, Istanbul Medipol University, Istanbul, Türkiye

Correspondence to:
Yeliz Guler, MD,
Department of Cardiology,
Basaksehir Cam and Sakura City Hospital,
Olimpiyat Bulvarı Yolu, 34480 Başakşehir,
Istanbul, Türkiye,
phone: +90 212 444 70 44,
e-mail: yelizguler829@gmail.com

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A 32-year-old male was admitted to our hospital due to chest pain. He experienced chest pain with ST-segment depression during the treadmill test. Coronary angiography was performed and revealed 70% long segment stenosis in the left anterior descending artery (LAD), and percutaneous intervention was planned (Figure 1A, Supplementary material, *Video S1*). After predilatation, a 2.75 × 28.0 mm stent was deployed, and the in-stent segments were postdilated with a 3.0 × 15 mm noncompliant balloon. At that point, angiography revealed extravasation of contrast material at the proximal stent segment (Figure 1B, Supplementary material, *Video S2*). The patient remained hemodynamically stable, but chest pain appeared. Prolonged balloon inflation and reversal of anticoagulation failed. A 3.5 × 19 mm graft stent (GS) was implanted via a GuideLiner catheter. Subsequent angiography showed the absence of extravasation at the proximal location of the stent but multiple focal jets of contrast extravasation at the distal stent segment (Figure 1C, Supplementary material, *Videos S3, S4*). Then we performed implantation of a 2.8 ×19.0 mm GS in the drainage site of the LAD stent (Figure 1D). The patient's hemodynamic condition was stable, and echocardiography showed no pericardial effusion. After the second GS implantation, the subsequent angiographic image revealed a dissection just before the proximal GS (Supplementary material, *Video S5*). A 3.0 × 23.0 mm stent was successfully deployed restoring normal antegrade flow (Figure 1E, 1F). The patient had an uneventful recovery.

In this case, we evaluated the stenosis as a mid-segment atherosclerotic LAD lesion with low risk of procedural complication due to less angulation and tortuosity. We applied nominal pressure created by the balloon, but subsequent angiography demonstrated apparent contrast extravasation first from the proximal stented segment and after the distal stented segment into the right ventricle. At the end of the procedure, we noticed a dissection on the angiogram just before the proximal GS, and we also deployed a coronary stent. In retrospect, the stenotic LAD segment might have had an intramyocardial course, which, in the presence of atherosclerosis, could explain why flow was tracked into the right ventricle. Following the GS implantation, an intimal tear completely penetrated the arterial wall leading to extravasation from multiple sites along the distal stented segment. Similarly, a proximal dissection, which is encountered as a final complication, may be associated with a corner dissection caused by the proximal GS or using a GuideLiner catheter, which may also represent the expansion upward of the ruptured segment causing intimal tear.

Cavity-spilling perforations are rare complications of PCI, and there are limited data in the literature about how they should be managed. Fortunately, they have a benign course since they are less often associated with pericardial tamponade or acute hemodynamic compromise. In this case, we encountered Ellis grade III coronary perforation, and our therapeutic approach was determined by the patient's hemodynamic stability, distal coronary artery flow, and size of the fistula [1–3]. Multiple overlapping stents may be required in cases of coronary artery perforations [4]. The main reasons can be stent malposition, disruption of the integrity of the GS coating at high pressure, and extension of the intimal tear proximally and distally. To avoid the last scenario, the GS length should not only cover the ruptured segment but also the proximal and distal parts to prevent further dissection or intimal tear.

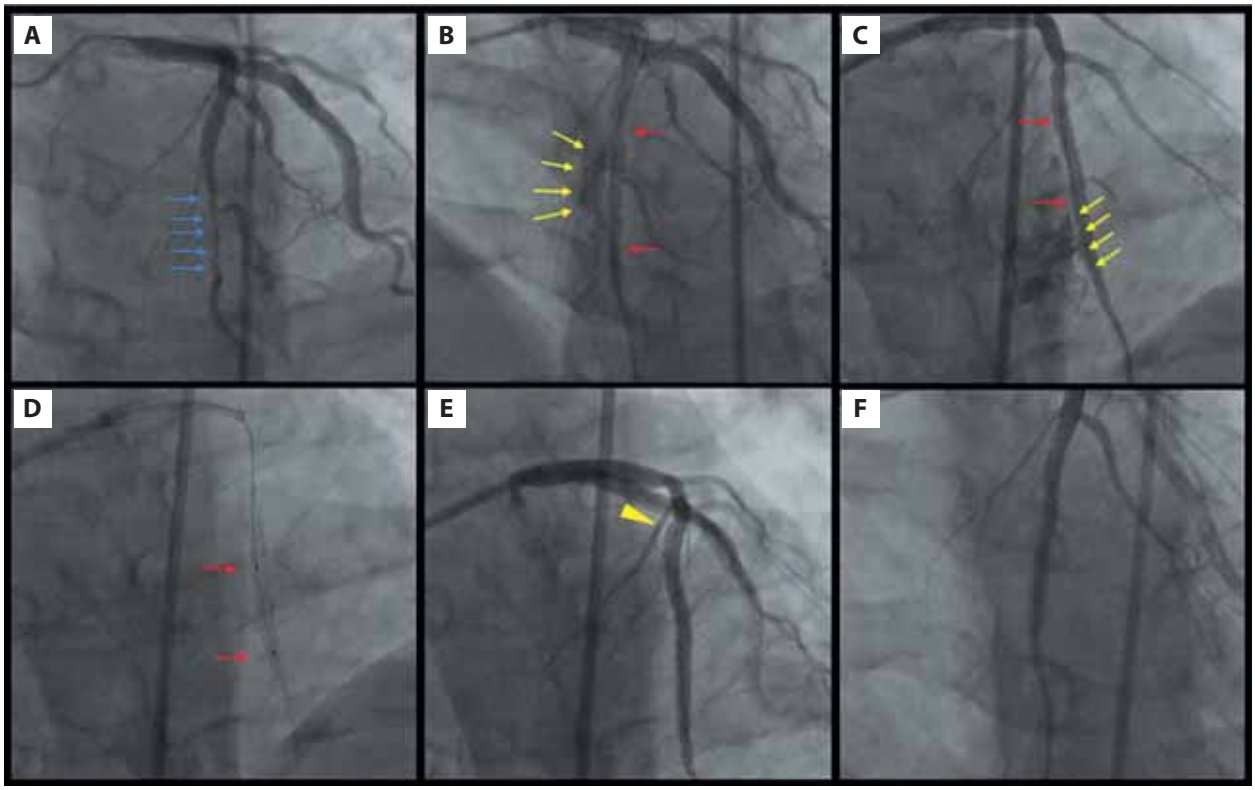

Figure 1. **A.** Coronary angiography showing left anterior descending artery (LAD) long segment stenosis (blue arrows). **B.** Angiographic image showing extravasation of contrast material into the right ventricle (yellow arrows). Red arrows show the proximal and distal zones of the coronary stent. **C.** Angiographic image after deployment of a covered stent showing the absence of extravasation at the proximal location of the LAD stent but progressively multiple focal jets of contrast extravasation at the distal stent segment (yellow arrows). Red arrows show the proximal and distal zones of the graft stent. **D.** Red arrows show the proximal and distal zones of the second graft stent. **E.** Angiographic image revealing a dissection just before the proximal graft stent (yellow arrowhead). **F.** Final angiogram

Supplementary material

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Article information

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REFERENCES

1. Ellis SG, Ajluni S, Arnold AZ, et al. Increased coronary perforation in the new device era. Incidence, classification, management, and outcome. Circulation. 1994; 90(6): 2725–2730, doi: 10.1161/01.cir.90.6.2725, indexed in Pubmed: 7994814.
2. Murthy A, Singh A, Driesman M. Acquired coronary cameral fistula due to post stent balloon dilatation: dual coronary artery perforations into the left ventricle—what is the right treatment? World J Cardiovasc Dis. 2014; 04(11): 548–555, doi: 10.4236/wjcd.2014.411066.
3. McCormick LM, Ko BS, Zaman S, et al. Persistent type III cavity-spilling coronary perforation due to covered stent malapposition. Cardiovasc Interv Ther. 2016; 31(4): 269–274, doi: 10.1007/s12928-015-0346-0, indexed in Pubmed: 26197781.
4. Lansky AJ, Yang Ym, Khan Y, et al. Treatment of coronary artery perforations complicating percutaneous coronary intervention with a polytetrafluoroethylene-covered stent graft. Am J Cardiol. 2006; 98(3): 370–374, doi: 10.1016/j.amjcard.2006.02.041, indexed in Pubmed: 16860026.

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