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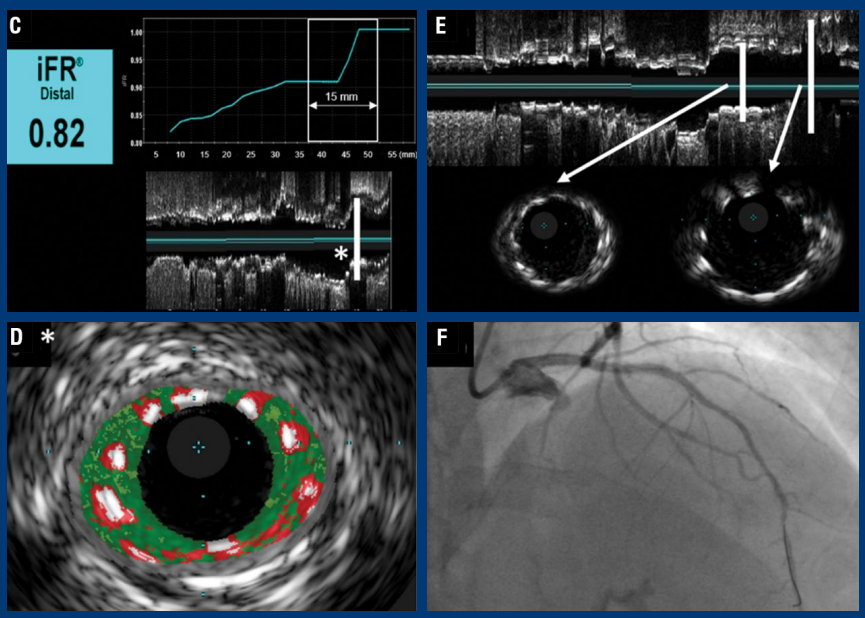

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EDITORIAL

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Does ticagrelor effectively inhibit platelets in patients undergoing mild therapeutic hypothermia or it does not?

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Out-of-hospital cardiac arrest (OHCA) is a common complication of acute myocardial infarction (MI) [1–9]. The results of studies on the impact of mild therapeutic hypothermia (MTH) in OHCA survivors are inconclusive [10–14]. Some of them confirm the efficacy of this method of treatment [11–13], while others, on the contrary, suggest the lack of superiority of MTH over temperature control in this subset of patients [14]. Therefore, the question "Mild therapeutic hypothermia after out-of-hospital cardiac arrest: What does really matter?" asked by Ratajczak is justified indeed [15].

Several factors, including patient age, baseline heart rhythm and neurological status, presence of cardiogenic shock, duration and effectiveness of cardiopulmonary resuscitation and hypothermia induction time were shown to influence clinical outcome in patients after OHCA treated with MTH [9, 15–20]. In patients additionally undergoing primary percutaneous coronary intervention (pPCI) due to MI, effective platelet inhibition may also have a relevant impact on clinical outcome due to increased risk of stent thrombosis in this subset of patients [21–32].

Recently, two pharmacokinetic studies with seemingly contradictory conclusions appeared in the "Cardiology Journal". First, Tomala et al. [33] confirms the effectiveness of ticagrelor to inhibit platelets in MI patients after OHCA treated with pPCI undergoing hypothermia. The other, by Umińska et al. [34], states that the antiplatelet effect of ticagrelor is attenuated and delayed in MI patients undergoing MTH and pPCI due to OHCA, in comparison with patients treated with pPCI for uncomplicated MI. As stressed in the first publication, in this clinical setting ticagrelor should be the drug of choice before clopidogrel due to its better absorption, faster metabolism, quicker onset of action, and its lack of requirement for metabolic activation [33]. However, in the previously published study [25], impaired bioavailability of ticagrelor and delayed maximal plasma concentration of the drug in patients undergoing MTH and pPCI due to OHCA were demonstrated. Impaired gastrointestinal absorption of ticagrelor in critically ill patients was suggested to be responsible for this finding. Moreover, the presence of different active metabolite (AR-C124910XX) formation rates in comparison with patients treated with primary PCI for uncomplicated MI, suggests diversity in ticagrelor metabolism and/or elimination in different subpopulations [25]. These results are in line with the second research by Umińska et al. [34], reporting significantly higher platelet reactivity in patients undergoing MTH, starting from the first hour up to 24 hours after ticagrelor loading dose administration. The greatest differences between patients undergoing MTH after OHCA and those with uncomplicated MI were observed between 2 and 12 hours after loading with ticagrelor. After

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24 hours, effective platelet inhibition was found in all patients in both groups, however the difference in platelet reactivity between groups persisted [34]. Tomala et al. [32] reported similar findings for a time range of 12–24 hours, however in this team's observation the difference disappeared 48–72 hours after loading. This finding led the authors to a conclusion quite different from one reached by Tomala et al. [33] and Umińska et al. [34]. The analysis of the methods and results of both studies shows, however, that despite different conclusions, both studies are consistent, and moreover, they complement each other.

In conclusion, indeed the differences in antiplatelet efficacy of ticagrelor, initially clearly marked up to 12 hours after the loading dose, gradually decreased until disappearing completely by 24 hours.

Conflict of interest: Jacek Kubica: speaker fee from AstraZeneca.

References

1. Szczerbinski S, Ratajczak J, Lach P, et al. Epidemiology and chronobiology of out-of-hospital cardiac arrest in a subpopulation of southern Poland: A two-year observation. Cardiol J. 2020; 27(1): 16–24, doi: 10.5603/CJ.a2018.0025, indexed in Pubmed: 29611174.
2. Szczerbiński S, Ratajczak J, Jasiewicz M, et al. Observational analysiS of out-of-hospital Cardiac Arrest occurRence and temporal variability patterns in subpopulation of southern POLand from 2006 to 2018: OSCAR-POL registry. Cardiol J. 2021 [Epub ahead of print], doi: 10.5603/CJ.a2021.0060, indexed in Pubmed: 34312830.
3. Berdowski J, Berg RA, Tijssen JGP, et al. Global incidences of out-of-hospital cardiac arrest and survival rates: Systematic review of 67 prospective studies. Resuscitation. 2010; 81(11): 1479–1487, doi: 10.1016/j.resuscitation.2010.08.006, indexed in Pubmed: 20828914.
4. Nadolny K, Bujak K, Kucap M, et al. The Silesian Registry of Out-of-Hospital Cardiac Arrest: Study design and results of a three-month pilot study. Cardiol J. 2020; 27(5): 566–574, doi: 10.5603/CJ.a2018.0140, indexed in Pubmed: 30444257.
5. Borkowska MJ, Smereka J, Safiejko K, et al. Out-of-hospital cardiac arrest treated by emergency medical service teams during COVID-19 pandemic: A retrospective cohort study. Cardiol J. 2021; 28(1): 15–22, doi: 10.5603/CJ.a2020.0135, indexed in Pubmed: 33140396.
6. Szczerbiński S. Observational, retrospective analysis of the circadian variability of out-of-hospital cardiac arrest within days of the week. Med Res J. 2020, doi: 10.5603/mrj.a2020.0020.
7. Nadolny K, Szczerbiński S, Ładny J, et al. Out-of-hospital cardiac arrest and COVID-19 pandemic. Med Res J. 2021; 6(2): 83–85, doi: 10.5603/mrj.2021.0029.
8. Ratajczak J, Łach P, Szczerbiński S, et al. Atmospheric conditions and the occurrence of out-of-hospital cardiac arrest in Poland — preliminary analysis of poorly understood phenomena. Med Res J. 2018; 3(3): 121–126, doi: 10.5603/mrj.a2018.0019.
9. Kołtowski Ł, Średniawa B, Tycińska A, et al. Predicting survival in out-of-hospital cardiac arrest patients undergoing targeted temperature management: The Polish Hypothermia Registry Risk Score. Cardiol J. 2021; 28(1): 95–100, doi: 10.5603/CJ.a2019.0035, indexed in Pubmed: 30994183.
10. Freund B, Kaplan PW. A review of the utility of a hypothermia protocol in cardiac arrests due to non-shockable rhythms. Cardiol J. 2017; 24(3): 324–333, doi: 10.5603/CJ.a2017.0016, indexed in Pubmed: 28150290.
11. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med. 2002; 346(8): 557–563, doi: 10.1056/NEJMoa003289, indexed in Pubmed: 11856794.
12. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med. 2002; 346(8): 549–556, doi: 10.1056/NEJMoa012689, indexed in Pubmed: 11856793.
13. Kozinski M, Pstragowski K, Kubica JM, et al. ACS network-based implementation of therapeutic hypothermia for the treatment of comatose out-of-hospital cardiac arrest survivors improves clinical outcomes: the first European experience. Scand J Trauma Resusc Emerg Med. 2013; 21: 22, doi: 10.1186/1757-7241-21-22, indexed in Pubmed: 23531402.
14. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33°C versus 36°C after cardiac arrest. N Engl J Med. 2013; 369(23): 2197–2206, doi: 10.1056/nejmoa1310519, indexed in Pubmed: 24237006.
15. Ratajczak J, Łach P, Umińska JM, et al. Mild therapeutic hypothermia after out-of-hospital cardiac arrest: What does really matter? Cardiol J. 2021; 28(2): 293–301, doi: 10.5603/CJ.a2019.0023, indexed in Pubmed: 30799547.
16. Kubica J, Pstrągowski K, Adamski P, et al. Mild therapeutic hypothermia for patients with acute coronary syndrome and cardiac arrest treated with percutaneous coronary intervention (UNICORN). The design and rationale for the prospective, observational, multicenter study. Med Res J. 2016; 1(1): 23–27, doi: 10.5603/mrj.2016.0004.
17. Pstrągowski K, Koziński M, Jabłoński M, et al. Optymalizacja postępowania w nagłym pozaszpitalnym zatrzymaniu krążenia w przebiegu ostrego zawału serca — opis przypadku i przegląd piśmiennictwa. Folia Cardiologica. 2011; 6: 27–276.
18. Umińska JM, Buszko K, Ratajczak J, et al. Comparison of temperature measurements in esophagus and urinary bladder in comatose patients after cardiac arrest undergoing mild therapeutic hypothermia. Cardiol J. 2020; 27(6): 735–741, doi: 10.5603/CJ.a2018.0115, indexed in Pubmed: 30246234.
19. Klimczuk T, Kubica J, Kasprzak M, et al. Łagodna hipotermia terapeutyczna po nagłym zatrzymaniu krążenia w przebiegu ostrego zespołu wieńcowego – doświadczenia z wdrażania metody. Folia Cardiologica. 2015; 10(1): 19–24, doi: 10.5603/fc.2015.0005.
20. Kubica A. Rationale of cardiopulmonary resuscitation training as an element of multilevel educational and motivational project (MEDMOTION). Disaster Emerg Med J. 2020, doi: 10.5603/demj.a2020.0017.
21. Umińska J, Koziński M, Pstrągowski K, et al. Platelet reactivity during mild therapeutic hypothermia in patients with acute myocardial infarction treated with ticagrelor: study protocol of a single-centre study. Med Res J. 2017; 1(4): 115–119, doi: 10.5603/mrj.2016.0021.

22. Kubica J, Adamski P, Paciorek P, et al. Treatment of patients with acute coronary syndrome: Recommendations for medical emergency teams: Focus on antiplatelet therapies. Updated experts' standpoint. Cardiol J. 2018; 25(3): 291–300, doi: 10.5603/CJ.a2018.0042, indexed in Pubmed: 29671864.
23. Kubica J. The optimal antiplatelet treatment in an emergency setting. Folia Medica Copernicana. 2014; 2(3): 73–76.
24. Trąbka-Zawicki A, Tomala M, Zeliaś A, et al. Adaptation of global hemostasis to therapeutic hypothermia in patients with out-of-hospital cardiac arrest: Thromboelastography study. Cardiol J. 2019; 26(1): 77–86, doi: 10.5603/CJ.a2017.0080, indexed in Pubmed: 28695976.
25. Umińska JM, Ratajczak J, Buszko K, et al. Impact of mild therapeutic hypothermia on bioavailability of ticagrelor in patients with acute myocardial infarction after out-of-hospital cardiac arrest. Cardiol J. 2020; 27(6): 780–788, doi: 10.5603/CJ.a2019.0024, indexed in Pubmed: 30799546.
26. Ibrahim K, Christoph M, Schmeinck S, et al. High rates of prasugrel and ticagrelor non-responder in patients treated with therapeutic hypothermia after cardiac arrest. Resuscitation. 2014; 85(5): 649–656, doi: 10.1016/j.resuscitation.2014.02.004, indexed in Pubmed: 24555950.
27. Kander T, Dankiewicz J, Friberg H, et al. Platelet aggregation and clot formation in comatose survivors of cardiac arrest treated with induced hypothermia and dual platelet inhibition with aspirin and ticagrelor; a prospective observational study. Crit Care. 2014; 18(5): 495, doi: 10.1186/s13054-014-0495-z, indexed in Pubmed: 25292183.
28. Schoergenhofer C, Hobl EL, Staudinger T, et al. Prasugrel in critically ill patients. Thromb Haemost. 2017; 117(8): 1582–1587, doi: 10.1160/TH17-03-0154, indexed in Pubmed: 28692105.
29. Liu Y, Kang S, Li X, et al. Modified ticagrelor loading doses according to the vasodilator-stimulated phosphoprotein phosphorylation index improve the clinical outcome in ST-elevation myocardial infarction patients with high on-treatment platelet reactivity. Cardiol J. 2021 [Epub ahead of print], doi: 10.5603/CJ.a2021.0105, indexed in Pubmed: 34581430.
30. Niezgoda P, Barańska M, Adamski P, et al. Influence of METHoxyflurane on ANtiplatelet Effect of ticagrelor in patients with unstable angina pectoris: Rationale and a protocol of a randomized clinical METHANE-SIRIO 4 study. Cardiol J. 2022; 29(2): 324–328, doi: 10.5603/CJ.a2021.0126, indexed in Pubmed: 34642919.
31. Kubica J, Adamski P, Gorog DA, et al. Low-dose ticagrelor with or without acetylsalicylic acid in patients with acute coronary syndrome: Rationale and design of the ELECTRA-SIRIO 2 trial. Cardiol J. 2022; 29(1): 148–153, doi: 10.5603/CJ.a2021.0118, indexed in Pubmed: 34622433.
32. Penela D, Magaldi M, Fontanals J, et al. Hypothermia in acute coronary syndrome: brain salvage versus stent thrombosis? J Am Coll Cardiol. 2013; 61(6): 686–687, doi: 10.1016/j.jacc.2012.10.029, indexed in Pubmed: 23265329.
33. Tomala MT, Trąbka-Zawicki A, Machnik A, et al. Ticagrelor effectively inhibits platelet aggregation in comatose survivors of cardiac arrest undergoing primary percutaneous coronary intervention treated with mild therapeutic hypothermia. Cardiol J. 2021 [Epub ahead of print], doi: 10.5603/CJ.a2021.0064, indexed in Pubmed: 34165181.
34. Umińska JM, Ratajczak J, Pstrągowski K, et al. The impact of mild therapeutic hypothermia on platelet reactivity in comatose survivors of cardiac arrest with acute myocardial infarction treated with ticagrelor. Cardiol J. 2022 [Epub ahead of print], doi: 10.5603/CJ.a2022.0029, indexed in Pubmed: 35514087.

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EXPERTS' VIEWPOINT

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Pre-hospital treatment of patients with acute coronary syndrome: Recommendations for medical emergency teams. Expert position update 2022

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Introduction

Recommendations for medical emergency teams regarding the pre-hospital management of patients with acute coronary syndrome (ACS) have been developed in 2017 by a broad representation of Polish experts in cardiology and emergency medicine [1]. These recommendations have been updated after the publication of the 2017 European Society of Cardiology (ESC) guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation (STEMI) and the 2017 update focused on dual antiplatelet therapy (DAPT) in coronary artery disease [2–4]. The 2020 ESC guidelines for the management of ACSs in patients presenting without persistent ST-segment elevation (NSTE-ACS) introduced several significant changes in treatment strategies [5].

The current expert position update aims to put the 2020 ESC guidelines into a Polish perspective and to provide practical recommendations for medical emergency teams.

Diagnosis and logistics of ACS patients

Emergency medical teams are responsible for early diagnosis, triage, transport and treatment of ACS patients [1–6]. In order to improve the quality of care and decrease adequate treatment delay, an early working diagnosis of ACS and risk stratification should be conducted at the earliest possible moment. The efficient treatment of ACS patients requires appropriate ambulance equipment and staff competences. All medical emergency system ambulances should be equipped with electrocardiogram (ECG) recorders, defibrillators, and at least one person trained in advanced life support. All ambulance personnel should be trained to recognize clinical symptoms of acute myocardial infarction (MI), record and transmit ECG, administer oxygen when appropriate, relieve pain, and provide basic life support [1, 2, 4].

Acute coronary syndrome may be associated with a wide variety of symptoms ranging from cardiac arrest, electrical or hemodynamic instability with cardiogenic shock due to ongoing ischemia or mechanical complications such as severe mitral regurgitation, to patients who are already pain free at the time of presentation. The major trigger for the diagnostic and therapeutic actions in patients with suspected ACS is acute chest discomfort, primarily characterized as pain, pressure, tightness, and burning. Chest pain-equivalent symptoms, such as dyspnea, epigastric pain or pain in the left arm, may also occur [5].

The resting 12-lead ECG is the first-line diagnostic tool in the assessment of patients with suspected ACS. It is recommended to perform it within 10 minutes after the first contact with the emergency medical services in a pre-hospital setting and to have it immediately interpreted by a qualified physician using remote technologies [1, 2, 4, 5].

The presence of persistent ST-segment elevation in two contiguous leads is considered one of the best indicators of ongoing MI with an occluded infarct artery [2]. If the standard leads are inconclusive, recording of additional leads (V7–V9 or V3R and V4R) should be performed as they can be the only ones to reveal left circumflex artery occlusion or right ventricular MI, respectively [5]. It is recommended to manage subjects with typical clinical symptoms of ongoing myocardial ischemia and left bundle branch block (LBBB) similar to STEMI patients, regardless of whether the bundle branch block has been previously known [2, 5]. In patients with right bundle branch block the interpretation of electrocardiographic changes is more specific as ST-elevation is indicative of STEMI, while ST-segment depression in lead I, aVL, and V5–V6 is indicative of NSTE-ACS [5]. Primary percutaneous coronary intervention (PCI) strategy is also recommended in the setting of other atypical electrocardiographic presentations combined with ongoing symptoms suggestive of myocardial ischemia, including: ventricular paced rhythm (during right ventricular pacing, the ECG shows LBBB pattern), isolated posterior MI (isolated ST depression > 1 mm in leads V1–V3 and ST-segment elevation (≥ 0.5 mm) in posterior chest wall leads V7–V9), ischemia due to left main coronary artery occlusion or multivessel disease (ST-segment depression ≥ 1 mm in 6 or more surface leads, coupled with ST-segment elevation in aVR and/or V1) [2, 5]. Characteristic ECG features of NSTE-ACS include ST-segment depression, transient ST-segment elevation, and T-wave changes however, ECG may remain normal in more than 30% of patients [5].

The ECG monitoring should be applied immediately in all patients with initial diagnosis of ACS in order to detect life-threatening arrhythmias and allow prompt defibrillation, if indicated [1, 2, 4].

Acute coronary syndromes are characterized by high clinical instability, therefore patients with initial diagnosis of ACS, even those who are not candidates for immediate coronary angiography and subsequent PCI at the time of initial diagnosis, should be transported to centers with invasive cardiology facilities regardless of changes in ECG [2, 5, 7–9]. Nevertheless, teleconsultation including transmission of patients' 12-lead ECG and clinical data to the destination center should be performed at the first medical contact [1, 2, 4, 10]. Teleconsultation, apart from the preliminary diagnosis and logistics aspects, should be used to coordinate pre-hospital therapy, especially regarding antiplatelet therapy and unfractionated heparin. This strategy is aimed to reduce treatment delay leading to mortality reduction in STEMI and very high-risk NSTE-ACS patients. This allows immediate activation of the interventional team and direct transportation of patients triaged for a primary PCI strategy to the catheterization laboratory, bypassing the emergency department [1, 2, 4, 11]. Therefore, the medical emergency system dispatcher should not change the choice of the destination center, unless, in his opinion, the choice made by the emergency medical team is incorrect. In this case, the change and its justification must be documented.

In locations where there is more than one hospital with an invasive cardiology unit, the selection of the destination center should be based both on the patient's clinical status and center category depending on its level of preparation for treatment of ACS patients. Local categorization of centers should take into account the following factors: the availability of invasive cardiology and cardiac surgery in one location, the number of cath labs available, the availability of hybrid rooms and circulatory support systems, and the number of beds in the intensive coronary care unit. Generally, ACS patients qualified for the immediate invasive strategy should be transferred to the nearest PCI center, however, whenever possible, direct transport of the highest risk patients (STEMI, NSTE-ACS of very high-risk, cardiogenic shock) to centers with both invasive cardiology and cardiac surgery facilities should be considered. It should be stressed however, that preference for this category of hospitals must not cause delay of invasive diagnostics [1, 4, 12].

Centers participating in the Managed Care after Acute Myocardial Infarction (KOS-zawał) network should be preferred as the target destination for all ACS patients due to comprehensive post-hospitalization care they provide. To ensure high quality of care in ACS patients, a working diagnosis, pivotal statements, decisions, medications, and time-points should be registered and monitored. Periodic evaluation at the local level (city/voivodeship) should cover the correctness of the initial diagnosis and treatment, the duration and causes of delays related to transport, diagnosis and treatment, the quality of cooperation between the emergency medical teams and hospital staff, and the target center choice correctness [2].

Chest pain management

Coronary revascularization is the most efficient analgesic treatment in patients with acute myocardial ischemia, regardless of ACS type. Patients presenting with STEMI or NSTE-ACS with recurrent or refractory chest pain despite medical treatment should be qualified to immediate invasive strategy [2, 5]. However, even in the most developed medical emergency systems with an access to extensive network of 24/7 PCI centers, the delay between the first medical contact and coronary revascularization may reach tens of minutes contributing to a prolonging chest discomfort. In order to cover the time until the culprit vessel is treated, a potent analgesic with a quick onset of action is necessary to provide timely and effective pain blockade.

The latest ESC guidelines on the treatment of STEMI recommend to titrate intravenous opioids to relieve pain in the pre-revascularization stage in patients with ongoing chest pain. Currently this constitutes a class IIa recommendation ("should be considered") with a level of evidence C ("consensus of the opinion of the experts and/or small studies, retrospective studies, registries") [2]. Notably, this recommendation has been downgraded from class I ("is recommended") compared with the previous edition of the ESC guidelines on STEMI [2, 13]. The 2020 ESC guidelines for the management of NSTE-ACS do not contain any recommendations regarding analgesic pharmacotherapy with opioids in patients with NSTE-ACS [5]. The former edition of these guidelines also did not provide any official recommendation regarding this topic, however the authors stated, that administration of

opioids is reasonable in NSTE-ACS patients with sustained severe chest pain who are waiting for urgent coronary angiography [14]. In this group sublingual or intravenous nitrates and early initiation of beta-blocker treatment are indicated, if ischemic symptoms are ongoing [5]. On the other hand, in the acute phase of STEMI nitrates have failed to show benefit and are not recommended, unless they are required for the control of heart failure symptoms or hypertension [2, 15].

Abundant experience with the use of morphine, its analgesic potency and wide availability explain why it remains the most commonly administered analgesic in patients with MI [16]. Nevertheless, morphine may cause adverse effects, including bradycardia, hypotension, and impairment of the intestinal propulsive function or even suppression of the respiratory function [17]. Additionally, morphine leads to impaired absorption of orally administered antiplatelet drugs, delay of anti-aggregatory effect and its reduction [18]. Noteworthy, this issue not only concerns clopidogrel, but also the newer P2Y12 receptor antagonists prasugrel and ticagrelor [19–21]. Although some studies suggest that morphine use may be related to increased infarct size, reinfarction rate and mortality, data from registries are ambiguous and randomized trials on this matter are lacking [22–27]. A meta-analysis of mostly observational studies has reported no association between morphine use in patients undergoing primary PCI for STEMI and adverse short-term clinical outcomes [28].

Recently, fentanyl has been proposed as an alternative to morphine in ACS patients with chest pain. However, in the setting of PCI fentanyl, similarly to morphine, leads to impairment of ticagrelor bioavailability and delay in its antiplatelet effect suggesting a class effect regarding the opioid-P2Y12 receptor inhibitor interaction [29]. Also, there is no difference in inhibition of platelet reactivity in ACS patients during the first 2 hours after a ticagrelor loading dose, suggesting no pharmacodynamic benefit from using fentanyl instead of morphine [30]. Interestingly, intravenous acetaminophen results in a comparable extent of pain relief when compared to fentanyl before and immediately after primary PCI for STEMI [31]. Still, although this approach increases the absorption of ticagrelor in patients with STEMI compared with fentanyl-treated patients, it does not improve the early antiplatelet response (before and just after primary PCI) [31]. Additionally, acetaminophen lacks anxiolytic effect that may be advantageous in the early phase of ACS treatment.

Due to the potentially harmful effect of oxygen in uncomplicated MI patients it should be used only in hypoxic patients with arterial oxygen saturation (SaO_2) < 90% [2]. In summary, routine use of opioids in ACS should be avoided and restricted only to a selected group of patients with severe, refractory chest pain. In case analgesic treatment is needed, withdrawal from morphine use or a routine switch to either fentanyl or acetaminophen should not be recommended. **Due to reasons explained above morphine should remain the first choice analgesic in ACS. Nevertheless, it has to be underlined that administration of this opioid should be limited only to patients with severe chest pain, and that the dose should be titrated to the minimal effective dosage in order to limit potential adverse effects of the drug. The timing and dosage of administered morphine should always be recorded and communicated to the medical staff of the destination cardiology center. In order to counteract adverse effects of opioids on absorption and platelet inhibition in ACS, administration of crushed tablets of ticagrelor, prasugrel or clopidogrel should be considered due to previously demonstrated acceleration of absorption and antiplatelet effect onset of P2Y12 receptor inhibitors when given in crushed form [32–35].** Additionally, administration of intravenous metoclopramide in opioid-treated ACS patients may also be considered to enhance absorption of antiplatelet agents from the gastrointestinal tract [36].

Antiplatelet treatment in ACS patients

Dual antiplatelet therapy including acetylsalicylic acid (ASA) and one of the P2Y12 receptor inhibitors, remains a standard of care in patients with ACS [2, 3, 5, 37].

ASA therapy in patients with ACS

Acetylsalicylic acid is an irreversible inhibitor of platelet cyclooxygenase isoenzyme type 1. According to the current guidelines, administration of an oral, rapidly absorbed ASA formulation in a loading dose of 150–300 mg or 75–250 mg intravenous ASA (if oral ingestion not possible) is recommended in all ACS patients with no contraindications (class of recommendation I, level of evidence A) [2, 5, 37]. The treatment should be applied as early as possible, i.e. upon the first medical contact. Subsequently, all patients should

Table 1. Contraindications for the use of P2Y12 receptor inhibitors in patients with acute coronary syndrome.

Contraindication	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor
Hypersensitivity to the P2Y12 receptor inhibitor	X	X	X	X
Active bleeding	X	X	X	X
Severe liver disorder	X	X	X	
History of ischemic stroke	Within 7 days	X		X
History of transient ischemic attack		X		X
History of intracranial hemorrhage		X	X	X
Indication for chronic oral anticoagulation		X	X	
Prior administration of other P2Y12 receptor inhibitor		X		X

receive chronic therapy with ASA 75–100 mg q.d. [2, 3, 5, 37, 38].

Platelet P2Y12 receptor inhibitors

Currently, three platelet P2Y12 receptor inhibitors are available in Poland: clopidogrel, prasugrel, and ticagrelor. Unfortunately, cangrelor, the only intravenous rapidly acting P2Y12 receptor inhibitor recommended in the most recent ESC guidelines, is still unavailable. Clopidogrel and prasugrel are pro-drugs and require hepatic activation into active metabolites irreversibly binding to the P2Y12 receptor, whereas ticagrelor and cangrelor are active drugs, which directly and reversibly block this receptor. Prasugrel and ticagrelor are preferentially recommended over clopidogrel due to their faster, more potent, and more uniform anti-aggregation effect, translating into better clinical outcomes [2, 3, 5, 37, 38]. When starting the treatment with P2Y12 receptor inhibitors one should always be aware of contraindications for these drugs (Table 1). Both prasugrel and ticagrelor are contraindicated in patients with prior hemorrhagic stroke, severe liver disease or those requiring chronic oral anticoagulation [2, 3, 5]. Moreover, prasugrel is also contraindicated in patients with a history of ischemic stroke or transient ischemic attack, it is generally not recommended for patients above 75 years of age or with body weight below 60 kg, but, if necessary, a reduced dose of 5 mg can be applied in these patients [2, 3, 5]. When neither of these agents is available or if they are contraindicated, clopidogrel should be administered instead [2, 3, 5]. Importantly, in ACS patients who were previously treated with clopidogrel or have received a loading dose of clopidogrel a switch to ticagrelor is indicated at a loading dose of 180 mg (class of recommendation I, level of evidence B) [37, 39].

Substantial percentage of ACS patients require long-term oral anticoagulation. The concomitant use of DAPT and oral anticoagulation increases the risk of bleeding complications 2- to 3-fold when compared to anticoagulation alone [40–43]. Clopidogrel is the only P2Y12 inhibitor to be used in combination with oral anticoagulants (acenocoumarol, apixaban, dabigatran, rivaroxaban, or warfarin) [2, 3]. Use of ticagrelor or prasugrel as a part of triple therapy is not recommended (class of recommendation III, level of evidence C) [2, 3, 5]. However, patients burdened with moderate-to-severe risk of stent thrombosis, who require concomitant oral anticoagulation may benefit from dual antithrombotic therapy comprising oral anticoagulant and prasugrel or ticagrelor instead of triple therapy (class of recommendation IIb, level of evidence C) [5].

Due to its rapid onset of action cangrelor appears to be the optimal P2Y12 receptor inhibitor for ACS patients requiring urgent invasive treatment [44, 45]. This compound may be considered in patients not pre-treated with oral P2Y12 receptor inhibitors at the time of PCI or in those who are considered unable to absorb oral agents, particularly in unconscious patients, patients with post-cardiac arrest syndrome, or patients treated with mild therapeutic hypothermia, when gastrointestinal absorption of medications is impaired [2, 5, 46–48]. Unfortunately, up to date cangrelor is not available in Poland.

In conservatively treated ACS patients ticagrelor is preferred over clopidogrel (class of recommendation IIa, level of evidence C), while prasugrel is not indicated (class of recommendation III, level of evidence B) [3].

Platelet P2Y12 receptor inhibitors in the treatment of patients with STEMI

ST-segment elevation MI is usually a result of sudden and complete occlusion of a coronary artery. Such immediate interruption in oxygen supply to the heart leads to rapidly progressing myocardial necrosis. **The main goal of STEMI treatment is to salvage as much cardiac muscle as possible, and this can be obtained by expeditious reperfusion of the culprit vessel, preceded by timely diagnosis and transportation to the catheterization laboratory without unnecessary delay.** Primary PCI remains the mainstay of coronary revascularization in patients with STEMI [2]. According to the ESC guidelines pre-hospital fibrinolysis is indicated in patients presenting early when anticipated STEMI diagnosis to PCI-mediated reperfusion time is > 120 minutes [2]. Nevertheless, in the Polish reality, where the density of invasive cardiology facilities is very high and transport times are short, the probability of such a situation is negligible. Moreover, the use of fibrinolytic drugs in ambulances was not approved by the Directive of the Minister of Health of Poland [49].

In the clinical setting of STEMI both potent P2Y12 inhibitors, prasugrel or ticagrelor, are preferred over clopidogrel. The use of clopidogrel should be limited to situations when neither of the stronger P2Y12 receptor inhibitors is available or when they are contraindicated (class of recommendation I, level of evidence A) [2]. Currently there is no evidence from randomized controlled trials indicating the optimal time point for initiation of antiplatelet treatment in STEMI [2]. Nevertheless, the available data suggest early initiation of P2Y12 receptor inhibitor treatment in order to obtain effective platelet inhibition by the time of PCI, especially that administration of P2Y12 inhibitors in pre-hospital management is considered to be safe [2, 38]. **Therefore, prasugrel 60 mg loading dose or ticagrelor 180 mg loading dose should be administered directly after the STEMI diagnosis is confirmed by ECG [2].** If unavailable or contraindicated clopidogrel 600 mg should be administered instead [2]. The ATLANTIC study has shown the pre-hospital loading with ticagrelor to be safe for STEMI patients [50]. Alternatively, in P2Y12-inhibitor naive patients undergoing PCI cangrelor (intravenous bolus of 30 mg/kg with subsequent of 4 mg/kg/min infusion lasting at least 2 h or duration of procedure, whichever is longer) may be considered (class of recommendation IIb, level of evidence A) [37]. However, up to date cangrelor is not available yet in Poland. Pre-hospital administration of DAPT should be especially avoided if there is a suspicion of active bleeding, mechanical complications of MI, acute aortic dissection or any other co-morbidities requiring emergency surgical operation.

Platelet P2Y12 receptor inhibitors in the treatment of patients with NSTE-ACS

Urgent coronary reperfusion is a mainstay of treatment for patients with STEMI, while in patients with NSTE-ACS the indications and recommended timeframes for invasive diagnostics and treatment depend primarily on risk stratification [2, 5]. The available evidence indicates that a routine invasive strategy reduces the risk of the composite ischemic endpoints, particularly in high-risk patients. Nevertheless, a routine invasive strategy does not reduce all-cause mortality in the overall population of NSTE-ACS patients, and it increases the risk of periprocedural complications [5]. The results of randomized controlled trials and their meta-analyses highlight the role of risk stratification in the decision-making process and support a routine invasive strategy only in very high and high-risk patients [51–55].

According to the ESC guidelines, immediate invasive strategy (< 2 h) should be applied in very high-risk NSTE-ACS patients (i.e., with at least one very high-risk criterion) [5]. The NSTE-ACS very high-risk criteria are defined as follows:

- Hemodynamic instability;
- Cardiogenic shock;
- Recurrent/refractory chest pain despite medical treatment;
- Life-threatening arrhythmias;
- Mechanical complications of MI;
- Acute heart failure clearly related to NSTE-ACS;
- ST-segment depression > 1 mm/6 leads plus ST-segment elevation aVR and/or V1.

Early invasive strategy (< 24 h) is recommended in high-risk patients. The NSTE-ACS high-risk criteria are defined as follows:

- Established NSTEMI diagnosis;
- Dynamic or presumably new contiguous ST/T-segment changes (symptomatic or silent);
- Resuscitated cardiac arrest without ST-segment elevation or cardiogenic shock;
- GRACE risk score > 140.

Similar to STEMI, DAPT, including ASA and one of the potent P2Y12 receptor inhibitors, is also recommended in patients with NSTE-ACS, unless

contraindicated, e.g., due to excessive bleeding risk (class of recommendation I, level of evidence A) [5]. The ISAR-REACT 5 trial compared two antiplatelet strategies: prasugrel-based vs. ticagrelor-based strategy in ACS patients for whom an invasive evaluation was planned. The trial demonstrated that the prasugrel-based strategy was associated with a reduced rate of composite of death, MI, or stroke, without an increase in the rate of bleeding complications [56]. Based on this single trial, the authors of the 2020 ESC guidelines on NSTE-ACS recommended prasugrel to be considered in preference to ticagrelor for NSTE-ACS patients who proceed to PCI after a diagnostic angiography was performed (class of recommendation IIa, level of evidence B) [5]. It should be highlighted, that the guidelines authors did not take into account serious limitations of the ISAR-REACT 5 trial [57–61] nor the results of the network meta-analysis of 12 randomized controlled trials by Navarese et al. [62] which clearly showed a similar reduction of ischemic events and increase of bleeding with both prasugrel and ticagrelor in comparison with clopidogrel. However, a significant mortality reduction was observed with ticagrelor only. Moreover, the meta-analysis showed that by excluding open label randomized controlled trials due to their limitations (e.g., ISAR-REACT 5), the mortality reduction with ticagrelor was strengthened without a significant increase of bleeding [62].

The 2020 ESC guidelines on NSTE-ACS suggest considering pre-treatment with a P2Y12 inhibitor in patients with NSTE-ACS who are not planned to undergo an early invasive strategy and do not have a high bleeding risk (class of recommendation IIb, level of evidence C) [5]. The same guidelines advocate against the use of routine pre-treatment with P2Y12 inhibitors in patients for whom coronary anatomy is not known and an early invasive management is planned (class of recommendation III, level of evidence A) [5].

In fact, supportive observations for a restrictive use of pre-treatment with P2Y12 receptor inhibitor are limited to prasugrel (ACCOAST trial) [63]. Therefore, prasugrel should not be administered prior to coronary angiography or when the patient is qualified for conservative treatment (class of recommendation III, level of evidence B) [37]. The prospective Swedish Coronary Angiography and Angioplasty Registry (SCAAR) [64] showed that pre-treatment of NSTE-ACS patients with P2Y12 receptor antagonists was not associated with improved clinical outcomes, but was associated with increased risk of bleeding in all consecutive patients who underwent PCI for NSTE-ACS (59894 patients with P2Y12 pre-treatment vs. 4963 patients without P2Y12 pre-treatment). However, whether pre-treatment with P2Y12 antagonists in selected high and very high-risk patients can improve clinical outcomes was not established in this study [64]. Moreover, the DUBIUS trial assessing efficacy and safety of pre-treatment vs. loading after angiography with oral P2Y12 receptor inhibitor in NSTE-ACS patients, was prematurely interrupted due to low incidence of ischemic and bleeding events and minimal numeric difference of event rates between the treatment groups [65].

According to the 2020 ESC guidelines, potent P2Y12 receptor inhibitors (ticagrelor or prasugrel) exhibit a fast onset of antiplatelet action, thereby allowing loading dose administration after diagnostic coronary angiography and directly before PCI [5]. However, the fast onset of action has been shown only in a stable setting [66–69], while in patients with MI the antiplatelet effect of both drugs was delayed, achieving satisfactory platelet inhibition in the majority of patients 2 hours after loading dose administration [17, 18, 70, 71]. Of note, even 4 hours after administration of the loading dose of ticagrelor high platelet reactivity (as assessed with VASP assay) was found in 7–37% of patients (depending on concomitant morphine administration) [17, 18, 70, 71]. Therefore, sufficient platelet inhibition at the time of PCI cannot be expected in patients in whom loading dose of ticagrelor or prasugrel was given after diagnostic coronary angiography and directly before PCI. This limitation can be overcome with cangrelor [5, 38, 44, 72, 73]. According to the ESC guidelines, due to its proven efficacy in preventing intra-procedural and postprocedural stent thrombosis cangrelor may be considered for use in P2Y12 receptor inhibitor-naive NSTE-ACS patients undergoing PCI (class of recommendation IIb, level of evidence A) [5, 37]. Unfortunately, cangrelor is still not available in Poland.

Due to conflicting evidence the routine pre-hospital administration of P2Y12 inhibitors in patients with NSTE-ACS is not recommended. However, even though early administration of P2Y12 receptor antagonists may increase the bleeding risk, the potential benefits for the selected NSTE-ACS patients may justify in-hospital administration of a ticagrelor loading dose before coronary angiography after an individual assessment. It has to be underlined though, that a decision on potential use of in-hospital pre-treatment

with ticagrelor should be left to the discretion of the treating physician.

Antiplatelet treatment after ACS

Dual antiplatelet therapy with ASA and P2Y12 receptor inhibitor should be maintained for 12 months after ACS, unless contraindications exist (class of recommendation I, level of evidence A) [2, 5]. In specific clinical scenarios, the duration of DAPT can be shortened, extended (> 12 months) or modified considering individual ischemic and bleeding risk, the occurrence of adverse events, comorbidities, and co-medications [2, 5, 62, 74–76]. Adding a second antithrombotic drug to ASA for long-term secondary prevention should be considered in patients with a high risk of ischemic events and without high bleeding risk (class of recommendation IIa, level of evidence A) — as a dual antithrombotic therapy (DATT). This strategy may be also considered in patients with at least a moderately increased risk of ischemic events and without high bleeding risk (class of recommendation IIb, level of evidence A) [5, 77]. A greater benefit in post-ACS patients may be expected with ASA and ticagrelor 60 mg b.i.d. when the therapy is continued after 12 months of DAPT without interruption or with short interruption only. On the other hand, a combination of ASA and rivaroxaban 2.5 mg b.i.d. seems to be a better option when indications for DATT appear after a longer time from ACS (more than 2 years) and/or from cessation of DAPT (more than 1 year), and in patients with multiple vascular bed atherosclerosis [78].

Conclusions

Dual antiplatelet therapy composed of ASA and a P2Y12 receptor inhibitor remains a mainstay of ACS therapy. The ESC guidelines recommend the use of potent P2Y12 inhibitors — prasugrel or ticagrelor over clopidogrel in all ACS patients, unless contraindicated, e.g., due to an excessive risk of bleeding [2, 5]. Clopidogrel is reserved for situations when prasugrel or ticagrelor are not available, cannot be tolerated or are contraindicated. Indications for ticagrelor are wider as compared with prasugrel, because ticagrelor can be used in conservatively treated ACS patients, patients pre-loaded with clopidogrel or on chronic clopidogrel therapy, as well as in those with previous ischemic stroke or transient ischemic attack, elderly (> 75 years of age) or those with low body mass (< 60 kg) [2, 3, 5]. Although, limited data on optimal timing of the P2Y12 receptor inhibitor initiation exist, there is a consistent recommendation that early administration — at the time of diagnosis — of a potent P2Y12 receptor inhibitor together with ASA and heparin is crucial in the management of all patients with STEMI [2]. In patients presenting with NSTE-ACS the latest 2020 ESC guidelines do not recommend the routine pre-treatment with a P2Y12 receptor inhibitor in patients in whom coronary anatomy is not known and an early invasive management is planned (class of recommendation III, level of evidence A) [5]. But, since the full antiplatelet effect is desired at the time of PCI and rapidly acting intravenous cangrelor is unavailable in Poland, in-hospital administration of ticagrelor loading dose before coronary angiography may be justified after an individual assessment. The use of prasugrel is not advised when the coronary anatomy is unknown what makes ticagrelor the drug of choice in the majority of ACS patients [37]. Moreover, ACS patients pre-treated with clopidogrel should be switched to ticagrelor when not contraindicated, but not to prasugrel which is recommended only in P2Y12 receptor inhibitor-naïve patients [3]. Importantly, in ACS patients undergoing coronary artery by-pass grafting procedure the use of ticagrelor provides the best safety profile, reducing the risk of adverse cardiovascular events, including death, yet not increasing the risk of coronary artery by-pass grafting-related bleeding when compared with clopidogrel [79].

Since the publication of the previous Recommendations for medical emergency teams a new Directive of the Minister of Health dated December 16, 2019 has been published [49]. Paramedics and emergency medical team members are allowed to (after ECG tele-transmission and consultation with the physician evaluating the ECG) administer as previously only clopidogrel and ticagrelor, but not prasugrel. In the periprocedural period ACS patients require anticoagulant treatment apart from DAPT, and according to the above-mentioned Directive of the Minister of Health, unfractionated heparin (70–100 U/kg) is the only anticoagulant agent that can be administered by paramedics and emergency medical team members.

This expert position is not fully in line with the recently published expert opinion of the Association of Cardiovascular Interventions and the Working Group on Cardiovascular Pharmacotherapy of the Polish Cardiac Society [80]. Nevertheless, the aforementioned expert opinion is only a summary of the 2020 ECS guidelines [5], while the present position paper is a proposal for the

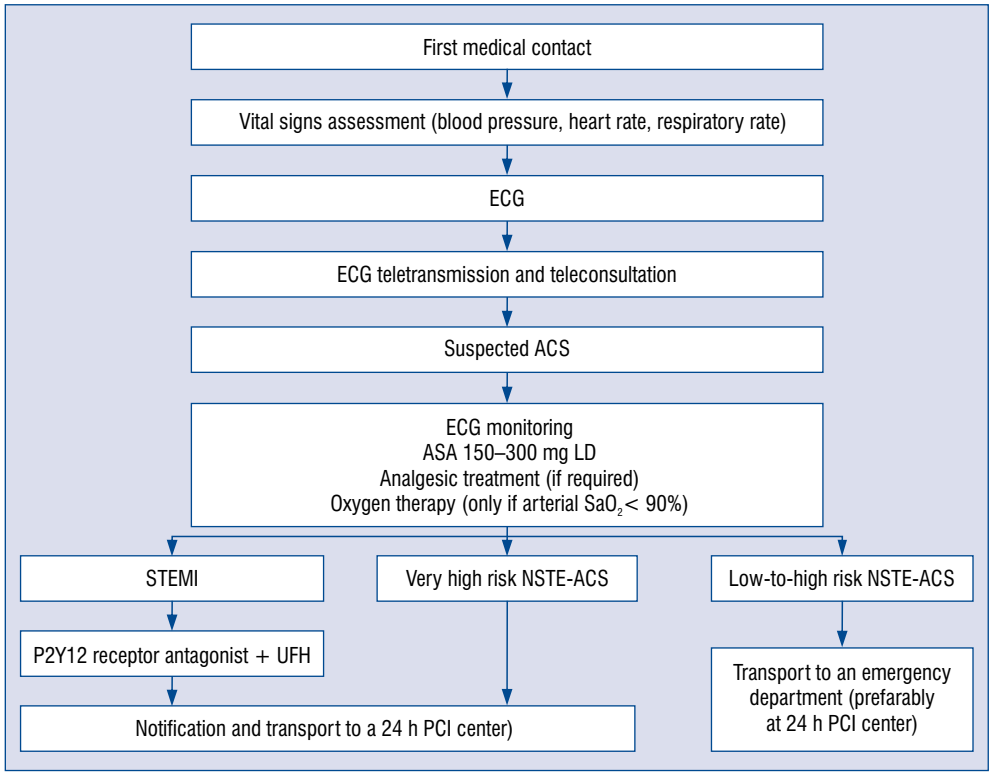

Figure 1. Algorithm for pre-hospital management of acute coronary syndromes (ACS); ASA — acetylsalicylic acid; ECG — electrocardiography; LD — loading dose; NSTE-ACS — non-ST-segment elevation acute coronary syndrome; PCI — percutaneous coronary intervention; SaO_2 — saturation of oxygen; STEMI — ST-segment elevation myocardial infarction; UFH — unfractionated heparin.

practical application of these recommendations in Polish conditions.

Pain management is an important part of the ACS emergency care. Titrated intravenous morphine remains the standard of care in STEMI patients [2]. While undertaking decision to administer morphine one should bear in mind the unwanted interaction between morphine and antiplatelet drugs as well as the fact that the most effective analgesic in ACS is urgent revascularization [17].

In the pre-hospital period patients with ACS may experience vomiting especially when given morphine. It carries the risk of loss of yet unabsorbed antiplatelet drugs. In such cases the time elapsed from drug intake to vomiting and the potential presence of tablets in the vomited content should be documented. The decision on administration of an additional dose of antiplatelet drugs should be left to the discretion of the physician at the destination hospital.

To conclude, ECG tele-transmission at first medical contact and consultation with experienced cardiologist enables pre-hospital administration of P2Y12 inhibitor loading dose added to ASA in all STEMI patients, while in NSTE-ACS patients in-hospital loading with P2Y12 inhibitor may be justified in selected patients (Fig. 1). Ticagrelor is the P2Y12 receptor inhibitor of choice in the vast majority of ACS patients.

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References

1. Kubica J, Adamski P, Paciorek P, et al. Anti-aggregation therapy in patients with acute coronary syndrome — recommendations for medical emergency teams. Experts' standpoint. Kardiol Pol. 2017; 75(4): 399–408, doi: 10.5603/KP.a2017.0057, indexed in Pubmed: 28421594.
2. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients present¬ing with ST-segment elevation: The Task Force for the manage¬ment 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.
3. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2018; 39(3): 213–260, doi: 10.1093/eurheartj/ehx419, indexed in Pubmed: 28886622.
4. Kubica J, Adamski P, Paciorek P, et al. Treatment of patients with acute coronary syndrome: Recommendations for medical emergency teams: Focus on antiplatelet therapies. Updated experts' standpoint. Cardiol J. 2018; 25(3): 291–300, doi: 10.5603/CJ.a2018.0042, indexed in Pubmed: 29671864.
5. Collet JP, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2021; 42(14): 1289–1367, doi: 10.1093/eurheartj/ehaa575, indexed in Pubmed: 32860058.
6. Borowicz A, Nadolny K, Bujak K, et al. Paramedic versus physician-staffed ambulances and prehospital delays in the management of patients with ST-segment elevation myocardial infarction. Cardiol J. 2021; 28(1): 110–117, doi: 10.5603/CJ.a2019.0072, indexed in Pubmed: 31313273.
7. Lopes RD, Siha H, Fu Y, et al. Diagnosing acute myocardial infarction in patients with left bundle branch block. Am J Cardiol. 2011; 108(6): 782–788, doi: 10.1016/j.amjcard.2011.05.006, indexed in Pubmed: 21726838.
8. Chan AW, Kornder J, Elliott H, et al. Improved survival associated with pre-hospital triage strategy in a large regional ST-segment elevation myocardial infarction program. JACC Cardiovasc Interv. 2012; 5(12): 1239–1246, doi: 10.1016/j.jcin.2012.07.013, indexed in Pubmed: 23257372.
9. Widimsky P, Rohác F, Stásek J, et al. Primary angioplasty in acute myocardial infarction with right bundle branch block: should new onset right bundle branch block be added to future guidelines as an indication for reperfusion therapy? Eur Heart J. 2012; 33(1): 86–95, doi: 10.1093/eurheartj/ehr291, indexed in Pubmed: 21890488.
10. Dhruva VN, Abdelhadi SI, Anis A, et al. ST-Segment Analysis Using Wireless Technology in Acute Myocardial Infarction (STAT-MI) trial. J Am Coll Cardiol. 2007; 50(6): 509–513, doi: 10.1016/j.jacc.2007.04.049, indexed in Pubmed: 17678733.
11. Bagai A, Jollis JG, Dauerman HL, et al. Emergency department bypass for ST-Segment-elevation myocardial infarction patients identified with a prehospital electrocardiogram: a report from the American Heart Association Mission: Lifeline program. Circulation. 2013; 128(4): 352–359, doi: 10.1161/CIRCULATIONAHA.113.002339, indexed in Pubmed: 23788525.
12. Welsh RC, Chang W, Goldstein P, et al. Time to treatment and the impact of a physician on prehospital management of acute ST elevation myocardial infarction: insights from the ASSENT-3 PLUS trial. Heart. 2005; 91(11): 1400–1406, doi: 10.1136/hrt.2004.054510, indexed in Pubmed: 15774607.
13. Steg PG, James SK, Atar D, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2012; 33(20): 2569–2619, doi: 10.1093/eurheartj/ehs215, indexed in Pubmed: 22922416.
14. Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J. 2016; 37(3): 267–315, doi: 10.1093/eurheartj/ehv320, indexed in Pubmed: 26320110.
15. ISIS-4: A randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58 050 patients with suspected acute myocardial infarction. Lancet. 1995; 345(8951): 669–685, doi: 10.1016/s0140-6736(95)90865-x.
16. Parodi G. Editor's Choice-Chest pain relief in patients with acute myocardial infarction. Eur Heart J Acute Cardiovasc Care. 2016; 5(3): 277–281, doi: 10.1177/2048872615584078, indexed in Pubmed: 25904757.
17. Kubica J, Kubica A, Jilma B, et al. Impact of morphine on antiplatelet effects of oral P2Y12 receptor inhibitors. Int J Cardiol. 2016; 215: 201–208, doi: 10.1016/j.ijcard.2016.04.077, indexed in Pubmed: 27128531.
18. Ostrowska M, Gorog D. Does morphine remain a standard of care in acute myocardial infarction? Med Res J. 2020; 5(1): 46–49, doi: 10.5603/mrj.a2020.0009.
19. Kubica J, Adamski P, Ostrowska M, et al. Influence of Morphine on Pharmacokinetics and Pharmacodynamics of Ticagrelor in Patients with Acute Myocardial Infarction (IMPRESSION): study protocol for a randomized controlled trial. Trials. 2015; 16(3): 198–252, doi: 10.1186/s13063-015-0724-z, indexed in Pubmed: 25925591.
20. Hobl EL, Stimpfl T, Ebner J, et al. Morphine decreases clopidogrel concentrations and effects: a randomized, double-blind, placebo-controlled trial. J Am Coll Cardiol. 2014; 63(7): 630–635, doi: 10.1016/j.jacc.2013.10.068, indexed in Pubmed: 24315907.
21. Parodi G, Bellandi B, Xanthopoulou I, et al. Morphine is associated with a delayed activity of oral antiplatelet agents in patients

with ST-elevation acute myocardial infarction undergoing primary percutaneous coronary intervention. Circ Cardiovasc Interv. 2015; 8(1), doi: 10.1161/CIRCINTERVENTIONS.114.001593, indexed in Pubmed: 25552565.
22. de Waha S, Eitel I, Desch S, et al. Intravenous morphine administration and reperfusion success in ST-elevation myocardial infarction: insights from cardiac magnetic resonance imaging. Clin Res Cardiol. 2015; 104(9): 727–734, doi: 10.1007/s00392-015-0835-2, indexed in Pubmed: 25725777.
23. Meine TJ, Roe MT, Chen AY, et al. Association of intravenous morphine use and outcomes in acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. Am Heart J. 2005; 149(6): 1043–1049, doi: 10.1016/j.ahj.2005.02.010, indexed in Pubmed: 15976786.
24. Puymirat E, Lamhaut L, Bonnet N, et al. Correlates of pre-hospital morphine use in ST-elevation myocardial infarction patients and its association with in-hospital outcomes and long-term mortality: the FAST-MI (French Registry of Acute ST-elevation and non-ST-elevation Myocardial Infarction) programme. Eur Heart J. 2016; 37(13): 1063–1071, doi: 10.1093/eurheartj/ehv567, indexed in Pubmed: 26578201.
25. Meine TJ, Roe MT, Chen AY, et al. Association of intravenous morphine use and outcomes in acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. Am Heart J. 2005; 149(6): 1043–1049, doi: 10.1016/j.ahj.2005.02.010, indexed in Pubmed: 15976786.
26. Iakobishvili Z, Porter A, Battler A, et al. Effect of narcotic treatment on outcomes of acute coronary syndromes. Am J Cardiol. 2010; 105(7): 912–916, doi: 10.1016/j.amjcard.2009.11.027, indexed in Pubmed: 20346305.
27. Gue YX, Spinthakis N, Farag M, et al. Impact of preadmission morphine on reinfarction in patients with ST-elevation myocardial infarction treated with percutaneous coronary intervention: a meta-analysis. Clin Pharmacol Ther. 2020; 108(1): 54–62, doi: 10.1002/cpt.1798, indexed in Pubmed: 31990051.
28. Batchelor R, Liu DH, Bloom J, et al. Association of periprocedural intravenous morphine use on clinical outcomes in ST-elevation myocardial infarction (STEMI) treated by primary percutaneous coronary intervention: Systematic review and meta-analysis. Catheter Cardiovasc Interv. 2020; 96(1): 76–88, doi: 10.1002/ccd.28561, indexed in Pubmed: 31654491.
29. Ibrahim K, Shah R, Goli RR, et al. Fentanyl delays the platelet inhibition effects of oral ticagrelor: full report of the PACIFY randomized clinical trial. Thromb Haemost. 2018; 118(8): 1409–1418, doi: 10.1055/s-0038-1666862, indexed in Pubmed: 29972861.
30. Senguttuvan NB, Suman F, Paneerselvam T, et al. Comparison of the effect of Morphine and Fentanyl in patients with acute coronary syndrome receiving Ticagrelor - The COMET (Comparison Morphine, Fentayl and Ticagrelor) randomized controlled trial. Int J Cardiol. 2021; 330: 1–6, doi: 10.1016/j.ijcard.2021.02.037, indexed in Pubmed: 33600846.
31. Tavenier AH, Hermanides RS, Ottervanger JP, et al. Impact of opioids on P2Y12 receptor inhibition in patients with ST-elevation myocardial infarction who are pre-treated with crushed ticagrelor: Opioids aNd crushed Ticagrelor In Myocardial infarction Evaluation (ON-TIME 3) trial. Eur Heart J Cardiovasc Pharmacother. 2022; 8(1): 4–12, doi: 10.1093/ehjcvp/pvaa095, indexed in Pubmed: 32730628.
32. Alexopoulos D, Barampoutis N, Gkizas V, et al. Crushed versus integral tablets of ticagrelor in ST-segment elevation myocardial infarction patients: a randomized pharmacokinetic/pharmacodynamic study. Clin Pharmacokinet. 2016; 55(3): 359–367, doi: 10.1007/s40262-015-0320-0, indexed in Pubmed: 26315810.
33. Parodi G, Xanthopoulou I, Bellandi B, et al. Ticagrelor crushed tablets administration in STEMI patients: the MOJITO study. J Am Coll Cardiol. 2015; 65(5): 511–512, doi: 10.1016/j.jacc.2014.08.056, indexed in Pubmed: 25660931.
34. Rollini F, Franchi F, Angiolillo DJ, et al. Crushed prasugrel tablets in patients with STEMI undergoing primary percutaneous coronary intervention: the CRUSH study. J Am Coll Cardiol. 2016; 67(17): 1994–2004, doi: 10.1016/j.jacc.2016.02.045, indexed in Pubmed: 27012781.
35. Niezgoda P, Sikora J, Barańska M, et al. Crushed sublingual versus oral ticagrelor administration strategies in patients with unstable angina. A pharmacokinetic/pharmacodynamic study. Thromb Haemost. 2017; 117(4): 718–726, doi: 10.1160/TH16-08-0670, indexed in Pubmed: 28203684.
36. Sikora J, Niezgoda P, Barańska M, et al. METoclopramide Administration as a Strategy to Overcome MORPHine-ticagrelOr Interaction in PatientS with Unstable Angina PectorIS-The METAMORPHOSIS Trial. Thromb Haemost. 2018; 118(12): 2126–2133, doi: 10.1055/s-0038-1675605, indexed in Pubmed: 30453344.
37. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019; 40(2): 87–165, doi: 10.1093/eurheartj/ehy394, indexed in Pubmed: 30165437.
38. Adamski P, Adamska U, Ostrowska M, et al. New directions for pharmacotherapy in the treatment of acute coronary syndrome. Expert Opin Pharmacother. 2016; 17(17): 2291–2306, doi: 10.1080/14656566.2016.1241234, indexed in Pubmed: 27677394.
39. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009; 361(11): 1045–1057, doi: 10.1056/NEJMoa0904327, indexed in Pubmed: 19717846.
40. Dans AL, Connolly SJ, Wallentin L, et al. Concomitant use of antiplatelet therapy with dabigatran or warfarin in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial. Circulation. 2013; 127(5): 634–640, doi: 10.1161/CIRCULATIONAHA.112.115386, indexed in Pubmed: 23271794.
41. Sørensen R, Hansen M, Abildstrom S, et al. Risk of bleeding in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel, and vitamin K antagonists in Denmark: a retrospective analysis of nationwide registry data. The Lancet. 2009; 374(9706): 1967–1974, doi: 10.1016/s0140-6736(09)61751-7.
42. Hansen ML, Sørensen R, Clausen MT, et al. Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. Arch Intern Med. 2010; 170(16): 1433–1441, doi: 10.1001/archinternmed.2010.271, indexed in Pubmed: 20837828.
43. Oldgren J, Budaj A, Granger CB, et al. Dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial. Eur Heart J. 2011; 32(22): 2781–2789, doi: 10.1093/eurheartj/ehr113, indexed in Pubmed: 21551462.
44. Tantry U, Chaudhary R, Kubica J, et al. Cangrelor for the treatment of patients with Arterial Thrombosis. Expert Opin Pharmacother. 2018; 19(12): 1389–1398, doi: 10.1080/14656566.2018.1506767, indexed in Pubmed: 30102083.
45. Kubica J, Kozinski M, Navarese EP, et al. Cangrelor: an emerging therapeutic option for patients with coronary ar-

tery disease. Curr Med Res Opin. 2014; 30(5): 813–828, doi: 10.1185/03007995.2014.880050, indexed in Pubmed: 24393016.
46. Umińska JM, Ratajczak J, Buszko K, et al. Impact of mild therapeutic hypothermia on bioavailability of ticagrelor in patients with acute myocardial infarction after out-of-hospital cardiac arrest. Cardiol J. 2020; 27(6): 780–788, doi: 10.5603/CJ.a2019.0024, indexed in Pubmed: 30799546.
47. Ratajczak J, Łach P, Umińska JM, et al. Mild therapeutic hypothermia after out-of-hospital cardiac arrest: What does really matter? Cardiol J. 2021; 28(2): 293–301, doi: 10.5603/CJ.a2019.0023, indexed in Pubmed: 30799547.
48. Tomala MT, Trąbka-Zawicki A, Machnik A, et al. Ticagrelor effectively inhibits platelet aggregation in comatose survivors of cardiac arrest undergoing primary percutaneous coronary intervention treated with mild therapeutic hypothermia. Cardiol J. 2021 [Epub ahead of print], doi: 10.5603/CJ.a2021.0064, indexed in Pubmed: 34165181.
49. Directive of the Minister of Health dated 16 December 2019 on medical rescue procedures and health services different than medical rescue procedures, which can be performed by paramedic.
50. Montalescot G, van ,t Hof AW, Lapostolle F, et al. Prehospital ticagrelor in ST-segment elevation myocardial infarction. N Engl J Med. 2014; 371(11): 1016–1027, doi: 10.1056/NEJMoa1407024, indexed in Pubmed: 25175921.
51. O'Donoghue M, Boden WE, Braunwald E, et al. Early invasive vs conservative treatment strategies in women and men with unstable angina and non-ST-segment elevation myocardial infarction: a meta-analysis. JAMA. 2008; 300(1): 71–80, doi: 10.1001/jama.300.1.71, indexed in Pubmed: 18594042.
52. Mehta SR, Cannon CP, Fox KAA, et al. Routine vs selective invasive strategies in patients with acute coronary syndromes: a collaborative meta-analysis of randomized trials. JAMA. 2005; 293(23): 2908–2917, doi: 10.1001/jama.293.23.2908, indexed in Pubmed: 15956636.
53. Fox KAA, Clayton TC, Damman P, et al. Long-term outcome of a routine versus selective invasive strategy in patients with non-ST-segment elevation acute coronary syndrome a meta-analysis of individual patient data. J Am Coll Cardiol. 2010; 55(22): 2435–2445, doi: 10.1016/j.jacc.2010.03.007, indexed in Pubmed: 20359842.
54. Fanning JP, Nyong J, Scott IA, et al. Routine invasive strategies versus selective invasive strategies for unstable angina and non-ST elevation myocardial infarction in the stent era. Cochrane Database Syst Rev. 2016(5): CD004815, doi: 10.1002/14651858.CD004815.pub4, indexed in Pubmed: 27226069.
55. Elgendy IY, Mahmoud AN, Wen X, et al. Meta-analysis of randomized trials of long-term all-cause mortality in patients with non-ST-elevation acute coronary syndrome managed with routine invasive versus selective invasive strategies. Am J Cardiol. 2017; 119(4): 560–564, doi: 10.1016/j.amjcard.2016.11.005, indexed in Pubmed: 27939385.
56. Schüpke S, Neumann FJ, Menichelli M, et al. Ticagrelor or prasugrel in patients with acute coronary syndromes. N Engl J Med. 2019; 381(16): 1524–1534, doi: 10.1056/nejmoa1908973.
57. Kubica J, Jaguszewski M. ISAR-REACT 5 — What have we learned? Cardiol J. 2019; 26(5): 427–428, doi: 10.5603/CJ.a2019.0090, indexed in Pubmed: 31536136.
58. Angoulvant D, Sabouret P, Savage MP. NSTE-ACS ESC guidelines recommend prasugrel as the preferred P2Y12 inhibitor: a contrarian view. Am J Cardiovasc Drugs. 2021; 21(5): 483–486, doi: 10.1007/s40256-021-00471-z, indexed in Pubmed: 33674980.
59. Crea F, Thiele H, Sibbing D, et al. Debate: Prasugrel rather than ticagrelor is the preferred treatment for NSTE-ACS patients who proceed to PCI and pretreatment should not be performed in patients planned for an early invasive strategy. Eur Heart J. 2021; 42(31): 2973–2985, doi: 10.1093/eurheartj/ehab277, indexed in Pubmed: 34110420.
60. Arslan F, Damman P, Zwart B, et al. 2020 ESC Guidelines on acute coronary syndrome without ST-segment elevation: Recommendations and critical appraisal from the Dutch ACS and Interventional Cardiology working groups. Neth Heart J. 2021; 29(11): 557–565, doi: 10.1007/s12471-021-01593-4, indexed in Pubmed: 34232481.
61. Kubica J, Jaguszewski M, Ostrowska M, et al. Creative scientific dispute — different points of view on the protocol and execution of the ISAR-REACT 5 trial. Med Res J. 2020; 5(1): 41–45, doi: 10.5603/mrj.a2020.0008.
62. Navarese EP, Khan SU, James S, et al. Comparative efficacy and safety of oral P2Y inhibitors in acute coronary syndrome: network meta-analysis of 52 816 patients from 12 randomized trials. Circulation. 2020; 142(2): 150–160, doi: 10.1161/CIRCULATIONAHA.120.046786, indexed in Pubmed: 32468837.
63. Montalescot G, Bolognese L, Dudek D, et al. Pretreatment with prasugrel in non-ST-segment elevation acute coronary syndromes. N Engl J Med. 2013; 369(11): 999–1010, doi: 10.1056/NEJMoa1308075, indexed in Pubmed: 23991622.
64. Dworeck C, Redfors B, Angerås O, et al. Association of pretreatment with P2Y12 receptor antagonists preceding percutaneous coronary intervention in non-ST-segment elevation acute coronary syndromes with outcomes. JAMA Netw Open. 2020; 3(10): e2018735, doi: 10.1001/jamanetworkopen.2020.18735, indexed in Pubmed: 33001202.
65. Tarantini G, Mojoli M, Varbella F, et al. Timing of oral P2Y inhibitor administration in patients with non-ST-segment elevation acute coronary syndrome. J Am Coll Cardiol. 2020; 76(21): 2450–2459, doi: 10.1016/j.jacc.2020.08.053, indexed in Pubmed: 32882390.
66. Gurbel PA, Bliden KP, Butler K, et al. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. Circulation. 2009; 120(25): 2577–2585, doi: 10.1161/CIRCULATIONAHA.109.912550, indexed in Pubmed: 19923168.
67. Buszko K, Kubica K, Hobl EL, et al. Pharmacokinetic modeling of morphine's effect on plasma concentrations of ticagrelor and its metabolite in healthy volunteers. Front Physiol. 2021; 12: 663170, doi: 10.3389/fphys.2021.663170, indexed in Pubmed: 34248659.
68. Hobl EL, Reiter B, Schoergenhofer C, et al. Morphine decreases ticagrelor concentrations but not its antiplatelet effects: a randomized trial in healthy volunteers. Eur J Clin Invest. 2016; 46(1): 7–14, doi: 10.1111/eci.12550, indexed in Pubmed: 26449338.
69. Hobl EL, Reiter B, Schoergenhofer C, et al. Morphine interaction with prasugrel: a double-blind, cross-over trial in healthy volunteers. Clin Res Cardiol. 2016; 105(4): 349–355, doi: 10.1007/s00392-015-0927-z, indexed in Pubmed: 26493304.
70. Schoergenhofer C, Hobl EL, Staudinger T, et al. Prasugrel in critically ill patients. Thromb Haemost. 2017; 117(8): 1582–1587, doi: 10.1160/TH17-03-0154, indexed in Pubmed: 28692105.
71. Adamski P, Sikora J, Laskowska E, et al. Comparison of bioavailability and antiplatelet action of ticagrelor in patients with ST-elevation myocardial infarction and non-ST-elevation myo-

cardial infarction: A prospective, observational, single-centre study. PLoS One. 2017; 12(10): e0186013, doi: 10.1371/journal.pone.0186013, indexed in Pubmed: 29023473.
72. Adamski P, Adamska U, Ostrowska M, et al. Evaluating current and emerging antithrombotic therapy currently available for the treatment of acute coronary syndrome in geriatric populations. Expert Opin Pharmacother. 2018; 19(13): 1415–1425, doi: 10.1080/14656566.2018.1510487, indexed in Pubmed: 30132731.
73. Ostrowska M, Kubica J, Adamski P, et al. Stratified approaches to antiplatelet therapies based on platelet reactivity testing. Front Cardiovasc Med. 2019; 6: 176, doi: 10.3389/fcvm.2019.00176, indexed in Pubmed: 31850373.
74. Kubica J, Adamski P, Gorog DA, et al. Prolonged antithrombotic therapy in patients after acute coronary syndrome: A critical appraisal of current European Society of Cardiology guidelines. Cardiol J. 2020; 27(6): 661–676, doi: 10.5603/CJ.a2020.0132, indexed in Pubmed: 33073857.
75. Kubica J, Adamski P, Niezgoda P, et al. A new approach to ticagrelor-based de-escalation of antiplatelet therapy after acute coronary syndrome. A rationale for a randomized, double-blind, placebo-controlled, investigator-initiated, multicenter clinical study. Cardiol J. 2021; 28(4): 607–614, doi: 10.5603/CJ.a2021.0056, indexed in Pubmed: 34096012.
76. Tubek S, Kuliczkowski W, Gąsior M, et al. Antiplatelets in acute coronary syndrome in Poland - from guidelines to clinical practice. Postepy Kardiol Interwencyjnej. 2021; 17(2): 141–154, doi: 10.5114/aic.2021.107492, indexed in Pubmed: 34400916.
77. Knuuti J, Wijns W, Saraste A, et al. ESC Scientific Document Group. 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.
78. Kubica J, Adamski P, Niezgoda P, et al. Prolonged antithrombotic therapy in patients after acute coronary syndrome: A critical appraisal of current European Society of Cardiology guidelines. Cardiol J. 2020; 27(6): 661–676, doi: 10.5603/CJ.a2020.0132, indexed in Pubmed: 33073857.
79. Held C, Asenblad N, Bassand JP, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes undergoing coronary artery bypass surgery: results from the PLATO (Platelet Inhibition and Patient Outcomes) trial. J Am Coll Cardiol. 2011; 57(6): 672–684, doi: 10.1016/j.jacc.2010.10.029, indexed in Pubmed: 21194870.
80. Barylski M, Legutko J, Lesiak M, et al. An expert opinion of the Association of Cardiovascular Interventions and the Working Group on Cardiovascular Pharmacotherapy of the Polish Cardiac Society related to the place of prasugrel in the prevention of cardiovascular events in patients with acute coronary syndromes. Kardiol Pol. 2022; 80(1): 113–122, doi: 10.33963/KP.a2022.0006, indexed in Pubmed: 35076081.

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Safety of coronary revascularization deferral based on fractional flow reserve and instantaneous wave-free ratio in patients with chronic kidney disease

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Abstract

Background: *The safety of revascularization deferral according to pressure wire examination in patients with chronic kidney disease (CKD) has not been fully established.*

Methods: *From a retrospective cohort of 439 patients in whom revascularization was deferred after physiological assessment, we examined the incidence of patient-oriented composite endpoint (POCE: all-cause death, myocardial infarction [MI] and unplanned revascularization) in patients with CKD (estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m^2) and without it.*

Results: *At 4 years of follow-up, the primary endpoint was met by 25.0% of patients with CKD and by 14.4% of patients without CKD (hazard ratio [HR] 1.56, 95% confidence interval [CI] 0.96–2.53, p = 0.071). The incidence of POCE was even higher in patients with an eGFR < 30 mL/min/1.73 m^2: 43.8% (HR 3.10, 95% CI 1.08–8.92, p = 0.036). However, no differences were observed in the incidence of MI (4.2% vs. 4.4% in non-CKD), target vessel revascularization (5.8% vs. 5.9%), and target vessel MI (0.8% vs. 4.6%).*

Conclusions: *Patients with CKD in whom pressure-wire evaluation led to deferral of coronary revascularization develop more POCE in the long term, compared to patients with normal renal function. However, the increase in POCE in patients with CKD was seldom related to deferred vessels, thus suggesting an epiphenomenon of an intrinsically higher cardiovascular risk of CKD patients.* (Cardiol J 2022, 29, 4: 553–562)

Key words: pressure wire, fractional flow reserve, instantaneous wave-free ratio, chronic kidney disease

Introduction

Physiological evaluation of coronary stenosis is a valuable tool to guide myocardial revascularization. Its safety has been widely demonstrated in the past years [1], shifting the process of treating coronary lesions from anatomical to physiological grounds. For more than two decades fractional flow reserve (FFR) was the only pressure-derived index available for functional stenosis assessment. More recently, instantaneous wave-free ratio (iFR), a non-hyperemic diastolic pressure ratio that overcomes some limitations of FFR [2, 3], was demonstrated to be non-inferior to FFR in clinical decision-making, contributing to more widespread use of pressure wire interrogation in real practice [4].

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One of the ways that pressure guidewire interrogation contributes to improved patient outcome is by avoiding unneeded revascularization procedures in functionally non-significant coronary stenoses. While the overall safety of myocardial revascularization deferral based on FFR and iFR has been well stablished [5, 6], there is a paucity of data regarding such an approach in subgroups of patients with high risk of coronary disease progression. One such subgroup is made up of patients with chronic kidney disease (CKD), which is associated with a higher burden of coronary atherosclerosis [7], faster disease progression [8], and higher incidence of cardiovascular events, compared with patients with normal renal function [9, 10].

The main aim of this study was to investigate whether deferral of coronary stenosis revascularization based on pressure guidewire interrogation is equally safe in patients with CKD and in patients with normal function. Additionally, we also wanted to investigate the long-term outcomes of revascularization deferral based on FFR or iFR in patients with and without CKD.

Methods

Study design and population selection

This is a single-center, retrospective study that collected all consecutive patients who underwent pressure-wire evaluation of angiographical stenosis (by visual estimation), and in whom treatment was deferred based on the result of this technique. Either FFR or iFR were performed, and patients were classified as FFR-deferred or iFR-deferred according to the method of pressure wire used for evaluation.

Different baseline characteristics were assessed. Serum creatinine was determined from blood samples in the 48 hours prior to the procedure. The estimated glomerular filtration rate (eGFR) was derived using the CKD-EPI formula. The cut-off value of 60 mL/min/1.73 m^2 was used to establish the presence or absence of CKD. Current clinical practice guidelines were used to define the different CKD stages [11].

Procedural aspects

Pressure wire assessment was performed with commercial guidewires available during the study period — Verrata (Phillips Healthcare, San Diego, California) and PressureWire X (St. Jude Medical, St. Paul, Minnesota) — and a standard technique as previously reported. An intracoronary bolus of nitrates (200 μg) was administered before FFR or iFR measurement. In cases in which FFR was performed, intravenous adenosine was infused with a rate of 140 μg/kg/min. At the end of each procedure, the presence of significant drift was ruled-out by placing the sensor of the pressure-wire at the tip of the guiding catheter.

In patients with stable angina, physiological evaluation was performed in the same procedure and all intermediate stenoses could be assessed. Serial stenoses were assessed as a single lesion and only those with non-ischemic values of pressure wire examination were deemed for inclusion in the present analysis. In patients with acute coronary syndromes, interrogation with a pressure wire was performed at a staged procedure only in non-culprit vessels. The cut-off points to defer revascularization were FFR > 0.80 or iFR > 0.89.

Endpoints

The primary endpoint was the combination of all-cause death, myocardial infarction (MI), or unplanned revascularization. Secondary endpoints were all-cause death, death due to cardiovascular causes, MI, and unplanned revascularization. Moreover, vessel-related endpoints such as target vessel MI and target vessel revascularization (TVR) were pre-specified as secondary endpoints. The minimum follow-up period was 2 years.

Statistical analysis

The population was divided based on the presence or absence of CKD, and the technique of pressure wire was used to defer revascularization (FFR or iFR).

Univariate analysis for baseline characteristics was done using the Pearson χ^2 test or Fisher's exact test for categorical variables, as appropriate. Comparison between continuous data was made using the Student-Fisher t-test or Wilcoxon's rank test in cases of non-normal distributions.

For the primary and secondary endpoints, a time-to-event analysis was performed using the Cox's proportional hazards model. Results are reported as hazard ratios (HR) with two-sided 95% confidence intervals (CI). Analyses were performed in an unadjusted manner as well as being adjusted by variables that were considered relevant: age, sex, the presence of diabetes mellitus, hypertension, tobacco use, clinical presentation, and the percentage of angiographic diameter stenosis.

The validity of the proportional hazards assumption was assessed using Schoenfeld residuals. No signs of violation of the proportional hazards

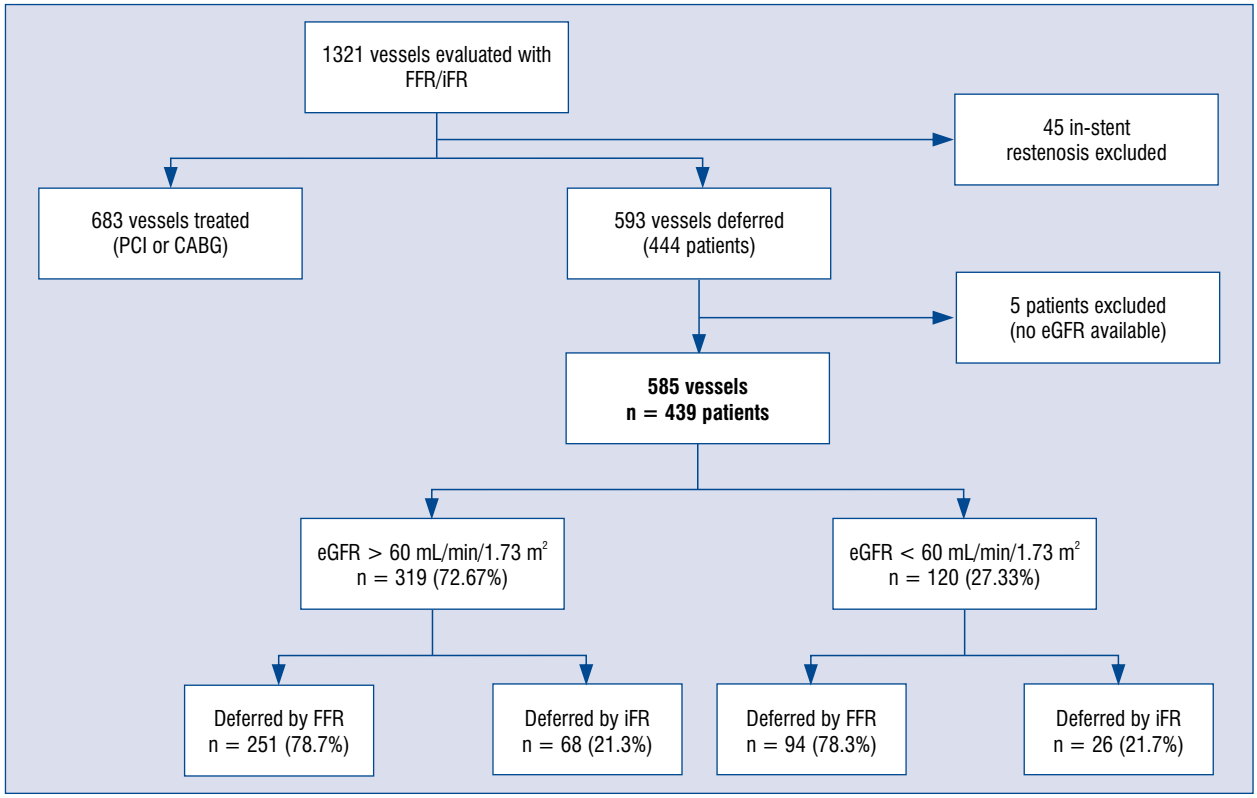

Figure 1. Flowchart of the study; CABG – coronary artery bypass grafting; FFR — fractional flow reserve; iFR — instantaneous wave-free ratio; eGFR — estimated glomerular filtration rate; PCI — percutaneous coronary intervention.

principle were found. Finally, cumulative hazards curves were created using the Kaplan-Meier method.

All statistical calculations were carried out with STATA 14 (StataCorp. 4905 Lakeway Drive. College Station, Texas. USA).

Results

Study population

From January 2012 to December 2016, a total of 1321 vessels underwent pressure-wire evaluation. From them, a total of 593 vessels (444 patients) were deferred according to the result of the pressure wire assessment. Five patients were excluded because of the unavailability of renal function data. A final cohort of 439 patients was included in the analysis (Fig. 1).

Baseline characteristics

Of the overall population, 120 (27.3%) patients had an eGFR of less than 60 mL/min/1.73 m^2. Sixteen of them (3.6%) had severe eGFR impairment (< 30 mL/min/1.73 m^2 or hemodialysis). Baseline characteristics are shown in Table 1.

Patients with eGFR < 60 mL/min/1.73 m^2 were significantly older (73.5 years vs. 66.6 years, $p < 0.001$) and had a higher prevalence of cardiovascular risk factors such as hypertension (79.2% vs. 69.9%, $p = 0.053$), diabetes mellitus (50.8% vs. 31.7%, $p < 0.001$), and peripheral vascular disease (16.7% vs. 5.6%, $p < 0.001$). They had higher rates of anticoagulation treatment (16.7% vs. 6.3%, $p = 0.003$) and less use of acetylsalicylic acid (ASA; 89.1% vs. 95.8%, $p = 0.008$).

Baseline angiographical characteristics and physiological results are shown in Table 2. Patients had a mean of 1.3 vessels interrogated in both groups. No differences were found in the mean values of FFR or iFR in either group, or in the type of vessel evaluated, the left anterior descendant (LAD) being the most frequently assessed. A less than 1% but statistically significant difference was seen in the percentage of angiographic stenosis (61.0% vs. 59.1%, $p = 0.027$), but this small disparity can be considered as clinically not relevant.

Table 1. Baseline characteristics.

	No CKD (eGFR > 60 mL/ /min/1.73 m^2)	CKD (eGFR < 60 mL/ /min/1.73 m^2)	P
Number of patients	319 (72.67%)	120 (27.33%)	—
Mean follow-up [months]	39.82 ± 0.6	38.12 ± 1.1	0.141
Age	66.55 ± 0.6	73.53 ± 0.8	< 0.001
Female sex	73 (22.9%)	31 (25.8%)	0.517
Hypertension	223 (69.9%)	95 (79.2%)	0.053
Dyslipidemia	201 (63.0%)	83 (69.2%)	0.229
Diabetes mellitus	101 (31.7%)	61 (50.8%)	< 0.001
Insulin therapy	17 (5.3%)	22 (18.3%)	< 0.001
Smoker (current and former)	194 (60.8%)	57 (47.5%)	0.012
Previous CABG	9 (2.8%)	3 (2.5%)	> 0.999*
Previous PCI	170 (49.0%)	48 (52.2%)	0.587
Previous MI	157 (49.2%)	61 (50.8%)	0.763
Peripheral vascular disease	18 (5.6%)	20 (16.7%)	< 0.001
Previous stroke	14 (4.4%)	7 (5.8%)	0.527
COPD	20 (6.3%)	10 (8.3%)	0.554
Statins	287 (93.8%)	106 (91.4%)	0.382
ACEIs/ARBs	234 (76.5%)	89 (76.7%)	0.956
Beta-blockers	243 (79.4%)	90 (77.6%)	0.682
Acetylsalicylic acid	299 (95.8%)	106 (89.1%)	0.008
Anticoagulation	10 (6.3%)	20 (16.7%)	0.003
Clinical presentation:			0.451
Stable angina	144 (45.1%)	59 (49.2%)	
Acute coronary syndrome	175 (54.9%)	61 (50.8%)	

Results are presented as number (%) or mean (± standard deviation). P values marked with asterisk (*) are calculated with Fisher's exact test. ACEIs — angiotensin-converter enzyme inhibitors; ARBs — angiotensin receptor blockers; CABG — coronary artery bypass grafting; CKD — chronic kidney disease; COPD — chronic obstructive pulmonary disease; eGFR — estimated glomerular filtration rate; MI — myocardial infarction; PCI — percutaneous coronary intervention

Outcomes in patients with and without CKD

The median follow-up was 42.1 (interquartile range [IQR] 26.6) and 43.0 (IQR 26.2) months in patients with and without CKD, respectively.

At 4 years, 30 (25.0%) patients with eGFR < 60 mL/min/1.73 m^2 met the primary endpoint (patient-oriented composite endpoint [POCE]: composite of all-cause death, MI, or unplanned revascularization), in comparison with 46 (14.4%) patients with eGFR > 60 mL/min/1.73 m^2 (Fig. 2A). The unadjusted HR was 1.81 (95% CI 1.15–2.84; p = 0.010). This difference was mainly driven by a higher rate of all-cause death (13.3% vs. 5.3%; p = 0.006) and cardiovascular death (5.8% vs. 1.3%; p = 0.012), and a less prominent but also higher rate of unplanned revascularization in patients with worse renal function (11.7% vs. 7.2%; p = 0.097; Table 3). No differences were observed in the incidence of MI (4.2% vs. 4.4%; p = 0.967). The adjusted multivariate analysis failed to reach statistical significance for the primary or the secondary endpoints but showed a trend towards a higher incidence of POCE in patients with eGFR < 60 mL/min/1.73 m^2, with a HR of 1.56 (95% CI 0.96–2.53; p = 0.071), and towards more frequent unplanned revascularizations (HR 1.91; 95% CI 0.93–3.93; p = 0.078).

Nevertheless, in the categorical analysis of the stages of CKD, the patients from stages G4 and G5 (eGFR of less than 30 mL/min/1.73 m^2) showed a marked increase in the incidence of POCE when compared to the reference category (stage G1: eGFR > 60 mL/min/1.73 m^2). In this case, the association remained significant in the adjusted analysis, with a HR of 3.10 (95% CI 1.08–8.92; p = 0.036; Table 4, Fig. 2B).

Interestingly, the higher event rate observed in patients with CKD was not related with the vessel

Table 2. Angiographic characteristics of the population.

	No CKD (eGFR > 60 mL/ /min/1.73 m^2)	CKD (eGFR < 60 mL/ /min/1.73 m^2)	P
Number of patients	319 (72.7%)	120 (27.3%)	—
Number of vessels	427 (73.0%)	158 (27.0%)	—
Mean of evaluated vessels (per patient)	1.34 ± 0.03	1.32 ± 0.05	0.990
Vessels evaluated per patient:			
1	230 (72.1%)	91 (75.8%)	0.432
2	73 (22.9%)	21 (17.5%)	0.220
3	13 (4.1%)	7 (5.8%)	0.431
4	3 (0.9%)	1 (0.8%)	> 0.999*
Percent of stenosis	59 ± 0.44	61 ± 0.76	0.027
Technique for deferral:			0.936
FFR	251 (78.7%)	94 (78.3%)	
iFR	68 (21.3%)	26 (21.7%)	
Mean FFR	0.87 (±0.003)	0.87 (±0.004)	0.435
Mean iFR	0.95 (±0.003)	0.94 (±0.005)	0.296
Vessel evaluated:			
Left main	19 (4.5%)	6 (3.8%)	0.729
LAD	178 (41.7%)	64 (40.5%)	0.797
LCX	133 (31.2%)	40 (25.3%)	0.170
RCA	91 (21.3%)	43 (27.2%)	0.131
Ramus intermedius	6 (1.4%)	5 (3.2%)	0.164
Multivessel disease (≥ 3 vessels)	60 (18.8%)	26 (21.7%)	0.501

Results are presented as number (%) or mean (± standard deviation). P values marked with asterisk (*) are calculated with Fisher's exact test. CKD — chronic kidney disease; eGFR — estimated glomerular filtration rate; FFR — fractional flow reserve; iFR — instantaneous free-wave ratio; LAD — left anterior descendant; LCX — left circumflex artery; RCA — right coronary artery

deferred by physiological evaluation. When assessing vessel-oriented outcomes, patients with eGFR < 60 mL/min/1.73 m^2 showed similar rates of TVR (5.8% vs. 5.0% in non-CKD patients) and target vessel MI (0.8% vs. 1.6% in non-CKD patients) related to the vessel left untreated on the grounds of non-ischemic FFR or iFR vales, both being non-statistically significant in the unadjusted and adjusted analysis (Fig. 2B, C).

Revascularization deferral based on FFR or iFR: Influence on patient outcomes

In the overall population, a total of 345 (78.6%) patients were deferred by FFR, and 94 (21.4%) were deferred by iFR, with a ratio between techniques similar in both groups with and without CKD (p = 0.936). The primary endpoint occurred in 64 (18.6%) patients in which the lesion was deferred by FFR, and in 12 (12.8%) patients deferred by iFR, with no differences between the techniques in patients with eGFR above or below 60 mL/min/1.73 m^2 (Fig. 3, Table 5). No significant differences in the incidence of other events were observed when comparing FFR and iFR deferral in patients with or without CKD.

Discussion

The main findings of the present study are as follows: i) in patients in whom revascularization of coronary stenosis has been deferred according to pressure-wire evaluation, the presence of CKD is associated with worse outcomes; ii) the excess in POCE observed in CKD patients is not caused by vessel-oriented events related to the deferred stenoses; and iii) no differences in outcomes were noted in CKD patients according to the physiological index (iFR or FFR) used in decision-making.

Overall, the findings of the study support the safety of pressure-guidewire based deferral of revascularization in patients with CKD, while highlighting the overall higher cardiovascular risk and worse prognosis of these patients, compared with those with normal renal function.

Table 3. Outcomes for patients with and without chronic kidney disease (CKD).

Endpoint	No CKD (eGFR > 60 mL/ /min/1.73m^2)	CKD (eGFR < 60 mL/ /min/1.73m^2)	Unadjusted HR and 95% CI	Unadjusted p value	Fully adjusted HR and 95% CI	Fully adjusted p value
MACE (all-cause death, infarction, revascularization)	46 (14.4%)	30 (25.0%)	**1.81 (1.15–2.84)**	**0.010**	**1.56 (0.96–2.53)**	**0.071**
All-cause death	17 (5.3%)	16 (13.3%)	**2.60 (1.31–5.15)**	**0.006**	**1.51 (0.75–3.04)**	**0.251**
Cardiovascular death	4 (1.3%)	7 (5.8%)	**4.84 (1.42–16.54)**	**0.012**	**2.83 (0.80–10.02)**	**0.106**
Myocardial infarction	14 (4.4%)	5 (4.2%)	**0.98 (0.35–2.72)**	**0.967**	**0.93 (0.31–2.74)**	**0.903**
Unplanned revascularization	23 (7.2%)	14 (11.7%)	**1.76 (0.90–3.41)**	**0.097**	**1.91 (0.93–3.96)**	**0.078**
Target vessel revascularization	16 (5.0%)	7 (5.8%)	**1.32 (0.54–3.24)**	**0.543**	**1.60 (0.60–4.28)**	**0.347**
Target vessel myocardial infarction	5 (1.6%)	1 (0.8%)	**0.56 (0.07–4.79)**	**0.596**	**0.61 (0.06–5.79)**	**0.666**

Events are shown as number (%). Analysis of unadjusted and adjusted hazard ratios (HR). Variables used for adjusted analysis: age, sex, hypertension, diabetes, tobacco use, clinical presentation, and percentage of angiographic stenosis. CI — confidence interval; eGFR — estimated glomerular filtration rate; MACE — major adverse cardiac events

Table 4. Outcomes of patients for different categories of chronic kidney disease (CKD).

Endpoint and CKD category [mL/min/1.73 m^2]	Events N (%)	Unadjusted HR and 95% CI	Unadjusted p value	Fully adjusted HR and 95% CI	Fully adjusted p value
MACE (all cause death, infarction, revascularization):					
Stage G1 (> 90)	10 (13.3%)	—	—	—	—
Stage G2 (60–90)	39 (16.0%)	1.19 (0.59–2.38)	0.630	1.00 (0.48–2.07)	0.998
Stage G3 (30–60)	24 (23.1%)	1.81 (0.87–3.79)	0.115	1.38 (0.61–3.10)	0.441
Stages G4 and G5 (< 30)	7 (43.8%)	4.07 (1.55–10.69)	0.004	3.10 (1.08–8.92)	0.036

Events are shown as n (%). Hazard ratios (HR) are derived having in consideration stage G1 as the reference. Variables used for adjusted analysis: age, sex, hypertension, diabetes, tobacco use, clinical presentation, and percentage of angiographic stenosis. CI — confidence interval; MACE — major adverse cardiac events

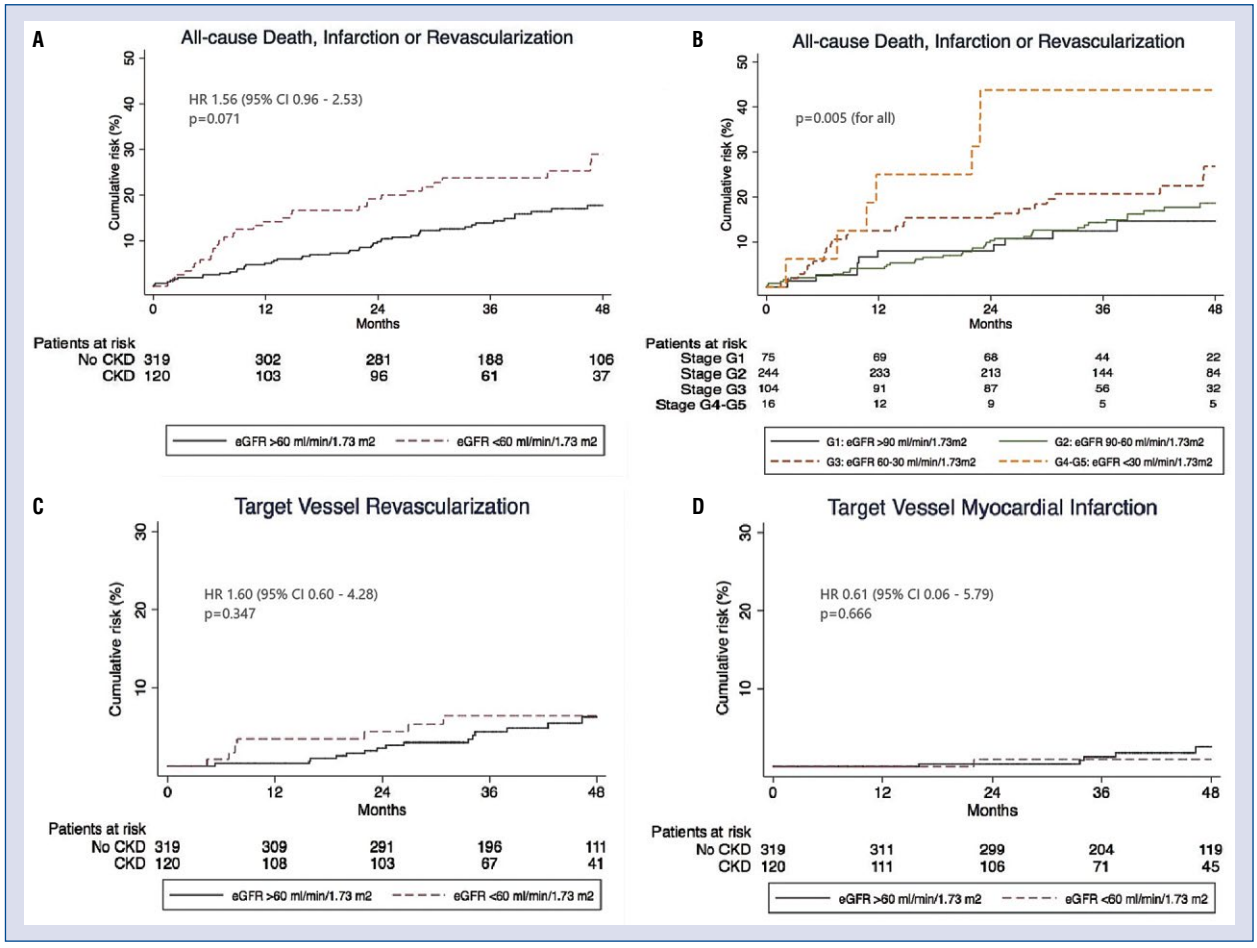

Figure 2. Kaplan-Meier survival plots comparing outcomes according to the presence or not of chronic kidney disease (CKD), and across CKD stages; **A.** Cumulative incidence of the primary endpoint (all-cause death, infarction, or unplanned revascularization) for the dichotomous variable CKD; **B.** Incidence of the primary endpoint for the different CKD stages; **C.** Incidence of target vessel revascularization for patients with or without CKD; **D.** Incidence of target vessel myocardial infarction; CI — confidence interval; eGFR — estimated glomerular filtration rate; HR — hazard ratio. For the individual HR of the different CKD categories (plot B), see Table 4.

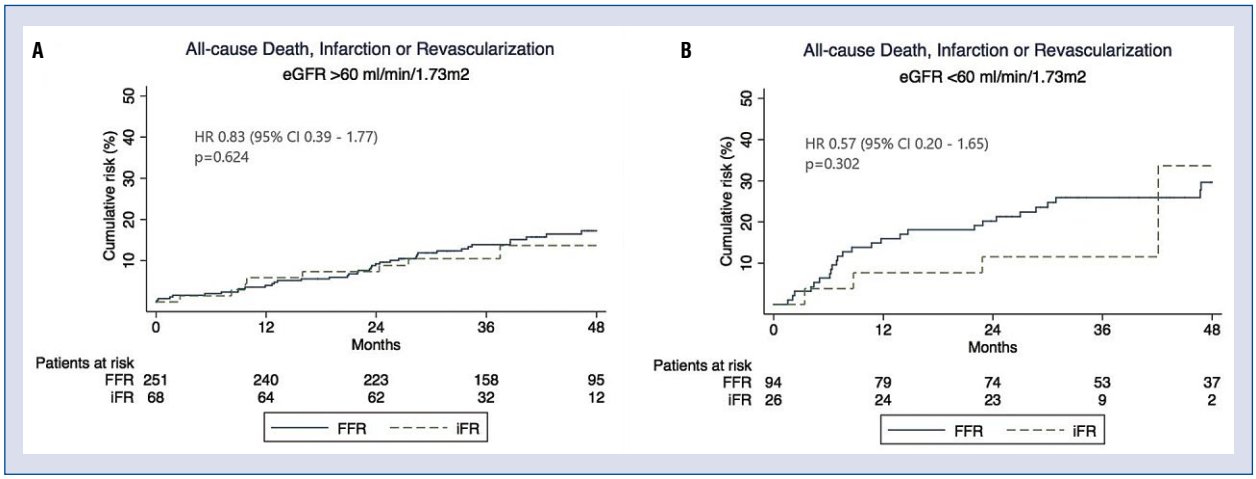

Figure 3. Kaplan-Meier survival plots comparing the technique used for revascularization deferral; **A.** Cumulative incidence of the primary endpoint in patients without chronic kidney disease (CKD) (estimated glomerular filtration rate [eGFR] > 60 mL/min/1.73 m^2) according to the technique of physiological assessment used (fractional flow reserve [FFR] or instantaneous wave-free ratio [iFR]); **B.** Cumulative incidence of the primary endpoint in patients with CKD (eGFR < 60 mL/min/1.73 m^2); CI — confidence interval; HR — hazard ratio.

Table 5. Outcomes for patients according to the technique of pressure wire used to defer treatment and the presence or absence of chronic kidney disease.

Endpoint	FFR deferred	iFR deferred	HR and 95% CI	P
MACE (death, MI, or revascularization):	64 (18.6%)	12 (12.8%)	0.73 (0.39–1.35)	0.310
> 60 mL/min/1.73 m^2	38 (15.1%)	8 (11.8%)	0.83 (0.39–1.77)	0.624
< 60 mL/min/1.73 m^2	26 (27.7%)	4 (15.4%)	0.57 (0.20–1.65)	0.302
All-cause mortality:	25 (7.3%)	8 (8.5%)	1.30 (0.59–2.89)	0.519
> 60 mL/min/1.73 m^2	12 (4.8%)	5 (7.4%)	1.67 (0.59–4.76)	0.333
< 60 mL/min/1.73 m^2	13 (13.8%)	3 (11.5%)	0.94 (0.27–3.33)	0.925
Cardiovascular mortality:	8 (2.3%)	3 (3.2%)	1.48 (0.39–5.59)	0.729
> 60 mL/min/1.73 m^2	2 (0.8%)	2 (2.9%)	4.15 (0.58–29.60)	0.156
< 60 mL/min/1.73 m^2	6 (6.4%)	1 (3.9%)	0.62 (0.07–5.16)	0.659
MI:	16 (4.7%)	3 (3.2%)	0.87 (0.25–3.00)	0.822
> 60 mL/min/1.73 m^2	12 (4.8%)	2 (2.9%)	0.74 (0.16–3.30)	0.690
< 60 mL/min/1.73 m^2	4 (4.3%)	1 (3.9%)	1.36 (0.14–12.88)	0.792
Revascularization:	33 (9.6%)	4 (4.3%)	0.48 (0.17–1.35)	0.161
> 60 mL/min/1.73 m^2	20 (8.0%)	3 (4.4%)	0.61 (0.18–2.05)	0.421
< 60 mL/min/1.73 m^2	13 (13.8%)	1 (3.9%)	0.28 (0.04–2.16)	0.223
TVR:	21 (6.1%)	2 (2.1%)	0.39 (0.09–1.71)	0.216
> 60 mL/min/1.73 m^2	14 (5.6%)	2 (2.9%)	0.62 (0.14–2.75)	0.533
< 60 mL/min/1.73 m^2	7 (7.5%)	0 (0%)	—	—
Target vessel MI:	4 (1.2%)	2 (2.1%)	2.57 (0.46–14.24)	0.280
> 60 mL/min/1.73 m^2	3 (1.2%)	2 (2.9%)	3.48 (0.58–21.03)	0.175
< 60 mL/min/1.73 m^2	1 (1.1%)	0 (0%)	—	—

Events are shown as number (%). CI — confidence interval; FFR — fractional flow reserve; HR — hazard ratio; iFR — instantaneous wave-free ratio; MACE — major adverse cardiac events MI — myocardial infarction; TVR — target vessel revascularization

Chronic kidney disease is an independent risk factor for coronary atherosclerosis and cardiovascular disease [9, 12]. Although impairment of renal function is associated with worse outcomes after myocardial revascularization [13, 14], the causes for this increased event rate are unclear. As stated in the introduction, there is a paucity of data on whether physiology-guided revascularization might contribute to better outcomes of CKD patients by avoiding unneeded interventions. Patients with CKD were underrepresented in pivotal studies supporting the value of FFR and iFR. In the FAME and FAME II trials no exclusion criteria were established based on renal function, but in the latter, the prevalence of defined CKD was less than 3% in the overall population.

From a theoretical standpoint, it might be possible that the diagnostic yield of both FFR and iFR is impaired in patients with CKD. Endothelial and microvascular dysfunction are common features of CKD, leading to impaired coronary vasodilator capacity [15] and higher microcirculatory resistances [16]. Coronary vasodilator dysfunction is an independent predictor of mortality in patients with CKD [17], with incremental diagnostic power over clinical assessment, left ventricular systolic function, and the presence of ischemia or non-viable myocardium. Due to this, the use of hyperemic-dependent diagnostic methods may be inadequate in establishing the true hemodynamic significance of coronary stenoses in CKD patients. On the other hand, iFR has demonstrated a closer correlation with coronary flow reserve (CFR) values than FFR. Because CFR is predictive of the risk of cardiovascular death regardless of CKD stage [18], it remains plausible that decision-making with FFR and iFR might be associated with differences in patient outcomes.

Few studies have focused on the use of physiology-based coronary indices in CKD patients. Tebaldi et al. [16] found that patients with CKD were more likely to have non-ischemic values of FFR, this being more frequent as renal function worsens. Conversely, a short report (n = 42) on hemodialysis patients [19] showed that the optimal cut-off value of FFR for detection of myocardial

ischemia (assessed with stress myocardial perfusion imaging techniques) was similar to the cut-off value in the overall population. However, because those studies were transversal in nature and lacked clinical follow-up of their study populations, the clinical impact of an FFR-based treatment strategy remains unknown.

In our study, we observed that patients with an eGFR of less than 60 mL/min/1.73 m^2 had a higher incidence of the primary endpoint (all-cause death, MI, or unplanned revascularization) when compared to patients with preserved renal function. Although in the adjusted analysis this association was not statistically significant, we could observe a trend ($p = 0.071$). This conclusion is further supported by the gradient effect that was observed in the staged analysis: as the renal function worsens, the incidence of POCE increases. We observed a 5% annual risk of POCE in the population with CKD, in contrast with a 3.6% annual risk in the non-CKD population. Both are comprised within the upper and lower limits of the incidence of 1-year major cardiovascular events estimated in previous studies of pressure wire-deferred vessels [6, 20].

This difference of POCE between CKD and non-CKD patients was mainly caused by an augmented risk of all cause death, cardiac death, and unplanned revascularizations, the incidence of MI being similar in both groups.

What is more relevant, even with this greater incidence of POCE and higher prevalence of comorbidities, there were no significant differences in vessel-oriented events (TVR or target vessel MI) related to the coronary artery interrogated with iFR or FFR. This supports our conclusion that, although patients with CKD are at high-risk for the development of cardiovascular events, deferring lesions according to pressure wire values is safe in terms of the incidence of MI or the necessity of unplanned revascularization in the evaluated vessel. In practice, at 4 years of follow-up, only half of the total amount of revascularizations in patients with renal insufficiency were performed in the previously interrogated vessel, in contrast with 69% in the non-CKD population. Furthermore, in CKD patients only 1 out of every 5 MIs during follow-up was attributable to the vessel assessed. Overall, these observations might reflect a wider progression of the disease in patients with CKD, not restricted to the vessel evaluated with pressure wire, and this leads to events related with other areas of the coronary tree.

In the sub-analysis regarding the technique used for physiological assessment, we conclude that, despite obvious limitations, the use of iFR to defer the treatment of intermediate coronary stenosis is associated with similar outcomes to those with the use of FFR, irrespective of the presence or absence of renal insufficiency. However, in this cohort the decision of whether to perform iFR or FFR was at the operator's discretion, and therefore we cannot exclude the occurrence of selection bias. Additionally, the sample number did not provide enough power to compare both techniques in different CKD stages. In order to precisely address the potential role of non-hyperemic indexes against FFR in more advanced renal insufficiency, a randomized study between both techniques is needed.

Limitations of the study

This study has various limitations. First, it is a single-center, retrospective, and observational study, and even if the results appear to be consistent, they should be considered as hypothesis-generating until further prospective randomized data becomes available. Second, eGFR estimated via creatinine levels could not be a reliable estimator of the baseline renal function in some cases. Although operators are discouraged to perform coronary angiography in the setting of acute renal failure, there was no previous data in order to exclude patients with recent worsening of eGFR. Third, the absence of randomization could have led to involuntary patient selection, avoiding the realization of angiography in patients with worse renal function. Fourth, because of the reduced number of patients with more severe CKD (eGFR < 30 mL/min/1.73 m^2), conclusions regarding secondary outcomes or the comparison between iFR and FFR in this subgroup were not feasible due to the lack of statistical power. And fifth, because FFR, iFR, and eGFR are continuous variables, the dichotomization in cut-off points always involves the loss of potentially relevant data. Limitations regarding comparison of FFR and iFR have been previously discussed.

On the other hand, our study provides real-world information about outcomes in daily practice, and the results mentioned above can fuel future investigations that will help to elucidate the best therapeutic strategies in CKD patients.

Conclusions

Patients with CKD and coronary lesions deferred upon pressure-wire evaluation have a higher risk of POCE than those with normal renal function, but these events are not related to the de-

ferred vessel. Pressure-wire evaluation is safe in terms of the risk of target vessel revascularization or target vessel MI in this population.

Conflict of interest: Dr. Travieso-Gonzalez, Dr. Casto-Mejia, Dr. Jeronimo-Baza, Dr. Perez-Vizcayno, Dr. Mejia-Rentería, Dr. Macaya, Dr. Tirado--Conte, Dr. Jimenez-Quevedo, Dr. Salinas, and Dr. Nuñez-Gil do not have disclosures. Dr. Nombela--Franco has served as proctor for Abbott and has received speaker honoraria from Edwards Lifesciences. Dr. Fernandez-Ortiz is a speaker at educational events funded by Medtronic, Biotronik, Biosensor, and Bayer. Dr. Escaned is a speaker and consultant for Abbott, Boston Scientific, and Phillips and has received personal fees from Phillips Volcano, Boston Scientific, and Abbott/St. Jude Medical. Dr. Gonzalo is a speaker at educational events funded by Abbott and Boston Scientific.

References

1. Tonino PAL, De Bruyne B, Pijls NHJ, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med. 2009; 360(3): 213–224, doi: 10.1056/NEJMoa0807611, indexed in Pubmed: 19144937.
2. Davies JE, Sen S, Dehbi H-M, et al. Use of the Instantaneous Wave-free Ratio or Fractional Flow Reserve in PCI. N Engl J Med. 2017; 376: 1824–1834.
3. Götberg M, Christiansen EH, Gudmundsdottir IJ, et al. Instantaneous Wave-free Ratio versus Fractional Flow Reserve to Guide PCI. N Engl J Med. 2017; 376(19): 1813–1823, doi: 10.1056/NEJMoa1616540, indexed in Pubmed: 28317438.
4. Lee HS, Lee JM, Nam CW, et al. Consensus document for invasive coronary physiologic assessment in Asia-Pacific countries. Cardiol J. 2019; 26(3): 215–225, doi: 10.5603/CJ.a2019.0054, indexed in Pubmed: 31225632.
5. Bech GJ, De Bruyne B, Pijls NH, et al. Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis: a randomized trial. Circulation. 2001; 103(24): 2928–2934, doi: 10.1161/01.cir.103.24.2928, indexed in Pubmed: 11413082.
6. Escaned J, Ryan N, Mejía-Rentería H, et al. Safety of the deferral of coronary revascularization on the basis of instantaneous wave-free ratio and fractional flow reserve measurements in stable coronary artery disease and acute coronary syndromes. JACC Cardiovasc Interv. 2018; 11(15): 1437–1449, doi: 10.1016/j.jcin.2018.05.029, indexed in Pubmed: 30093050.
7. Sugiyama T, Kimura S, Ohtani H, et al. Impact of chronic kidney disease stages on atherosclerotic plaque components on optical coherence tomography in patients with coronary artery disease. Cardiovasc Interv Ther. 2017; 32(3): 216–224, doi: 10.1007/s12928-016-0408-y, indexed in Pubmed: 27339299.
8. Bundy JD, Chen J, Yang W, et al. Risk factors for progression of coronary artery calcification in patients with chronic kidney disease: The CRIC study. Atherosclerosis. 2018; 271: 53–60, doi: 10.1016/j.atherosclerosis.2018.02.009, indexed in Pubmed: 29459266.
9. Go AS, Chertow GM, Fan D, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004; 351(13): 1296–1305, doi: 10.1056/NEJMoa041031, indexed in Pubmed: 15385656.
10. Fried LF, Shlipak MG, Crump C, et al. Renal insufficiency as a predictor of cardiovascular outcomes and mortality in elderly individuals. J Am Coll Cardiol. 2003; 41(8): 1364–1372, doi: 10.1016/s0735-1097(03)00163-3, indexed in Pubmed: 12706933.
11. Levey AS, Coresh J, Bolton K, et al. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. Am J Kidney Dis. 2002; 39: S1–S266.
12. Pereg D, Tirosh A, Shochat T, et al. Mild renal dysfunction associated with incident coronary artery disease in young males. Eur Heart J. 2008; 29(2): 198–203, doi: 10.1093/eurheartj/ehm525, indexed in Pubmed: 18079138.
13. Milojevic M, Head SJ, Mack MJ, et al. The impact of chronic kidney disease on outcomes following percutaneous coronary intervention versus coronary artery bypass grafting in patients with complex coronary artery disease: five-year follow-up of the SYNTAX trial. EuroIntervention. 2018; 14(1): 102–111, doi: 10.4244/EIJ-D-17-00620, indexed in Pubmed: 29155387.
14. Best P, Lennon R, Ting H, et al. The impact of renal insufficiency on clinical outcomes in patients undergoing percutaneous coronary interventions. J Am Coll Cardiol. 2002; 39(7): 1113–1119, doi: 10.1016/s0735-1097(02)01745-x.
15. Chade AR, Brosh D, Higano ST, et al. Mild renal insufficiency is associated with reduced coronary flow in patients with non-obstructive coronary artery disease. Kidney Int. 2006; 69(2): 266––271, doi: 10.1038/sj.ki.5000031, indexed in Pubmed: 16408115.
16. 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.
17. Murthy VL, Naya M, Foster CR, et al. Coronary vascular dysfunction and prognosis in patients with chronic kidney disease. JACC Cardiovasc Imaging. 2012; 5(10): 1025–1034, doi: 10.1016/j.jcmg.2012.06.007, indexed in Pubmed: 23058070.
18. Charytan DM, Skali H, Shah NR, et al. Coronary flow reserve is predictive of the risk of cardiovascular death regardless of chronic kidney disease stage. Kidney Int. 2018; 93(2): 501–509, doi: 10.1016/j.kint.2017.07.025, indexed in Pubmed: 29032954.
19. Hirose K, Chikamori T, Hida S, et al. Application of pressure-derived myocardial fractional flow reserve in chronic hemodialysis patients. J Cardiol. 2018; 71(1): 52–58, doi: 10.1016/j.jjcc.2017.05.007, indexed in Pubmed: 29183566.
20. Sen S, Ahmad Y, Dehbi HM, et al. Clinical events after deferral of LAD revascularization following physiological coronary assessment. J Am Coll Cardiol. 2019; 73(4): 444–453, doi: 10.1016/j.jacc.2018.10.070, indexed in Pubmed: 30704577.

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Efficacy and safety of bioresorbable scaffolds in patients with coronary bifurcation lesions: A systematic review and meta-analysis

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Abstract

Background: *Bioresorbable scaffolds (BRS) were considered to be beneficial for coronary bifurcation lesions regarding the avoidance of lateral branch opening incarceration after complete absorption. However, data is limited in this setting. The aim of this meta-analysis was to evaluate the short (6-month) and medium-term (1-year) outcomes of BRS in patients with coronary bifurcation lesions.*

Methods: *PubMed, EMBASE, Web of Science, Cochrane library databases were searched to find the studies of BRS implantation in patients with coronary bifurcation lesions. The effective outcome was target lesion revascularization. The safety outcomes included major adverse cardiovascular events, target vessel revascularization, myocardial infarction, definite or probable scaffold thrombosis, and cardiac death.*

Results: *A total of 1204 patients involved in 12 studies were included. The pooled estimate rate of target lesion revascularization as efficacy outcome was highly consistent between 6-month and 1-year follow-up, which was 4.74% (95% CI 2.36–9.54%, I^2 = 41.5%, p = 0.14) and 4.37% (95% CI 3.05–5.69%, I^2 = 4.6%, p = 0.39). The pooled estimated rate of major adverse cardiovascular events as safety outcome was 5.50% and 7.31% for both 6-month and 1-year follow-up. The pooled estimated rate of target vessel revascularization, myocardial infarction, definite or probable scaffold thrombosis, and cardiac death at 1-year follow-up was 5.92%, 2.52%, 1.69%, and 0.42%.*

Conclusions: *The application of BRS for coronary bifurcation lesions is acceptable in efficacy outcome, but the high rate of scaffold thrombosis remains of concern (Registered by PROSPERO, CRD42019140341).* (Cardiol J, 2022; 29, 4: 563–573)

Key words: bioresorbable scaffolds, coronary bifurcation lesions, percutaneous coronary intervention, meta-analysis

Introduction

Bifurcation lesions are common complex coronary artery lesions, accounting for 15–20% of percutaneous coronary intervention (PCI), and are also one of the most challenging lesions in interventional cardiology from the point of view for procedural success rate and long-term cardiac events [1]. Drug-eluting stents (DES) are currently recommended for the treatment of coronary bifurcation lesions [2]. However, the DES can lead to inflammation, poor adherence and impaired vasodilation, which may also limit the possibility of re-intervention after permanent implantation. In

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addition, the risks of late stent thrombosis and in-stent restenosis are still the major factors affecting the efficacy of coronary artery disease especially coronary bifurcation lesions [3, 4].

The emergence of bioresorbable scaffolds (BRS), which can be traced back to 1980s may be conducive to this problem with the following advantages: shorter arterial healing time than DES implantation, late lumen expansion can reduce the risk of restenosis and avoidance of long-term jailing for side branch stent after complete resorption of scaffold wire within 2–3 years following implantation [4]. Meanwhile, it is believed that restoration of vascular patency may be more important for treatment of coronary bifurcation lesions in the absence of permanent implants [5]. Additional potential advantages include easier imaging (cardiac computed tomography or magnetic resonance imaging) and increased lumen area [6].

The applications of BRS are being extended to more complex lesions in the real-world study. However, there is still a lack of randomized controlled trials for coronary bifurcation lesions; the available data are limited to observational studies of conclusion conflict [7, 8]. The current expert consensus only provided a limited recommendation for the application of this new technology in coronary bifurcation lesions [1, 2, 9]. Given the advantages and clinical setting of BRS, a hypothesis to be beneficial for patients with coronary bifurcation lesions was established. Therefore, this systematic review and meta-analysis was designed to evaluate the efficacy and safety of BRS for the short- (6-month) and medium-term (1-year) in patients with those.

Methods

Search strategy

The present systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) consensus statement [10] and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) consensus statement [11]. PubMed, EMBASE, Web of Science, Cochrane library databases were searched with the following keywords: "coronary bifurcation lesion*" AND "bioresorbable scaffold*" OR "bioresorbable vascular stent*" (**Suppl. File S1**) with no language restrictions from inception to September 21, 2019. The references from relevant articles were scanned for additional studies not identified in the initial database search. An automated reminder from the PubMed was set up to track the latest publications. All reports were independently screened by two investigators (X.Y. Liang and Y. Li) to determine whether they met the inclusion criteria and any disagreement was resolved by consultation. The study protocol was registered in PROSPERO (CRD42019140341).

Selection criteria

The inclusion criteria were as follows: (1) patients with at least one coronary bifurcation lesion (*de novo* bifurcation lesion involving a side-branch ≥ 2 mm by visual estimation in diameter); (2) at least 1 BRS implanted; (3) at least 9 patients were included in the study; (4) trials reported clinical outcomes for at least 6 months; (5) included at least 1 clinical outcome, such as target lesion revascularization (TLR), major adverse cardiovascular events (MACE), target vessel revascularization (TVR), myocardial infarction (MI), definite or probable scaffold thrombosis (ST) or cardiac death.

The exclusion criteria included: (1) experimental studies on animals; (2) case report, conference abstract, review or expert opinions; (3) incomplete description (no complete report for patient characteristics and clinical outcomes of coronary bifurcation lesions); (4) duplicate publication or duplicate studies (if duplicate studies were identified, only the most exhaustive and recent reports were retained).

Data extraction

Baseline characteristics, lesion and procedural characteristics for patients, as well as numbers of events, were independently extracted from the original publications by 4 investigators (X.Y. Liang, Y. Li, W.J. Zhang, and X. Qiao). Divergences were resolved through discussions with the third party (Z.L. Wang).

Outcomes and definitions

The effective outcome was TLR, defined as any repeated PCI or coronary artery bypass grafting (CABG) for the segment of previously treated or in the adjacent 5 mm. The safety outcomes were MACE, TVR, any MI, definite or probable ST, and cardiac death. The MACE was defined according to the definitions of the original trials. The TVR was defined as repeat PCI or CABG in the target vessel. The MI was defined according to the universal definition [12]. The definite or probable ST was classified according to the Academic Research Consortium criteria [13]. Deaths that could not be attributed to another cause was regarded as cardiac death.

Quality assessment

Depending on the type of study included, the Newcastle-Ottawa scale checklist [14] and the Joanna Briggs Institute Critical Appraisal Checklist for Case Series (https://joannabriggs.org/research/critical-appraisal-tools.html) were used to assess the quality of non-randomized studies and case series. The quality of all studies was independently evaluated by 2 investigators (X.Y. Liang and Y. Li) and any dispute was settled by a third party through negotiations (Z.L. Wang). Furthermore, GRADE-profiler 3.2.2 was performed to appraise the quality of the evidence as high, moderate, low or very low grades [15]. As analyses were based on previously published studies, ethical approval and patient consent were not required.

Statistical analysis

Statistical analysis was performed on the pooled data of all included studies. The metaprop command was used to calculate combined rate with 95% confidence interval (95% CI). The normality test was employed for untransformed proportion (PRAW) and the rate transformed by Natural Logar Transformed Proportion, Logit Transformed Proportion, Arcsine Transformed Proportion or Freeman-Tukey Double Arcsine Transformed before the metaprop analysis, and the method close to the normal distribution was selected according to the results. Meta-analyses of dichotomous variables were expressed as odds ratio (OR) and 95% CI. Heterogeneity was assessed by the Higgins I^2 test, and random-effects model was applied to calculate the statistic effects. Publication bias was evaluated by visual estimation of funnel plots and the Egger's test at the $p < 0.05$ level of significance. The sensitivity analysis was performed by omitting one study from the analysis at a time. The subgroup analysis was utilized to explore the effect of different conditions (acute coronary syndrome [ACS] or not, diabetes mellitus [DM] or not) on outcomes. The p-value threshold of two-tailed significance was 0.05. Analyses were performed with R 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria and Stata SE 14.0 (StataCorp LP, College Station, Texas).

Results

Search results and characteristics

At first, 532 articles were retrieved, which were reduced to 144 studies after screening the title and abstract. Finally, 12 studies are included in the quantitative synthesis after excluding most unrelated studies (Fig. 1) [7, 8, 16–25]. Among them, the Desolve 150 BRS (Elixir, US) was used in one study [22], while others used the second-generation everolimus-eluting bioresorbable vascular scaffolds (ABSORB; Abbott Vascular, Santa Clara, CA, USA). A total of 1,204 patients met the inclusion criteria and were included, of whom 1,014 (84.2%) were male patients, 573 (47.6%) patients with ACS and 369 (30.7%) patients with DM in Table 1. The lesion and procedure features are listed in Table 2. The quality assessments for studies are reported in **Supplementary Tables S1 and S2**. GRADE quality assessment is provided in **Supplementary Table S3**.

The effective outcome

Five studies provided data on the effective outcome of TLR at 6-month follow-up and the pooled estimate rate of TLR is 4.74% (95% CI 2.36–9.54%, $I^2 = 41.5\%$, $p = 0.14$; Fig. 2). A significant asymmetry was observed in the funnel plot by visual estimation (**Suppl. Fig. S1a**). However, the publication bias was not detected by the Egger's test ($p = 0.81$). The sensitivity analysis shows that the pooled estimate rate was reduced from 4.74% to 3.53% and heterogeneity of the remaining studies had changed significantly ($I^2 = 0\%$) when a study was omitted (**Suppl. Fig. S2**). The effective outcome for 1 year was followed-up in 8 studies, which shows that the pooled estimate rate of TLR was 4.37% (95% CI 3.05–5.69%, $I^2 = 4.6\%$, $p = 0.39$) (Fig. 2). For this outcome, no asymmetry is identified in the funnel plot by visual estimation (**Suppl. Fig. S1b**), and no significant publication bias was found by the Egger's test ($p = 0.11$).

The safety outcomes

The safety outcomes are presented (Fig. 3). The pooled estimate rate of MACE was 5.50% (95% CI 0.56–10.45%, $I^2 = 41.2\%$, $p = 0.15$) at 6-month follow-up and 7.31% (95% CI 4.69–9.92%, $I^2 = 36.9\%$, $p = 0.16$) at 1-year follow-up. The sensitivity analysis shows that the pooled estimate rate of MACE at 6-month follow-up had decreased from 5.50% to 3.89% and heterogeneity of the remaining studies had changed significantly ($I^2 = 0\%$) after omitting one study (**Suppl. Fig. S2b**). The initial pooled estimate rates of TVR and MI at 1-year follow-up were 5.92% (95% CI 3.62–8.22%, $I^2 = 15.5\%$, $p = 0.31$) and 2.52% (95% CI 1.32–3.73%, $I^2 = 28.6\%$, $p = 0.19$). The pooled estimate rate was 1.69% (95% CI 0.80–2.58%, $I^2 = 0\%$, $p = 0.49$) for the definite or probable ST and 0.42% (95% CI 0–0.95%, $I^2 = 0\%$, $p = 0.97$) for

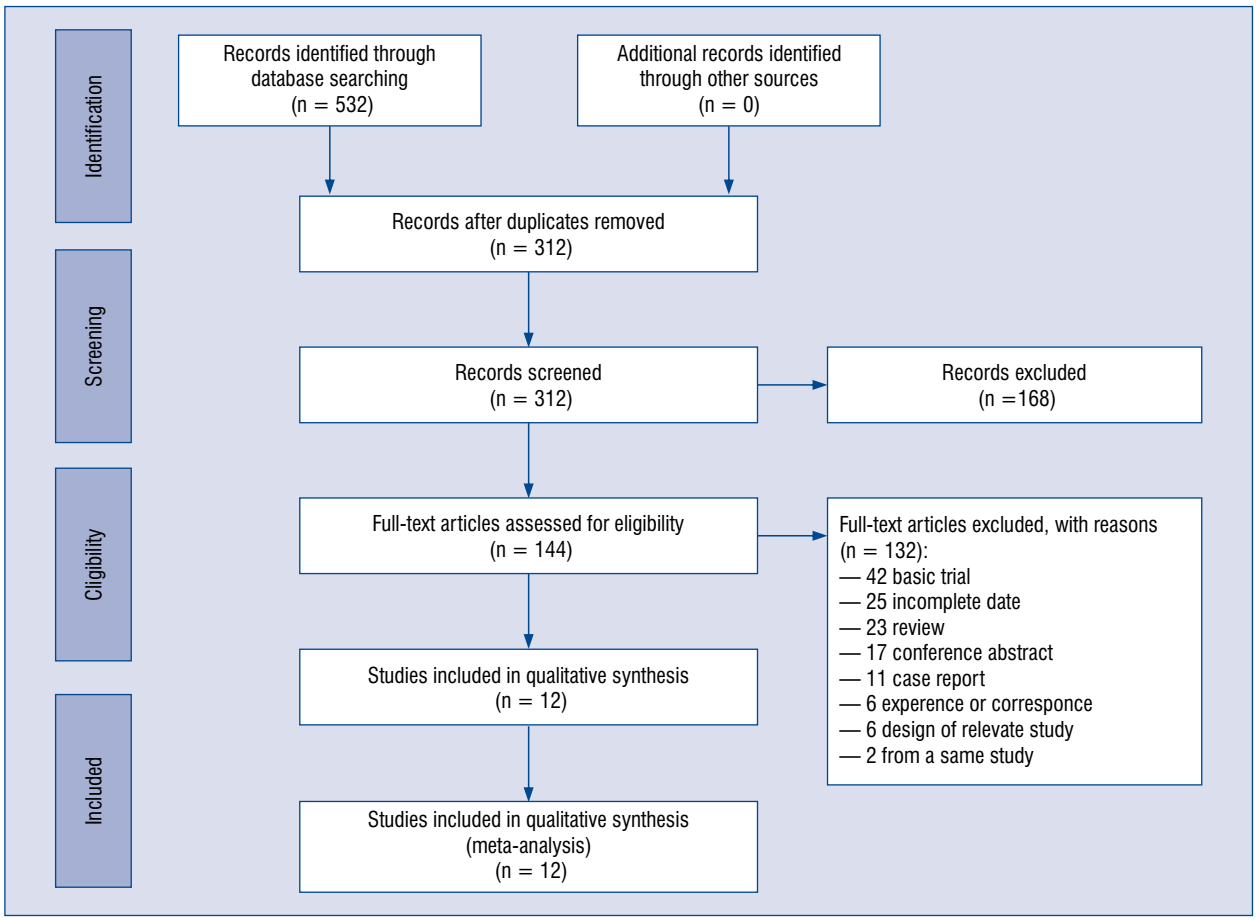

Figure 1. Flow chart of study selection.

cardiac death without publication bias at 1-year follow-up. The effects of the simple and complex strategies on the definite or probable ST are extracted and analyzed in 5 studies, which shows that there was no statistical significance between the simple and complex strategies (OR = 0.86, 95% CI 0.248–2.624; I^2 = 0%, p = 0.981; Fig. 4).

Subgroup analysis

Two subgroup analyses were performed according to the median proportion of patients with ACS and DM in the 12 studies included. The ACS was stratified according to whether the median proportion exceeded 40.35%, the DM was stratified according to whether the median proportion exceeded 28.85%. The results showed that the pooled estimate rate of MI, definite or probable ST and cardiac death was increased in patients with ACS and DM (3.82% vs. 1.54%, 2.52% vs. 1.28% and 0.66% vs. 0.35% for the subgroup of ACS vs. non-ACS, respectively; 4.04% vs. 2.03, 3.01% vs. 1.54% and 1.06% vs. 0.40% for the subgroup of DM vs. non-DM, respectively), which increase nearly or more than twice (**Suppl. Figs. S3 and S4**). The effect on TLR, MACE and TVR is not significant for both ACS and DM subgroups (**Suppl. Figs. S5 and S6**).

Discussion

According to available research, this is the first systematic review and meta-analysis involving the application of BRS for patients with coronary bifurcation lesions. The major findings are as follows: (1) the pooled estimated rate of TLR as the effective outcome of BRS for patients with those is acceptable at short- and medium-term follow-up; (2) a majority of the safety outcomes (MACE, TVR, MI and cardiac death) have reached the safety effect size; (3) the rate of definite or probable ST remains a concern. However, these findings are only based on observational studies with very low GRADE quality. Therefore, this estimate is very uncertain, and additional

Table 1. Baseline patient's characteristics.

	De Paolis et al. 2016	Elabbassi et al. 2019	Grundeken et al. 2015	Holck et al. 2019	Kawamoto et al. 2015	Naganuma et al. 2017	Ojeda et al. 2016	Paradies et al. 2018	Suárez et al. 2016	Tanaka et al. 2016 (1)	Tanaka et al. 2016 (2)	Wiebe et al. 2016	Average
Age (years)	59.61 ± 10.79	58 ± 12	62.3 ± 9.29	64 ± 13	62.5 ± 11.1	61.6 ± 11.6	57 ± 10	59.4 ± 15.4	57 ± 9	63 ± 11	61.8 ± 10.2	65	60.9
Male (%)	81.4	87.3	100	80	89.1	81	82	78	87	88.1	92.7	85.7	86.0
Hypertension (%)	55.9	69.8	40	40	63	73.7	54	56	54	62.4	68.3	78.6	59.6
Dyslipidemia (%)	52	76.2	50	90	63	56.7	—	16	58	67.3	61	57.1	58.8
Diabetes (%)	15.7	57.1	20	30	27.7	25.3	60	68	23	27.7	39	35.7	35.8
Smoking (%)	41.2	47.6	10	50	13.4	22.5	49	68	45	17.8	7.3	35.7	34.0
Family history (%)	29.4	1.6	—	—	42	34.6	—	—	25	35.6	31.7	35.7	29.5
Previous MI (%)	22.5	48.2	40	—	26.1	—	4	18	—	22.8	26.8	25.8	26.0
Prior PCI (%)	14.7	24	30	30	44.5	36.7	10	26	—	38.6	48.8	35.7	30.8
Prior CABG (%)	2	1.5		10	6.7	3.5	—		—	6.9	2.4	10.7	5.5
LVEF (%)	—	48 ± 11	—	57 ± 7	54.9 ± 7	53.6 ± 8.6	59 ± 10	—	57 ± 9	56 ± 7	53.5 ± 9.8	—	54.9
ACS (%)	57.8	68.3	20	10	11.8	34.3	—	51	81	12.9	7.3	46.4	36.4
STEMI (%)	18.6	6	2O	0	1.7	30	37	12	29	—	—	14.3	16.5
NSTEMI (%)	—	—	0	10	0	32	18	30	52	—	—	14.3	19.5
UA (%)	—	—	0	0	10.1	12.8	32	8		—	—	17.6	11.5
SCAD (%)	42.2	31.7	80	90	88.2	65.7	18	49	19	87.1	92.7	53.6	59.8

(1) Tanaka A., Jabbour R.J. et.al., (2) Tanaka A., Latib A. et al.; MI — myocardial infarction; PCI — percutaneous coronary intervention; CABG — coronary artery bypass grafting; LVEF — left ventricular ejection fraction; ACS — acute coronary syndromes; STEMI — ST-segment elevation myocardial infarction; NSTEMI — non-ST-segment elevation myocardial infarction; UA — unstable angina; SCAD — stable coronary artery disease

Table 2. Lesion and procedural characteristics.

	De Paolis et al. 2016	Elabbassi et al. 2019	Grundeken et al. 2015	Holck et al. 2019	Kawamoto et al. 2015	Naganuma et al. 2017	Ojeda et al. 2016	Paradies et al. 2018	Suárez et al. 2016	Tanaka et al. 2016 (1)	Tanaka et al. 2016 (2)	Wiebe et al. 2016	Average
Bifurcation site:													
LAD (%)	68.2	59	90	70	69.7	69.5	50.5	81	65	73	81	50	68.9
LCX (%)	24.3	23.8	0	10	16.7	19.9	23	12	23	14.8	9.5	35.7	17.7
RCA (%)	5.6	9.5	10	0	7.6	5.6	26	6	7	12.2	4.8	14.3	9.1
LM (%)	1.9	8%	0	20	6.1	5	0.5	1	4	0	4.8	0	3.6
TRUE bifurcation (%)	42	66.7[a]	50	20	57.3	44.7	30	24	45	42.6	90.5	35.7[a]	44.6
Number of bifurcations	107	63	11	10	132	302	190	110	230	115	42	33	112.1
Simple strategy (%)	93.4	31.7	0	80	75	86.1	—	87.3	96.1	100	0	81.5	66.5
Complex strategy (%)	6.6	—	100	20	17.4	13.9	—	12.7	3.5	0	100	18.5	29.3
Intravascular imaging (%)	—	68	—	—	83.3	—	94	89.9	—	90.4	92.9	—	86.4
IVUS (%)	—	7.7	—	—	82.7	22.2	—	68.1	—	89.6	90.5	—	60.1
OCT (%)	19.6	60.3	90	80	—	21.2	—	21.8	44.8	12.2	23.8	25.9	41.5
MV pre-dilation (%)	84.1	96.8	100	70	99.2	95.4	—	96	—	98.3	100	88.9	92.9
MV post-dilation (%)	59.8	—	70	80	100	61.3	39	74	49	100	100	33.3	69.7
POT (%)	35.5	57.1	50	100	—	—	—	—	—	—	—	14.8	51.5
Device success (%)	99.1	—	91	90	—	—	—	—	—	—	—	97.1	94.3
SB pre-dilation (%)	23.4	—	90	—	31.8	96.2	0	12.3	—	21.7	100	40.7	49.1
SB post-dilation (%)	—	—	10	—	31.8	75	—	—	40	—	—	25.9	36.5

(1) Tanaka A., Jabbour R.J. et.al., (2) Tanaka A., Latib A. et al.; LAD — left anterior descending artery; LCX — left circumflex artery; RCA — right coronary artery; LM — left main coronary artery; IVUS — intravascular ultrasound; OCT — optical coherence tomography; MV — main vessel; SB — side-branch; POT — proximal optimization technique. TRUE bifurcation was defined as Medina 1.1.1/1.0.1/0.1.1; [a]Medina 1.1.1. Simple strategy was defined as single stenting or provisional strategy. Complex strategy was defined as T-stenting, TAP — T-stenting and small protrusion technique, Culotte, Mini-crush, V-stenting, Skirt, hybrid strategy of BVS (ABSORB; Abbott Vascular, Santa Clara, CA, USA) and drug-eluting stent or three stents.

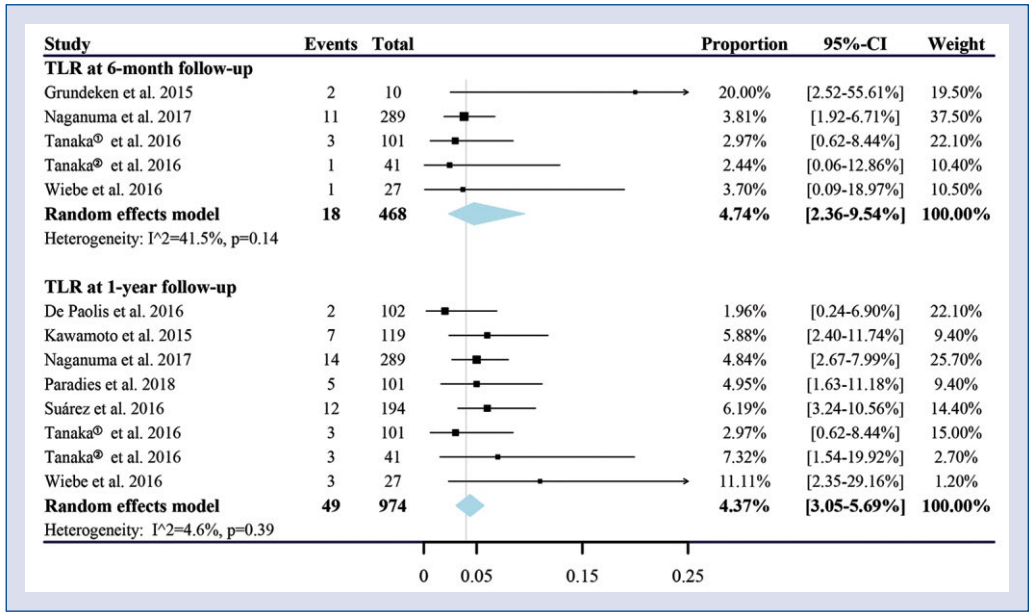

Figure 2. Primary endpoints for studies included; CI — confidence interval; TLR — target lesion revascularization.

randomized trials are required to provide higher quality evidence.

The BRS has the characteristic of complete absorption and is known as the fourth revolution in the history of coronary intervention, which changed the long-term problem of permanent implantation and achieved complete revascularization/restoration of vascular patency. The Igaki-Tamai stent was the first biodegradable stent to be included in human trials with long-term (> 10 year) clinical outcomes and intravascular ultrasound data, which had acceptable MACE and ST rates without stent recoil and vessel remodeling [26]. It revealed a promising early result. More than 10 BRS with different backbone, different coating drug dose, different strut thickness, different vessel coverage area and different complete resorption time have been tested in clinical practice to date. However, these scaffolds are still in clinical research and lack of powerful evidence. Most experience came from bioresorbable vascular scaffolds (BVS) of Abbott, whereas poor clinical results for ST and low market share led to its delisting in 2017. This appears to place a veil over the use of BRS. However, two recently published randomized controlled trials showed optimistic results. One was the ABSORB IV trial [27], which showed that BVS resulted in non-inferior rates of target lesion failure and angina pectoris compared with metallic DES, another was the implanted NeoVas BRS that indicted non-inferior to metallic DES for angiographic in-segment late loss and clinical outcomes [28]. The NeoVas BRS is a new generation BRS, which could elute sirolimus from a poly-D, l-lactide coating. Nonetheless, these do not include coronary bifurcation lesions.

Currently, there is limited evidence to investigate the clinical results of BRS in coronary bifurcation lesions, although Stankovic and Lassen [5] believed that BRS might better provide profit in this specific lesion. The incidence of TLR and majority safety outcomes for BRS was acceptable compared with first- and second-generation DES in coronary bifurcation lesions 29, 30]. Another notable problem is that the results were obtained on the basis that the side branch was more than at least 2 mm, regardless of intervention or not. The BRS was designed with increased strut thickness, which is easier to protrude into the side branch and occlude it. Therefore, the coronary bifurcation lesions should be selected cautiously when BRS was used, which were supported by studies from Muramatsu et al. [31] and Ojeda et al. [21]. The rate of MACE was significantly lower at 1-year follow-up in this meta-analysis than that of the second-generation DES (6.91% vs. 12.1%), which might be due to different event definitions rather than an obvious advantage. It should also be emphasized that the incidence of definite or probable ST implanted BRS was significantly higher than that of second-generation DES (1.61% vs. 0.7% with 1st-stent, 1.4% with 2nd-stent). The same results were drawn in simple lesions, which needs to be addressed to reduce

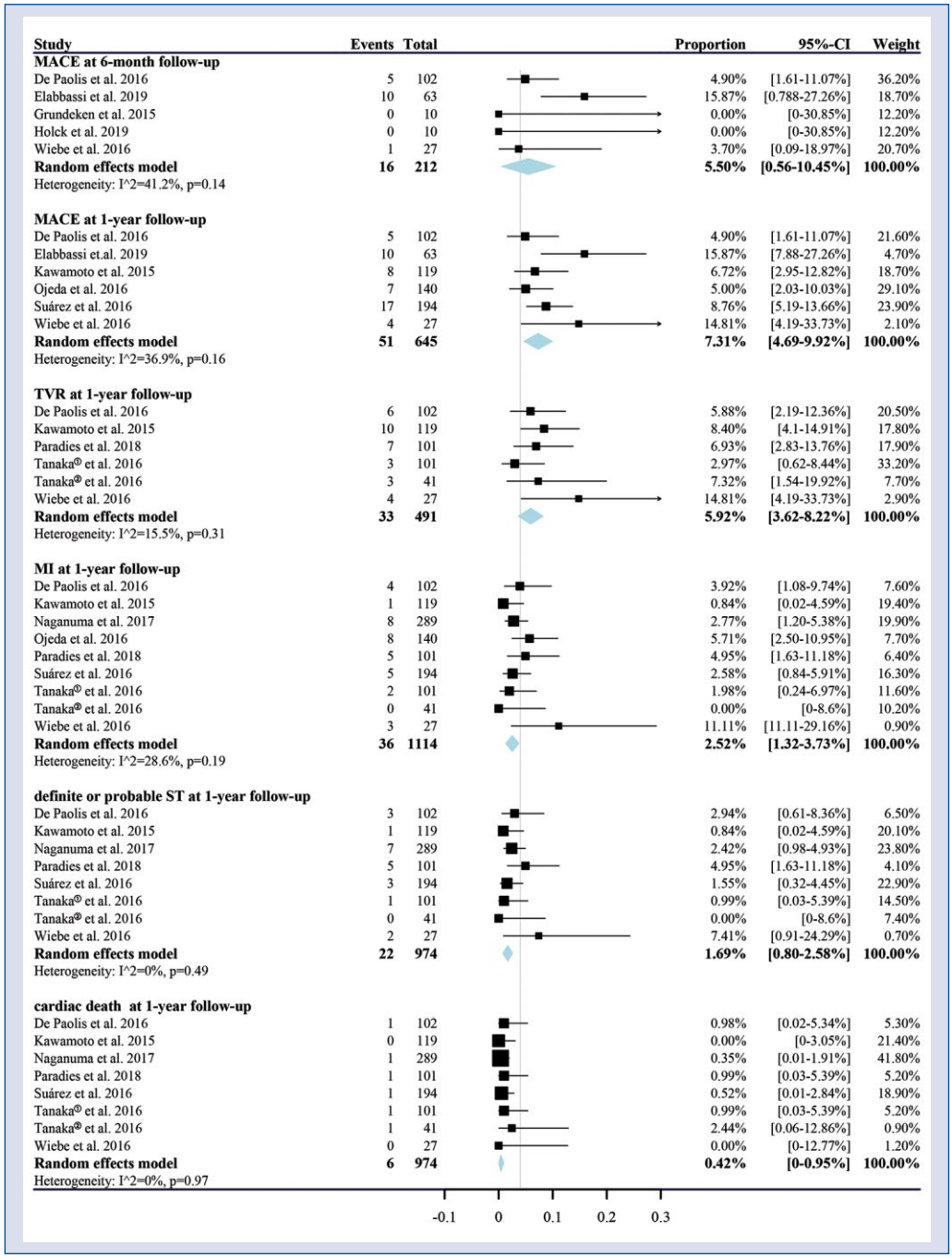

Figure 3. Secondary endpoints for studies included; CI — confidence interval; MACE — major adverse cardiac events; MI — myocardial infarction; TVR — target vessel revascularization; ST — scaffold thrombosis.

the rate of definite or probable ST. First of all, this result can be improved by more appropriate lesion selection and standard implantation techniques (pre-dilation, sizing and post-dilation technique). In addition, the provisional strategy was recommended for bifurcation lesions according to present consensus and guidelines [1, 2]. This study did not provide further recommendations for simple and complex strategies, but the simple strategy (single stent or provisional strategy) is obviously more popular. Previous research has shown that premature discontinuation of antiplatelet therapy exacerbated risk of scaffold thrombosis [8]. The 2018 ESC/EACTS Guidelines recommended that dual antiplatelet therapy should be considered for at least 12 months and up to the presumed full absorption of BRS [2]. Although the BRS was designed to reduce the duration of long-term an-

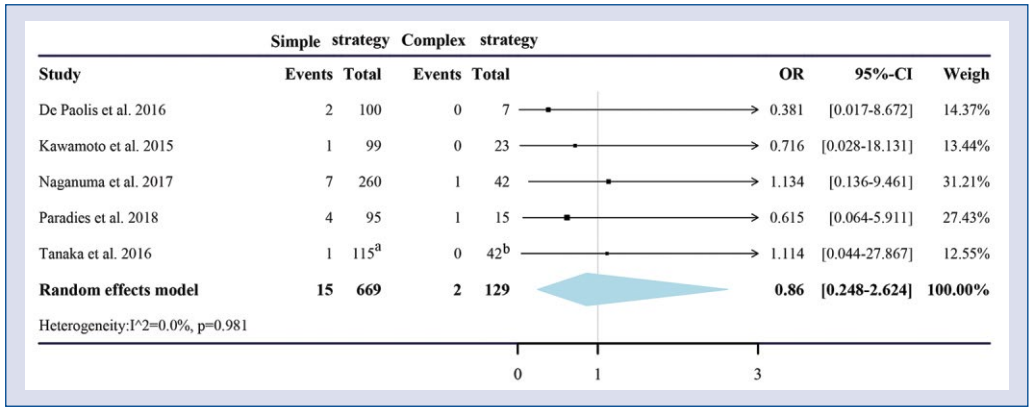

Figure 4. Effects of simple and complex strategies on definite or probable scaffold thrombosis for studies included ([a]Data from [24]; [b]Data from [25]); CI — confidence interval; OR — odds ratio.

tiplatelet therapy, this may occur after complete stent degradation. The result of a registry study, BVS LATE (NCT02939872), intended to evaluate the optimal duration of antiplatelet therapy after BVS implantation is to be expected. Preliminary subgroup analysis showed that ACS and DM were risk factors of partial safety outcomes, which were similar to the coronary bifurcation lesions substudy from GHOST EU Registry [20]. This suggests a more conservative approach to patient selection.

Nevertheless, the results must be interpreted cautiously before there is insufficient evidence to support them. Firstly, considering the difference of baseline characteristics and the BRS types, as well as varied definitions of clinical outcome, the event rates might be influenced. Secondly, most of these results were from European, and may require data from more regional and ethnic populations to determine whether the results can be extrapolated. In addition, these data were only observational studies from specific clinical centers which had better implantation technology and higher operation success rates. Furthermore, the proportion of intravascular imaging varies greatly, which has an important impact on of procedure and incidence of postoperative events, and is an important reason for the differences in the results of the studies. Therefore, it also needs to be evaluated by randomized controlled trials. Meanwhile, BRS should be implanted cautiously in patients with a high risk of bleeding who cannot tolerate dual antiplatelet therapy for 12 months. Furthermore, the quality of evidence and the strength of recommendation for the studies included were very low according to GRADE criteria, which was because of limitations of the single-arm observational study design, lack of indirect evidence from a control group, and inaccurate results due to small sample sizes. However, the purpose of this meta-analysis was to summarize the evidence, it should not be widely used in clinical practice without further evidence.

Limitation of the study

The limitations of this meta-analysis should be considered. Firstly, the studies included were single-arm or observational studies with small sample sizes, most of which were single-center data, which significantly decreased the level of evidence for study. Secondly, the absorbable scaffolds implanted in the meta-analysis were not uniform, with BVS dominating, and no magnesium — BRS were included. These differences may affect the results of study. Thirdly, the data of subgroup analysis were based on the median of patients with DM and ACS in the single-arm study, which was not supported by the specific evidence, the results should be interpreted carefully. Fourthly, due to the limitations of current clinical studies, the duration of dual antiplatelet therapy and the optimal strategy in this study had not been clearly explained. Lastly, longer-term results after the stents complete absorption have also not been reported.

Conclusions

This meta-analysis shows that the application of BRS for coronary bifurcation lesions is acceptable in efficacy outcome and most safety outcomes, but the high rate of ST remains a concern. The efficacy and safety of BRS on coronary bifurcation

lesions should be explored in large-scale randomized controlled trials in the future.

Conflict of interest: None declared

References

1. Lassen JF, Holm NR, Banning A, et al. Percutaneous coronary intervention for coronary bifurcation disease: 11th consensus document from the European Bifurcation Club. EuroIntervention. 2016; 12(1): 38–46, doi: 10.4244/EIJV12I1A7, indexed in Pubmed: 27173860.
2. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. ESC Scientific Document Group, ESC Scientific Document Group. 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.
3. McFadden EP, Stabile E, Regar E, et al. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. Lancet. 2004; 364(9444): 1519–1521, doi: 10.1016/S0140-6736(04)17275-9, indexed in Pubmed: 15500897.
4. Colleran R, Byrne RA. Bioresorbable vascular scaffolds in coronary bifurcation lesions: only in expert hands. Rev Esp Cardiol (Engl Ed). 2016; 69(6): 543–546, doi: 10.1016/j.rec.2016.03.011, indexed in Pubmed: 27157886.
5. Stankovic G, Lassen JF. When and how to use BRS in bifurcations? EuroIntervention. 2015; 11 Suppl V: V185–V187, doi: 10.4244/EIJV11SVA44, indexed in Pubmed: 25983163.
6. Iqbal J, Onuma Y, Ormiston J, et al. Bioresorbable scaffolds: rationale, current status, challenges, and future. Eur Heart J. 2014; 35(12): 765–776, doi: 10.1093/eurheartj/eht542, indexed in Pubmed: 24366915.
7. De Paolis M, Felix C, van Ditzhuijzen N, et al. Everolimus-eluting bioresorbable vascular scaffolds implanted in coronary bifurcation lesions: Impact of polymeric wide struts on side-branch impairment. Int J Cardiol. 2016; 221: 656–664, doi: 10.1016/j.ijcard.2016.06.153, indexed in Pubmed: 27423087.
8. Wiebe J, Dörr O, Bauer T, et al. Everolimus-eluting bioresorbable scaffold implantation for the treatment of bifurcation lesions: Implications from early clinical experience during daily practice. Cardiovasc Revasc Med. 2016; 17(5): 313–317, doi: 10.1016/j.carrev.2016.03.011, indexed in Pubmed: 27085220.
9. Ormiston JA, Kassab G, Finet G, et al. Bench testing and coronary artery bifurcations: a consensus document from the European Bifurcation Club. EuroIntervention. 2018; 13(15): e1794–e1803, doi: 10.4244/EIJ-D-17-00270, indexed in Pubmed: 29131803.
10. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Medicine. 2009; 6(7): e1000097, doi: 10.1371/journal.pmed.1000097.
11. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000; 283(15): 2008–2012, doi: 10.1001/jama.283.15.2008, indexed in Pubmed: 10789670.
12. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Eur Heart J. 2012; 33(20): 2551–2567, doi: 10.1093/eurheartj/ehs184, indexed in Pubmed: 22922414.
13. Cutlip DE, Windecker S, Mehran R, et al. Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation. 2007; 115(17): 2344–2351, doi: 10.1161/CIRCULATIONAHA.106.685313, indexed in Pubmed: 17470709.
14. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010; 25(9): 603–605, doi: 10.1007/s10654-010-9491-z, indexed in Pubmed: 20652370.
15. Atkins D, Best D, Briss PA, et al. GRADE Working Group. Grading quality of evidence and strength of recommendations. BMJ. 2004; 328(7454): 1490, doi: 10.1136/bmj.328.7454.1490, indexed in Pubmed: 15205295.
16. Elabbassi W, Chowdhury MA, Hatala R. Use of Bioresorbable Vascular Scaffold technology in treating coronary bifurcation lesions: A report about long-term clinical results and review of available literature. Bratisl Lek Listy. 2019; 120(8): 545–551, doi: 10.4149/BLL_2019_088, indexed in Pubmed: 31379174.
17. Grundeken MJ, Hassell ME, Kraak RP, et al. Treatment of coronary bifurcation lesions with the Absorb bioresorbable vascular scaffold in combination with the Tryton dedicated coronary bifurcation stent: evaluation using two- and three-dimensional optical coherence tomography. EuroIntervention. 2015; 11(8): 877–884, doi: 10.4244/EIJY14M08_15, indexed in Pubmed: 25169592.
18. Holck EN, Fox-Maule C, Barkholt TO, et al. Procedural findings and early healing response after implantation of a self-apposing bioresorbable scaffold in coronary bifurcation lesions. Int J Cardiovasc Imaging. 2019; 35(7): 1199–1210, doi: 10.1007/s10554-019-01537-5, indexed in Pubmed: 31053981.
19. Kawamoto H, Latib A, Ruparelia N, et al. Clinical outcomes following bioresorbable scaffold implantation for bifurcation lesions: Overall outcomes and comparison between provisional and planned double stenting strategy. Catheter Cardiovasc Interv. 2015; 86(4): 644–652, doi: 10.1002/ccd.26045, indexed in Pubmed: 26013748.
20. Naganuma T, Colombo A, Lesiak M, et al. Bioresorbable vascular scaffold use for coronary bifurcation lesions: A substudy from GHOST EU registry. Catheter Cardiovasc Interv. 2017; 89(1): 47–56, doi: 10.1002/ccd.26634, indexed in Pubmed: 27414021.
21. Ojeda S, Pan M, Suárez de Lezo J, et al. Patency of coronary side branches covered by an everolimus-eluting bioresorbable vascular scaffold: clinical outcomes and computed tomography scan follow-up. EuroIntervention. 2016; 11(11): e1283–e1290, doi: 10.4244/EIJV11I11A250, indexed in Pubmed: 26865446.
22. Paradies V, Vlachojannis GJ, Royaards KJ, et al. Angiographic and midterm outcomes of bioresorbable vascular scaffold for coronary bifurcation lesions. Am J Cardiol. 2018; 122(12): 2035–2042, doi: 10.1016/j.amjcard.2018.09.003, indexed in Pubmed: 30360886.
23. Suárez de Lezo J, Martín P, Pan M, et al. Bioresorbable vascular scaffold for the treatment of coronary bifurcation lesions: immediate results and 1-year follow-up. Rev Esp Cardiol (Engl Ed). 2016; 69(6): 554–562, doi: 10.1016/j.rec.2015.12.004, indexed in Pubmed: 26949014.
24. Tanaka A, Jabbour RJ, Kawamoto H, et al. Preliminary report of clinical outcomes after single crossover bioresorbable scaffold implantation without routine side branch strut dilation. Catheter Cardiovasc Interv. 2016; 88(6): 865–870, doi: 10.1002/ccd.26586, indexed in Pubmed: 27219102.

25. Tanaka A, Latib A, Kawamoto H, et al. Clinical outcomes following bifurcation double-stenting with bioresorbable scaffolds. Catheter Cardiovasc Interv. 2016; 88(6): 854–862, doi: 10.1002/ccd.26579, indexed in Pubmed: 27184769.
26. Nishio S, Kosuga K, Igaki K, et al. Long-term (>10 years) clinical outcomes of first-in-human biodegradable poly-l-lactic acid coronary stents: Igaki-Tamai stents. Circulation. 2012; 125(19): 2343–2353, doi: 10.1161/CIRCULATIONAHA.110.000901, indexed in Pubmed: 22508795.
27. Stone GW, Ellis SG, Gori T, et al. ABSORB IV Investigators. Blinded outcomes and angina assessment of coronary bioresorbable scaffolds: 30-day and 1-year results from the ABSORB IV randomised trial. Lancet. 2018; 392(10157): 1530–1540, doi: 10.1016/S0140-6736(18)32283-9, indexed in Pubmed: 30266412.
28. Han Y, Xu Bo, Fu G, et al. A randomized trial comparing the neovas sirolimus-eluting bioresorbable scaffold and metallic everolimus-eluting stents. JACC Cardiovasc Interv. 2018; 11(3): 260–272, doi: 10.1016/j.jcin.2017.09.037, indexed in Pubmed: 29413240.
29. Ferenc M, Buettner HJ, Gick M, et al. Clinical outcome after percutaneous treatment of de novo coronary bifurcation lesions using first or second generation of drug-eluting stents. Clin Res Cardiol. 2016; 105(3): 230–238, doi: 10.1007/s00392-015-0911-7, indexed in Pubmed: 26329585.
30. Lee JM, Hahn JY, Kang J, et al. Differential prognostic effect between first- and second-generation drug-eluting stents in coronary bifurcation lesions: patient-level analysis of the korean bifurcation pooled cohorts. JACC Cardiovasc Interv. 2015; 8(10): 1318–1331, doi: 10.1016/j.jcin.2015.05.014, indexed in Pubmed: 26315734.
31. Muramatsu T, Onuma Y, García-García HM, et al. Incidence and short-term clinical outcomes of small side branch occlusion after implantation of an everolimus-eluting bioresorbable vascular scaffold: an interim report of 435 patients in the ABSORB-EXTEND single-arm trial in comparison with an everolimus-eluting metallic stent in the SPIRIT first and II trials. JACC Cardiovasc Interv. 2013; 6(3): 247–257, doi: 10.1016/j.jcin.2012.10.013, indexed in Pubmed: 23517836.

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Efficacy and safety of PCSK9 inhibition in cardiovascular disease: A meta-analysis of 45 randomized controlled trials

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Abstract

Background: *Safety concerns about proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors make physicians reluctant to prescribe agents for patients. The present aim was to assess the efficacy and safety of alirocumab, evolocumab and bococizumab in patients with atherosclerotic cardiovascular disease (ASCVD).*

Methods: *Medline, the Cochrane Library and Clinicaltrials.gov were searched for 45 randomized controlled trials, involving 97,297 patients.*

Results: *Compared with the control group, PCSK9 inhibitors could significantly reduce low-density lipoprotein cholesterol, total cholesterol, triglycerides and increase high-density lipoprotein cholesterol. Alirocumab was associated with lower incidence of unstable angina ($p < 0.05$) and myocardial infarction ($p < 0.05$), compared with the control group. Alirocumab (odds ratio [OR] 0.76, 95% confidence interval [CI] 0.60–0.97, $p < 0.05$), evolocumab (OR 0.79, 95% CI 0.66–0.95, $p < 0.05$) and bococizumab (OR 0.60, 95% CI 0.42–0.84, $p < 0.05$) were associated with lower incidence of stroke, compared with control group. The incidence of injection-site reactions was significantly higher in alirocumab (OR 1.68, 95% CI 1.45–1.93, $p < 0.05$), evolocumab (OR 1.64, 95% CI 1.41–1.91, $p < 0.05$) and bococizumab (OR 8.03, 95% CI 6.85–9.41, $p < 0.05$) group than in the control group.*

Conclusions: *Alirocumab and evolocumab could ameliorate lipid profile and reduce the risk of cardiac disorders and stroke with satisfactory safety and tolerability. However, injection-site reactions should be paid attention to.* (Cardiol J 2022; 29, 4: 574–581)

Key words: proprotein convertase subtilisin/kexin type 9, efficacy, safety, meta-analysis

Introduction

Statins were recommended as a first-line therapy for cardiovascular disease (CVD) and substantially decreased the risk for CVD events. But, a high proportion of patients did not achieve optimal levels of low-density lipoprotein cholesterol (LDL-C) or may have had high residual CVD risk despite high-intensity statin therapy. An optional approach is to choose other LDL-C lowering agents for these patients on the basis of statins.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) promotes the degradation of low-density lipoprotein receptors (LDLR) at the surface of hepatocytes by binding to LDLR in lysosomes/endosomes. PCSK9 inhibitors have emerged as an effective strategy to reduce LDL-C and other lipid parameters. Alirocumab and evolocumab appeared to reduce nonfatal major adverse cardiac event (MACE) and be well tolerated [1]. But, further development of bococizumab was discontinued because of no significant reduction in cardiovas-

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cular events and high incidence of injection-site reactions with bococizumab [2, 3]. Physicians were still worried about the efficacy and safety of PCSK9 inhibitors and reluctant to prescribe for atherosclerotic cardiovascular disease (ASCVD) patients. With the increase in evidence in recent years, this meta-analysis was therefore performed to evaluate the efficacy and safety of PCSK9 inhibitors (alirocumab, evolocumab, bococizumab) currently available in clinical practice.

Methods

Search strategy

This meta-analysis was performed in accordance with the Preferred Reporting of Systematic Reviews and Meta-Analysis (PRISMA) statement [4]. Pubmed, the Cochrane Library database, Clinicaltrials.gov from March 2012 to March 2021 were searched using the following search items: "evolocumab'', "AMG 145'', "alirocumab'', "SAR236553", "REGN727'', "bococizumab" and "RN316/PF-04950615". The search pattern is shown in **Supplementary Table S2.**

Study selection

Two independent investigators screened article titles and full-text according to the inclusion criteria. Discrepancies were resolved by discussion and consensus. Risk of bias of was assessed by using the Cochrane Risk of Bias tool [5].

No language, follow-up or study size were imposed as restrictions in the searches. Alirocumab, evolocumab, bococizumab were all included in the analyses.

Inclusion criteria was set based on the PICOS schema. The PICOS items were as follows: (P) patients with hypercholesterolemia or CVD; (I) PCSK9 inhibitors, evaluated the efficacy and safety of PCSK9 inhibitors (alirocumab or evolocumab or bococizumab); (C) control, evaluated the efficacy and safety of control (placebo or usual care or ezetimibe); (S) randomized controlled trials (RCTs).

The exclusion criteria: abstracts, reviews, and case reports; no report of efficacy and safety assessments.

Data extraction

The following data were extracted: sample size, age, design, follow-up duration, lipid profiles (LDL-C, total cholesterol [TC], triglycerides [TG], high-density lipoprotein cholesterol [HDL-C]), unstable angina (UA), myocardial infarction (MI), stroke, injection site reaction, myalgia.

Statistical analysis

Review Manager software 5.3 was used to calculate all statistical analyses. I^2 statistic were used to assess heterogeneity in the analysis. If $I^2 < 50\%$, a fixed-effect model was used; otherwise, a random-effect model was applied. Publication bias was examined by using the funnel plot. For dichotomous data, odds ratios were used. Continuous data (lipid outcomes) were expressed as mean difference of percentage change from baseline and 95% confidence interval (CI). $P < 0.05$ was considered statistically significant. The risk of bias was estimated by using the parameters: sequence generation, concealment of group allocation, blinding during outcome assessment, selective reporting and intention-to-treat analysis [6].

Results

Initially, a total of 1820 studies were searched, of which 82 studies were excluded because of duplication and 893 studies failed to meet the inclusion criteria. Finally, a total of 45 RCTs involving 97,297 patients were included. Of these, 21 RCTs were treated with alirocumab, 21 RCTs were treated with evolocumab, and 3 RCTs were treated with bococizumab. The study selection flow diagram is shown in Figure 1. Characteristics of the included studies are shown in **Supplementary Table S1 ([S1–S45]).**

Lipid profile

Triglycerides, TC, LDL-C, and HDL-C were reported in 42 studies with a total of 92,681 patients, of which 21 studies were treated with alirocumab, 18 studies were treated with evolocumab and 3 studies were treated with bococizumab. Compared with control group, alirocumab reduced LDL-C by –51.29% (95% CI –55.83 to –46.75, $p < 0.05$), TC by –30.31% (95% CI –34.26 to –26.36, $p < 0.05$), TG by –10.31% (95% CI –13.81 to –6.81, $p < 0.05$) and increased HDL-C by 5.63% (95% CI 4.86 to 6.40, $p < 0.05$). Compared with control group, evolocumab reduced LDL-C by –53.99% (95% CI –58.45 to –49.54, $p < 0.05$), TC by –34.2% (95% CI –36.18 to –32.21, $p < 0.05$), TG by –8.86% (95% CI –13.17 to –4.55, $p < 0.05$) and increased HDL-C by 7.05% (95% CI 5.55 to 8.54, $p < 0.05$). Compared with control group, bococizumab reduced LDL-C by –56.96% (95% CI –60.69 to –53.23, $p < 0.05$), TC by –38.96% (95% CI –43.33 to –34.58, $p < 0.05$), TG by –17.64% (95% CI –20.79 to –14.48, $p < 0.05$) and increased HDL-C by 5.98% (95% CI 4.86 to 7.11, $p < 0.05$) (Table 1).

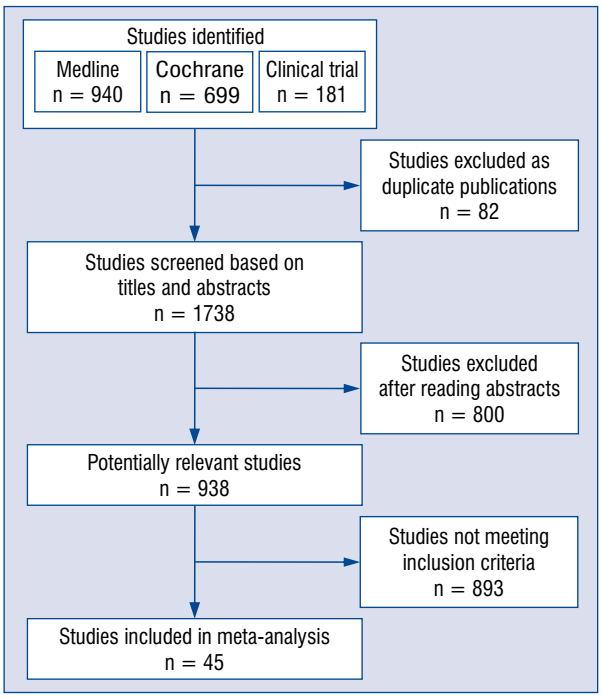

Figure 1. Selection flow diagram. In total, 1820 studies were identified. Finally, 45 studies were selected.

Cardiac disorders

Unstable angina and MI were considered as cardiac disorders. UA were reported in 13 studies with a total of 57,717 patients, of which 6 studies treated with alirocumab, 4 studies treated with evolocumab and 3 studies treated with bococizumab. MI were reported in 16 studies with a total of 90,355 patients, of which 8 studies treated with alirocumab, 6 studies treated with evolocumab and 2 studies treated with bococizumab. UA was less common in the alirocumab group (odds ratio [OR] 0.69, 95% CI 0.48 to 0.98, $p < 0.05$) (Fig. 2A), as was the frequency of MI (OR 0.85, 95% CI 0.76 to 0.95, $p < 0.05$) (Fig. 2B). There was no significant difference in the risk of UA between evolocumab and control group (OR 0.66, 95% CI 0.42 to 1.03, $p > 0.05$) (Fig. 2C). However, evolocumab was associated with lower risk of MI (OR 0.73, 95% CI 0.65 to 0.82, $p < 0.05$) (Fig. 2D). No statistically significant difference in UA (OR 0.82, 95% CI 0.67 to 1.00, $p = 0.05$) (Fig. 2E) and MI (OR 0.94, 95% CI 0.78 to 1.14, $p > 0.05$) (Fig. 2F) was found between bococizumab and control.

Stroke

The incidence of stroke was significantly lower in alirocumab (OR 0.76, 95% CI 0.60 to 0.97, $p < 0.05$) (Fig. 3A), evolocumab (OR 0.79, 95% CI

Table 1. Percent change of lipid profiles with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors versus control.

	Alirocumab					Evolocumab					Bococizumab				
	No. of patients		MD	95% CI	Test for overall effect	No. of patients		MD	95% CI	Test for overall effect	No. of patients		MD	95% CI	Test for overall effect
	Alirocumab	Control				Evolocumab	Control				Bococizumab	Control			
LDL-C	13928	11953	–51.29	–55.83 to –46.75	P < 0.05	18498	16416	–53.99	–58.45 to –49.54	P < 0.05	16125	15810	–56.96	–60.69 to –53.23	P < 0.05
TC	4466	2491	–30.31	–34.26 to –26.36	P < 0.05	17959	16081	–34.2	–36.18 to –32.21	P < 0.05	16125	15810	–38.96	–43.33 to –34.58	P < 0.05
TG	4466	2491	–10.31	–13.81 to –6.81	P < 0.05	18280	16200	–8.86	–13.17 to –4.55	P < 0.05	16125	15810	–17.64	–20.79 to –14.48	P < 0.05
HDL-C	4466	2491	5.63	4.86 to 6.40	P < 0.05	18280	16200	7.05	5.55 to 8.54	P < 0.05	16125	15810	5.98	4.86 to 7.11	P < 0.05

CI — confidence interval; HDL-C — high density lipoprotein cholesterol; LDL-C — low density lipoprotein cholesterol; MD — mean difference; TC — total cholesterol; TG — triglycerides

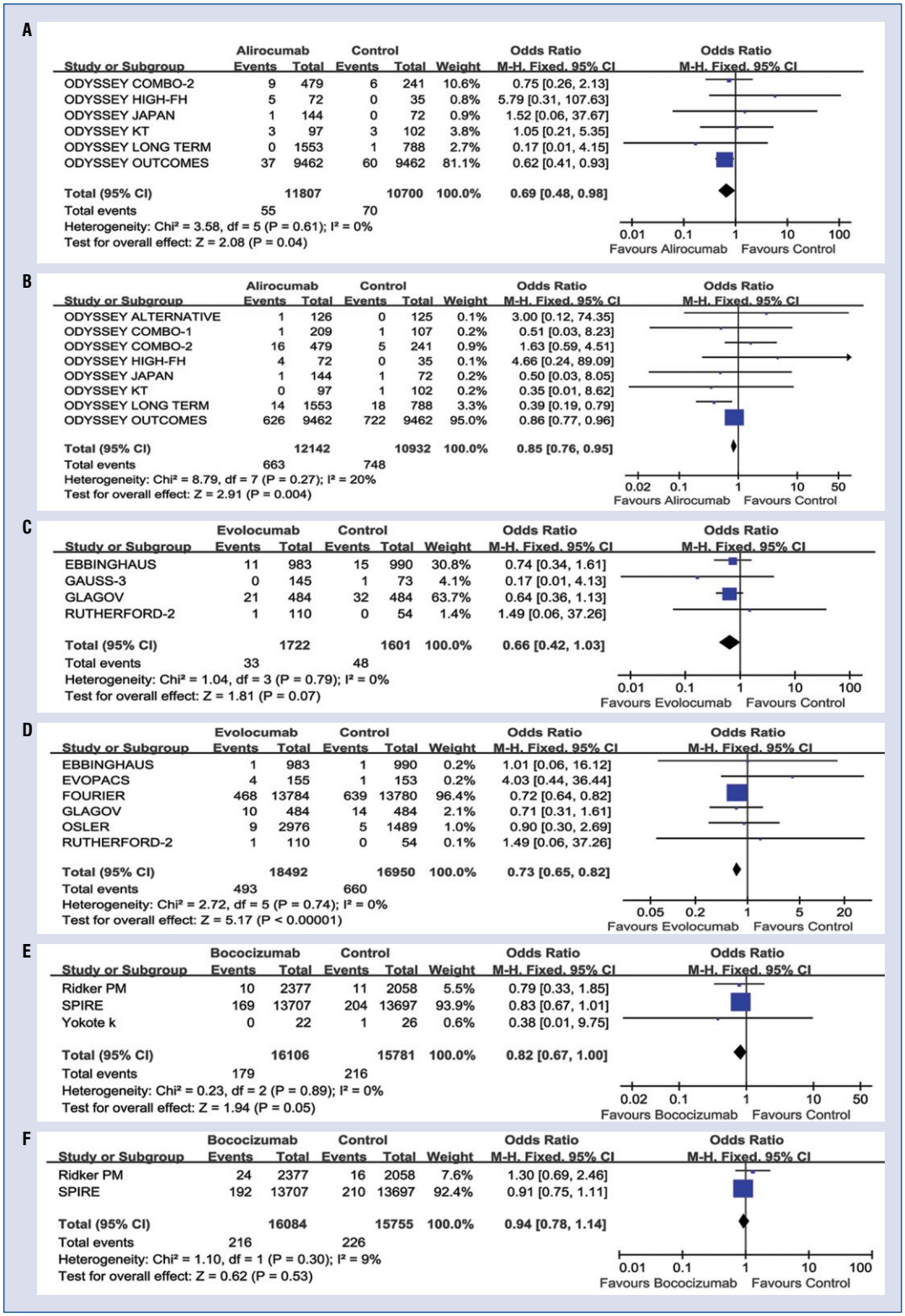

Figure 2. Forest plots of cardiac disorders with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors versus control. The odds ratio (OR) of unstable angina (UA) in alirocumab and control group differ significantly (OR 0.69, 95% confidence interval [CI] 0.48 to 0.98, $p < 0.05$) (**A**). The OR of myocardial infarction (MI) in alirocumab and control group differ significantly (OR 0.85, 95% CI 0.76 to 0.95, $p < 0.05$) (**B**). There was no significant difference in the risk of UA between evolocumab and control group (OR 0.66, 95% CI 0.42 to 1.03, $p > 0.05$) (**C**). Evolocumab was associated with lower risk of MI (OR 0.73, 95% CI 0.65 to 0.82, $p < 0.05$) (**D**). No statistically significant difference in UA (OR 0.82, 95% CI 0.67 to 1.00, $p = 0.05$) (**E**) and MI (OR 0.94, 95% CI 0.78 to 1.14, $p > 0.05$) (**F**) was found between bococizumab and control.

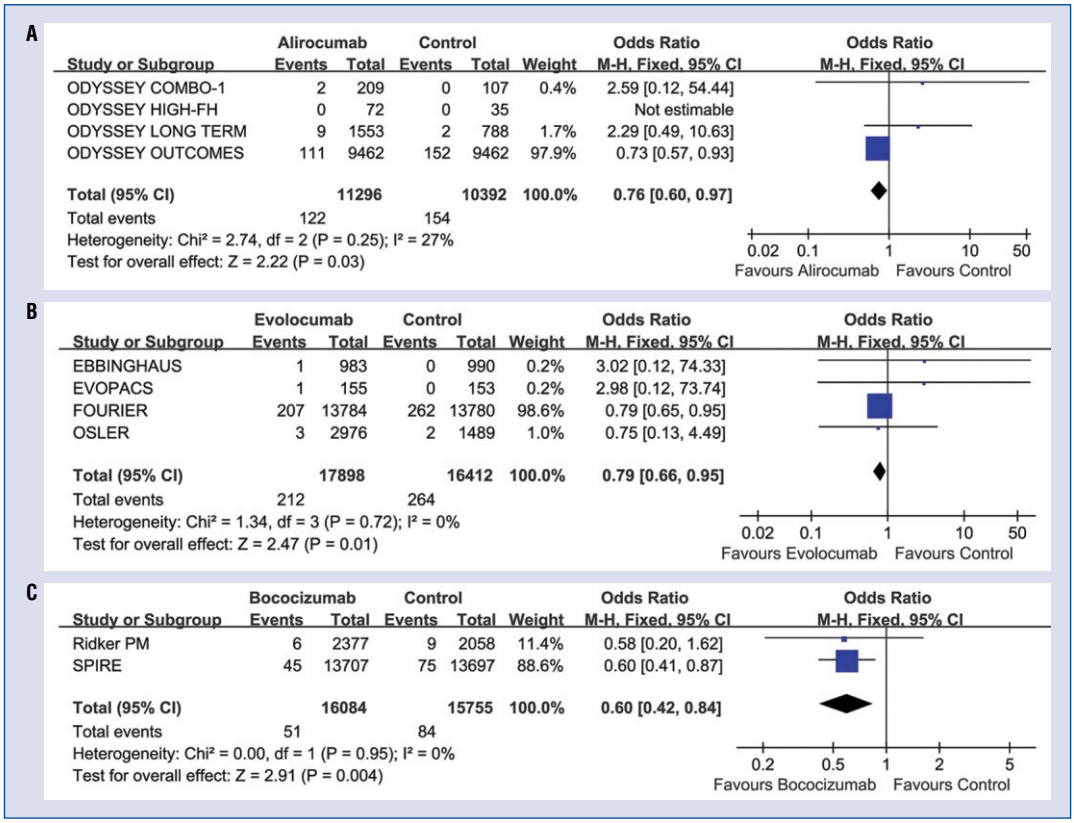

Figure 3. Forest plots of stroke with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors versus control. Stroke were reported in 10 studies with a total of 87,837 patients, of which 4 studies treated with alirocumab, 4 studies treated with evolocumab and 2 studies treated with bococizumab. The incidence of stroke was significantly lower in alirocumab (odds ratio [OR] 0.76, 95% confidence interval [CI] 0.60 to 0.97, $p < 0.05$) (**A**), evolocumab (OR 0.79, 95% CI 0.66 to 0.95, $p < 0.05$) (**B**) and bococizumab (OR 0.60, 95% CI 0.42 to 0.84, $p < 0.05$) (**C**) group than in control group.

0.66 to 0.95, $p < 0.05$) (Fig. 3B), and bococizumab (OR 0.60, 95% CI 0.42 to 0.84, $p < 0.05$) (Fig. 3C) group than in control group.

Safety

The safety concerns included injection-site reactions and myalgia. Injection-site reactions included dryness, discoloration, erythema, exfoliation, hematoma, hemorrhage, edema, pain, rash, sweeling, urticaria, vesicles or bruising at the injection site. The incidence of injection-site reactions was significantly higher in alirocumab (OR 1.68, 95% CI 1.45 to 1.93, $p < 0.05$) (Fig. 4A), evolocumab (OR 1.64, 95% CI 1.41 to 1.91, $p < 0.05$) (Fig. 4B), and bococizumab (OR 8.03, 95% CI 6.85 to 9.41, $p < 0.05$) (Fig. 4C) group than in control group. Compared with control group, alirocumab (OR 1.18, 95% CI 0.92 to 1.53, $p > 0.05$) (Fig. 5A), evolocumab (OR 1.09, 95% CI 0.85 to 1.38, $p > 0.05$) (Fig. 5B), and bococizumab (OR 1.05, 95% CI 0.92 to 1.20, $p > 0.05$) (Fig. 5C) group had no significant difference in the incidence of myalgia.

Discussion

In the current study, it was found that PCSK9 inhibitors could lead to marked reduction in LDL-C, TC, TG, and increase in HDL-C. Alirocumab, evolocumab and bococizumab could reduce LDL-C > 50%, increase HDL-C > 5%. PCSK9 inhibitors could ameliorate the lipid profile. The present results about lipid changes were consistent with the meta-analysis by Zhang et al. [7].

This meta-analysis has shown that alirocumab and evolocumab probably have beneficial effects on cardiovascular outcomes. The current study demonstrated that evolocumab could reduce the incidence of MI, but did not have significant benefit with respect to UA. It was considered that this result should be interpreted with caution.

According to available research, this is the first meta-analysis to demonstrate the efficacy and safety of bococizumab. Injection-site reactions occurred in 8.4% of patients with bococizumab. Meanwhile, the rate of injection-site reactions for

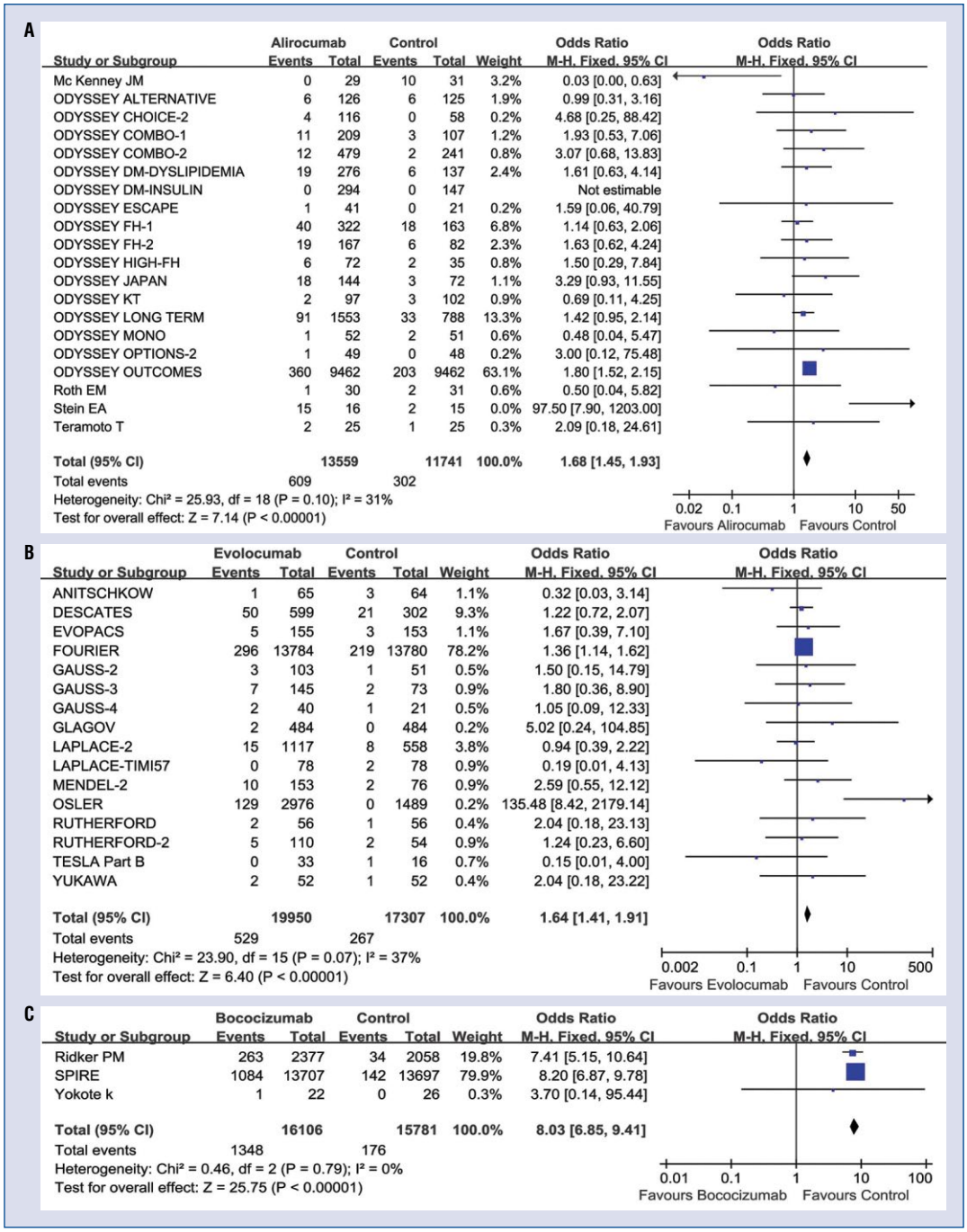

Figure 4. Forest plots of injection site reaction with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors versus control. Injection-site reactions were reported in 38 studies with a total of 94,444 patients, of which 19 studies treated with alirocumab, 16 studies treated with evolocumab and 3 studies treated with bococizumab. The incidence of injection-site reactions in alirocumab (odds ratio [OR] 1.68, 95% confidence interval [CI] 1.45 to 1.93, $p < 0.05$) (**A**), evolocumab (OR 1.64, 95% CI 1.41 to 1.91, $p < 0.05$) (**B**) and bococizumab (OR 8.03, 95% CI 6.85 to 9.41, $p < 0.05$) (**C**) group was significantly higher than in control group.

alirocumab and evolocumab therapy were 4.5% and 2.7%, respectively. Alirocumab, evolocumab and bococizumab had no significant difference in the incidence of myalgia. In the current analysis, it was found that bococizumab was not associated with reduction of cardiovascular events. These findings observed in the current analysis was similar to that observed in the SPIRE study [2]. It was thought that this was the reason why the sponsors decided to discontinue the clinical development of

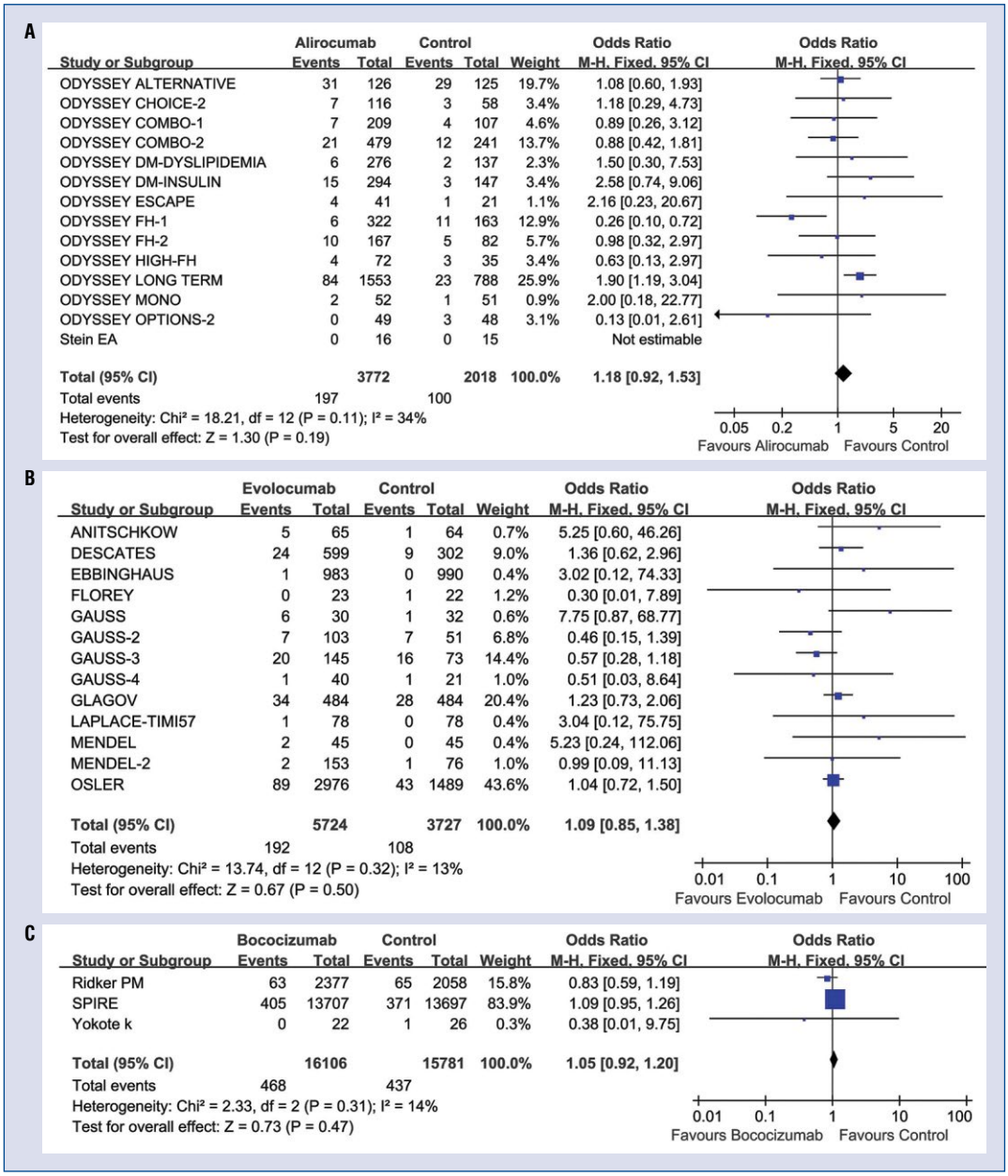

Figure 5. Forest plots of myalgia with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors versus control. Myalgia was reported in 30 studies with a total of 47,128 patients, of which 14 studies treated with alirocumab, 13 studies treated with evolocumab and 3 studies treated with bococizumab. Compared with control group, alirocumab group (odds ratio [OR] 1.18, 95% confidence interval [CI] 0.92 to 1.53, p > 0.05) (**A**), evolocumab group (OR 1.09, 95% CI 0.85 to 1.38, p > 0.05) (**B**) and bococizumab group (OR 1.05, 95% CI 0.92 to 1.20, p > 0.05) (**C**) had no significant difference in the incidence of myalgia.

bococizumab. More RCTs are needed to provide more evidence to prove the efficacy and safety of bococizumab.

PCSK9 is expressed in atherosclerotic plaques and might promote atherosclerosis by stimulating inflammation and endothelial dysfunction [8]. The present study found that alirocumab and evolocumab could reduce the risk of cardiovascular events and stroke, which may be related to their ability to ameliorate the blood lipid profile, inhibit PCSK9 expression in plaques, and inhibit inflammation. These findings were very encouraging and demonstrated conclusive evidence in favor of alirocumab and evolocumab therapy for CVD patients with acceptable safety concerns. In real-world practice, evolocumab has been prescribed

with favorable safety and tolerability outcomes [9]. However, more randomized clinical evidence was needed to explore the efficacy of bococizumab.

Limitations of the study

There are several limitations that should be taken into account in this analysis. First, the dose of PCSK9 inhibitors and different follow-up duration may have affected heterogeneity to the results. The shortest follow-up period was 8 weeks, the longest was 134 weeks. Second, the pooling of data in control group was a mixture of placebo or ezetimibe. Third, definitions of efficacy and safety were nonuniform in the included studies.

Clinical perspective

In our opinion, there is enough evidence with alirocumab and evolocumab on cardiovascular events and lipid profile to approve of using them.

Adverse events of PCSK9 inhibitors were mild and acceptable in patients with CVD. PCSK9 inhibitors were generally safe and well tolerated.

Conclusions

In conclusion, the present meta-analysis revealed that, compared with no PCSK9 inhibitors management, treatment with alirocumab and evolocumab could ameliorate lipid profile in ASCVD and reduce the risk of cardiac disorders and stroke. However, injection-site reactions should be paid attention to.

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Conflict of interest: None declared

References

1. Turgeon RD, Tsuyuki RT, Gyenes GT, et al. Cardiovascular Efficacy and Safety of PCSK9 Inhibitors: Systematic Review and Meta-analysis Including the ODYSSEY OUTCOMES Trial. Can J Cardiol. 2018; 34(12): 1600–1605, doi: 10.1016/j.cjca.2018.04.002, indexed in Pubmed: 30527147.
2. Ridker PM, Revkin J, Amarenco P, et al. Cardiovascular efficacy and safety of bococizumab in high-risk patients. N Engl J Med. 2017; 376(16): 1527–1539, doi: 10.1056/NEJMoa1701488, indexed in Pubmed: 28304242.
3. Ridker PM, Tardif JC, Amarenco P, et al. Lipid-Reduction variability and antidrug-antibody formation with bococizumab. N Engl J Med. 2017; 376(16): 1517–1526, doi: 10.1056/NEJMoa1614062, indexed in Pubmed: 28304227.
4. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Medicine. 2009; 6(7): e1000097, doi: 10.1371/journal.pmed.1000097.
5. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011; 343: d5928, doi: 10.1136/bmj.d5928, indexed in Pubmed: 22008217.
6. Higgins JPT, Green S (eds). Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. 2011. http://www.cochrane-handbook.org (accessed 21 March 2011).
7. Zhang XL, Zhu QQ, Zhu Li, et al. Safety and efficacy of anti-PCSK9 antibodies: a meta-analysis of 25 randomized, controlled trials. BMC Med. 2015; 13: 123, doi: 10.1186/s12916-015-0358-8, indexed in Pubmed: 26099511.
8. Li J, Liang X, Wang Y, et al. Investigation of highly expressed PCSK9 in atherosclerotic plaques and ox-LDL-induced endothelial cell apoptosis. Mol Med Rep. 2017; 16(2): 1817–1825, doi: 10.3892/mmr.2017.6803, indexed in Pubmed: 28656218.
9. Koskinas KC, Windecker S, Pedrazzini G, et al. Design of the randomized, placebo-controlled evolocumab for early reduction of LDL-cholesterol levels in patients with acute coronary syndromes (EVOPACS) trial. Clin Cardiol. 2018; 41(12): 1513–1520, doi: 10.1002/clc.23112, indexed in Pubmed: 30421481.

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The impact of readiness to discharge from hospital on adherence to treatment in patients after myocardial infarction

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Abstract

Background: *The healthcare professionals involved in in-hospital treatment of myocardial infarction (MI) are also responsible to patients for their education before leaving the hospital. This education aims to modify patient behaviour in order to reduce relevant risk factors and improve self-control and adherence to medications. The aim of the study was to analyse the relationship between readiness for discharge from hospital and adherence to treatment at follow-up in MI patients.*

Methods: *An observational, single-center, MI cohort study with 6-month follow-up was conducted between May 2015 and July 2016. The Readiness for Hospital Discharge after Myocardial Infarction Scale (RHD-MIS) and the Adherence in Chronic Diseases Scale (ACDS) were applied.*

Results: *Two hundred and thirteen patients aged 30–91 years (62.91 ± 11.26) were enrolled in the study. The RHD-MIS general score ranged from 29 to 69 points (51.16 ± 9.87). A high level of readiness was found in 66 (31%) patients, intermediate in 92 (43.2%), and low in 55 (25.8%) of patients. Adherence level assessed with the ACDS 6-months after discharge from hospital ranged from 7 to 28 points (23.34 ± 4.06). An increase in objective assessment of patient knowledge according to RHD-MIS subscale resulted in significantly higher level of adherence at the follow-up visit ($p = 0.0154$); R Spearman = 0.16671, $p = 0.015$; p for trend = 0.005. During the 6-month follow-up 3 (1.41%) patients died and 17 (7.98%) were hospitalized for a subsequent acute coronary syndrome.*

Conclusions: *This study provided preliminary evidence of a long-term association between the results of assessment of readiness for discharge from hospital and adherence to treatment in patients after MI.*
(Cardiol J 2022; 29, 4: 582–590)

Key words: readiness for discharge from the hospital, adherence, myocardial infarction, coronary artery disease, antiplatelet treatment, questionnaire, scale

Introduction

Adherence to medications after discharge from hospital is required for effective treatment of chronic diseases, including ischemic heart disease [1]. It is estimated that up to 60–80% of patients do not follow recommendations during long-term therapy [1–3], making it impossible to achieve therapy goals. In order to achieve patient's active involvement in the therapeutic process, it is necessary to provide the patient with some elementary knowledge about the disease and its treatment.

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Therefore, effective health education is essential for successful therapy [4, 5]. The healthcare professionals involved with in-hospital treatment of patients with myocardial infarction (MI) are also responsible for their preparation for discharge from hospital including education aimed to modify the risk factor profile, improve self-control and adherence to treatment [6–10]. In order to evaluate the effectiveness of preparation for the discharge procedure, the Readiness for Hospital Discharge after Myocardial Infarction Scale (RHD-MIS) was developed [11]. It is not clear, however, to what extent the level of readiness to discharge in patients after MI affects their subsequent adherence to therapeutic recommendations.

Presented data were collected as a part of a wider master project titled 'The influence of education on adherence'. Some results of the project have already been published [12, 13].

The aim of this study was to evaluate the long-term relationship between readiness for discharge from hospital and adherence to treatment in MI patients.

Methods

An observational, single-center, cohort study with 6-month follow-up was conducted at the Jurasz University Hospital in Bydgoszcz, Poland. The master project titled 'The influence of education on adherence' was approved by The Bioethics Committee of the Collegium Medicum, Nicolaus Copernicus University in Torun (No. KB 312/2015 of 21/04/2015). The research was performed in accordance with the Declaration of Helsinki and International Conference on Harmonization/Good Clinical Practice and applicable regulatory requirements. Consecutive patients treated with percutaneous coronary intervention (PCI) due to MI between May 2015 and July 2016 were considered eligible for the study. Subjects with cognitive or physical impairment, prisoners, soldiers, and patients remaining in any personal relationship with researchers were excluded. A written informed consent was acquired from all study participants before enrollment [12]. All patients during hospitalization and follow-up were treated according to current guidelines of the European Society of Cardiology [10]. Patients enrolled in the study received in-hospital education as a part of an in-hospital rehabilitation program, and were then seen in the out-patient clinic every 2 months up to 6 months after hospital discharge. Patients who missed their follow-up visit were contacted by phone and telephone follow-up was performed. The information regarding re-hospitalization or death of study participants was retrieved from the National Health Fund [12].

An in-hospital standardized educational program, which was a pivotal element of the procedure in patient preparation for discharge, was conducted by educational nurses in cooperation with physiotherapists, dietitians and physicians in all patients. The program includes information regarding pathophysiology of coronary artery disease, symptoms and treatment of the disease, diet, physical activity, and plan for outpatient control visits. Readiness for discharge from hospital was assessed with the RHD-MIS [11]. Adherence to treatment at follow-up was evaluated with The Adherence in Chronic Diseases Scale (ACDS) [14, 15]. Both scales were developed and validated in patients after MI [11, 15] and are available free of charge on the website of the Department of Health Promotion, Collegium Medicum, Nicolaus Copernicus University, Poland (https://www.cm.umk.pl/wydzialy/wydzial-nauk-o-zdrowiu/jednostki-wydzialowe/katedra-i-zaklad-promocji-zdrowia.html).

The RHD-MIS consists of three subscales: (1) subjective, and (2) objective assessment of patient knowledge about the disease, and (3) patient expectations [11]. A score from 0 to 3 was assigned for each of 23 RHD-MIS items. The questionnaire also contains non-scored questions regarding patients' opinions related to disease, treatment and prevention. A total RHD-MIS score of more than 57 points indicates high readiness for discharge, less than 44 points — low readiness, while medium readiness was defined as scores between 44 and 57 points. The previously reported an alpha-Cronbach coefficient of 0.789 indicates high reliability and homogeneity of this questionnaire. Moreover, internal consistency analysis of the RHD-MIS, three areas confirmed the appropriateness of the subscale distinction [11, 12].

Adherence to medication was assessed with standardized, self-reported questionnaire — the ACDS. The scale includes 7 questions with sets of 5 suggested answers to each question. Depending on the answer, each item of the scale is awarded 0–4 points. A score of more than 26 points reflects high adherence to treatment, while scores of 21–26, and less than 21 points respectively, correspond to intermediate and low adherence. According to the validation study, the ACDS questionnaire has a satisfactory level of reliability and homogeneity (alpha-Cronbach coefficient of 0.752) [13]. The ACDS is designed for surveying

adults treated for chronic diseases and reflects the actual implementation of a treatment plan regarding pharmacotherapy.

The first section of RHD-MIS, as well as the entire ACDS were completed by patients under the supervision of a data collecting nurse.

All enrolled patients were evaluated with the RHD-MIS on the day of discharge from hospital, while the ACDS was assessed 6-months after discharge [12]. Concordance between the subjective and objective assessment of knowledge with the RHD-MIS was recognized when the results of both subscales were in the same score ranges (high and high, intermediate and intermediate, or low and low); extremely different scores (high and low) of subjective and objective assessment of knowledge were defined as extreme discordance; any other combination of subscale results was classified as discordant.

In order to ensure accuracy and completeness of data collection, special care was taken to assure study participants of anonymity and confidentiality of the information obtained from both questionnaires. The data collecting staff also did their best to avoid influencing patient responses [12]. All data collection, including supervision of questionnaire completion, was performed by three co-authors of this paper (AKo, PM and ŁP).

Statistical analysis

Statistical analysis was performed using Statistica 12.0 software (StatSoft, Tulsa, USA). Medians with interquartile ranges and means with standard deviations were used for continuous variables presentation. Normality of data distribution was verified with the Shapiro-Wilk test. Due to a lack of normal distribution of the investigated continuous variables, non-parametric tests were used for statistical analysis. The Mann-Whitney unpaired rank sum test was applied for comparisons between the two groups. Comparisons between three or more groups were performed with the Kruskal-Wallis one-way analysis of variance for assessment of heterogeneity. For evaluation of trends the Jonckheere-Terpstra test was used. The degree of association between two variables was assessed with the Spearman rank correlation test. The results were considered significant at $p < 0.05$ [12].

Results

General results

The study population consisted of 213 patients (59 women and 154 men) aged from 30 to 91 years (average 62.91 ± 11.26 years), with complete data collected at baseline hospitalization and at follow-up visit (Fig. 1) [12].

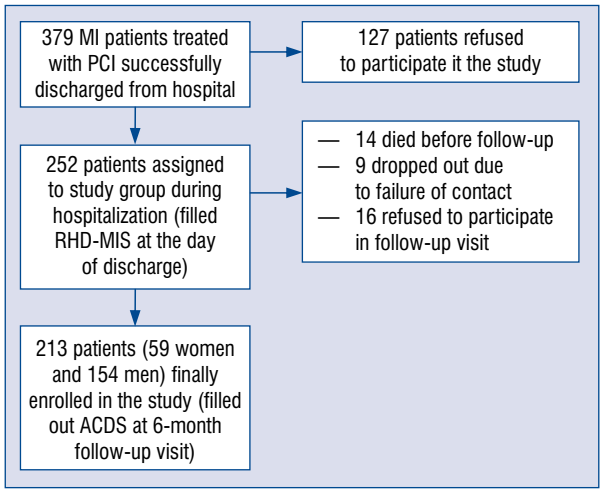

Figure 1. A study flow chart; MI — myocardial infarction; PCI — percutaneous coronary intervention; ACDS — Adherence in Chronic Diseases Scale; RHD-MIS — Readiness for Hospital Discharge after Myocardial Infarction Scale.

Out of 379 consecutive patients who met the inclusion criteria during hospitalization and were successfully discharged from hospital, 166 individuals were not enrolled in the study (127 of them did not provide their consent for participation in the study, 14 died after discharge from hospital, but before the follow-up visit, 9 were lost to follow-up due to failure of contact, and 16 refused to participate in follow-up or provided incomplete answers precluding data analysis) [12]. Only 37 (17.4%) patients participated in a rehabilitation program after discharge. The characteristics of the study population is shown in Table 1 [12].

The level of readiness for discharge from hospital was assessed with the RHD-MIS general score which ranged from 29 to 69 points with a median of 52 and an average score of 51.16 ± 9.87. A high level of readiness was found in 66 (31%) patients, intermediate in 92 (43.2%), and low in 55 (25.8%) of patients. The results obtained with each of the three subscales are shown in Table 2.

According to multiple comparison tests, none of the analyzed sociodemographic nor clinical factors were associated with the RHD-MIS general score. Regarding the RHD-MIS subscales, knowledge about coronary artery disease according to an objective assessment was associated with gender (higher for female; $p = 0.012$) and with place of

Table 1. Study population characteristics.

Parameter	Variable	Total sample (n = 213)
Gender	Female	59 (27.7%)
	Male	154 (72.3%)
Age	< 65	119 (55.87%)
	≥ 65	94 (43.13%)
Education	Primary	26 (12.21%)
	Vocational	77 (36.15%)
	Secondary	79 (37.09%)
	Higher	31 (14.55%)
Employment status	Employed	86 (40.38%)
	Unemployed	13 (6.1%)
	OA pensioner	86 (40.38%)
	DLA recipient	28 (13.1%)
Economic status	Very good	12 (5.63%)
	Acceptable	190 (89.2%)
	Bad	11 (5.16%)
	Very bad	0 (0.0%)
Place of residence*	City	112 (52.58%)
	Town	45 (21.13%)
	Village	56 (26.29%)
Marital status	Unmarried	21 (9.86%)
	Married	163 (76.53%)
	Widowed	29 (13.62%)
Living status	Alone	25 (11.74%)
	With family	188 (88.26%)
Prior hospitalization for CAD	Yes	131 (61.50%)
	No	82 (38.5%)
History of CAD	Yes	100 (46.95%)
	No	113 (53.05%)
Prior MI	Yes	60 (28.17%)
	No	153 (71.83%)
Prior PCI	Yes	80 (37.56%)
	No	133 (62.44%)
Prior CABG	Yes	32 (15.02%)
	No	181 (84.98%)
Hypertension	Yes	157 (73.71%)
	No	56 (26.29%)
Hyperlipidemia	Yes	145 (68.08%)
	No	68 (31.92%)
Smoking status	Yes (current)	74 (34.74%)
	No (current)	139 (65.26%)
	Ex-smoker	51 (23.94%)
Family burden	Yes	128 (60.09%)
	No	85 (39.91%)
Diabetes	Yes	61 (28.64%)
	No	152 (71.36%)

*City > 100,000 inhabitants; Town ≤ 100,000 inhabitants; OA — old age; DLA — disability living allowance; CAD — coronary artery disease; MI — myocardial infarction; PCI — percutaneous coronary intervention; CABG — coronary artery bypass grafting

residence (higher for city dwellers; p = 0.025). Economic status was found to have an impact on patient expectations (higher for lower status; p = = 0.014); no association between the factors analyzed and subjective assessment of knowledge was found. Detailed results concerning those factors have been previously published [12].

The results of ACDS were influenced by age (higher for patients < 65 years of age; p = 0.0005) and previous MI (lower for patients with MI before the index event; p = 0.005).

A comparison of subjective and objective assessment of patient knowledge revealed concordance in 90 (42.3%) subjects, while discordance was observed in 123 (57.7%) patients. Moreover, an extreme mismatch (low and high level) occurred in 24 (11.3%) patients (Table 3).

The adherence to prescribed medication assessment with the ACDS at 6 months after discharge from the hospital resulted in a score from 7 to 28 (median of 24 points; average of 23.34 ± ± 4.06). A score of over 26 points classified as high was obtained by 56 (26.3%) patients, an intermediate score (between 21 and 26 points) was found in 106 (49.8%) subjects and in 51 (23.9%) patients the score was under 21 points was defined as low.

Detailed results

A comparison of RHD-MIS general score according to ACDS scores in all patients enrolled in the study did not reveal any significant differences, only a trend (p = 0.038) suggesting higher adherence at follow-up in patients with a higher level of readiness for discharge was found (Table 2). However, in subjects showing concordance between subjective and objective assessment of patient knowledge, higher ACDS results were associated with higher RHD-MIS general scores (ACDS score of 22.64 ± 4.83, 23.34 ± 2.94, and 24.97 ± 3.55 for low, intermediate and high RHD-MIS general score, respectively, p = 0.018). The comparison of these ACDS scores showed differences for low vs. high (p = 0.023) and intermediate vs. high (p = 0.014), but not for low vs. intermediate (p = 0.099) RHD-MIS general score.

Among the RHD-MIS subscales, the increase in objective assessment of patients resulted in significantly higher level of adherence at follow-up visit (p = 0.0154); R Speraman = 0.16671, p = 0.015; p for trend = 0.005. The results of the remaining RHD-MIS subscales did not show a relationship with ACDS results. Nevertheless, the high result of RHD-MIS general score as well as high results of all subscales of RHD-MIS were

Table 2. Readiness for Hospital Discharge after Myocardial Infarction Scale (RHD-MIS) scores with regard to Adherence in Chronic Diseases Scale (ACDS) score level.

ACDS	RHD-MIS General score	RHD-MIS subscales scores		
		Subjective knowledge	Objective knowledge	Patient expectations
Low score (n = 51)	49.06 ± 10.45	17.24 ± 3.35	15.47 ± 3.59	16.35 ± 7.34
Intermediate score (n = 106)	51.29 ± 9.57	17.75 ± 3.17	15.49 ± 3.42	18.05 ± 6.67
High score (n = 56)	52.84 ± 9.70	18.34 ± 3.18	16.73 ± 3.17	17.77 ± 7.25

Table 3. Readiness for Hospital Discharge after Myocardial Infarction Scale (RHD-MIS) regarding patient knowledge — concordance of subjective and objective assessment.

Level of knowledge	Objective low	Objective intermediate	Objective high
Subjective low	22 (10.3%)	22 (10.3%)	8 (3.8%)
Subjective intermediate	15 (7.0%)	32 (15.0%)	11 (5.2%)
Subjective high	16 (7.5%)	51 (23.9%)	36 (16.9%)

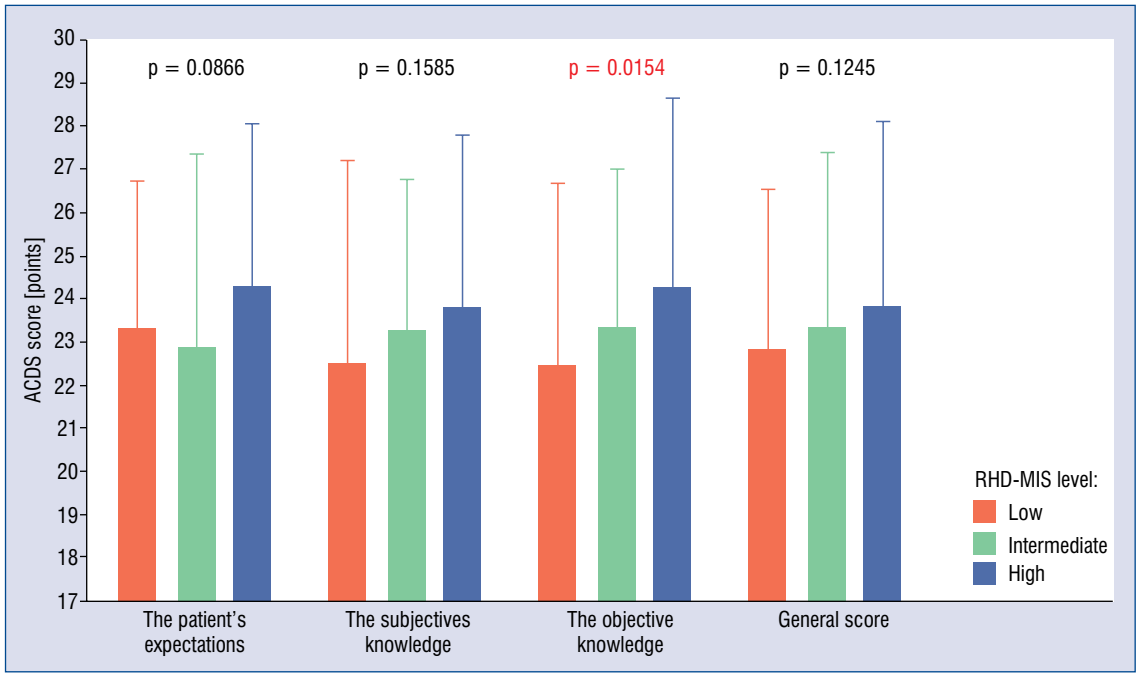

Figure 2. Comparison of Adherence in Chronic Diseases Scale (ACDS) scores with regard to Readiness for Hospital Discharge after Myocardial Infarction Scale (RHD-MIS) results (general score and subscale scores).

associated with the highest adherence level according to ACDS (Fig. 2).

RHD-MIS and ACDS scores were analysed according to patient opinions expressed in non-scored RHD-MIS items (Figs. 3, 4). Due to the distribution of answers, answers "Yes" and "I guess so" were combined and compared vs. answers "I do not" and "I'm not sure". The statistical analysis of RHD-MIS was not performed for the first opinion (A), as almost all patients (210 vs. 3) answered "Yes" or "I guess so". For all remaining opinions significant differences regarding RHD-MIS were

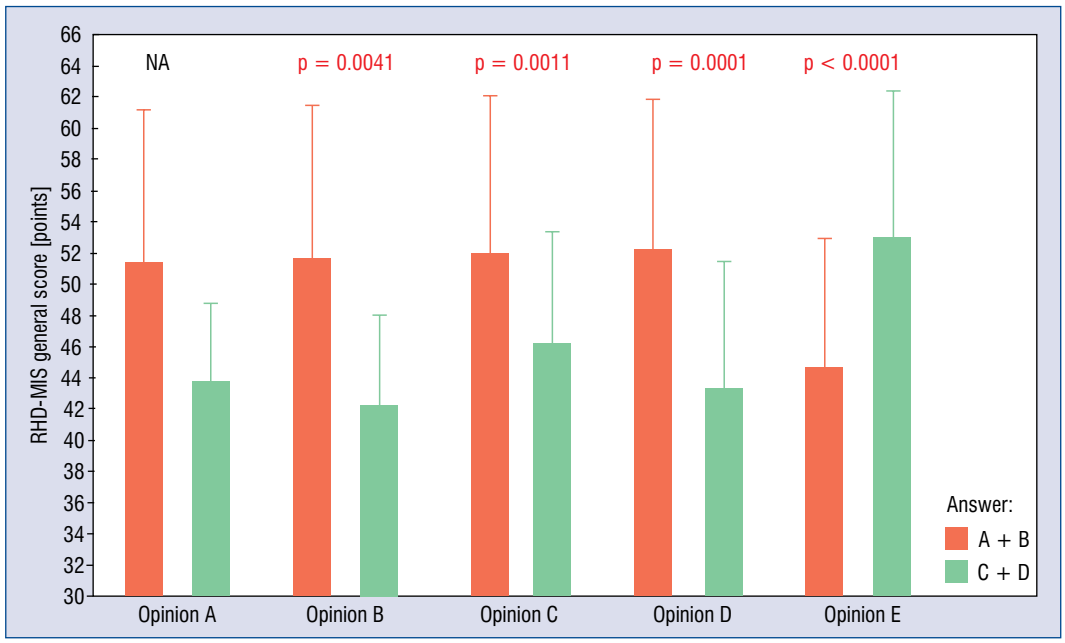

Figure 3. Readiness for Hospital Discharge after Myocardial Infarction Scale (RHD-MIS) general score with regard to patients' opinions; NA — not applicable
Opinion A. Do you think that the illness being the reason for your hospitalisation is serious?
Opinion B. Do you think that despite the medication, you need to change your lifestyle to prevent illness recurrence?
Opinion C. Do you think that systematic medication reduces the risk of reinfarction?
Opinion D. Can you rely on the help of family or other people to comply with your doctor's recommendations?
Opinion E. Do you think your return home is associated with additional hazards?

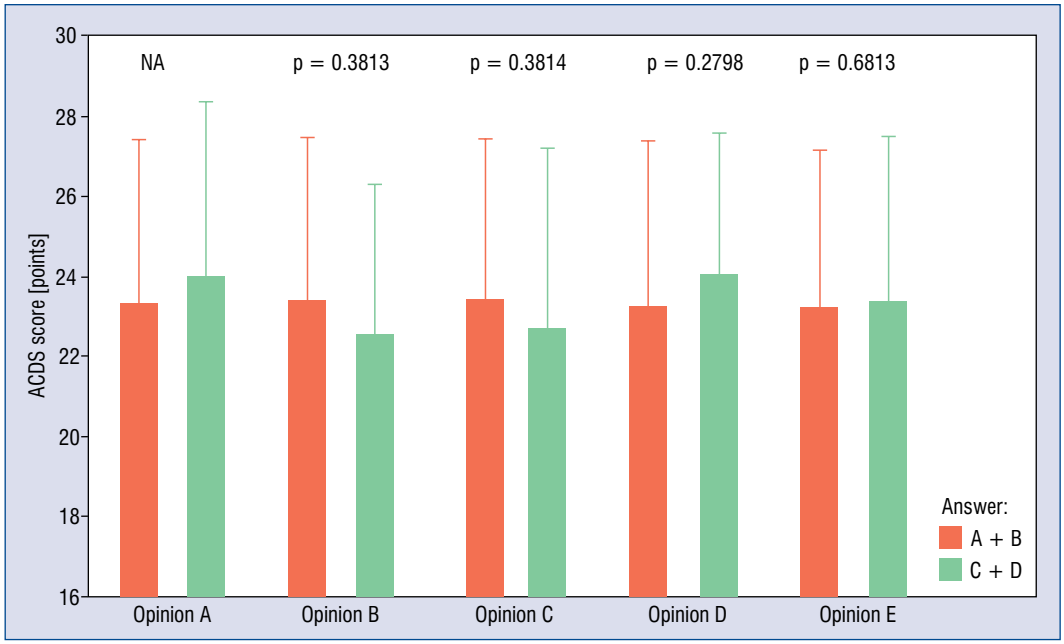

Figure 4. Adherence in Chronic Diseases Scale (ACDS) score with regard to patients' opinions; NA — not applicable
Opinion A. Do you think that the illness being the reason for your hospitalisation is serious?
Opinion B. Do you think that despite the medication, you need to change your lifestyle to prevent illness recurrence?
Opinion C. Do you think that systematic medication reduces the risk of reinfarction?
Opinion D. Can you rely on the help of family or other people to comply with your doctor's recommendations?
Opinion E. Do you think your return home is associated with additional hazards?

found (Fig. 2); for B, C, and D the mean score was higher with answers "Yes" and "I guess so", while for opinion E it was higher with answers "I do not" and "I'm not sure" (Fig. 3). The ACDS scores did not differ with regard to patient opinions (Fig. 4).

Moreover, significant differences in scores of RHD-MIS sub-scale 1 (subjective assessment of patient knowledge about the disease) were observed between patients answering "Yes" and "I guess so" vs. "I do not" and "I'm not sure" for the following opinions: B (Do you think that besides taking medication, lifestyle changes are also necessary to prevent illness recurrence?): 17.90 ± ± 3.22 vs. 15.11 ± 1.96, p = 0.0033; C (Do you think that systematic medication taking reduces the risk of reinfarction?): 18.27 ± 3.03 vs. 14.94 ± 2.86, p < 0.0001; D (Can you rely on help from your family or other people to comply with your doctor's recommendations?): 18.17 ± 2.98 vs. 15.50 ± 3.24, p = 0.0001; and E (Do you think your return home is associated with additional hazards?): 17.09 ± ± 3.00 vs. 17.98 ± 3.27, p = 0.0377. Similar differences in RHD-MIS subscale 3 (patient expectations) scores were found for the following opinions: C (17.79 ± 7.25 vs. 16.29 ± 5.13, p = 0.0353), D (18.18 ± 6.98 vs. 13.38 ± 5.59, p = 0.0003), and E (12.70 ± 6.56 vs. 18.91 ± 6.50, p < 0.0001). No significant differences in ACDS score were found with regard to patient opinions expressed in the non-scored RHD-MIS items.

During 6-month follow-up 3 (1.41%) patients died and 17 (7.98%) were hospitalized for a subsequent acute coronary syndrome (ACS). Adherence levels assessed with ACDS were similar irrespective of occurrence or absence of ACS at follow-up (22.30 ± 3.81 vs. 23.56 ± 3.92; p = 0.130).

Discussion

Therapy according to medical guidelines has shown to be effective with regard to a reduction in illness symptoms and in the prevention of complications, however the rates of long-term adherence to pharmacotherapy tend to be as low as 50–60%, regardless of the of illness, the regimen of treatment and the applied criteria [9, 16]. Available evidence suggests that patients early after hospitalization remain particularly vulnerable. Adverse events, including serious medication errors and hospital readmissions, occurred in nearly 20% of patients within 3 weeks after discharge [17]. Thus, effective preparation of patients for discharge from hospital is of great importance.

The association between readiness for discharge from the hospital and adherence to treatment assessed 6 months after discharge in patients treated for MI was the primary finding of this study. However, direct impact of readiness for discharge on clinical outcome during 6 months of follow-up was not able to be determined. This may partly be attributed to inadequate preparation for discharge of patient and his/her, poor coordination of discharge transition, and unsuccessful patient self-management at home [18].

Extensive preparation for discharge including teaching should be a standard of hospital care. However, several barriers to retention of learning at discharge have to be taken into account, including complexity of managing medical care at home, an overwhelming amount of information, the timing of teaching, as well as content relevance to personal concerns and needs [19, 20]. Although patients are prone to report receiving adequate information prior to discharge, the gaps in knowledge needed is identified when tested with questionnaires. For patients enrolled the present study the readiness for discharge level was judged high with RHD-MIS in about 1/3 of patients while low in 1/4 of the study population. Moreover, according to a subjective assessment the level of patient knowledge was almost two-fold higher when compared to an objective assessment of patient knowledge.

Multiple factors may contribute to adverse events after discharge, including an overwhelming quantity of information received by patients on their final hospitalization day as well as fragmented and inconsistent communication [17]. A growing body of literature suggests that to ensure patient understanding, satisfaction and safety, discharge planning should start at the time of admission [21]. Ineffective planning for discharge may result in confusion experienced by patients and their families, coping difficulties, and an increased readmission rate [22]. The implementation of a discharge planning procedure, including an assessment of patient readiness for discharge, is the first step in improving the effectiveness of hospital discharge [23, 24].

It has been previously demonstrated that the views of nurses and patients about what is important in cardiac rehabilitation are often different [25, 26]. Moreover, models of illness represented by patients, which influence their understanding of cardiac problems, frequently differ from models represented by professionals [27, 28]. Therefore, the RHD-MIS was designed as a complex tool taking into account not only the perspective of the

patient, but also of the nurse evaluating readiness for hospital discharge, as well as expectations and opinions of the patient [11]. Discordance was found between patient self-assessment and nurse assessment of patient knowledge in almost 60% of cases, including approximately 11% of extreme discordance.

Weiss et al. [18] showed that nurse assessment of discharge readiness was more strongly associated with post-discharge readmissions and emergency department visit utilization than patient self-assessment. Since patients with low knowledge level, according to the RHD-MIS subscale for objective assessment, are at increased risk of low adherence to treatment, they require additional motivation activities and educational intervention to avert adverse outcomes [13, 19, 29, 30].

Limitations of the study

The study was designed as a single center study, therefore the population may not be representative for other hospitals. The relatively low number of adverse clinical events at post-discharge follow-up did not permit showing any effect on readiness for discharge from hospital on clinical outcome.

Conclusions

The results of this study provide preliminary evidence of an association between assessment of readiness for discharge from hospital and adherence to treatment at long-term follow-up in patients after MI. Further testing of readiness for discharge assessment, coupled with preventive interventions targeted at improvement of adherence to treatment is needed to support rationale for implementation of such a strategy into the discharge procedure.

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Conflict of interest: None declared

References

1. Desai N, Choudhry N. Impediments to adherence to post myocardial infarction medications. Curr Cardiol Rep. 2012; 15(1), doi: 10.1007/s11886-012-0322-6.
2. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. 2005; 353(5): 487–497, doi: 10.1056/NEJMra050100, indexed in Pubmed: 16079372.
3. Haynes RB, McDonald HP, Garg AX. Helping patients follow prescribed treatment: clinical applications. JAMA. 2002; 288(22): 2880–2883, doi: 10.1001/jama.288.22.2880, indexed in Pubmed: 12472330.
4. Kubica A. Problems of long-term antiplatelet therapy after coronary stent implantation. Adv Interv Cardiol. 2009; 5: 158–161.
5. Kubica A, Obońska K, Fabiszak T, et al. Adherence to antiplatelet treatment with P2Y12 receptor inhibitors. Is there anything we can do to improve it? A systematic review of randomized trials. Curr Med Res Opin. 2016; 32(8): 1441–1451, doi: 10.1080/03007995.2016.1182901, indexed in Pubmed: 27112628.
6. Visser A, Deccache A, Bensing J. Patient education in Europe: united differences. Patient Educ Couns. 2001; 44(1): 1–5, doi: 10.1016/s0738-3991(01)00111-2, indexed in Pubmed: 11390150.
7. Jackevicius CA, Li P, Tu JV. Prevalence, predictors, and outcomes of primary nonadherence after acute myocardial infarction. Circulation. 2008; 117(8): 1028–1036, doi: 10.1161/CIRCULATIONAHA.107.706820, indexed in Pubmed: 18299512.
8. Forster AJ, Murff HJ, Peterson JF, et al. The incidence and severity of adverse events affecting patients after discharge from the hospital. Ann Intern Med. 2003; 138(3): 161–167, doi: 10.7326/0003-4819-138-3-200302040-00007, indexed in Pubmed: 12558354.
9. Kubica A, Kochman W, Bogdan M, et al. The influence of undergone percutaneous coronary interventions, and earlier hospitalizations with myocardial infarction on the level of knowledge and the effectiveness of health education in patients with myocardial infarction. Adv Interv Cardiol. 2009; 5: 25–30.
10. Steg PG, James SK, Atar D, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2012; 33(20): 2569–2619, doi: 10.1093/eurheartj/ehs215, indexed in Pubmed: 22922416.
11. Buszko K, Kosobucka A, Michalski P, et al. The readiness for hospital discharge of patients after acute myocardial infarction: a new self-reported questionnaire. Med Res J. 2017; 2(1): 20–28, doi: 10.5603/mrj.2017.0004.
12. Kosobucka A, Kasprzak M, Michalski P, et al. Relation of the Readiness for Hospital Discharge after Myocardial Infarction Scale to socio-demographic and clinical factors. An observational study. Med Res J. 2018; 3(1): 32–37, doi: 10.5603/mrj.2018.0006.
13. Kosobucka A, Michalski P, Pietrzykowski Ł, et al. Adherence to treatment assessed with the Adherence in Chronic Diseases Scale in patients after myocardial infarction. Patient Prefer Adherence. 2018; 12: 333–340, doi: 10.2147/PPA.S150435, indexed in Pubmed: 29551891.
14. Kubica A, Kosobucka A, Michalski P, et al. The adherence in chronic diseases scale-a new tool to monitor implementation of a treatment plan. Folia Cardiol. 2017; 12: 19–26.
15. Buszko K, Obońska K, Michalski P, et al. The Adherence Scale in Chronic Diseases (ASCD). The power of knowledge: the key to successful patient — health care provider cooperation. Med Res J. 2016; 1(1): 37–42, doi: 10.5603/mrj.2016.0006.
16. DiMatteo MR. Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research. Med Care. 2004; 42(3): 200–209, doi: 10.1097/01.mlr.0000114908.90348.f9, indexed in Pubmed: 15076819.
17. Forster AJ, Murff HJ, Peterson JF, et al. Adverse drug events occurring following hospital discharge. J Gen Intern Med. 2005; 20(4): 317–323, doi: 10.1111/j.1525-1497.2005.30390.x, indexed in Pubmed: 15857487.
18. Weiss M, Yakusheva O, Bobay K. Nurse and patient perceptions of discharge readiness in relation to postdischarge utilization. Med Care. 2010; 48(5): 482–486, doi: 10.1097/MLR.0b013e3181d5feae, indexed in Pubmed: 20393364.

19. Weiss ME, Piacentine LB, Lokken L, et al. Perceived readiness for hospital discharge in adult medical-surgical patients. Clin Nurse Spec. 2007; 21(1): 31–42, doi: 10.1097/00002800-200701000-00008, indexed in Pubmed: 17213738.
20. Paterson B, Kieloch B, Gmiterek J. ‚They never told us anything': postdischarge instruction for families of persons with brain injuries. Rehabil Nurs. 2001; 26(2): 48–53, doi: 10.1002/j.2048-7940.2001.tb01925.x, indexed in Pubmed: 12035699.
21. Patel H, Mourad M. Demystifying discharge: Assessing discharge readiness to predict day of discharge. J Hosp Med. 2015; 10(12): 832–833, doi: 10.1002/jhm.2445, indexed in Pubmed: 26434568.
22. Horwitz LI, Moriarty JP, Chen C, et al. Quality of discharge practices and patient understanding at an academic medical center. JAMA Intern Med. 2013; 173(18): 1715–1722, doi: 10.1001/jamainternmed.2013.9318, indexed in Pubmed: 23958851.
23. Tyler A, Boyer A, Martin S, et al. Development of a discharge readiness report within the electronic health record-A discharge planning tool. J Hosp Med. 2014; 9(8): 533–539, doi: 10.1002/jhm.2212, indexed in Pubmed: 24825848.
24. Weiss ME, Costa LL, Yakusheva O, et al. Validation of patient and nurse short forms of the Readiness for Hospital Discharge Scale and their relationship to return to the hospital. Health Serv Res. 2014; 49(1): 304–317, doi: 10.1111/1475-6773.12092, indexed in Pubmed: 23855675.
25. Normington K, Goodwin S. A personalised approach to cardiac rehabilitation. Prof Nurse. 2000; 15(7): 432–436, indexed in Pubmed: 11129924.
26. Kubica A, Kasprzak M, Obońska K, et al. Discrepancies in assessment of adherence to antiplatelet treatment after myocardial infarction. Pharmacology. 2015; 95(1-2): 50–58, doi: 10.1159/000371392, indexed in Pubmed: 25592409.
27. Gassner LA, Dunn S, Piller N. Patients' interpretation of the symptoms of myocardial infarction: implications for cardiac rehabilitation. Intensive Crit Care Nurs. 2002; 18(6): 342–354, doi: 10.1016/s0964-3397(02)00072-1, indexed in Pubmed: 12526872.
28. Smith J, Liles C. Information needs before hospital discharge of myocardial infarction patients: a comparative, descriptive study. J Clin Nurs. 2007; 16(4): 662–671, doi: 10.1111/j.1365-2702.2006.01689.x, indexed in Pubmed: 17402947.
29. Kubica A, Kasprzak M, Siller-Matula J, et al. Time-related changes in determinants of antiplatelet effect of clopidogrel in patients after myocardial infarction. Eur J Pharmacol. 2014; 742: 47–54, doi: 10.1016/j.ejphar.2014.08.009, indexed in Pubmed: 25199965.
30. Scott JT, Thompson DR. Assessing the information needs of post-myocardial infarction patients: a systematic review. Patient Educ Couns. 2003; 50(2): 167–177, doi: 10.1016/s0738-3991(02)00126-x, indexed in Pubmed: 12781932.

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Comparative effects of fentanyl versus morphine on platelet inhibition induced by ticagrelor in patients with ST-segment elevation myocardial infarction: Full results of the PERSEUS randomized trial

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Abstract

Background: *Morphine reduces absorption and delays action onset of potent oral $P2Y_{12}$ receptor inhibitors in patients with ST-segment elevation myocardial infarction (STEMI). We sought to determine the differential effects of fentanyl compared to morphine on the pharmacodynamics and pharmacokinetics of ticagrelor in STEMI patients undergoing primary percutaneous coronary intervention (PCI).*

Methods: *PERSEUS (NCT02531165) was a prospective, single-center, open-label, randomized controlled study. Patients with STEMI who required analgesia were randomly assigned in a 1:1 ratio to treatment with intravenous fentanyl or morphine after ticagrelor loading dose (LD) administration. The primary endpoint was platelet reactivity at 2 hours after ticagrelor LD assessed by $P2Y_{12}$ reaction units (PRU).*

Results: *The study was prematurely stopped in June 2017 after enrolment of 38 out of 56 planned patients. PRU at 2 hours following ticagrelor LD was 173.3 ± 89.7 in the fentanyl group and 210.3 ± 76.4 in the morphine group ($p = 0.179$). At 4 hours, PRU was significantly lower among patients treated with fentanyl as compared to those treated with morphine (90.1 ± 97.4 vs. 168.0 ± 72.2; $p = 0.011$). Maximal plasma concentrations of ticagrelor and its active metabolite AR-C124910XX tended to be delayed and numerically lower among patients treated with morphine compared to fentanyl. Total exposures to ticagrelor and AR-C124910XX within 6 hours after ticagrelor LD were numerically greater among patients treated with fentanyl compared to those treated with morphine.*

Conclusions: *In patients with STEMI undergoing primary PCI, fentanyl did not improve platelet inhibition at 2 hours after ticagrelor pre-treatment compared with morphine. Fentanyl may, however, accelerate ticagrelor absorption and increase platelet inhibition at 4 hours compared to morphine.* (Cardiol J 2022; 29, 4: 591–600)

Key words: fentanyl, pharmacodynamics, pharmacokinetics, ST-segment elevation myocardial infarction, ticagrelor

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Introduction

Dual antiplatelet therapy combining acetylsalicylic acid (ASA) and a $P2Y_{12}$ receptor antagonist is a cornerstone in the pharmacological treatment of patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI) [1]. Early optimal $P2Y_{12}$ receptor inhibition has been shown to improve coronary reperfusion before primary PCI and clinical outcomes compared to a delayed $P2Y_{12}$ inhibition strategy in patients with STEMI [2]. However, platelet inhibitory effects induced by potent oral $P2Y_{12}$ receptor antagonists are delayed in patients with STEMI [3, 4]. Recent pharmacological studies have demonstrated that morphine further reduces absorption, delays onset of action, and decreases antiplatelet effects of oral $P2Y_{12}$ inhibitors among STEMI patients undergoing primary PCI [4–7], which potentially results in an increased risk of stent-related adverse outcomes [8].

Fentanyl is a potent, fast-acting, and effective intravenous synthetic opioid agent [9], which is frequently used for procedural analgesia during cardiac catheterization procedures [10]. Recently, fentanyl has been shown to reduce ticagrelor absorption and delay platelet inhibition compared with placebo in patients with chronic coronary syndrome [11, 12], but the potential influence of fentanyl on ticagrelor absorption and platelet inhibition in patients with acute STEMI remains uncertain. We recently reported the main results for the primary and selected prespecified secondary endpoints from the Platelet Inhibition after Pre-hospital Ticagrelor using Fentanyl compared to Morphine in patients with ST-segment elevation Myocardial Infarction undergoing Primary Percutaneous Coronary Intervention (PERSEUS) randomized trial, which compared fentanyl versus morphine regarding ticagrelor pharmacokinetics and pharmacodynamics among STEMI patients undergoing primary PCI, and demonstrated that fentanyl did not improve platelet inhibition at 2 hours compared with morphine [13]. However, the full results from the PERSEUS trial have not been published to date. Herein, we report baseline demographic and procedural characteristics of the study population, patient self-reported pain scores, complete platelet function results, and prespecified coronary reperfusion outcomes.

Methods

Study design and patient population

PERSEUS was an investigator-initiated, prospective, single-center, open-label, randomized controlled trial. A detailed description of the study rationale and design has been previously published [14]. Briefly, patients with STEMI undergoing primary PCI within 12 hours of symptoms' onset were eligible for inclusion. Key inclusion and exclusion criteria have been reported previously [14]. Patients on chronic $P2Y_{12}$ receptor antagonist or oral anticoagulation therapy, or who received glycoprotein IIb/IIIa inhibitors were excluded. In addition, patients with medical conditions that may adversely affect gastrointestinal absorption and metabolic activation of oral $P2Y_{12}$ receptor inhibitors, including comatose patients or those with cardiogenic shock, were excluded. All patients were pre-treated with ASA (loading dose [LD] 500 mg), ticagrelor (LD 180 mg), and unfractionated heparin (LD 5000 IU or 70–100 IU per kg of body weight) at the time of STEMI diagnosis. Patients requiring analgesia for pain relief (visual analogue scale [VAS] score ≥ 3) were randomly assigned in a 1:1 ratio to treatment with intravenous fentanyl (50–100 μg) or morphine (4–8 mg) using a centralized telephone treatment allocation. Additional doses of fentanyl (25 μg, every 2–5 min) or morphine (2 mg, every 5–15 min) were administrated to achieve adequate analgesia (VAS score < 3). All patients underwent primary PCI according to institutional standards. The choice of vascular access site, periprocedural anticoagulation regimen, and procedural techniques was left to the discretion of the treating physician. After primary PCI, all patients received a maintenance dose of ASA (100 mg daily) indefinitely. A ticagrelor maintenance dose (90 mg twice daily) was initiated 12 hours after the LD and was recommended for at least 12 months. The study protocol complied with the Declaration of Helsinki. The study protocol was approved by the local Ethics Committee at Lausanne University Hospital, Switzerland (Project ID: PB_2016-00291). All enrolled patients provided written informed consent for participation. The trial was registered with ClinicalTrials.gov, identifier NCT02531165.

Pharmacodynamic assessments

Blood samples were collected at baseline and at 1, 2, 4, 6, and 12 hours after ticagrelor LD admin-

istration [13]. Platelet reactivity was determined as $P2Y_{12}$ reaction units (PRU) using the VerifyNow® $P2Y_{12}$ function assay (Accumetrics, Inc., San Diego, California, USA) at 1, 2, 4, 6, and 12 hours, and platelet reactivity index (PRI) using the Vasodilator-Stimulated-phosphoprotein Phosphorylation (VASP) assay (Biocytex, Inc., Marseille, France) at 1, 2, and 4 hours after ticagrelor LD administration [14]. High on-treatment platelet reactivity (HTPR) was defined as PRU ≥ 240 or PRI ≥ 50% [15].

Pharmacokinetic assessments

Plasma concentrations of ticagrelor and its major active metabolite AR-C124910XX were determined by a blinded external laboratory (Covance Laboratories, Indianapolis, Indiana, USA) at 1, 2, 4, 6, and 12 hours after ticagrelor pre-treatment using high-performance liquid chromatography combined with tandem mass spectrometry detection in the negative ion mode after protein precipitation extraction. A detailed description of blood samples collection and preparation has been reported previously [13]. Baseline ticagrelor and AR-C124910XX plasma concentrations were presumed to be zero because subjects on chronic $P2Y_{12}$ receptor inhibitors were excluded. The lower limits of quantification for ticagrelor and AR-C124910XX were 1 ng/mL and 2.5 ng/mL, respectively.

Study endpoints

The primary endpoint was platelet reactivity assessed by PRU at 2 hours after ticagrelor LD administration. Prespecified secondary endpoints include platelet reactivity assessed by PRU at 1, 4, 6, and 12 hours after ticagrelor LD, the proportion of patients with HTPR at 1, 2, 4, 6, and 12 hours after ticagrelor LD, the peak plasma concentration (C_{max}) of ticagrelor and AR-C124910XX at 1, 2, 4, 6, and 12 hours after ticagrelor LD, the time to peak plasma concentration (T_{max}) for ticagrelor and AR-C124910XX, the area under the plasma concentration-time curve for ticagrelor and AR-C124910XX during the first 6 hours after ticagrelor LD (AUC_{0-6}), the proportion of patients with thrombolysis in myocardial infarction (TIMI) grade 3 flow in the infarct-related artery before primary PCI, and the proportion of patients with ≥ 70% ST-segment elevation resolution after primary PCI. Data collection and monitoring have been described previously [14]. Study endpoints were independently adjudicated by a clinical events committee blinded to treatment assignment.

Sample size calculation

At the time of the study design, there was no reference study examining the effects of fentanyl on the pharmacodynamics and pharmacokinetics of $P2Y_{12}$ receptor inhibitors in patients with STEMI treated with primary PCI. Based on the results of previous studies [4–7], we assumed a mean PRU value of 190 at 2 hours after ticagrelor administration in STEMI patients undergoing primary PCI after receiving analgesia with morphine. We presumed that platelet reactivity assessed by PRU at 2 hours after ticagrelor loading dose administration would be lower in patients receiving fentanyl as compared to morphine (PRU 160 ± ± 40; absolute platelet reactivity difference, 30 PRU; relative platelet reactivity difference, 16%) due to differential involvement of μ-opioid receptor sites and responsible regions between fentanyl and morphine, which results in varying effects on gastrointestinal motility and degrees of induced dysmotility [14]. Assuming a two-sided statistical significance level of 0.05 and 95% confidence interval (CI), we calculated that enrolment of a total of 56 patients (28 in both study groups) would provide 80% power to demonstrate a significant difference in PRU values at 2 hours after ticagrelor LD administration between treatment arms.

Statistical analysis

All analyses were performed according to the intention-to-treat principle. The results are presented as percentages for categorical variables and mean ± standard deviation or medians (interquartile range [IQR]) for continuous data with normal and skewed distributions, respectively. Comparisons between categorical data were performed using Fisher's exact test, whereas Student's t-test and the Mann-Whitney test were used for comparisons of continuous and ordinal data, as appropriate. Comparisons between paired samples were performed using paired sample t-test or Wilcoxon sum rank test. Statistical significance was considered for p values < 0.05. All statistical analyses were performed using SPSS software (SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 5.0 for Windows (GraphPad Software, La Jolla CA, USA).

Results

Between December 18, 2015 and June 22, 2017, 38 patients were included and randomly assigned to treatment with fentanyl (n = 19) or morphine

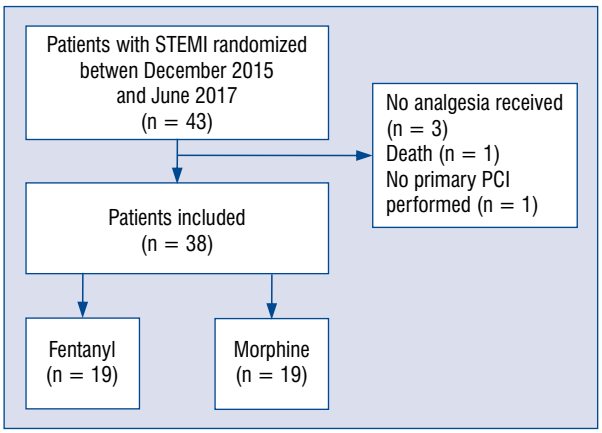

Figure 1. Patient flow chart according to the CONSORT statement; PCI — percutaneous coronary intervention; STEMI — ST-segment elevation myocardial infarction.

(n = 19) (Fig. 1). The study was prematurely stopped due to a slower than anticipated patient enrolment rate after inclusion of 38 (68%) of the 56 patients planned. Patient baseline and procedural characteristics were similar between the two treatment groups (Table 1). Median age was 68.6 ± 13.1 years in the fentanyl group and 65.2 ± 16.2 years in the morphine group (p = 0.46). Median reperfusion delays from STEMI diagnosis to primary PCI and from ticagrelor loading dose administration to primary PCI did not differ between patients treated with fentanyl or morphine. Infarct-related coronary artery characteristics and final myocardial infarct size, as assessed by peak troponin levels, were comparable between the two treatment groups. Finally, mean self-reported VAS pain score was similar in the fentanyl and the morphine groups, both at the time of randomization (4.8 ± 5.5 vs. 6.3 ± 1.7; p = 0.50) and before PCI (2.4 ± 2.6 vs. 1.9 ± 2.3; p = 0.57).

Pharmacodynamic assessment

The primary endpoint, mean PRU at 2 hours after ticagrelor LD, was 173.3 ± 89.7 in patients treated with fentanyl and 201.3 ± 76.4 among those receiving morphine (p = 0.179). Mean PRU values were significantly lower with fentanyl at 4 hours compared with morphine (90.1 ± 97.4 vs. 168.0 ± ± 72.2; p = 0.011). However, the differences in mean PRU values did not significantly differ at 6 hours (79.3 ± 89.1 vs. 122.2 ± 80.3; p = 0.14) and 12 hours (51.3 ± 53.3 vs. 83.3 ± 63.8; p = 0.11) after ticagrelor LD administration between patients treated with fentanyl and those receiving morphine (Table 2). The rates of HTPR were similar throughout the 6 hours after ticagrelor LD administration between patients treated with fentanyl or morphine (Fig. 2). PRI at 1, 2, and 4 hours after ticagrelor LD administration among patients treated with fentanyl or morphine are reported in Table 2.

Pharmacokinetic assessment

The pharmacokinetic profile of ticagrelor and AR-C124910XX among patients treated with fentanyl or morphine after ticagrelor LD administration are detailed in Table 3. Overall, mean C_{max} for ticagrelor and AR-C124910XX within 12 hours of ticagrelor pre-treatment did not significantly differ between patients treated with fentanyl or morphine (Table 3). Mean C_{max} for the active metabolite AR-C124910XX was, however, significantly lower at 6 hours (154.8 ± 128.5 vs. 74.6 ± 63.4 ng/mL; p = 0.011) among patients treated with fentanyl as compared to those receiving morphine (Table 3). Median T_{max} for ticagrelor (6 h; IQR 4–12 vs. 12 h; IQR 4–12; p = 0.325) and AR-C124910XX (6 h; IQR 4–12 vs. 12 h; IQR 6–12; p = 0.070) were similar among patients treated with fentanyl and morphine (Table 3). Total exposures to ticagrelor (1386 ng × h/ /mL; IQR 96–2765 vs. 579 ng × h/mL; IQR 74–1108; p = 0.108) and AR-C124910XX (293 ng × h/mL; IQR 17–881 vs. 71 ng × h/mL; IQR 17–225; p = 0.080) within 6 hours of ticagrelor pre-treatment were numerically greater among patients treated with fentanyl versus morphine (Table 3).

Coronary perfusion outcomes

TIMI grade < 3 flow in the infarct-related artery before primary PCI was found in 18 (94.7%) patients in the fentanyl group and in 18 (94.7%) patients in the morphine group (p = 1.00) (Fig. 3). Following ticagrelor LD administration, ST-segment elevation resolution < 70% after primary PCI was observed in 9 (60%) patients in the fentanyl group and in 8 (50%) patients in the morphine group (p = 0.47) (Fig. 3).

Discussion

In the PERSEUS randomized trial, fentanyl did not improve platelet inhibition at 2 hours after ticagrelor LD administration compared to morphine among patients with STEMI undergoing primary PCI. Despite the premature study termination resulting in loss of statistical power, there was consistent pharmacodynamic and pharmacokinetic evidence that fentanyl may be associated with a more favorable ticagrelor absorption profile than morphine. The use of fentanyl in symptomatic patients with STEMI, who were pre-treated with

Table 1. Patient baseline and procedural characteristics.

Characteristics	Fentanyl (n = 19)	Morphine (n = 19)	P
Age [years]	68.6 ± 13.1	65.2 ± 16.2	0.46
Male	13 (68.4%)	14 (73.7%)	0.72
Body mass index [kg/m^2]	26.7 ± 5.7	26.5 ± 3.7	0.93
Hypertension	8 (42.1%)	10 (52.6%)	0.51
Dyslipidemia	7 (36.9%)	8 (42.1%)	0.74
Diabetes mellitus	3 (15.8%)	3 (15.8%)	1.00
Current smoker	9 (47.4%)	8 (42.1%)	0.74
Prior coronary artery disease	1 (5.3%)	3 (15.7%)	0.29
Prior myocardial infarction	1 (5.3%)	4 (21.1%)	0.15
Prior PCI	0 (0%)	3 (15.7%)	–
Prior CABG	0 (0%)	0 (0%)	–
Prior stroke	0 (0%)	0 (0%)	–
Peripheral arterial disease	1 (5.3%)	2 (10.5%)	0.55
Chronic kidney disease	2 (10.5%)	2 (10.5%)	1.00
Medication at admission:			
Oral anticoagulation	0 (0%)	1 (5.3%)	–
Acetylsalicylic acid	4 (21.1%)	7 (36.8%)	0.28
Statin	5 (26.3%)	7 (36.8%)	0.48
Beta-blocker	2 (10.5%)	4 (21.1%)	0.37
ARB/ACE inhibitor	4 (21.1%)	4 (21.1%)	1.00
Vital signs:			
Systolic BP [mmHg]	128.9 ± 27.1	121.1 ± 21.2	0.33
Diastolic BP [mmHg]	73.0 ± 15.2	70.7 ± 11.3	0.60
Heart rate [bpm]	77.5 ± 20.3	75.9 ± 12.6	0.77
STEMI diagnosis to primary PCI time [min] (median, IQR)	108.0 (24.2)	105.0 (22.4)	0.74
Ticagrelor loading dose to primary PCI time [min] (median, IQR)	72.5 (32.4)	84.5 (20.3)	0.17
Cardiogenic shock	2 (10.5%)	1 (5.3%)	0.52
Infarct-related coronary vessel:			
Left anterior descending artery	7 (36.8%)	8 (42.1%)	0.74
Left circumflex artery	4 (21.1%)	3 (15.8%)	0.67
Right coronary artery	8 (42.1%)	7 (36.8%)	0.74
Other	0 (0%)	1 (5.3%)	–
Peak troponin level [ng/L] (median, IQR)	6719.9 ± 6463.6	6211.4 ± 8934.4	0.84
Visual Analogue Scale score:			
At randomization	4.8 ± 5.5	6.3 ± 1.7	0.50
Before PCI	2.4 ± 2.6	1.9 ± 2.3	0.57

Values are mean ± standard deviation, n (%), or median [interquartile range (IQR)]. ACE — angiotensin converting enzyme; ARB — angiotensin receptor blockers; BP — blood pressure; CABG — coronary artery bypass grafting; PCI — percutaneous coronary intervention; STEMI — ST-segment elevation myocardial infarction

ticagrelor, may accelerate ticagrelor absorption, and result in significantly increased platelet inhibition at 4 hours compared to morphine. To our knowledge, PERSEUS represents the first direct randomized comparison between fentanyl and morphine with regards to the pharmacodynamic and pharmacokinetic response to ticagrelor in STEMI patients requiring analgesia.

Rapid-onset and effective platelet P2Y$_{12}$ receptor inhibition represents the mainstay of pharmacological treatment in patients with STEMI undergoing primary PCI [1]. However, antiplatelet

Table 2. Pharmacodynamic assessment with $P2Y_{12}$ reaction units and platelet reactivity index after ticagrelor loading dose (LD) administration in patients treated with fentanyl versus morphine.

	Fentanyl (n = 19)	Morphine (n = 19)	P
$P2Y_{12}$ reaction units			
At baseline	188.89 ± 47.51	205.00 ± 49.16	0.331
At 1 hour post LD	187.84 ± 87.56	202.47 ± 66.87	0.566
At 2 hours post LD	173.26 ± 89.69	201.32 ± 76.41	0.179
At 4 hours post LD	90.11 ± 97.42	168.00 ± 72.24	0.011
At 6 hours post LD	79.33 ± 89.10	122.17 ± 80.34	0.139
At 12 hours post LD	51.33 ± 53.29	83.33 ± 63.81	0.112
Platelet reactivity index			
At 1 hour post LD	56.52 ± 26.93	76.35 ± 16.39	0.013
At 2 hours post LD	54.27 ± 27.45	64.82 ± 24.28	0.237
At 4 hours post LD	34.38 ± 27.42	52.12 ± 30.60	0.086

Values are mean ± standard deviation

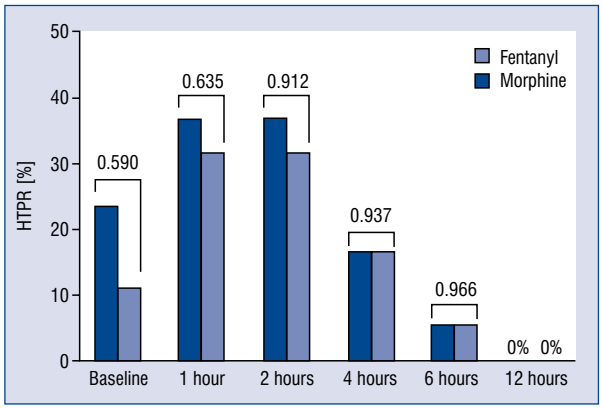

Figure 2. High on-treatment platelet reactivity rates following ticagrelor loading dose administration in patients treated with fentanyl versus morphine; HTPR — high on-treatment platelet reactivity as assessed by the VerifyNow $P2Y_{12}$ assay. Histograms represent rates.

inhibitory effects induced by potent oral $P2Y_{12}$ receptor antagonists are substantially delayed in STEMI patients [3, 4] owing to impaired gastrointestinal absorption [16]. The results of the present analysis are consistent with previous pharmacological studies indicating that intravenous opioid agents delay the absorption and the onset of action of orally administered $P2Y_{12}$ receptor antagonists in patients undergoing primary PCI for STEMI, which results in reduced plasma concentrations, delayed antiplatelet effects, and increased platelet reactivity of oral $P2Y_{12}$ receptor inhibitors [3, 7]. In the IMPRESSION randomized trial [7], morphine co-administration with ticagrelor was associated with reduced total exposure to ticagrelor and its active metabolite, which resulted in delayed and attenuated maximal plasma concentrations of ticagrelor compared to placebo among patients with acute myocardial infarction. The adverse pharmacological effects of morphine on oral $P2Y_{12}$ receptor antagonists are likely caused by the inhibition of normal muscular activity of the gastrointestinal tract in patients with STEMI [17, 18]. Our findings confirm that the delayed and reduced antiplatelet effects of potent oral $P2Y_{12}$ receptor inhibitors in STEMI patients treated with intravenous opioid agents are mainly attributed to an altered pharmacokinetic profile, which reduces total exposure to oral $P2Y_{12}$ receptor inhibitors within the first hours after LD administration.

The clinical implications of the pharmacological interaction between μ-opioid receptor agonists and $P2Y_{12}$ receptor inhibitors in patients with acute coronary syndrome (ACS) remain controversial. In the FAST-MI registry, in-hospital and 1-year rates of major adverse ischemic outcomes were similar between STEMI patients who received, as compared to those who did not receive, prehospital morphine, but the risk of myocardial re-infarction during admission was significantly higher among patients pretreated with morphine [19]. Conversely, morphine was associated with higher risk-adjusted in-hospital and 30-day rates of ischemic events among patients with non ST-elevation ACS pretreated with clopidogrel in the EARLY ACS trial [20], thus disclosing the need for future research on alternatives to morphine in ACS patients requiring analgesia. Different strategies have been proposed

Table 3. Pharmacokinetic assessment of ticagrelor and AR-C124910XX after ticagrelor loading dose (LD) administration in patients treated with fentanyl versus morphine.

	Fentanyl (n = 19)	Morphine (n = 19)	P
Ticagrelor			
T_{max} [h]	6 (4–12)	12 (4–12)	0.325
C_{max} [ng/mL]			0.202
at 1 hour post LD	184.8 ± 361.6	32.3 ± 56.7	0.078
at 2 hours post LD	245.1 ± 390.7	107.6 ± 246.7	0.203
at 4 hours post LD	425.3 ± 450.4	294.0 ± 551.2	0.439
at 6 hours post LD	550.7 ± 506.6	327.1 ± 372.1	0.489
at 12 hours post LD	425.1 ± 423.6	371.1 ± 295.7	0.666
AUC_{0-6} [ng × h/mL]	1386 (96–2765)	579 (74–1108)	0.108
AR-C124910XX			
T_{max} [h]	6 (4–12)	12 (6–12)	0.070
C_{max} [ng/mL]			0.308
at 1 hour post LD	22.7 ± 44.9	24.5 ± 13.4	0.095
at 2 hours post LD	42.7 ± 72.8	27.0 ± 45.6	0.129
at 4 hours post LD	99.9 ± 112.9	66.9 ± 68.3	0.083
at 6 hours post LD	154.8 ± 128.5	74.6 ± 63.4	0.011
at 12 hours post LD	141.1 ± 125.1	121.0 ± 104.1	0.504
AUC_{0-6} [ng × h/mL]	293 (17–881)	71 (17–225)	0.080

Values are mean ± standard deviation or median [interquartile range (IQR)]. AUC_{0-6} — area under the plasma concentration-time curve at 6 hours after ticagrelor loading dose; C_{max} — peak plasma concentration; T_{max} — time to peak plasma concentration

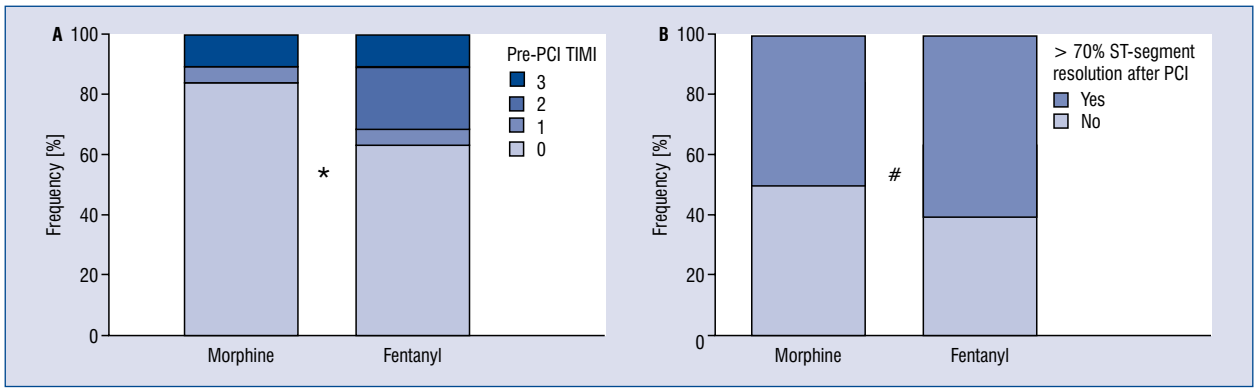

Figure 3. Coronary perfusion outcomes before primary percutaneous coronary intervention (PCI) in patients treated with fentanyl versus morphine. Proportion of patients with thrombolysis in myocardial infarction (TIMI) flow grade 0 to 3 in the infarct-related artery (**A**), and with or without ≥ 70% ST-segment elevation resolution (**B**) before primary PCI; *p-value for comparison of TIMI flow grade 3 between the fentanyl and morphine groups = 0.34; #p-value for comparison of > 70% ST-segment resolution after PCI between the fentanyl and morphine groups = 0.58.

to bridge the initial gap in platelet inhibition and overcome high on-treatment residual platelet reactivity associated with the use of oral $P2Y_{12}$ inhibitors in STEMI patients, including upstream $P2Y_{12}$ receptor antagonist administration [21], escalating $P2Y_{12}$ receptor inhibitor LD regimens [16], intravenous $P2Y_{12}$ receptor antagonists [22], use of glycoprotein IIb/IIIa inhibitors [23], or co-administration of a prokinetic agent [24]. To date, it remained uncertain whether intravenous opioid agents such as fentanyl have similar adverse pharmacological effects on orally administered $P2Y_{12}$ receptor antagonists in patients with STEMI. Recent evidence indicates that μ-opioid receptor

agonists have differential pharmacological profiles and exert their effects by involvement of different μ-opioid receptor sites and varying degrees of gastrointestinal dysmotility [25]. Fentanyl is a potent, fast-acting, and effective intravenous synthetic opioid agent [9], which displays different pharmacological dose-response curves and mitigates gastrointestinal motility inhibition compared to morphine [25], hence theoretically improving the absorption and the bioavailability of orally administered drugs. In the PACIFY trial, fentanyl has been shown to reduce plasma concentration and delay antiplatelet effects of ticagrelor compared with placebo, but the study only included patients undergoing PCI for chronic coronary syndrome [11, 12]. To the best of our knowledge, PERSEUS is the first head-to-head randomized trial designed to specifically compare the pharmacological effects of fentanyl versus morphine in patients with STEMI undergoing primary PCI after pre-treatment with a potent oral $P2Y_{12}$ receptor inhibitor. The present study suggests potential differences in the pharmacological responses to ticagrelor between STEMI patients who received fentanyl or morphine for pain relief after ticagrelor pre-treatment. Overall, peak and time-to-peak plasma concentrations for ticagrelor and its major active metabolite AR-C124910XX after ticagrelor pre-treatment tended to be numerically higher and faster, respectively, among STEMI patients treated with fentanyl as compared to those receiving morphine. In addition, total exposures to ticagrelor and AR-C124910XX within 6 hours of ticagrelor pre-treatment were numerically greater among patients treated with fentanyl versus morphine. The observed numerical differences in ticagrelor pharmacokinetic profiles between fentanyl- and morphine-treated patients yielded a significantly increased platelet inhibition at 4 hours after ticagrelor pre-treatment among patients treated with fentanyl as compared to those receiving morphine. Interestingly, the analgesic effect of fentanyl-treated patients was similar to the effect observed with morphine, which lends further support to the preferential use of fentanyl rather than morphine in symptomatic STEMI patients undergoing primary PCI.

Limitations of the study

The results of the present study should be interpreted bearing in mind several limitations. Due to the premature termination of the trial and the smaller than anticipated sample size, the study results should be interpreted with appropriate caution and considered as hypothesis-generating. Notwithstanding, our pharmacodynamic findings suggest potential for an improved platelet inhibition at 4 hours with fentanyl after ticagrelor LD administration among STEMI patients as compared to morphine. The present study was not powered to assess pain outcomes between the fentanyl and morphine groups. As per study protocol, we defined HTPR as PRU $\geq$ 240 assessed by VerifyNow® platelet function assay according to consensus evidence available at the time of the study design [15]. However, we found similar results with regards to platelet reactivity when defining HTPR as PRU $\geq$ 208. Finally, this study was not powered for clinical endpoints, and larger studies are needed to explore whether the observed differences in ticagrelor pharmacodynamic and pharmacokinetic profiles induced by fentanyl versus morphine may translate into different clinical outcomes.

Conclusions

In patients with STEMI undergoing primary PCI after ticagrelor pre-treatment, fentanyl did not improve platelet inhibition at 2 hours compared with morphine. Taking into account the loss of power due to premature study termination, we found pharmacodynamic and pharmacokinetic evidence that fentanyl has the potential to reduce ticagrelor absorption delay and improve platelet inhibition compared to morphine. Future, properly powered studies should investigate the comparative clinical effects of fentanyl versus morphine in symptomatic STEMI patients undergoing primary PCI.

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no role in the study data analysis or interpretation. The data supporting these findings are available from the corresponding author on reasonable request.

Conflict of interest: Juan F. Iglesias reports research grants to the institution and personal fees from AstraZeneca during the conduct of the study; grants and personal fees from Biotronik, Philips Volcano, and AstraZeneca, and personal fees from Terumo, Medtronic, and Cardinal Health, outside the submitted work; Marco Valgimigli reports grants and personal fees from Abbott, Terumo, and AstraZeneca, personal fees from Bayer, Daiichi Sankyo, Amgen, Alvimedica, Idorsia, Coreflow, Vifor, Bristol-Myers Squibb, and iVascular, and grants from Medicare, outside the submitted work; Sophie Degrauwe reports grants and personal fees from Biotronik, outside the submitted work. All other authors declare no conflicts of interest.

References

1. 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.
2. Bellemain-Appaix A, Bégué C, Bhatt DL, et al. The efficacy of early versus delayed P2Y12 inhibition in percutaneous coronary intervention for ST-elevation myocardial infarction: a systematic review and meta-analysis. EuroIntervention. 2018; 14(1): 78–85, doi: 10.4244/EIJ-D-17-00852, indexed in Pubmed: 29469030.
3. Alexopoulos D, Xanthopoulou I, Gkizas V, et al. Randomized assessment of ticagrelor versus prasugrel antiplatelet effects in patients with ST-segment-elevation myocardial infarction. Circ Cardiovasc Interv. 2012; 5(6): 797–804, doi: 10.1161/CIRCINTERVENTIONS.112.972323, indexed in Pubmed: 23169985.
4. Parodi G, Valenti R, Bellandi B, et al. Comparison of prasugrel and ticagrelor loading doses in ST-segment elevation myocardial infarction patients: RAPID (Rapid Activity of Platelet Inhibitor Drugs) primary PCI study. J Am Coll Cardiol. 2013; 61(15): 1601–1606, doi: 10.1016/j.jacc.2013.01.024, indexed in Pubmed: 23500251.
5. Hobl EL, Stimpfl T, Ebner J, et al. Morphine decreases clopidogrel concentrations and effects: a randomized, double-blind, placebo-controlled trial. J Am Coll Cardiol. 2014; 63(7): 630–635, doi: 10.1016/j.jacc.2013.10.068, indexed in Pubmed: 24315907.
6. Parodi G, Bellandi B, Xanthopoulou I, et al. Morphine is associated with a delayed activity of oral antiplatelet agents in patients with ST-elevation acute myocardial infarction undergoing primary percutaneous coronary intervention. Circ Cardiovasc Interv. 2015; 8(1), doi: 10.1161/CIRCINTERVENTIONS.114.001593, indexed in Pubmed: 25552565.
7. Kubica J, Adamski P, Ostrowska M, et al. Morphine delays and attenuates ticagrelor exposure and action in patients with myocardial infarction: the randomized, double-blind, placebo-controlled IMPRESSION trial. Eur Heart J. 2015; 37(3): 245–252, doi: 10.1093/eurheartj/ehv547, indexed in Pubmed: 26491112.
8. Furtado RHM, Nicolau JC, Guo J, et al. Morphine and cardiovascular outcomes among patients with non-ST-segment elevation acute coronary syndromes undergoing coronary angiography. J Am Coll Cardiol. 2020; 75(3): 289–300, doi: 10.1016/j.jacc.2019.11.035, indexed in Pubmed: 31976867.
9. Schug SA, Ting S. Fentanyl formulations in the management of pain: an update. Drugs. 2017; 77(7): 747–763, doi: 10.1007/s40265-017-0727-z, indexed in Pubmed: 28337672.
10. Lavi S, Jolly SS, Bainbridge D, et al. Sedation, analgesia, and anaesthesia variability in laboratory-based cardiac procedures: an international survey. Can J Cardiol. 2014; 30(6): 627–633, doi: 10.1016/j.cjca.2014.03.034, indexed in Pubmed: 24882533.
11. McEvoy J, Ibrahim K, Kickler T, et al. Effect of intravenous fentanyl on ticagrelor absorption and platelet inhibition among patients undergoing percutaneous coronary intervention. Circulation. 2018; 137(3): 307–309, doi: 10.1161/circulationaha.117.031678, indexed in Pubmed: 29046319.
12. Ibrahim K, Shah R, Goli RR, et al. Fentanyl delays the platelet inhibition effects of oral ticagrelor: full report of the PACIFY randomized clinical trial. Thromb Haemost. 2018; 118(8): 1409–1418, doi: 10.1055/s-0038-1666862, indexed in Pubmed: 29972861.
13. Iglesias JF, Valgimigli M, Carbone F, et al. Effects of fentanyl versus morphine on ticagrelor-induced platelet inhibition in patients with st-segment elevation myocardial infarction: the PERSEUS randomized trial. Circulation. 2020; 142(25): 2479–2481, doi: 10.1161/CIRCULATIONAHA.120.049287, indexed in Pubmed: 33347326.
14. Degrauwe S, Roffi M, Lauriers N, et al. Influence of intravenous fentanyl compared with morphine on ticagrelor absorption and platelet inhibition in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: rationale and design of the PERSEUS randomized trial. Eur Heart J Cardiovasc Pharmacother. 2019; 5(3): 158–163, doi: 10.1093/ehjcvp/pvy031, indexed in Pubmed: 30101278.
15. Bonello L, Tantry US, Marcucci R, et al. Consensus and future directions on the definition of high on-treatment platelet reactivity to adenosine diphosphate. J Am Coll Cardiol. 2010; 56(12): 919–933, doi: 10.1016/j.jacc.2010.04.047, indexed in Pubmed: 20828644.
16. Franchi F, Rollini F, Cho JR, et al. Impact of escalating loading dose regimens of ticagrelor in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: results of a prospective randomized pharmacokinetic and pharmacodynamic investigation. JACC Cardiovasc Interv. 2015; 8(11): 1457–1467, doi: 10.1016/j.jcin.2015.02.030, indexed in Pubmed: 26404199.
17. Nimmo WS, Heading RC, Wilson J, et al. Inhibition of gastric emptying and drug absorption by narcotic analgesics. Br J Clin Pharmacol. 1975; 2(6): 509–513, doi: 10.1111/j.1365-2125.1975.tb00568.x, indexed in Pubmed: 9953.
18. Giannopoulos G, Deftereos S, Kolokathis F, et al. P2Y12 receptor antagonists and morphine: a dangerous liaison? . Circ Cardiovasc Interv. 2016; 9: e004229, doi: 10.1161/CIRCINTERVENTIONS.116.004229, indexed in Pubmed: 27586412.
19. Puymirat E, Lamhaut L, Bonnet N, et al. Correlates of pre-hospital morphine use in ST-elevation myocardial infarction patients and its association with in-hospital outcomes and long-term mortality: the FAST-MI (French Registry of Acute ST-elevation and non-ST-elevation Myocardial Infarction) programme. Eur Heart J.

2016; 37(13): 1063–1071, doi: 10.1093/eurheartj/ehv567, indexed in Pubmed: 26578201.
20. Furtado RHM, Nicolau JC, Guo J, et al. Morphine and cardiovascular outcomes among patients with non-ST-segment elevation acute coronary syndromes undergoing coronary angiography. J Am Coll Cardiol. 2020; 75(3): 289–300, doi: 10.1016/j.jacc.2019.11.035, indexed in Pubmed: 31976867.
21. Montalescot G, van ,t Hof AW, Montalescot G, et al. Prehospital ticagrelor in ST-segment elevation myocardial infarction. N Engl J Med. 2014; 371(11): 1016–1027, doi: 10.1056/NEJMoa1407024, indexed in Pubmed: 25175921.
22. Franchi F, Rollini F, Rivas A, et al. Platelet inhibition with cangrelor and crushed ticagrelor in patients with ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention. Circulation. 2019; 139(14): 1661–1670, doi: 10.1161/CIRCULATIONAHA.118.038317, indexed in Pubmed: 30630341.
23. Valgimigli M, Tebaldi M, Campo G, et al. Prasugrel versus tirofiban bolus with or without short post-bolus infusion with or without concomitant prasugrel administration in patients with myocardial infarction undergoing coronary stenting: the FABOLUS PRO (Facilitation through Aggrastat By drOpping or shortening Infusion Line in patients with ST-segment elevation myocardial infarction compared to or on top of PRasugrel given at loading dOse) trial. JACC Cardiovasc Interv. 2012; 5(3): 268–277, doi: 10.1016/j.jcin.2012.01.006, indexed in Pubmed: 22440491.
24. Saad M, Meyer-Saraei R, de Waha-Thiele S, et al. Impact of morphine treatment with and without metoclopramide coadministration on ticagrelor-induced platelet inhibition in acute myocardial infarction: the randomized monAMI trial. Circulation. 2020; 141(16): 1354–1356, doi: 10.1161/CIRCULATIONAHA.119.042816, indexed in Pubmed: 32310699.
25. Mori T, Shibasaki Y, Matsumoto K, et al. Mechanisms that underlie μ-opioid receptor agonist-induced constipation: differential involvement of μ-opioid receptor sites and responsible regions. J Pharmacol Exp Ther. 2013; 347(1): 91–99, doi: 10.1124/jpet.113.204313, indexed in Pubmed: 23902939.

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Outcomes and predictive value of the 2MACE score in patients with atrial fibrillation treated with rivaroxaban in a prospective, multicenter observational study: The EMIR study

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Abstract

Background: *The aim of the study was to evaluate the performance of the 2MACE in patients with atrial fibrillation (AF) treated with rivaroxaban and to improve the accuracy of 2MACE.*

Methods: *This was a post-authorization and observational study of AF adults treated with rivaroxaban for ≥ 6 months. The primary endpoint was any of the major adverse cardiac events (MACE), namely, cardiovascular death, non-fatal myocardial infarction, and myocardial revascularization. The area under the curve (AUC) was calculated to evaluate the performance of 2MACE, and a new score, 2MACER to predict MACE.*

Results: *A total of 1433 patients were included (74.2 ± 9.7 years, CHA_2DS_2-VASc 3.5 ± 1.5, 26.9% 2MACE ≥ 3). The annual event rates (follow-up 2.5 years) were 1.07% for MACE, 0.66% for thromboembolic events and 1.04% for major bleeding. Patients with 2MACE ≥ 3 (vs. < 3) had higher risk of stroke/systemic embolism/transient ischemic attack (odds ratio [OR] 5.270; 95% confidence interval [CI] 2.216–12.532), major bleeding (OR 4.624; 95% CI 2.163–9.882), MACE (OR 3.202; 95% CI 1.548–6.626) and cardiovascular death (OR 3.395; 95% CI 1.396–8.259). 2MACE was recalculated giving 1 more point to patients with baseline a glomerular filtration rate < 50 mL/min/1.73 m^2 (2MACER); (2MACER vs. 2MACE: IDI 0.1%, p = 0.126; NRI 23.9%, p = 0.125; AUC: 0.651 [95% CI 0.547–0.755] vs. 0.638 [95% CI 0.534–0.742], respectively; p = 0.361).*

Conclusions: *In clinical practice, AF patients anticoagulated with rivaroxaban exhibit a low risk of events. 2MACE score acts as a modest predictor of a higher risk of adverse outcomes in this population. 2MACER did not significantly increase the ability of 2MACE to predict MACE.* (Cardiol J 2022; 29, 4: 601–609)

Key words: atrial fibrillation, bleeding, major adverse cardiac events (MACE), stroke, rivaroxaban

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Introduction

Patients with atrial fibrillation (AF) have a 4- to 5-fold increased risk of stroke. However, this risk can be substantially reduced with long-term anticoagulation therapy [1, 2]. In addition, AF is an important predictor of other important cardiovascular (CV) events, including myocardial infarction (MI) and an independent predictor of CV death [3, 4]. Thus, the most recent European guidelines recommend a comprehensive approach in the management of patients with AF, with the aim of reducing not only the risk of stroke, but also that of MI and heart failure (HF) [2].

Although a higher CHA_2DS_2-VASc score has been associated with a greater risk of CV events, this scale has been designed to assess thromboembolic risk in the AF population, but not the risk of CV events. By contrast, the 2MACE score (2 points for metabolic syndrome and age ≥ 75 years, and 1 point for MI/revascularization, congestive HF/ejection fraction ≤ 40%, and thromboembolism-stroke/ /transient ischemic attack [TIA]) has been specifically developed to predict the risk of major adverse cardiac events (MACE) in patients with AF. A 2MACE score ≥ 3 has the best combination of specificity and sensitivity for predicting MACE [5]. Nevertheless, the 2MACE score is affected by limitations (i.e., the original cohort was Caucasian, and all patients were treated with vitamin K antagonists [VKAs]), thus potentially restricting its use in clinical practice [5]. As a result, an improved score for such events is desirable.

In patients taking VKA, the risk of MACE increases as control of anticoagulation worsens [6]. Direct oral anticoagulants (DOACs) overcome the main limitations of VKAs and are now widely prescribed [7]. Results from pivotal studies show that DOACs have a better efficacy and safety profile than warfarin in patients with AF [8]. Although the information provided by clinical trials is of great interest, studies performed in clinical practice assess the efficacy and safety of a drug for treatment of AF under real-world conditions. However, few real-world data are available on the role of rivaroxaban in comprehensive CV protection (i.e., against thromboembolic events and MI or HF) [9–11].

In summary, the dearth of information about the 2MACE score in patients treated with DOACs makes it necessary to assess the performance of the score in a population receiving DOACs and to determine whether 2MACE can be improved by including additional risk factors or by removing some of the existing ones. The EMIR study (***E****studio observacional para la identificación de los factores de riesgo asociados a eventos cardiovasculares* ***mayores*** *en pacientes con f****i****brilación auricular no valvular tratados con un anticoagulante oral directo [****R****ivaroxaban]* ["Observational study to identify risk factors associated with major cardiovascular events in patients with nonvalvular atrial fibrillation treated with a direct oral anticoagulant [rivaroxaban]") [12] was designed to evaluate the performance of 2MACE for assessing CV risk in AF patients treated with rivaroxaban. The primary endpoint was any of the MACE: CV death, non-fatal MI, or myocardial revascularization. In addition, the study also evaluated the potential for increasing the accuracy of the 2MACE score either by incorporating additional risk factors or by replacing some of the existing ones.

Methods

EMIR was a post-authorization, observational, and non-interventional study, conducted in 79 centers (hospitals and private clinics) throughout Spain. The study population comprised adult patients with AF treated with rivaroxaban for at least 6 months before inclusion. All patients had to give written informed consent before being enrolled in the study. The exclusion criteria were participation in an investigational program with interventions outside routine clinical practice, initiation of treatment with rivaroxaban after the start of the inclusion period, presence of prosthetic heart valves or severe valve disease, severe cognitive impairment, chronic infections, systemic autoimmune diseases, active cancer, or severe liver failure. The study was approved by the local Institutional Review Boards.

Data were collected at 4 study visits over 2 years and 6 months: baseline visit, follow-up 1 (at year 1), follow-up 2 (at year 2), and final visit (after 2 years and 6 months or early termination). All the study visits coincided with the patients' routine visits to monitor their disease. Only data available from daily clinical practice were collected, and there were no requests for additional visits, laboratory tests, or diagnostic tests.

Baseline data were recorded using an electronic case report form specially designed for this study. The data recorded included biodemographic data, physical examination findings, risk stratification ($CHADS_2$, CHA_2DS_2-VASc, HAS-BLED, and 2MACE score), CV risk factors, concomitant vascular disease, and other comorbidities. In addition, conditions that increased the risk of bleed-

ing, non-severe dementia, laboratory data (most recent hemoglobin, platelet, renal function values within the prior 3 months), and rivaroxaban dose were documented. Dependency was classified as autonomous (no dependency), partial dependency for daily activities, or complete dependency for daily activities. Baseline clinical characteristics were also analyzed according to age, diabetes, hypertension, and renal function (MDRD-4 formula).

MACE (primary endpoint), defined as a combination of non-fatal MI, revascularization, and CV death, were recorded during follow-up. In addition, thromboembolic events (ischemic stroke, TIA, systemic embolism, and MI), death (all-cause and CV), pulmonary embolism, major bleeding (following the International Society of Thrombosis and Hemostasis definition) [13], and fatal bleeding were reported. Annual event rates were calculated. Incidence and annual rate (patient/year) of events (stroke + systemic embolism + TIA, major bleeding, and MACE) were analyzed. A scientific committee independently evaluated and classified the events.

Statistical methods

The aim of the present study was to assess the performance of the 2MACE score in a population treated with rivaroxaban. The sample size was planned that would enable us to obtain a minimum number of MACE comparable with the events of the study carried out by Pastori et al. [5], which included an original cohort of 1,019 patients with 111 MACE and a validation cohort including 1,089 patients, 68 with MACE. A sample size of 1,500 patients was proposed for this study, assuming a maximum loss to follow-up of 10% and considering two extreme scenarios. In the minimum scenario, it was assumed a loss to follow-up of 10% and a MACE rate of 2%; in the maximum scenario, a loss to follow-up of 5% was considered and a MACE rate of 2.5%. These assumptions yielded 1,350 patients in the minimum scenario and 1,425 patients in the maximum scenario. Given that the overall follow-up period was 2.5 years, we estimated 89 events in the maximum scenario and 68 events in the minimum scenario.

Qualitative variables are expressed as absolute and relative frequencies; quantitative variables are expressed as measures of central tendency and dispersion (mean and standard deviation). Categorical variables were compared using the χ^2 test or the Fisher exact test, when appropriate. When 2 means were compared, the t test or the Mann-Whitney test was used, as applicable.

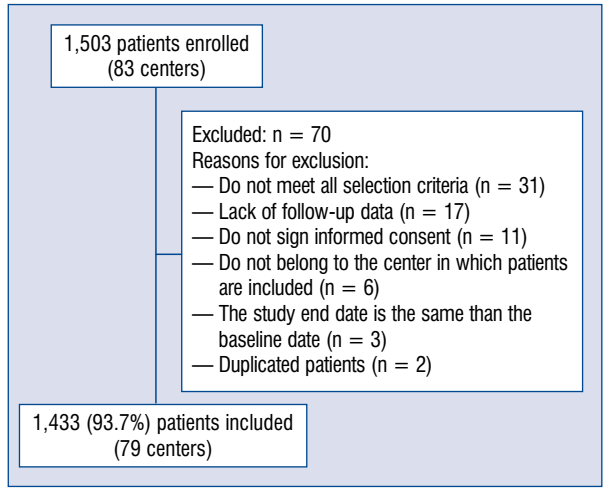

Figure 1. Study flow chart.

To assess the potential for increasing the accuracy of the 2MACE score either by incorporating additional risk to the 2MACE or replacing some of the existing factors, the feasibility of these factors was initially explored using bivariate models. The multivariate models started to be constructed by introducing those factors with $p < 0.150$ in the bivariates by the automatic variable selection method by steps forward. Only the significant factors were finally considered to build the model. A logistic regression analysis was used to evaluate the association between specific variables and events during follow-up, and the odds ratio (OR) along with the 95% confidence interval (CI) were calculated. The receiver operating characteristic (ROC) curves were then plotted the sensitivity, specificity, cutoff points for 2MACE were calculated and the new score, if necessary, as well as integrated discrimination index (IDI) and net reclassification index (NRI). Statistical significance was set at 0.05. The data were analyzed using the statistical package SPSS (v18.0 or superior).

Results

A total of 1,503 patients were enrolled from 79 participating centers. After exclusion of 70 patients for various reasons (i.e., not fulfilling selection criteria, lack of follow-up data, duplicate patients, not belonging to the center, not signing informed consent), 1,433 (93.7%) patients were eventually included in the analysis (Fig. 1).

The clinical characteristics of the study population at baseline are presented in Table 1. Mean age was 74.2 ± 9.7 years, 55.5% of patients were

Table 1. Clinical characteristics of the study population at baseline.

	Total (N = 1,433; 100%)
Biodemographic data	
Age [years]:	74.2 ± 9.7
≥ 75	691 (48.2%)
≥ 85	453 (31.6%)
Sex (male)	795 (55.5%)
Level of dependency:	
No dependency	1,251 (89.9%)
Partial dependency	126 (9.1%)
Total dependency	14 (1.0%)
Type of AF:	
Paroxysmal	578 (40.6%)
Persistent	259 (18.2%)
Long-standing persistent	53 (3.7%)
Permanent	535 (37.5%)
Physical examination	
Systolic blood pressure [mmHg]	131.6 ± 16.4
Diastolic blood pressure [mmHg]	76.3 ± 10.5
Heart rate [bpm]	71.9 ± 14.8
Body mass index [kg/m^2], median (IQR)	28.4 (25.7–31.9)
Risk stratification	
$CHADS_2$ score	2.0 ± 1.2
CHA_2DS_2-VASc score	3.5 ± 1.5
2MACE score:	1.8 ± 1.4
≥ 3	385 (26.9%)
HAS-BLED score	1.6 ± 1.0
Cardiovascular risk factors	
Hypertension	1,137 (79.3%)
SBP > 160 mmHg	53 (4.7%)
Hyperlipidemia	790 (55.1%)
Diabetes	388 (27.1%)
Smoking:	121 (8.4%)
Current	75 (5.2%)
Ex-smoker < 1 year	23 (1.6%)
Ex-smoker > 1 year	23 (1.6%)
Vascular disease	
Heart failure	326 (22.7%)
Ischemic heart disease	235 (16.4%)
Revascularization	183 (12.8%)
Prior cerebrovascular disease	179 (12.5%)
Peripheral artery disease	58 (4.0%)
Aortic plaque	45 (3.1%)
Venous thromboembolic disease	31 (2.2%)
Prior systemic embolism	14 (1.0%)

→

Table 1 (cont.). Clinical characteristics of the study population at baseline.

	Total (N = 1,433; 100%)
Other conditions/comorbidities	
Kidney failure*	350 (24.7%)
Labile INR	374 (26.1%)
Drug or alcohol use	130 (9.1%)
Medication usage predisposing to bleeding**	123 (8.6%)
Cancer	80 (5.6%)
Falls in the previous 2 years	88 (6.1%)
Previous major bleeding:	46 (3.2%)
Gastrointestinal	17 (1.2%)
Intracranial	8 (0.6%)
Hematuria	8 (0.6%)
Gingival	3 (0.2%)
Joint-muscular	3 (0.2%)
No severe cognitive impairment	33 (2.3%)
Liver failure	10 (0.7%)
Biochemical parameters	
Hemoglobin [g/dL]	14.1 ± 1.6
Platelets [×10^{12}/L]	17.8 ± 58.7
Creatinine [mg/dL]	1.0 ± 0.4
Glomerular filtration rate (MDRD-4) [mL/min/1.73 m^2]	74.9 ± 21.7
Glomerular filtration rate (CKD-EPI) [mL/min/1.73 m^2]	69.7 ± 18.4
Creatinine clearance (Cockcroft-Gault) [mL/min]	74.6 ± 30.5

*Glomerular filtration rate < 60 mL/min/1.73 m^2; by MDRD-4; **Nonsteroidal anti-inflammatory drugs or antiplatelet agents at least once a week; AF — atrial fibrillation; IQR — interquartile range; INR — international normalized ratio; SBP — systolic blood pressure

men, 40.6% had paroxysmal AF, 37.5% permanent AF, mean CHA_2DS_2-VASc score was 3.5 ± ± 1.5, mean HAS-BLED 1.6 ± 1.0, and 26.9% had a 2MACE score ≥ 3. Cardiovascular risk factors were very common (79.3% hypertension, 27.1% diabetes), as was vascular disease (24.7% kidney failure, 22.7% HF, 16.4% ischemic heart disease [IHD]). Baseline clinical characteristics were analyzed according to age, diabetes, HF, renal function, and 2MACE score (Table 2, **Suppl. Table 1**). Compared with younger patients, those aged 75 years or older were more commonly women, more frequently had HF and permanent AF. They also had higher CHA_2DS_2-VASc and HAS-BLED scores and more frequently had a 2MACE score ≥ 3. Patients with diabetes were more commonly men and more frequently had hypertension, HF, and peripheral

artery disease. In addition, their CHA_2DS_2-VASc and HAS-BLED scores were higher and they more frequently had a 2MACE score ≥ 3. Patients with HF were older, more frequently had diabetes, peripheral artery disease, and permanent AF, as well as higher CHA_2DS_2-VASc and HAS-BLED scores and a 2MACE score ≥ 3. Patients with kidney failure were older and more commonly women. They also had hypertension, HF, and permanent AF more frequently, with higher CHA_2DS_2-VASc and HAS-BLED scores. In addition, their 2MACE score was mostly ≥ 3, although they less frequently had diabetes. Patients with a 2MACE score ≥ 3 (vs. < 3) were older, had more hypertension, diabetes, HF, prior cerebrovascular disease, peripheral artery disease and kidney failure, with higher CHA_2DS_2-VASc and HAS-BLED scores.

Overall, 1,105 (77.1%) patients were taking rivaroxaban 20 mg once daily, and the remaining 328 (22.9%) were taking rivaroxaban 15 mg. After a median follow-up of 2.5 (2.2–2.6) years, 234 patients discontinued the study prematurely. Eighty-seven (6.1%) patients died during the study, 23.0% (20/87) from CV causes, including progressive chronic HF (13/87, 14.9%). The annual rates of relevant events were calculated based on 1,425 patients and were as follows: death, 2.73%; thromboembolic events, 0.66%; MACE, 1.07%; major bleeding, 1.04%; and fatal bleeding, 0.06%. The annual rates of relevant events were analyzed according to age, diabetes, HF, renal function, and 2MACE score. Annual rates of stroke + systemic embolism + TIA were higher in elderly and diabetic patients and also in those with a 2MACE score ≥ 3. Major bleeding was more common in elderly patients and patients with kidney failure and a 2MACE score ≥ 3. Overall, the risk of stroke, systemic embolism or TIA (OR 5.270; 95% CI 2.216–12.532), major bleeding (OR 4.624; 95% CI 2.163–9.882), MACE (OR 3.202; 95% CI 1.548–6.626) and CV death (OR 3.395; 95% CI 1.396–8.259) was higher in those patients with 2MACE ≥ 3 compared to those patients with 2MACE < 3 (Table 3, **Suppl. Fig. 1A–D**, **Suppl. Table 2**).

Multivariate logistic regression analysis was performed to study the potential association between new CV risk factors and MACE. Ischemic heart disease (OR 3.411; 95% CI 1.599–7.275; p = 0.002), kidney failure (OR 2.530; 95% CI 1.165–5.492; p = 0.019), and HF (OR 3.402; 95% CI 1.593–7.266; p = 0.002) were independently associated with MACE in the overall population. A second multivariate model developed by replacing IHD for IHD and antiplatelet treatment (the rest of the variables were included as in the first analysis) revealed that combined IHD and antiplatelet treatment (OR 9.067; 95% CI 3.842––21.397; p < 0.001), kidney failure (OR 2.561; 95% CI 1.163–5.640; p = 0.020), and HF (OR 3.842; 95% CI 1.807–8.170; p < 0.001) were independent predictive factors (**Suppl. Table 3**).

The area under the curve (AUC) of 2MACE was 0.638 (95% CI 0.534–0.742; p = 0.01). Considering a cut-off = 3 for 2MACE score, sensitivity was 0.533 and specificity 0.737. As IHD and HF are already included in 2MACE score, 2MACE score was recalculated giving 1 more point to the patients with baseline estimated glomerular filtration rate < 50 mL/min/1.73 m^2 by MDRD-4. The new score was called 2MACER (R due to renal impairment). The mean 2MACER score was 1.9 ± 1.5 and (vs. 1.8 ± 1.4 of 2MACE score) and 32.2% had a 2MACER score ≥ 3 (vs. 26.9% with 2MACE score ≥ 3).

The ROC curves for 2MACE and 2MACER scores to predict MACE outcomes are presented in **Supplementary Figure 2**. Both scales were also compared, and the IDI and NRI are in **Supplementary Table 4**. The AUC for 2MACE was 0.638 (95% CI 0.534–0.742) and for 2MACER was 0.651 (95% CI 0.547–0.755), p = 0.361 between the global areas under the two ROC curves. IDI was 0.1%; p = 0.126 and NRI was 23.9%; p = 0.125.

Discussion

This study shows that in a stable AF population treated with rivaroxaban, 2MACE score may be helpful in detecting those patients at high risk of adverse outcomes. The prediction of important CV events is modestly improved if the 2MACE score is modified by the addition of 1 point for the estimated glomerular filtration rate < 50 ml/min. The most important message for the clinician is that patients with AF that are already optimally protected from embolic/stroke events by stable treatment with rivaroxaban are still at risk for HF and MI. This risk can be better characterized by considering the past history of IHD, HF and renal insufficiency, with no need for more complex risk calculators.

Despite anticoagulation, patients with AF have a significant residual risk of CV events [14]. The CHA_2DS_2-VASc score has been specifically developed to determine stroke risk, but not the risk of CV events. In this context, the 2MACE score could help to identify AF patients at risk for CV events [5]. Both scales provide complementary

Table 2. Baseline clinical characteristics according to the 2MACE score.

	Total (n = 1,433; 100%)	2MACE < 3 (n = 1,048; 73.1%)	2MACE ≥ 3 (n = 385; 26.9%)	P
Biodemographic data				
Age [years]	74.2 ± 9.7	72.3 ± 9.6	79.2 ± 7.9	< 0.001
Sex (male)	795 (55.5%)	573 (54.7%)	222 (57.7%)	0.313
Permanent AF	535 (37.5%)	363 (34.6%)	172 (44.7%)	< 0.001
Risk stratification				
CHA_2DS_2-VASc score	3.5 ± 1.5	3.0 ± 1.2	4.9 ± 1.4	< 0.001
HAS-BLED score	1.6 ± 1.0	1.4 ± 0.9	2.1 ± 1.0	< 0.001
Cardiovascular risk factors				
Hypertension	1,137 (79.3%)	808 (77.1%)	329 (85.5%)	< 0.001
Diabetes	388 (27.1%)	231 (22.0%)	157 (40.8%)	< 0.001
Vascular disease				
Heart failure	326 (22.7%)	176 (16.8%)	150 (38.9%)	< 0.001
Prior cerebrovascular disease	179 (12.5%)	42 (4.0%)	137 (35.6%)	< 0.001
Peripheral artery disease	58 (4.0%)	26 (2.5%)	32 (8.3%)	< 0.001
Other conditions/comorbidities				
Kidney failure*	350 (24.7%)	222 (21.4%)	128 (33.5%)	< 0.001

*Glomerular filtration rate < 60 mL/min/1.73 m^2 by MDRD-4; AF — atrial fibrillation

Table 3. Incidence and annual rates of events categorized by 2MACE score.

	Patients with 2MACE < 3 (n = 1,048) Annual rate of events (n = 1,042; accumulated time = 2359.90 years)	Patients with 2MACE ≥ 3 (n = 385) Annual rate of events (n = 383; accumulated time = 824.47 years)	P	Odds ratio (95% CI)
Stroke + SE + TIA				
N events [N patients (%)]	8 [8 (0.8)]	15 [15 (3.9)]	< 0.001	**5.270**
Annual rate of events	0.34	1.82	< 0.001	**(2.216–12.532)**
Major bleeding				
N events [N patients (%)]	12 [11 (1.0)]	21 [18 (4.7)]	< 0.001	**4.624**
Annual rate of events	0.51	2.55	< 0.001	**(2.163–9.882)**
MACE				
N events [N patients (%)]	16 [14 (1.3)]	18 [16 (4.2)]	< 0.001	**3.202**
Annual rate of events	0.68	2.18	0.001	**(1.548–6.626)**
Myocardial infarction				
N events [N patients (%)]	3 [3 (0.3)]	2 [2 (0.5)]	0.615	1.819
Annual rate of events	0.13	0.24	0.771	(0.303–10.928)
Revascularization				
N events [N patients (%)]	4 [4 (0.4)]	5 [5 (1.3)]	0.064	3.434
Annual rate of events	0.17	0.61	0.112	(0.917–12.856)
Cardiovascular (cardiac) death				
N events [N patients (%)]	9 [9 (0.9)]	11 [11 (2.9)]	0.004	**3.395**
Annual rate of events	0.38	1.33	0.011	**(1.396–8.259)**

CI — confidence interval; MACE — major adverse cardiovascular events; SE — systemic embolism; TIA — transient ischemic attack

information. In the present study, patients with a 2MACE score ≥ 3 (vs. < 3) had higher annual rates of MACE, CV mortality, fatal HF, stroke + systemic embolism + TIA, and major bleeding. This finding is in line with those of previous studies, which have shown that AF patients with a high 2MACE score have a greater risk of all-cause mortality, CV mortality, MACE, coronary artery disease, and severe coronary artery disease [5, 15–19]. The majority of studies [5, 15–17], but not all [20], have shown a relatively high capacity of 2MACE score to predict CV events in AF patients, that was slightly superior to that found in the current study. This small difference between this study and previous data may be because patients in previous studies were mainly anticoagulated with VKA but not with DOACs, which have a better risk-benefit profile [5, 8, 15–17]. Moreover, low rates of adverse events were recorded herein, despite the high thromboembolic risk of the study patients. These data strongly suggest that adapting the 2MACE score to patients taking DOACs may be of interest, and the addition of renal failure to 2MACE score (2MACER), could slightly improve the accuracy to predict MACE. In the original Pastori cohort, the c-index was 0.79 in the internal derivation cohort and 0.66 in the external validation cohort [5]. In the present study, c-index was 0.638 for 2MACE and 0.651 for 2MACER, very close to the external validation cohort.

Data herein, showed that patients with IHD and concomitant treatment with antiplatelet agents were at especially high risk of CV events. There are at least three possible explanations for this observation. First, baseline characteristics reflect the increased risk of patients with recent acute coronary syndrome or myocardial revascularization. These patients clearly have a higher risk of MACE, such as death, non-fatal MI, new revascularizations or HF. Accordingly, the higher MACE rates would be related to the CV condition itself, rather than the combination of acetylsalicylic acid or P2Y12 inhibitors with rivaroxaban [21]. Second, the combined antithrombotic regimen could lead to additional major bleeding and indirectly higher rates of death or non-fatal HF admissions [22]. Third, there may be polivascular patients, with a known higher risk for additional events [21]. Although some of these findings are not new, this should be further explored.

In the present study, the clinical profile was similar to that found in other real-life studies [11, 23–28], indicating that the current data were representative of patients with AF taking rivaroxaban in clinical practice, and, consequently, that these results can be extended to this population. With regard to outcomes, annual event rates were low (MACE, 1.07%; thromboembolic events, 0.66%; major bleeding, 1.04%). In a study of patients taking VKAs, annual rates of stroke/TIA and MACE were 1.1% and 2.9%, respectively, after a median follow-up of 30.8 months. Of note, rates of MACE increased as control of the international normalized ratio worsened [6]. In a German registry of patients taking DOACs, the annual incidence of MACE (not including revascularization) was 2% in a population with a mean $CHADS_2$ of 2 [10]. In the rivaroxaban arm of the ROCKET-AF trial, rates for thromboembolic events, and major bleeding were 1.7, and 3.6 per 100 patient-years, respectively [29]; in the XANTUS study, these values were 1.8 and 2.1 per 100 patient-years, respectively [11]. Therefore, in clinical practice, thromboembolic and bleeding events are less common than in the pivotal clinical trial, and even less frequent in the Spanish population. Although these numbers could be explained by differences in clinical profile, the fact is that in routine practice, event rates are lower with DOACs than with VKAs.

Limitations of the study

This study is subject to the limitations associated with the population selected. The patients may have differed from those of Pastori's cohort in that they were recruited after at least 6 months of receiving rivaroxaban. In addition, their potentially higher CV risk could prevent the results of this uncontrolled study from being extrapolated to other populations. Clinical evidence indicates that the use of rivaroxaban may also be a limitation in that the number of expected events may be lower than with VKAs, although according to our calculation it was sufficient to assess the performance of the primary and secondary objectives. Another limitation was that the objective of improving the accuracy of the 2MACE score was not validated (internally or externally), because it was an exploratory objective that should be confirmed in further investigations. As this was an observational study, no control group was available, and the presence of residual confounding factors could not be excluded. However, patients were recruited consecutively after an office consultation, thus reducing the possibility of selection bias.

Conclusions

Although a 2MACE score ≥ 3 predicts a higher risk of adverse CV outcomes in AF patients treated

with rivaroxaban, the capacity of 2MACE to estimate major thrombotic outcomes, such as CV death, MI, and myocardial revascularization, is modest in this setting. The new 2MACER score slightly increases the ability to predict MACE in this population. On the other hand, whereas rivaroxaban is used in elderly patients with a high thromboembolic risk and many comorbidities, the rate of adverse events, including death, MACE, thromboembolic complications, and bleeding (major and fatal) is low.

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References

1. Miyasaka Y, Barnes ME, Bailey KR, et al. Mortality trends in patients diagnosed with first atrial fibrillation: a 21-year community-based study. J Am Coll Cardiol. 2007; 49(9): 986–992, doi: 10.1016/j.jacc.2006.10.062, indexed in Pubmed: 17336723.
2. Hindricks G, Potpara T, Dagres N, et al. ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2021; 42(5): 373–498, doi: 10.1093/eurheartj/ehaa612, indexed in Pubmed: 32860505.
3. Soliman EZ, Safford MM, Muntner P, et al. Atrial fibrillation and the risk of myocardial infarction. JAMA Intern Med. 2014; 174(1): 107–114, doi: 10.1001/jamainternmed.2013.11912, indexed in Pubmed: 24190540.
4. Soliman EZ, Lopez F, O'Neal WT, et al. Atrial Fibrillation and Risk of ST-Segment-Elevation Versus Non-ST-Segment-Elevation Myocardial Infarction: The Atherosclerosis Risk in Communities (ARIC) Study. Circulation. 2015; 131(21): 1843–1850, doi: 10.1161/CIRCULATIONAHA.114.014145, indexed in Pubmed: 25918127.
5. Pastori D, Farcomeni A, Poli D, et al. Cardiovascular risk stratification in patients with non-valvular atrial fibrillation: the 2MACE score. Intern Emerg Med. 2016; 11(2): 199–204, doi: 10.1007/s11739-015-1326-1, indexed in Pubmed: 26471883.
6. Pastori D, Pignatelli P, Saliola M, et al. Inadequate anticoagulation by vitamin K antagonists is associated with major adverse cardiovascular events in patients with atrial fibrillation. Int J Cardiol. 2015; 201: 513–516, doi: 10.1016/j.ijcard.2015.08.054, indexed in Pubmed: 26318513.
7. Bassand JP, Apenteng PN, Atar D, et al. GARFIELD-AF: a worldwide prospective registry of patients with atrial fibrillation at risk of stro,ke. Future Cardiol. 2021; 17(1): 19–38, doi: 10.2217/fca-2020-0014, indexed in Pubmed: 32696663.
8. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014; 383(9921): 955–962, doi: 10.1016/S0140-6736(13)62343-0, indexed in Pubmed: 24315724.
9. Camm AJ, Amarenco P, Haas S, et al. XANTUS: rationale and design of a noninterventional study of rivaroxaban for the prevention of stroke in patients with atrial fibrillation. Vasc Health Risk Manag. 2014; 10: 425–434, doi: 10.2147/VHRM.S63298, indexed in Pubmed: 25083135.
10. Hecker J, Marten S, Keller L, et al. Effectiveness and safety of rivaroxaban therapy in daily-care patients with atrial fibrillation. Results from the Dresden NOAC Registry. Thromb Haemost. 2016; 115(5): 939–949, doi: 10.1160/TH15-10-0840, indexed in Pubmed: 26791999.
11. Camm AJ, Amarenco P, Haas S, et al. XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation. Eur Heart J. 2016; 37(14): 1145–1153, doi: 10.1093/eurheartj/ehv466, indexed in Pubmed: 26330425.

12. Fernández M, Marín F, Rafols C, et al. Thromboembolic and bleeding events with rivaroxaban in clinical practice in Spain: impact of inappropriate doses (the EMIR study). J Comp Eff Res. 2021; 10(7): 583–593, doi: 10.2217/cer-2020-0286.
13. Schulman S, Kearon C. Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost. 2005; 3(4): 692–694, doi: 10.1111/j.1538-7836.2005.01204.x, indexed in Pubmed: 15842354.
14. Violi F, Soliman EZ, Pignatelli P, et al. Atrial fibrillation and myocardial infarction: a systematic review and appraisal of pathophysiologic mechanisms. J Am Heart Assoc. 2016; 5(5), doi: 10.1161/JAHA.116.003347, indexed in Pubmed: 27208001.
15. Szymańska A, Płatek AE, Semczuk-Kaczmarek K, et al. Usefulness of the 2MACE score as a predictor of long-term all-cause mortality in patients with atrial fibrillation. Pol Arch Intern Med. 2020; 130(7-8): 635–639, doi: 10.20452/pamw.15431, indexed in Pubmed: 32539310.
16. Rivera-Caravaca JM, Marín F, Esteve-Pastor MA, et al. Usefulness of the 2MACE score to predicts adverse cardiovascular events in patients with atrial fibrillation. Am J Cardiol. 2017; 120(12): 2176–2181, doi: 10.1016/j.amjcard.2017.09.003, indexed in Pubmed: 29111209.
17. Polovina M, Đikić D, Vlajković A, et al. Adverse cardiovascular outcomes in atrial fibrillation: Validation of the new 2MACE risk score. Int J Cardiol. 2017; 249: 191–197, doi: 10.1016/j.ijcard.2017.09.154, indexed in Pubmed: 28986061.
18. Pastori D, Biccirè FG, Lip GY, et al. Relation of atrial fibrillation to angiographic characteristics and coronary artery disease severity in patients undergoing percutaneous coronary intervention. Am J Cardiol. 2021; 141: 1–6, doi: 10.1016/j.amjcard.2020.11.006, indexed in Pubmed: 33220321.
19. Ding WY, Lip GYH, Pastori D, et al. Effects of atrial fibrillation and chronic kidney disease on major adverse cardiovascular events. Am J Cardiol. 2020; 132: 72–78, doi: 10.1016/j.amjcard.2020.07.004, indexed in Pubmed: 32773222.
20. Pastori D, Rivera-Caravaca JM, Esteve-Pastor MA, et al. Comparison of the 2MACE and TIMI-AF scores for composite clinical outcomes in anticoagulated atrial fibrillation patients. Circ J. 2018; 82(5): 1286–1292, doi: 10.1253/circj.CJ-17-1318, indexed in Pubmed: 29553090.
21. Eikelboom J, Connolly S, Bosch J, et al. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. N Engl J Med. 2017; 377(14): 1319–1330, doi: 10.1056/nejmoa1709118.
22. So CH, Eckman MH. Combined aspirin and anticoagulant therapy in patients with atrial fibrillation. J Thromb Thrombolysis. 2017; 43(1): 7–17, doi: 10.1007/s11239-016-1425-5, indexed in Pubmed: 27665101.
23. Martí E, Segado A, Pastor-Galán I, et al. Use of rivaroxaban for the prevention of stroke in patients with nonvalvular atrial fibrillation in Spain. Future Cardiol. 2018; 14(3s): 3–8, doi: 10.2217/fca-2018-0020, indexed in Pubmed: 29848095.
24. Pérez Cabeza AI, González Correa JA, Chinchurreta Capote PA, et al. Drug persistence and outcomes in a cohort of patients with nonvalvular atrial fibrillation treated with rivaroxaban after 2 years of follow-up in clinical practice. Future Cardiol. 2018; 14(3s): 9–16, doi: 10.2217/fca-2018-0021, indexed in Pubmed: 29848094.
25. Muñiz Lobato S, Tarrazo Tarrazo C, González Fernández E, et al. Clinical profile, adequacy of dosage and thromboembolic and bleeding outcomes in patients with nonvalvular atrial fibrillation treated with rivaroxaban in a regional hospital of Asturias, Spain. Future Cardiol. 2018; 14(3s): 17–24, doi: 10.2217/fca-2018-0022, indexed in Pubmed: 29848093.
26. Gavín Sebastián O, Izuzquiza Fernández M, Martínez Fernández R, et al. Anticoagulation with rivaroxaban in a hematology unit: clinical profile, events and discontinuation rates in real-life patients with nonvalvular atrial fibrillation. Future Cardiol. 2018; 14(3s): 25–30, doi: 10.2217/fca-2018-0023, indexed in Pubmed: 29848092.
27. Cerezo-Manchado JJ, Navarro-Almenzar B, Elvira-Ruiz G, et al. Effectiveness and safety of rivaroxaban in a cohort of 142 patients with nonvalvular atrial fibrillation treated with rivaroxaban for the prevention of stroke. Future Cardiol. 2018; 14(3s): 31–37, doi: 10.2217/fca-2018-0024, indexed in Pubmed: 29848091.
28. Brun Guinda D, Callen García Ó, Ondiviela Pérez J, et al. Clinical profile, management and outcomes in a cohort of elderly and highly comorbid patients with nonvalvular atrial fibrillation treated with rivaroxaban in routine practice. Future Cardiol. 2018; 14(3s): 39–45, doi: 10.2217/fca-2018-0025, indexed in Pubmed: 29848090.
29. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011; 365(10): 883–891, doi: 10.1056/NEJMoa1009638, indexed in Pubmed: 21830957.

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The diagnostic and prognostic value of copeptin in patients with acute ischemic stroke and transient ischemic attack: A systematic review and meta-analysis

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Abstract

Background: *Stroke is the second main cause of mortality and the third leading cause of mortality and permanent disability combined. Many potential biomarkers have been described to contribute to the diagnosis, prognosis of outcomes, and risk stratification after stroke. Copeptin is an inactive peptide that is produced in an equimolar ratio to arginine vasopressin in response to the activation of the endogenous stress system.*

Methods: *The present study is a systematic review and meta-analysis to assess plasma copeptin concentrations, diagnostic and prognostic values for risk stratification after acute ischemic stroke and transient ischemic attack.*

Results: *Mean copeptin level in stroke vs. non-stroke groups varied and amounted to 19.8 ± 17.4 vs. 9.7 ± 6.6 pmol/L, respectively (mean differences [MD]: 12.75; 95% confidence interval [CI]: 5.00 to 20.49; $p < 0.001$), in good vs. poor outcome 12.0 ± 3.6 vs. 29.4 ± 14.5 (MD: −8.13; 95% CI: −8.37 to −7.88; $p < 0.001$) and in survive vs. non-survive stroke patients: 13.4 ± 3.2 vs. 33.0 ± 12.3, respectively (MD: −13.43; 95% CI: −17.82 to −9.05; $p < 0.001$).*

Conclusions: *The above systematic review and meta-analysis suggests that monitoring the copeptin levels may help predict the long-term prognosis of ischemic stroke efficiently. Determining the copeptin level may help individualize the management of ischemic stroke patients, keep stroke risk lower, reduce post-stroke complications, including patient death, and minimize healthcare costs.* (Cardiol J 2022; 29, 4: 610–618)

Key words: copeptin, C-terminal (pre)pro-vasopressin, prognostic biomarker, acute ischemic stroke, systematic review, meta-analysis

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Introduction

Stroke is the second main cause of mortality and the third leading cause of mortality and permanent disability combined [1]. Unfortunately, despite significant progress in the clinical management of stroke patients and the invaluable role of imaging studies, there is still a lack of reliable blood biomarkers for use in diagnosis and prognosis of outcome in this patient population [2]. Many potential biomarkers have been described to contribute to risk stratification after stroke [3]. Of these, markers of inflammation (procalcitonin and mannose-binding lectin), atherogenesis (adipocyte fatty acid-binding protein), stress response (copeptin and cortisol), and the natriuretic peptide should be mentioned. These markers were most consistently associated with poorer outcomes after stroke and added a prognostic value to the established prognostic factors. However, there are some concerns about the methodological or statistical quality of these studies, thus limiting the applicability of this data to clinical practice [3]. It raises the need for further research into the most promising markers.

A transient ischemic attack (TIA) is a strong predictor of stroke. Survivors often require long-term care and are at high risk of recurrent stroke [4]. Early assessment of the risk of stroke recurrence is critical in determining a patient's prognosis. Rapidly measurable biomarkers may play a role in helping to predict the development and consequences of stroke, which is significant in optimal differentiation of patient care and allocation of healthcare resources [5].

Arginine vasopressin (AVP) is a non-cardiac plasma marker of cardiovascular disease. It is secreted from the posterior pituitary gland in response to changes in plasma osmolality and co-stimulates adrenocorticotropin along with corticotropin-releasing hormone, thereby influencing the stress response [6]. This non-osmotic pathway is likely how AVP and copeptin can be used as predictive markers [7]. However, the challenge with AVP is its instability outside the human body and challenges in measurements. Copeptin, the C-terminal part of (pre)pro-vasopressin, is a surrogate marker for AVP. It is more stable at room temperature and easier to measure [8]. Elevated copeptin concentration was associated with higher mortality in patients with heart failure and poorer prognosis in patients after acute myocardial infarction [9, 10]. It was also described to have clinical implications in non-cardiovascular diseases such as polydipsia-polyuria syndrome, multiple sclerosis, sepsis, or preeclampsia [11–15]. Due to the positive relationship of increases in the copeptin level in patients with acute ischemic stroke and TIA, it is assumed that copeptin is a good marker for differential diagnosis between stroke, TIA, and stroke-mimics diseases [16]. Moreover, an elevated copeptin concentration was related to worse prognosis in patients after stroke and to a higher incidence of recurrent TIA or stroke after a TIA event [2]. However, some studies demonstrated the lack of any significant association between the copeptin concentrations and stroke incidence [17].

Therefore, the present systematic review and meta-analysis was performed to assess the diagnosis and prognostic value of plasma copeptin concentrations for risk stratification after acute ischemic stroke and TIA.

Methods

This systematic review and meta-analysis were done according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement [18]. All analyses were based on previously published studies; thus, ethical approval or patient consent was unsuitable for this meta-analysis.

Literature search and selection

Comprehensive systematic searches of online electronic databases, including PubMed, Scopus, Web of Science, Cochrane Library, and Google Scholar from the databases inception to November 21, 2021, were performed. The literature was searched using the following keywords: "C-terminal pro-vasopressin" OR "copeptin" AND "stroke" OR "ischemic attack" OR "TIA" OR "transient ischemic stroke" OR "recurrent cerebrovascular event". All records were searched by two researchers (P.S. and N.B.) separately. They solved disagreements through discussion with a third researcher (L.S.). The search of databases was limited to English publications. No limitation was set for the age of participants in the searched articles. Reference lists in each publication involved were also manually checked to identify eligible studies.

The inclusion criteria were: (1) studies focused on the value of copeptin in predicting mortality in patients with stroke or studies focused on the value of copeptin in: (a) stroke vs. non-stroke patients; (b) re-events TIA vs. non-re-events TIA; (c) ischemic vs. hemorrhagic stroke; (d) stroke/TIA vs. mimic; (3) randomized controlled trials or non-randomized trials. Studies were excluded if: (1) they did not

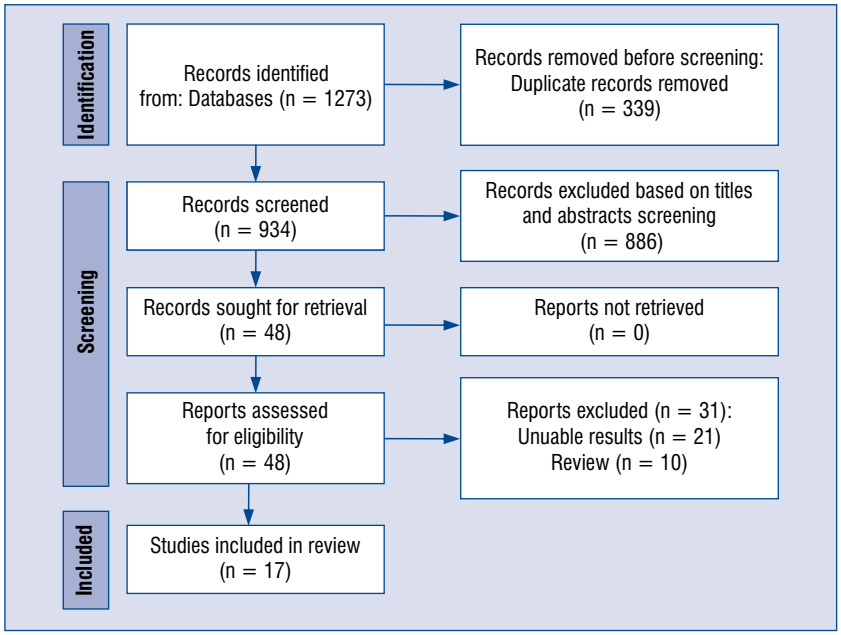

Figure 1. Database search and selection of studies according to Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.

present a comparator group; (2) references were in the form of reviews, letters, editorials, conference articles, or duplicated publications.

Quality assessment and data extraction

Two authors (N.B. and L.S.) independently extracted data from relevant articles: first author name, year of publication, region of the cohort, patient characteristics (i.e., no. of patients, age, sex), type of cerebrovascular event, and copeptin levels. They resolved discrepancies through discussion with the third researcher (A.G.). Data were recorded from included studies using a Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) specific predefined report form. When data about the primary outcomes were missing, the plan was to contact the corresponding author of the original study.

Data items, outcomes, design strengths, and weaknesses across the studies were compared. The risk of bias at the study level was assessed for each study using the Cochrane ROBINS-I bias assessment tool [19]. The ROBINS-I tool examines seven bias domains due to: (1) confounders; (2) selection of participants; (3) classification of interventions; (4) deviations from intended interventions; (5) missing data; (6) measurements of outcomes; (7) selection of the reported results. The Robvis application was used to visualize the risk of bias assessments [20].

Statistical analysis

Mean differences (MD) with 95% confidence intervals (CIs) for continuous data were used. When the continuous outcome was reported in a study as median, range, and interquartile range, means and standard deviations were estimated using the formula described by Hozo et al. [21]. For dichotomous data, odds ratios (OR) as the effect measure with 95% CI were utilized. We assessed heterogeneity statistically using I^2 (no heterogeneity, I^2: 0–25%; moderate heterogeneity, I^2: 25–50%; large heterogeneity, I^2: 50–75%; extreme heterogeneity, I^2: 5–100%). The random-effects model was used for $I^2 > 50\%$; otherwise, the fixed effects model was employed. Potential publication bias was sought using a funnel plot if over 10 trials were included for an outcome. For continuous outcomes, the Egger test was used to detect funnel plot asymmetry [22]. All analyses were performed using Stata software, version 15.0 (College Station, TX, USA) as well as with the Review Manager software version 5.4 (Nordic Cochrane Center, Cochrane Collaboration). $P < 0.05$ (two-tailed) was considered significant.

Results

Characteristics of the articles

A flowchart of the publication selection process is presented in Figure 1. The database search-

Table 1. Characteristics of included trials.

Study	Country	Study design	No. of patients	Age	Sex, female
De Marchis et al. 2013 [24]	Switzerland/Germany	Prospective, multicenter, cohort study	783	70.6 ± 3.3	298 (38.1%)
De Marchis et al. 2014 [2]	Switzerland/Germany	Prospective, multicenter, cohort study	302	68.8 ± 3.2	112 (37.1%)
Deboevere et al. 2019 [25]	France	Prospective, observational, monocenter study	135	59.4 ± 5.9	79 (58.5%)
Dong et al. 2013 [26]	China	Prospective, observational cohort study	125	71 ± 4	56 (44.8%)
Katan et al. 2009 [27]	Switzerland	Prospective observational study	359	74 ± 3.3	149 (41.5%)
Katan et al. 2011 [28]	Switzerland	Prospective observational study	107	70.3 ± 3.2	60 (56.1%)
Katan et al. 2016 [17]	Switzerland	Nested case-control study	516	69.5 ± 3.1	326 (63.2%)
Perovic et al. 2017 [29]	Croatia	Case-control study	172	76.2 ± 2.7	100 ((58.1%)
Sun et al. 2018 [30]	China	Case-control study	238	61.5 ± 2.7	92 (38.7%)
Tang et al. 2017 [5]	China	Post hoc analysis	405	Not specified	Not specified
Tu et al. 2013 [31]	China	Prospective cohort study	189	66.5 ± 4.7	72 (55.0%)
Urwyler et al. 2010 [32]	Switzerland	Prospective cohort study	362	74.5 ± 3	145 (40.1%)
von Recum et al. 2015 [33]	Germany	Prospective cohort study	36	68 ± 6.3	16 (44.4%)
Wang et al. 2014 [16]	China	Prospective cohort study	275	68.8 ± 3.2	135 (49.1%)
Wang et al. 2016 [34]	China	Prospective cohort study	247	65.3 ± 3.8	108 (43.7%)
Wendt et al. 2015 [23]	Germany	Prospective cohort study	561	72.7 ± 13.7	302 (53.8%)
Zhang et al. 2013 [35]	China	Prospective cohort study	245	73 ± 64.8	103 (42.0%)

es and citation tracking yielded 1273 hits. After a title review and removal of duplicate studies, screening excluded 934 articles and 48 full-text articles remained. Some articles did not meet the inclusion criteria; on this basis, 31 full-text papers with insufficient data for extraction were excluded. After screening for all the probable factors, 5057 patients were finally included from 17 studies [2, 5, 16, 17, 23–35].

Table 1 summarizes the 17 articles included in the systemic review and their methodologies. All studies were conducted between 2009 and 2019 in China [5, 16, 26, 30, 31, 34, 35], Switzerland [17, 27, 28, 32], Germany [23, 33], Switzerland and Germany [2, 24], France [25], and Croatia [29]. The risk of bias of these studies was low (n = 14) or moderate (n = 3) (**Suppl. Figs. S1 and S2**).

Search results

Five trials reported copeptin levels in stroke vs. non-stroke groups. In most of the studies, the non-stroke patients group consisted of healthy subjects, except for studies conducted by Deboevere et al. [25] where the non-stroke group, contained patients visiting emergency department for a new episode of dizziness with the exclusion of stroke diagnosis based on brain imaging, and DeMarchis et al. [2] in which the patients who did not experience a stroke within 3 months after the index TIA were investigated. Mean copeptin level in stroke vs. non-stroke groups varied and amounted to 19.8 ± 17.4 vs. 9.7 ± 6.6 pmol/L, respectively (MD: 12.75; 95% CI: 5.00 to 20.49; $p < 0.001$; Fig. 2).

Eight studies reported copeptin levels in good vs. poor outcomes. The definitions used by

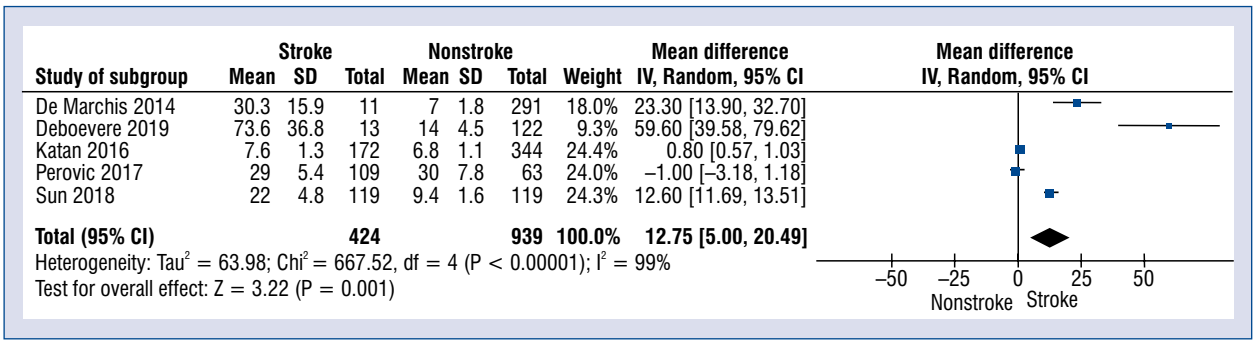

Figure 2. Forest plot of copeptin levels in stroke and non-stroke groups. The center of each square represents the weighted mean differences for individual trials, and the corresponding horizontal line stands for a 95% confidence interval (CI). The diamond represents pooled results; SD — standard deviation.

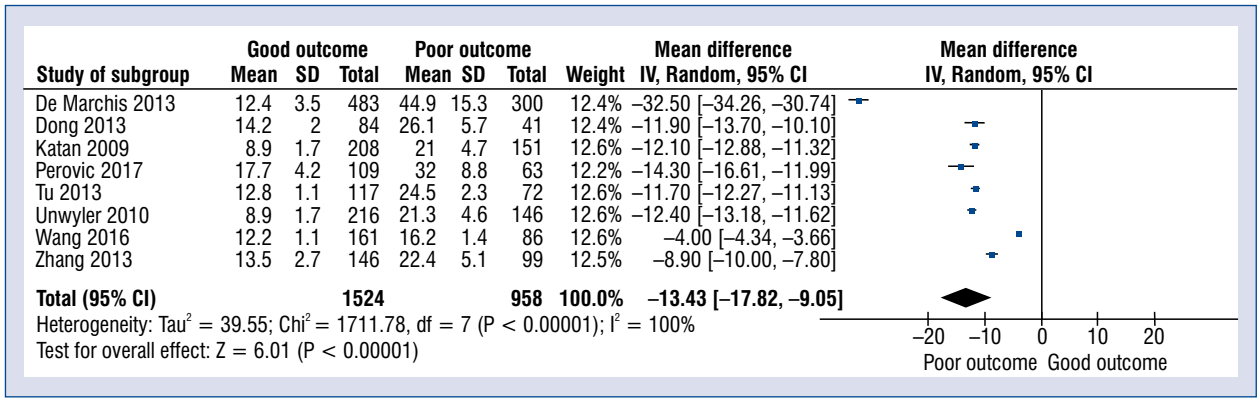

Figure 3. Forest plot of copeptin levels in good and poor outcome groups. The center of each square represents the weighted mean differences for individual trials, and the corresponding horizontal line stands for a 95% confidence interval (CI). The diamond represents pooled results; SD — standard deviation.

each study were utilized to classify neurologic outcomes. This categorization incorporated modified Rankin Scale (classified as good: 0 to 2, poor: > 2) and Barthel Index (good: 60 or more, poor: less than 60) outcome scales. The result was assessed after 1 year/3 months (90 days) or when the patients were discharged from the baseline. Pooled analysis showed that the copeptin level in the good outcome group was 12.0 ± 3.6 pmol/L and was statistically significantly lower than in the poor outcome group 29.4 ± 14.5 pmol/L (MD: −8.13; 95% CI: −8.37 to −7.88; p < 0.001; Fig. 3).

Six studies reported copeptin levels in survive vs. non-survive stroke patients which was 13.4 ± ± 3.2 vs. 33.0 ± 12.3 pmol/L, respectively (MD: −13.43; 95% CI: −17.82 to −9.05; p < 0.001; Fig. 4).

Copeptin levels in no-re-events vs. re-events TIA varied and amounted to 13.8 ± 7.6 vs. 22.8 ± ± 11.4 pmol/L, respectively (MD: −7.31; 95% CI: −11.30 to −3.33; p < 0.001; Fig. 5).

Additional analysis showed that two studies [23, 33] reported copeptin levels between the stroke/TIA group and the mimic group. Pooled analysis showed that lower copeptin levels were observed in stroke/TIA group compared to mimic group (14.8 ± 5.1 vs. 18.1 ± 25.9, respectively; MD: 1.27; 95% CI: 0.18 to 2.36; p = 0.02).

Discussion

The main finding of the meta-analysis was that the level of copeptin was significantly higher in groups with stroke as compared to the groups in which stroke did not occur (MD: 12.75; 95% CI: 5.00 to 20.49; p < 0.001). Furthermore, copeptin concentration analyzed in relation to good or poor outcomes was statistically significantly lower in the group with good results than in the group with poor results. On this basis, it was found that a higher blood biomarker level contributed to the poor results

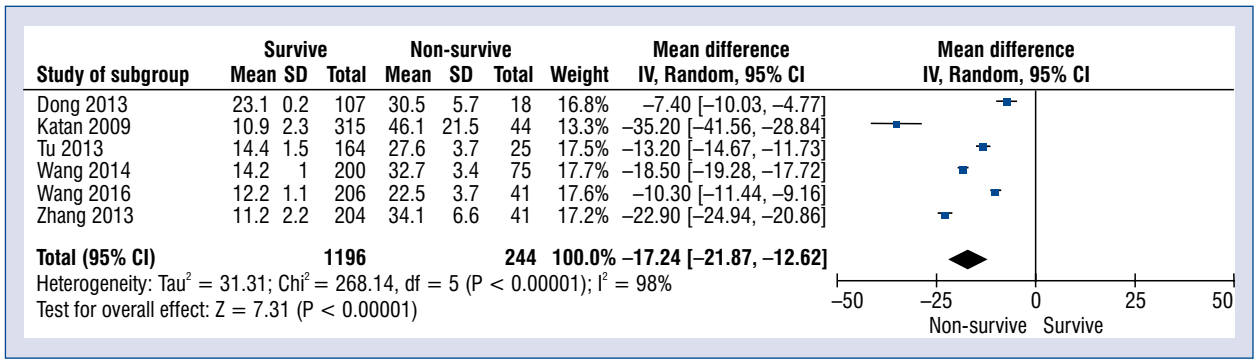

Figure 4. Forest plot of copeptin levels in survive vs. non-survive groups. The center of each square represents the weighted mean differences for individual trials, and the corresponding horizontal line stands for a 95% confidence interval (CI). The diamond represents pooled results; SD — standard deviation.

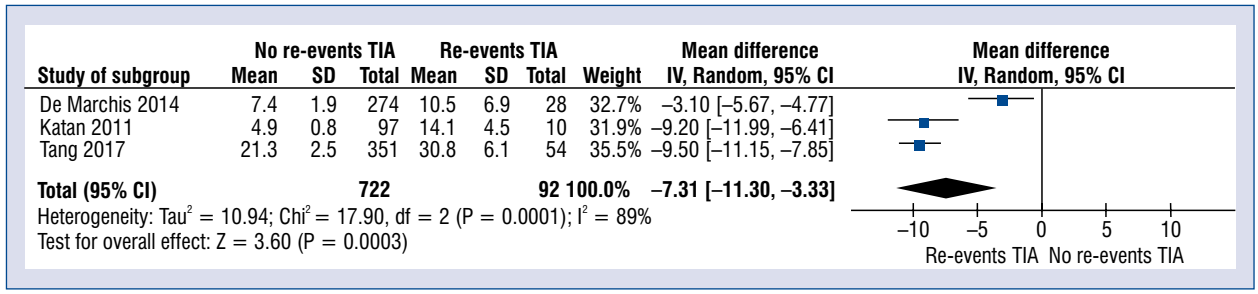

Figure 5. Forest plot of copeptin levels in no re-events transient ischemic attack (TIA) vs. re-events TIA groups. The center of each square represents the weighted mean differences for individual trials, and the corresponding horizontal line stands for a 95% confidence interval (CI). The diamond represents pooled results; SD — standard deviation.

(MD: −8.13; 95% CI: −8.37 to 7.88; p < 0.001). The findings of the meta-analysis are in line with the conclusions of the first published meta-analysis assessing the prognostic value of copeptin in acute stroke [36]. Thirteen relevant studies involving 2746 patients included in the meta-analysis showed that increased plasma copeptin levels have been associated with an increased risk of adverse outcomes and mortality after stroke. The relationship between copeptin concentrations and survival in patients after stroke was also evaluated in our meta-analysis. Based on the data embodied in the included studies, it was concluded that an increase in the level of this biomarker in plasma, reduces the chances of patients' survival after stroke (MD: −13.43; 95% CI: −17.82 to −9.05; p < 0.001). The studies included in the meta-analysis examined all-cause mortality, while it would be ideal to consider cause-specific mortality. However, it is difficult in clinical practice to obtain reliable data about the cause of death.

From the pathophysiologic viewpoint, the AVP works through the V1a, V1b, and V2 receptors. The influence on V1a receptors is associated with vasoconstriction. Copeptin is found in the circulation in equimolar amounts to AVP. It is a very stable peptide, and it is easy to estimate [37]. Copeptin correlates positively with the initial infarct volume measured in the brain by computed tomography (CT) or brain magnetic resonance imaging (MRI). AVP stimulates V1a and V2 receptors, which trigger platelet aggregation, vasoconstriction, and water retention. The above process results, are hypovolemic or normovolemic hyponatremia, and low plasma osmolality may occur [38]. Hyponatremia is a common condition in patients after stroke. It is estimated that 40–45% of stroke patients develop hyponatremia during hospitalization. This electrolyte disturbance is associated with severe complications, such as cerebral edema, which may increase the risk of poor outcomes and death in post-stroke patients. However, it is still unclear whether the appropriate restoration of sodium levels improves outcomes in patients after stroke [39]. Likewise, there is a close relationship be-

tween copeptin levels and cerebral edema, which develops early after the focal ischemia onset and is correlated with infarct volume. The AVP V1a receptor is involved in the pathogenesis of secondary brain injury following acute ischemia by exacerbating cerebral edema. The relationship between the copeptin concentration in serum and AVP level and cerebral edema development. The blocking of AVP receptors reduces cerebral edema with ischemia and trauma.

It is essential to mention that one study, which was not included in the analysis, sought to assess the temporal profile of copeptin in relation to revascularization techniques and the development of cerebral edema and hemorrhagic transformation by evaluation upon admission, at 24 hours, and between the third and fifth day of hospitalization. Initial copeptin rise was substantially associated with stroke severity. Copeptin decremental course was noticeably steeper in patients receiving a combined reperfusion strategy, than in patients receiving single reperfusion therapy or a conservative approach in the following days [40].

The concentration of copeptin were further analyzed in patients with a recurrent TIA and in patients who experienced a TIA once. In the studies by De Marchis et al. [2, 24], TIA was defined as a neurological dysfunction caused by focal cerebral ischemia that lasts less than 24 hours, regardless of whether diffusion-weighted MRI revealed an ischemic lesion. On the contrary, von Recum et al. [33] introduced the term of transient symptoms with infarction in the case of visible lesions in brain imaging with resolving symptoms within 24 hours, following the criteria of the World Health Organization for TIA definition. Previous studies have indicated that copeptin levels can differentiate patients with TIA after the first episode into patients with high or low risk for stroke recurrence. This could allow appropriate treatment to be tailored for particular groups of patients [41]. The level of copeptin in the present meta-analysis was lower in the group of subjects without a recurring event of a TIA (MD: −7.31; 95% CI: −11.30 to −3.33; $p < 0.001$). Based on this, it can be assumed that this biomarker can predict a TIA recurrence. Further studies are required to adjudicate these data's clinical utility and find cut-off points for different treatment approaches. The exact mechanism behind the association between copeptin levels and the recurrence of cerebrovascular events, remains unknown. However, several hypotheses have been presented. Copeptin appeared to capture unknown risk variables in addition to the ABCD2 score. Additionally, the activation of the stress axis was more apparent in patients with a more severe "ischemic danger" (as indicated by a diffusion-weighted imaging and/or patients with longer-lasting and more severe symptoms) [2]. These patient groups were known to be at a higher risk of recurrent cerebrovascular incidents [28]. Copeptin levels that are high in patients with significant artery atherosclerosis may also indicate unstable vascular plaques [41].

Copeptin may aid in predicting ischemic stroke and TIA outcomes, however, its utility in distinguishing between cerebral ischemia and stroke mimics has not been proven. However, researchers demonstrated that prospective biomarker research is feasible in a prehospital setting [23] without causing time delays in patient care and thus providing valuable recommendations for future studies of noninvasive tests, aimed at quickly distinguishing stroke from stroke mimics.

There are some limitations of this meta-analysis that have to be considered. First, observational studies are always characterized by some degree of risk of bias that cannot be entirely eliminated. Second, the methods of measuring copeptin concentration could have affected the results of the current meta-analysis. The measuring method was specified in only 7 out of 17 studies eligible for analysis. Three of them used KRYPTOR test, which is the most appropriate according to the study conducted by Sailer et al. [42] because it is highly accurate in non-healthy subjects. The sandwich-type immunoassay (ELISA) was used in 3 studies, and the CT-proAVP-luminescence--immunoassay was used in 1 study.

Contrary to the KRYPTOR test, sandwich--type immunoassay (ELISA) and the CT-proAVP-luminescence-immunoassay have poorer diagnostic values in detecting copeptin levels. Moreover, included studies did not provide serial measurements of copeptin; thus, further studies need to evaluate whether serial copeptin measurements will bring additional benefits in stratifying the risk of acute stroke patients. Finally, other potential biases and confounders could not be entirely excluded in the present meta-analysis since the outcomes may also have depended on the severity and etiology of the cerebrovascular event, its treatment, how the comorbidities were managed, and the professionalism and experience in the centers where the patients were treated. Thus, despite results consistent with others in the literature and including a large group of patients, the current analysis should be treated with caution because all possible confounding variables could be not accounted for.

Copeptin measurement is still not used in the routine care of post-stroke patients despite years of increasing evidence on the association of copeptin with unfavorable outcomes after stroke. Studies that reported an association of copeptin with post-stroke outcomes, tended to include a small study population, which decreased the significance of the results. In addition, copeptin is also elevated in other diseases, such as heart failure and infections, acting as a body stress marker [17]. Researchers do not always consider all potential factors that may affect copeptin levels, which increases the risk of bias. Cut-off points for copeptin are necessary for clinical utility and have not been well established to date. Current studies suggest that copeptin could play a subsidiary role to other current prognostic factors or as a panel with other biomarkers [31]. However, this requires further large-scale, well-designed studies that consider multiple confounding factors and aim to establish the actual clinical utility of copeptin in stroke patients.

Conclusions

The above systematic review and meta-analysis suggest that monitoring copeptin concentrations, may help predict long-term prognosis of TIA and ischemic stroke efficiently. Thus, copeptin is a prospective blood biomarker that could be determined along with other established risk factors in patients with stroke or TIA. Therefore, it can reduce post-stroke complications by identifying patients requiring more intensive care. Furthermore, individualization of stroke treatment based on copeptin concentration, may reduce mortality after stroke and healthcare costs associated with stroke patient management. Nevertheless, more studies with better data reliability are needed before copeptin measurements may be used in routine clinical practice.

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Conflict of interest: None declared

References

1. Feigin VL, Stark BA, Johnson CO, et al. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Neurol. 2021; 20(10): 795–820, doi: 10.1016/S1474-4422(21)00252-0, indexed in Pubmed: 34487721.
2. De Marchis GM, Weck A, Audebert H, et al. Copeptin for the prediction of recurrent cerebrovascular events after transient ischemic attack: results from the CoRisk study. Stroke. 2014; 45(10): 2918–2923, doi: 10.1161/STROKEAHA.114.005584, indexed in Pubmed: 25169950.
3. Montellano FA, Ungethüm K, Ramiro L, et al. Role of blood-based biomarkers in ischemic stroke prognosis: a systematic review. Stroke. 2021; 52(2): 543–551, doi: 10.1161/STROKEAHA.120.029232, indexed in Pubmed: 33430636.
4. Coutts SB. Diagnosis and management of transient ischemic attack. Continuum (Minneap Minn). 2017; 23(1, Cerebrovascular Disease): 82–92, doi: 10.1212/CON.0000000000000424, indexed in Pubmed: 28157745.
5. Tang WZ, Wang XB, Li HT, et al. Serum copeptin predicts severity and recurrent stroke in ischemic stroke patients. Neurotox Res. 2017; 32(3): 420–425, doi: 10.1007/s12640-017-9754-5, indexed in Pubmed: 28555260.
6. Frank E, Landgraf R. The vasopressin system — from antidiuresis to psychopathology. Eur J Pharmacol. 2008; 583(2-3): 226–242, doi: 10.1016/j.ejphar.2007.11.063, indexed in Pubmed: 18275951.
7. Katan M, Morgenthaler N, Widmer I, et al. Copeptin, a stable peptide derived from the vasopressin precursor, correlates with the individual stress level. Neuro Endocrinol Lett. 2008; 29(3): 341–346, indexed in Pubmed: 18580851.
8. Morgenthaler NG, Struck J, Alonso C, et al. Assay for the measurement of copeptin, a stable peptide derived from the precursor of vasopressin. Clin Chem. 2006; 52(1): 112–119, doi: 10.1373/clinchem.2005.060038, indexed in Pubmed: 16269513.
9. Zhong Y, Wang R, Yan L, et al. Copeptin in heart failure: review and meta-analysis. Clin Chim Acta. 2017; 475: 36–43, doi: 10.1016/j.cca.2017.10.001, indexed in Pubmed: 28982590.
10. Yalta K, Yalta T, Sivri N, et al. Copeptin and cardiovascular disease: a review of a novel neurohormone. Int J Cardiol. 2013; 167(5): 1750–1759, doi: 10.1016/j.ijcard.2012.12.039, indexed in Pubmed: 23298558.
11. Fenske W, Refardt J, Chifu I, et al. A copeptin-based approach in the diagnosis of diabetes insipidus. N Engl J Med. 2018; 379(5): 428–439, doi: 10.1056/NEJMoa1803760, indexed in Pubmed: 30067922.
12. Winzeler B, Christ-Crain M. Use of coetin in the diagnosis of olyuria-olydisia syndrome - Authors' reply. Lancet (London, England). 2020; 395: 267–268.
13. Koseoglu M, Ozben S, Gozubatik-Celik G, et al. Plasma copeptin levels in patients with multiple sclerosis. J Clin Neurosci. 2020; 78: 143–146, doi: 10.1016/j.jocn.2020.04.095, indexed in Pubmed: 32345514.
14. Gomes DA, de Almeida Beltrão RL, de Oliveira Junior FM, et al. Vasopressin and copeptin release during sepsis and septic shock. Peptides. 2021; 136: 170437, doi: 10.1016/j.peptides.2020.170437, indexed in Pubmed: 33181268.
15. Bellos I, Pergialiotis V, Papapanagiotou A, et al. Association between serum copeptin levels and preeclampsia risk: A meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2020; 250: 66–73, doi: 10.1016/j.ejogrb.2020.04.051, indexed in Pubmed: 32388342.
16. Wang CW, Wang JL, Zhang Yi, et al. Plasma levels of copeptin predict 1-year mortality in patients with acute ischemic stroke. Neuroreport. 2014; 25(18): 1447–1452, doi: 10.1097/WNR.0000000000000290, indexed in Pubmed: 25383462.
17. Katan M, Moon YP, Paik MC, et al. Procalcitonin and midregional proatrial natriuretic peptide as markers of ischemic stroke: The

Northern Manhattan study. Stroke. 2016; 47(7): 1714–1719, doi: 10.1161/STROKEAHA.115.011392, indexed in Pubmed: 27197849.
18. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. Int J Surg. 2021; 88: 105906, doi: 10.1016/j.ijsu.2021.105906, indexed in Pubmed: 33789826.
19. Sterne JAc, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016; 355: i4919, doi: 10.1136/bmj.i4919, indexed in Pubmed: 27733354.
20. McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. Res Synth Methods. 2021; 12(1): 55–61, doi: 10.1002/jrsm.1411, indexed in Pubmed: 32336025.
21. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 2005; 5: 13, doi: 10.1186/1471-2288-5-13, indexed in Pubmed: 15840177.
22. Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Database Syst Rev. 2019; 10: ED000142, doi: 10.1002/14651858.ED000142, indexed in Pubmed: 31643080.
23. Wendt M, Ebinger M, Kunz A, et al. Copeptin levels in patients with acute ischemic stroke and stroke mimics. Stroke. 2015; 46(9): 2426–2431, doi: 10.1161/STROKEAHA.115.009877, indexed in Pubmed: 26251255.
24. De Marchis GM, Katan M, Weck A, et al. Copeptin adds prognostic information after ischemic stroke: results from the CoRisk study. Neurology. 2013; 80(14): 1278–1286, doi: 10.1212/WNL.0b013e3182887944, indexed in Pubmed: 23468541.
25. Deboevere N, Marjanovic N, Sierecki M, et al. Value of copeptin and the S-100b protein assay in ruling out the diagnosis of stroke-induced dizziness pattern in emergency departments. Scand J Trauma Resusc Emerg Med. 2019; 27(1): 72, doi: 10.1186/s13049-019-0651-1, indexed in Pubmed: 31387626.
26. Dong X, Tao DB, Wang YX, et al. Plasma copeptin levels in Chinese patients with acute ischemic stroke: a preliminary study. Neurol Sci. 2013; 34(9): 1591–1595, doi: 10.1007/s10072-013-1291-2, indexed in Pubmed: 23354601.
27. Katan M, Fluri F, Morgenthaler NG, et al. Copeptin: a novel, independent prognostic marker in patients with ischemic stroke. Ann Neurol. 2009; 66(6): 799–808, doi: 10.1002/ana.21783, indexed in Pubmed: 20035506.
28. Katan M, Nigro N, Fluri F, et al. Stress hormones predict cerebrovascular re-events after transient ischemic attacks. Neurology. 2011; 76(6): 563–566, doi: 10.1212/WNL.0b013e31820b75e6, indexed in Pubmed: 21228295.
29. Perovic E, Mrdjen A, Harapin M, et al. Diagnostic and prognostic role of resistin and copeptin in acute ischemic stroke. Top Stroke Rehabil. 2017; 24(8): 614–618, doi: 10.1080/10749357.2017.1367454, indexed in Pubmed: 28845746.
30. Sun H, Huang D, Wang H, et al. Association between serum copeptin and stroke in rural areas of Northern China: a matched case-control study. Dis Markers. 2018; 2018: 9316162, doi: 10.1155/2018/9316162, indexed in Pubmed: 30402171.
31. Tu WJ, Dong X, Zhao SJ, et al. Prognostic value of plasma neuroendocrine biomarkers in patients with acute ischaemic stroke. J Neuroendocrinol. 2013; 25(9): 771–778, doi: 10.1111/jne.12052, indexed in Pubmed: 23701638.
32. Urwyler SA, Schuetz P, Fluri F, et al. Prognostic value of copeptin: one-year outcome in patients with acute stroke. Stroke. 2010; 41(7): 1564–1567, doi: 10.1161/STROKEAHA.110.584649, indexed in Pubmed: 20508186.
33. von Recum J, Searle J, Slagman A, et al. Copeptin: limited usefulness in early stroke differentiation? Stroke Res Treat. 2015; 2015: 768401, doi: 10.1155/2015/768401, indexed in Pubmed: 26167332.
34. Wang CB, Zong M, Lu SQ, et al. Plasma copeptin and functional outcome in patients with ischemic stroke and type 2 diabetes. J Diabetes Complications. 2016; 30(8): 1532–1536, doi: 10.1016/j.jdiacomp.2016.07.030, indexed in Pubmed: 27554438.
35. Zhang JL, Yin CH, Zhang Y, et al. Plasma copeptin and long-term outcomes in acute ischemic stroke. Acta Neurol Scand. 2013; 128(6): 372–380, doi: 10.1111/ane.12132, indexed in Pubmed: 23614762.
36. Choi KS, Kim HJ, Chun HJ, et al. Prognostic role of copeptin after stroke: a systematic review and meta-analysis of observational studies. Sci Rep. 2015; 5: 11665, doi: 10.1038/srep11665, indexed in Pubmed: 26119473.
37. Baranowska B, Kochanowski J. Copeptin: a new diagnostic and prognostic biomarker in neurological and cardiovascular diseases. Neuro Endocrinol Lett. 2019; 40(5): 207–214, indexed in Pubmed: 32112544.
38. Oraby M, Soliman R, Elkareem RA, et al. Copeptin: a potential blood biomarker for acute ischemic stroke. Egypt J Neurol Psychiatry Neurosurg. 2021; 57(1), doi: 10.1186/s41983-021-00393-2.
39. Liamis G, Barkas F, Megapanou E, et al. Hyponatremia in acute stroke patients: pathophysiology, clinical significance, and management options. Eur Neurol. 2019; 82(1-3): 32–40, doi: 10.1159/000504475, indexed in Pubmed: 31722353.
40. Spagnolello O, De Michele M, Lorenzano S, et al. Copeptin kinetics in acute ischemic stroke may differ according to revascularization strategies: pilot data. Stroke. 2019; 50(12): 3632–3635, doi: 10.1161/STROKEAHA.119.025433, indexed in Pubmed: 31630623.
41. Purroy F, Suárez-Luis I, Cambray S, et al. The determination of copeptin levels helps management decisions among transient ischaemic attack patients. Acta Neurol Scand. 2016; 134(2): 140–147, doi: 10.1111/ane.12523, indexed in Pubmed: 26471428.
42. Sailer CO, Refardt J, Blum CA, et al. Validity of different copeptin assays in the differential diagnosis of the polyuria-polydipsia syndrome. Sci Rep. 2021; 11(1): 10104, doi: 10.1038/s41598-021-89505-9, indexed in Pubmed: 33980941.

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Usefulness of soluble endothelial protein C receptor combined with left ventricular global longitudinal strain for predicting slow coronary flow: A case-control study

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Abstract

Background: *Slow coronary flow (SCF) is an angiographic entity characterized by delayed coronary opacification without an evident obstructive lesion in the epicardial coronary artery. However, patients with SCF have decreased left ventricular (LV) global longitudinal strain (GLS). SCF is associated with inflammation, and soluble endothelial protein C receptor (sEPCR) is a potential biomarker of inflammation. Therefore, under evaluation herein, was the relationship between SCF and sEPCR and the predictive value of sEPCR and LV GLS for SCF was investigated.*

Methods: *Twenty-eight patients with SCF and 34 controls were enrolled. SCF was diagnosed by the thrombolysis in myocardial infarction frame count (TFC). The plasma level of sEPCR was quantified using enzyme-linked immunosorbent assay. LV GLS was measured by two-dimensional speckle-tracking echocardiography.*

Results: *Plasma sEPCR was significantly higher in patients with SCF than in controls and was positively correlated with the mean TFC ($r = 0.67$, $p < 0.001$) and number of involved vessels ($r = 0.61$, $p < 0.001$). LV GLS was decreased in patients with SCF compared to that in controls. sEPCR level (OR = 3.14, 95% CI 1.55–6.36, $p = 0.001$) and LV GLS (OR = 1.44, 95% CI 1.02–2.04, $p = 0.04$) were independent predictors of SCF. sEPCR predicted SCF (area under curve [AUC]: 0.83); however, sEPCR > 9.63 ng/mL combined with LV GLS > −14.36% demonstrated better predictive power (AUC: 0.89; sensitivity: 75%; specificity: 91%).*

Conclusions: *Patients with SCF have increased plasma sEPCR and decreased LV GLS. sEPCR may be a useful potential biomarker for SCF, and sEPCR combined with LV GLS can better predict SCF.*
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Key words: slow coronary flow, endothelial protein C receptor, global longitudinal strain, left ventricle

Introduction

Slow coronary flow (SCF) is an angiographic phenomenon characterized by delayed coronary opacification with normal or near-normal epicardial coronary arteries, which is different from the delay observed in other pathological conditions, such as acute myocardial infarction stenting, coronary

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artery ectasia, or myocardial dysfunction [1, 2]. Although SCF is only observed in 1–7% of patients undergoing coronary angiography because of suspected cardiovascular disease, it has been associated with recurrent chest pain, repeat coronary angiography, life-threatening arrhythmias, and even sudden cardiac death [3–5]. Therefore, patients with SCF should be closely monitored for any abnormalities.

Slow coronary flow has been reported to be related to clinical cardiovascular events, which significantly hamper the patient's quality of life [5]. Moreover, although there are no evident obstructive lesions in the epicardial coronary artery, several investigators have observed fibromuscular hyperplasia, medial hypertrophy, endothelial edema, thickening, and coronary microvessel degeneration in biopsy samples of patients with SCF [3]. However, because the precise pathophysiological mechanisms of SCF have not yet been elucidated, no standard and effective treatment approach exists for this condition. Therefore, it is vital to study the pathogenesis and pathophysiological processes involved in SCF, and, furthermore, identify novel biomarkers and therapeutic targets to halt disease progression in SCF.

Currently, the thrombolysis in myocardial infarction frame count (TFC) method using coronary angiography remains the only effective and accurate tool for the diagnosis and assessment of SCF [6]. However, due to its invasiveness and high cost, this method does not permit long-term follow-up and dynamic treatment evaluation. Therefore, an inexpensive, simple, and feasible alternative for SCF detection is warranted.

A previous study assessed left ventricular (LV) myocardial systolic function by noninvasive and inexpensive echocardiography and demonstrated that patients with SCF have decreased LV global longitudinal strain (GLS) [7]. Therefore, it was hypothesized that analyzing LV GLS may be an effective approach for predicting SCF.

Although several previous studies have hypothesized that inflammation, early-stage coronary atherosclerosis, endothelial dysfunction, or microvascular reserve anomalies may contribute to the etiopathogenesis of SCF, a clear pathophysiological mechanism has not been demonstrated, and a precise biomarker of SCF remains unknown [8, 9]. It has been reported that inflammation may be a major factor in many cardiovascular events, and may be associated with coronary artery disease. In the past few years, numerous studies have reported on the role of inflammation in SCF [10–12]. Therefore, it was further hypothesized that inflammation is involved in the development of SCF.

Endothelial protein C receptor (EPCR) is a 46-kDa, type 1 transmembrane glycoprotein, which has been observed in high concentrations in the endothelial membranes of the aorta, heart, and lungs. Soluble EPCR (sEPCR) is a molecule generated at the endothelial surface by cleavage of the extracellular portion of the protein C receptor, particularly due to inflammation, and has been suggested to be a potential biomarker of inflammation [13]. Elevated sEPCR levels are associated with the presence of coronary artery disease and myocardial infarction [14]. However, no study has, as yet, investigated the relationship between sEPCR levels and SCF.

Therefore, the aim of this study was to evaluate the correlation between sEPCR and SCF and investigate the predictive value of sEPCR and LV GLS for SCF.

Methods

Study population

This is a case-controlled study of the Department of Cardiology at the documented hospital between January 2018 and November 2018. Patients with normal or near-normal (less than 40% stenosis) epicardial coronary arteries were consecutively included in this study when coronary angiography was performed to determine the presence of obstructive coronary artery disease because of typical angina, coronary risk factors, or abnormal electrocardiography changes. Exclusion criteria were as follows: coronary artery spasm or ectasia; a previous history of myocardial infarction; LV ejection fraction (EF) $< 52\%$ in males or $< 54\%$ in females; abnormal heart structure (valvular dysfunction, cardiomyopathies, or congenital heart disease); pericardial effusion; any arrhythmia (atrioventricular conduction abnormalities, bundle branch block, ventricular pre-excitation, atrial fibrillation, or paced rhythm); uncontrolled hypertension (systolic blood pressure $>$ 160 mmHg or diastolic blood pressure $>$ 105 mmHg); hyperthyroidism or hypothyroidism; malignancy; autoimmune disease; infection; pulmonary, hepatic, or renal disorder; hematological disorder; positive results on an exercise test (to distinguish SCF from syndrome X), and poor echocardiographic images.

Based on the TFC, patients were divided into two groups: (1) the SCF group, with TFC $>$ 27 in one or more vessels, and (2) the control group, with TFC $\leq$ 27 in all vessels [6]. Patients with in-

calculable TFC or any hemodynamic changes that might affect the TFC during coronary angiography were also excluded from the study.

All examinations were performed by investigators who were blinded to the clinical status of the patients. Written informed consent was obtained from all patients before enrollment. The study protocol was approved by the China Medical University Ethics Committee, and was conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki.

Blood evaluations

Peripheral venous blood samples were obtained from a forearm vein after at least 12 hours of overnight fasting before coronary angiography. Routine blood tests were performed as routine procedures in the Laboratory Department of the hospital. The red blood cell count, red cell distribution width, platelet count, and platelet distribution width were analyzed using a Beckman Coulter LH 780 analyzer (Miami, FL, USA). Triglycerides, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and fasting blood glucose were analyzed using a Siemens ADVIA 2400 analyzer (Tarrytown, NY, USA). The serum sEPCR level was measured by using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Lanji Biotech, Shanghai, China), in accordance with the manufacturer's instructions.

Coronary angiography and TFC calculation

Coronary angiography was performed using the General Electric Innova 3100 (Milwaukee, WI, USA). A femoral approach was used, with the standard Judkins technique and multiple angulated views. Iohexol (350/100 mL) was used as a contrast agent and was manually injected intravenously at the same rate of 3–4 mL/s for the left coronary artery and 2–3 mL/s for the right coronary artery (RCA). The same contrast medium was used in all patients.

In accordance with the method first described by Gibson et al. [6], the flow rate of each major coronary artery was quantitatively evaluated by TFC, including the left anterior descending artery (LAD), left circumflex coronary artery (LCx), and RCA. TFC, recorded at 30 frames per second, was the number of frames from the time (in seconds) at which the contrast medium filled > 70% the proximal coronary artery lumen to the time at which it reached the distal end. The distal end was defined as the distal bifurcation for the LAD, the distal bifurcation of the segment with the longest total distance for the LCx, and the first branch of the posterolateral artery for the RCA.

The TFC was assessed by two separate cardiologists and any disagreement was resolved by a third observer. Since the LAD is usually longer than are the LCx and RCA, the TFC of the LAD was divided by 1.7 to obtain the corrected TFC of the LAD (cLAD). The mean TFC for each patient was calculated by averaging of the TFCs for the RCA, LCx, and cLAD.

Echocardiography

A standard echocardiographic examination was performed using a Vivid E9 ultrasound system (GE Healthcare, Waukesha, WI, USA) equipped with a M5S phased-array probe within 72 hours after coronary angiography. Standard two-dimensional cine loops were recorded for offline analysis using an EchoPAC work station (GE Healthcare).

In accordance with the recommendations of the American Society of Echocardiography [15], the LVEF (by the biplane modified Simpson method), left atrial (LA) volume index, mitral E, mitral A, and mitral average e' were measured. Further, mitral E/A and mitral average E/e' were calculated. Two-dimensional speckle-tracking echocardiography (STE) was performed in accordance with the common standard from the consensus document of the EACVI/ASE/Industry Task Force [16]. LV GLS was obtained by averaging the end-systolic strains of all LV myocardial segments.

Statistical analysis

All statistical analyses were performed using the SPSS 17.0 software package (SPSS version 17, SPSS Inc., Chicago, IL). Data are presented as the mean ± standard deviation (SD) for continuous variables and as the frequency (percentage) for categorical variables. For independent-samples, the Student t-test was used to evaluate differences in continuous variables between the two groups. Categorical variables were compared using the χ^2 or Fisher exact test, as appropriate. The Spearman or Pearson correlation coefficients were obtained, as appropriate. Least squares linear regression was used to evaluate univariable and multivariable correlation with plasma sEPCR level. An enter multivariate logistic regression analysis was performed to identify independent predictors of SCF; results are expressed as the odds ratio (OR) and 95% confidence interval (CI). Receiver operating characteristic curve (ROC) analyses were performed to evaluate the diagnostic effects distinguishing patients with and without CSF and

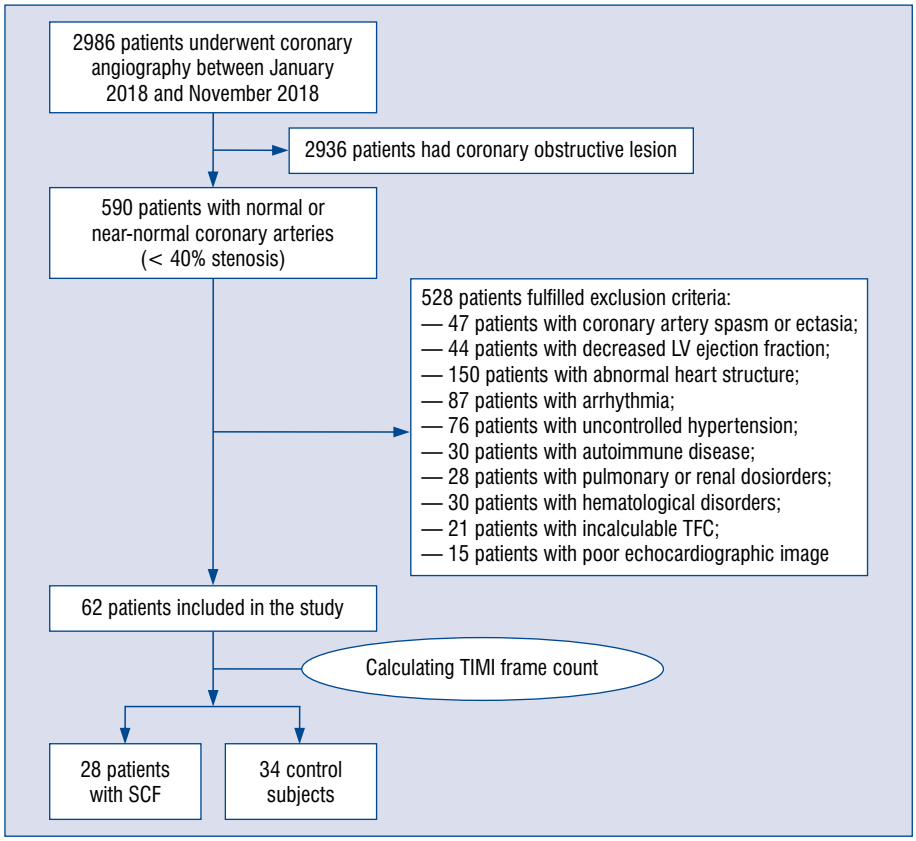

Figure 1. Patient recruitment flowchart; LV — left ventricle; TFC — thrombolysis in myocardial infarction frame count; SCF — slow coronary flow.

to determine appropriate cutoff values. For all parameters, $p < 0.05$ (two-tailed) was considered to indicate statistical significance.

Results

The study flowchart is shown in Figure 1. A total of 28 patients with SCF and 34 age- and sex-matched controls were enrolled in the study. The demographic, routine biochemical data, medications, and angiographic findings of the study population are shown in Table 1. There were no differences in baseline characteristics between the groups. Patients with SCF had significantly higher TFC values for the cLAD, LCx, and RCA, and a higher mean TFC, than those in controls. There was one-, two-, and three-vessel involvement in 14%, 57%, and 29% of the patients, respectively.

Although there was no difference in the LVEF between the groups, the LV GLS was decreased in patients with SCF compared to that in controls (–14.89% ± 2.94 vs. –16.97% ± 2.56, $p = 0.004$). Additionally, it was found that patients with SCF had decreased mitral average e' compared to that in controls, but the difference failed to reach significance (Table 2).

Plasma sEPCR levels were significantly higher in patients with SCF than in controls (10.39 ± 1.84 vs. 8.24 ± 1.20 ng/mL, $p < 0.001$). Moreover, the plasma sEPCR level was positively correlated with the mean TFC ($r = 0.67$, $p < 0.001$) and the number of involved vessels ($r = 0.61$, $p < 0.001$; Fig. 2). After adjusting for baseline covariates including age, sex, body mass index, systolic blood pressure, smoking history, fasting blood glucose and blood lipid, multivariate linear regression analysis showed the associations between plasma sEPCR level with mean TFC and the number of involved vessels were still significant (Table 3).

Logistic regression analysis confirmed that the plasma sEPCR level (OR = 3.14, 95% CI: 1.55–6.36, $p = 0.001$) and LV GLS (OR = 1.44, 95% CI: 1.02–2.04, $p = 0.04$) were independent predictors of SCF, after adjusting for age, sex, body mass index, and other variables with $p < 0.10$ on univariate analysis, including red blood cell count, statin use, and mitral average e' (Table 4).

Table 1. Comparison of baseline characteristics and angiographic findings.

	Controls (n = 34)	SCF (n = 28)	P
Demographics:			
Age [years]	56.24 ± 6.76	58.11 ± 6.58	0.28
Female sex	18 (53%)	10 (36%)	0.17
Body mass index [kg/m^2]	25.31 ± 3.67	24.63 ± 3.09	0.44
Medical history:			
Smoking	8 (24%)	11 (39%)	0.18
Hypertension	11 (32%)	5 (18%)	0.19
Diabetes mellitus	3 (9%)	4 (14%)	0.69
Laboratory values:			
Triglycerides [mmol/L]	1.44 ± 0.56	1.29 ± 0.58	0.31
Total cholesterol [mmol/L]	4.23 ± 0.84	4.01 ± 0.59	0.26
LDL cholesterol [mmol/L]	2.67 ± 0.72	2.52 ± 0.57	0.39
HDL cholesterol [mmol/L]	1.19 ± 0.25	1.15 ± 0.30	0.61
Fasting blood glucose [mmol/L]	5.36 ± 0.72	5.63 ± 1.02	0.23
Red blood cell count [10^{12}/L]	4.48 ± 0.39	4.66 ± 0.43	0.09
Red cell distribution width [%]	12.65 ± 1.07	12.60 ± 0.63	0.83
Platelet count [10^9/L]	230.44 ± 60.75	215.86 ± 57.61	0.34
Platelet distribution width [%]	11.75 ± 1.81	11.88 ± 1.48	0.78
Medications:			
ASA	23 (68%)	14 (50%)	0.16
ACEI	12 (35%)	6 (21%)	0.23
ARB	3 (9%)	2 (7%)	0.81
Beta-blockers	29 (47%)	14 (25%)	0.16
Calcium channel blocker	15 (60%)	19 (56%)	0.75
Statin	21 (62%)	11 (39%)	0.08
Nitrates	10 (29%)	6 (21%)	0.48
Levocarnitine/trimetazidine	17 (50%)	8 (29%)	0.10
TFC:			
cLAD	23.24 ± 3.71	44.25 ± 14.88	**< 0.001**
LCx	20.35 ± 3.67	32.64 ± 12.27	**< 0.001**
RCA	23.56 ± 3.83	38.32 ± 14.19	**< 0.001**
Mean	22.65 ± 3.28	40.26 ± 4.87	**< 0.001**
Vessel involved:			
1-vessel		4 (14%)	
2-vessel		16 (57%)	
3-vessel		8 (29%)	

Values are shown as means ± standard deviation or percentages. SCF — slow coronary flow; LDL — low-density lipoprotein; HDL — high--density lipoprotein; ASA — acetylsalicylic acid; ACEI — angiotensin-converting enzyme inhibitor; ARB — angiotensin II receptor blocker; TFC — thrombolysis in myocardial infarction frame count; cLAD — corrected left anterior descending coronary artery; LCx — left circumflex coronary artery; RCA — right coronary artery

Receiver operating characteristic curve analysis indicated that both sEPCR (area under curve [AUC]: 0.83) and LV GLS (AUC: 0.67) could predict SCF. However, sEPCR > 9.63 ng/mL combined with LV GLS > –14.36% demonstrated better predictive power (AUC: 0.89; sensitivity: 75%; specificity: 91%; Fig. 3).

Discussion

Under investigation was the relationship between the sEPCR level and SCF, and newly demonstrated the following: (1) the plasma sEPCR level was significantly higher in the SCF group than in controls, and was significantly correlated with

Table 2. Comparison of left ventricular function.

	Controls (n = 34)	SCF (n = 28)	P
LV end-diastolic volume [mL]	91.65 ± 22.07	96.51 ± 20.42	0.38
LV ejection fraction [%]	64.85 ± 4.21	64.00 ± 4.06	0.43
LV GLS [%]	–16.97 ± 2.56	–14.89 ± 2.94	**0.004**
LA volume index [mL/m^2]	28.06 ± 4.89	31.22 ± 6.33	0.11
Mitral E [cm/s]	62.79 ± 14.70	61.82 ± 17.30	0.81
Mitral E/A	0.90 ± 0.28	0.95 ± 0.31	0.56
Mitral average e' [cm/s]	9.12 ± 1.67	8.35 ± 1.75	0.09
Mitral average E/e'	7.02 ± 1.85	7.58 ± 2.26	0.29

Values are shown as means ± standard deviation. SCF — slow coronary flow; LV — left ventricle; GLS — global longitudinal strain; LA — left atrium; E — early diastolic flow velocity; A — late diastolic flow velocity; e' — early diastolic annular velocity

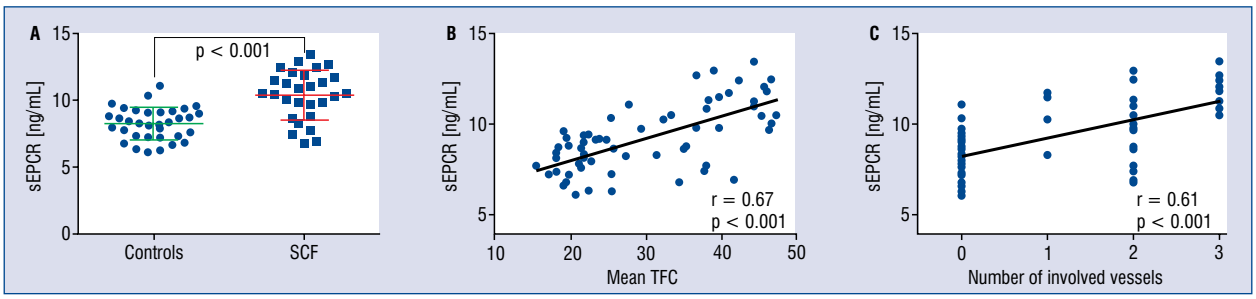

Figure 2. Relationship between soluble endothelial protein C receptor (sEPCR) level and slow coronary flow (SCF). The plasma sEPCR level was significantly higher in patients with SCF than in controls (**A**) and was positively correlated with the mean thrombolysis in myocardial infarction frame count (TFC) (**B**) and number of involved vessels (**C**).

Table 3. Associations between plasma soluble endothelial protein C receptor (sEPCR) level with mean thrombolysis in myocardial infarction frame count (TFC) and number of involved vessels on multivariate analysis.

	Mean TFC	Number of involved vessels
Model 1		
β [95% CI]	0.12 [0.09–0.16]	1.01 [0.68–1.33]
P	**< 0.001**	**< 0.001**
Model 2		
β [95% CI]	0.12 [0.09–0.16]	1.02 [0.68–1.35]
P	**< 0.001**	**< 0.001**
Model 3		
β [95% CI]	0.12 [0.08–0.16]	1.02 [0.68–1.37]
P	**< 0.001**	**< 0.001**
Model 4		
β [95% CI]	0.12 [0.08–0.16]	1.05 [0.67–1.42]
P	**< 0.001**	**< 0.001**

β —regression coefficient; CI — confidence interval. Model 1 — unadjust; Model 2 — adjust for model 1 plus age, sex, body mass index; Model 3 — adjust for model 2 plus systolic blood pressure and smoking history; Model 4 — adjust for model 3 plus fasting blood glucose, triglycerides, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol

the mean TFC and number of involved vessels; (2) sEPCR and LV GLS were independent predictors for SCF; and (3) sEPCR combined with LV GLS can better predict SCF.

Li et al. [17] reported that patients with SCF have increased levels of C-reactive protein and interleukin-6. Moreover, elevations in leukocyte levels, neutrophil to lymphocyte ratio, and myeloperoxidase level in patients with SCF have also been reported [18, 19]. These findings suggest that inflammation might be a major contributing factor in SCF. However, although these inflammatory factors have excellent sensitivity, they lack specificity.

There are two forms of EPCR: membrane-bound EPCR (mEPCR) and sEPCR. On the one hand, mEPCR is bound to the endothelial layer, and can augment protein C activation to play a key role in anticoagulant, anti-inflammatory, and antiapoptotic activity [20]. On the other hand, sEPCR can attenuate mEPCR and inhibit the activities of activated protein C, and plays a major role in procoagulant activity and proinflammatory properties [14]. sEPCR is known to be involved in inflamma-

Table 4. Factors predicting slow coronary flow on multivariate analysis.

	Model 1		Model 2		Model 3	
	OR [95% CI]	P	OR [95% CI]	P	OR [95% CI]	P
Age	1.06 [0.97–1.15]	0.19	1.12 [0.99–1.26]	0.07	1.08 [0.94–1.26]	0.28
Sex	0.37 [0.12–1.13]	0.08	0.45 [0.09–2.22]	0.33	0.27 [0.04–1.90]	0.19
Body mass index	0.94 [0.80–1.10]	0.44	0.95 [0.76–1.19]	0.67	0.84 [0.64–1.11]	0.23
Red blood cell count			1.56 [0.22–11.05]	0.66	2.51 [0.24–26.88]	0.45
sEPCR			2.65 [1.50–4.68]	**0.001**	3.14 [1.55–6.36]	**0.001**
Statin			0.58 [0.13–2.63]	0.48	0.73 [0.13–4.03]	0.72
Mitral average e'					0.79 [0.48–1.31]	0.36
LV GLS					1.44 [1.02–2.04]	**0.04**

Data are presented as odds ratio (OR) and 95% confidence interval [95% CI]. Abbreviations — see Table 2 and 3. Model 1 included age, sex and body mass index; Model 2 included Model 1 plus red blood cell count, sEPCR and statin; Model 3 included Model 2 plus mitral average e' and LV GLS.

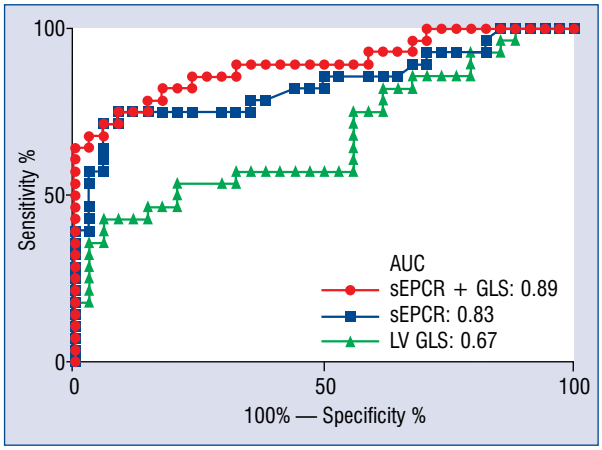

Figure 3. Receiver-operating characteristic curve analysis of soluble endothelial protein C receptor (sEPCR) and left ventricle global longitudinal strain (LV GLS) for predicting slow coronary flow; AUC — area under the curve.

tion, binding to activated neutrophils by neutrophil proteinase 3 and Mac-1 (CD11b/CD18a); activated neutrophils can contribute toward increased local thrombogenic activity, leading to distal embolization and microvascular plugging [13, 21]. The present study results show that patients with SCF have higher plasma sEPCR levels. These findings further strengthen the argument that inflammation plays a significant role in the development of SCF.

In the present study, the plasma sEPCR level had a strong positive correlation with the mean TFC and number of involved vessels. Thus, patients with SCF with greater TFCs and a greater number of involved vessels had higher plasma sEPCR levels. These findings suggest that slower coronary flow and a greater number of involved vessels represent more severe and diffuse inflammation in patients with SCF. Therefore, anti-inflammatory treatment may be considered as a potential approach in treatment for patients with SCF. However, whether such therapies can relieve symptoms and improve survival warrants further prospective investigations with larger sample sizes.

Speckle-tracking echocardiography-derived LV GLS can be considered as a noninvasive approach to detect early subclinical changes in LV global systolic function, even with normal LVEF. Moreover, it has been recommended by the American Society of Echocardiography. As with sEPCR, LV GLS were also found to be an independent predictor of SCF, and sEPCR combined with LV GLS demonstrated better predictive power than for that of sEPCR or LV GLS alone. Thus, the combination of serological testing and imaging examination may provide an inexpensive, simple, and feasible alternative for detecting SCF.

Limitations of the study

The major limitations of the present study are the small sample size and recruitment of patients from a single center. This might limit the generalizability of the present findings. Thus, large-scale, prospective, multicenter studies are warranted to verify and validate the role of sEPCR as a potential biomarker for SCF and confirm the predictive value of sEPCR combined with LV GLS for SCF.

Conclusions

Patients with SCF have an increased plasma sEPCR level and decreased LV GLS. sEPCR may

play an important role in the pathogenesis of SCF and is a potential biomarker for SCF. Moreover, sEPCR combined with LV GLS can better predict SCF. Further studies are warranted to analyze the clinical significance of an increased plasma sEPCR level and investigate the therapeutic efficacy of anti-inflammatory agents.

Funding

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Conflict of interest: None declared

References

1. Tambe AA, Demany MA, Zimmerman HA, et al. Angina pectoris and slow flow velocity of dye in coronary arteries--a new angiographic finding. Am Heart J. 1972; 84(1): 66–71, doi: 10.1016/0002-8703(72)90307-9, indexed in Pubmed: 5080284.
2. Wang X, Nie SP. The coronary slow flow phenomenon: characteristics, mechanisms and implications. Cardiovasc Diagn Ther. 2011; 1(1): 37–43, doi: 10.3978/j.issn.2223-3652.2011.10.01, indexed in Pubmed: 24282683.
3. Mangieri E, Macchiarelli G, Ciavolella M, et al. Slow coronary flow: clinical and histopathological features in patients with otherwise normal epicardial coronary arteries. Cathet Cardiovasc Diagn. 1996; 37(4): 375–381, doi: 10.1002/(SICI)1097-0304(199604)37:4<375::AID-CCD7>3.0.CO;2-8, indexed in Pubmed: 8721694.
4. Beltrame JF, Limaye SB, Horowitz JD. The coronary slow flow phenomenon--a new coronary microvascular disorder. Cardiology. 2002; 97(4): 197–202, doi: 10.1159/000063121, indexed in Pubmed: 12145474.
5. Saya S, Hennebry TA, Lozano P, et al. Coronary slow flow phenomenon and risk for sudden cardiac death due to ventricular arrhythmias: a case report and review of literature. Clin Cardiol. 2008; 31(8): 352–355, doi: 10.1002/clc.20266, indexed in Pubmed: 17957738.
6. Gibson CM, Cannon CP, Daley WL, et al. TIMI frame count: a quantitative method of assessing coronary artery flow. Circulation. 1996; 93(5): 879–888, doi: 10.1161/01.cir.93.5.879, indexed in Pubmed: 8598078.
7. Wang Y, Ma C, Zhang Y, et al. Assessment of left and right ventricular diastolic and systolic functions using two-dimensional speckle-tracking echocardiography in patients with coronary slow-flow phenomenon. PLoS One. 2015; 10(2): e0117979, doi: 10.1371/journal.pone.0117979, indexed in Pubmed: 25706989.
8. Wang X, Geng LL, Nie SP. Coronary slow flow phenomenon: A local or systemic disease? Medical Hypotheses. 2010; 75(3): 334–337, doi: 10.1016/j.mehy.2010.03.016, indexed in Pubmed: 20385447.
9. Chaudhry MA, Smith M, Hanna EB, et al. Diverse spectrum of presentation of coronary slow flow phenomenon: a concise review of the literature. Cardiol Res Pract. 2012; 2012: 383181, doi: 10.1155/2012/383181, indexed in Pubmed: 22645695.
10. Fragasso G, Maranta F. The light of inflammation in the darkness of the coronary slow flow phenomenon. Anadolu Kardiyol Derg. 2013; 13(1): 45–47, doi: 10.5152/akd.2013.030, indexed in Pubmed: 23154121.
11. Li JJ, Xu Bo, Li ZC, et al. Is slow coronary flow associated with inflammation? Med Hypotheses. 2006; 66(3): 504–508, doi: 10.1016/j.mehy.2005.09.028, indexed in Pubmed: 16288834.
12. Yurtdaş M, Yaylali YT, Kaya Y, et al. Increased plasma high-sensitivity C-reactive protein and myeloperoxidase levels may predict ischemia during myocardial perfusion imaging in slow coronary flow. Arch Med Res. 2014; 45(1): 63–69, doi: 10.1016/j.arcmed.2013.10.019, indexed in Pubmed: 24316393.
13. Fink K, Busch HJ, Bourgeois N, et al. Mac-1 directly binds to the endothelial protein C-receptor: a link between the protein C anticoagulant pathway and inflammation? PLoS One. 2013; 8(2): e53103, doi: 10.1371/journal.pone.0053103, indexed in Pubmed: 23408932.
14. Tanalp AC, Oduncu V, Erkol A, et al. Soluble endothelial protein C receptor levels and protein C activity in patients with acute ST-segment elevation myocardial infarction. Coron Artery Dis. 2013; 24(3): 209–216, doi: 10.1097/MCA.0b013e32835e5c45, indexed in Pubmed: 23377316.
15. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015; 28(1): 1–39.e14, doi: 10.1016/j.echo.2014.10.003, indexed in Pubmed: 25559473.
16. Voigt JU, Pedrizzetti G, Lysyansky P, et al. Definitions for a Common Standard for 2D Speckle Tracking Echocardiography: Consensus Document of the EACVI/ASE/Industry Task Force to Standardize Deformation Imaging. J Am Soc Echocardiogr. 2015; 28(2): 183–193, doi: 10.1016/j.echo.2014.11.003.
17. Li JJ, Qin XW, Li ZC, et al. Increased plasma C-reactive protein and interleukin-6 concentrations in patients with slow coronary flow. Clin Chim Acta. 2007; 385(1-2): 43–47, doi: 10.1016/j.cca.2007.05.024, indexed in Pubmed: 17706955.
18. Aksan G, Soylu K, Aksoy O, et al. The relationship between neutrophil gelatinase-associated lipocalin levels and the slow coronary flow phenomenon. Coron Artery Dis. 2014; 25(6): 505––509, doi: 10.1097/MCA.0000000000000121, indexed in Pubmed: 24801557.
19. Yayla Ç, Akboğa MK, Gayretli Yayla K, et al. A novel marker of inflammation in patients with slow coronary flow: lymphocyte-to-monocyte ratio. Biomark Med. 2016; 10(5): 485–493, doi: 10.2217/bmm-2016-0022, indexed in Pubmed: 27089433.
20. Esmon CT. Protein C anticoagulant system--anti-inflammatory effects. Semin Immunopathol. 2012; 34(1): 127–132, doi: 10.1007/s00281-011-0284-6, indexed in Pubmed: 21822632.
21. Kurosawa S, Esmon CT, Stearns-Kurosawa DJ. The soluble endothelial protein C receptor binds to activated neutrophils: involvement of proteinase-3 and CD11b/CD18. J Immunol. 2000; 165(8): 4697–4703, doi: 10.4049/jimmunol.165.8.4697, indexed in Pubmed: 11035113.

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Effects of trimetazidine in patients with severe chronic heart failure with reduced left ventricular ejection fraction: A prospective, randomized, open-label, cross-over study

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Abstract

Background: *Trimetazidine (TMZ) modulates cardiac metabolism, but its use in heart failure remains controversial. The aim of the study was to evaluate the effects of TMZ on exercise capacity, left ventricular ejection fraction (LVEF), mortality, and quality of life in stable patients with heart failure with reduced left ventricular ejection fraction (HFrEF).*

Methods: *Forty-five patients with stable advanced HFrEF treated with optimal medical therapy were randomized in a prospective, single-center, open-label, cross-over study of TMZ (35 mg b.i.d.) on top of standard medical therapy or standard pharmacotherapy for two periods of 30 days and one period of 6 months. Initially and at the end of each period all patients underwent the following: exercise testing, six-minute walk test (6MWT), two-dimensional-echocardiography, and quality of life assessment.*

Results: *The mean age of patients was 58.2 ± 10.6 years. Etiology of HFrEF was ischemic in 66.6% of patients. After 6 months no significant changes were observed in either group with regards to peak VO_2 uptake, 6MWT, LVEF, or quality of life. TMZ had no effect on mortality or cardiovascular events.*

Conclusions: *The additional use of TMZ on top of standard medical therapy in stable advanced HFrEF patients was not associated with significant changes in mortality, exercise capacity, LVEF, or quality of life.* (Cardiol J 2022; 29, 4: 627–636)

Key words: trimetazidine, heart failure, cardiac metabolism, exercise capacity, echocardiography, prognosis

Introduction

Chronic heart failure (CHF) is one of the major challenges for healthcare systems in developed countries. Recently, the prevalence of CHF has increased from 5.7 to 6.5 million in Americans aged ≥ 20 years [1]. Despite improvements in CHF therapy, the prognosis is poor, with 5-year survival reaching 61% in patients with CHF after myocardial infarction [2]. It has been shown that CHF is a syndrome characterized by metabolic abnormalities in the myocardium that lead to energy starvation [3]. Progression of heart failure is associated with the decrease of free fatty acid beta-oxidation

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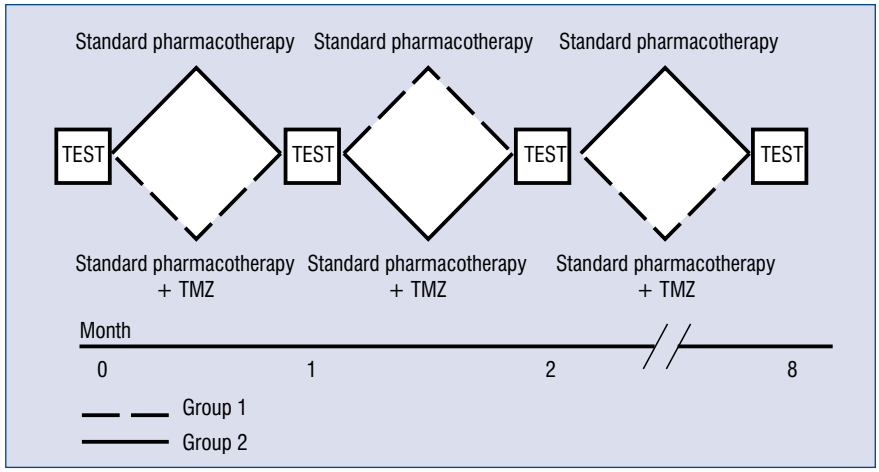

Figure 1. Study design. Standard pharmacotherapy = beta-blocker and angiotensin converting enzyme inhibitor or angiotensin receptor blocker and aldosterone blocker, if not contraindicated; TMZ — trimetazidine.

and promotion of glucose oxidation [3]. Metabolic alterations that occur in CHF mandate the potential use of metabolic modulators.

Trimetazidine (TMZ) has been evaluated in randomized trials and several meta-analyses in CHF patients. It has been observed that TMZ on top of standard pharmacotherapy reduces morbidity and mortality in patients with chronic heart failure with reduced left ventricular ejection fraction (HFrEF) [4–8]. Moreover, some studies suggest that TMZ may reduce the symptoms in New York Heart Association (NYHA) classification and increase the exercise duration in CHF [9, 10]. Some studies also indicate that TMZ may improve cardiopulmonary stress testing results and six-minute walk test (6MWT) distance [11, 12].

The available results of TMZ in CHF patients were derived mainly from retrospective analyses and small studies. There has been only one study assessing the effects of TMZ on cardiopulmonary stress testing and echocardiography in patients with nonischemic CHF [13]. Moreover, the data on beneficial role of TMZ in CHF are conflicting [13]. There are insufficient data from prospective analyses to support the use of TMZ in HFrEF. The aim of the study was to evaluate the effects of TMZ on exercise capacity, left ventricular ejection fraction (LVEF), cardiovascular mortality, and quality of life in CHF patients.

Methods

Patients were randomized to TMZ (35 mg b.i.d.) on top of medical therapy for 1 month followed by medical therapy alone for another month and then TMZ for 6 months (Group 1) and to medical therapy for 1 month followed by additional TMZ for another month and then medical therapy without TMZ for 6 months (Group 2) according to a computer-generated random list (Fig. 1) (Research randomizer, https://www.randomizer.org/). A wash-out period of 1 month was chosen to avoid any potential effect of TMZ on heart function after TMZ cessation. The primary endpoint of the study was change in mean LVEF. Secondary endpoints included changes in exercise capacity and quality of life. Inclusion criteria were as follows: 1) ischemic or nonischemic CHF for at least 1 year prior to randomization; 2) LVEF ≤ 35% evaluated in two-dimensional (2D) echocardiography at the index visit; 3) at least one documented CHF exacerbation within 12 months prior to randomization; 4) stable course of CHF with NYHA class II or III, defined as no exacerbation of CHF symptoms and/or no modifications of treatment for at least 3 months prior to randomization; and 5) age ≥ 18 years. Exclusion criteria were as follows: 1) primary valvular disease; 2) neurological disorders; 3) severe kidney disease, with estimated glomerular filtration rate (eGFR) < 30 mL/kg/min; 4) frailty syndrome; 5) presence of coronary lesions suitable for revascularization; 6) alcohol abuse; and 7) pregnancy.

Initially and during each visit cardiopulmonary stress testing (Medisoft Ergocard, Belgium) and 6MWT were performed in all patients. Symptom severity was assessed with the use of NYHA classification. LVEF was calculated automatically and using biplane Simpson's method in 2D

echocardiography (Vivid 6, GE Healthcare, USA). The MacNew heart disease health-related quality of life questionnaire was used to measure quality of life. Blood samples were also taken for further analyses. Adverse events associated with TMZ were monitored by a safety committee. The study was approved by Local Ethics Committee (NKBBN/346/2012).

Statistical analysis

Continuous variables are presented as mean ± standard deviation and categoric variables as percentages (%). All statistical analyses were performed with STATA, version 13.1 (Statacorp, Texas, USA). Baseline parameters in two groups were compared by two-sample t-test or Mann-Whitney test. In order to assess the effects of TMZ in the study group mixed models with random effects analysis was applied. To investigate the possible treatment, carry-over, sequence, and period effects, the 'pkcross' function in STATA software was used.

The results of the analyses are presented as changes in values of specific parameters at various time points in both groups.

In order to evaluate the impact of TMZ on survival a Kaplan-Meier estimator and log-rank test to make comparisons between groups were applied. The effect of TMZ on survival and cardiovascular (CV) risk (CV hospitalization, implantable cardioverter-defibrillator [ICD] appropriate intervention(s), CV death) was assessed using a discreet-time hazard model. The significance level was set at $p \leq 0.05$.

Power calculation was based on a paired t-test assuming a two-sided level of significance $\alpha = 0.05$, power 1-$\beta = 0.80$. For the effect size calculation we assumed an expected mean LVEF change of 5% and a standard deviation of 8% in changes in LVEF from baseline to 6 months after treatment with the required sample size of n = 20. To compensate for potential drop-out, we increased the total number of patients for this study to n = 45.

Results

Forty-five patients with HFrEF were recruited in a prospective, single-center, open-label, cross-over study. All patients received standard pharmacotherapy for at least 6 months prior to randomization with β-blocker, angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB), aldosteron blocker and diuretics, digoxin, and ivabradine were indicated. The mean age of study group was 58.2 ± 10.6 years. The majority of patients were male (n = 43, 95.6%). There were no significant differences in basal characteristics in both groups except creatinine level (Table 1). Visits number 2, 3, and 4 were completed by 95.3%, 86.7%, and 73.3% of patients, respectively. Five patients were lost to follow-up. One patient was diagnosed with intracranial aneurysm and was referred to surgery, while 3 patients had CHF exacerbation and were not able to complete visit 4. Three patients died due to CV reasons, and 19 patients had 22 CV events (hospitalizations due to CV reasons, ICD intervention due to ventricular tachycardia). One patient experienced gastro-intestinal side effects that were attributed to TMZ.

Exercise capacity

Additional use of TMZ had no effect on peak oxygen consumption (VO_2 peak) and VO_2 at the anaerobic threshold in both groups (Fig. 2A, B). Reduction of slope of minute ventilation versus carbon dioxide production (VE/VCO_2 slope) after 1-month treatment with TMZ in Group 1 was observed (47.2 ± 2.4 vs. 40.9 ± 2.5 at 1 month, $p = 0.07$; Fig. 2C). No effect of TMZ on 6MWT distance was noted in either group (Fig. 2D). There was a significant reduction in NYHA classification at visit 2 in Group 2, and a similar tendency was observed in Group 1 at visit 3 (2.4 ± 0.1 vs. 2.0 ± 0.1, $p < 0.01$ and 2.4 ± 0.1 vs. 2.1 ± 0.1, respectively). In addition, patients in Group 2 at visit 4 experienced a significant increase in symptom severity in NYHA class (2.1 ± 0.1 vs. 2.4 ± 0.1, $p < 0.05$; Fig. 3D).

Echocardiography

Patients in Group 1 at visit 4 had a tendency towards LVEF increase (24.6 ± 1.4% vs. 26.7 ± 1.5%, $p = 0.059$). Moreover, no significant effect of TMZ on left ventricular end-diastolic diameter (LVEDD) and left ventricular end-systolic diameter (LVESD) was found. Patients from Group 2 at visit 2 had significant increase in LVESD (60.0 ± 1.8 mm vs. 64.7±1.9 mm, $p < 0.05$). Interestingly, this effect in Group 2 was not confirmed during the following 6 months of observation on standard pharmacotherapy alone (Fig. 3A–C).

Laboratory evaluation

There were no differences in B-type natriuretic peptide (BNP) level at various time points in both groups. A significant rise in C-reactive protein (CRP) level was observed in patients in Group 1

Table 1. Baseline characteristics.

	Group I (n = 22)	Group II (n = 23)	P
Age [years]	59 ± 9.6	57.3 ± 11.6	NS
Gender, male	22 (48.9%)	21 (46.7%)	NS
CHF duration [years]	3.5 ± 3.13	3.17 ± 1.72	NS
CHF etiology:			
Ischemic	15 (33.3%)	15 (33.3%)	NS
Nonischemic	7 (15.6%)	8 (17.8%)	NS
Concomitant diseases:			
Diabetes	3 (6.7%)	8 (17.8%)	NS
Hypertension	11 (24.4%)	12 (26.7%)	NS
Chronic kidney disease	8 (18.2%)	6 (13.6%)	NS
COPD	3 (6.8%)	2 (4.6%)	NS
CRT	7 (15.9%)	3 (6.8%)	NS
NYHA (mean ± SD)	2.3 ± 0.5	2.4 ± 0.5	NS
NYHA II	16 (35.6%)	13 (28.9%)	NS
NYHA III	6 (13.3%)	10 (22.2%)	NS
BMI [kg/m^2]	27.5 ± 5.1	28.8 ± 3.7	NS
BNP [pg/mL]	694.2 ± 746.8	575.0 ± 502.5	NS
Hemoglobin [g/L]	13.9 ± 1.5	14.5 ± 1.5	NS
Red cell width	15.1 ± 1.7	15.3 ± 2.1	NS
Sodium [mmol/L]	138.5 ± 2.4	137.3 ± 3.2	NS
hs-CRP [mg/L]	2.9 ± 1.9	3.2 ± 2.5	NS
Creatinine [mg/dL]	1.3 ± 0.3	1.1 ± 0.2	< 0.05
eGFR [mL/kg/1.73 m^2]	63.6 ± 18.7	72.3 ± 16.5	NS
Sinus rhythm	10 (24.4%)	16 (39%)	NS
LVEF [%]	23.6 ± 5.9	22.5 ± 6.7	NS
VO2 peak [mL/kg/min]	11.7 ± 3.7	12.3 ± 3.9	NS
VO2 (AT) [mL/kg/min]	8.8 ± 2.6	9.2 ± 1.9	NS
VE/VCO2 slope	46.7 ± 12.9	40.5 ± 10.9	NS
6MWT (m)	392.7 ± 108.4	377.7 ± 91.3	NS
Seattle Heart Failure Model:			
Mortality 1 year [%]	6.4 ± 5.7	6.1 ± 4.9	NS
Mortality 2 years [%]	12.2 ± 10.3	11.7 ± 9.3	NS
Mortality 5 years [%]	28.9 ± 20.3	27.9 ± 19.6	NS
Mean life expectancy [years]	11.6 ± 6.5	11.8 ± 6.6	NS
Beta-blocker	22 (100%)	23 (100%)	NS
MRA	19 (86.4%)	23 (100%)	NS
ACEI	20 (90.9%)	20 (86.9%)	NS
ARB	2 (9.1%)	3 (13.04%)	NS

ACEI — angiotensin converting enzyme inhibitor; ARB — angiotensin receptor blocker; BMI — body mass index; BNP — B-type natriuretic peptide; CHF — chronic heart failure; COPD — chronic obstructive pulmonary disease; CRT — cardiac resynchronization therapy; eGFR — estimated glomerular filtration rate; hs-CRP — high-sensitivity C-reactive protein; LVEF — left ventricular ejection fraction; MRA — mineralocorticoid receptor antagonist; NYHA — New York Heart Association; VO2 peak — peak oxygen uptake; 6MWT — six-minute walk test

after 1-month TMZ treatment (2.5 ± 1.2 mg/L vs. 6.4 ± 1.2 mg/L). Moreover, in Group 1 there was a tendency towards CRP reduction after a 1-month period without TMZ (6.4 ± 1.2 mg/L vs. 3.2 ± 1.3 mg/L, p = 0.071). No effects on CRP were found in a 6-month period with TMZ in Group 1 (Fig. 4A, B).

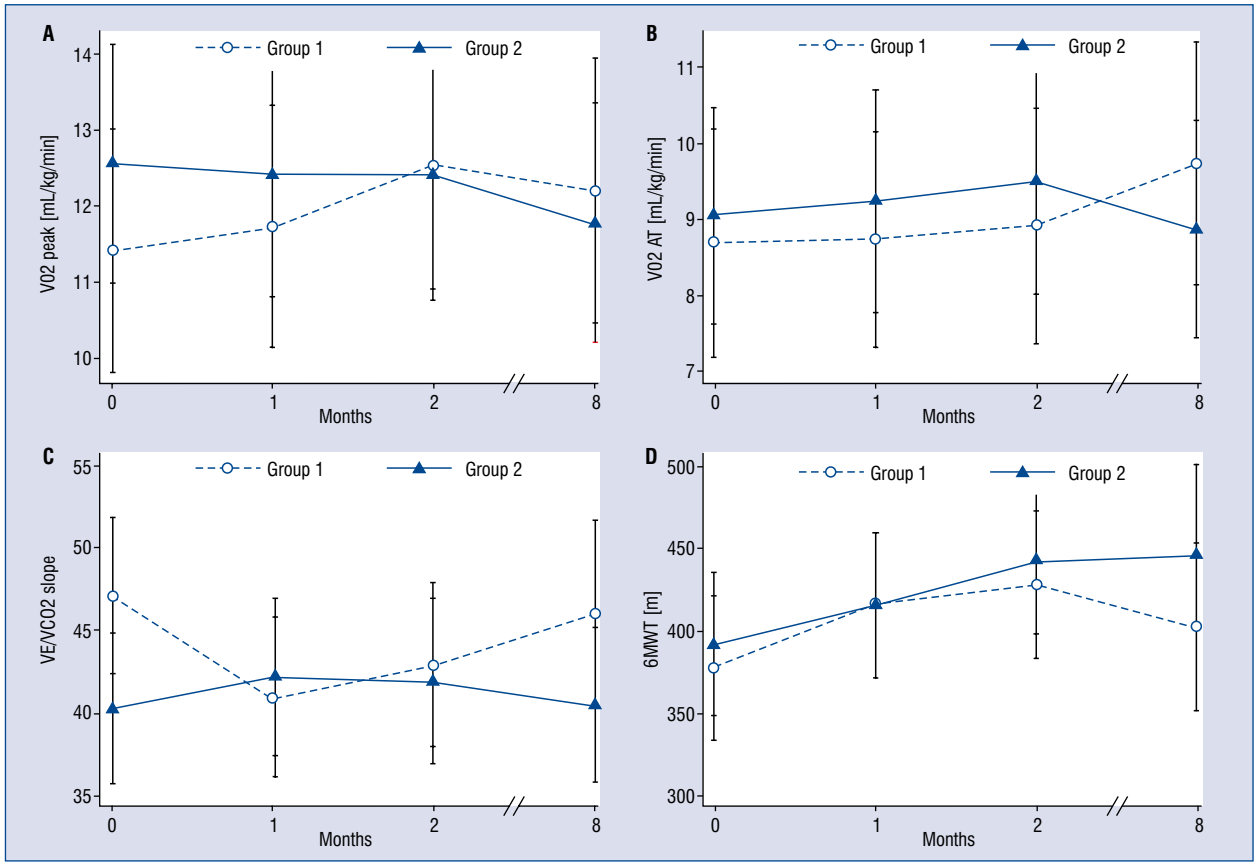

Figure 2. Peak oxygen consumption (VO_2 peak), VO_2 in anaerobic threshold (AT), slope of minute ventilation versus carbon dioxide production (VE/VCO_2 slope), and six-minute walk test (6MWT) values in both groups at various time points.

Mortality and cardiovascular events

No impact on CV mortality of TMZ was observed (odds ratio [OR]: 2.22, 95% confidence interval [CI] 0.2–24.5). In addition, TMZ was not associated with any significant effects on CV events, including CV deaths (OR 0.5, 95% CI 0.2–1.2; Fig. 4C, D).

Health-related quality of life

Patients in Group 1 had significant deterioration of quality of life during 6-month TMZ treatment in MacNew Global (5.5 ± 0.2 points vs. 5.1 ± ± 0.2 points, $p < 0.05$), MacNew Physical (5.0 ± ± 0.2 points vs. 4.6 ± 0.3 points, $p < 0.04$), MacNew Social (5.5 ± 0.2 points vs. 4.9 ± 0.2 points, $p < < 0.05$), and a tendency towards decreased MacNew Emotional (5.9 ± 0.2 points vs. 5.5 ± 0.2 points, $p = 0.066$). Moreover, a significant decrease in MacNew Emotional after 6-month treatment with standard medical therapy was also noted in Group 2 (5.7 ± 0.2 points vs. 5.3 ± 0.2 points, $p < 0.05$; Fig. 5A–D).

Analysis of patients who responded with LVEF increase after TMZ administration

Patients, who experienced an increase in LVEF of at least 5% at any time due to TMZ administration in comparison to other patients had the following initially: significantly lower BNP level (262.3 ± ± 282.7 pg/mL vs. 714.1 ± 653.9 pg/mL; $p < 0.05$), lower 1-year and 2-year mortality (3.6 ± 4.5% vs. 6.9 ± 5.3%; $p < 0.05$; and 6.9 ± 7.9% vs. 13.2 ± ± 9.7%, respectively; $p < 0.05$), and improved predicted life expectancy according to Seattle Heart Failure Model (15.5 ± 7.3 years vs. 10.7 ± 6.0 years; $p < 0.05$). In addition, patients who had LVEF ≥ 5% during TMZ treatment in comparison to other patients had a tendency towards more frequent occurrence of diabetes mellitus or pre-diabetes and arterial hypertension (55.6% vs. 22.2%; $p = 0.063$ and 77.8% vs. 44.4%, $p = 0.077$, respectively), a tendency towards higher hemoglobin level (15.1 ± ± 1.1 g/L vs. 13.9 ± 1.6 g/L, $p = 0.055$), and a tendency towards lower red cell width value (14.2 ± ± 1.4 vs. 15.4 ± 1.9, $p = 0.076$) (Table 2).

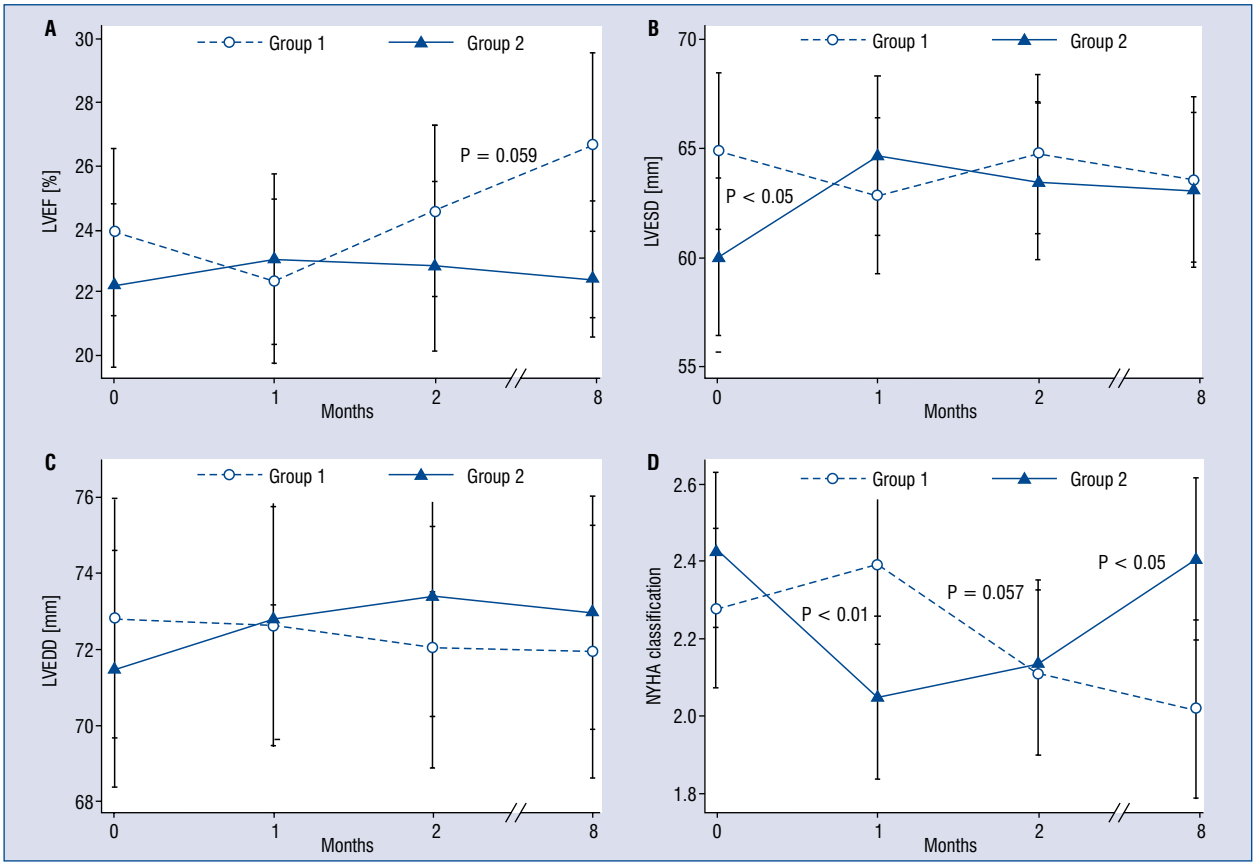

Figure 3. Left ventricular ejection fraction (LVEF), left ventricular end-systolic diameter (LVESD), left ventricular end--diastolic diameter (LVEDD), and New York Heart Association (NYHA) values in both groups at various time points.

Discussion

In this prospective, randomized, open-label study the use of TMZ on top of standard medical therapy in patients with severe HFrEF did not result in any significant improvement in exercise capacity, left ventricle contractility and left ventricular diameters, or quality of life. In addition, TMZ had no impact on CV events and CV mortality.

In recent years many studies have shown that TMZ has led to improvements in exercise capacity in CHF patients. Momen et al. [14] included in their study 98 patients with ischemic HFrEF. A significantly higher percentage of patients in NYHA class I and II was reported in the group that received TMZ for 6 months in comparison to patients receiving placebo (22% vs. 8%, p = 0.03 for NYHA I class and 56% vs. 34%, p = 0.01 for NYHA II class, respectively). Moreover, these effects were also reported in a study in patients with dilated cardiomyopathy, who were randomized to TMZ 20 mg t.i.d. on top of standard CHF pharmacotherapy vs. standard CHF pharmacotherapy [10]. At 3 months, reduced NYHA class (from 2.25 ± 0.5 to 1.85 ± 0.46, p = 0.001) and increased 6MWT distance (from 349.8 ± 89.6 m to 402.1 ± 87.6 m, p = 0.001) were observed in the group that received TMZ. In addition, a meta-analysis by Gao et al. [6] suggested that TMZ on top of standard pharmacotherapy resulted in reduced NYHA classification (weighted mean difference [WMD] 0.41, 95% CI 0.51–0.31, p < 0.01) and increased exercise duration (WMD 30.26 s; 95% CI 8.77–51.75; p < 0.01). Our study results with regards to NYHA class and 6MWT were partly consistent with those of Di Napoli et al. [15], who reported no changes in NYHA class after 6-month treatment with TMZ, but a significant improvement in exercise capacity in patients receiving TMZ was found. Another study included 60 patients with dilated cardiomyopathy, who were randomized to two groups: one received TMZ 35 mg b.i.d. and the other was given placebo. At 6 months, no significant improvements with regards to NYHA class, 6MWT, and VO_2 peak in patients receiving TMZ were noted [13].

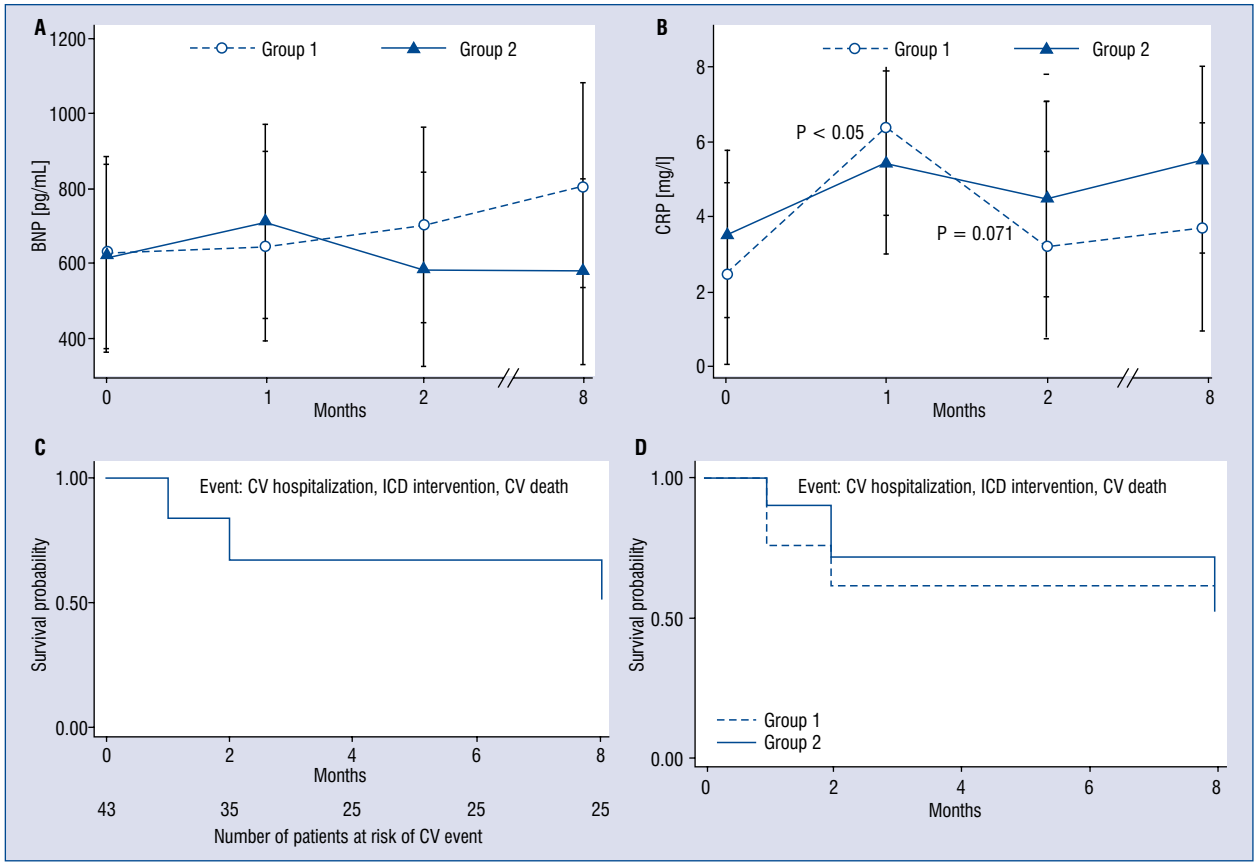

Figure 4. B-type natriuretic peptide (BNP), C-reactive protein (CRP) and cardiovascular (CV) events in both groups at various time points; ICD — implantable cardioverter defibrillator.

We found no significant effect of TMZ on cardiopulmonary stress testing. There are insufficient data in the literature concerning the effects of TMZ on cardiopulmonary stress testing in CHF patients, and 6MWT and total exercise duration (TED) were mainly used to assess the impact of TMZ on exercise capacity. Our study is therefore one of the few observations on TMZ effects with regards to cardiopulmonary stress testing. Zhao et al. [8] in a meta-analysis of studies including subgroup of patients with CHF and coronary artery disease reported a significant increase in TED (WMD of 50.01 [n = 214, 95% CI 44.77–55.25, $p < 0.001$]). Interestingly, TMZ treatment was also associated with significant increase in pVO_2 (n = = 204, WMD 2.41, 95% CI 1.76–3.06, $p < 0.00001$), METS (n = 611, WMD 1.33, 95% CI 0.38–2.28, $p = 0.006$), and 6-MWT (n = 218, WMD 62.46, 95% CI 35.86–89.05, $p < 0.00001$) in patients with coronary disease [8]. In another meta-analysis, however, no significant effect of TMZ on TED was observed [4]. In our study the initially low VO_2 peak values indicate that the study group had an advanced CHF. It cannot be excluded, therefore, that the lack of anticipated beneficial effects of TMZ with regards to cardiopulmonary parameters, 6MWT distance, and NYHA class may be associated with the severity of CHF and irreversible changes that occurred in myocardium.

Our study revealed a tendency towards LVEF increase in patients who received TMZ for 6 months. Moreover, patients who responded with LVEF increase ≥ 5% to TMZ treatment had initially lower BNP level, lower 1-year and 2-year mortality and higher life expectancy according to Seattle Heart Failure Model in comparison to patients without increase in LVEF ≥ 5% during TMZ administration. This observation may indicate that there is a higher probability of LVEF improvement due to TMZ treatment in patients with less advanced CHF. In addition, there was a tendency towards higher incidence of diabetes or pre-diabetes and hypertension in patients with increased LVEF ≥ 5% in comparison to subjects without increased LVEF ≥ 5% on TMZ. The results of studies the concerning TMZ effects in patients with CHF and

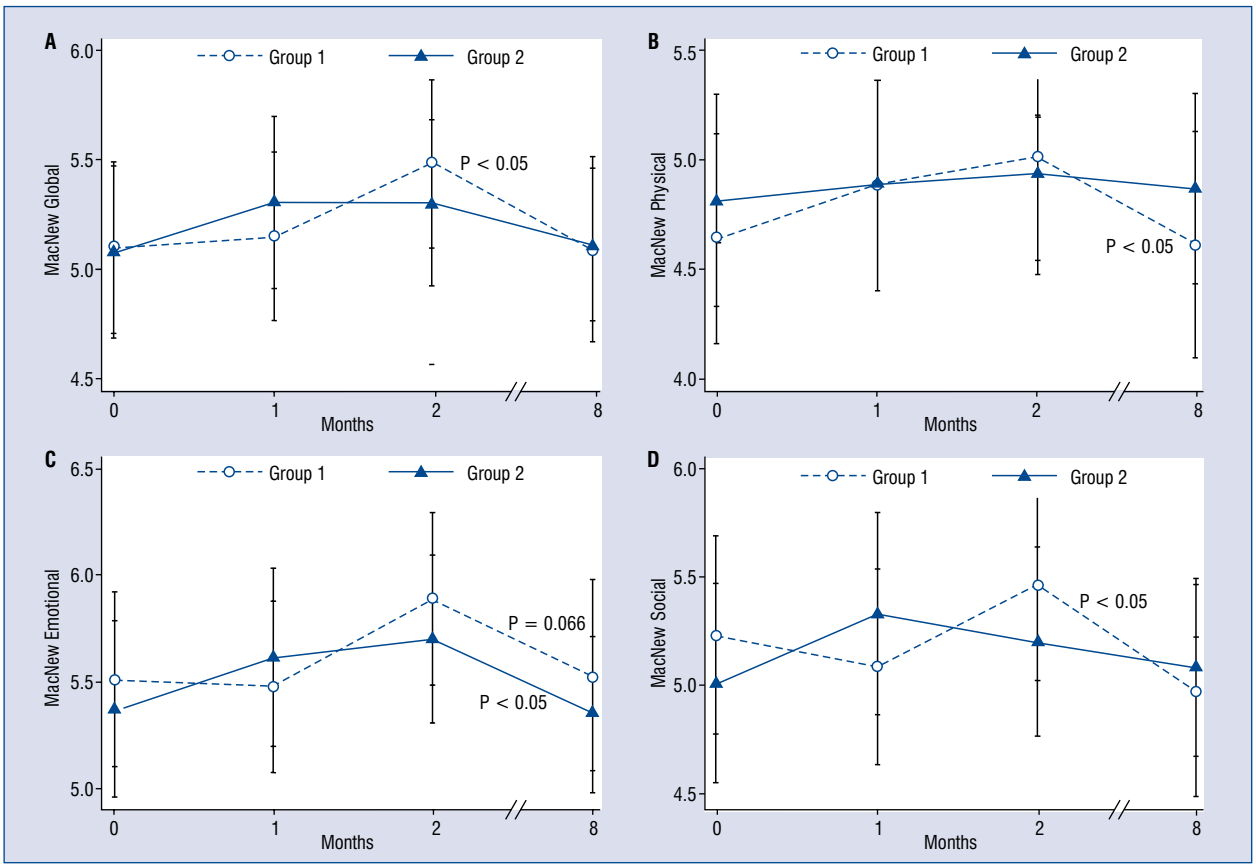

Figure 5. MacNew health-related quality of life.

diabetes are unclear. Thrainsdottir et al. [16] in a small group of ischemic CHF patients with diabetes found no effects of TMZ with regards to LVEF, while Gunes et al. [17] reported a significant correlation between LVEF rise during TMZ treatment and diabetes occurrence ($r = 0.524$, $p < 0.001$).

The data concerning the effects of TMZ on left ventricular function are conflicting. The majority of available studies in CHF reported beneficial effects of TMZ on LVEF. Gao et al. [6] observed that TMZ treatment resulted in LVEF improvements both in ischemic and non-ischemic patients (WMD 7.37%, 95% CI 6.05–8.7, $p < 0.01$ and WMD 8.72%, 95% CI 5.51–11.92, $p < 0.01$, respectively). In addition, TMZ treatment was associated with significant left ventricular end-systolic volume (LVESV) reduction (WMD 10.37 mL; 95% CI 15.46–5.29, $p < 0.01$) [6]. In other meta-analysis, a significant increase in LVEF (WMD 7.29%, 95% CI 6.49–8.09, $p < 0.01$), reduction of LVESV (WMD –17.09 mL, 95% CI –20.15 to –14.04, $p < 0.01$), and reduction of left ventricular end-diastolic volume (WMD –11.24 mL, 95% CI –14.06 to –8.42, $p < 0.01$) was found. On the other hand, there were also studies that did not find any significant effects of TMZ on LVEF in CHF patients [13, 15].

We observed no significant effect of TMZ on CV events and mortality in patients with HFrEF. Meta-analyses and retrospective studies including larger numbers of participants provided data on the beneficial effect of TMZ in terms of mortality reduction. Grajek et al. [7] included 326 patients with CHF and reported significant mortality reduction in patients using TMZ (relative risk [RR] = = 0.283, $p < 0.0001$). Moreover, Fragasso et al. [18] analyzed the effect of TMZ on morbidity and mortality during 3-year follow-up. This study confirmed 11.3% improved global survival ($p = 0.015$) and 8.5% improved survival for CV death ($p = 0.05$) in the TMZ group. Interestingly, the observed rate of hospitalization for CV causes was also reduced by 10.4% at 5 years ($p < 0.0005$) with increased hospitalization-free survival of 7.8 months [18]. Other meta-analysis also corroborated that TMZ had a significant positive effect on mortality (RR 0.29, 95% CI 0.17–0.49, $p < 0.00001$) and resulted

Table 2. Comparison of patients with LVEF ≥ 5% and patients without LVEF ≥ 5% during trimetazidine treatment.

Variable	ΔLVEF ≥ 5% (n = 9)	ΔLVEF < 5% (n = 36)	P
Age [years]	58.4 ± 9.7	58.4 ± 10.9	NS
Male	9 (100%)	34 (94.4%)	NS
CHF duration [years]	3 ± 2.1	3.4 ± 2.6	NS
Coronary artery disease	5 (55.6%)	25 (69.4%)	NS
Diabetes or prediabetes	5 (55.6%)	8 (22.2%)	0.063
Hypertension	7 (77.8%)	16 (44.4%)	0.077
Chronic kidney disease	3 (33.3%)	11 (30.6%)	NS
COPD	0	5 (13.9%)	NS
CRT	1 (11.1%)	9 (25%)	NS
NYHA II	6 (66.7%)	23 (63.9%)	NS
NYHA III	3 (33.3%)	13 (36.1%)	NS
BMI [kg/m^2]	27.1 ± 4.1	27.9 ± 4.5	NS
BNP [pg/mL]	262.3 ± 282.7	714.1 ± 653.9	0.025
Hemoglobin [g/L]	15.1 ± 1.1	13.9 ± 1.6	0.055
Red cell width	14.2 ± 1.4	15.4 ± 1.9	0.076
Sodium [mmol/L]	137.2 ± 3.2	138 ± 2.8	NS
hs-CRP [mg/L]	3.1 ± 2.4	3.1 ± 2.2	NS
Creatinine [mg/dL]	1.1 ± 0.2	1.2 ± 0.3	NS
eGFR [mL/kg/1.73 m^2]	76.8 ± 18.4	65.8 ± 17.4	NS
Initial HR ≤ 75/min	4 (44.4%)	19 (52.8%)	NS
Sinus rhythm	5 (62.5%)	21 (61.8%)	NS
Optimal pharmacotherapy	4 (44.4%)	18 (50%)	NS
LVEF [%]	23.1 ± 6.6	23.1 ± 6.4	NS
LVEDD [mm]	71.3 ± 4.5	72.6 ± 8.9	NS
LVESD [mm]	61.8 ± 5.9	61.6 ± 9.9	NS
Seattle Heart Failure Model:			
Mortality 1 year [%]	3.6 ± 4.5	6.9 ± 5.3	0.03
Mortality 2 years [%]	6.9 ± 7.9	13.2 ± 9.7	0.03
Mortality 5 years [%]	17.9 ± 16.8	31.0 ± 19.7	NS
Mean life expectancy (years)	15.5 ± 7.3	10.7 ± 6.0	0.047

BMI — body mass index; BNP — B-type natriuretic peptide; CHF — chronic heart failure; COPD — chronic obstructive pulmonary disease; CRP — C-reactive protein; CRT — cardiac resynchronization therapy; eGFR — estimated glomerular filtration rate; hs-CRP — high-sensitivity C-reactive protein; HR — heart rate, LVEDD — left ventricular end-diastolic diameter; LVEF — left ventricular ejection fraction; LVESD — left ventricular end-systolic diameter; NYHA — New York Heart Association

in reduction of CV events and hospitalizations (RR 0.42, 95% CI 0.30–0.58, p < 0.00001) [6].

We observed no positive effect of TMZ on quality of life. The deterioration of quality of life in Group 1 after 6-month TMZ treatment may be a result of the patients' disappointment with the lack of anticipated beneficial effects of TMZ. Lack of improvements in exercise capacity and echocardiography may have led to emotional exhaustion. In addition, perceived exercise capacity deterioration during TMZ treatment may explain the significant reduction in the MacNew Physical subscale. The majority of studies evaluating TMZ in CHF reported beneficial effects of TMZ on quality of life with the use of visual-analogue scale [19–21]. Winter et al. [13], on the other hand, reported no beneficial effect of TMZ administration on quality of life.

Limitations of the study

The lack of a double-blind, placebo-controlled study and the relatively small sample size may be considered as limitations of the study. The exercise

capacity assessment, however, was performed by using objective methods such as cardiopulmonary stress testing or 6MWT, and these results were also accompanied by echocardiography and laboratory tests. Moreover, the majority of studies that focused on TMZ in CHF were open-label and largely underpowered.

In addition, the study was conducted in the period 2012–2016. At that time sacubitril/valsartan (ARNI) was not available in Poland. Therefore, we were not able to test TMZ efficacy in patients receiving ARNI.

The study group was statistically efficient due to cross-over methodology. This is one of the few prospective, randomized, cross-over evaluations of TMZ in advanced HFrEF.

Conclusions

Trimetazidine on top of standard pharmacotherapy in CHF patients, irrespective of CHF etiology, did not lead to any beneficial effects on CV events, including mortality, it was not associated with beneficial effect in exercise capacity, and it had no positive effect on quality of life in stable patients with severe HFrEF. Presumably, patients with less advanced stage of CHF may have a better response to TMZ, resulting in left ventricle contractility improvement.

Conflict of interest: None declared

References

1. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. Circulation. 2017; 135(10): e146–e603, doi: 10.1161/CIR.0000000000000485, indexed in Pubmed: 28122885.
2. Gerber Y, Weston SA, Enriquez-Sarano M, et al. Mortality associated with heart failure after myocardial infarction: a contemporary community perspective. Circ Heart Fail. 2016; 9(1): e002460, doi: 10.1161/CIRCHEARTFAILURE.115.002460, indexed in Pubmed: 26699392.
3. Neubauer S. The failing heart--an engine out of fuel. N Engl J Med. 2007; 356(11): 1140–1151, doi: 10.1056/NEJMra063052, indexed in Pubmed: 17360992.
4. Zhou X, Chen J. Is treatment with trimetazidine beneficial in patients with chronic heart failure? PLoS One. 2014; 9(5): e94660, doi: 10.1371/journal.pone.0094660, indexed in Pubmed: 24797235.
5. Zhang L, Lu Y, Jiang H, et al. Additional use of trimetazidine in patients with chronic heart failure: a meta-analysis. J Am Coll Cardiol. 2012; 59(10): 913–922, doi: 10.1016/j.jacc.2011.11.027, indexed in Pubmed: 22381427.
6. Gao D, Ning N, Niu X, et al. Trimetazidine: a meta-analysis of randomised controlled trials in heart failure. Heart. 2011; 97(4): 278–286, doi: 10.1136/hrt.2010.208751, indexed in Pubmed: 21134903.
7. Grajek S, Michalak M. The effect of trimetazidine added to pharmacological treatment on all-cause mortality in patients with systolic heart failure. Cardiology. 2015; 131(1): 22–29, doi: 10.1159/000375288, indexed in Pubmed: 25832112.
8. Zhao Y, Peng L, Luo Y, et al. Trimetazidine improves exercise tolerance in patients with ischemic heart disease: a meta-analysis. Herz. 2016; 41(6): 514–522, doi: 10.1007/s00059-015-4392-2, indexed in Pubmed: 26668006.
9. Sisakian H, Torgomyan A, Barkhudaryan A. The effect of trimetazidine on left ventricular systolic function and physical tolerance in patients with ischaemic cardiomyopathy. Acta Cardiol. 2007; 62(5): 493–499, doi: 10.2143/AC.62.5.2023413, indexed in Pubmed: 17982971.
10. Jatain S, Kapoor A, Sinha A, et al. Metabolic manipulation in dilated cardiomyopathy: Assessing the role of trimetazidine. Indian Heart J. 2016; 68(6): 803–808, doi: 10.1016/j.ihj.2016.04.023, indexed in Pubmed: 27931551.
11. Di Napoli P, Di Giovanni P, Gaeta MA, et al. Trimetazidine and reduction in mortality and hospitalization in patients with ischemic dilated cardiomyopathy: a post hoc analysis of the Villa Pini d'Abruzzo Trimetazidine Trial. J Cardiovasc Pharmacol. 2007; 50(5): 585–589, doi: 10.1097/FJC.0b013e31814fa9cb, indexed in Pubmed: 18030070.
12. Belardinelli R, Lacalaprice F, Faccenda E, et al. Trimetazidine potentiates the effects of exercise training in patients with ischemic cardiomyopathy referred for cardiac rehabilitation. Eur J Cardiovasc Prev Rehabil. 2008; 15(5): 533–540, doi: 10.1097/HJR.0b013e328304feec, indexed in Pubmed: 18797405.
13. Winter JL, Castro PF, Quintana JC, et al. Effects of trimetazidine in nonischemic heart failure: a randomized study. J Card Fail. 2014; 20(3): 149–154, doi: 10.1016/j.cardfail.2014.01.004, indexed in Pubmed: 24412523.
14. Momen A, Ali M, Karmakar PK, et al. Effects of sustained-release trimetazidine on chronically dysfunctional myocardium of ischemic dilated cardiomyopathy: Six months follow-up result. Indian Heart J. 2016; 68(6): 809–815, doi: 10.1016/j.ihj.2016.03.021, indexed in Pubmed: 27931552.
15. Di Napoli P, Di Giovanni P, Gaeta MA, et al. Beneficial effects of trimetazidine treatment on exercise tolerance and B-type natriuretic peptide and troponin T plasma levels in patients with stable ischemic cardiomyopathy. Am Heart J. 2007; 154(3): 602.e1–602.e5, doi: 10.1016/j.ahj.2007.06.033, indexed in Pubmed: 17719313.
16. Thrainsdottir IS, von Bibra H, Malmberg K, et al. Effects of trimetazidine on left ventricular function in patients with type 2 diabetes and heart failure. J Cardiovasc Pharmacol. 2004; 44(1): 101–108, doi: 10.1097/00005344-200407000-00014, indexed in Pubmed: 15175564.
17. Gunes Y, Guntekin U, Tuncer M, et al. Improved left and right ventricular functions with trimetazidine in patients with heart failure: a tissue Doppler study. Heart Vessels. 2009; 24(4): 277–282, doi: 10.1007/s00380-008-1118-x, indexed in Pubmed: 19626400.
18. Fragasso G, Rosano G, Baek SH, et al. Effect of partial fatty acid oxidation inhibition with trimetazidine on mortality and morbidity in heart failure: results from an international multicentre retrospective cohort study. Int J Cardiol. 2013; 163(3): 320–325, doi: 10.1016/j.ijcard.2012.09.123, indexed in Pubmed: 23073279.
19. Fragasso G, Salerno A, Lattuada G, et al. Effect of partial inhibition of fatty acid oxidation by trimetazidine on whole body energy metabolism in patients with chronic heart failure. Heart. 2011; 97(18): 1495–1500, doi: 10.1136/hrt.2011.226332, indexed in Pubmed: 21700755.
20. Marazzi G, Gebara O, Vitale C, et al. Effect of trimetazidine on quality of life in elderly patients with ischemic dilated cardiomyopathy. Adv Ther. 2009; 26(4): 455–461, doi: 10.1007/s12325-009-0024-7, indexed in Pubmed: 19396409.
21. Vitale C, Wajngaten M, Sposato B, et al. Trimetazidine improves left ventricular function and quality of life in elderly patients with coronary artery disease. Eur Heart J. 2004; 25(20): 1814–1821, doi: 10.1016/j.ehj.2004.06.034, indexed in Pubmed: 15474696.

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Lymphopenia and mortality among patients undergoing coronary angiography: Long-term follow-up study

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Abstract

Background: *Lymphopenia is associated with adverse prognosis in chronic disease states that are related to immune dysregulation. We aimed to determine the association between lymphopenia and mortality in patients presenting to coronary angiography and investigate whether elevated red blood cell distribution width (RDW), an established cardiovascular prognostic marker, further refines risk stratification.*

Methods: *Retrospective analysis of patients undergoing coronary angiography for evaluation or treatment of coronary artery disease between 2003 and 2018. Mortality risk associated with relative (1000–1500/μL) or severe (< 1000/μL) lymphopenia was analyzed using adjusted Cox proportional hazards regression models.*

Results: *Overall, 15,179 patients aged 65 ± 12 years underwent coronary angiography. During a median follow-up of 8 years, 4253 patients died. Compared to normal lymphocyte count, the adjusted hazard ratio (HR) for mortality was 1.31 (95% confidence interval [CI] 1.21–1.41) and 1.97 (95% CI 1.75–2.22) for relative and severe lymphopenia, respectively. The increase in mortality associated with severe lymphopenia was significant in patients presenting in the non-acute setting (HR 2.18, 95% CI 1.74–2.73), ST-segment elevation myocardial infarction (STEMI) (HR 1.59, 95% CI 1.15–2.21), or unstable angina/non-STEMI (HR 2.00, 95% CI 1.70–2.34); p-value for interaction 0.626. The association of lymphopenia with mortality remained significant after additional adjustment to RDW. High RDW (> 14.5%) was associated with reduced survival, and it improved the predictive accuracy of lymphocytes count with an increase in Harrell's Concordance statistic from 0.634 (SE = 0.005) to 0.672 (SE = 0.005), p < 0.001.*

Conclusions: *Lymphopenia is associated with increased risk of mortality during long-term follow-up in patients undergoing coronary angiography, regardless of the coronary presentation. High RDW may enhance the predictive ability of lymphopenia.* (Cardiol J 2022; 29, 4: 637–646)

Key words: lymphopenia, coronary angiography, mortality, prognosis, red cell distribution width

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Introduction

Lymphopenia was demonstrated in observational studies to be associated with malignancies, infections, systemic autoimmune diseases, and worse clinical outcomes [1–5]. Early studies have shown that a low relative lymphocyte count, measured as the percentage of total leukocytes, is inversely associated with the risk of cardiovascular disease (CVD) states, particularly heart failure [6–10]. More recent findings further suggest that the measurement of absolute lymphocyte count by itself may risk stratify for mortality in the setting of the general population, especially when associated with other immunohematologic abnormalities [11, 12]. However, the extent to which absolute lymphopenia is associated with survival in patients with coronary artery disease (CAD) is less known [13]. In the current study, we aimed to investigate the association between absolute lymphocyte count and mortality in the real-world clinical practice of patients presenting to coronary angiography for evaluation and treatment of CAD, with both acute and non-acute coronary syndromes (ACS). In addition, we wished to examine whether elevated red blood cell distribution width (RDW), which has emerged as a useful prognostic parameter in CVDs, further refines risk prediction beyond lymphocyte count [14–17].

Methods

Study population

Retrospective analysis of the cardiac catheterization laboratory database at Carmel Medical Center, Haifa, Israel, between January 2000 and December 2018, was performed. Included were patients who were referred to coronary angiography for the assessment and/or treatment of CAD. Only the first angiography of each patient during the study period was included. This analysis was restricted to patients who are members of the Clalit Health Service (CHS), the largest non-for-profit health care provider in Israel, for whom we had full access to outcomes data during follow-up and other variables that were not originally collected at the time of coronary angiography. Patients with elevated lymphocyte count > 5000/μL and patients in whom laboratory values of white blood cells and red cell distribution width (RDW) counts in the year prior to angiography were unavailable were excluded. Final study population included 15,179 patients.

The study population was classified into three groups of angiographic indications: (a) unstable angina pectoris (UAP) or acute non-ST-segment elevation myocardial infarction (NSTEMI), (b) acute ST-segment elevation myocardial infarction (STEMI), and (c) evaluation and/or treatment of CAD with stable clinical presentation (non-ACS). The primary study endpoint was long-term mortality. The cause of death was not consistently available, and therefore we included all-cause and not cardiovascular death. Data on vital status was retrieved from the Ministry of the Interior. Cohort participants were followed up until reaching the occurrence of study outcome or end of follow-up in December 2019, whichever came first.

The study database was approved by Carmel Medical Center Ethics Committee with waiving of the need for individual patient consent due to the retrospective nature of the study.

Study variables and definition of terms

Demographic data, clinical variables, risk factors, and comorbidities were most often prospectively collected from patients' medical files at the time of coronary angiography. Data that was not originally collected were retrieved from computerized database of CHS. The results of all complete blood cell counts performed during the year prior to the date of coronary angiography were retrieved from the CHS laboratory database. We used 1-year median levels to calculate the absolute lymphocyte count, neutrophil-to-lymphocyte ratio (NLR), and RDW, in order to assess their association with mortality. The absolute lymphocyte count was evaluated in three ways: (a) classification to normal lymphocyte count > 1500/μL (reference category); relative lymphopenia 1000–1500/μL; severe lymphopenia < 1000/μL, (b) quintiles of lymphocyte count with the highest quintile serving as reference, and (c) lymphocyte levels included in the model as a continuous variable. For the purpose of the current study, elevated RDW values were defined as > 14.5% [15].

Data analysis

Continuous data are reported as means and standard deviation or median and interquartile range (IQR), and categorical variables as numbers and percentages. One-way ANOVA test was used to compare continuous variables and χ^2 to compare categorical variables. For each lymphocytes group, the number of events and the incidence rates of death per 100 person-years were calculated. Median follow-up was estimated using subjects alive at end of follow-up. Kaplan-Meier curves were used to estimate the long-term cumulative incidence of

death according to the lymphocyte count categories, with comparison between curves performed using the log-rank test. The association between lymphocyte count and mortality over time was evaluated using Cox proportional hazards regression models to estimate the hazard ratio (HR) with 95% confidence interval (CI), using three models adjusting for (a) age and gender, (b) multivariable adjustment including demographics, clinical characteristics, and baseline comorbidities, and (c) with additional adjustment to RDW.

We performed additional sensitivity analyses by repeating the multivariable models using the most adjacent lymphocyte count performed before coronary angiography instead of median 1-year levels, and by further adjusting the multivariable model to NLR, a marker of inflammation that was found to be independently associated with increased risk of mortality in various cardiovascular diseases [18]. Exploratory analysis was performed by examining the association between lymphopenia and all-cause mortality stratified by the acuity of coronary presentation (STEMI, UAP/NSTEMI, non-ACS), and according to age decades, with calculation of p-values for interaction between subgroups.

In order to further assess the association of lymphocyte count with mortality, absolute lymphocyte count was additionally modeled as a continuous variable. First, a linearity assumption on the relationship between lymphocyte count and mortality was tested using a likelihood ratio test, comparing two nested Cox regression models: one including only linear effect and the second including also quadratic and cubic terms, and the non-linearity was detected. Then, for graphical presentation of the association, a smoothed plot of adjusted HR (relative to a reference value of 2000/μL, the overall median count) was estimated along with point-wise 95% CI. For this purpose, the lymphocyte count was flexibly modeled in a Cox regression using a restricted cubic spline function with five knots corresponding to the 5%, 25%, 50%, 75%, and 95% percentiles of lymphocyte count [19]. We repeated the analysis separately for each of the three clinical presentation types: STEMI, UAP/NSTEMI, and non-ACS, and we tested the interaction between presentation type and lymphocyte count.

To assess the predictive accuracy of lymphocyte counts with and without the addition of RDW into a Cox regression model, Harrell's concordance statistic was used, as implemented in the R survival package [20]. Concordance statistic along with standard error (SE) were presented, and further compared using appropriate Z contrast.

The results were considered statistically significant when the two-sided p-value was < 0.05. SPSS statistical software version 20.0, SAS version 9.4 software, and MEDCALC version 16.8.4 were used to perform all statistical analyses.

Results

A total of 15,179 patients undergoing coronary angiography for evaluation and/or treatment of CAD were included in the study. Their mean age was 65 ± 12 years, and 72% were males. Baseline patients' characteristics are shown in Table 1, classified according to lymphocyte category (normal lymphocyte count, relative lymphopenia, and severe lymphopenia). Compared to those with normal lymphocyte count, subjects with lymphopenia were older. The prevalence of chronic kidney disease, hypertension, prior cancer, vascular disease, congestive heart failure, chronic obstructive lung disease, RDW levels, as well as presentation with ACS, increased with the reduction in lymphocyte count. In contrast, lymphopenia was associated with lower rates of hyperlipidemia, obesity, smoking, and Arab ethnicity.

The association between lymphopenia and mortality

Overall, 4253 (28%) patients died during a median follow-up of 8 years (IQR 4–12.2 years). Crude incidence rates of death increased progressively in patients with relative and severe lymphopenia compared to those with normal lymphocyte count, and in an inverse dose-response manner across lymphocyte quintiles: 7.16, 4.12, 3.20, 2.76, and 2.37 events per 100 person-years, respectively (Table 2). Kaplan-Meier plots displaying the distribution of time to mortality by the three lymphocyte categories are presented in Figure 1 (log rank $p < 0.001$). In a multivariable Cox proportional hazard regression analysis, the adjusted HR (95% CI) for long-term mortality was 1.31 (1.21–1.41) for relative lymphopenia and 1.97 (1.75–2.22) for severe lymphopenia, compared to subjects with normal lymphocyte counts (Table 2). In addition, compared to the highest lymphocyte quintile, the HRs for mortality increased in a graded manner (p for trend across quintiles < 0.001) and when analyzed as a continuous variable with an HR (95% CI) of 1.23 (1.17–1.29), $p < 0.001$ for each 100-lymphocyte cell count decrease. However, lymphocyte count appears

Table 1. Patient characteristics according to lymphocyte count.

Variable	Overall population N = 15179	Normal lymphocyte count 1500–5000/μL N = 11875 (78.2%)	Relative lymphopenia 1000–1500/μL N = 2739 (18%)	Severe lymphopenia < 1000/μL N = 565 (3.7%)	P
Age [years]	65 ± 12	64 ± 11	70 ± 11	73±11	< 0.001
Women	4359 (28.7%)	3448 (29%)	778 (28.4%)	133 (23.5%)	0.017
Hypertension	11088 (73%)	8542 (71.9%)	2097 (76.6%)	449 (79.5%)	< 0.001
Hyperlipidemia	11021 (72.6%)	8696 (73.2%)	1945 (71%)	380 (67.3%)	0.001
Smoker	3495 (23%)	3114 (26.2%)	327 (11.9%)	54 (9.6%)	< 0.001
Diabetes	5972 (39.3%)	4703 (39.6%)	1045 (38.2%)	24 (39.6%)	0.370
Ethnicity (Arab)	2801 (18.5%)	2438 (20.5%)	300 (11%)	63 (11.2%)	< 0.001
Obesity	4726 (31.1%)	3929 (33.1%)	672 (24.5%)	125 (22.1%)	< 0.001
Old myocardial infarction	8127 (53.5%)	6163 (51.9%)	1600 (58.4%)	364 (64.4%)	< 0.001
Chronic kidney disease	1651 (10.9%)	1002 (8.4%)	492 (18%)	157 (27.8%)	< 0.001
Creatinine > 1.4 mg/dL	1302 (8.6%)	769 (6.5%)	386 (14.1%)	147 (26%)	< 0.001
PVD	992 (6.5%)	681 (5.7%)	252 (9.2%)	59 (10.4%)	< 0.001
CABG	1725 (11.4%)	1270 (10.7%)	368 (13.4%)	87 (15.4%)	< 0.001
ACS	8077 (53.2%)	6080 (51.2%)	1611 (58.8%)	386 (68.3%)	< 0.001
Cancer	1684 (11.1%)	1042 9 (8.8%)	506 (18.5%)	136 (24.1%)	< 0.001
Heart failure	2843 (10.7%)	1892 (15.9%)	725 (26.5%)	226 (40%)	< 0.001
COPD	1088 (7.2%)	799 (6.7%)	225 (8.2%)	64 (11.3%)	< 0.001
RDW median (IQR)	13.7 (13.2–14.4)	13.6 (13.1–14.3)	14.0 (13.3–14.7)	14.4 (13.6–15.6)	< 0.001
WBC median (IQR)	7.9 (6.6–9.4)	8.1 (7.0–9.6)	6.8 (5.7–8.1)	6.7 (5.4–8.4)	< 0.001

ACS — acute coronary syndrome; CABG — coronary artery bypass graft surgery; COPD — chronic obstructive pulmonary disease; IQR — interquartile range; PVD — peripheral vascular disease; RDW — red cell distribution width; WBC — white blood cells

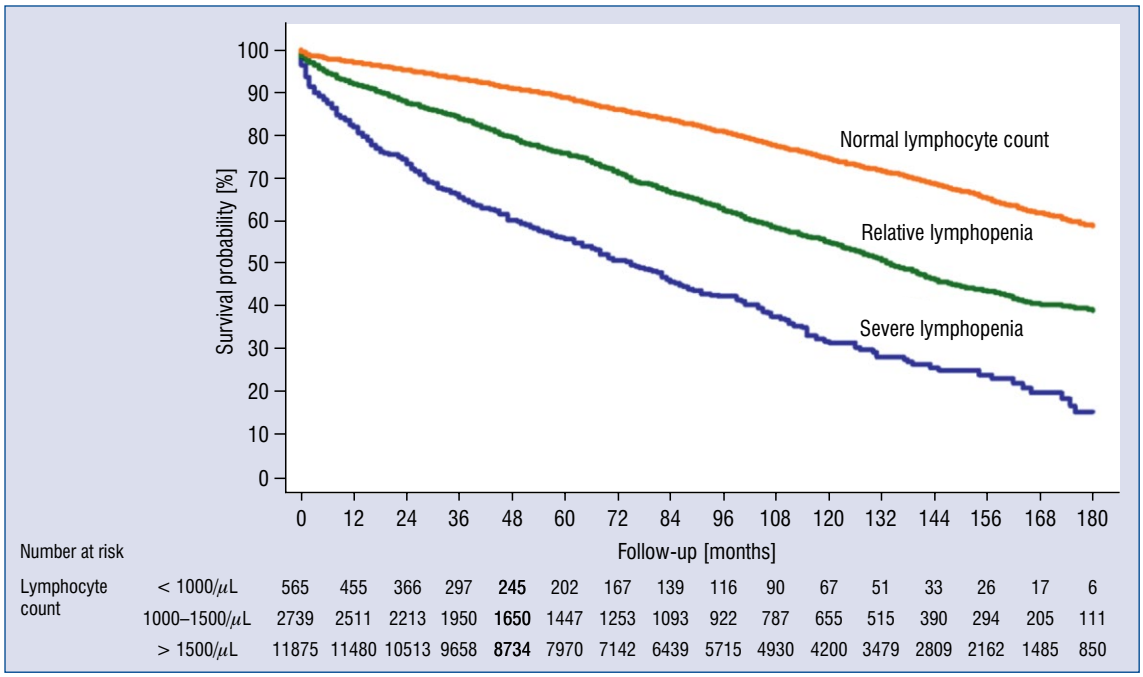

Figure 1. Long-term survival as a function of lymphocyte count.

Table 2. Crude incidence rates and multivariate Cox proportional regression models for the association between lymphocyte counts and long-term mortality.

Lymphocyte count	No. of death/ /patients (%)	Incidence rate per 100 person--years	Age and gender adjusted HR	Multivariable* adjusted HR	Multivariable+ RDW adjusted HR
Three categories					
Normal lymphocyte count	2864/11875 (24.1%)	3.04	Reference	Reference	Reference
Relative lymphopenia	1073/2739 (39.2%)	6.12	1.41 (1.32–1.52) P < 0.001	1.31 (1.21–1.41) P < 0.001	1.26 (1.17–1.36) P < 0.001
Severe lymphopenia	316/565 (55.9%)	12.32	2.47 (2.19–2.78) P < 0.001	1.97 (1.75–2.22) P < 0.001	1.84 (1.63–2.07) P < 0.001
Quintiles					
Q1 < 1495/μL	1304/3031 (43%)	7.16	1.64 (1.49–1.82) P < 0.001	1.47 (1.33–1.63) P < 0.001	1.42 (1.28–1.57) P < 0.001
Q2 1495–1825/μL	885/3034 (29.2%)	4.12	1.13 (1.01–1.25) P = 0.027	1.10 (0.99–1.23) P = 0.071	1.10 (0.99–1.23) P = 0.068
Q3 1826–2175/μL	756/3037 (24.9%)	3.20	1.01 (0.91–1.13) P = 0.846	(0.92–1.14) P = 0.715	(0.92–1.15) P = 0.612
Q4 2276–2650/μL	693/3038 (22.8%)	2.76	0.97 (0.87–1.08) P = 0.515	0.97 (0.87–1.09) P = 0.616	0.98 (0.88–1.09) P = 0.685
Q5 > 2650/μL	615/3039 (20.2%)	2.37	Reference	Reference	Reference
Continuous					
HR is for each decrease of 100/μL in lymphocyte count			1.32 (1.25–1.38) P < 0.001	1.23 (1.17–1.29) P < 0.001	1.20 (1.14–1.26) P < 0.001

HR — hazard ratio; Q — quintile; RDW — red cell distribution width
Normal lymphocyte count > 1500/μL; relative lymphopenia 1000–1500/μL; severe lymphopenia < 1000/μL
*Adjusted for age, gender, ethnicity, hypertension, hyperlipidemia, smoking, diabetes, chronic kidney disease, obesity, cancer, chronic obstructive pulmonary disease, heart failure, peripheral vascular disease, previous myocardial infarction, acute coronary syndrome

to have a nonlinear reversed J-shaped relationship with all-cause mortality (p for nonlinearity < 0.0001). A smoothed plot of adjusted HR (relative to the overall median lymphocyte value of 2000/μL) is presented in Figure 2.

The magnitude of the adjusted HR (95% CI) for death associated with severe lymphopenia decreased with increasing age (p for interaction < 0.001): 3.25 (2.24–4.71) in those aged ≤ 60 years, 2.32 (1.73–3.12) in ages > 60 to 70 years, 1.84 (1.53–2.22) in ages > 70 to 80 years, and 1.75 (1.41–2.17) in patients aged > 80 years (Fig. 3).

We reached similar results performing sensitivity analysis, in which the association with mortality was evaluated using the most recent lymphocyte count tested before angiography instead of the median values of all lymphocyte counts in the year prior to angiography (in this period a median of three tests [IQR 2–5 tests] were available for each patient): multivariable adjusted HR (95% CI) for mortality was 1.65 (1.48–1.83), p < 0.001 for severe lymphopenia and 1.29 (1.20–1.39), p < 0.001 for relative lymphopenia. Moreover, the

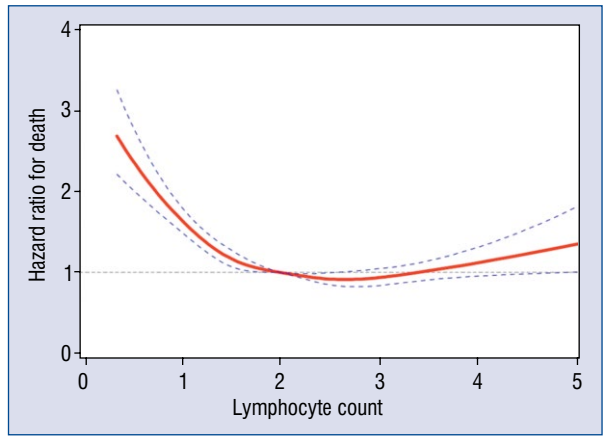

Figure 2. Association between lymphocyte count and adjusted hazard ratio for mortality based on restricted cubic spline model, in the overall population.

significant association of lymphopenia with mortality was retained after the addition of NLR to the multivariable model, both when added as median NLR levels: relative lymphopenia, HR 1.18 (95%

Table 3. Association of lymphocyte count with mortality according to age decades.

Age groups [years]	Normal lymphocyte count Deaths/at risk (%) Adjusted* HR (95% CI) P value	Relative lymphopenia Deaths/at risk (%) Adjusted* HR (95% CI) P value	Severe lymphopenia Deaths/at risk (%) Adjusted* HR (95% CI) P value
≤ 60	492/4632 (10.6%) Reference	87/527 (16.5%) 1.33 (1.05–1.69) P = 0.017	32/78 (41%) 3.25 (2.24–4.71) P < 0.001
> 60 to 70	808/3768 (21.4%) Reference	216/774 (27.9%) 1.45 (1.24–1.69) P < 0.001	50/133 (37.6%) 2.32 (1.73–3.12) P < 0.001
> 70 to 80	1078/2637 (40.9%) Reference	453/942 (48.1%) 1.27 (1.14–1.42) P < 0.001	128/206 (62.1%) 1.84 (1.53–2.22) P < 0.001
> 80	486/838 (58%) Reference	317/496 (63.9%) 1.23 (1.06–1.42) P = 0.006	106/148 (71.6%) 1.75 (1.41–2.17) P < 0.001

CI — confidence interval; HR — hazard ratio
P for interaction between age and lymphocyte count < 0.001
*Adjusted for age, gender, ethnicity, hypertension, hyperlipidemia, smoking, diabetes, chronic kidney disease, obesity, cancer, chronic obstructive pulmonary disease, heart failure, peripheral vascular disease, previous myocardial infarction, acute coronary syndrome

CI 1.10–1.28), p < 0.001 and severe lymphopenia, HR 1.45 (95% CI 1.25–1.69), p < 0.001 or as NLR tertiles: relative lymphopenia, HR 1.11 (95% CI 1.02–1.20), p = 0.015 and severe lymphopenia, HR 1.62 (95% CI 1.42–1.84), p < 0.001.

Lymphopenia and mortality, according to acuity of coronary presentation

Similar to the overall population, crude incidence rates of death and adjusted HRs for mortality were higher in patients with relative lymphopenia, and more so in severe lymphopenia, compared to normal lymphocyte count, in each of the three coronary presentations (non-ACS, UAP/NSTEMI, or STEMI) (Fig. 4). Severe lymphopenia was associated with an adjusted HR (95% CI) for mortality of 2.18 (1.74–2.73) in patients with non-ACS, 2.00 (1.70–2.34) in those with UAP/NSTEMI, and 1.59 (1.15–2.21) in patients presenting with acute STEMI. The p-value for interaction between lymphocyte count and coronary presentation in relation to mortality was non-significant (p = 0.626). **Supplementary Figure S1** further presents a smoothed plot of adjusted HRs for mortality according the coronary presentations based on restricted cubic spline model.

RDW and refinement of mortality risk

Red blood cell distribution width levels were higher in patients with lymphopenia (Table 1). The independent association between lymphopenia and mortality remained significant after further adjustment for RDW in the multivariable model, both in the overall study population (Table 2) and when separately analyzed in the three categories of coronary presentation (model 2 in Fig. 4). Survival probabilities over time in each of the lymphocyte count categories (normal lymphocyte levels, relative lymphopenia, or severe lymphopenia) were lower in patients with high RDW levels > 14.5% compared to those with RDW levels ≤ 14.5% (**Suppl. Fig. S2**). The discrimination ability of the lymphocyte count for mortality was improved with the addition of RDW count; the Harrell's concordance statistic significantly increased from 0.634 (SE = 0.005) to 0.672 (SE = 0.005), p < 0.001 for the change in the concordance statistic. The addition of RDW to lymphocyte count increased the discriminatory capacity for mortality in each of the three coronary presentations (STEMI: from 0.623 [SE = 0.014] to 0.665 [SE = 0.0014]; UAP/NSTEMI: from 0.646 [SE = 0.007] to 0.688 [SE = 0.006]; non-ACS: from 0.610 [SE = 0.008] to 0.653 [SE = 0.008], p < 0.001 for all comparisons).

Discussion

In the present study we analyzed the association between absolute lymphocyte count and long-term mortality in patients presenting to coronary angiography in both the acute and non-acute setting. Lymphopenia, especially when severe, was associated with increased long-term mortality, even after adjusting to chronic disease states such

Table 4. Association of lymphocyte count with mortality, according to coronary presentation.

Coronary presentation	Normal lymphocyte count	Relative lymphopenia	Severe lymphopenia
Non-ACS			
Deaths/at risk (%)	1288/5795 (22.2%)	381/1128 (33.8%)	86/179 (48%)
Model 1	Reference	1.30 (1.15–1.46)	2.18 (1.74–2.73)
		P < 0.001	P < 0.001
Model 2	Reference	1.25 (1.11–1.41)	1.94 (1.55–2.44)
		P < 0.001	P < 0.001
UAP/NSTEMI			
Deaths/at risk (%)	1267/4753 (26.7%)	561/1292 (43.4%)	185/286 (64.7%)
Model 1	Reference	1.39 (1.25–1.54)	2.00 (1.70–2.34)
		P < 0.001	P < 0.001
Model 2	Reference	1.33 (1.20–1.48)	1.81 (1.54–2.12)
		P < 0.001	P < 0.001
STEMI			
Deaths/at risk (%)	309/1327 (23.3%)	131/319 (41.1%)	45/100 (45%)
Model 1	Reference	1.10 (0.89–1.37)	1.59 (1.15–2.21)
		P = 0.370	P = 0.005
Model 2	Reference	1.05 (0.84–1.30)	1.54 (1.11–2.14)
		P = 0.693	P < 0.001

ACS — acute coronary syndrome; NSTEMI — non-ST-segment elevation myocardial infarction; STEMI — ST-segment elevation myocardial infarction; UAP — unstable angina pectoris
P for interaction between lymphocyte count and coronary presentation = 0.626
Model 1: Hazard ratios (95% confidence intervals) adjusted for age, gender, ethnicity, hypertension, hyperlipidemia, smoking, diabetes, chronic kidney disease, obesity, cancer, chronic obstructive pulmonary disease, heart failure, peripheral vascular disease, previous myocardial infarction
Model 2: Hazard ratios (95% confidence intervals) adjusted as model 1 + red cell distribution width

as cancer, heart failure, and vascular diseases, and regardless of the acuity of the coronary presentation. The magnitude of the increase in the risk of death associated with severe lymphopenia was more prominent in younger age groups. Moreover, elevated RDW levels were additively associated with reduced survival, and further refined risk prediction improving the discriminatory capacity of absolute lymphocyte count for mortality.

Lymphopenia is a common hematological finding observed in systemic inflammatory states, malignancies, and autoimmune diseases [1–5]. Early studies have shown that a low relative lymphocyte count, measured as the percentage of total leukocytes, is predictive of adverse outcomes in CVD states, particularly heart failure [6–10]. Relatively few studies have evaluated absolute lymphocyte count as a prognostic biomarker, demonstrating its ability to stratify risk for mortality in the general population [11, 12]. Our findings extend the prognostic value of absolute lymphopenia to patients undergoing coronary angiography for evaluation and/or treatment of CAD with both ACS and non-ACS. The increase in mortality seemed to be less pronounced in patients presenting with acute STEMI, although the interaction between lymphocyte count and coronary presentation was not statistically significant. Only a few analyses of very small-scale have evaluated the prognostic significance of lymphopenia in patients with CAD, including stable clinical presentation [21], unstable angina [22], mechanical complications after myocardial infarction [23], and no-reflow phenomenon [24]. In addition, total white blood cell count was shown to be an independent predictor of death and myocardial infarction in patients with, or at high risk of, CAD, with greater predictive ability provided by high neutrophil or low lymphocyte counts [13]. In the current analysis the increased mortality risk associated with lymphopenia remained significant after adjustment to NLR, demonstrating the independent predictive ability of absolute lymphopenia, which is more intuitive for bedside calculation than NLR.

Several mechanistic pathways may connect lymphopenia to adverse prognosis in CAD. Lymphocytes have been suggested to play a role in the

modulation of the inflammatory response throughout the atherosclerotic process [25]. In response to physiologic stress there is a release of cortisol, catecholamines, and proinflammatory cytokines, which may lead to lymphopenia [26–28]. Activation of the immune system during myocardial ischemia or infarction may be accompanied by an increase of lymphocyte apoptosis, which was shown to be present in atherosclerotic lesions and becomes increasingly frequent with the development and destabilization of the atherosclerotic plaque [29]. Lymphopenia may also be aggravated by redistribution of T cells from the circulation to lymphoid tissues [30]; it may induce compensatory proliferation of antigen-experienced T cells, which could increase the risk of cardiovascular disease [31]. On the other hand, an optimal lymphocyte count may reflect an immune system that is more capable of providing protection against cardiovascular diseases [12].

Lymphocyte count is known to decline with age [32], and this was also observed in the current analysis. Nevertheless, we found a higher relative risk for mortality associated with severe lymphopenia in younger age groups, with a significant interaction between age and lymphocyte count in the context of mortality during long-term follow-up. A similar trend was recently shown by Warny et al. [11] in the setting of the general population; it was suggested that additional factors including poor immune surveillance, blood transfusions, and iatrogenic causes such as medications might contribute to the difference in mortality risk between age groups.

Red blood cell distribution width is a measure of red cell size variability. Its use in the clinical setting is mainly for the differential diagnosis of micro- and normocytic anemias [33]. However, in recent years multiple studies have shown significant associations between RDW and clinical outcomes in a variety of populations, particularly cardiovascular morbidity and mortality [34, 35]. An elevated RDW may reflect chronic inflammation, ultimately leading to altered iron homeostasis and erythropoietin resistance. Associations between RDW, inflammatory markers, and impaired iron mobilization were demonstrated in heart failure [36, 37]. In the United Kingdom Biobank study, examining healthy volunteers, the incidence of CAD and all-cause mortality began to increase with RDW values > 13% and was the highest (3-fold higher) in participants with RDW value > 15% [38]. A meta-analysis of 21 studies concluded that high RDW levels are associated with increased risk of mortality and cardiovascular events also in patients with established CAD [39]. Zidar et al. [12] recently demonstrated in the setting of the general population that the risks associated with abnormal immunohematologic parameters including lymphopenia, RDW, and C-reactive protein may be synergistic with each other. Our findings are in line with these results, demonstrating improved risk prediction in patients with CAD when both lymphocytes and RDW levels are taken into account.

Strengths and limitations

Strengths of the current analysis include the large number of CAD patients investigated with both acute and non-acute presentations and the long follow-up period. In addition, the classification of lymphocytes as both categorical and continuous variables may have reduced potential bias. Several limitations should also be noted. The study does not prove a causal relation between lymphopenia and mortality, due to its retrospective observational design. In addition, although significant adjustment was made for confounding variables including malignancies, heart failure, and other vascular diseases, we cannot exclude residual confounding. We did not account for infectious causes or autoimmune diseases that are known to be associated with inflammatory markers. Parameters of immune activation such as C-reactive protein levels were not available, although we did adjust our data to NLR, an indicator of inflammation and oxidative stress that did not neutralize the independent association of lymphopenia with mortality. Moreover, we used median levels of all lymphocyte counts in the year prior to angiography, and therefore our results may not reflect the association of lymphocyte count during ACS with mortality. However, we did perform sensitivity analysis using the most recent lymphocyte count tested before angiography, achieving similar results. Finally, causes of death were not available, and therefore we could not evaluate the association of lymphopenia with specific causes of death.

Conclusions

Absolute lymphopenia, especially when severe, may identify patients presenting to coronary angiography who are at higher risk for mortality during long-term follow-up. This association, observed in both acute and non-acute coronary presentations, was more significant in younger age groups and was aggravated in patients with elevated RDW levels enhancing the predictive

ability of lymphopenia. Routinely obtained immunohematologic blood indices have potential utility in clinical practice as biomarkers for long-term risk prediction in patients with CAD.

Conflict of interest: None declared

References

1. Fogar P, Sperti C, Basso D, et al. Decreased total lymphocyte counts in pancreatic cancer: an index of adverse outcome. Pancreas. 2006; 32(1): 22–28, doi: 10.1097/01.mpa.0000188305.90290.50, indexed in Pubmed: 16340740.
2. Ray-Coquard I, Cropet C, Van Glabbeke M, et al. Lymphopenia as a prognostic factor for overall survival in advanced carcinomas, sarcomas, and lymphomas. Cancer Res. 2009; 69(13): 5383–5391, doi: 10.1158/0008-5472.CAN-08-3845, indexed in Pubmed: 19549917.
3. Saroha S, Uzzo RG, Plimack ER, et al. Lymphopenia is an independent predictor of inferior outcome in clear cell renal carcinoma. J Urol. 2013; 189(2): 454–461, doi: 10.1016/j.juro.2012.09.166, indexed in Pubmed: 23041457.
4. Hepburn AL, Narat S, Mason JC. The management of peripheral blood cytopenias in systemic lupus erythematosus. Rheumatology (Oxford). 2010; 49(12): 2243–2254, doi: 10.1093/rheumatology/keq269, indexed in Pubmed: 20823093.
5. Warny M, Helby J, Nordestgaard BG, et al. Lymphopenia and risk of infection and infection-related death in 98,344 individuals from a prospective Danish population-based study. PLoS Med. 2018; 15(11): e1002685, doi: 10.1371/journal.pmed.1002685, indexed in Pubmed: 30383787.
6. Rudiger A, Burckhardt OA, Harpes P, et al. The relative lymphocyte count on hospital admission is a risk factor for long-term mortality in patients with acute heart failure. Am J Emerg Med. 2006; 24(4): 451–454, doi: 10.1016/j.ajem.2005.10.010, indexed in Pubmed: 16787804.
7. Ommen SR, Hodge DO, Rodeheffer RJ, et al. Predictive power of the relative lymphocyte concentration in patients with advanced heart failure. Circulation. 1998; 97(1): 19–22, doi: 10.1161/01.cir.97.1.19, indexed in Pubmed: 9443426.
8. Acanfora D, Gheorghiade M, Trojano L, et al. Relative lymphocyte count: a prognostic indicator of mortality in elderly patients with congestive heart failure. Am Heart J. 2001; 142(1): 167–173, doi: 10.1067/mhj.2001.115792, indexed in Pubmed: 11431674.
9. Huehnergarth KV, Mozaffarian D, Sullivan MD, et al. Usefulness of relative lymphocyte count as an independent predictor of death/urgent transplant in heart failure. Am J Cardiol. 2005; 95(12): 1492–1495, doi: 10.1016/j.amjcard.2005.02.022, indexed in Pubmed: 15950581.
10. Vaduganathan M, Ambrosy AP, Greene SJ, et al. Predictive value of low relative lymphocyte count in patients hospitalized for heart failure with reduced ejection fraction: insights from the EVEREST trial. Circ Heart Fail. 2012; 5(6): 750–758, doi: 10.1161/CIRCHEARTFAILURE.112.970525, indexed in Pubmed: 23051949.
11. Warny M, Helby J, Nordestgaard BG, et al. Incidental lymphopenia and mortality: a prospective cohort study. CMAJ. 2020; 192(2): E25–E33, doi: 10.1503/cmaj.191024, indexed in Pubmed: 31932337.
12. Zidar DA, Al-Kindi SG, Liu Y, et al. Association of lymphopenia with risk of mortality among adults in the US general population. JAMA Netw Open. 2019; 2(12): e1916526, doi: 10.1001/jamanetworkopen.2019.16526, indexed in Pubmed: 31790569.
13. Horne BD, Anderson JL, John JM, et al. Which white blood cell subtypes predict increased cardiovascular risk? J Am Coll Cardiol. 2005; 45(10): 1638–1643, doi: 10.1016/j.jacc.2005.02.054, indexed in Pubmed: 15893180.
14. Al-Najjar Y, Goode KM, Zhang J, et al. Red cell distribution width: an inexpensive and powerful prognostic marker in heart failure. Eur J Heart Fail. 2009; 11(12): 1155–1162, doi: 10.1093/eurjhf/hfp147, indexed in Pubmed: 19926599.
15. Saliba W, Barnett-Griness O, Rennert G. Red cell distribution width and all-cause mortality in patients with atrial fibrillation: A cohort study. J Arrhythm. 2017; 33(1): 56–62, doi: 10.1016/j.joa.2016.06.001, indexed in Pubmed: 28217230.
16. Dabbah S, Hammerman H, Markiewicz W, et al. Relation between red cell distribution width and clinical outcomes after acute myocardial infarction. Am J Cardiol. 2010; 105: 312–317.
17. Arbel Y, Weitzman D, Raz R, et al. Red blood cell distribution width and the risk of cardiovascular morbidity and all-cause mortality. A population-based study. Thromb Haemost. 2014; 111(2): 300–307, doi: 10.1160/TH13-07-0567, indexed in Pubmed: 24173039.
18. Bhat T, Teli S, Rijal J, et al. Neutrophil to lymphocyte ratio and cardiovascular diseases: a review. Expert Rev Cardiovasc Ther. 2013; 11(1): 55–59, doi: 10.1586/erc.12.159, indexed in Pubmed: 23259445.
19. Heinzl H, Kaider A. Gaining more flexibility in Cox proportional hazards regression models with cubic spline functions. Comput Methods Programs Biomed. 1997; 54(3): 201–208, doi: 10.1016/s0169-2607(97)00043-6, indexed in Pubmed: 9421665.
20. Therneau T (2020). A Package for Survival Analysis in R. R package version 3.1-11. https://CRAN.R-project.org/package=survival.
21. Ommen SR, Gibbons RJ, Hodge DO, et al. Usefulness of the lymphocyte concentration as a prognostic marker in coronary artery disease. Am J Cardiol. 1997; 79(6): 812–814, doi: 10.1016/s0002-9149(96)00878-8, indexed in Pubmed: 9070569.
22. Zouridakis EG, Garcia-Moll X, Kaski JC. Usefulness of the blood lymphocyte count in predicting recurrent instability and death in patients with unstable angina pectoris. Am J Cardiol. 2000; 86(4): 449–451, doi: 10.1016/s0002-9149(00)00963-2, indexed in Pubmed: 10946041.
23. Widmer A, Linka AZ, Attenhofer Jost CH, et al. Mechanical complications after myocardial infarction reliably predicted using C-reactive protein levels and lymphocytopenia. Cardiology. 2003; 99(1): 25–31, doi: 10.1159/000068448, indexed in Pubmed: 12589119.
24. Dogan NB, Ozpelit E, Akdeniz S, et al. Simple clinical risk score for no-reflow prediction in patients undergoing primary Percutaneous Coronary Intervention with acute STEMI. Pak J Med Sci. 2015; 31(3): 576–581, doi: 10.12669/pjms.313.7484, indexed in Pubmed: 26150847.
25. Núñez J, Miñana G, Bodí V, et al. Low lymphocyte count and cardiovascular diseases. Curr Med Chem. 2011; 18(21): 3226–3233, doi: 10.2174/092986711796391633, indexed in Pubmed: 21671854.
26. Thomson SP, McMahon LJ, Nugent CA. Endogenous cortisol: a regulator of the number of lymphocytes in peripheral blood. Clin Immunol Immunopathol. 1980; 17(4): 506–514, doi: 10.1016/0090-1229(80)90146-4, indexed in Pubmed: 7192197.

27. Ulich TR, Keys M, Ni RX, et al. The contributions of adrenal hormones, hemodynamic factors, and the endotoxin-related stress reaction to stable prostaglandin analog-induced peripheral lymphopenia and neutrophilia. J Leukoc Biol. 1988; 43(1): 5–10, doi: 10.1002/jlb.43.1.5, indexed in Pubmed: 3275734.
28. Gordon AS. Some aspects of hormonal influences upon the leukocytes. Ann N Y Acad Sci. 1955; 59(5): 907–927, doi: 10.1111/j.1749-6632.1955.tb45990.x, indexed in Pubmed: 13259358.
29. Hofmann U, Frantz S. Role of lymphocytes in myocardial injury, healing, and remodeling after myocardial infarction. Circ Res. 2015; 116(2): 354–367, doi: 10.1161/CIRCRESAHA.116.304072, indexed in Pubmed: 25593279.
30. Toft P, Svendsen P, Tønnesen E, et al. Redistribution of lymphocytes after major surgical stress. Acta Anaesthesiol Scand. 1993; 37(3): 245–249, doi: 10.1111/j.1399-6576.1993.tb03708.x, indexed in Pubmed: 8517098.
31. Le Campion A, Gagnerault MC, Auffray C, et al. Lymphopenia-induced spontaneous T-cell proliferation as a cofactor for autoimmune disease development. Blood. 2009; 114(9): 1784–1793, doi: 10.1182/blood-2008-12-192120, indexed in Pubmed: 19561321.
32. Linton PJ, Dorshkind K. Age-related changes in lymphocyte development and function. Nat Immunol. 2004; 5(2): 133–139, doi: 10.1038/ni1033, indexed in Pubmed: 14749784.
33. Bessman JD, Gilmer PR, Gardner FH. Improved classification of anemias by MCV and RDW. Am J Clin Pathol. 1983; 80(3): 322—326, doi: 10.1093/ajcp/80.3.322, indexed in Pubmed: 6881096.
34. Fava C, Cattazzo F, Hu ZD, et al. The role of red blood cell distribution width (RDW) in cardiovascular risk assessment: useful or hype? Ann Transl Med. 2019; 7: 581.
35. Salvagno GL, Sanchis-Gomar F, Picanza A, et al. Red blood cell distribution width: A simple parameter with multiple clinical applications. Crit Rev Clin Lab Sci. 2015; 52(2): 86–105, doi: 10.3109/10408363.2014.992064, indexed in Pubmed: 25535770.
36. Allen LA, Felker GM, Mehra MR, et al. Validation and potential mechanisms of red cell distribution width as a prognostic marker in heart failure. J Card Fail. 2010; 16: 230–238.
37. Förhécz Z, Gombos T, Borgulya G, et al. Red cell distribution width in heart failure: prediction of clinical events and relationship with markers of ineffective erythropoiesis, inflammation, renal function, and nutritional state. Am Heart J. 2009; 158(4): 659–666, doi: 10.1016/j.ahj.2009.07.024, indexed in Pubmed: 19781428.
38. Pilling LC, Atkins JL, Kuchel GA, et al. Red cell distribution width and common disease onsets in 240,477 healthy volunteers followed for up to 9 years. PLoS One. 2018; 13(9): e0203504, doi: 10.1371/journal.pone.0203504, indexed in Pubmed: 30212481.
39. Su C, Liao LZ, Song Y, et al. The role of red blood cell distribution width in mortality and cardiovascular risk among patients with coronary artery diseases: a systematic review and meta-analysis. J Thorac Dis. 2014; 6: 1429–1440.

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ST-elevation versus non-ST-elevation myocardial infarction after combined use of statin with renin–angiotensin system inhibitor: Data from the Korea Acute Myocardial Infarction Registry

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Abstract

Background: *Limited data are available comparing the combined effects of statins and renin–angiotensin system inhibitor (RASI) between patients with ST-segment elevation myocardial infarction (STEMI) and those with non-STEMI (NSTEMI). We compared the effects of statins combined with RASI in STEMI and NSTEMI patients after stent implantation during a 2-year follow-up period.*

Methods: *A total of 21,890 acute myocardial infarction (AMI) patients who underwent successful stent implantation and who received statins with RASI were enrolled. They were separated into the STEMI group (n = 12,490) and the NSTEMI group (n = 9400). The major clinical endpoint was the occurrence of major adverse cardiac events (MACEs) defined as all-cause death, recurrent myocardial infarction (Re-MI), and any repeat revascularization.*

Results: *Two propensity score-matched groups (5891 pairs, n = 11,782, C-statistic = 0.821) were generated. Even though the cumulative incidences of MACE, Re-MI, total repeat revascularization were similar between the two groups, the cumulative incidences of all-cause death (hazard ratio [HR] 1.407; 95% confidence interval [CI] 1.106–1.790; p = 0.005) and cardiac death (HR 1.311; 95% CI 0.983–1.749; p = 0.046) were significantly higher in the NSTEMI group.*

Conclusions: *In this study, statin with RASI combination therapy was more beneficial to the STEMI patients than to the NSTEMI patients in reducing all-cause death and cardiac death.* (Cardiol J 2022; 29, 4: 647–659)

Key words: non-ST-segment elevation myocardial infarction, renin–angiotensin system, statin, ST-segment elevation myocardial infarction

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Introduction

Intensive statin therapy has produced greater reductions in the risks of cardiovascular death, non-fatal myocardial infarction (MI), ischemic stroke, and coronary revascularization than less intensive statin therapy in patients with acute coronary syndrome [1–3]. Moreover, stains are recommended for all acute MI (AMI) patients, regardless of cholesterol concentration at presentation [4–6]. More recently, Kim et al. [7] reported that statin therapy was more effective in reducing the cumulative risks of major adverse cardiac events (MACEs), all-cause death, and target vessel revascularization (TVR) in a ST-segment elevation myocardial infarction (STEMI) group than in a non-STEMI (NSTEMI) group in Korean patients with AMI after successful drug-eluting stent (DES) implantation. Current guidelines recommended that angiotensin-converting enzyme inhibitors (ACEIs) should be prescribed within the first 24 hours for all AMI patients with left ventricular (LV) systolic dysfunction, unless contraindicated. Furthermore, the patients who do not tolerate ACEIs should be given angiotensin receptor blockers (ARBs) [5, 6, 8, 9]. A previous report [10] showed that the mortality reduction capability of renin–angiotensin system inhibitors (RASIs) was more prominent in STEMI patients compared with NSTEMI patients. Hence, combination therapy with statins and RASIs may be an important treatment modality in patients with hypertension, hypercholesterolemia, diabetes, metabolic syndrome, or obesity, to reduce or prevent cardiovascular disease [11, 12]. Nevertheless, the data concerning long-term clinical outcomes of statin with RASI combination therapy in patients with STEMI and NSTEMI after stent implantation are limited. Therefore, we compared the effects of statins combined with RASI in STEMI and NSTEMI patients after successful percutaneous coronary intervention (PCI) over a 2-year follow-up period.

Methods

Study design and population

The study population of this non-randomized, multicenter, observational, retrospective cohort study was obtained from the Korea AMI Registry (KAMIR). KAMIR was designed to capture real-world treatment practices and the short- and long-term outcomes of AMI patients; to evaluate the current epidemiology and analyze the prognostic factors of AMI; and to improve the long-term prognosis of the individual patients. Eligible patients were ≥ 18 years of age at the time of hospital admission [13]. A total of 45,863 AMI patients who underwent successful stent implantation from November 2005 to June 2015 were evaluated. This study protocol was approved by the ethics committee at each participating center, and informed consent was obtained from all individual participants prior to enrollment. These processes were conducted according to the ethical guidelines of the 1975 Declaration of Helsinki. The exclusion criteria were as follows: (1) incomplete laboratory results (n = 10,506, 22.9%); (2) lost to follow-up (n = 2562, 5.6%); (3) statin and RASI had not been prescribed (n = 2392, 5.2%); (4) statin only prescribed (n = 4409, 9.6%); and (5) RASI only prescribed (n = 4185, 9.1%). Finally, a total of 21,890 AMI patients who underwent successful stent implantation and who had been prescribed both statin and RASI were enrolled. Among these, 12,490 (57.1%) were STEMI patients and the remaining 9400 (42.9%) were NSTEMI patients (Fig. 1). Any information concerning adverse events in these 21,890 participants with AMI including the time intervals and the types of events after the index PCI, which occurred during the follow-up period, was monitored at the outpatient clinic, by phone calls, or by reviewing the patients' charts at each participating center, and all participants completed a 2-year clinical follow-up [14].

PCI procedure and medical treatment

Diagnostic coronary angiography and PCI were performed after an administration of unfractionated heparin (50–100 IU/kg) according to standard technique [15]. Before PCI, all patients received loading doses of acetylsalicylic acid (ASA) 200–300 mg and clopidogrel 300–600 mg; alternatively, ticagrelor 180 mg or prasugrel 60 mg was administered. Moreover, dual antiplatelet therapy (DAPT), such as a daily dose of 100 mg ASA and 75 mg clopidogrel or ticagrelor 90 mg twice daily or prasugrel 5–10 mg/day, was recommended for more than 12 months after PCI. The choice of triple antiplatelet therapy (cilostazol 100 mg twice daily added to DAPT) was determined by the discretion of the individual operators [10]. The statins and their doses were as follows: 10–40 mg of atorvastatin, 5–10 mg of rosuvastatin, 2–4 mg of pitavastatin, 10–40 mg of simvastatin, 10–40 mg of pravastatin, 80 mg fluvastatin, and 50–100 mg lovastatin per day. The RASI used and their doses were as follows: 12.5–75 mg of captopril, 2.5–10 mg of ramipril, 2–8 mg of perindopril, 1.25–5 mg of cilazapril, 5–10 mg of imidapril, 7.5–15 mg of moexipril, 2.5–10 mg of

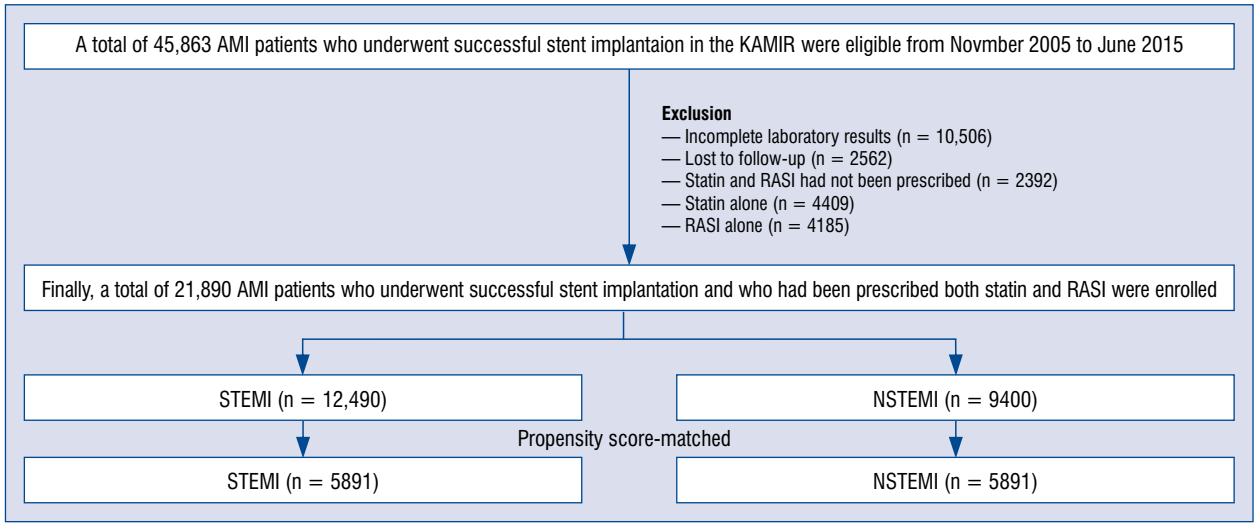

Figure 1. Flow chart; AMI — acute myocardial infarction; KAMIR — Korea Acute Myocardial Infarction Registry; NSTEMI — non-ST-segment elevation myocardial infarction; RASI — renin–angiotensin system inhibitor; STEMI — ST-segment elevation myocardial infarction.

enalapril, 5–10 mg of lisinopril, 10 mg of fosinopril, 3.75–7.5 mg of zofenopril, 25–100 mg of losartan, 150–300 mg of irbesartan, 40–160 mg of valsartan, 40–80 mg of telmisartan, 10–20 mg of olmesartan, 4–32 mg of candesartan, 600 mg of eprosartan, and 30–120 mg of fimasartan per day.

Study definitions and clinical outcomes

According to the current guidelines [6, 8], STEMI was defined as follows: ongoing chest pain and admission electrocardiogram showing ST-segment elevation in at least 2 contiguous leads of ≥ 2 mm (0.2 mV) in men or ≥ 1.5 mm (0.15 mV) in women in leads V2–V3 and/or of ≥ 1 mm (0.1 mV) in other contiguous chest leads or the limb leads; or new-onset left bundle branch block [8]. NSTEMI was defined as follows: absence of persistent ST-segment elevation with increased cardiac biomarkers and appropriate clinical context [6]. In the present study, early invasive treatment strategy was defined as performing PCI within 24 hours after admission [10]. The major clinical endpoint was the occurrence of MACEs, defined as all-cause death, recurrent myocardial infarction (Re-MI), and any coronary repeat revascularization during a 2-year follow-up period. Any coronary repeat revascularization comprised target lesion revascularization (TLR), TVR, and non-TVR. All-cause death was classified as cardiac death (CD) or non-CD. Re-MI was defined as the presence of clinical symptoms, electrocardiographic changes, or abnormal imaging findings of MI combined with an increase in the creatine kinase myocardial band (CK-MB) fraction above the upper normal limits or an increase in troponin-T/troponin-I to greater than the 99th percentile of the upper normal limit after the index PCI [10]. The definitions of TLR, TVR, and non-TVR were previously published [10].

Statistical analyses

For continuous variables, differences between groups were evaluated with the unpaired t-test. Data are expressed as mean ± standard deviation. For discrete variables, differences are expressed as counts and percentages, and were analyzed with χ^2 test or Fisher's exact test between the groups. Various clinical outcomes were estimated using the Kaplan-Meier method, and differences between the two groups were compared by the log-rank test. To adjust for potential confounders, propensity score-matched (PSM) analysis was performed. We tested all available variables that could be of potential relevance: baseline clinical, laboratory, angiographic, and procedural characteristics (Table 1). The C-statistic for PSM was 0.821. Subjects were matched with a caliper width equal to 0.01. The procedure yielded 5891 matched pairs except for the serum levels of CK-MB and troponin-I. Many patients were excluded during this PSM analysis; to overcome this limitation, we performed multivariate analysis. Any variable with a p value of < 0.001 in univariate analysis and conventional risk factors of a poor outcome in the AMI population were considered as potential confounding factors and entered into the multivariate analysis (Table 2). Using Kaplan-Meier analysis, the differences

Table 1. Baseline clinical, laboratory, angiographic, and procedural characteristics.

Variables	Total study population			Propensity score-matched patients		
	STEMI (n = 12,490)	NSTEMI (n = 9400)	P	STEMI (n = 5891)	NSTEMI (n = 5891)	P
Age [years]	61.9 ± 12.6	64.2 ± 12.0	< 0.001	63.3 ± 12.5	63.3 ± 12.2	0.654
Men	9638 (77.2%)	6622 (70.4%)	< 0.001	4361 (74.0%)	4350 (73.8%)	0.817
LVEF [%]	51.5 ± 10.8	54.6 ± 11.1	< 0.001	53.5 ± 10.9	53.8 ± 11.0	0.136
BMI [kg/m^2]	24.2 ± 3.1	24.2 ±3.1	0.448	24.1 ± 3.0	24.2 ± 3.0	0.525
SBP [mmHg]	129.1 ± 27.8	135.1 ± 26.3	< 0.001	132.6 ± 26.8	132.8 ± 26.1	0.587
DBP [mmHg]	79.2 ± 16.8	81.1 ± 15.3	< 0.001	80.2 ± 15.8	80.4 ± 15.5	0.624
Cardiogenic shock	645 (5.2%)	154 (1.6%)	< 0.001	129 (2.2%)	137 (2.3%)	0.620
CPR on admission	358 (2.9%)	133 (1.4%)	< 0.001	119 (2.0%)	105 (1.8%)	0.345
Hypertension	5831 (46.7%)	5117 (54.4%)	< 0.001	3010 (51.1%)	3004 (51.0%)	0.912
Diabetes mellitus	2944 (23.6%)	2762 (29.4%)	< 0.001	1568 (26.6%)	1582 (26.9%)	0.771
Dyslipidemia	1383 (11.1%)	1246 (13.3%)	< 0.001	723 (12.3%)	692 (11.7%)	0.380
Previous MI	334 (2.7%)	458 (4.9%)	< 0.001	226 (3.8%)	213 (3.6%)	0.527
Previous PCI	514 (4.1%)	701 (7.5%)	< 0.001	332 (5.6%)	332 (5.6%)	1.000
Previous CABG	38 (0.3%)	63 (0.7%)	< 0.001	27 (0.5%)	29 (0.5%)	0.789
Previous HF	71 (0.6%)	131 (1.4%)	< 0.001	46 (0.8%)	41 (0.7%)	0.591
Previous CVA	637 (5.1%)	670 (7.1%)	< 0.001	353 (6.0%)	362 (6.1%)	0.728
Current smokers	6067 (48.6%)	3620 (38.5%)	< 0.001	2549 (43.3%)	2546 (43.2%)	0.956
CK-MB [mg/dL]	171.3 ± 216.0	65.3 ± 168.6	< 0.001	101.4 ± 214.8	82.0 ± 207.2	< 0.001
Troponin-I [ng/mL]	59.6 ± 126.9	23.1 ± 43.5	< 0.001	37.8 ± 155.3	28.6 ± 52.4	< 0.001
NT-proBNP [pg/mL]	1497.5 ± 2832.4	2101.7 ± 4751.4	< 0.001	1748.2 ± 3636.7	1761.3 ± 3162.3	0.836
hs-CRP [mg/dL]	10.9 ± 51.0	11.9 ± 55.9	0.207	11.5 ± 52.0	11.1 ± 45.3	0.616
Serum creatinine [mg/L]	1.05 ± 1.00	1.09 ± 1.16	0.007	1.06 ± 1.00	1.07 ± 1.07	0.667
Blood glucose [mg/dL]	170.8 ± 72.3	158.5 ± 76.2	< 0.001	162.4 ± 65.1	161.2 ± 79.5	0.348
Total cholesterol [mg/dL]	186.8 ± 43.4	185.0 ± 45.6	0.004	185.9 ± 43.6	185.7 ± 45.9	0.818
Triglyceride [mg/L]	136.4 ± 113.3	136.3 ± 108.3	0.943	136.4 ± 112.8	137.2 ± 113.6	0.702
HDL cholesterol [mg/L]	44.2 ± 19.3	43.5 ± 15.4	0.001	43.8 ± 19.4	43.6 ± 16.3	0.638
LDL cholesterol [mg/L]	119.0 ± 38.8	117.7 ± 39.4	0.016	117.9 ± 38.8	117.8 ± 39.9	0.874
Discharge medications:						
ASA	12430 (99.5%)	9341 (99.4%)	0.142	5859 (99.5%)	5856 (99.4%)	0.713
Clopidogrel	11212 (89.8%)	8340 (88.7%)	0.013	5263 (89.3%)	5247 (89.1%)	0.635
Ticagrelor	727 (5.8%)	625 (6.6%)	0.012	366 (6.2%)	365 (6.2%)	0.970
Prasugrel	438 (3.5%)	344 (3.7%)	0.547	208 (3.5%)	223 (3.8%)	0.462
Cilostazol	3077 (24.6%)	2202 (23.4%)	0.038	1366 (23.2%)	1386 (23.5%)	0.663
Beta-blockers	10824 (86.7%)	8082 (86.0%)	0.145	5094 (86.5%)	5114 (86.8%)	0.588
CCB	549 (4.4%)	824 (8.8%)	< 0.001	354 (6.0%)	350 (5.9%)	0.876
Angiographic and procedural characteristics						
PCI within 24 hours	11668 (93.4)	7444 (79.2)	< 0.001	5203 (88.3)	5213 (88.5)	0.774
Infarct-related artery:						
Left main	112 (0.9%)	188 (2.0%)	< 0.001	73 (1.2%)	75 (1.3%)	0.869
Left anterior descending	6535 (52.3%)	3988 (42.4%)	< 0.001	2885 (49.0%)	2869 (48.7%)	0.768
Left circumflex	1138 (9.1%)	2603 (27.7%)	< 0.001	932 (15.8%)	932 (15.8%)	1.000
Right coronary artery	4705 (37.7%)	2621 (27.9%)	< 0.001	2001 (34.0%)	2015 (34.2%)	0.786
Treated vessel:						
Left main	196 (1.6%)	332 (3.5%)	< 0.001	133 (2.3%)	129 (2.2%)	0.803
Left anterior descending	7414 (59.4%)	5202 (55.3%)	< 0.001	3436 (58.3%)	3444 (58.5%)	0.881
Left circumflex	2027 (16.2%)	3733 (39.7%)	< 0.001	1535 (26.1%)	1504 (25.5%)	0.514
Right coronary artery	5301 (42.4%)	3486 (37.1%)	< 0.001	2415 (41.0%)	2414 (41.0%)	0.985

→

Table 1 (cont.). Baseline clinical, laboratory, angiographic, and procedural characteristics.

Variables	Total study population			Propensity score-matched patients		
	STEMI (n = 12,490)	NSTEMI (n = 9400)	P	STEMI (n = 5891)	NSTEMI (n = 5891)	P
Treated vessel:						
Left main	196 (1.6%)	332 (3.5%)	< 0.001	133 (2.3%)	129 (2.2%)	0.803
Left anterior descending	7414 (59.4%)	5202 (55.3%)	< 0.001	3436 (58.3%)	3444 (58.5%)	0.881
Left circumflex	2027 (16.2%)	3733 (39.7%)	< 0.001	1535 (26.1%)	1504 (25.5%)	0.514
Right coronary artery	5301 (42.4%)	3486 (37.1%)	< 0.001	2415 (41.0%)	2414 (41.0%)	0.985
ACC/AHA lesion type:						
Type B1	1745 (14.0%)	1448 (15.4%)	0.003	875 (14.9%)	908 (15.4%)	0.396
Type B2	3706 (29.7%)	3418 (36.4%)	< 0.001	1969 (33.4%)	1984 (33.7%)	0.770
Type C	5911 (47.3%)	3752 (39.9%)	< 0.001	2543 (43.2%)	2488 (42.2%)	0.306
Extent of coronary artery disease:						
1-vessel	6534 (52.3%)	4040 (43.2%)	< 0.001	2809 (47.7%)	2774 (47.1%)	0.518
2-vessel	3701 (29.6%)	3212 (34.2%)	< 0.001	1882 (31.9%)	1895 (32.2%)	0.797
≥ 3-vessel	2255 (18.1%)	2148 (22.9%)	< 0.001	1200 (20.4%)	1222 (20.7%)	0.616
Multi-vessel disease	5956 (47.7%)	5360 (57.0%)	< 0.001	3082 (52.3%)	3117 (52.9%)	0.518
Drug-eluting stents:						
BMS	834 (6.7%)	534 (5.7%)	0.003	344 (5.8%)	358 (6.1%)	0.586
SES	1941 (15.5%)	1207 (12.8%)	< 0.001	782 (13.3%)	815 (13.8%)	0.374
PES	1667 (13.3%)	1123 (11.9%)	0.002	747 (12.7%)	716 (12.2%)	0.386
ZES	2780 (22.3%)	2006 (21.3%)	0.104	1254 (21.3%)	1273 (21.6%)	0.670
EES	3548 (28.4%)	3168 (33.7%)	< 0.001	1939 (32.9%)	1885 (32.0%)	0.288
BES	1012 (8.1%)	1002 (10.7%)	< 0.001	543 (9.2%)	541 (9.2%)	0.949
Stent diameter [mm]	3.20 ± 0.42	3.10 ± 0.42	< 0.001	3.14 ± 0.41	3.14 ± 0.42	0.572
Stent length [mm]	26.1 ± 9.1	26.7 ± 11.2	< 0.001	26.5 ± 9.9	26.5 ± 10.4	0.965
Number of stents	1.41 ± 0.72	1.60 ± 0.88	< 0.001	1.51 ± 0.80	1.52 ± 0.79	0.811

Values are mean ± standard deviation or number (%). The p values for continuous data were obtained from analysis of the unpaired t-test. The p values for categorical data were obtained from chi-square test. STEMI — ST-segment elevation myocardial infarction; NSTEMI — non-STEMI; LVEF — left ventricular ejection fraction; BMI — body mass index; SBP — systolic blood pressure; DBP — diastolic blood pressure; CPR — cardiopulmonary resuscitation; PCI — percutaneous coronary intervention; MI — myocardial infarction; CABG — coronary artery bypass graft; CVA — cerebrovascular accident; HF — heart failure; CK-MB — creatine kinase myocardial band; NT-proBNP — N-terminal pro-B-type natriuretic peptide; hs-CRP — high-sensitivity-C-reactive protein; HDL — high-density lipoprotein; LDL — low-density lipoprotein; ASA — acetylsalicylic acid; CCB — calcium channel blockers; ACC/AHA — American College of Cardiology/American Heart Association; BMS — bare-metal stent; SES — sirolimus-eluting stent; PES — paclitaxel-eluting stent; ZES — zotarolimus-eluting stent; EES — everolimus-eluting stent; BES — biolimus-eluting stent

between the groups were compared using the log-rank test. For all analyses, a two-sided $p < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS software, version 20 (IBM; Armonk, NY, USA) [7].

Results

Baseline clinical, laboratory, angiographic, and procedural characteristics

In the total study population, the mean age of the NSTEMI group was greater than that of the STEMI group (64.2 ± 12.0 years vs. 61.9 ± 12.6 years, $p < 0.001$, Table 1). The following values were higher in the STEMI group than in the NSTEMI group: number of men; value of cardiogenic shock, cardiopulmonary resuscitation (CPR), and current smokers; levels of CK-MB, troponin I, blood glucose, total cholesterol, high-density lipoprotein (HDL)-cholesterol, and low-density lipoprotein (LDL)-cholesterol; prescription rates of clopidogrel and cilostazol; numbers of PCI within 24 hours, left anterior descending artery (LAD, infract-related artery [IRA] and treated vessel) and right coronary artery (RCA, IRA and treated vessel); and numbers of American College of Cardiology/American Heart Association (ACC/AHA) type C and 1-vessel disease. By contrast, the NSTEMI

Table 2. Clinical outcomes by Kaplan-Meier analysis and Cox-proportional hazard ratio analysis up to 2 years.

Outcomes	Cumulative events at 2-year (%)				
	STEMI	NSTEMI	Log-rank	Hazard ratio (95% CI)	P
Total study population					
MACEs	851 (7.2)	728 (8.3)	0.003	1.159 (1.050–1.280)	0.003
All-cause death	228 (1.9)	255 (2.9)	< 0.001	1.512 (1.265–1.808)	< 0.001
Cardiac death	164 (1.4)	170 (1.9)	0.002	1.398 (1.128–1.733)	0.002
Re-MI	181 (1.5)	149 (1.7)	0.319	1.117 (0.899–1.387)	0.319
Total repeat revascularization:	507 (4.3)	399 (4.7)	0.310	1.070 (0.939–1.220)	0.310
TLR	160 (1.4)	122 (1.4)	0.774	1.035 (0.818–1.310)	0.774
TVR	294 (2.5)	244 (2.8)	0.153	1.132 (0.955–1.341)	0.154
Non-TVR	222 (1.9)	162 (1.9)	0.933	0.991 (0.810–1.214)	0.933
Propensity score-matched patients					
MACEs	414 (7.4)	452 (8.2)	0.132	1.108 (0.969–1.266)	0.132
All-cause death	114 (2.0)	158 (2.9)	0.005	1.407 (1.106–1.790)	0.005
Cardiac death	82 (1.4)	106 (1.9)	0.046	1.311 (0.983–1.749)	0.046
Re-MI	94 (1.7)	90 (1.7)	0.847	0.972 (0.728–1.298)	0.847
Total repeat revascularization:	241 (4.4)	252 (4.7)	0.485	1.065 (0.893–1.271)	0.485
TLR	85 (1.5)	71 (1.3)	0.308	0.849 (0.619–1.163)	0.308
TVR	150 (2.7)	150 (2.8)	0.871	1.019 (0.813–1.278)	0.871
Non-TVR	98 (1.8)	107 (2.0)	0.444	1.113 (0.846–1.464)	0.444
Multivariate analysis*					
MACEs	851 (7.2)	728 (8.3)	0.003	1.081 (0.965–1.210)	0.178
All-cause death	228 (1.9)	255 (2.9)	< 0.001	1.528 (1.264–1.852)	0.001
Cardiac death	164 (1.4)	170 (1.9)	0.002	1.406 (1.146–1.802)	0.020
Re-MI	181 (1.5)	149 (1.7)	0.319	1.021 (0.798–1.308)	0.866
Total repeat revascularization:	507 (4.3)	399 (4.7)	0.310	0.975 (0.839–1.134)	0.746
TLR	160 (1.4)	122 (1.4)	0.774	0.857 (0.653–1.124)	0.264
TVR	294 (2.5)	244 (2.8)	0.153	0.979 (0.805–1.190)	0.830
Non-TVR	222 (1.9)	162 (1.9)	0.933	0.963 (0.764–1.213)	0.748

*Adjusted by age, men, LVEF, SBP, DBP, cardiogenic shock, CPR on admission, hypertension, diabetes, dyslipidemia, previous history of MI, PCI, CABG, HF, and CVA, current smoker, serum level of CK-MB, troponin I, NT-proBNP, blood glucose, CCB, PCI within 24 hours, IRA, treated vessel, ACC/AHA type B2, and C lesion, the extent of coronary artery disease, types of stents (SES, EES, and BES), stent diameter, stent length, and number of stents. STEMI — ST-segment elevation myocardial infarction; NSTEMI — non-STEMI; CI — confidence interval; MACE — major adverse cardiac events; Re-MI — re-myocardial infarction; TLR — target lesion revascularization: TVR — target vessel revascularization; Non-TVR — non-TVR; LVEF — left ventricular ejection fraction; SBP — systolic blood pressure; DBP — diastolic blood pressure; CPR — cardiopulmonary resuscitation; MI — myocardial infarction; PCI — percutaneous coronary intervention; CABG — coronary artery bypass graft; HF — heart failure; CVA — cerebrovascular accidents; CK-MB — creatine kinase myocardial band; NT-proBNP — N-terminal pro-B-type natriuretic peptide; CCB — calcium channel blockers; IRA — infarct-related artery; ACC/AHA — American College of Cardiology/ /American Heart Association; SES — sirolimus-eluting stent; EES — everolimus-eluting stents; BES — biolimus-eluting stents

group showed higher values than the STEMI group for the following: left ventricular ejection fraction (LVEF, 54.6 ± 11.1% vs. 51.5 ± 10.8%, $p < 0.001$); systolic blood pressure; diastolic blood pressure; number of patients with hypertension, diabetes, dyslipidemia, previous history of MI, PCI, coronary artery bypass graft, heart failure (HF), and cerebrovascular accident; levels of serum N-terminal pro-B-type natriuretic peptide and serum creatinine; prescription rates of ticagrelor and calcium channel blockers; the number of left main coronary artery (LM, IRA and treated vessel), left circumflex artery (LCx, IRA and treated vessel); and the frequency of multi-vessel disease (MVD). Bare-metal stents (BMS) and first-generation DESs were more frequently deployed in the STEMI group, and the everolimus-eluting stents and biolimus-eluting stents were more frequently de-

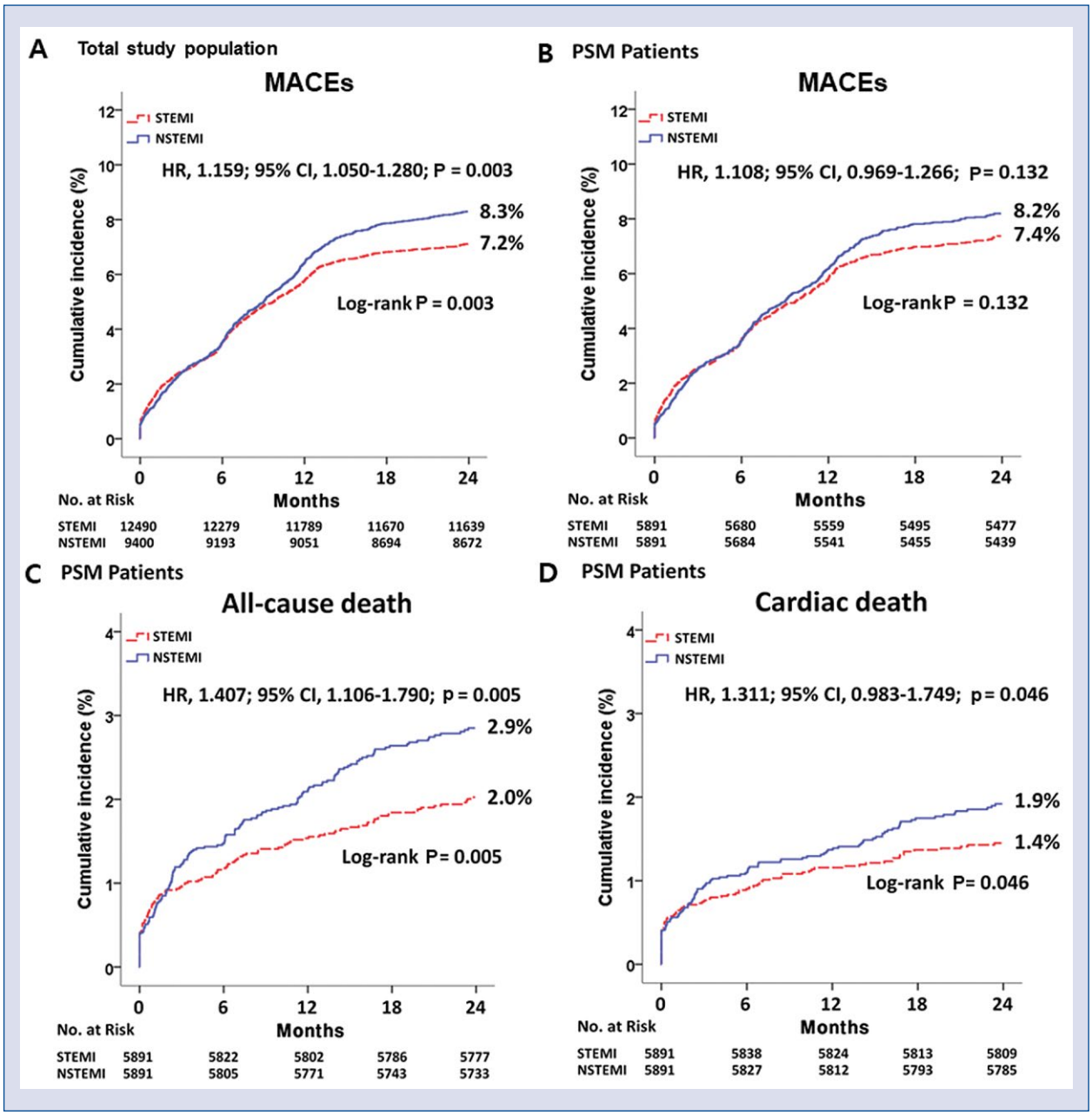

Figure 2. Kaplan-Meier analysis for major adverse cardiac events (MACEs) (**A**, **B**), all-cause death (**C**), and cardiac death (**D**); PSM — propensity score-matched; HR — hazard ratio; CI — confidence interval; NSTEMI — non-ST--segment elevation myocardial infarction; STEMI — ST-segment elevation myocardial infarction.

ployed in the NSTEMI group. After PSM analysis, baseline differences between the two groups were well balanced. However, the blood levels of CK-MB and troponin I levels were not well balanced.

Clinical outcomes

In the total study population, the cumulative incidence of MACEs (hazard ratio [HR] 1.159; 95% confidence interval [CI] 1.050–1.280; p = 0.003, Fig. 2A), all-cause death (HR 1.512; 95% CI 1.265–1.808; p < 0.001), and CD (HR 1.398; 95% CI 1.128–1.733; p = 0.002) were higher in the NSTEMI group than in the STEMI group. After PSM analysis, the cumulative incidence of MACEs was not significantly different between the groups (Fig. 2B). However, the cumulative incidences of all-cause death (HR 1.407; 95% CI 1.106–1.790; p = 0.005, Fig. 2C) and CD (HR 1.311; 95% CI 0.983–1.749; p = 0.046, Fig. 2D) were significantly higher in the NSTEMI group

than in the STEMI group. Before and after PSM analysis, the cumulative incidences of Re-MI, any repeat revascularization, TLR, TVR, and non-TVR were not statistically different between the groups. Figure 3 shows subgroup analysis for MACEs at 2 years. In cases of male sex (HR 1.13; 95% CI 1.00–1.27; p = 0.047), low LVEF (< 50%, HR 1.47; 95% CI 1.26–1.71; p < 0.001), cardiogenic shock (HR 1.17; 95% CI 1.06–1.29; p = 0.002), and PCI within 24 hours (HR 1.15; 95% CI 1.03–1.28; p = 0.012) statins combined with RASI showed greater reduction in MACEs for patients with STEMI than for those with NSTEMI. Advanced age (≥ 65 years), low LVEF (< 50%), diabetes, CPR on admission, N-terminal pro-B-type natriuretic peptide, serum creatinine, total cholesterol, triglyceride, LDL-cholesterol, PCI within 24 hours, BMS, and MVD were meaningful independent risk factors for both all-cause death and CD in PSM patients (Table 3).

Discussion

According to current guidelines [5, 6, 8, 9], more than 80% of the patients with AMI received statin therapy in Korea [16]. Similarly, more than 50% of these patients received RASI therapy to reduce cardiovascular mortality [17]. However, the comparative studies regarding long-term clinical outcomes of statin with RASI combination therapy between STEMI and NSTEMI after stent implantation have not been reported. We believe this may be the first report focusing on this issue. Moreover, the present study confirms that statin combined with RASI was more effective in patients with STEMI rather than in patients with NSTEMI with respect to all-cause death and CD rates over a 2-year follow-up.

The key findings of this study are as follows: First, after PSM analysis, the cumulative incidences of all-cause death and CD were significantly higher in patients with NSTEMI than in those with STEMI after combined statin and RASI therapy. Second, the cumulative incidences of MACEs, Re-MI, and any repeat revascularization including TLR, TVR, and non-TVR were not significantly different between the two groups after PSM analysis. Third, advanced age (≥ 65 years), male sex, low LVEF (< 50%), diabetes, CPR on admission, PCI within 24 hours, BMS, and MVD were independent risk factors for both all-cause death and CD in PSM patients.

Statins both reduce LDL-cholesterol and decrease the occurrences of cardiovascular death, non-fatal MI, and repeat coronary revascularization by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase activity, as well as other not fully understood processes [3, 18, 19]. The beneficial effects of statins are evident in both STEMI and NSTEMI patients [5, 6, 8, 9]. However, data comparing the long-term prognosis of STEMI and NSTEMI patients, especially those focused on the usage of statins, are limited. In the era of DES, Kim et al. [7] demonstrated that MACEs and mortality reduction capacity of statin therapy was prominent compared with statin non-use, and statins were more effective in patients with STEMI compared with NSTEMI. Regardless of STEMI or NSTEMI, RASI provides mortality reduction benefit by diminishing the rate of progressive LV dilation and remodeling, especially in patients with LV dysfunction [5, 6]. Even though Kim et al. [10] reported greater reduction in mortality following RASI in STEMI patients than in NSTEMI patients after successful PCI, long-term clinical outcome data comparing the status of STEMI and NSTEMI patients post successful stent implantation after combined statin and RASI therapy are also limited. Koh et al. [20] suggested that combined statins and RASI may improve endothelial function, insulin resistance, and atherosclerosis. In our study, the cumulative incidences of all-cause death (HR 1.407; 95% CI 1.106–1.790; p = 0.005) and CD (HR 1.311; 95% CI 0.983–1.749; p = 0.046) were also significantly higher in the NSTEMI group than in the STEMI group. Taken together, these results suggest that RASI monotherapy or statins combined with RASI was more beneficial for STEMI patients than for NSTEMI patients in terms of reduced mortality. Statins decrease the production of oxygen-derived free radicals by reducing LDL-cholesterol, increasing nitric oxide (NO) synthesis, promoting antioxidant effects, and inhibiting upregulation of angiotensin II type 1 (AT1) receptor expression. RASI inhibits binding of angiotensin II to the AT1 receptor and induces decreased production of oxygen-derived free radicals. Accumulated bradykinins after ACEI treatment lead to increased stimulation of NO production [20]. NO production may be a shared process for both statins and RASI. Kim et al. [10] showed that RASI after PSM was more effective in reducing all-cause death (HR 1.386; 95% CI 1.114–1.725; p = 0.003) and CD (HR 1.358; 95% CI 1.041–1.7770; p = 0.024) in patients with STEMI compared with NSTEMI after PSM. However, we found that statins combined with RASI did not show greater relative risk reduction of all-cause

Table 3. Multivariate Cox-proportional regression analysis for predictors of all-cause death and cardiac death in propensity score-matched patients.

Variables	All-cause death		Cardiac death	
	HR (95% CI)	P	HR (95% CI)	P
STEMI vs. NSTEMI	2.822 (2.102–3.789)	< 0.001	2.643 (1.858–3.759)	< 0.001
Age ≥ 65 years	2.617 (1.945–3.521)	< 0.001	2.491 (1.748–3.551)	< 0.001
Male	1.009 (0.774–1.315)	0.949	1.057 (0.770–1.450)	0.733
LVEF < 50%	1.961 (1.531–2.510)	< 0.001	1.887 (1.403–2.540)	< 0.001
Systolic blood pressure	0.991 (0.982–0.999)	0.024	0.992 (0.983–1.002)	0.121
Diastolic blood pressure	1.012 (0.999–1.026)	0.072	1.010 (0.994–1.027)	0.204
Hypertension	1.186 (0.916–1.535)	0.196	1.236 (0.905–1.689)	0.183
Diabetes mellitus	1.522 (1.184–1.956)	0.001	1.453 (1.074–1.967)	0.015
Dyslipidemia	1.140 (0.758–1.715)	0.528	1.086 (0.693–1.702)	0.720
Cardiogenic shock	1.074 (0.517–2.233)	0.847	1.372 (0.524–3.591)	0.519
CPR on admission	3.289 (2.034–5.318)	< 0.001	4.001 (2.322–6.895)	< 0.001
CK-MB	1.000 (0.999–1.001)	0.814	1.000 (0.999–1.001)	0.969
Troponin-I	1.000 (1.000–1.001)	0.407	1.000 (1.000–1.001)	0.497
NT-proBNP	1.001 (1.000–1.002)	< 0.001	1.002 (1.001–1.003)	< 0.001
hs-CRP	1.001 (0.999–1.003)	0.256	1.000 (0.998–1.003)	0.766
Serum creatinine	1.128 (1.074–1.186)	< 0.001	1.124 (1.057–1.195)	< 0.001
Total cholesterol	0.994 (0.991–0.997)	< 0.001	0.992 (0.989–0.996)	< 0.001
Triglyceride	0.996 (0.994–0.998)	< 0.001	0.996 (0.994–0.999)	0.001
HDL-cholesterol	0.993 (0.982–1.003)	0.173	0.994 (0.981–1.006)	0.308
LDL-cholesterol	0.994 (0.991–0.998)	0.001	0.993 (0.989–0.997)	0.001
Beta-blocker	1.562 (1.038–2.353)	0.033	1.600 (0.978–2.617)	0.061
PCI within 24 hours	1.483 (1.167–1.885)	0.001	1.395 (1.046–1.860)	0.024
LAD (IRA)	1.122 (0.752–1.676)	0.572	1.020 (0.633–1.643)	0.934
LAD (treated)	1.120 (0.744–1.686)	0.586	1.065 (0.659–1.721)	0.796
ACC/AHA type B2/C lesion	1.124 (0.824–1.533)	0.461	1.007 (0.703–1.442)	0.970
BMS	3.104 (1.905–5.056)	< 0.001	2.481 (1.360–4.527)	0.003
SES	1.940 (1.048–3.591)	0.035	2.041 (0.974–4.275)	0.059
PES	1.343 (0.755–2.389)	0.316	1.142 (0.591–2.210)	0.692
ZES	1.128 (0.702–1.813)	0.618	1.084 (0.616–1.909)	0.780
EES	1.150 (0.725–1.824)	0.552	1.112 (0.642–1.924)	0.706
BES	1.066 (0.606–1.874)	0.825	1.196 (0.598–2.390)	0.613
MVD	1.301 (1.003–1.687)	0.048	1.343 (0.981–1.840)	0.042
Stent diameter	0.856 (0.630–1.162)	0.317	0.714 (0.490–1.040)	0.079
Stent length	0.999 (0.987–1.012)	0.883	0.998 (0.983–1.013)	0.791

HR — hazard ratio; CI — confidence interval; STEMI — ST-segment elevation myocardial infarction; NSTEMI — non-STEMI; LVEF — left ventricular ejection fraction; CPR — cardiopulmonary resuscitation; CK-MB — creatine kinase myocardial band; NT-proBNP — N-terminal pro-B-type natriuretic peptide; hs-CRP — high sensitivity-C-reactive protein; HDL — high-density lipoprotein; LDL — low-density lipoprotein; PCI — percutaneous coronary intervention; LAD — left anterior descending coronary artery; IRA — infarct-related artery; ACC/AHA — American College of Cardiology/American Heart Association; BMS — bare-metal stent; SES — sirolimus-eluting stent; PES — paclitaxel-eluting stent; ZES — zotarolimus-eluting stent; EES — everolimus-eluting stent; BES — biolimus-eluting stent; MVD — multivessel disease

death (40.7% vs. 38.6%) or CD (31.1% vs. 35.8%) compared with the results of Kim et al. [10]. We speculated that one of the major causative factors for the similar relative risk reduction potency for all-cause death and CD in these two studies (Kim et al. [10] and the present study) is related, at least in part, with this shared NO production process [19]. This has included suggestion that this similar NO mediated protective mechanism may be attenuated their effects on endothelium each

other. However, this supposition supports the need for further study to confirm these findings. Other possible factor for these results was the presence of BMS. BMS was not included in the Kim et al. [10] study. However, the proportion of BMS in the total study population was low, and BMS was an independent significant predictor for both all-cause death and cardiac death in PSM patients (Table 3). Nevertheless, with regard to the beneficial effect of statin monotherapy by reducing MACEs, all-cause death, and TVR in patients with STEMI [7], statin and RASI combination therapy showed an additional beneficial effect on reducing the cumulative incidence of CD (HR 1.311; 95% CI 0.983–1.749; p = 0.046) in this study.

On PSM analysis, many patients (10,108/ /21,890, 46.2%) were excluded and the serum CK-MB and troponin-I levels were not well-matched. To overcome these limitations, we performed standard multivariate analysis. Nevertheless, the results of multivariate analysis were similar to the results of the PSM analysis. After multivariate analysis, the cumulative incidences of all-cause death (HR 1.528; 95% CI 1.264–1.852; p = 0.001) and CD (HR 1.406; 95% CI 1.146– –1.802; p = 0.020) were significantly higher in NSTEMI patients than in STEMI patients. The cumulative incidences of MACEs, Re-MI, and any repeat revascularization were similar between the two groups (Table 2).

The condition of the STEMI group was worse than that of the NSTEMI group with respect to baseline characteristics. The values of cardiogenic shock (5.2% vs. 1.6%, p < 0.001) and CPR on admission (2.9% vs. 1.4%, p < 0.001); the number of current smokers (48.6% vs. 38.5%, p < 0.001), LAD (IRA, treated vessel), RCA (IRA, treated vessel), and ACC/AHA type C; and the levels of CK-MB, troponin I were significantly higher in the STEMI group. However, the cumulative incidences of all-cause death and CD were significantly lower in the STEMI group than in the NSTEMI group. These results were associated with the beneficial effects of RASI and were compatible with those of the OPTIMAAL study [21]. In the OPTIMAAL study, the clinical benefit of RASI was larger in the high-risk patient subgroup, including anterior MI, decreased LVEF (≤ 40%), HF, prior MI, and tachycardia. On subgroup analysis, for patients who had decreased LVEF and who were in cardiogenic shock, statin combined with RASI reduced MACEs in patients with STEMI more than in those with NSTEMI (Fig. 3).

Another considerable factor for determining the cumulative incidences of all-cause death and CD was the treatment strategy. In the present study, 93.5% (11,627/12,490) of the STEMI patients had undergone primary PCI, and about 79.2% (7444/9400) of the NSTEMI patients had received early invasive treatment. The higher incidence of primary PCI may be associated with favorable all-cause death rates and CD in STEMI patients. Currently, the reasons for the higher incidence of death in NSTEMI during long-term follow-up remain poorly understood [22, 23]. In patients with NSTEMI, studies recommended that a selective invasive strategy may be preferable in selected patients to improve long-term outcomes [24, 25].

KAMIR is a nationwide, prospective, observational, on-line registry in South Korea that has been compiling data since November 2005. More than 50 high-volume university and community hospitals with facilities for primary PCI and onsite cardiac surgery have participated [13]. Therefore, we believe the population of this study is sufficiently large to provide reasonably accurate results. Furthermore, the results of this comparative study may persuade interventional cardiologists of the benefits of statins combined with RASI with respect to reducing all-cause death and CD in STEMI patients compared with those in NSTEMI patients after PCI.

Limitations of the study

Our study had several limitations. First, there may be some under-reporting and/or missed data because of the non-randomized retrospective nature of the study. Second, our study was based on medications at discharge, and the registry data did not include full detailed data concerning the starting time of statin or RASI therapy, changes in prescription doses, long-term adherence, or discontinuation during the follow-up period; therefore, these factors may contribute bias. Third, we could not provide serial follow-up results compared with initial laboratory results because of limitations related to the registry data; this too may introduce bias. Fourth, we reported 2-year clinical outcomes between the two groups in this study; nevertheless, a 2-year follow-up period is relatively short for the determination of long-term major clinical outcomes. Finally, the long inclusion period could also have influenced the patient's profile and may have biased the results, because RASI, AT1, and statins in recent years have been modernized in late generations with, generally, better bioprofile.

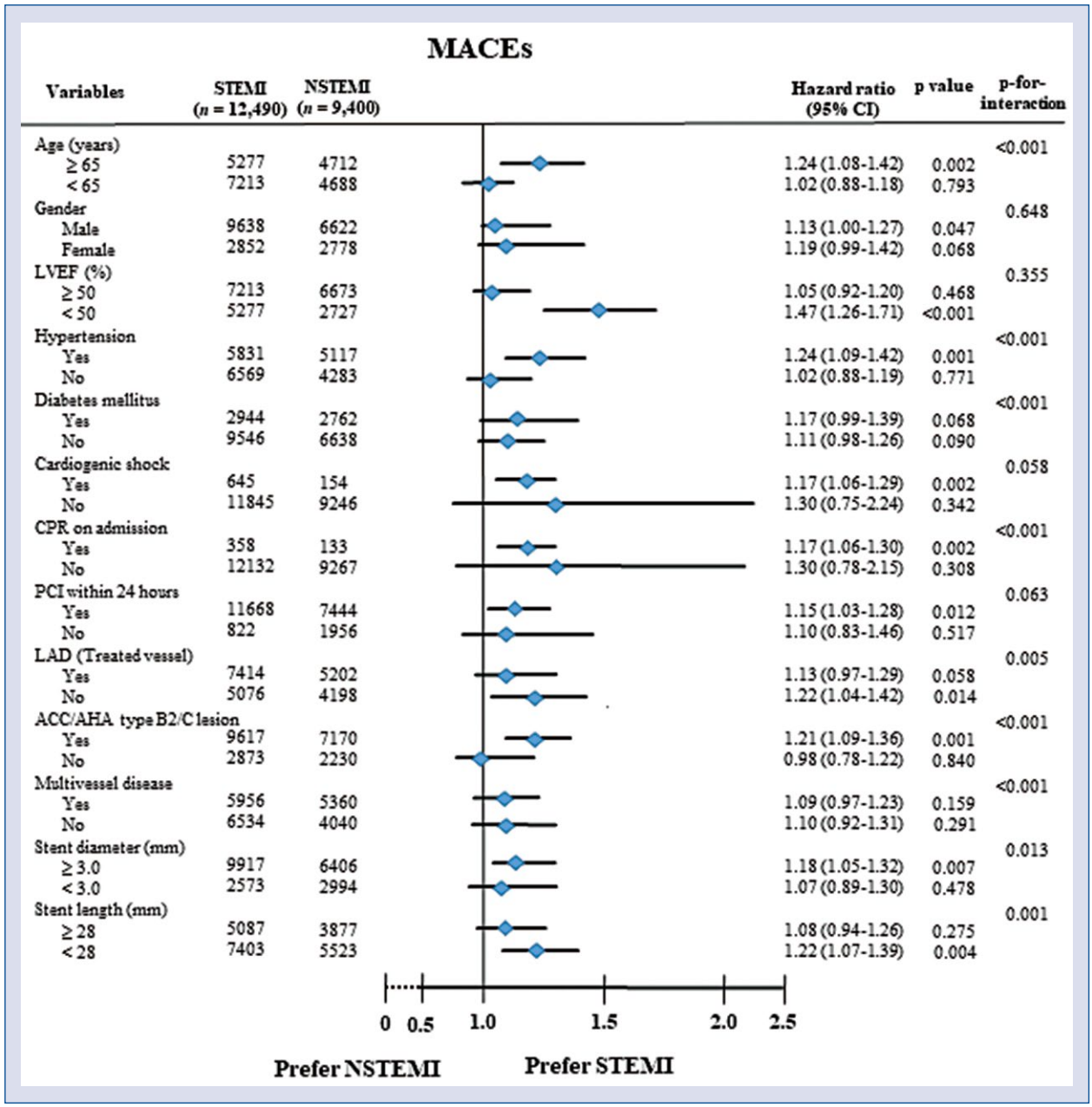

Figure 3. Subgroup analysis for major adverse cardiac events (MACEs); CI — confidence interval; NSTEMI — non-ST-segment elevation myocardial infarction; STEMI — ST-segment elevation myocardial infarction; LVEF — left ventricular ejection fraction; CPR — cardiopulmonary resuscitation; PCI — percutaneous coronary intervention; LAD — left anterior descending artery; ACE/AHA — American College of Cardiology/American Heart Association.

Conclusions

In conclusion, despite the fact that the cumulative incidences of MACEs, Re-MI, and any repeat revascularization including TLR, TVR, and non-TVR were not statistically significantly different between the two groups, with respect to all-cause death and CD rates during a 2-year follow-up period, combined use of statin with RASI was more effective in patients with STEMI than in those with NSTEMI. However, further studies are warranted to elucidate this focus.

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References

1. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med. 2004; 350(15): 1495–1504, doi: 10.1056/NEJMoa040583, indexed in Pubmed: 15007110.
2. Baigent C, Blackwell l, Emberson J. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. Lancet. 2010; 376(9753): 1670–1681, doi: 10.1016/s0140-6736(10)61350-5.
3. Larsen AI, Tomey MI, Mehran R, et al. Comparison of outcomes in patients with ST-segment elevation myocardial infarction discharged on versus not on statin therapy (from the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction Trial). Am J Cardiol. 2014; 113(8): 1273–1279, doi: 10.1016/j.amjcard.2014.01.401, indexed in Pubmed: 24576541.
4. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J. 2016; 37(29): 2315–2381, doi: 10.1093/eurheartj/ehw106, indexed in Pubmed: 27222591.
5. 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.
6. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC Guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014; 64(24): e139–e228, doi: 10.1016/j.jacc.2014.09.017, indexed in Pubmed: 25260718.
7. Kim YH, Her AY, Jeong MHo, et al. Different statin effects of ST-elevation versus non-ST-elevation acute myocardial infarction after stent implantation. Am J Med Sci. 2020; 359(3): 156–167, doi: 10.1016/j.amjms.2019.12.004, indexed in Pubmed: 32089157.
8. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013; 127(4): e362–e425, doi: 10.1161/CIR.0b013e3182742cf6, indexed in Pubmed: 23247304.
9. Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J. 2016; 37(3): 267–315, doi: 10.1093/eurheartj/ehv320, indexed in Pubmed: 26320110.
10. Kim YH, Her AY, Jeong MHo, et al. Impact of renin-angiotensin system inhibitors on long-term clinical outcomes in patients with acute myocardial infarction treated with successful percutaneous coronary intervention with drug-eluting stents: comparison between STEMI and NSTEMI. Atherosclerosis. 2019; 280: 166–173, doi: 10.1016/j.atherosclerosis.2018.11.030, indexed in Pubmed: 30529829.
11. Lee HY, Sakuma I, Ihm SH, et al. Statins and renin-angiotensin system inhibitor combination treatment to prevent cardiovascular disease. Circ J. 2014; 78(2): 281–287, doi: 10.1253/circj.cj-13-1494, indexed in Pubmed: 24401609.
12. Koh KK, Sakuma I, Hayashi T, et al. Renin-angiotensin system inhibitor and statins combination therapeutics: what have we learnt? Expert Opin Pharmacother. 2015; 16(7): 949–953, doi: 10.1517/14656566.2015.1019464, indexed in Pubmed: 25747324.
13. Kim Y, Ahn Y, Cho MC, et al. Current status of acute myocardial infarction in Korea. Korean J Intern Med. 2019; 34(1): 1–10, doi: 10.3904/kjim.2018.381, indexed in Pubmed: 30612415.
14. Kim YH, Her AY, Jeong MHo, et al. Two-year outcomes of statin therapy in patients with acute myocardial infarction with or without dyslipidemia after percutaneous coronary intervention in the era of new-generation drug-eluting stents within Korean population: Data from the Korea Acute Myocardial Infarction Registry. Catheter Cardiovasc Interv. 2019; 93(7): 1264–1275, doi: 10.1002/ccd.27985, indexed in Pubmed: 30474346.
15. Grech ED. ABC of interventional cardiology: percutaneous coronary intervention. II: the procedure. BMJ. 2003; 326(7399): 1137–1140, doi: 10.1136/bmj.326.7399.1137, indexed in Pubmed: 12763994.
16. Won KB, Hur SH, Nam CW, et al. Evaluation of the impact of statin therapy on the obesity paradox in patients with acute myocardial infarction: A propensity score matching analysis from the

Korea Acute Myocardial Infarction Registry. Medicine (Baltimore). 2017; 96(35): e7180, doi: 10.1097/MD.0000000000007180, indexed in Pubmed: 28858077.

17. Kim YH, Her AY, Jeong MH, et al. Clinical outcomes at 2 years between beta-blockade with ACE inhibitors or arbs in patients with AMI who underwent successful PCI with DES: a retrospective analysis of 23,978 patients in the korea AMI registry. Am J Cardiovasc Drugs. 2019; 19(4): 403–414, doi: 10.1007/s40256-019-00326-8, indexed in Pubmed: 30788675.
18. Athyros VG, Kakafika AI, Tziomalos K, et al. Pleiotropic effects of statins: clinical evidence. Curr Pharm Des. 2009; 15(5): 479––489, doi: 10.2174/138161209787315729, indexed in Pubmed: 19199976.
19. Baigent C, Keech A, Kearney PM. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. Lancet. 2005; 366(9493): 1267–1278, doi: 10.1016/s0140-6736(05)67394-1.
20. Koh KK, Han SH, Oh PC, et al. Combination therapy for treatment or prevention of atherosclerosis: focus on the lipid-RAAS interaction. Atherosclerosis. 2010; 209(2): 307–313, doi: 10.1016/j.atherosclerosis.2009.09.007, indexed in Pubmed: 19800624.
21. Dickstein K, Kjekshus J. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Lancet. 2002; 360(9335): 752–760, doi: 10.1016/s0140-6736(02)09895-1.
22. Hasdai D, Behar S, Wallentin L, et al. A prospective survey of the characteristics, treatments and outcomes of patients with acute coronary syndromes in Europe and the Mediterranean basin; the Euro Heart Survey of Acute Coronary Syndromes (Euro Heart Survey ACS). Eur Heart J. 2002; 23(15): 1190–1201, doi: 10.1053/euhj.2002.3193, indexed in Pubmed: 12127921.
23. Polonski L, Gasior M, Gierlotka M, et al. A comparison of ST elevation versus non-ST elevation myocardial infarction outcomes in a large registry database: are non-ST myocardial infarctions associated with worse long-term prognoses? Int J Cardiol. 2011; 152(1): 70–77, doi: 10.1016/j.ijcard.2010.07.008, indexed in Pubmed: 20684999.
24. Kofoed KF, Kelbæk H, Hansen PR, et al. Early versus standard care invasive examination and treatment of patients with non-ST-segment elevation acute coronary syndrome. Circulation. 2018; 138: 2741–2750, doi: 10.1161/CIRCULATIONAHA, indexed in Pubmed: 30565996.
25. Hoedemaker NPG, Damman P, Woudstra P, et al. Early invasive versus selective strategy for non-ST-Segment elevation acute coronary syndrome: the ICTUS trial. J Am Coll Cardiol. 2017; 69(15): 1883–1893, doi: 10.1016/j.jacc.2017.02.023, indexed in Pubmed: 28408018.

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Predictors of the voltage derived left atrial fibrosis in patients with long-standing persistent atrial fibrillation

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Abstract

Background: *Left atrial (LA) arrhythmogenic substrate beyond the pulmonary veins (PV) seems to play a crucial role in the maintenance of atrial fibrillation (AF). The aim of this study was to evaluate the association of selected parameters with the presence and extent of voltage-defined LA fibrosis in patients with long-standing persistent AF (LSPAF) undergoing catheter ablation.*

Methods: *One hundred and sixteen consecutive patients underwent high density-high resolution voltage mapping of the LA with a multielectrode catheter following PV isolation and restoration of sinus rhythm with cardioversion. A non-invasive dataset, such as clinical variables, two- and three-dimensional echocardiography determined LA size and function and fibrillatory-wave amplitude on a standard surface electrocardiogram were obtained during AF before ablation.*

Results: *Low-voltage areas (LVA; 15 cm^2 [IQR 8–31]) were detected in 56% of patients. Twenty nine percent of them presented mild, 43% moderate and 28% severe global LVA burden. In univariate analysis, age ≥ 57 years old, female sex, body surface area ≤ 1.76 m^2, valvular heart disease, moderate mitral regurgitation, chronic coronary syndrome, hypothyroidism, CHA_2DS_2-VASc score ≥ 3 and ≥ 4 predicted the presence of LVA. In multivariate analysis only female sex, valvular heart disease and CHA_2DS_2-VASc ≥ 4 remained statistically significant. AF duration, LA size and function and fibrillatory-waves amplitude were neither associated with the prediction of the LVA, nor severe LVA burden.*

Conclusions: *A LSPAF diagnosis does not indicate the presence of voltage defined fibrosis in many cases. Simple non-invasive screening of the LSPAF population could predict LVA prevalence.* (Cardiol J 2022; 29, 4: 660–669)

Key words: atrial fibrillation, long-standing persistent atrial fibrillation, voltage mapping, left atrial fibrosis, low-voltage areas

Introduction

Left atrial (LA) arrhythmogenic substrate beyond the pulmonary veins (PVs) seems to play a crucial role in the maintenance of atrial fibrillation (AF). Bipolar voltage mapping has been shown to be a useful method to assess the incidence of low-voltage areas (LVA), most commonly considered a marker for the presence of atrial fibrosis [1]. However, the incidence of voltage-derived LA remodelling in patients with long-standing persistent AF (LSPAF), as well as factors that may noninvasively unmask LVA, has not been thoroughly investigated. The aim of this study was to evaluate the presence and extent of voltage defined LA fibrosis among an LSPAF population by creating high-density high-resolution contact voltage maps acquired with a multielectrode catheter. Moreover, to correlate LVA burden with clinical variables, two- (2D) and three-dimensional (3D) echocardiography determined LA size and function and fibrillatory waves (f-waves) amplitude on a standard surface electrocardiogram (ECG) in order to check the feasibility of noninvasively predicting the presence of an arrhythmogenic substrate.

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Methods

Study population

The prospective cohort study included 116 consecutive patients with continuous AF of duration greater than 12 months who had undergoing radiofrequency ablation at the documented center. Patients with any previous ablation for AF, cardiac surgery affecting the atria, severe valvular disease or mechanical valve, known pulmonary hypertension, history of myocarditis or pericarditis were excluded. The clinical characteristics of the overall population is summarized in Table 1. The study complied with the Declaration of Helsinki, all patients provided written, informed consent and the study protocol was approved by a local institutional review board.

Echocardiography examination

Transthoracic echocardiography was performed on the day of the ablation using a Vivid E9 ultrasound system (GE Vingmed Ultrasound AS) by a single experienced echocardiographist. All 2D and M-mode measurements of the left atrium and ventricle were performed according to recent recommendations [2]. Valvular heart disease was considered as the presence of any moderate regurgitation exclusively. 3D LA volume analysis was made using the dedicated image processing software 4D auto LVQ (GE Healthcare), adjusted manually and corrected using a volume waveform tool. 3D LA systolic (emptying fraction, stroke volume) and diastolic (expansion index) function were calculated by system software. All echocardiographic variables were indexed to body surface area (BSA) where appropriate.

Atrial f-waves amplitude measurement

A standard surface ECG at the lead gain of 1 mV/10 mm and sweep speed of 50 mm/s was analysed. F-wave amplitude was measured on V1 precordial lead with computer-assisted electronic calliper software (Cardio Calipers, Iconico) from wave peak-to-trough by a single physician. The maximal, minimal and mean amplitude, as well as amplitude dispersion of all measured f-waves in a single 5-second ECG recording was reported, except f-waves which overlapped with QRS and T waves and was indexed to BSA. Mean f-waves amplitude < 0.1 mV was considered as fine when ≥ 0.1 mV was a coarse AF pattern [3].

Voltage mapping protocol

An LA respiration-gated shell was created using CARTO®3 electroanatomical platform (Biosense-Webster) with the geometry filling threshold set at 16 using a Pentaray duodecapolar catheter with a 2–6–2 mm electrode spacing configuration (Biosence-Webster) which offers the highest mapping resolution among all multipolar catheters that work with the CARTO3 system. The mitral annulus was defined with a ThermocoolSmartTouch catheter (Biosence-Webster) by electrogram characteristics (local atrial-ventricular amplitude ratio < 0.1 with a ventricular electrogram > 1.5 mV). The ventricular portion of the shell was always erased to avoid an overestimation of the total LA surface area (TSA). An encircling isolation of ipsilateral PV pairs (PVI), uniformly delivered ≤ 15 mm away from the PVs ostia, was performed as the initial step in all patients with a SmartTouch catheter. Then, a direct current shock was applied to restore sinus rhythm in all patients. If AF failed to be cardioverted or recurred shortly following cardioversion (n = 12.9% of the total study population), the subject was excluded from analysis. Finally, 116 patients were found to be suitable for further evaluation. Following confirmation of PVI in sinus rhythm, a high-density (2876 ± ± 1058 points per map), high-resolution bipolar LA voltage mapping, during proximal coronary sinus pacing at 600 ms cycle length, with a Pentaray catheter acquired with a CONFIDENSE™ module (Biosence-Webster) was performed. To ensure detailed mapping the distance filling threshold was set at 5 mm, the density acquisition filter at 1 mm and catheter location stability at 4 mm. A tissue proximity filter was always enabled during mapping in order to reject points not found to be in close proximity to the tissue. Point collection was only allowed when both bipoles on a single spline had adequate catheter-tissue contact. Moreover, internal point filter software was used to limit data acquisition. Only mapping sites that were within a distance of 5 mm from the acquired LA shell contributed to the voltage map. Further discrete voltage mapping using a SmartTouch catheter, covering less than 10% of the TSA, at sites presenting inadequate Pentaray-tissue contact was performed if necessary. Electrograms were only accepted if contact force was ≥ 6 g and catheter location stability did not exceed 2 mm. Electrogram amplitude ≥ 0.5 mV was defined as normal and < 0.5 mV as both moderately and severely diseased tissue [4]. All points presenting low voltage were visually inspected and those incorrectly annotated were deleted from the map in the presence of atrial ectopy, uncaptured coronary sinus pacing, noise, ventricular and atrial farfield. All gaps in the map

Table 1. Patient characteristics.

	Entire study group	LVA (+) N = 65 (56%)	LVA (–) N = 51 (44%)	P	Severe LVA (+) N = 18 (16%)	Severe LVA (–) N = 98 (84%)	P
Known uninterrupted AF duration [months]	24 (12–40.5) [range 12–204]	24 (14–48)	24 (12–36)	NS	24 (14–48)	24 (12–36)	NS
History of failed direct current cardioversion	63 (54%)	35 (54%)	28 (55%)	NS	9 (50%)	54 (55%)	NS
Age [years]	63 (57–68) [range 37–79]	**65 (60–69)**	**61 (53–65)**	**0.0015**	**67 (65–71)**	**62 (57–66)**	**0.0002**
Females	23 (20%)	**19 (29%)**	**4 (8%)**	**0.041**	**8 (44%)**	**15 (15%)**	**0.009**
BSA [m^2]	2.12 (1.96–2.22)	2.1 (2.0–2.2)	2.16 (2.03–2.3)	0.09	**2 (1.9–2.16)**	**2.15 (2–2.22)**	**0.024**
Body mass index [kg/m^2]	30.3 (27.5–32)	29.7(27.5–32)	30.7 (27.7–32.6)	NS	30.3 (26.8–31.8)	30.4 (27.6–32.2)	NS
Hypertension	47 (41%)	55 (85%)	43 (84%)	NS	18 (100%)	80 (82%)	0.07
Valvular heart disease	35 (30%)	**35 (54%)**	**12 (24%)**	**0.001**	11 (61%)	36 (37%)	0.07
Moderate mitral regurgitation	21 (18%)	**25 (39%)**	**10 (20%)**	**0.02**	8 (44%)	26 (27%)	NS
Moderate tricuspid regurgitation	26 (22%)	15 (23%)	6 (12%)	NS	9 (50%)	47 (48%)	NS
Confirmed chronic coronary syndrome	7 (6%)	20 (31%)	6(12%)	**0.015**	6 (33%)	20 (20%)	NS
Heart failure	27 (23%)	16 (25%)	11 (22%)	NS	2 (11%)	26 (27%)	NS
eGFR [$mL/min/1.73\ m^2$]	84 (71–94)	82 (69–89)	87 (71–95)	NS	79 (70–89)	84 (70–95)	NS
Diabetes	26 (22%)	16 (25%)	10 (20%)	NS	5 (28%)	21 (21%)	NS
Hypothyroidism	15 (13%)	12 (18%)	3 (6%)	0.08	4 (22%)	11 (11%)	NS
CHA_2DS_2-VASc ≤ 1	40 (34%)	**17 (26%)**	**23 (45%)**	**0.03**	**1 (6%)**	**39 (40%)**	**0.006**
CHA_2DS_2-VASc ≥ 2	74 (64%)	46 (71%)	28 (55%)	0.07	15 (83%)	59 (60%)	0.07
CHA_2DS_2-VASc ≥ 3	43 (37%)	**30 (46%)**	**13(25%)**	**0.02**	**12 (67%)**	**31 (32%)**	**0.007**
CHA_2DS_2-VASc ≥ 4	16 (14%)	**15 (23%)**	**1 (2%)**	**0.03**	**8 (44%)**	**8 (8%)**	**0.0004**
Left ventricular ejection fraction (%)	60 (55–65)	60 (53–63)	60 (55–65)	NS	60 (55–61)	60 (50–65)	NS
LA antero-posterior diameter [mm]	47 (45–50) [range 37–63]	47 (44–50)	47 (45–50)	NS	47 (43–49)	47 (45–50)	NS
BSA indexed value [mm/m^2]	22 (20.7–24.7)	22 (21–25)	22 (20–24)	NS	24 (21–26)	22 (21–24)	NS
2D LA maximum length [mm]	67 (64–73)	67 (64–72)	68 (64–74)	NS	66 (64–72)	68 (64–73)	NS
BSA indexed value [mm/m^2]	32 (30–35)	33 (31–34)	31 (28–35)	NS	34 (32–36)	32 (29–35)	NS
2D LA maximum area [cm^2]	28 (25–32)	28 (26–32)	28 (25–34)	NS	28 (24–32)	28 (26–32)	NS
BSA indexed value [cm^2/m^2]	13 (12–16)	14 (12–16)	13 (11–16)	NS	14 (12–16)	13 (12–16)	NS
2D maximum volume [mL]	100 (86–127)	101 (87–126)	91 (84–132)	NS	101 (84–124)	101 (85–127)	NS
BSA indexed value [mL/m^2]	48 (38–60)	50 (41–60)	47 (37–63)	NS	51 (39–63)	48 (38–60)	NS

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Table 1 (cont.). Patient characteristics.

	Entire study group	LVA (+) N = 65 (56%)	LVA (–) N = 51 (44%)	P	Severe LVA (+) N = 18 (16%)	Severe LVA (–) N = 98 (84%)	P
3D LA maximum volume [mL]	87 (74–107) [range 41–148]	88 (74–107)	86 (71–111)	NS	95 (78–112)	86 (70–105)	NS
BSA indexed value [mL/m^2]	42 (35–50)	44 (35–50)	39 (34–54)	NS	**45 (39–57)**	**41 (34–49)**	**0.04**
2D LA minimum length [mm]	64 (61–70)	64 (61–68)	65 (60–72)	NS	63 (61–69)	64 (61–69)	NS
BSA indexed value [mm/m^2]	31 (28–33)	31 (29–33)	30 (27–33)	NS	32 (30–34)	31 (28–33)	NS
2D LA minimum area [cm^2]	26 (22–29)	26 (23–28)	25 (22–31)	NS	26 (22–28)	26 (22–29)	NS
BSA indexed value [cm^2/m^2]	12 (11–14)	13 (11–14)	12 (10–14)	NS	14 (11–15)	12 (11–14)	NS
2D minimum volume [mL]	89 (69–102)	89 (67–99)	87 (70–110)	NS	91 (71–103)	87 (69–100)	NS
BSA indexed value [mL/m^2]	42 (32–50)	45 (32–51)	40 (32–51)	NS	47 (33–53)	40 (32–50)	NS
3D LA minimum volume [mL]	68 (53–83)	69 (54–83)	66 (52–86)	NS	69 (58–95)	66 (52–81)	NS
BSA indexed value [mL/m^2]	33 (25–38)	34 (26–38)	32 (23–41)	NS	34 (29–47)	32 (24–38)	NS
3D LA ejection fraction [%]	23 (16–28)	22 (16–28)	23 (16–30)	NS	25 (19–28)	22 (16–28)	NS
3D LA stroke volume [mL]	20 (13–26)	20 (16–25)	20 (11–27)	NS	21 (18–28)	19 (12–25)	NS
3D LA expansion index [%]	30 (20–41)	30 (21–39)	31 (19–45)	NS	33 (30–40)	29 (19–41)	NS
Enlarged LA [2D LAVI > 34 mL/m^2]	101 (87%)	**59 (91%)**	**42 (82%)**	**0.01**	17 (94%)	84 (86%)	NS
Severely enlarged LA [2D LAVI > 48 mL/m^2]	56 (48%)	34 (52%)	22 (43%)	NS	11 (61%)	45 (46%)	NS
f-waves maximum amplitude [mV]	0.11 (0.09–0.14)	0.1 (0.08–0.14)	0.12 (0.09–0.15)	NS	0.1 (0.08–0.12)	0.11 (0.09–0.15)	NS
BSA indexed value [mV/m^2]	0.05 (0.04–0.07)	0.05 (0.04–0.07)	0.05(0.04–0.07)	NS	0.05 (0.04–0.06)	0.05 (0.04–0.07)	NS
f-waves minimum amplitude [mV]	0.06 (0.05–0.08)	0.05 (0.05–0.08)	0.07 (0.05–0.08)	NS	0.05 (0.05–0.08)	0.06 (0.05–0.08)	NS
BSA indexed value [mV/m^2]	0.03 (0.02–0.04)	0.03 (0.02–0.04)	0.03 (0.02–0.04)	NS	0.03 (0.02–0.04)	0.03 (0.02–0.0.04)	NS
f-waves mean amplitude [mV]	0.08 (0.06–0.1)	0.08 (0.06–0.1)	0.09 (0.07–0.1)	NS	0.08 (0.07–0.01)	0.09 (0.06–0.1)	NS
BSA indexed value [mV/m^2]	0.04 (0.03–0.05)	0.04 (0.03–0.05)	0.04 (0.03–0.05)	NS	0.04 (0.03–0.05)	0.04 (0.03–0.05)	NS
f-waves dispersion [mV]	0.05 (0.03–0.07)	0.05 (0.03–0.06)	0.05 (0.03–0.07)	NS	0.04 (0.03–0.05)	0.05 (0.03–0.07)	NS
Fine AF pattern	72 (62%)	41 (63%)	31 (61%)	NS	13 (72%)	59 (60%)	NS

LVA — low voltage areas; AF — atrial fibrillation; 2D/3D — two/three-dimensional echocardiography; eGFR — estimated glomerular filtration rate; LA — left atrium; LV — left ventricle; BSA — body surface area; LAVI — left atrial volume index; f-waves — atrial fibrillatory waves on a standard surface electrocardiogram

Table 2. Predictors of left atrium remodeling.

	Predictors of LA remodeling				Predictors of severe LA remodeling			
	Univariate		Multivariate		Univariate		Multivariate	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Known uninterrupted AF duration	1.003 (0.990–1.017)	NS			1.005 (0.989–1.021)	NS		
Age	**1.09 (1.034–1.149)**	**0.006**			**1.165 (1.062–1.277)**	**0.002**		
Females	**2.2 (1.238–3.920)**	**0.003**	**2.41(1.341–4.482)**	**0.004**	**2.104 (1.226–3.611)**	**0.009**	**2.441 (1.207–4.938)**	**0.013**
BSA	**0.122 (0.015–0.994)**	**0.044**			**0.019 (0.001– 0.404)**	**0.008**		
Body mass index	0.931 (0.835–1.038)	NS			0.939 (0.806–1.095)	NS		
Hypertension	1.012 (0.610–1.678)	NS			1.403 (0.673–1.965)	NS		
Valvular heart disease	**1.981 (1.319–2.974)**	**0.0006**	**1.862 (1.202–2.883)**	**0.005**	1.632 (0.973–2.736)	NS		
Moderate MR	**1.601 (1.045–2.452)**	**0.03**			1.450 (0.867–2.427)	NS		
Moderate TR	1.500 (0.897–2.509)	NS			1.167 (0.631–2.156)	NS		
Chronic coronary syndrome	**1.826 (1.107–3.012)**	**0.012**			1.396 (0.807–2.416)	NS		
Heart failure	1.09 (0.704–1.687)	NS			0.604 (0.280–1.304)	NS		
eGFR	0.983 (0.960–1.007)	NS			0.985 (0.954–1.016)	NS		
Diabetes	1.157 (0.741–1.808)	NS			1.188 (0.672–2.099)	NS		
Hypothyroidism	**1.903 (0.982–3.690)**	**0.04**			1.503 (0.794–2.845)	NS		
CHA_2DS_2-VASc ≤1	**0.657 (0.444–0.970)**	**0.03**			**0.298 (0.107–0.834)**	**0.02**		
CHA_2DS_2-VASc ≥2	1.410 (0.961–2.070)	NS			**1.818 (0.941–3.489)**	**0.048**		
CHA_2DS_2-VASc ≥3	**1.583 (1.063–2.357)**	**0.02**			**2.079 (1.219–3.547)**	**0.005**		
CHA_2DS_2-VASc ≥4	**3.873 (1.381–10.859)**	**0.0003**	**3.157 (1.091–9.140)**	**0.034**	**3.0 (1.665–5.406)**	**0.003**		
LVEF	0.990 (0.961–1.037)	NS			1.039 (0.979–1.102)	NS		
LA antero-posterior diameter	0.984 (0.910–1.064)	NS			0.989 (0.888–1.101)	NS		
BSA indexed value	1.069 (0.942–1.213)	NS			1.157 (0.977–1.370)	NS		
2D LA maximum length	0.985 (0.925–1.049)	NS			0.973 (0.989–1.055)	NS		
BSA indexed value	1.040 (0.945–1.144)	NS			1.073 (0.942–1.222)	NS		
2D LA maximum area	0.987 (0.913–1.068)	NS			0.980 (0.844–1.088)	NS		
BSA indexed value	1.021 (0.875–1.192)	NS			1.050 (0.859– 1.285)	NS		
2D maximum volume	1.0 (0.987–1.013)	NS			0.988 (0.982–1.015)	NS		
BSA indexed value	1.004 (0.977–1.031)	NS			1.004 (0.969–1.039)	NS		
3D LA maximum volume	1.0 (0.983–1.016)	NS			1.014 (0.993–1.035)	NS		
BSA indexed value	1.004 (0.969–1.040)	NS			1.042 (0.995–1.091)	NS		

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Table 2 (cont.). Predictors of left atrium remodeling.

	Predictors of LA remodeling				Predictors of severe LA remodeling			
	Univariate		Multivariate		Univariate		Multivariate	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
3D LA ejection fraction	0.986 (0.946–1.028)	NS			1.015 (0.962–1.071)	NS		
3D LA stroke volume	0.994 (0.955–1.036)	NS			1.037 (0.985–1.093)	NS		
3D LA expansion index	0.989 (0.965–1.014)	NS			1.012 (0.982–1.044)	NS		
Enlarged LA	1.452 (0.835–2.524)	NS			1.683 (0.591–4.797)	NS		
Severely enlarged LA	1.202 (0.832–1.739)	NS			1.360 (0.814–2.274)	NS		
f-waves maximum amplitude	0.892 (0.560–1.223)	NS			1.103 (0.724–1.679)	NS		
BSA indexed value	0.732 (0.343–1.560)	NS			1.263 (0.559–2.853)	NS		
f-waves mean amplitude	0.501 (0.177–1.414)	NS			0.402 (0.075–2.167)	NS		
BSA indexed value	0.404 (0.052–3.125)	NS			0.388 (0.017–9.1)	NS		
Fine AF pattern	1.072 (–0.734–1.568)	NS			1.294 (0.743–2.253)	NS		

CI — confidence interval; LVEF — left ventricular ejection fraction; MR — mitral regurgitation; OR — odds ratio; TR — tricuspid regurgitation; other abbreviations — see Table 1

were filled and areas of apparent low voltage were confirmed using an ablation catheter. Extension of all areas showing low-voltage potentials at least 5 mm away from the ablation lesion set was measured with dedicated CARTO3 system software. The global LVA burden was calculated as the sum of all LVA and then expressed as the percentage of TSA. It was decided to exclude the following areas from TSA calculations: (a) tubular and antral portion of PVs inside the ablation encirclement, (b) a left atrial appendage (LAA), which, in the majority of cases, contributes a great deal to TSA and has been always found to present high voltage in the present study cohort, (c) an area adjacent to the fossa ovalis that always presents low voltage as containing little myocardium. The appendage was defined as an anatomical structure around the LAA orifice, determined internally from within the LA in a reconstructed shell.

The extent of global LVA burden was arbitrarily considered as mild (< 5% of the TSA), moderate (5–20% of the TSA) and severe (> 20% of the TSA) on the basis of current observation that all detected LVA can be easily ablated if occupying less than 20% of the TSA.

The LA was segmented into five areas, i.e. septum, anterior, posterior, inferior and lateral wall and LAA adopting the landmarks proposed by Huo et al. [5].

Statistical analysis

Continuous data with non-normal distribution is expressed as median and interquartile range (IQR). The categorical variables are presented as values and percentages. Comparisons between groups were performed with either the Mann–Whitney U-test or the χ^2 test as appropriate. Univariate and multivariate logistic regression analyses were used to determine factors associated with the existence of LVA. Only variables with a p-value of < 0.05 in univariate analysis were included for further evaluation in a multivariate model, using a stepwise forward regression. Receiver operating characteristic analysis was used to determine the optimal cut-off value to predict the existence of LVA. Statistical significance for all tests was accepted at a p value < 0.05. A statistical analysis was performed using the Statistica 13.3 software (StatSoft).

Results

Low-voltage areas (15 cm^2 [8–31]; 11% [5–22] of the TSA) were detected in 56% of the patients. Twenty nine percent of patients with LVA presented mild, 43% moderate and 28% severe global LVA

burden. Fifty-seven percent of patients with LVA presented a disseminated pattern of remodeling including at least 3 LA segments. In 3% of patients LVA were limited to 2 segments, and a single segment was affected in 29% (90% the posterior wall, 5% the anterior wall and 5% the inferior wall). The posterior wall was involved in 78.5% of cases (6 cm^2 [5–13]), the anterior LA in 52.3% (8 cm^2 [3–12]), the septum in 49.2% (8 cm^2 [3–11]), the inferior wall in 40% (8 cm^2 [4–10]), and the lateral LA in 23% [4.3 cm^2 [3–8]). The lateral LVA was only noted when there was already LVA elsewhere.

Patients with LVA were more frequently female, older, presented valvular heart disease, moderate mitral regurgitation, chronic coronary syndrome, CHA_2DS_2-VASc score ≥ 3 and ≥ 4 and enlarged LA whilst less often CHA_2DS_2-VASc score ≤ 1 (Table 1).

In the univariate analysis, more advanced age, female sex, lower BSA values, valvular heart disease, moderate mitral regurgitation, chronic coronary syndrome, hypothyroidism, CHA_2DS_2-VASc score ≥ 3 and ≥ 4 predicted the presence of LVA. However, CHA_2DS_2-VASc score ≤ 1 predicted the absence of LVA. A cut-off value of 57 years old predicted LVA incidence with 90% sensitivity and 65% specificity. Whereas, 1.76 m^2 BSA cut-off value with 100% sensitivity and specificity. In the multivariate analysis, only female sex, valvular heart disease and CHA_2DS_2-VASc score ≥ 4 remained statistically significant (Table 2).

Patients with severe LVA were more often female, older, presented lower BSA values, CHA_2DS_2-VASc score ≥ 3 and ≥ 4, higher 3D LA indexed maximum volume, whilst less frequently CHA_2DS_2-VASc score ≤ 1 (Table 1).

The severe LVA burden was associated with older age, female sex, lower BSA values, CHA_2DS_2-VASc score ≥ 2, ≥ 3 and ≥ 4 in the univariate analysis. CHA_2DS_2-VASc score ≤ 1 predicted the absence of severe LVA. A cut-off value of 64 years old predicted severe LVA incidence with 89% sensitivity and 39% specificity, whereas 1.89 m^2 BSA cut-off value with 89% sensitivity and 88% specificity. In the multivariate analysis, only female sex remained statistically significant (Table 2).

Atrial fibrillation duration, LA and LV size and function, f-wave amplitude, AF ECG patterns were neither associated with prediction of the LVA nor severe LVA burden.

Discussion

The key findings of the study were that LSPAF diagnosis does not necessarily equate to extensive voltage-derived LA remodeling and that the best predictors of LVA were female sex, CHA_2DS_2-VASc score > 4 and valvular heart disease. According to available research, this is the first attempt to assess the incidence of voltage-derived LA fibrosis among a large unselected LSPAF population undergoing AF ablation and to correlate LVA burden with non-invasive pre-ablation parameters. Contemporary data concerning the incidence of voltage-defined LA remodeling describe paroxysmal [6–9], persistent [10–16] or a mixed AF population [4, 5, 17–27] in which LSPAF patients are regularly underrepresented. Moreover, patients with severely enlarged atria, very long AF duration, who are elderly, with moderate valvular regurgitation or heart failure are commonly excluded [1, 6, 8, 10, 11, 13, 14, 19, 27]. In addition, presented herein, is a standardized mapping protocol in order to optimize data accuracy.

The prevalence and distribution of LVA

In previous studies the prevalence of LVA was 10–63% in paroxysmal AF (PAF) [4, 8, 18, 19, 20, 25] and 35–100% in persistent AF (PsAF) population [4, 10, 12, 17, 18, 20, 25]. The mean extent of LVA was 5–45 cm^2 in PAF [1, 18, 20, 25] and 12–72 cm^2 in PsAF [1, 12, 13, 15, 16, 18, 20, 25] when reported. In the present study LVA burden was relatively low and there are at least two possible explanations for this. 1) It might be attributed to the voltage mapping approach. The lack of standardized methodology for defining LVA results in significant heterogeneity in voltage mapping strategies among studies, in particular rhythm during mapping, pre or post PVI analysis, mapping density and resolution, catheter-tissue contact verification, analysis of automatically acquired points, and finally electrogram amplitude cut-off value. It is well known that multielectrode mapping catheters with a small electrodes size and spacing provide much higher mapping resolution of an atrial scar [24]. The accuracy of voltage mapping could further increase with catheter-tissue contact verification and manual point verification [25] and finally high-density acquisition [24]. All of the issues were incorporated into the current approach. 2) This might reflect a heterogeneity of the atrial substrate among the AF population.

In the present cohort, LVA were most often located at the posterior wall which is not in line with other studies, where the anterior wall and septum were generally affected [1, 4, 7, 8, 11, 13, 15–17, 20, 23, 24]. Moreover, the posterior wall was the most common single remodeling site. Therefore, it can

be speculated that voltage-derived fibrosis begins at the posterior wall and spreads gradually around the LA. Furthermore, lateral LA, usually a very rare location of LVA [4, 8, 11, 20, 23] was affected in relatively many cases, but was never found at a single remodeling site. It can be hypothesized that it is the last affected area when the disseminated pattern of LVA is present. LVA inside the LAA was not found as this was previously reported [11, 20].

The predictors of LVA

Previous studies have shown evidence of LVA with several markers [1, 4, 7, 8, 12, 15, 18, 20, 22–26]. Intuitively voltage-defined LA remodeling burden would be expected to increase with a longer AF duration time, increased atrial size, decreased LA function, advanced age, the presence of structural heart disease or many concomitant comorbidities and a fine AF pattern. Further, aforementioned discussion about these potential correlations in the light of the present study results was undertaken.

Many studies demonstrated that there is a positive association between LVA and AF persistence [1, 4, 7, 13, 18, 20, 22, 24]. The underlying mechanism decreasing LA voltage is usually explained by tachycardia induced functional changes that over time result in electrical and structural atrial remodeling [28]. However other studies demonstrated LVA among the PAF population [1, 4, 6–9, 17–23]. It was also reported that even the successful elimination of AF fails to halt the progression of fibrosis [29], suggesting that abnormal LA substrate is not the result of arrhythmia alone. Additionally, some studies indicated that the persistence of AF was not a marker of LVA [15, 17, 23, 25, 26]. These findings are in line with the present study results, as there was no correlation between AF duration and detection of LVA. This indicates that there are other factors causing atrial remodeling beside AF and atrial structural changes that could be the cause, and not the consequence of AF.

Many studies reported an association between LA enlargement and LVA [3, 8, 13, 15, 23–27] expressed with LA diameter, area or volume. In the current dataset there was no association between LA size expressed in many various parameters and LVA, despite the fact that 87% of patients had enlarged and 48% severely enlarged LA based on widely accepted 2D indexed LA volume [2]. A detailed LA size assessment with 3D echocardiography, which is more accurate than 2D echocardiography and correlates well with cardiac computed tomography and magnetic resonance imaging [2], did not affect the results. Moreover, 3D derived LA systolic and diastolic function was not associated with LVA. However, due to the limited normative data describing LA function [2] it is hard to assess if the patients presented a decreased LA function pattern. A possible explanation of the present findings is that LVA might be attributed to LA structural, rather than functional remodeling. It was observed that LA remodeling in the AF population, manifesting as a change in atrial size, differs from the consequence of other causes, as it is at least partially reversible [27]. In the current study cohort lack of LVA despite LA enlargement was limited to patients without underlying structural heart disease and it can be speculated that LA enlargement resulted exclusively from LSPAF. Alternatively, the presence of structural heart disease, such as any moderate valvular regurgitation (primary or functional due to annular dilatation as the consequence of LA enlargement [30]) probably resulted in voltage-defined LA fibrosis. LA enlargement was secondary to this scenario as a consequence of valvular regurgitation, AF or a combination of both. A direct pathophysiological relationship of mitral regurgitation with LA LVA seems obvious, however such a relationship with tricuspid regurgitation is not easy to explain. This could be a manifestation of long-standing increased pulmonary pressure and LA pressure overload [31].

There are some studies that found an association between LVA and age [1, 4, 7, 13, 15, 23–26]. However, the data seem to be ambiguous [8, 20]. The present study showed that age does not correlate with LVA incidence which supports the hypothesis that any age contribution to voltage-derived remodeling development is limited.

In the majority of studies there is an association between LVA and female sex [1, 4, 7, 8, 15, 20, 24]. The findings herein, are in line with this data. It could be assumed that females are genetically favored for atrial fibrosis [32] and/or undergo AF ablation in an advanced state of the disease [33].

In the present dataset many classical risk factors failed to predict LVA in multivariate analysis. However, a combination of these factors expressed as a high CHA_2DS_2-VASc score > 4 was in fact predictive. This highlights the multifactorial nature of LVA development and the interplay between risk factors. In previous studies a mean risk score of 2.5–2.6 was an independent predictor for LVA [7, 13, 18] or remained not predictive at all [34].

Fibrillatory wave amplitude on surface ECG could potentially unmask atrial LVA as it is dependent on the magnitude of the underlying voltage, which is related to the magnitude of remaining viable

atrial muscle [3]. However, in this study such a correlation was not found. What may be considered one major factor, is that atrial activity recorded in lead V1 does not reflect left atrial activity exclusively, but rather right atrial or global atrial activity.

Limitations of the study

Voltage mapping was limited to patients who were able to maintain sinus rhythm following PVI and cardioversion. Therefore, this may have reduced the overall LVA burden. Voltage mapping following PVI may have excluded a part of LA with low voltages and could have reduced the overall LVA burden. Voltages < 0.5 mV were considered to correlate well with different degrees of LA structural defect, based on previous descriptions. However, this cut-off value has not been clearly validated. It is too early to exclude the extent to which the LA fibrosis in our patient cohort might have been detected or reclassified to normal when compared to other methods for detecting LA fibrosis, especially cardiac magnetic resonance imaging [35]. Females were strongly underrepresented in our population.

Conclusions

The present study showed that a diagnosis of LSPAF does not indicate the presence of LVA in many cases and that neither long AF duration, LA enlargement, nor ECG parameters correlate with LVA presence or extent. Given the fact that many electrophysiologists incorporate voltage mapping to guide AF ablation to improve results, and presuming that patients without evidence of LVA may be sufficiently treated with PVI alone, this study provides important new insight into the promise: 1) Patients with LSPAF should not be excluded from voltage map-guided ablation procedures on the basis of long AF duration, advanced age, LA enlargement or fine AF ECG pattern; 2) Many LSPAF patients do not require voltage-derived substrate modification following PVI and therefore can avoid excessive ablation; 3) Simple non-invasive screening of the LSPAF population could predict LVA prevalence and help in further decision making.

However, it is still unclear if voltage-defined fibrosis presence and its extent can be useful markers in a decision as to whether a patient requires additional PV ablation.

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References

1. Blandino A, Bianchi F, Grossi S, et al. Left atrial substrate modification targeting low-voltage areas for catheter ablation of atrial fibrillation: a systematic review and meta-analysis. Pacing Clin Electrophysiol. 2017; 40(2): 199–212, doi: 10.1111/pace.13015, indexed in Pubmed: 28054377.
2. 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. Eur Heart J Cardiovasc Imaging. 2015; 16(3): 233–270, doi: 10.1093/ehjci/jev014, indexed in Pubmed: 25712077.
3. Nault I, Lellouche N, Matsuo S, et al. Clinical value of fibrillatory wave amplitude on surface ECG in patients with persistent atrial fibrillation. J Interv Card Electrophysiol. 2009; 26(1): 11–19, doi: 10.1007/s10840-009-9398-3, indexed in Pubmed: 19404588.
4. Rolf S, Kircher S, Arya A, et al. Tailored atrial substrate modification based on low-voltage areas in catheter ablation of atrial fibrillation. Circ Arrhythm Electrophysiol. 2014; 7(5): 825–833, doi: 10.1161/CIRCEP.113.001251, indexed in Pubmed: 25151631.
5. Huo Y, Gaspar T, Pohl M, et al. Prevalence and predictors of low voltage zones in the left atrium in patients with atrial fibrillation. Europace. 2018; 20(6): 956–962, doi: 10.1093/europace/eux082, indexed in Pubmed: 28605524.
6. Vlachos K, Efremidis M, Letsas KP, et al. Low-voltage areas detected by high-density electroanatomical mapping predict recurrence after ablation for paroxysmal atrial fibrillation. J Cardiovasc Electrophysiol. 2017; 28(12): 1393–1402, doi: 10.1111/jce.13321, indexed in Pubmed: 28884923.
7. Masuda M, Fujita M, Iida O, et al. Left atrial low-voltage areas predict atrial fibrillation recurrence after catheter ablation in patients with paroxysmal atrial fibrillation. Int J Cardiol. 2018; 257: 97–101, doi: 10.1016/j.ijcard.2017.12.089, indexed in Pubmed: 29506746.
8. Wang XH, Li Z, Mao JL, et al. Low voltage areas in paroxysmal atrial fibrillation: The prevalence, risk factors and impact on the effectiveness of catheter ablation. Int J Cardiol. 2018; 269: 139–144, doi: 10.1016/j.ijcard.2018.07.076, indexed in Pubmed: 30060968.
9. Zhou W, Wang L, Zhou Bo, et al. Catheter ablation of paroxysmal atrial fibrillation using high-density mapping-guided substrate modification. Pacing Clin Electrophysiol. 2018; 41(12): 1630–1634, doi: 10.1111/pace.13524, indexed in Pubmed: 30353561.

10. Wang XH, Li Z, Mao JL, et al. A novel individualized substrate modification approach for the treatment of long-standing persistent atrial fibrillation: preliminary results. Int J Cardiol. 2014; 175(1): 162–168, doi: 10.1016/j.ijcard.2014.05.022, indexed in Pubmed: 24874911.
11. Yang G, Yang B, Wei Y, et al. Catheter ablation of nonparoxysmal atrial fibrillation using electrophysiologically guided substrate modification during sinus rhythm after pulmonary vein isolation. Circ Arrhythm Electrophysiol. 2016; 9(2): e003382, doi: 10.1161/CIRCEP.115.003382, indexed in Pubmed: 26857907.
12. Jadidi AS, Lehrmann H, Keyl C, et al. Ablation of persistent atrial fibrillation targeting low-voltage areas with selective activation characteristics. Circ Arrhythm Electrophysiol. 2016; 9(3), doi: 10.1161/CIRCEP.115.002962, indexed in Pubmed: 26966286.
13. Yamaguchi T, Tsuchiya T, Fukui A, et al. Efficacy of left atrial voltage-based catheter ablation of persistent atrial fibrillation. J Cardiovasc Electrophysiol. 2016; 27(9): 1055–1063, doi: 10.1111/jce.13019, indexed in Pubmed: 27235000.
14. Yang B, Jiang C, Lin Y, et al. STABLE-SR (Electrophysiological Substrate Ablation in the Left Atrium During Sinus Rhythm) for the Treatment of Nonparoxysmal Atrial Fibrillation: A Prospective, Multicenter Randomized Clinical Trial. Circ Arrhythm Electrophysiol. 2017; 10(11), doi: 10.1161/CIRCEP.117.005405, indexed in Pubmed: 29141843.
15. Ammar-Busch S, Buiatti A, Tatzber A, et al. Predictors of low voltage areas in persistent atrial fibrillation: is it really a matter of time? J Interv Card Electrophysiol. 2020; 57(3): 345–352, doi: 10.1007/s10840-018-0471-7, indexed in Pubmed: 30374659.
16. Kumagai K, Toyama H, Zhang Bo. Effects of additional ablation of low-voltage areas after Box isolation for persistent atrial fibrillation. J Arrhythm. 2019; 35(2): 197–204, doi: 10.1002/joa3.12169, indexed in Pubmed: 31007783.
17. Kottkamp H, Berg J, Bender R, et al. Box isolation of fibrotic areas (BIFA): a patient-tailored substrate modification approach for ablation of atrial fibrillation. J Cardiovasc Electrophysiol. 2016; 27(1): 22–30, doi: 10.1111/jce.12870, indexed in Pubmed: 26511713.
18. Yagishita A, Gimbel JR, De Oliveira S, et al. Long-Term outcome of left atrial voltage-guided substrate ablation during atrial fibrillation: a novel adjunctive ablation strategy. J Cardiovasc Electrophysiol. 2017; 28(2): 147–155, doi: 10.1111/jce.13122, indexed in Pubmed: 27862561.
19. Kircher S, Arya A, Altmann D, et al. Individually tailored vs. standardized substrate modification during radiofrequency catheter ablation for atrial fibrillation: a randomized study. Europace. 2018; 20(11): 1766–1775, doi: 10.1093/europace/eux310, indexed in Pubmed: 29177475.
20. Schreiber D, Rieger A, Moser F, et al. Catheter ablation of atrial fibrillation with box isolation of fibrotic areas: Lessons on fibrosis distribution and extent, clinical characteristics, and their impact on long-term outcome. J Cardiovasc Electrophysiol. 2017; 28(9): 971–983, doi: 10.1111/jce.13278, indexed in Pubmed: 28635186.
21. Huang D, Li JB, Zghaib T, et al. The Extent of Left Atrial Low-Voltage Areas Included in Pulmonary Vein Isolation Is Associated With Freedom from Recurrent Atrial Arrhythmia. Can J Cardiol. 2018; 34(1): 73–79, doi: 10.1016/j.cjca.2017.10.012, indexed in Pubmed: 29275886.
22. Ahmed-Jushuf F, Murgatroyd F, Dhillon P, et al. The impact of the presence of left atrial low voltage areas on outcomes from pulmonary vein isolation. J Arrhythm. 2019; 35(2): 205–214, doi: 10.1002/joa3.12174, indexed in Pubmed: 31007784.
23. Matsuda Y, Masuda M, Asai M, et al. Impact of renal dysfunction on left atrial low-voltage areas in patients with atrial fibrillation. Circ J. 2019; 83(5): 985–990, doi: 10.1253/circj.CJ-18-1277, indexed in Pubmed: 30853681.
24. Kosiuk J, Dinov B, Kornej J, et al. Prospective, multicenter validation of a clinical risk score for left atrial arrhythmogenic substrate based on voltage analysis: DR-FLASH score. Heart Rhythm. 2015; 12(11): 2207–2212, doi: 10.1016/j.hrthm.2015.07.003, indexed in Pubmed: 26144350.
25. Nery PB, Al Dawood W, Nair GM, et al. Characterization of low-voltage areas in patients with atrial fibrillation: insights from high-density intracardiac mapping. Can J Cardiol. 2018; 34(8): 1033–1040, doi: 10.1016/j.cjca.2018.04.008, indexed in Pubmed: 30056843.
26. Kishima H, Mine T, Fukuhara E, et al. The association between left atrial stiffness and low-voltage areas of left atrium in patients with atrial fibrillation. Heart Vessels. 2019; 34(11): 1830–1838, doi: 10.1007/s00380-019-01423-z, indexed in Pubmed: 31049675.
27. Hohendanner F, Romero I, Blaschke F, et al. Extent and magnitude of low-voltage areas assessed by ultra-high-density electroanatomical mapping correlate with left atrial function. Int J Cardiol. 2018; 272: 108–112, doi: 10.1016/j.ijcard.2018.07.048, indexed in Pubmed: 30017527.
28. Wijffels MC, Kirchhof CJ, Dorland R, et al. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation. 1995; 92(7): 1954–1968, doi: 10.1161/01.cir.92.7.1954, indexed in Pubmed: 7671380.
29. Teh AW, Kistler PM, Lee G, et al. Long-term effects of catheter ablation for lone atrial fibrillation: progressive atrial electroanatomic substrate remodeling despite successful ablation. Heart Rhythm. 2012; 9(4): 473–480, doi: 10.1016/j.hrthm.2011.11.013, indexed in Pubmed: 22079885.
30. Silbiger JJ. Mechanistic insights into atrial functional mitral regurgitation: Far more complicated than just left atrial remodeling. Echocardiography. 2019; 36(1): 164–169, doi: 10.1111/echo.14249, indexed in Pubmed: 30620100.
31. Iacuzio L, Essayagh B, Civaia F, et al. Right-Sided heart structural and functional remodeling in mitral regurgitation secondary to mitral valve prolapse. Am J Cardiol. 2018; 122(12): 2095–2103, doi: 10.1016/j.amjcard.2018.08.062, indexed in Pubmed: 30293652.
32. Begg GA, Lip GYH, Plein S, et al. Circulating biomarkers of fibrosis and cardioversion of atrial fibrillation: A prospective, controlled cohort study. Clin Biochem. 2017; 50(1-2): 11–15, doi: 10.1016/j.clinbiochem.2016.09.008, indexed in Pubmed: 27622867.
33. Patel D, Mohanty P, Di Biase L, et al. Outcomes and complications of catheter ablation for atrial fibrillation in females. Heart Rhythm. 2010; 7(2): 167–172, doi: 10.1016/j.hrthm.2009.10.025, indexed in Pubmed: 20022814.
34. Park JH, Joung B, Son NH, et al. The electroanatomical remodelling of the left atrium is related to CHADS2/CHA2DS2VASc score and events of stroke in patients with atrial fibrillation. Europace. 2011; 13(11): 1541–1549, doi: 10.1093/europace/eur135, indexed in Pubmed: 21576128.
35. Chen J, Arentz T, Cochet H, et al. Extent and spatial distribution of left atrial arrhythmogenic sites, late gadolinium enhancement at magnetic resonance imaging, and low-voltage areas in patients with persistent atrial fibrillation: comparison of imaging vs. electrical parameters of fibrosis and arrhythmogenesis. Europace. 2019; 21(10): 1484–1493, doi: 10.1093/europace/euz159, indexed in Pubmed: 31280323.

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Heart failure with preserved ejection fraction update: A review of clinical trials and new therapeutic considerations

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Abstract

Between 2013 and 2016 there were approximately 6.2 million adults in the United States living with heart failure; nearly half had an ejection fraction that was preserved. Despite the high prevalence of heart failure with preserved ejection fraction (HFpEF), our understanding of this disease is limited and it still carries significant morbidity and mortality worldwide. At present, physicians are burdened by the inconclusive benefits of currently available treatment options. Recently the scientific community has seen an influx of new pathophysiology studies and outcome trials that have reshaped our understanding of HFpEF as a complex, multi-systemic disease. Pharmacological trials involving beta-blockers, angiotensin II receptor antagonists, aldosterone antagonists, and angiotensin-neprilysin inhibitors have demonstrated encouraging results, but have yet to reach the significance of advancements made in the treatment of heart failure with reduced ejection fraction. This review aims to summarize landmark clinical trials that have influenced current treatment guidelines, and reports on emerging evidence supporting/refuting new treatment modalities including pharmacotherapy, lifestyle modification and device therapy. (Cardiol J 2022; 29, 4: 670–679)

Key words: heart failure, heart failure with preserved ejection fraction, HFpEF, diastolic heart failure, clinical trials

Introduction

Approximately half of patients with heart failure (HF) have a left ventricular ejection fraction (LVEF) that is preserved [1, 2]. HF with preserved ejection fraction (HFpEF) is a clinical syndrome affecting millions of people worldwide, whose pathophysiology is still poorly understood. Diagnosis relies on a combination of symptomatology, echocardiographic evidence, exclusion of noncardiac causes of dyspnea, and in some cases invasive hemodynamic measurements. According to the latest guidelines, there is inconclusive evidence for the benefit of any pharmacotherapy in reducing morbidity, mortality or HF hospitalizations in these patients [3, 4]. This review provides an update on HFpEF, addressing the epidemiology, pathophysiology, diagnosis and current management strategies

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based on a review of clinical trials and provides therapeutic rationale for new treatment options.

Definition

HFpEF is a clinical syndrome in which patients have signs and symptoms of HF, a normal LVEF (≥ 50%), elevated natriuretic peptide levels, and evidence of diastolic dysfunction or relevant structural heart disease. Diastolic dysfunction is characterized by structural changes such as an increase in left ventricular (LV) wall thickness and/or left atrial (LA) size which result in abnormal LV filing and elevated LV filling pressure (LVFP) [1, 3, 5]. The stratification of patients according to LVEF is important because patients within their respective dichotomy often share similar underlying etiologies and co-morbidities, which has implications on selection of therapy and prognosis [2].

Epidemiology

The American Heart Association (AHA) estimated that between 2013 and 2016 there were approximately 6.2 million adults in the United States living with HF [6]. Nearly half had a preserved ejection fraction (EF) [1, 2]. Recent data suggests the age-specific incidence of HF may be decreasing, however longitudinal studies from Mayo Clinic using the Olmsted County Cohort, the Framingham Heart Study, and the Cardiovascular Health Study, have all shown a proportional increase in the prevalence of HFpEF over the past two decades [7–9]. It is well documented that the risk of HFpEF increases with age and is related to conditions such as hypertension, obesity, and coronary artery disease (CAD). Multimorbidity is ubiquitous in HFpEF with approximately half of patients having five or more major comorbidities. Conceivably, HFpEF patients experience a higher proportion of non-cardiovascular (CV) deaths, albeit the majority of deaths are CV in etiology. Unlike heart failure with reduced ejection fraction (HFrEF) where there is a predilection for the male gender, the prevalence of HFpEF is equal among men and women [3, 9].

Pathophysiology

Although HFpEF is common, the pathophysiology remains largely unknown. Coronary microvascular dysfunction is an important factor in disease development, however recent data has also pointed towards extracardiac pathologies [1, 10]. Obesity and diabetes mellitus, which often coexist, cause intramyocardial inflammation that results in epicardial fat expansion and LV fibrosis that may play an essential role in the pathophysiology of HFpEF [1, 10].

One demonstrable hemodynamic abnormality that characterizes HFpEF patients is increased LVFP due to diastolic dysfunction, defined as the inability to fill the LV to an adequate end-diastolic volume at acceptably low pressures [1, 11, 12]. In mild cases of HFpEF, LVFP is only elevated during exertion [1, 11, 13]. Ventricular diastolic function can be conceptualized as the sum of early active LV relaxation and late passive 'stiffness', related to myocardial structural tension [11, 14]. HFpEF patients have prolonged active LV relaxation that is more apparent with exertion [1, 11, 15, 16]. They also lose LV suction, a phenomenon caused by intraventricular pressure gradients determined by the speed of relaxation, velocity of mitral annular longitudinal motion, LV "untwisting", and end-systolic volume (ESV) achieved during the preceding contraction cycle. Loss of LV suction means that LA hypertension becomes necessary to drive LV filling [1, 11, 17]. Ventricular diastolic stiffness also serves as an important factor driving elevated LVFP. Previously, it was thought to be determined by collagen quantity and qualities of extracellular matrix, however recent data theorizes that myocytes are responsible for increased stiffness via phosphorylation of the sarcomeric protein titin [11, 18].

Reduced systolic function is also implicated in HFpEF pathophysiology [1, 11]. Despite preserved LVEF, studies have identified subtle abnormalities in systolic function, made evident by tissue Doppler and strain-based imaging [11, 17]. Systolic dysfunction promotes LA hypertension by reducing early LV suction due to elevated ESV while also directly leading to reduced anterograde flow. Chronically elevated LVFP correlates with secondary LA dysfunction and remodeling [1, 11]. When LA dysfunction occurs, HFpEF patients lose the barrier between the LV and pulmonary circulation leading to pulmonary hypertension and right HF [1, 11, 19]. Additionally, one third of the HFpEF patients develop right ventricular dysfunction that confers an increased risk for adverse outcomes via systemic venous congestion causing intestinal edema, congestive hepatopathy and cardiorenal syndrome [11, 20].

Autopsy studies in HFpEF patients have shown reduced coronary microvascular density and the degree of reduction correlates with the magnitude of myocardial fibrosis [1, 13]. Vascular

abnormalities are common [21], such as the inability of peripheral vessels to dilate appropriately, leading to greater afterload and increased ESV. This, in part, is caused by endothelial dysfunction and decreased nitric oxide levels [1, 11]. HFpEF patients also exhibit changes in skeletal muscle, manifesting as sarcopenia and decreased oxygen utilization [1, 21]. Other rarely considered causes of HFpEF are infiltrative cardiomyopathies, such as amyloidosis. The disease pathophysiology is distinct from what is discussed above. While generally thought to be rare, the prevalence of wild-type transthyretin cardiac amyloidosis is estimated to be 13% to 19% among HFpEF patients [1].

Diagnosis

Since there is no single test or biomarker that identifies HFpEF, diagnosis continues to be a challenge. In addition to clinical suspicion, three important criteria are essential. Patients must present with one or more symptoms of HF (i.e., dyspnea, orthopnea, edema). Next, using Doppler echocardiography or invasive hemodynamic testing, a quantitative assessment of preserved LVEF and elevated LVFP is required. Finally, all other etiologies that can explain the clinical symptoms of HF such as obesity, pulmonary disease, cardiomyopathy, pericardial or valvular heart disease must be excluded [5]. Once the aforementioned criteria are met, the H2FPEF or HFA-PEFF scores can be calculated to further discriminate HFpEF from other noncardiac causes of unexplained dyspnea [22, 23].

The H2FPEF score [22] uses 6 clinical and echocardiographic features that predict HF: body mass index > 30 kg/m^2, use of two or more antihypertensives, presence of atrial fibrillation, age > 60, Doppler echocardiographic estimated pulmonary artery systolic pressure > 35 mmHg and E/e' ratio > 9. Each variable is assigned a point value totaling a maximum of 9 points. A score < 2 predicts low likelihood of HFpEF, while a score > 6 predicts high likelihood. Calculation of the HFA-PEFF score [23] is the second step in an advanced algorithm which involves pretest assessment, diagnostic work-up, functional testing and etiologic investigation. The score comprises functional and morphologic parameters evaluated by echocardiography or cardiac magnetic resonance imaging, in addition to different threshold serum natriuretic peptide levels. The sum of points across all three domains is calculated (2 points for major criteria, 1 point for minor criteria), with a maximum of 2 points for each domain. Scores from 0 to 6 predict the probability of HFpEF with a score ≥ 5 considered diagnostic and ≤ 1 excluding the diagnosis. Intermediate scores of 2–4 require evaluation with exercise stress echocardiography or invasive hemodynamic measurements [23]. The applicability and prognostic value of these scoring systems has been validated such that they can help identify patients who may benefit from certain pharmacotherapies as well as predict the risk of HF hospitalization or death [24–27].

Trials

Beta-blockers

The SENIORS trial [28] investigated the use of nebivolol, a beta-1-selective blocker, in elderly patients (≥ 70 years) with HF, looking at a primary composite outcome of all-cause mortality and CV hospitalization. One third of the 2128 participants had LVEF > 35%. After a median follow-up of 21 months, the primary endpoint was seen in 31.1% and 35.3% of patients receiving nebivolol or placebo, respectively (hazard ratio [HR] 0.86; 95% confidence interval [CI]: 0.74–0.99; p = 0.039). Although the trial did not assess exercise capacity, it concluded that nebivolol was well tolerated and effective in reducing morbidity and mortality in elderly patients across a spectrum of measured LVEF [28]. The ELANDD trial [29] explored the effects of nebivolol, particularly nitric oxide-mediated vasodilation, on exercise capacity in HFpEF patients. The multicenter randomized controlled trial (RCT) recruited 116 participants and assigned them to either 6-month treatment with nebivolol or placebo. No improvement in the primary endpoint, change in 6-minute walk test (6MWT) distance, was seen between groups (from 420 ± 143 to 428 ± 141 m with nebivolol vs. from 412 ± 123 to 446 ± 119 m with placebo; p = 0.004 for interaction). A significant correlation was seen between the change in peak exercise heart rate and peak oxygen consumption ($\dot{V}O_2$) (r = 0.391; p = 0.003). Overall treatment with nebivolol resulted in an unfavorable outcome on exercise capacity, likely owing to negative chronotropic effects [29]. J-DHF [30], a prospective randomized, open, blinded-endpoint study, assessed the efficacy of carvedilol vs. placebo in HFpEF patients, looking at a composite outcome of CV death and CV hospitalization. Participants receiving carvedilol were further subdivided into standard-dose (> 7.5 mg/day) and low-dose (≤ 7.5 mg/day) groups. After a median follow-up of 3.2 years, the primary outcome occurred in 24.2% and 27.2% of patients

in the carvedilol and placebo groups, respectively (HR 0.902; 95% CI: 0.546–1.488; p = 0.6854). In the standard-dose group, the composite primary endpoint was significantly reduced compared to placebo (HR 0.539; 95% CI: 0.303–0.959; p = 0.0356), whereas in the low-dose group the same endpoint was comparable to placebo. The study was underpowered and failed to show prognostic benefit after treatment with carvedilol. However, administration of standard-dose carvedilol was associated with a reduction in CV death or CV hospitalization which may incite further study [30].

Angiotensin-converting-enzyme inhibitors/angiotensin receptor blockers

The CHARM-Preserved trial [31], a multicenter study across 26 European countries, studied the efficacy of candesartan, looking at a primary composite outcome of CV death and HF hospitalization. 3023 HFpEF participants were randomized 1:1 to receive candesartan (target dose 32 mg once daily) or placebo. After a median follow-up of 36.6 months, the primary endpoint was seen in 22% and 24% of patients in the candesartan and placebo groups respectively (HR 0.86; 95% CI: 0.74–1.00; p = 0.051). Although no clear benefit was seen, there was a modest reduction in HF hospitalization rate (HR 0.84; 95% CI: 0.70–1.00; p = 0.051), prompting a class IIb recommendation by the American College of Cardiology/American Heart Association (ACC/AHA) for treatment of HFpEF with angiotensin receptor blockers (ARBs) [4, 31]. PEP-CHF [32], a double-blinded, multicenter RCT, looked at the effects of perindopril in patients aged ≥ 70 years with diastolic dysfunction confirmed by Doppler echocardiography. 850 participants were divided into two treatment groups, perindopril (4 mg once daily) or placebo, and monitored for a mean follow-up of 26.2 months. No significant reduction in the primary endpoint, a composite of all-cause mortality and HF hospitalization, was observed (HR 0.92; 95% CI: 0.70–1.21; p = 0.55). The study was insufficiently powered resulting from many patients leaving early to start open-label angiotensin-converting-enzyme inhibitors [32]. In the I-PRESERVE trial, Massie et al. [33] assessed the efficacy of irbesartan in HFpEF patients, looking at a composite endpoint of all-cause mortality or CV hospitalization. 4128 participants from 25 countries across 5 continents were randomly assigned 1:1 to receive irbesartan (300 mg once daily) or placebo. After a mean follow-up of 49.5 months, the primary endpoint occurred in 36% and 37% of patients in the respective treatment groups (HR 0.95; 95% CI: 0.86–1.05; p = 0.35). The trial failed to replicate the therapeutic benefits of ARB therapy seen in the CHARM-Preserved Trial [33].

Mineralocorticoid receptor antagonists

TOPCAT [34], an international RCT, investigated treatment of HFpEF with mineralocorticoid receptor antagonists (MRAs). The trial enrolled 3445 patients aged ≥ 50 years with LVEF ≥ 45%, and HF hospitalization within 12 months or elevated natriuretic peptide levels within 60 days of randomization. It consisted of 1767 participants from the United States, Canada, Brazil, Argentina, grouped as the Americas, and 1678 participants from Russia/Georgia. Patients were treated with spironolactone (15–45 mg once daily) or placebo during mean follow-up of 3.3 years, and the primary outcome was a composite of CV death, aborted cardiac arrest or HF hospitalization. Secondary outcomes included all-cause mortality or hospitalization, hyperkalemia (> 5.5 mmol/L), hypokalemia (< 3.5 mmol/L), serum creatinine level > 2 times baseline and above the upper limit of normal, and serum creatinine 3.0 mg/dL or greater [34]. Dose adjustments of spironolactone were limited by elevations in serum creatinine and potassium, therefore one-third of participants discontinued therapy but continued study participation. The overall incidence of the primary composite outcome was not reduced by treatment; events occurred in 18.6% and 20.4% of patients in the spironolactone and placebo groups, respectively (p = 0.14). Importantly, there was a lower incidence of HF hospitalization in the spironolactone group when compared to placebo (206 [12.0%] vs. 245 [14.2%]; HR 0.83; 95% CI: 0.69–0.99; p = 0.04) [34]. A post hoc analysis identified significant regional variations, almost a 4-fold difference, in clinical outcomes of patients from Russia/Georgia compared to the Americas [34, 35]. Demographic characteristics revealed that trial results may have been confounded by enrollment of two distinctly different populations. Patients from Russia/Georgia were younger, had less atrial fibrillation, diabetes mellitus, and chronic kidney disease, but were more likely to have had prior myocardial infarction or HF hospitalization. Differences also included lower baseline LVEF and creatinine but higher diastolic blood pressure. When comparing outcome measures, patients from the Americas experienced hyperkalemia and doubling of creatinine more frequently with spironolactone but had fewer hypokalemic events. Rates of the primary composite outcome were also significantly reduced by spironolactone therapy in patients from the Americas but were

unaffected in patients from Russia/Georgia [35]. It was concluded that spironolactone therapy may improve prognosis by lowering rates of CV death and HF hospitalization, with an incremental added risk of hyperkalemia and renal impairment [35, 36].

Nitrates

The first trial to examine nitrate therapy for HFpEF was NEAT-HFpEF [37], a multicenter crossover study that tested the effects of extended-release isosorbide mononitrate (ISMN) vs. placebo on daily activity. 110 participants were randomly assigned to either a 6-week dose-escalation regimen of ISMN (30 mg to 60 mg to 120 mg once daily) or placebo, followed by crossover to the opposite group for 6 weeks. The primary endpoint was daily activity level measured by patient-worn accelerometers, specifically average daily accelerometer units during the 120-mg phase of ISMN. Secondary endpoints included hours of activity per day during the maximum dose phase, daily accelerometer units during all three phases, quality of life (QOL) scores, 6MWT distance, and natriuretic peptide levels. Subgroup analysis revealed that in the group receiving the maximum dose of ISMN, there was a significant decrease in hours of activity per day compared to placebo (−0.30 hours; [−0.55 to −0.05]; p = 0.02). During all dose phases, activity in the ISMN group was lower than in the placebo groups and the decline was dose-dependent (−439 accelerometer units; [−792 to −86]; p = 0.02). There were no significant between-group differences in the secondary outcome measures, but the results were numerically unfavorable to nitrates. Overall treatment with ISMN did not improve submaximal exercise capacity, QOL scores, or natriuretic peptide levels [37–39]. In fact, nitrate therapy may be detrimental in HFpEF patients due to an increased risk for CV events [38, 40]. NEAT-HFpEF may have been limited by its dose-escalation strategy because HFpEF patients are hypersensitive to rapid changes in hemodynamics [38]. INDIE-HFpEF [41], a follow-up trial with similar design, also failed to show any benefits of inorganic nitrates on exercise capacity. There was no improvement in peak oxygen consumption, daily activity levels, health status, functional class (New York Heart Association [NYHA]), cardiac filling pressures or natriuretic peptide levels in HFpEF patients treated with nebulized nitrate therapy for 4 weeks.

Angiotensin-neprilysin inhibition

PARAGON-HF [42], was a prospective comparison of angiotensin-neprilysin inhibition vs. ARB therapy in patients with NYHA class II–IV HF, LVEF ≥ 45%, elevated natriuretic peptide levels, and structural heart disease. It hoped to replicate the results of its predecessor, PARADIGM-HF, which demonstrated significant benefits of sacubitril/valsartan compared to submaximal doses of enalapril in HFrEF patients [43]. Solomon et al. [42] organized a double-blinded, active-comparator trial, in which 4822 HFpEF participants from 848 centers in 43 countries, were randomized 1:1 to receive sacubitril/valsartan (target dose 97 mg of sacubitril with 103 mg of valsartan twice daily) or valsartan (target dose 160 mg twice daily). The primary endpoint was a reduction in incidence of HF hospitalization or death. After a median follow-up of 35 months there were 894 primary events in 526 patients receiving sacubitril/valsartan and 1009 events in 557 patients receiving valsartan (HR 0.87; 95% CI: 0.75–1.01; p = 0.06). Concerning the primary composite outcome, sacubitril/valsartan therapy did not result in a statistically significant benefit, however, among 12 prespecified subgroups, there was possible benefit for women and patients with lower EF (45–57%) [42, 44]. Despite using a framework for interpretation of treatment heterogeneity in subgroups, and evaluation of key considerations such as biological plausibility, age-related arterial stiffening, and incidence of risk factors predisposing to HF exacerbations, the mechanistic basis for sex-related benefits remains unclear [44].

SGLT-2 inhibition

The efficacy of sodium-glucose co-transporter 2 (SGLT-2) inhibitors in patients with HFrEF with and without diabetes has been well established in DAPA-HF and EMPEROR-Reduced trials [45, 46]. Dapagliflozin and empagliflozin showed lower rates of hospitalization and mortality benefit in patients with HFrEF [45, 46]. PRESERVED-HF was designed to study whether dapagliflozin improves symptoms, physical limitations and exercise capacity in patients with HFpEF irrespective of diabetes status [47]. 324 patients with an LVEF ≥ 45% were randomized 1:1 to receive dapagliflozin or placebo. The primary endpoint was improvement of Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CS) a self-administered instrument that quantifies HF-related symptoms, physical function, QOL and social life, higher scores reflecting better health status [47]. Dapagliflozin led to an improvement in KCCQ-CS at 12 weeks by 5.8 points (95% CI 2.3–9.2; p = 0.001) [47]. The EMPEROR-Preserved trial built on its predecessor EMPEROR-Reduced. EMPEROR-Preserved

was a multicenter, double-blind, randomized clinical trial that randomized 5988 patients with an LVEF > 40% 1:1 to receive either empagliflozin or placebo, in addition to usual therapy [48]. The primary endpoint was a composite outcome of CV death or hospitalization for HF and occurred in 13.8% of patients in the empagliflozin group and in 17.1% of patients in the placebo group (HR 0.79; 95% CI: 0.69–0.90; p < 0.001), number needed to treat 31 (95% CI: 20–69) [48]. The benefit was mainly driven by reduced HF hospitalizations with a secondary outcome of reduced CV death not reaching statistical significance [48]. The authors did not provide subgroup analyses to separate patients with HFmrEF and HFpEF. PRESERVED-HF and EMPEROR-Preserved demonstrated that the beneficial effects of SGLT-2 inhibitors also apply to patients with HFpEF, however, the outcomes are more modest in comparison to those with HFrEF. Most recently sotagliflozin has had promising results in patients with HF evaluated in two large randomized clinical trials, SCORED and SOLOIST--WHF. The SCORED trial was a multicenter, double blinded, randomized clinical trial comparing sotagliflozin to placebo in patients with diabetes and chronic kidney disease. The primary endpoints were total number of deaths due to CV causes, hospitalizations for HF and urgent visits for HF. After a follow up period of 16 months, the total primary end-point events were 5.6 and 7.5 per 100 patient-years in the sotalgliflozin and placebo groups, respectively (HR 0.74; 95% CI: 0.6–0.88; p < 0.001) [49]. The SOLOIST-WHF was a multicenter, double blinded, randomized clinical trial that compared sotafliflozin to placebo in patients with type 2 diabetes mellitus and HF. The primary end-points were total number of deaths due to CV causes, hospitalizations for HF and urgent visits for HF. After a follow up period of 9 months, the rate of primary end-point events in the sotagliflozin and placebo groups were 51.0 vs. 76.3, respectively (HR 0.67; 95% CI: 0.52–0.85; p < 0.0010 [50]. Bhatt et al. [50] performed a pooled analysis of both SCORED and SOLOIST--WHF trials stratified by EF with primary end--points of total number of deaths from CV causes and hospitalization. They noted that for patients with HFpEF (EF > 50%) there was a 30% reduction in total number of deaths due to CV causes, hospitalizations and urgent visits for HF [51].

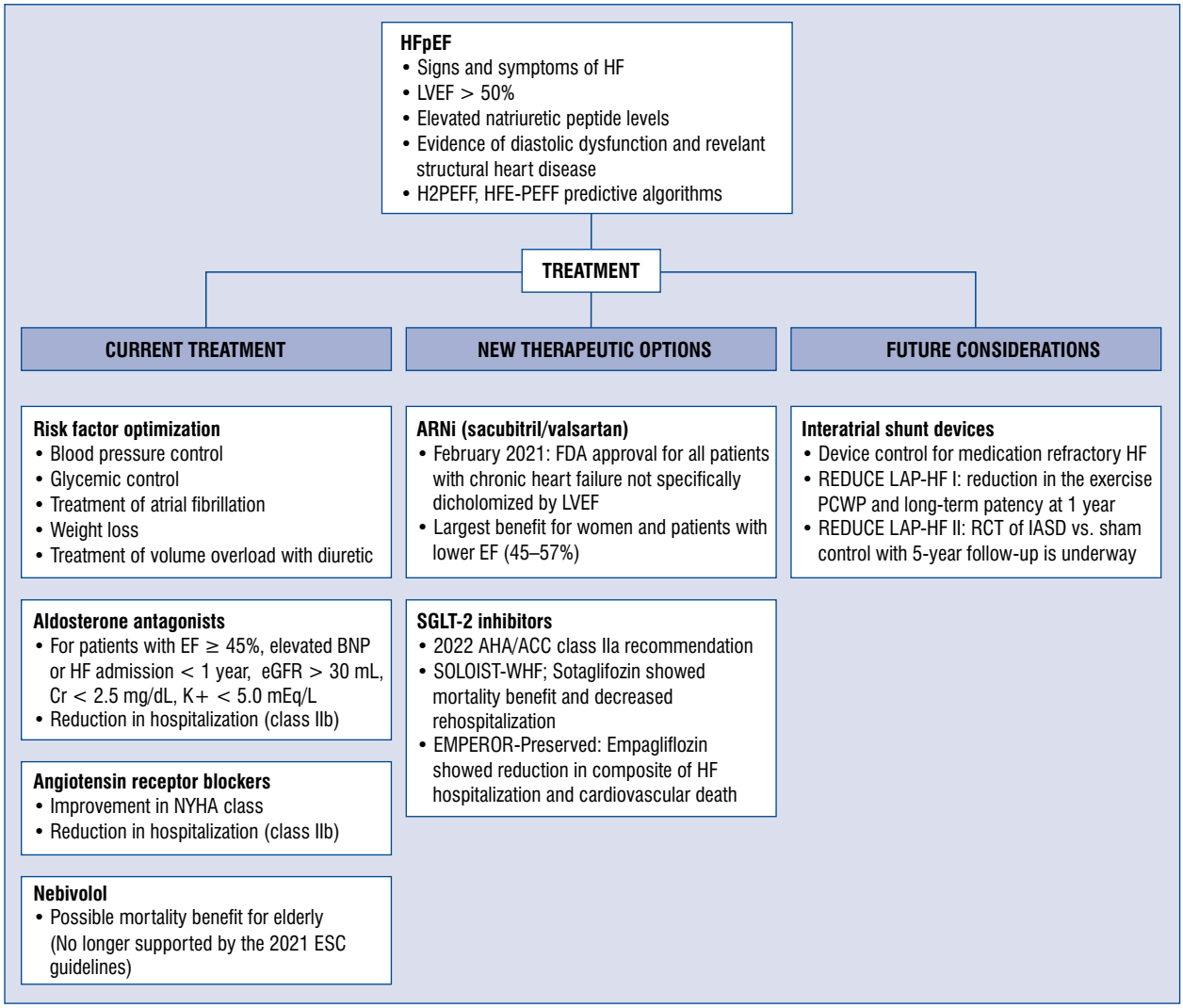
Guideline recommendations

Guidelines on the management of HFpEF from the ACC/AHA (2022) [4] and European Society of Cardiology (ESC) (2021) [3], suggest there is inconclusive evidence that treatment with any pharmacotherapy reduces morbidity, mortality or HF related hospitalizations. The consensus is a focus on management of underlying comorbidities which contribute to the development of HF and prevention of symptom progression. Both societies agree on the importance of controlling blood pressure, maintaining healthy body weight, managing volume overload with diuretics, optimizing glycemic control, and treating atrial fibrillation [3, 4]. For symptomatic treatment, only diuretics have shown convincing benefit. Improvement in NYHA class has only otherwise been seen with candesartan [31] The ACC/AHA advocates a class IIa recommendation for use of SGLT-2 inhibitors as well as management of atrial fibrillation and a class IIb recommendation for treatment of select patients with ARBs, angiotensin receptor blocker neprilylisn inhibitor and MRAs to reduce HF hospitalization (Central illustration) [4, 31, 34]. Treatment with candesartan reduced HF hospitalizations in the CHARM-Preserved trial, but it is unclear whether the objective benefits of ARB therapy are class specific or limited to candesartan. Based on findings from the TOPCAT trial, treatment with MRAs can be effective in patients with EF ≥ 45%, elevated natriuretic peptide levels or HF admission within the last year, estimated glomerular filtration rate > 30 mL/min, creatinine < 2.5 mg/dL, and potassium < 5.0 mEq/L [4, 34, 35]. As opposed to the 2016 guidelines, the ESC no longer names candesartan, spironolactone, digoxin and nebivolol as effective therapeutic options for reducing HF hospitalization [3, 28, 49]. The 2021 update to the ESC HF guidelines takes an aggressive approach and only supports the use of diuretics for symptomatic relief in congested patients with HFpEF [3]. Based on results from the NEAT-HFpEF and RELAX trials, the ACC/AHA refutes any benefit of using nitrates or phosphodiesterase inhibitors for improvement of activity level or QOL [4, 37, 50]. Regarding patients with diabetes, the ESC recommends using SGLT-2 inhibitors to prevent HF hospitalizations [3, 51].

New considerations

Expanded indications for sacubitril/valsartan

Subgroup analysis of the PARAGON-HF trial demonstrated a heterogeneous treatment effect of sacubitril/valsartan, with statistically significant benefits seen in women and patients with lower EF [42, 44]. A subsequent pooled meta-analysis that



Central illustration. Overview of current guideline directed management, new therapeutic options and future considerations for the treatment of heart failure with preserved ejection fraction (HFpEF); ACC — American College of Cardiology; AHA — American Heart Association; ARNi — angiotensin receptor blocker neprilylisn inhibitor; BNP — B-type natriuretic peptide; Cr — creatinine; EF — ejection fraction; eGFR — estimated glomerular filtration rate; ESC — European Society of Cardiology; FDA — Food and Drug Administration; HF — heart failure; IASD — interatrial shunt device; K+ — potassium; LVEF — left ventricular ejection fraction; NYHA — New York Heart Association; PCWP — pulmonary capillary wedge pressure; RCT — randomized control trial; SGLT-2 — sodium-glucose co-transporter 2.

combined the PARAGON-HF and PARADIGM-HF trials, identified a graded benefit of angiotensin-neprilysin inhibition depending on measured EF. Patients with lower EF benefited most from therapy, however benefits also extended to patients with mildly reduced EF. In women, therapeutic effects of sacubitril/valsartan extended to a higher LVEF range [44, 52, 53]. In February 2021, in light of the aforementioned observations, the Food and Drug Administration approved an expansion of the indications for ENTRESTO® (sacubitril/valsartan) to all patients with chronic HF not specifically dichotomized by LVEF (Central illustration) [54, 55]. Millions of HFpEF patients previously deemed ineligible were now qualified to receive treatment. This recommendation should be considered carefully because it is based on a subgroup analysis that involves a trial that did not reach its primary endpoint. At present, there are no plans to study sacubitril/valsartan vs. an active comparator in a cohort of patients believed to benefit most from therapy.

Optimal exercise training regimen

Mueller et al. [56] questioned whether different modes of exercise had different effects on change in $\dot{V}O_2$. They conducted a prospective, multicenter RCT, assigning HFpEF patients to one of three treatment groups: high-intensity interval training, moderate continuous training, and guideline-based physical activity. Patients were followed for 12 months and the primary endpoint was change in peak $\dot{V}O_2$ after 3 months, with the minimal clinically important difference set at 2.5 mL/kg/min. The study failed to meet significance, delineating no benefit of alternative training regimens. After 12 months, no statistically or clinically significant changes in metrics of cardiorespiratory fitness, diastolic function, QOL scores, or natriuretic peptide levels were observed [56, 57].

Device therapy

Mechanical reduction of LA pressure is an important therapeutic target in HFpEF. It is achieved by transcatheter implantation of an interatrial shunt device (IASD) and monitored by invasive hemodynamic measurement of workload corrected exercise pulmonary capillary wedge pressure (PCWP) [58]. REDUCE LAP-HF [58], an open-label, single-arm study of IASDs in 64 adult patients with chronic symptomatic HF and LVEF > 40%, provided evidence of clinical efficacy and safety at 6 and 12 months [59]. A subsequent parallel-group, sham-controlled RCT (REDUCE-LAP HF I) [60] corroborated these findings showing reductions in exercise PCWP and long-term patency of devices at 12 months. Due to the small sample size of 44 patients, the trial was underpowered to detect clinically significant differences in HF hospitalization rates, functional capacity, QOL scores, or 6MWT distance [61]. A pooled analysis of these two trials concluded that implantation of IASDs improves pulmonary vascular function at rest and during exercise without compromising systemic perfusion [62]. REDUCE LAP-HF II [63], a comprehensive trial enrolling 608 patients randomized 1:1 to IASD vs. sham control, with plans for 5-year follow-up, is underway and will provide further insight about the potential of device therapy for medication refractory HFpEF (Central illustration).

Conclusions

Our understanding of the pathophysiology and management of HFpEF is limited. Epidemiologic studies have demonstrated a high prevalence of HFpEF [1, 2] and this provides a unique opportunity to affect the lives of many. Several ongoing studies are in search of therapeutic modalities that will improve prognosis and QOL. Recent expansion of the indications for sacubitril/valsartan to all patients with chronic HF [54, 55], has made this therapeutic modality available to a larger population. Promising results from trials involving the use of SGLT-2 inhibitors in patients with HFpEF have earned this drug class a class IIa recommendation in 2022 ACA/AHA guidelines for possible reduction in HF hospitalizations and CV mortality [4]. At present SGLT-2 inhibitors are the only medications with a class IIa recommendation making them the mainstay of HFpEF management [4]. Current trial involving IASDs [63] is also showing early promise. Future studies with intelligent subgroup design and specific phenotyping, could provide answers that explain the enigmatic pathophysiology of HFpEF and uncover treatment strategies which offer patients hope and empower clinicians.

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References

1. Pfeffer MA, Shah AM, Borlaug BA. Heart failure with preserved ejection fraction in perspective. Circ Res. 2019; 124(11): 1598–1617, doi: 10.1161/CIRCRESAHA.119.313572, indexed in Pubmed: 31120821.
2. Shah SJ, Kitzman DW, Borlaug BA, et al. Phenotype-Specific treatment of heart failure with preserved ejection fraction: a multiorgan roadmap. Circulation. 2016; 134(1): 73–90, doi: 10.1161/CIRCULATIONAHA.116.021884, indexed in Pubmed: 27358439.
3. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2016; 18(8): 891–975, doi: 10.1002/ejhf.592, indexed in Pubmed: 27207191.
4. Heidenreich PA, Bozkurt B, Aguilar O, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. J Card Fail. 2022; 28(5): e1–e167, doi: 10.1016/j.cardfail.2022.02.010, indexed in Pubmed: 35378257.
5. Reddy YNV, Borlaug BA. Heart failure with preserved ejection fraction. Curr Probl Cardiol. 2016; 41(4): 145–188, doi: 10.1016/j.cpcardiol.2015.12.002, indexed in Pubmed: 26952248.
6. Virani SS, Alonso A, Benjamin EJ, et al. Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. Circulation. 2020; 141(9): e139–e596, doi: 10.1161/CIR.0000000000000757, indexed in Pubmed: 31992061.
7. Gerber Y, Weston SA, Redfield MM, et al. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. JAMA Intern Med. 2015; 175(6): 996–1004, doi: 10.1001/jamainternmed.2015.0924, indexed in Pubmed: 25895156.
8. Tsao CW, Lyass A, Enserro D, et al. Temporal trends in the incidence of and mortality associated with heart failure with

preserved and reduced ejection fraction. JACC Heart Fail. 2018; 6(8): 678–685, doi: 10.1016/j.jchf.2018.03.006, indexed in Pubmed: 30007560.
9. Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. Nat Rev Cardiol. 2017; 14(10): 591–602, doi: 10.1038/nrcardio.2017.65, indexed in Pubmed: 28492288.
10. Tomasoni D, Adamo M, Anker MS, et al. Heart failure in the last year: progress and perspective. ESC Heart Fail. 2020 [Epub ahead of print], doi: 10.1002/ehf2.13124, indexed in Pubmed: 33277825.
11. Borlaug BA. The pathophysiology of heart failure with preserved ejection fraction. Nat Rev Cardiol. 2014; 11(9): 507–515, doi: 10.1038/nrcardio.2014.83, indexed in Pubmed: 24958077.
12. Borlaug BA, Kass DA. Invasive hemodynamic assessment in heart failure. Cardiol Clin. 2011; 29(2): 269–280, doi: 10.1016/j.ccl.2011.03.003, indexed in Pubmed: 21459248.
13. Borlaug BA, Olson TP, Lam CSP, et al. Global cardiovascular reserve dysfunction in heart failure with preserved ejection fraction. J Am Coll Cardiol. 2010; 56(11): 845–854, doi: 10.1016/j.jacc.2010.03.077, indexed in Pubmed: 20813282.
14. Borlaug BA, Kass DA. Mechanisms of diastolic dysfunction in heart failure. Trends Cardiovasc Med. 2006; 16(8): 273–279, doi: 10.1016/j.tcm.2006.05.003, indexed in Pubmed: 17055383.
15. Westermann D, Kasner M, Steendijk P, et al. Role of left ventricular stiffness in heart failure with normal ejection fraction. Circulation. 2008; 117(16): 2051–2060, doi: 10.1161/CIRCULATIONAHA.107.716886, indexed in Pubmed: 18413502.
16. Phan TT, Abozguia K, Nallur Shivu G, et al. Heart failure with preserved ejection fraction is characterized by dynamic impairment of active relaxation and contraction of the left ventricle on exercise and associated with myocardial energy deficiency. J Am Coll Cardiol. 2009; 54(5): 402–409, doi: 10.1016/j.jacc.2009.05.012, indexed in Pubmed: 19628114.
17. Tan YuT, Wenzelburger F, Lee E, et al. The pathophysiology of heart failure with normal ejection fraction: exercise echocardiography reveals complex abnormalities of both systolic and diastolic ventricular function involving torsion, untwist, and longitudinal motion. J Am Coll Cardiol. 2009; 54(1): 36–46, doi: 10.1016/j.jacc.2009.03.037, indexed in Pubmed: 19555838.
18. Hidalgo C, Granzier H. Tuning the molecular giant titin through phosphorylation: role in health and disease. Trends Cardiovasc Med. 2013; 23(5): 165–171, doi: 10.1016/j.tcm.2012.10.005, indexed in Pubmed: 23295080.
19. Phan TT, Abozguia K, Shivu GN, et al. Increased atrial contribution to left ventricular filling compensates for impaired early filling during exercise in heart failure with preserved ejection fraction. J Card Fail. 2009; 15(10): 890–897, doi: 10.1016/j.cardfail.2009.06.440, indexed in Pubmed: 19944366.
20. Melenovsky V, Hwang SJ, Lin G, et al. Right heart dysfunction in heart failure with preserved ejection fraction. Eur Heart J. 2014; 35(48): 3452–3462, doi: 10.1093/eurheartj/ehu193, indexed in Pubmed: 24875795.
21. Haykowsky MJ, Kouba EJ, Brubaker PH, et al. Skeletal muscle composition and its relation to exercise intolerance in older patients with heart failure and preserved ejection fraction. Am J Cardiol. 2014; 113(7): 1211–1216, doi: 10.1016/j.amjcard.2013.12.031, indexed in Pubmed: 24507172.
22. Reddy YNV, Carter RE, Obokata M, et al. A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. Circulation. 2018; 138(9): 861–870, doi: 10.1161/CIRCULATIONAHA.118.034646, indexed in Pubmed: 29792299.
23. Pieske B, Tschöpe C, de Boer RA, et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur Heart J. 2019; 40(40): 3297–3317, doi: 10.1093/eurheartj/ehz641, indexed in Pubmed: 31504452.
24. Segar MW, Patel KV, Berry JD, et al. Generalizability and implications of the HFPEF score in a cohort of patients with heart failure with preserved ejection fraction. Circulation. 2019; 139(15): 1851–1853, doi: 10.1161/CIRCULATIONAHA.118.039051, indexed in Pubmed: 30958721.
25. Myhre PL, Vaduganathan M, Claggett BL, et al. Application of the H FPEF score to a global clinical trial of patients with heart failure with preserved ejection fraction: the TOPCAT trial. Eur J Heart Fail. 2019; 21(10): 1288–1291, doi: 10.1002/ejhf.1542, indexed in Pubmed: 31332920.
26. Selvaraj S, Myhre PL, Vaduganathan M, et al. Application of diagnostic algorithms for Heart Failure with preserved ejection fraction to the community. JACC Heart Fail. 2020; 8(8): 640–653, doi: 10.1016/j.jchf.2020.03.013, indexed in Pubmed: 32535127.
27. Barandiarán Aizpurua A, Sanders-van Wijk S, Brunner-La Rocca HP, et al. Validation of the HFA-PEFF score for the diagnosis of heart failure with preserved ejection fraction. Eur J Heart Fail. 2020; 22(3): 413–421, doi: 10.1002/ejhf.1614, indexed in Pubmed: 31472035.
28. Flather MD, Shibata MC, Coats AJS, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J. 2005; 26(3): 215–225, doi: 10.1093/eurheartj/ehi115, indexed in Pubmed: 15642700.
29. Conraads VM, Metra M, Kamp O, et al. Effects of the long-term administration of nebivolol on the clinical symptoms, exercise capacity, and left ventricular function of patients with diastolic dysfunction: results of the ELANDD study. Eur J Heart Fail. 2012; 14(2): 219–225, doi: 10.1093/eurjhf/hfr161, indexed in Pubmed: 22147202.
30. Yamamoto K, Origasa H, Hori M. Effects of carvedilol on heart failure with preserved ejection fraction: the Japanese Diastolic Heart Failure Study (J-DHF). Eur J Heart Fail. 2013; 15(1): 110––118, doi: 10.1093/eurjhf/hfs141, indexed in Pubmed: 22983988.
31. Yusuf S, Pfeffer M, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet. 2003; 362(9386): 777–781, doi: 10.1016/s0140-6736(03)14285-7.
32. Cleland JGF, Tendera M, Adamus J, et al. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J. 2006; 27(19): 2338–2345, doi: 10.1093/eurheartj/ehl250, indexed in Pubmed: 16963472.
33. Massie BM, Carson PE, McMurray JJ, et al. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med. 2008; 359(23): 2456–2467, doi: 10.1056/NEJMoa0805450, indexed in Pubmed: 19001508.
34. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med. 2014; 370(15): 1383–1392, doi: 10.1056/NEJMoa1313731, indexed in Pubmed: 24716680.
35. Pfeffer MA, Claggett B, Assmann SF, et al. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. Circulation. 2015; 131(1): 34–42, doi: 10.1161/CIRCULATIONAHA.114.013255, indexed in Pubmed: 25406305.
36. Desai AS, Liu J, Pfeffer MA, et al. Incident hyperkalemia, hypokalemia, and clinical outcomes during spironolactone treatment of heart failure with preserved ejection fraction: analysis of the TOPCAT trial. J Card Fail. 2018; 24(5): 313–320, doi: 10.1016/j.cardfail.2018.03.002, indexed in Pubmed: 29572190.
37. Redfield MM, Anstrom KJ, Levine JA, et al. Isosorbide mononitrate in heart failure with preserved ejection fraction. N Engl J Med. 2015; 373(24): 2314–2324, doi: 10.1056/NEJMoa1510774, indexed in Pubmed: 26549714.
38. Wagdy K, Hassan M. NEAT HFpEF: Organic nitrates fail to deliver. Glob Cardiol Sci Pract. 2016; 2016(1): e201601, doi: 10.21542/gcsp.2016.1, indexed in Pubmed: 29043251.

39. Oeser C. Heart failure: Nitrates reduce activity levels in HFpEF. Nat Rev Cardiol. 2016; 13(1): 2, doi: 10.1038/nrcardio.2015.176, indexed in Pubmed: 26606959.
40. Tsujimoto T, Kajio H. Use of nitrates and risk of cardiovascular events in patients with heart failure with preserved ejection fraction. Mayo Clin Proc. 2019; 94(7): 1210–1220, doi: 10.1016/j.mayocp.2018.11.032, indexed in Pubmed: 31272569.
41. Borlaug BA, Anstrom KJ, Lewis GD, et al. Effect of inorganic nitrite vs placebo on exercise capacity among patients with heart failure with preserved ejection fraction: the INDIE-HFpEF randomized clinical trial. JAMA. 2018; 320(17): 1764–1773, doi: 10.1001/jama.2018.14852, indexed in Pubmed: 30398602.
42. Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin-Neprilysin inhibition in heart failure with preserved ejection fraction. N Engl J Med. 2019; 381(17): 1609–1620, doi: 10.1056/NEJMoa1908655, indexed in Pubmed: 31475794.
43. 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.
44. McMurray JJV, Jackson AM, Lam CSP, et al. Effects of sacubitril-valsartan versus valsartan in women compared with men with heart failure and preserved ejection fraction: insights from PARAGON-HF. Circulation. 2020; 141(5): 338–351, doi: 10.1161/CIRCULATIONAHA.119.044491, indexed in Pubmed: 31736337.
45. 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, doi: 10.1056/NEJMoa2022190, indexed in Pubmed: 32865377.
46. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019; 381(21): 1995–2008, doi: 10.1056/NEJMoa1911303, indexed in Pubmed: 31535829.
47. Nassif ME, Windsor SL, Borlaug BA, et al. The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: a multicenter randomized trial. Nat Med. 2021; 27(11): 1954–1960, doi: 10.1038/s41591-021-01536-x, indexed in Pubmed: 34711976.
48. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med. 2021; 385(16): 1451–1461, doi: 10.1056/NEJMoa2107038, indexed in Pubmed: 34449189.
49. Bhatt DL, Szarek M, Pitt B, et al. Sotagliflozin in patients with diabetes and chronic kidney disease. N Engl J Med. 2021; 384(2): 129–139, doi: 10.1056/NEJMoa2030186, indexed in Pubmed: 33200891.
50. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. N Engl J Med. 2021; 384(2): 117–128, doi: 10.1056/NEJMoa2030183, indexed in Pubmed: 33200892.
51. SOTAGLIFLOZIN shows benefit for difficult-to-treat form of heart failure [Internet]. American College of Cardiology. 2021. https://www.acc.org/about-acc/press-releases/2021/05/17/03/52/sotagliflozin-shows-benefit-for-difficult-to-treat-form-of-heart-failure (Cited 2022 May 1).
52. Solomon SD, Vaduganathan M, L Claggett B, et al. Sacubitril/Valsartan across the spectrum of ejection fraction in heart failure. Circulation. 2020; 141(5): 352–361, doi: 10.1161/CIRCULATIONAHA.119.044586, indexed in Pubmed: 31736342.
53. Bozkurt B, Ezekowitz J. Substance and substrate: LVEF and sex subgroup analyses of PARAGON-HF and PARADIGM-HF trials. Circulation. 2020; 141(5): 362–366, doi: 10.1161/CIRCULATIONAHA.120.045008, indexed in Pubmed: 32011927.
54. Novartis Entresto® granted expanded indication in chronic heart failure by FDA. MultiVu. https://www.multivu.com/players/English/8848351-novartis-entresto-fda-approval/ (Accessed March 29, 2021).
55. ENTRESTO [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; February 2021.
56. Mueller S, Winzer EB, Duvinage A, et al. Effect of high-intensity interval training, moderate continuous training, or guideline-based physical activity advice on peak oxygen consumption in patients with heart failure with preserved ejection fraction: a randomized clinical trial. JAMA. 2021; 325(6): 542–551, doi: 10.1001/jama.2020.26812, indexed in Pubmed: 33560320.
57. Pandey A, Kitzman DW. Searching for the optimal exercise training regimen in heart failure with preserved ejection fraction. JAMA. 2021; 325(6): 537–539, doi: 10.1001/jama.2020.26347, indexed in Pubmed: 33560307.
58. Hasenfuß G, Hayward C, Burkhoff D, et al. A transcatheter intracardiac shunt device for heart failure with preserved ejection fraction (REDUCE LAP-HF): a multicentre, open-label, single-arm, phase 1 trial. Lancet. 2016; 387(10025): 1298–1304, doi: 10.1016/s0140-6736(16)00704-2.
59. Kaye DM, Hasenfuß G, Neuzil P, et al. One-Year outcomes after transcatheter insertion of an interatrial shunt device for the management of heart failure with preserved ejection fraction. Circ Heart Fail. 2016; 9(12): e003662, doi: 10.1161/CIRCHEARTFAILURE.116.003662, indexed in Pubmed: 27852653.
60. Feldman T, Mauri L, Kahwash R, et al. Transcatheter interatrial shunt device for the treatment of heart failure with preserved ejection fraction (REDUCE LAP-HF i [reduce elevated left atrial pressure in patients with heart failure]): a phase 2, randomized, sham-controlled trial. Circulation. 2018; 137(4): 364–375, doi: 10.1161/CIRCULATIONAHA.117.032094, indexed in Pubmed: 29142012.
61. Shah SJ, Feldman T, Ricciardi MJ, et al. One-Year safety and clinical outcomes of a transcatheter interatrial shunt device for the treatment of heart failure with preserved ejection fraction in the reduce elevated left atrial pressure in patients with heart failure (REDUCE LAP-HF I) trial: a randomized clinical trial. JAMA Cardiol. 2018; 3(10): 968–977, doi: 10.1001/jamacardio.2018.2936, indexed in Pubmed: 30167646.
62. Obokata M, Reddy YNV, Shah SJ, et al. Effects of interatrial shunt on pulmonary vascular function in heart failure with preserved ejection fraction. J Am Coll Cardiol. 2019; 74(21): 2539–2550, doi: 10.1016/j.jacc.2019.08.1062, indexed in Pubmed: 31753198.
63. Berry N, Mauri L, Feldman T, et al. Transcatheter InterAtrial Shunt Device for the treatment of heart failure: Rationale and design of the pivotal randomized trial to REDUCE Elevated Left Atrial Pressure in Patients with Heart Failure II (REDUCE LAP-HF II). Am Heart J. 2020; 226: 222–231, doi: 10.1016/j.ahj.2019.10.015, indexed in Pubmed: 32629295.

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Overview of mitral valve replacement versus mitral valve repair due to ischemic papillary muscle rupture: A meta-analysis inspired by a case report

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Abstract

Background: *Papillary muscle rupture (PMR) is an infrequent but catastrophic complication after myocardial infarction (MI). Surgical procedure is considered the optimal treatment, despite high risk. However, the gold standard technique is still a major dilemma. Therefore, a meta-analysis was carried out to assess and provide an overview comparing mitral valve replacement (MVR) and mitral valve repair (MVr) for PMR post-MI.*

Methods: *A systematic literature search was performed. Data were extracted and verified using a standardized data extraction form. Meta-analysis was realized mainly using RevMan 5.4 software.*

Results: *From four observational studies 1640 patients were identified; 81% underwent MVR and 19% MVr. Operative mortality results were significantly higher in MVR group than the MVr group. MVR was performed under emergency conditions and patients admitted in cardiogenic shock or who required the use of mechanical cardiac support underwent MVR. MVr had shorter time of hospitalization and similar incidence of postoperative complications than MVR. No significant differences existed between the two procedures regarding cardiopulmonary bypass time.*

Conclusions: *Mitral valve repair appears to be a viable alternative to MVR for post-MI PMR, given that it has lower operative mortality, shorter time of hospitalization and similar incidence of short-term postoperative complications than MVR. However, it needs to be pointed out that MVR was associated with the most critical clinical condition following PMR. There is uncertainty regarding the overall survival and improvement of the quality of life between the procedures. Nevertheless, further completed investigation is required.* (Cardiol J 2022; 29, 4: 680–690)

Key words: ischemic papillary muscle rupture, mitral valve repair, mitral valve replacement, meta-analysis

Introduction

A case of papillary muscle rupture post-myocardial infarction

A previously healthy 55-year-old man was referred to hospital with chest pain and shortness of breath starting after intensive exertion. The electrocardiogram upon admission revealed sinus tachycardia (120 bpm) with a 3 mm ST depression in leads II, III, aVF, from V3 to V6, and ST elevation in leads I and aVR (Fig. 1A). Additionally, transthoracic echocardiography showed preserved

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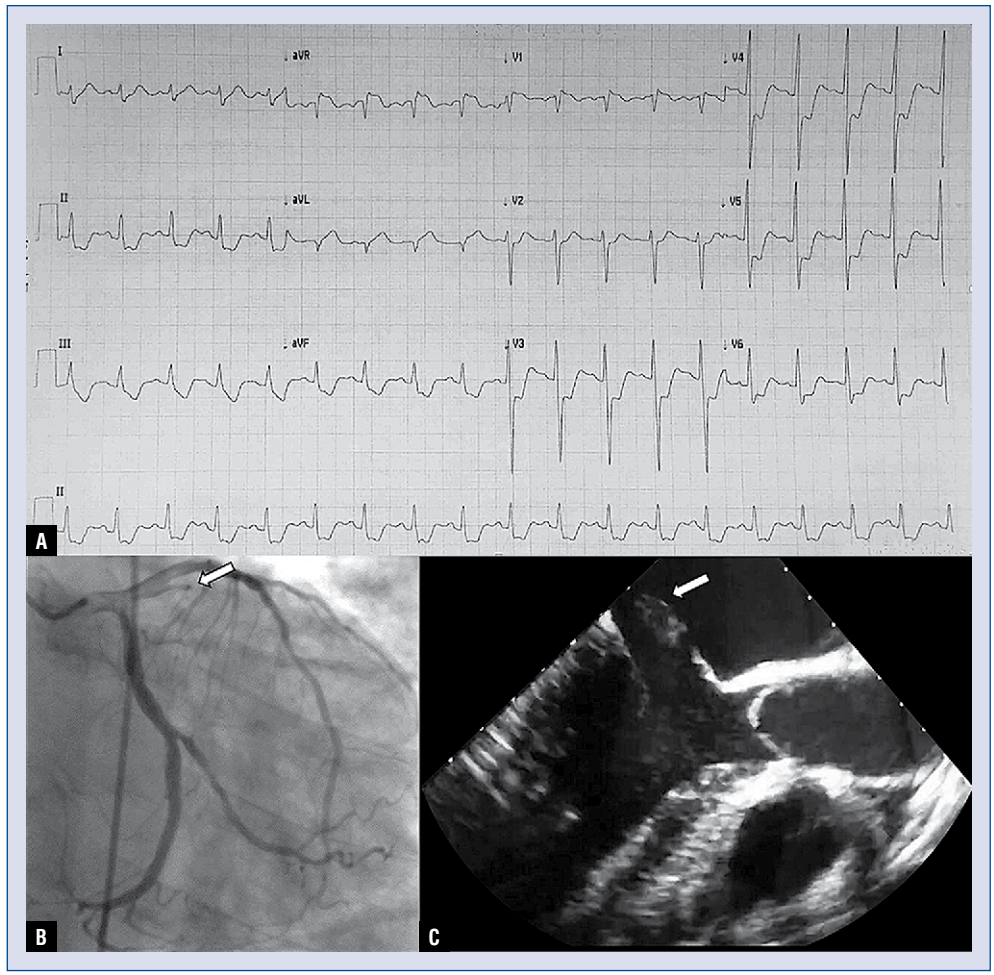


Figure 1. A. Twelve-lead electrocardiogram; **B.** Angiographic image. Right anterior oblique caudal view of the left coronary artery. Arrow indicates site of vessel occlusion; **C.** Transoesophageal echocardiogram. Three-chamber view during systole; arrow indicates ruptured papillary muscle fragment prolapsed in the left atrium.

left ventricular ejection fraction without regional wall motion abnormalities, moderate-severe posteriorly directed mitral regurgitation (MR) and an absence of pericardial effusion. Since the clinical scenario suggested acute non-ST-segment elevation myocardial infarction (NSTEMI) complicated by papillary muscle dysfunction, the patient underwent emergency cardiac angiography, which showed small intermediate and marginal branch occlusion; percutaneous coronary intervention (PCI) was not feasible due to their small sizes (Fig. 1B). After the intensive care unit admission, the patient's condition suddenly worsened, showing signs and symptoms of acute heart failure. In order to better evaluate the MR mechanism, transoesophageal echocardiogram was performed, detecting severe acute MR with anterolateral papillary muscle rupture (PMR) (Fig. 1C). The patient experienced cardiogenic shock and respiratory distress requiring sedation, mechanical ventilation and hemodynamic support with vasopressors and intra-aortic balloon pump counterpulsation (IABP). As the patient's condition worsened, a quick decision about whether to perform surgery and about which surgical techniques to choose — mitral valve replacement (MVR) or mitral valve repair (MVr) — was required.

Given your knowledge of the patient and the points made by the experts, which approach would you choose?...

Ischemic PMR is a life-threatening mechanical complication following acute myocardial infarction (MI) [1, 2].

Papillary muscle rupture, although rare, is responsible for 1–5% of deaths in patients with acute MI [2].

The APEX-AMI trial found a 0.26% incidence of PMR following acute MI; more recently that rate

was 0.029%, according to data derived from the National Inpatient Sample in the USA (2005–2014) [3, 4]. Epidemiological data suggest that since the introduction of an up-to-date approach to acute MI, which includes primary PCI, the incidence of mechanical complications after an acute MI, as PMR, has successfully decreased [3, 5].

Almost all cases of PMR occur in the mitral valve, whereas ischemic tricuspid regurgitation caused by PMR is extremely rare [6].

As widely reported in literature, the posterior--medial papillary muscle is the most vulnerable: whereas the antero-lateral papillary muscle has a dual blood supply from the diagonal branches of the left anterior descending artery (LAD) and the obtuse marginal branches of the circumflex artery (Cx), the posteromedial one has a single blood supply from the posterior descending artery, usually deriving from the right coronary artery (RCA) or, less frequently, from Cx [7, 8]. Therefore, the posterior-medial PMR occurs 6–12 times more frequently than the antero-lateral one.

Austen et al. [9], who performed the first valvular replacement in this setting (1965), described the patient's critical condition after PMR with a rapidly deteriorating course. Without adequate diagnosis and treatment, acute heart failure cardiogenic shock and death occurred within a few hours [9].

A high degree of suspicion and early echocardiography are pivotal for a rapid diagnosis.

As medical treatment is associated with very poor survival, surgery remains the cornerstone of treatment [2] and provides the best chance for a successful outcome [10], as recommended in current guidelines [11, 12].

However, because of the rarity of ischemic PMR, few reports have been published on this topic and the choice of MVR versus MVr is controversial [2, 13]. Clinical evaluation and procedures were performed in different centers by different surgeons who might have assessed the clinical conditions differently. No systematic comparison was carried out between these two techniques, making any conclusive analysis of potential inference of the type of surgery difficult to be applicable. Thus, the optimal surgical strategy for an ischemic PMR remained unclear.

Hence, the present study aims to analyze the available studies which report the clinical outcomes of MVR or MVr after ischemic PMR with the ambition of descrambling and comparing these evidences in order to examine if the hazards and complications deemed by surgeons hold true and, if not, hopefully supply a more robust perspective (Central illustration).

Methods

Search strategy

All published and unpublished randomized clinical trials/observational studies were searched in MEDLINE/PubMed, Embase and Cochrane Library from January 2000 up to November 2020. Previous studies were excluded, since the treatment of acute MI has changed (such as the introduction of primary PCI) and has developed over time and the incidence of mechanical complications, including PMR, has decreased.

Literature searches were performed by using Medical Subject Heading terms and free text terms: "ischemic papillary muscle rupture", "acute myocardial infarction", "acute mitral valve regurgitation", "severe mitral valve regurgitation", "ischemic mitral insufficiency", "emergency cardiac surgery", "mechanical complications after myocardial infarction", "mitral valve replacement", "mitral valve surgery", "mitral valve surgical correction", "mitral valve surgical treatment", "mitral valve repair", "mitral valvuloplasty", "mitral valve reconstruction". A systematic literature review was planned according to the PICO format [14]: Population: all men and women who experienced MI and PMR; Intervention: patients underwent MVR; Comparison: patients underwent MVr; Outcomes of interest: operative mortality, urgency of surgery, cardiopulmonary bypass time, use of mechanical support, postoperative course.

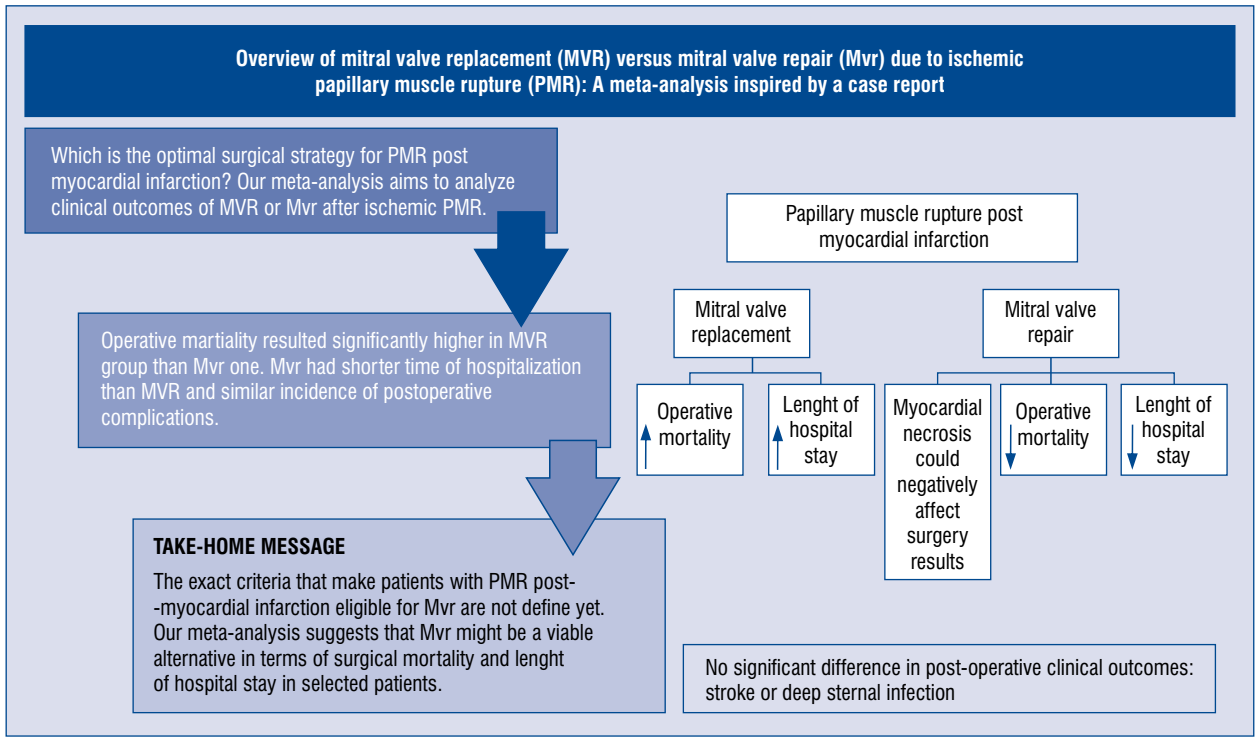
This systematic review and meta-analysis was planned and performed in accordance with the Preferred Reporting Items for Systemic Review and Meta-Analysis (PRISMA) statement and Cochrane Handbook for Systematic Reviews of Intervention [15, 16].

Studies were included if the following criteria were met: PMR after MI; comparison between MVR and MVr; availability of data about the present outcomes were considered.

Studies were excluded if presented: no direct comparison of MVR versus MVr; chronic ischemic MR; patient undergoing mitral valve surgery for etiologies other than ischemic PMR.

Data were extracted using a standardized data extraction form based on the template of Cochrane good practice data extraction [16].

The following data were extracted from each study: study name, publication date, country, bias, study design, inclusion and exclusion criteria,



Central illustration. Central Illustration summarizes the whole manuscript in a visual way.

total patient numbers and sample numbers, mean age, sex and the concomitant diseases including hypertension, diabetes. The following outcome variables were analyzed: operative mortality, the urgency of surgery, cardiogenic shock at admission, the incidence of the use of IABP, cardiopulmonary bypass time, the incidence of stroke and deep sternal infection, the length of hospital stay. Any discrepancies were settled in group discussion.

Bias risk assessment and quality of evidence

According to evidence-based medicine, a critical analysis of a study aims to evaluate the internal validity, clinical relevance and the applicability of a published study. Methodological quality was assessed with the Newcastle-Ottawa Scale (NOS) which consists of 8 items with 3 subscales and the total maximum score of these 3 subsets is 9 [17]. Studies which scored ≥ 7 in high-quality study were considered, as it is commonly used, since a standard criterion for what represents a high-quality study has not been universally established yet [18].

As recommended by Cochrane Handbook [16], the software GRADE profiler was further used to validate the quality of evidence of the included retrospective studies.

Statistical analysis

Statistical analysis was performed by RevMan software, version 5.4.1 and Comprehensive Meta-Analysis software v3.

When reporting the results of clinical studies, some researchers may choose the five-number summary (including the sample median, the first and third quartiles, and minimum and maximum values) rather than the sample mean and standard deviation, particularly for skewed data. To convert the five-number summary back to the sample mean and standard deviation a method proposed by Shi et al. [19] was used.

Relevant data of clinical outcomes were obtained from each study in order to generate forest plots. Some studies did not report data categorized by type of surgery.

Dichotomous variables were analyzed using the odds ratios (OR) with 95% confidence intervals (CI), and the Mantel–Haenszel [20] method combines the relevant outcomes. Continuous variables were analyzed using the weighted mean difference (WMD) reported with 95% CI. Pooled estimates were calculated with a DerSimonian–Laird random-effect model approach [21]. This method assumes the treatment effect being estimated follows some random distribution, rather than estimating some

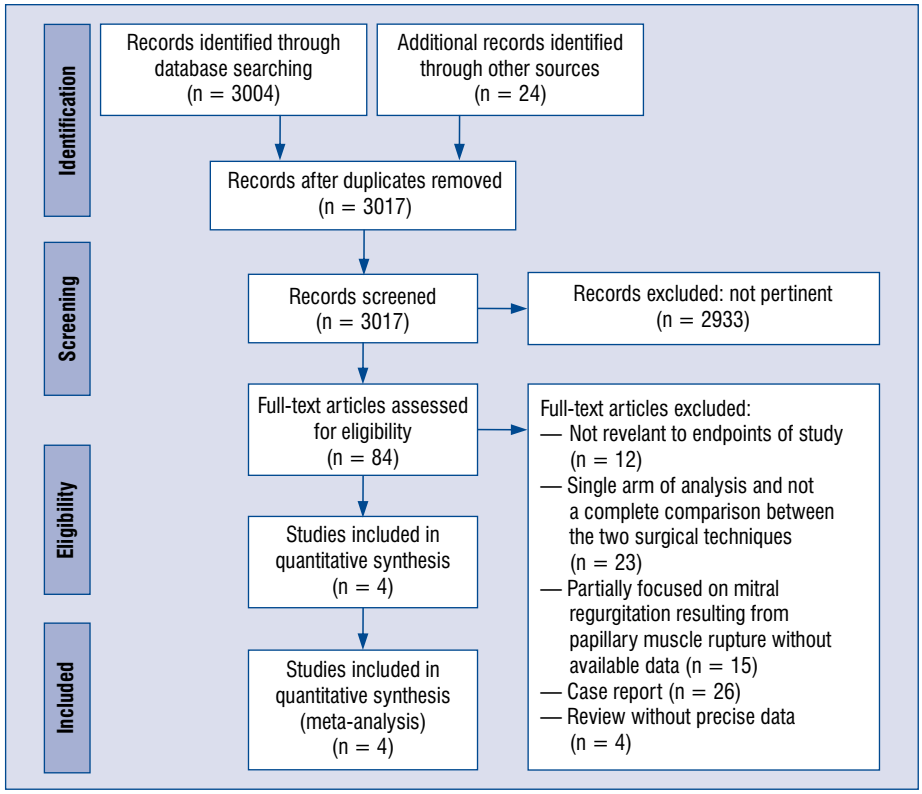


Figure 2. Preferred Reporting Items for Systemic Review and Meta-Analysis (PRISMA) flow diagram. Display of the screening process; four retrospective and nonrandomized studies were selected.

common fixed treatment effect as in a fixed-effects meta-analysis.

The pooled effects were determined by the Z-test and p-value < 0.05 was considered to point out statistical significance of all tests.

Heterogeneity among studies was analyzed: Forest plots were visually examined looking for overlap in the CI and the Cochrane chi-squared test and inconsistency (I^2) were used to assess heterogeneity among studies. In accordance with Higgins I^2 values, values below 30–40% were considered as low heterogeneity (most of the variation observed could be plausibly due to random error); I^2 values between 30–75% as moderate heterogeneity; I^2 values between 75–100% as considerable heterogeneity [16]. A chi-squared test-based Q test was also performed and p-value < 0.10 was considered to identify the presence of heterogeneity.

Publication bias was analyzed according to Egger et al. [22]; Egger's test p-value was interpreted suggestive for publication bias at values < 0.10.

Sensitivity analysis was performed to examine whether overall findings are robust enough to potentially influence decision-making: one or more studies were excluded and results were compared from random and fixed models to assess whether such exclusions significantly change the estimate of the effect.

Results

From this systematic research, a total of 3017 references were identified, and duplicates were removed by using EndNote X7. The remaining quotations were screened by the title, excluding articles that did not have any agreement according to participants and interventions required in inclusion criteria (predominantly mitral valve degenerative disease); when title was doubtful, we proceeded to the research in the abstract of the inclusion and exclusion criteria. 84 articles were selected but, following the full-text assessment, 80 of these papers were excluded, leaving 4 studies for inclusion into the present meta-analysis. Figure 2 displays the aforementioned screening process. Methodological quality was assessed with NOS and all the studies were considered to be of high quality.

Four studies provided a total sample of 1640 patients, 1326 (81%) of whom underwent MVR and 314 (19%) underwent MVr.

Baseline characteristics did not differ markedly between MVR patients and the MVr group. According to the present analysis the population was homogeneous regarding gender (OR = 0.55; 95% CI: 0.26–1.15; p = 0.11) and mean age (pooled mean MVR: 67.21 ± 10.49; pooled mean MVr: 64.8 ± 11.29; OR = 1.84; 95% CI: –1.30–4.98; p = 0.25) with no significant difference between the two groups. Likewise, the incidence of hypertension and diabetes did not show significant differences between the two population groups (respectively OR = 1.09; 95% CI: 0.83–1.45; p = 0.53 and OR = 1.31; 95% CI: 0.95–1.8; p = 0.1).

As widely reported in literature the most affected papillary muscle was the posterior-medial one because it has a single blood supply from the posterior descending artery deriving from RCA or Cx [7, 8]. Indeed, Bouma et al. [23] reported 28 (58%) cases of Cx involvement; 19 (40%) cases of RCA involvement and 1 (2%) case of LAD involvement. Fujita et al. [12] performed coronary angiogram in 89% of 196 patients and the remaining patients underwent surgery without coronary angiogram, likely due to lack of time. They reported 90 (51.7%) cases of Cx involvement; 82 (47.1%) cases of RCA involvement.

Herein, primary outcome was operative mortality (OP), defined as death within 30 days after surgery or in-hospital death. Combining data from 4 studies [12, 13, 23, 24], totaling 1640 patients, the OP in patients undergoing MVR was significantly higher than MVr (OR = 5.47; 95% CI: 3.27–9.13; p < 0.00001). This finding featured low heterogeneity (I^2 = 0%, Cochran's Q test p-value = 0.66) (Fig. 3A). Publication bias was not highlighted (Egger's test p-value = 0.55).

The sensitivity analyses showed that the overall results and conclusions were not affected by the different decisions that could be made during the review process; therefore, the results of this outcome can be regarded with a higher degree of certainty.

Two studies [12, 24], totaling 1538 patients, provided data on the percentage of patients admitted to the emergency room in cardiogenic shock (CS) condition (58%). This latter percentage rose up to 59% if we also considered data from Bouma et al. [23], excluded from this analysis because they did not categorize this outcome for MVR vs MVr. CS, defined as systolic blood pressure < 90 mmHg with adequate volume and clinical features or laboratory signs of hypoperfusion, is a high-acuity, low-cardiac-output state resulting in life-threatening end-organ hypoperfusion and hypoxia [25]. The combined result of these studies demonstrated that for patients in CS condition at hospital admission MVR was significantly more frequently performed than MVr (OR = 7.87; 95% CI: 5.76–10.73; p < 0.00001). This evidence was with low heterogeneity (I^2 = 0%, Cochran's Q test p-value = 0.51) (Fig. 3B).

In addition, the combined result of these same studies [12, 24], demonstrated that MVR was significantly more frequently performed as emergency surgery than MVr (OR = 6.04; 95% CI: 4.31–8.46; p < 0.00001) (Fig. 3C); on the other hand, MVr was significantly more frequently performed as urgent surgery than MVR (OR = 0.41; 95% CI: 0.31–0.53; p < 0.00001) (Fig. 3D). This evidence featured low heterogeneity (respectively I^2 = 0%, Cochran's Q test p-value = 0.50; I^2 = 0%, Cochran's Q test p-value = 0.82).

Combining data from three studies [12, 13, 24], 1592 patients, regarding the use of IABP, a mechanical circulatory device developed to mitigate the adverse outcomes of CS until treating the underlying cause, a significantly higher incidence in patients undergoing MVR than MVr (OR = = 5.01; 95% CI: 3.79–6.62; p < 0.0001) resulted with low heterogeneity (I^2 = 0%, Cochran's Q test p-value = 0.82) (Fig. 4A).

The combined results of two studies [12, 13], 250 patients, revealed that MVR had a longer time of hospitalization, compared to MVr (OR = 3.9; 95% CI: 1.1–6.69; p = 0.006). No heterogeneity emerged (I^2 = 0%, Cochran's Q test p-value = 0.75) (Fig. 4B).

Postoperative data mainly include short-term postoperative complications (stroke and deep sternal infection). The incidence of these latter was compared in two reports [12, 24], totaling 1538 patients. According to the present analysis, no significant difference existed regarding the incidence of stroke (OR = 1.62; 95% CI: 0.71–3.69; p = 0.25) (Fig. 4C), and deep sternal infection between the groups (OR = 0.6; 95% CI: 0.08–4.48; p = 0.62) (Fig. 4D). These findings were with no heterogeneity (respectively I^2 = 18%, Cochran's Q test p-value = 0.27; I^2 = 0%, Cochran's Q test p-value = 0.37).

Pooling data from three studies [12, 13, 24], totaling 1592 patients, there seemed to be no statistical significance in cardiopulmonary bypass time between the two groups. This finding was with high heterogeneity (I^2 = 81%, Cochran's Q

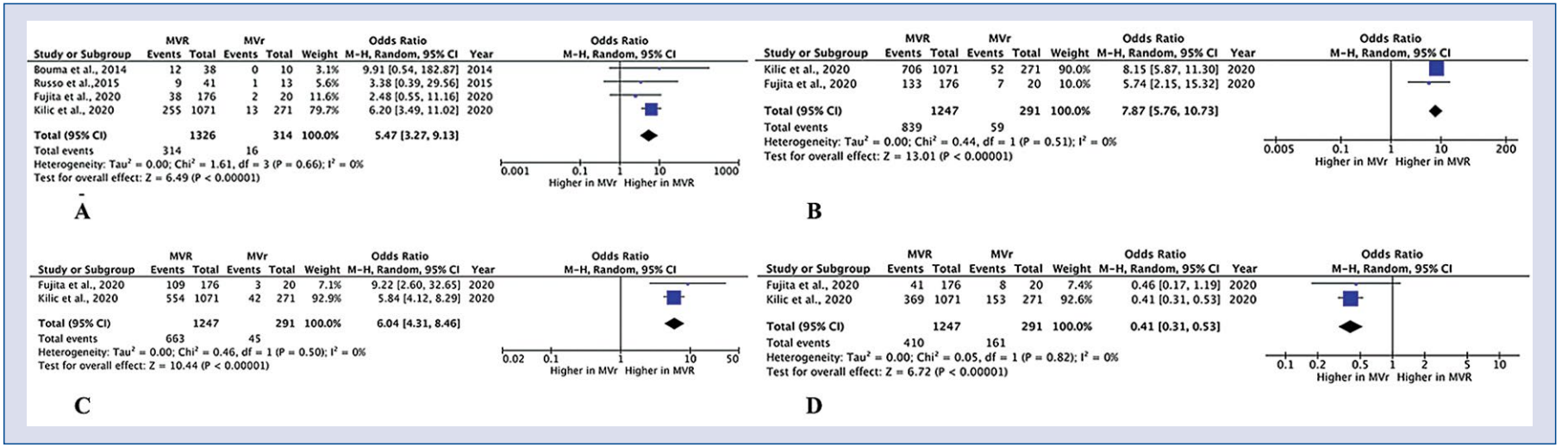


Figure 3. Forest plot; **A.** Operative mortality; **B.** Incidence of cardiogenic shock at admission; **C.** Emergency surgery; **D.** Urgent surgery.

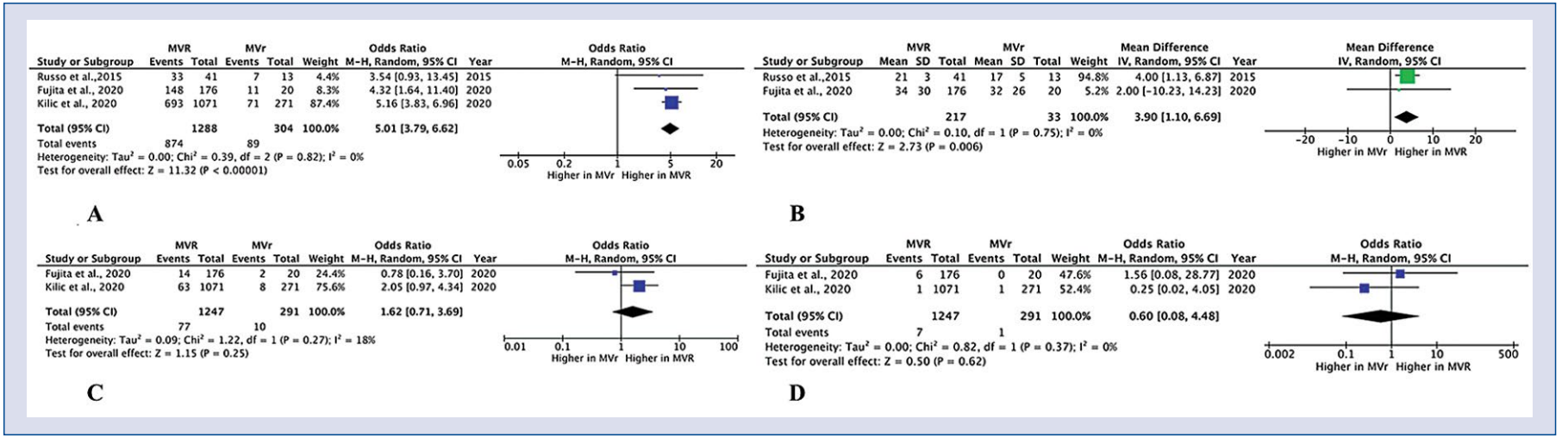


Figure 4. Forest plot; **A.** Intra-aortic balloon pump counterpulsation use; **B.** Length of hospital stay; **C.** Incidence of stroke; **D.** Deep sternal infection.

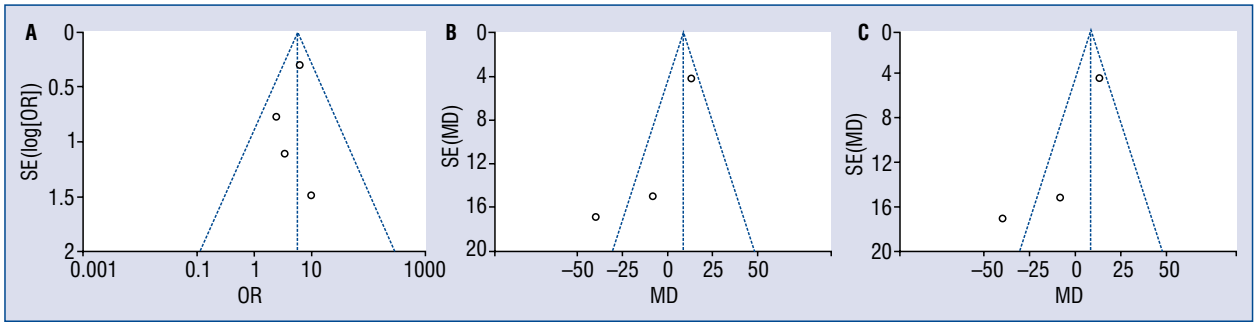


Figure 5. Funnel plot; **A.** Operative mortality; **B.** Cardiopulmonary bypass time with high heterogeneity; **C.** Assessed using the "Trim and Fill" method; MD — mean difference; OR — odds ratio; SE — standard error.

test p-value = 0.005) (Fig. 5A). An asymmetry of the analysis was evident at the visual inspection of the funnel plot (Fig. 5B). Using the "Trim and Fill" method the influence of the small study on the pooled effect was not relevant when the analysis was repeated omitting this study [26, 27]. A visual inspection of the other funnel plot analysis showed no asymmetry (Fig. 5C).

Bias of included studies

Fujita et al. [12], did not clearly define the clinical diagnosis of MI and CS condition, and did not report how the diagnosis of MR and PMR was performed and exclusion criteria was not clearly defined.

Russo et al. [13], compared MVR and MVr just for a few of our outcomes.

Bouma et al. [23], did not categorize all of the outcomes and patient baseline characteristics into MVR and MVr, resulting in missing and unavailable data.

Kilic et al. [24], did not accurately state the definition of MI and how the diagnosis of ischemic MR and PMR was performed.

These studies contained limitations related to multicenter and retrospective format of data collection.

Discussion

Two surgical techniques in 1640 patients were evaluated, of whom 81% underwent MVR and 19% MVr. During the extensive period of analysis (2000–2020), this difference may be due to the more recent experience in MVr than MVR technique and also to the procedural concerns about necrosis extent of left ventricular wall which could negatively affect MVr results [28].

It is appropriate to point out that baseline patient characteristics are homogeneous, regarding mean age, gender and common comorbidities, achieving relatively reliable results.

The meta-analysis demonstrated that OP in patients undergoing MVR was significantly higher than MVr (Fig. 3A). However, it is important to highlight that the critical condition of patients before MVR, could affect OP outcome. Indeed, according to the present results, MVR was performed in the most critical condition by different surgeons: it was performed much more often than MVr in patients admitted in CS and under emergency conditions (Fig. 3B and 3C, respectively). Similarly, the use of IABP, as an important bridge to surgery for further hemodynamic support, in patients undergoing MVR was also significantly higher than MVr (Fig. 4A).

In support of this way forward, Kishon et al. [29], reported that when emergency surgery is performed during the acute phase of MI, MVR is recommended as the first choice because the cardiac muscle around the ruptured papillary muscle is vulnerable, making MVr a difficult and time-consuming procedure. However, according to the authors, MVr might be considered in selected patients who had residual healthy papillary muscle and good quality left ventricular wall tissue around the rupture [29].

Mitral valve repair might be a viable alternative to MVR when also considering the other outcomes that are explored herein: patients who underwent MVR had a longer hospitalization than patients who underwent MVr (Fig. 4B); there was no significant difference in the incidence of short-term post-operative complications (Fig. 4C, D), and no procedure extended surgical time.

The association of coronary artery bypass grafting (CABG) might represent a protective or

detrimental factor for patient outcome. Simultaneous CABG was performed in 65% of patients involved in the current meta-analysis, with no differences regarding type of procedure being performed. There is no established consensus to perform concomitant CABG because many patients with PMR have single branch lesions and not extensive MI. This meta-analysis did not explore, due to the scarcity of data, long-term survival which would be probably the most effective tool for defining the effect of concomitant CABG in the two surgical procedures. However, one of the included studies demonstrated improvements in early death rate, particularly in patients who underwent simultaneous CABG [13].

Overall completeness and limitations

GRADE profiler software was used for an overall assessment of the certainty of evidence. The GRADE ratings represent how inconsistency, indirectness, imprecision and publication bias affect confidence in the results of the review. Apart from the high bias risk in confounding factors and patient selection, that are typical of retrospective studies, the current study determined that the evidence provided by these studies is still of an acceptable quality.

Despite the benefits of a pooled analysis, such as higher statistical power, there are some limitations with the present current meta-analysis study.

First and foremost, the retrospective studies included in meta-analysis carried inherent biases such as the selection bias given by their observational nature.

Secondly, some centers might have had funding restrictions which would bias their choice of surgery, along with the surgeon's experience, who might have differently oriented the assessment of surgical choice. However, due to the severity of valve disease with hemodynamic instability, a randomized study would be difficult to carry out.

The perioperative course and management are a delicate and relevant point of discussion, however, the postoperative complications considered in the current analysis, based on data available, was incomplete, particularly regarding the presence of low cardiac output syndrome, or the use of temporary support.

Even data regarding the use of imaging techniques such as echocardiography in the selected study were lacking; intra- or perioperative echocardiographic assessment during both MVr and MVR could help to make a joint, high-impact decision with the surgeon, in a time-sensitive manner and a dynamic clinical situation. Evaluation should include analysis of pre-repair functional anatomy, quantification of valvular dysfunction, identification of predictors of both short and long-term failure of surgical repair [30].

During surgery, as reported by many authors, echocardiography, in particular transesophageal echocardiography, provides real-time information on both morphology and hemodynamics without exposure to radiation or media contrast and is essential for intraoperative monitoring and assistance, for example, in evaluating the sizing of the annuloplasty ring [31].

Another limitation faced was the scarcity of categorization for the various MVr techniques described in literature, such as annuloplasty, suture of the ruptured papillary muscle head or the use of other techniques, such as chordal transfer.

A further limitation pointed out by the present study was the absence of randomized or matched population studies with long-term follow-up, so long-term survival could not be analyzed. The only study which concisely reported this outcome was Russo et al. [13]; they described no differences between MVR and MVr in terms of 5-year survival and an insignificant trend for higher survival, free of congestive heart failure, with MVr.

Another important aspect, which accounts mainly for the surgical strategy, is the role of the preservation of subvalvular apparatus in case of MVR. These patients may indeed experience post-MI ventricular maladaptive remodeling and, therefore, the absence of the mitro-ventricular continuity secondary to complete native valve excision, might affect the post-procedural left ventricular ejection fraction and remodeling.

In general, it has been shown that MVR with preservation of subvalvular apparatus maintains postoperative left ventricular contractile function and improves outcome [32].

In the Bouma et al. [33] study in patients undergoing MVR for post-MI PMR, partial or complete preservation of the subvalvular apparatus, independently predicted and significantly improved overall long-term survival.

This aspect entails a remarkable relevance also and above all in ischemic settings but, in papers considered in the current meta-analysis, no mention was made about this.

The optimal techniques for surgical repair of mitral valve have varied over time and even across continents. Beginning with suture annuloplasty, then commissural fusion with suture, and open leaflet plication, techniques of mitral valve repair have continued to multiply and progress.

The American correction has gained popularity over the past several years as many authors reported [34].

Freedom from reoperation and freedom from recurrent significant mitral regurgitation at 10 years have been reported at 90.1% for American correction than 93.9% of the French correction [35].

However, MVr techniques continue to evolve. In papers selected for our work the difference between various repair techniques was not deeply analyzed, therefore we did not focus on it.

As we mentioned previously, patients with papillary muscle rupture, usually in cardiogenic shock, cannot survive a few days, so the vast majority of them must be treated in emergency conditions and it becomes difficult to do a randomized study comparing valve replacement and valve repair and the different techniques of shelter.

The present study would like to lay the foundations for new accurate studies that can confirm the current evidence that MVr should be considered not only in stable patients, because it could be a valid option in selected patients even in emergency conditions.

Conclusions

Briefly back to the clinical case: within a few hours, the patient experienced refractory cardiogenic shock, so that an expedited MVR was performed. Post-operative course was uneventful, and patient was discharged in good clinical conditions. MVR was deemed to be the best option, because the complete rupture of papillary muscle was evident and myocardial tissue with acute ongoing ischemia could lead to unpredictable results. The case showed how even an isolated lesion of small coronary branches may cause PMR and a dramatic clinical scenario so that a prompt diagnosis and an early surgical intervention are crucial, especially in patients with hemodynamic instability.

Despite surgeons' choice to further opt for MVR, the current meta-analysis suggests that MVr might be a viable alternative in terms of surgical mortality and length of hospital stay in selected patients. Considering clinical outcomes across the two groups, there were no significant differences in short-term postoperative complications. Only a randomized study comparing the two procedures can define which techniques are superior, but, starting from the available data, this study suggests not considering acute MI as a contraindication, *per se,* to valve repair [13]. However, being conscious that not all patients are suitable candidates for MVr due to critical clinical conditions at hospital admission, infarct size, characteristics of PMR (complete or partial), and many other factors, such as age and preoperative comorbidities, are reasons for further investigation. In conclusion, in more stable and selected patients, MVr may be considered.

Conflict of interest: None declared

References

1. Thompson CR, Buller CE, Sleeper LA, et al. Cardiogenic shock due to acute severe mitral regurgitation complicating acute myocardial infarction: a report from the SHOCK Trial Registry. SHould we use emergently revascularize Occluded Coronaries in cardiogenic shocK? J Am Coll Cardiol. 2000; 36(3 Suppl A): 1104–1109, doi: 10.1016/s0735-1097(00)00846-9, indexed in Pubmed: 10985712.
2. Kutty RS, Jones N, Moorjani N. Mechanical complications of acute myocardial infarction. Cardiol Clin. 2013; 31(4): 519–531, vii, doi: 10.1016/j.ccl.2013.07.004, indexed in Pubmed: 24188218.
3. French JK, Hellkamp AS, Armstrong PW, et al. Mechanical complications after percutaneous coronary intervention in ST-elevation myocardial infarction (from APEX-AMI). Am J Cardiol. 2010; 105(1): 59–63, doi: 10.1016/j.amjcard.2009.08.653, indexed in Pubmed: 20102891.
4. Bhardwaj B, Sidhu G, Balla S, et al. Outcomes and hospital utilization in patients with papillary muscle rupture associated with acute myocardial infarction. Am J Cardiol. 2020; 125(7): 1020–1025, doi: 10.1016/j.amjcard.2019.12.051, indexed in Pubmed: 31973809.
5. Badheka AO, Patel NJ, Grover P, et al. Impact of annual operator and institutional volume on percutaneous coronary intervention outcomes: a 5-year United States experience (2005-2009). Circulation. 2014; 130(16): 1392–1406, doi: 10.1161/CIRCULATIONAHA.114.009281, indexed in Pubmed: 25189214.
6. Kanemitsu S. Repair of tricuspid papillary muscle rupture after percutaneous coronary intervention. Multimed Man Cardiothorac Surg. 2018, doi: 10.1510/mmcts.2018.035, indexed in Pubmed: 30549514.
7. Barbour DJ, Roberts WC. Rupture of a left ventricular papillary muscle during acute myocardial infarction: analysis of 22 necropsy patients. J Am Coll Cardiol. 1986; 8(3): 558–565, doi: 10.1016/s0735-1097(86)80182-6, indexed in Pubmed: 3745700.
8. Voci P, Bilotta F, Caretta Q, et al. Papillary muscle perfusion pattern. A hypothesis for ischemic papillary muscle dysfunction. Circulation. 1995; 91(6): 1714–1718, doi: 10.1161/01.cir.91.6.1714, indexed in Pubmed: 7882478.
9. Austen WG, Sanders CA, Averill JH, et al. Ruptured papillary muscle. Report of a case with successful mitral valve replacement. Circulation. 1965; 32(4): 597–601, doi: 10.1161/01.cir.32.4.597, indexed in Pubmed: 5826931.
10. Mokadam NA, Stout KK, Verrier ED. Management of acute regurgitation in left-sided cardiac valves. Tex Heart Inst J. 2011; 38(1): 9–19, indexed in Pubmed: 21423463.
11. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017; 38(36): 2739–2791, doi: 10.1093/eurheartj/ehx391, indexed in Pubmed: 28886619.
12. Fujita T, Yamamoto H, Kobayashi J, et al. Mitral valve surgery for ischemic papillary muscle rupture: outcomes from the Japan

cardiovascular surgery database. Gen Thorac Cardiovasc Surg. 2020; 68(12): 1439–1446, doi: 10.1007/s11748-020-01418-y, indexed in Pubmed: 32588291.
13. Russo A, Suri RM, Grigioni F, et al. Clinical outcome after surgical correction of mitral regurgitation due to papillary muscle rupture. Circulation. 2008; 118(15): 1528–1534, doi: 10.1161/CIRCULATIONAHA.107.747949, indexed in Pubmed: 18809799.
14. Richardson WS, Wilson MC, Nishikawa J, et al. The well-built clinical question: a key to evidence-based decisions. ACP J Club. 1995; 123(3): A12–A13, indexed in Pubmed: 7582737.
15. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015; 4: 1, doi: 10.1186/2046-4053-4-1, indexed in Pubmed: 25554246.
16. Higgins JPT, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.1. 2020. https://training.cochrane.org/handbook/current.
17. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2013. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
18. Islam MdM, Iqbal U, Walther B, et al. Benzodiazepine use and risk of dementia in the elderly population: a systematic review and meta-analysis. Neuroepidemiology. 2016; 47(3-4): 181–191, doi: 10.1159/000454881, indexed in Pubmed: 28013304.
19. Shi J, Luo D, Weng H, et al. Optimally estimating the sample standard deviation from the five-number summary. Res Synth Methods. 2020; 11(5): 641–654, doi: 10.1002/jrsm.1429, indexed in Pubmed: 32562361.
20. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst. 1959; 22(4): 719–748, indexed in Pubmed: 13655060.
21. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986; 7(3): 177–188, doi: 10.1016/0197-2456(86)90046-2, indexed in Pubmed: 3802833.
22. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997; 315(7109): 629–634, doi: 10.1136/bmj.315.7109.629, indexed in Pubmed: 9310563.
23. Bouma W, Wijdh-den Hamer IJ, Koene BM, et al. Predictors of in-hospital mortality after mitral valve surgery for post-myocardial infarction papillary muscle rupture. J Cardiothorac Surg. 2014; 9: 171, doi: 10.1186/s13019-014-0171-z, indexed in Pubmed: 25322911.
24. Kilic A, Sultan I, Chu D, et al. Mitral valve surgery for papillary muscle rupture: outcomes in 1342 patients from The Society of Thoracic Surgeons Database. Ann Thorac Surg. 2020; 110(6): 1975–1981, doi: 10.1016/j.athoracsur.2020.03.097, indexed in Pubmed: 32376352.
25. van Diepen S, Katz JN, Albert NM, et al. Contemporary management of cardiogenic shock: a scientific statement from the American Heart Association. Circulation. 2017; 136(16): e232–e268, doi: 10.1161/CIR.0000000000000525, indexed in Pubmed: 28923988.
26. Duval S, Tweedie R. A nonparametric "Trim and Fill" method of accounting for publication bias in meta-analysis. JASA. 2000; 95(449): 89, doi: 10.2307/2669529.
27. Peters JL, Sutton AJ, Jones DR, et al. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. J Clin Epidemiol. 2008; 61(10): 991–996, doi: 10.1016/j.jclinepi.2007.11.010, indexed in Pubmed: 18538991.
28. Chevalier P, Burri H, Fahrat F, et al. Perioperative outcome and long-term survival of surgery for acute post-infarction mitral regurgitation. Eur J Cardiothorac Surg. 2004; 26(2): 330–335, doi: 10.1016/j.ejcts.2004.04.027, indexed in Pubmed: 15296892.
29. Kishon Y, Oh JK, Schaff HV, et al. Mitral valve operation in postinfarction rupture of a papillary muscle: immediate results and long-term follow-up of 22 patients. Mayo Clin Proc. 1992; 67(11): 1023–1030, doi: 10.1016/s0025-6196(12)61116-1, indexed in Pubmed: 1434862.
30. Mahmood F, Matyal R. A quantitative approach to the intraoperative echocardiographic assessment of the mitral valve for repair. Anesth Analg. 2015; 121(1): 34–58, doi: 10.1213/ANE.0000000000000726, indexed in Pubmed: 26086507.
31. Orihashi K. Intraoperative transesophageal echocardiography. Kyobu Geka. 2018 ; 71(10): 763–768, indexed in Pubmed: 30310024.
32. David TE. Papillary muscle-annular continuity: is it important? J Card Surg. 1994; 9(2 Suppl): 252–254, doi: 10.1111/j.1540-8191.1994.tb00937.x, indexed in Pubmed: 8186577.
33. Bouma W, Hamer IWd, Koene B, et al. Long-term survival after mitral valve surgery for post-myocardial infarction papillary muscle rupture. J Cardiothorac Surg. 2015; 10(1), doi: 10.1186/s13019-015-0213-1, indexed in Pubmed: 25622516.
34. Woo YJ, MacArthur JW. Simplified nonresectional leaflet remodeling mitral valve repair for degenerative mitral regurgitation. J Thorac Cardiovasc Surg. 2012; 143(3): 749–753, doi: 10.1016/j.jtcvs.2011.08.024, indexed in Pubmed: 21943963.
35. Schubert SA, Mehaffey JH, Charles EJ, et al. Mitral valve repair: the French correction versus the American correction. Surg Clin North Am. 2017; 97(4): 867–888, doi: 10.1016/j.suc.2017.03.009, indexed in Pubmed: 28728720.

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Trimethylamine-N-oxide versus echocardiographic, biochemical and histopathological indices of heart failure in patients with severe aortic stenosis: Rationale and design of the prospective, observational TASTE study

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Background

Trimethylamine N-oxide (TMAO) has recently gained increasing scientific interest in the field of cardiovascular disease. An association between elevated plasma concentration of TMAO and an increased prevalence of diabetes, atherosclerosis and ischemic heart disease was observed [1, 2]. TMAO originates from the liver, which oxidizes trimethylamine (TMA), TMAO precursor. TMA is produced by conversion of L-carnitine, betaine and choline by intestinal symbiotic bacteria [3]. The rich source of the nutrients includes red meat, eggs and cheese. Recently, several studies have shown that TMA is deleterious for the circulatory system, and that TMAO may be a surrogate marker only [3, 4]. Nevertheless, an interventional study conducted by Gawrys-Kopczyska et al. [5] reported that TMAO applied to heart failure (HF) rats reduced mortality, which was associated with diuretic, natriuretic and hypotensive effects [5, 6]. Hence, unlike its precursor — TMA, TMAO might exert some favourable effects on the cardiovascular system. However, the role of TMAO in the pathogenesis of human diseases remains to be defined.

Aortic stenosis (AS) is the most common organic valvular heart disease, affecting approximately 7.6 million people over 75 years of age in North America and Europe alone [7]. The prevalence of AS is expected to increase due to an ageing population [8]. In the course of AS, aortic valve orifice gradually narrows, leading to chronic left ventricular (LV) pressure overload, LV hypertrophy and fibrosis [9]. Once AS symptoms

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(including HF symptoms, syncope, and/or angina) occur, if the patient is left untreated, the annual mortality oscillates around 25%, with an average survival of 2 to 3 years [10]. Hence, symptomatic patients with severe AS should promptly undergo either surgical aortic valve replacement (SAVR) or transcatheter aortic valve implantation (TAVI) [11]. The choice of the method of treatment (SAVR vs. TAVI) is mainly determined by the patients' individual risk of surgery, as assessed by the Heart Team [11]. SAVR is preferred in patients under 75 years old and with low perioperative risk, while TAVI is recommended in high-risk patients not suitable for SAVR, as assessed by the Heart Team [12]. Noteworthy, adverse LV remodeling due to AS is partially reversible after interventional treatment [13, 14]. However, in some patients, LV remodeling with LV dysfunction (mainly diastolic, but also systolic in patients with a long history of severe AS) and HF symptoms persists after intervention [14]. The course of reversible remodeling might be evaluated using circulating markers of cardiac fibrosis such as matrix metalloproteinase 2 and 9 (MMP-9, MMP-2), collagen I C-terminal telopeptide (CITP) and galectin-3 (gal-3) [15–17]. Uremic toxins such as indoxyl sulphate (IS) were also shown to exacerbate fibrosis and proliferation of cardiomyocytes [18, 19].

To some extent, LV pressure overload in patients with AS may resemble hydrostatic pressure affecting deep-sea marine animals [20, 21]. Based on the fact that TMAO plays a protective role in marine animals, it was hypothesized herein, that TMAO might play a role in protection of the heart against pressure overload in patients with AS. The primary aim of the present study is to investigate the association between serum and urine TMAO concentrations, and (i) echocardiographic, (ii) biochemical and (iii) histopathological indices of HF in patients with severe AS referred for SAVR or TAVI. The secondary aim of the study is to evaluate the relationship between baseline TMAO concentrations and changes in clinical status, echocardiographic and biochemical parameters after interventional treatment of severe AS.

Methods

Study design

The TASTE (TMAO in severe Aortic STenosis: association with Echocardiographic, biochemical and histopathological indices of heart failure) study is a prospective, observational study. The recruitment phase started in January 2019 and its duration was expected to be 24 months, however, due to the coronavirus disease 2019 (COVID-19) pandemic, it has been prolonged for another 24 months.

Selection of participants

Inclusion and exclusion criteria are listed in Table 1. Patients are enrolled among those (i) aged from 18 to 99 years, (ii) admitted to the department of cardiology or cardiac surgery in a tertiary referral, university hospital due to severe AS, and (iii) qualified for treatment with either SAVR or TAVI by the Heart Team. Patients with HF due to causes other than AS, patients with coexisting significant aortic regurgitation and those who underwent myocardial infarction within the last 3 months or coronary revascularization within the last month are excluded from the study. Since TMAO is excreted by the urinary tract, patients with chronic kidney disease (CKD) with estimated glomerular filtration rate (eGFR) < 45 mL/ /min/1.73 m^2, calculated using the Modification of Diet in Renal Disease (MDRD) formula, are excluded as well. Finally, because the intestinal metabolism of TMAO is affected by the state of gastrointestinal tract and its microbiota, patients with acute or chronic gastrointestinal diseases, autoimmune disease, treated with antibiotics within the last 2 months or taking dietary supplements within the last 7 days are excluded from the study. All patients provide written informed consent.

Study schedule

The study schedule is presented in Figure 1. Screening and eligibility check are performed after qualification for treatment (TAVI or SAVR). All patients screened are registered in the screening log. Patients not eligible for enrolment are registered as a screen failure with a reason for failure and not followed-up.

Patients enrolled in the study are evaluated at 4 time points: (i) prior to SAVR or TAVI, (ii) 5–7 days after the procedure (before hospital discharge) (follow-up visit 1), (iii) 1 month after the procedure (follow-up visit 2), and (iv) 6 months after the procedure (follow-up visit 3). At each visit, data regarding medical history and concomitant pharmacotherapy are collected, a thorough physical examination is conducted, transthoracic echocardiogram (TTE) is performed, and blood and urine samples are collected for laboratory tests.

Laboratory tests

Venous blood is collected to EDTA tubes to prepare plasma and to clotting activator tubes

Table 1. Eligibility criteria, laboratory and non-biochemical parameters assessed in the TASTE study.

Complete blood count	**Heart failure**	**Inflammatory markers**
	NT-proBNP	C-reactive protein
Fibrosis	**Renal function**	**Glucose and lipid metabolism**
MMP-2	Creatinine	Fasting glucose[1]
MMP-9	eGFR[2]	Lipid profile[1]
CIPT	Urea in blood	
Gal-3		
Hepatic function	**Metabolites**	**Other parameters**
ALT	TMAO[3]	Potassium and sodium[1]
AST	TMA[3]	Thyroid-stimulating hormone[1]
	IS[3]	Fibrinogen[1]
Main echocardiographic parameters	**Left heart catheterization (in patients undergoing TAVI)**	**Exclusion criteria**
E/e' (assessment of LV filling pressures)	End-diastolic and end-systolic LV and aortic pressures	Heart failure etiology other than AS
e' (lateral and septal)	**Inclusion criteria**	Chronic intestinal disease
S' (LV)	Age between 18 and 99 years	Coexisting, hemodynamically significant aortic regurgitation
LV GLS	Informed consent to participate in the study	Myocardial infarction within the last 3 months
LAVI	Severe AS, defined as AVA < 1.0 cm^2 or indexed AVA < 0.6 cm^2/m^2 as calculated by the continuity equation on transthoracic echocardiography, regardless of transvalvular gradient, with or without coexisting symptoms of heart failure	Coronary revascularization within the last month or planned during TAVI or SAVR
LV EDV		Chronic kidney disease with eGFR < 45 mL/min/1.73 m^2
LV ESV		Acute gastrointestinal disease within the last month
RV and RA dimensions		Active neoplastic disease
S' (RV)		Chronic inflammatory disease
LAVI		Autoimmune disease
TAPSE	Qualification for SAVR or TAVI by the Heart Team in accordance with European Society of Cardiology guidelines [11]	Antibiotic therapy within the last 2 months
TRV and estimated SPAP		Dietary supplements within the last 7 days
Histopathological study (in patients undergoing SAVR)		
Severity of myocardial fibrosis		

[1]Parameters assessed only at enrolment.
[2]eGFR is calculated based on serum creatinine using the Modification of Diet in Renal Disease (MDRD) formula.
[3]Concentrations of these parameters will be measured both in serum and urine.
ALT — alanine transaminase; AS — aortic stenosis; AST — aspartate aminotransferase; AVA — aortic valve area; CITP — collagen I C-terminal telopeptide; eGFR — estimated glomerular filtration rate; Gal-3 — galectin-3; IS — indoxyl sulfate; MMP-2, MMP-9 — matrix metalloproteinase 2 and 9; NT-proBNP — N-terminal prohormone of B-type natriuretic peptide; TMAO — trimethylamine-N-oxide; TMA — trimethylamine; LV — left ventricular; e' — early diastolic mitral annular velocity (lateral and septal); S' — systolic mitral annular velocity; GLS — global longitudinal strain; LAVI — left atrial volume index; EDV — end-diastolic volume; ESV — end-systolic volume; RV — right ventricular; RA — right atrial; SAVR — surgical aortic valve replacement; SPAP — systolic pulmonary artery pressure; TAPSE — tricuspid annular plane systolic; TAVI — transcatheter aortic valve implantation; TRV — tricuspid regurgitation velocity

to prepare serum. Urine is collected to sterile urine cups. For standard laboratory tests, blood is transferred to the accredited hospital laboratory. For TMAO analysis, EDTA-anticoagulated blood is centrifuged for 15 min at 2,000 g within 60 min after blood collection to prepare plasma [22]. Both plasma and urine are aliquoted and stored in a freezer at −80°C until analyzed. The analysis is performed in the Center of Preclinical Research and Technology, Medical University of Warsaw. All collected samples are coded with a unique number and will be analyzed in one block by operators blinded to patient data. Concentrations of TMAO in plasma and urine will be measured using a Waters Acquity Ultra Performance Liquid Chromatograph coupled with a Waters TQ-S Triple-Quadrupole Mass Spectrometer. The mass spectrometer will be operated in the multiple-reaction monitoring--positive electrospray ionization mode, as previously described [23].

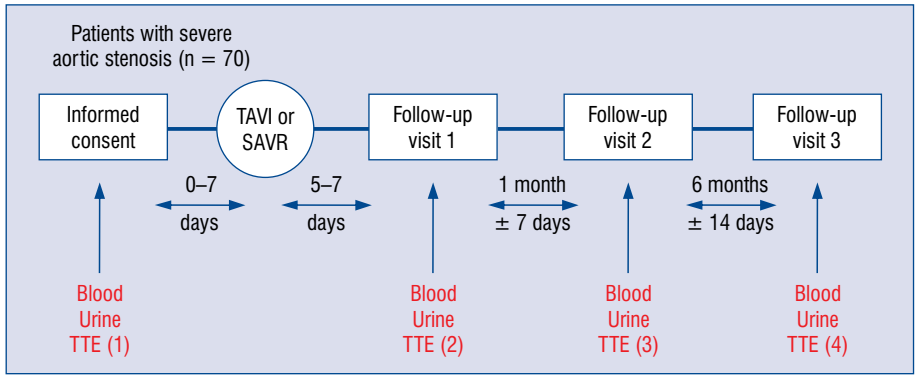

Figure 1. Study schedule; SAVR — surgical aortic valve replacement; TAVI — transcatheter aortic valve implantation; TTE — transthoracic echocardiography.

Echocardiographic examination

Each patient undergoes TTE at four prespecified time points. Echocardiographic examination includes evaluation of: (i) LV end-diastolic and end-systolic dimensions and volumes, LV wall thickness and LV mass index, (ii) LV systolic function, including assessment of LV ejection fraction (EF; using biplane Simpson's method) and global longitudinal strain, (iii) LV diastolic function (using tissue Doppler imaging [TDI]) and estimated left atrial pressure, (iv) left atrial dimension and indexed volume, (v) right ventricular size and systolic function (tricuspid annular plane systolic excursion, S' from TDI), right atrial size, (vi) maximal and mean aortic gradients, aortic valve area (AVA), indexed AVA, indexed LV stroke volume, (vii) presence and severity of aortic regurgitation or — after intervention — paravalvular leaks, (viii) function of other heart valves, and (ix) probability of pulmonary hypertension. At follow-up visit 2 (7 days after the procedure), echocardiographic assessment may not include all the above parameters due to limited visualization.

Severe AS is defined as AVA < 1.0 cm^2 or indexed AVA < 0.6 cm^2/m^2 as calculated by the continuity equation on TTE. The study includes both patients with high-gradient severe AS, and those with low-flow, low-gradient severe AS, regardless of LVEF. In patients with low-flow, low-gradient AS and reduced LVEF to differentiate between true severe AS and pseudo-severe AS, dobutamine stress echocardiography is typically performed, and in patients with low-flow, low-gradient AS and preserved LVEF — computed tomography with assessment of aortic valve calcium score, as recommended by the European Society of Cardiology (ESC) guidelines [11].

Histopathological evaluation

In patients undergoing SAVR, biopsy of interventricular septum is performed during surgery (a specimen of ~2 mm in diameter) for histopathological evaluation of myocardial fibrosis. The material is temporarily stored in 5% solution of formalin and transferred to the Department of Physiology and Experimental Pathophysiology, Medical University of Warsaw for histopathological evaluation. All collected samples are coded with a unique number and will be analyzed in one block by operators blinded to patient data. Microscopic examination of each sample will include assessment of myocardial morphology and interstitial fibrosis or inflammation. Only samples containing at least 50% of the cardiac muscle tissue will be examined.

Left heart catheterization

In patients undergoing TAVI, before and after prosthesis implantation end-diastolic and end-systolic LV and aortic pressures are measured.

Endpoints

The primary endpoint of this study is the association between serum and urine TMAO concentrations and (i) echocardiographic, (ii) biochemical and (iii) histopathological indices of HF. This will be assessed by (i) comparing clinical, echocardiographic, biochemical and histopathological variables in patients with TMAO concentrations above and below median, and (ii) analyzing correlations between TMAO concentrations and those parameters (for continuous variables). TMAO concentrations will also be correlated with LV pressures measured invasively during TAVI. The secondary endpoints include relationship between baseline TMAO

concentrations and post-treatment clinical status, echocardiographic and biochemical parameters in 6-month follow-up. This will include assessment whether TMAO is an independent predictor of clinical and/or echocardiographic improvement at 6 months. Clinical improvement will be defined as an improvement of at least 1 New York Heart Association class. In addition, changes in serum and urine TMAO, TMA and IS concentrations after the procedure will be analyzed in relation to other biochemical and echocardiographic changes. Clinical end-points, including all-cause death, HF death, HF hospitalizations and other cardiovascular hospitalizations will be recorded.

Sample size

Because insufficient data are available to assess the association between the concentration of TMAO and severity of echocardiographic, biochemical and histopathological features of HF in patients with severe AS, the calculation was based on two previous studies [24, 25]. Required sample size was calculated by a power test at a significance level of 0.05 with the following assumptions (i) the expected correlation coefficient R 0.35, (ii) nominal test power 0.8, (iii) p-value considered significant 0.05. Based on this sample size estimation, a total of 62 patients should be enrolled in the trial. Assuming that up to 15% of patients may be potentially lost to follow-up, we estimated that 70 patients should be enrolled in the trial. As of January 2021, 26 patients have been included in the study.

Legal considerations

The study protocol was approved by the Bioethical Committee of the Medical University of Warsaw, and registered in the ClinicalTrials database (NCT04406805). The study is conducted according to good clinical practice, the ethical principles described in the Declaration of Helsinki, the requirements of the European Medicines Agency and local legal and regulatory requirements. Data storage is conducted in compliance with local data protection laws. Authorities may request access to the study documentation in case of an inspection or audit. Documentation can be copied during inspection or audit only in case the identity of the participant has been made unrecognizable.

Statistical analysis

Statistical analysis was conducted using IBM SPSS Statistics, version 24.0 (IBM). Categorical variables will be presented as number and percentage and compared using the χ^2 test. The Shapiro-Wilk test will be used to assess normal distribution of continuous variables. Continuous variables will be presented as mean and standard deviation or median with interquartile range and compared using an unpaired t-test or the Mann-Whitney U test. The Pearson or Spearman correlation coefficient will be used to analyze a correlation between serum and urine TMAO concentration and continuous echocardiographic, biochemical and histopathological variables. The analyses will also include a comparison of patient groups with TMAO concentrations above and below the median, and patients with and without echocardiographic and clinical improvement at 6 months. The Cox regression model will be used to determine the prognostic ability of TMAO to predict echocardiographic, clinical and biochemical improvement at 6 months. Mortality and other adverse events will be reported descriptively. A p-value below 0.05 will be considered significant.

Discussion

The TASTE study is the first clinical study to evaluate the association between concentrations of TMAO and TMA and the severity of HF in patients with AS in an investigator-blinded way [22]. Recently, it has been shown that TMA, but not TMAO reduced rat cardiomyocytes viability, likely due to its disturbing effect on proteins, whereas a concomitant treatment with TMAO protected cardiomyocytes against the deleterious effect of TMA. Therefore, TMA but not TMAO seems to be a toxin and a marker of cardiovascular risk [22]. This study is expected to shed a light on the respective roles of TMA and TMAO in cardiovascular disease in a human model of pressure overload (AS). Noteworthy, the study offers an opportunity to assess the correlation of TMA and TMAO with the histopathology of human heart tissue. The state-of-the art methods to analyze TMAO and TMA will account for the reliability of results.

In this study, other promising markers of cardiac fibrosis will also be measured, such as MMP-9, MMP-2, CITP, gal-3 and IS. Indoxyl sulphate is considered to be a molecule linking CKD and HF, involved in the pathogenesis of the cardiorenal syndrome (CRS) [18, 26]. CRS is a condition characterized by kidney and HF, where the failure of one organ may induce dysfunction of the other, thus further accelerating the progressive failure of both organs [27]. Given the fact that AS and CKD often coexist, and that over half of patients have an improvement in eGFR after interventional treatment

of severe AS, assessment of IS concentrations in this study offers a unique possibility to investigate its role in the development of CRS in patients with severe AS [18, 28, 29].

TASTE is expected to determine whether TMAO and/or TMA reflect the severity of HF in AS patients, or predict clinical and echocardiographic improvement after interventional treatment of AS. This could be yet another step to understand the role of TMAO and TMA in cardiovascular disease [30]. If the association between TMAO and the severity of HF is confirmed, TASTE might provide a basis for future studies aimed to develop new methods for cardiac muscle protection by increasing the concentration of TMAO, for example by diet or supplements rich in TMAO precursors, and to diminish the detrimental effect of LV pressure overload on LV structure and function in patients with AS or arterial hypertension. Altogether, TMAO may be the key to discover new, breakthrough ways to prevent and/or treat HF. The findings of this study might potentially change the present paradigm of TMAO as a cardiovascular risk marker and trigger a debate on the protective effects of TMAO.

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Conflict of interest: None declared

References

1. Ufnal M, Zadlo A, Ostaszewski R. TMAO: A small molecule of great expectations. Nutrition. 2015; 31(11-12): 1317–1323, doi: 10.1016/j.nut.2015.05.006.
2. Lever M, George PM, Slow S, et al. Betaine and trimethylamine-n-oxide as predictors of cardiovascular outcomes show different patterns in diabetes mellitus: an observational study. PLoS One. 2014; 9(12): e114969, doi: 10.1371/journal.pone.0114969, indexed in Pubmed: 25493436.
3. Jaworska K, Bielinska K, Gawrys-Kopczynska M, et al. TMA (trimethylamine), but not its oxide TMAO (trimethylamine-oxide), exerts haemodynamic effects: implications for interpretation of cardiovascular actions of gut microbiome. Cardiovasc Res. 2019; 115(14): 1948–1949, doi: 10.1093/cvr/cvz231, indexed in Pubmed: 31504256.
4. Jaworska K, Konop M, Hutsch T, et al. Trimethylamine but not trimethylamine oxide increases with age in rat plasma and affects smooth muscle cells viability. J Gerontol A Biol Sci Med Sci. 2020; 75(7): 1276–1283, doi: 10.1093/gerona/glz181, indexed in Pubmed: 31411319.
5. Gawrys-Kopczynska M, Konop M, Maksymiuk K, et al. TMAO, a seafood-derived molecule, produces diuresis and reduces mortality in heart failure rats. Elife. 2020; 9, doi: 10.7554/eLife.57028, indexed in Pubmed: 32510330.
6. Huc T, Drapala A, Gawrys M, et al. Chronic, low-dose TMAO treatment reduces diastolic dysfunction and heart fibrosis in hypertensive rats. Am J Physiol Heart Circ Physiol. 2018; 315(6): H1805–H1820, doi: 10.1152/ajpheart.00536.2018, indexed in Pubmed: 30265149.
7. Osnabrugge RLJ, Mylotte D, Head SJ, et al. Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study. J Am Coll Cardiol. 2013; 62(11): 1002–1012, doi: 10.1016/j.jacc.2013.05.015, indexed in Pubmed: 23727214.
8. Iung B, Baron G, Butchart EG, et al. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. Eur Heart J. 2003; 24(13): 1231–1243, doi: 10.1016/s0195-668x(03)00201-x, indexed in Pubmed: 12831818.
9. Dweck MR, Boon NA, Newby DE. Calcific aortic stenosis: a disease of the valve and the myocardium. J Am Coll Cardiol. 2012; 60(19): 1854–1863, doi: 10.1016/j.jacc.2012.02.093, indexed in Pubmed: 23062541.
10. Otto CM, Lind BK, Kitzman DW, et al. Association of aortic-valve sclerosis with cardiovascular mortality and morbidity in the elderly. N Engl J Med. 1999; 341(3): 142–147, doi: 10.1056/NEJM199907153410302, indexed in Pubmed: 10403851.
11. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017; 38(36): 2739–2791, doi: 10.1093/eurheartj/ehx391, indexed in Pubmed: 28886619.
12. Joseph J, Naqvi SY, Giri J, et al. Aortic stenosis: pathophysiology, diagnosis, and therapy. Am J Med. 2017; 130(3): 253––263, doi: 10.1016/j.amjmed.2016.10.005, indexed in Pubmed: 27810479.
13. Treibel TA, Kozor R, Schofield R, et al. Reverse myocardial remodeling following valve replacement in patients with aortic stenosis. J Am Coll Cardiol. 2018; 71(8): 860–871, doi: 10.1016/j.jacc.2017.12.035, indexed in Pubmed: 29471937.
14. Kayama S, Aratake S, Sawamura S, et al. Medium and long-term prognosis of transcatheter aortic valve implantation from the perspective of left ventricular diastolic function. Cardiol J. 2019; 26(1): 29–35, doi: 10.5603/CJ.a2018.0005, indexed in Pubmed: 29570210.
15. Bjørnstad JL, Neverdal NO, Vengen OA, et al. Alterations in circulating activin A, GDF-15, TGF-beta3 and MMP-2, -3, and -9 during one year of left ventricular reverse remodelling in patients operated for severe aortic stenosis. Eur J Heart Fail. 2008; 10(12): 1201–1207, doi: 10.1016/j.ejheart.2008.09.010, indexed in Pubmed: 18996047.
16. Kupari M, Laine M, Turto H, et al. Circulating collagen metabolites, myocardial fibrosis and heart failure in aortic valve stenosis. J Heart Valve Dis. 2013; 22(2): 166–176, indexed in Pubmed: 23798204.
17. Zhong X, Qian X, Chen G, et al. The role of galectin-3 in heart failure and cardiovascular disease. Clin Exp Pharmacol Physiol. 2019; 46(3): 197–203, doi: 10.1111/1440-1681.13048, indexed in Pubmed: 30372548.
18. Fu Q, Cao L, Li H, et al. Cardiorenal syndrome: pathophysiological mechanism, preclinical models, novel contributors and potential therapies. Chin Med J (Engl). 2014; 127(16): 3011–3018, indexed in Pubmed: 25131243.
19. Lekawanvijit S, Kompa AR, Manabe M, et al. Chronic kidney disease-induced cardiac fibrosis is ameliorated by reducing circulating levels of a non-dialysable uremic toxin, indoxyl sulfate. PLoS One. 2012; 7(7): e41281, doi: 10.1371/journal.pone.0041281, indexed in Pubmed: 22829936.

20. Organ CL, Otsuka H, Bhushan S, et al. Choline diet and its gut microbe-derived metabolite, trimethylamine N-oxide, exacerbate pressure overload-induced heart failure. Circ Heart Fail. 2016; 9(1): e002314, doi: 10.1161/CIRCHEARTFAILURE.115.002314, indexed in Pubmed: 26699388.
21. Ufnal M, Jazwiec R, Dadlez M, et al. Trimethylamine-N-oxide: a carnitine-derived metabolite that prolongs the hypertensive effect of angiotensin II in rats. Can J Cardiol. 2014; 30(12): 1700–1705, doi: 10.1016/j.cjca.2014.09.010, indexed in Pubmed: 25475471.
22. Jaworska K, Hering D, Mosieniak G, et al. TMA, A Forgotten Uremic Toxin, but Not TMAO, Is Involved in Cardiovascular Pathology. Toxins (Basel). 2019; 11(9), doi: 10.3390/toxins11090490, indexed in Pubmed: 31454905.
23. Jaworska K, Huc T, Samborowska E, et al. Hypertension in rats is associated with an increased permeability of the colon to TMA, a gut bacteria metabolite. PLoS One. 2017; 12(12): e0189310, doi: 10.1371/journal.pone.0189310, indexed in Pubmed: 29236735.
24. Yancey PH, Siebenaller JF. Co-evolution of proteins and solutions: protein adaptation versus cytoprotective micromolecules and their roles in marine organisms. J Exp Biol. 2015; 218(Pt 12): 1880–1896, doi: 10.1242/jeb.114355, indexed in Pubmed: 26085665.
25. Burg MB, Ferraris JD. Intracellular organic osmolytes: function and regulation. J Biol Chem. 2008; 283(12): 7309–7313, doi: 10.1074/jbc.R700042200, indexed in Pubmed: 18256030.
26. Konopelski P, Ufnal M. Indoles: gut bacteria metabolites of tryptophan with pharmacotherapeutic potential. Curr Drug Metab. 2018; 19(10): 883–890, doi: 10.2174/1389200219666180427164731, indexed in Pubmed: 29708069.
27. Lekawanvijit S, Krum H. Cardiorenal syndrome: acute kidney injury secondary to cardiovascular disease and role of protein-bound uraemic toxins. J Physiol. 2014; 592(18): 3969–3983, doi: 10.1113/jphysiol.2014.273078, indexed in Pubmed: 24907309.
28. Reuillard A, Garrouste C, Pereira B, et al. Evolution of chronic kidney disease after surgical aortic valve replacement or transcatheter aortic valve implantation. Arch Cardiovasc Dis. 2019; 112(3): 162–170, doi: 10.1016/j.acvd.2018.10.003, indexed in Pubmed: 30655226.
29. Vavilis G, Bäck M, Occhino G, et al. Kidney dysfunction and the risk of developing aortic stenosis. J Am Coll Cardiol. 2019; 73(3): 305–314, doi: 10.1016/j.jacc.2018.10.068, indexed in Pubmed: 30678761.
30. Winther SA, Øllgaard JC, Tofte N, et al. Utility of plasma concentration of trimethylamine n-oxide in predicting cardiovascular and renal complications in individuals with type 1 diabetes. Diabetes Care. 2019; 42(8): 1512–1520, doi: 10.2337/dc19-0048, indexed in Pubmed: 31123156.

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STUDY PROTOCOL

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Safety and efficacy of His bundle pacing validated by extracardiac vagal nerve stimulation (HIS-STORY)

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Background

Growing interest in His bundle pacing (HBP) is being seen worldwide. HBP is an attractive option for permanent cardiac pacing as it maintains a physiological pattern of ventricular activation and thus may prevent the development of right ventricular pacing-induced cardiomyopathy. The permanent HBP procedure has a two-decade track record and has been refined and improved along the way [1]. However, despite general optimism on 'physiological pacing', concerns about the performance, safety, and clinical benefits of HBP still exist. In the 2021 European Society of Cardiology (ESC) guidelines on cardiac pacing an abstaining prevails and there is no first-class recommendation with HBP as first-line therapy [2].

Hypothesized herein, that in a situation of vagal surge some patients with HBP may be endangered by loss of capture due to parasympathetic influence on His-Purkinje system (HPS). For this group of patients a change to left bundle branch pacing, which is usually not selective, thereby assuring direct ventricular myocardium stimulation, or implantation of the back-up right ventricular electrode may be necessary. Another reasonable approach, based on a relatively novel therapeutic technique — cardioneuroablation (CNA), i.e., percutaneous radiofrequency ablation of the parasympathetic ganglionated plexi of the heart [3]. The implementation of extracardiac vagal nerve stimulation (ECANS) and recently introduced ultrasound-guided ECANS (US-ECANS) enables validation of impact of right and left vagal nerve stimulation on parameters of automaticity and conduction [4]. Although, ECANS is associated with sinus asystole or atrioventricular (AV) block during atrial pacing, the incidence of vagally mediated HBP exit block and changes in pacing threshold have not been investigated.

To test the present hypothesis it was decided to conduct a study on the effects of ECANS on pacing parameters in patients with permanent HBP [5]. The aim of this clinical investigation is to assess efficacy of HBP during strong activation of parasympathetic system. As ECANS is a novel, non-standardized diagnostic method, another aim of the study is an assessment of effects of left-

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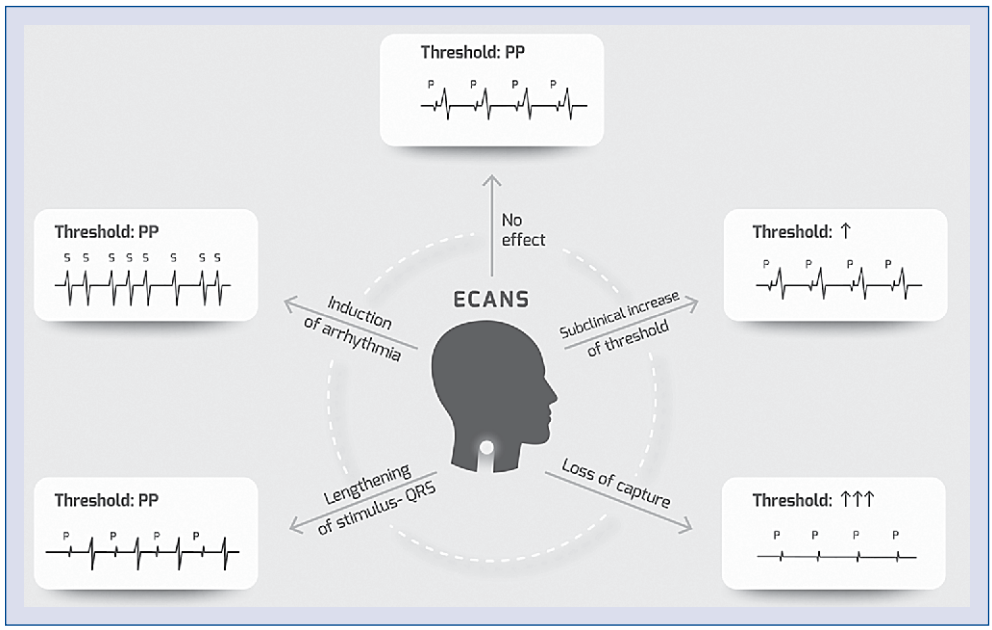

Figure 1. Possible effects of vagus nerve stimulation on His bundle pacing and underlying heart rhythm; ECANS — extracardiac autonomic (vagal) nerve stimulation; PP — permanently programmed values; ↑ — increase of threshold below PP; ↑↑↑ — increase of threshold above PP.

versus right-sided ECANS on underlying rhythm and/or HBP parameters.

Methods

HIS-STORY is an investigator-initiated, prospective, multicenter, randomized, interventional clinical study. All the measured parameters, as well as demographic and clinical data will be recorded in the study database. All patients will provide an informed consent form. Patients with indications for permanent pacing, according to the latest ESC guidelines, will be enrolled. All participants will undergo permanent pacemaker implantation for HBP. Subsequently, an invasive electrophysiological study (EPS) and ECANS will be performed under general anesthesia. The study will recruit patients with existing HBP systems and also those in whom a HBP device will be implanted just before the EPS/ECANS procedure. ECANS can be performed from right or left interior jugular vein (IJV) at two levels: at the level of jugular foramen (superior ECANS) or at the level of the angle of mandible (inferior ECANS). Superior ECANS can be fluoroscopy-guided only, however inferior ECANS can be guided by fluoroscopy, ultrasound (US) or both. This study has a factorial design and 2×2 randomization and will be performed thus: patients will be randomized to begin superior ECANS from the right or left IJV; a second randomization will assess the feasibility of the US-guided inferior ECANS. Patients will be randomized into two groups, blinded to the main operator; to undergo US-guided inferior ECANS or to undergo sham US-guidance. During ECANS, pacing parameters will be tested using a dedicated programmer and will be compared with baseline values. Possible effects of ECANS are depicted in the Figure 1. Patients with an exit block or an increase in a pacing threshold of an HBP electrode will be further managed by electrophysiologists from the research group. The management will be based on clinical relevance and share-decision making with the patient and may involve observation, pacemaker reprogramming, pacemaker upgrade with a back-up pacing electrode implantation, or cardioneuroablation. Moreover, additional substrates for supraventricular and ventricular arrhythmias will be managed according to shareddecision-making with the patient. Ablations for any arrhythmias will, however, be performed only if they will be clinically justified and indicated by the current ESC guidelines. Study protocol was approved by the Local Bioethical Committee and is registered on clinicaltrials.gov (NCT04816864; https://clinicaltrials. gov/ct2/show/NCT04816864). Enrollment began on January 02, 2021, and the study was registered on March 25, 2021.

Table 1. Inclusion and exclusion criteria for the HIS-STORY study.

Inclusion criteria	Exclusion criteria
Signed informed consent form	Age below 18 years
Age of 18 years or older	Contraindications to invasive electrophysiology study
Effective and stable His bundle pacing	Contraindications to general anesthesia
Sinus rhythm during the intervention procedure	Contraindications to atropine administration (e.g., glaucoma)
	Persistent atrial fibrillation or atrial flutter
	Pregnancy
	Diseases that may cause autonomic system neuropathy
	Use of medications that may affect the parasympathetic system
	A history of cardiac surgery
	A history of ablation due to arrhythmia

Study population

The target study population is 60. Inclusion and exclusion criteria are shown in Table 1.

Intervention

The study intervention will consist of three steps, all of which will be performed under general anesthesia:

— EPS with the measurement of parameters of AV conduction and programmed atrial and/or ventricular pacing;
— ECANS of the right and the left vagus nerve (from the right and left IJV, respectively; patients will be randomized to begin ECANS from either the right or the left side) performed during: 1) the patient's spontaneous heart rhythm (if present); 2) HBP with permanently programmed impulse parameters; 3) HBP at a pacing threshold of +0.1 V; and 4) 5 min after intravenous injection of atropine (0.02–0.04 mg/kg);
— EPS with the measurement of parameters of AV conduction and programmed atrial and ventricular pacing.

ECANS

A steerable quadripolar catheter will be inserted through the right femoral vein and advanced under fluoroscopic guidance to the right and left jugular vein at the level of the jugular foramen. The tip of the catheter will be directed medially and 5 s of stimulation with square wave pulsed of 50 μs at a frequency of 50 Hz and amplitude of 0.5 to 1.0 V/kg (max: 70 V) will be delivered. Subsequently the catheter will be pulled back under fluoroscopic guidance so that the tip will be at level of the angle of mandible (inferior ECANS). In accordance with prior randomization the US operator will guide the main operator to place the tip near the vagus nerve or only pretend to do so. Timing of the ECANS will be at the discretion of the US operator, so that the main operator will stay blinded for sham or US-guided ECANS. In patients with subclavian, vena cava superior or IJV thrombosis associated with the lead detailed imaging and clinical management will be performed and ability to cannulate IJV will be recorded.

Endpoints

Primary outcome measures:

— Loss of HBP capture or significant increase in pacing threshold, i.e., above the permanently programmed impulse amplitude of HBP electrode induced by ECANS.

Secondary outcome measures:

— A nonsignificant increase in pacing threshold, that is, below the permanently programmed impulse amplitude of HBP electrode induced by ECANS;
— Prolongation of the stimulus–QRS interval during HBP induced by ECANS;
— Any arrhythmia induced within 30 s after ECANS.

Statistical analysis

For statistical analysis Statistica (Statsoft Polska, Krakow, Poland) software will be used.

The continuous variables will be presented as means and standard deviations or medians and interquartile ranges due to their distribution and compared with the Student t-test or the Mann-Whitney U test. Discrete variables will be presented as numbers and percentages and compared with the χ^2 test.

The presented outcomes will be assessed as to their presence or absence. The logistic regres-

sion analysis and classification and regression trees analysis will be performed to find factors associated with the outcomes. The models will be constructed using variables which differ in univariate analysis with $p < 0.15$ or clinically significant.

The multivariable analysis will be performed for the continuous dependent variables. P less than 0.05 will be considered as significant.

Discussion

It has been shown that hyperactivity of the parasympathetic system might induce AV conduction disturbances. Zyśko et al. [6] analyzed electrocardiographic characteristics of AV conduction abnormalities induced by neurocardiogenic reflex during tilt-testing and found AV blocks in 3.9% of patients. Taking into account that even 40% of the general population experiences at least one episode of syncope during their life and that about 20% of all syncopes are reflex syncope, vagally mediated functional AV block does not seem to be an uncommon clinical condition [7]. Moreover, excessive vagal tone has been shown to be responsible not only for transient but also for some permanent AV block cases [4]. Therefore, some patients with indications for permanent cardiac pacing who have received the HBP may actually have vagally mediated functional AV conduction abnormalities. Although the impact of ECANS on sinus and AV node electrophysiological properties is well-known, the incidence of functional, vagally mediated reflexes on HPS remain unexplained [8]. In the literature, however, plenty of evidence on vagal innervation and influence on ventricular tissue exists [9, 10]. Similar prospective studies have been performed, however they were assessing the impact of ECANS on the conduction system and electrophysiological properties inferior or superior to HPS [11, 12]. Therefore, the present study might provide new insight into our knowledge of parasympathetic innervation of the conduction tissue. Moreover, some clinically important hypothesis will be tested, as aforementioned remarks raise suspicion that in some patients, vagal surge might be strong enough to hyperpolarize conduction tissue below the AV node level, thereby causing an acute increase in the capture threshold and even exit block. Such patients are in danger of transient loss of ventricular pacing.

Limitations of the study

Iatrogenic high parasympathetic tone induced by vagal nerve stimulation might never be experienced by the patient in natural, real-life circumstances, thereby increases in pacing thresholds or loss of capture may not necessarily be clinically important.

Conflict of interest: Sebastian Stec: author of several patents and shareholder of Medicine S.A. No specific product of the company will be used in this study. All other authors have no conflict of interest to declare.

References

1. Deshmukh P, Casavant D, Romanyshyn M, et al. Permanent, direct His-bundle pacing. Circulation. 2000; 101(8): 869–877, doi: 10.1161/01.cir.101.8.869.
2. Glikson M, Nielsen J, Kronborg M, 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.
3. Pachon JC, Pachon EI, Pachon JC, et al. „Cardioneuroablation"--new treatment for neurocardiogenic syncope, functional AV block and sinus dysfunction using catheter RF-ablation. Europace. 2005; 7(1): 1–13, doi: 10.1016/j.eupc.2004.10.003, indexed in Pubmed: 15670960.
4. Wileczek A, Polewczyk A, Kluk M, et al. Ultrasound-guided imaging for vagus nerve stimulation to facilitate cardioneuroablation for the treatment of functional advanced atrioventricular block. Indian Pacing Electrophysiol J. 2021; 21(6): 403–406, doi: 10.1016/j.ipej.2021.06.008, indexed in Pubmed: 34186197.
5. Pachon M JC, Pachon M EI, Santillana P TG, et al. Simplified method for vagal effect evaluation in cardiac ablation and electrophysiological procedures. JACC Clin Electrophysiol. 2015; 1(5): 451–460, doi: 10.1016/j.jacep.2015.06.008, indexed in Pubmed: 29759475.
6. Zyśko D, Gajek J, Koźluk E, et al. Electrocardiographic characteristics of atrioventricular block induced by tilt testing. Europace. 2009; 11(2): 225–230, doi: 10.1093/europace/eun299, indexed in Pubmed: 18987129.
7. Aksu T, Guler TE, Bozyel S, et al. Potential usage of cardioneuroablation in vagally mediated functional atrioventricular block. SAGE Open Med. 2019; 7: 2050312119836308, doi: 10.1177/2050312119836308, indexed in Pubmed: 30906551.
8. Stec S, Dobaj Ł, Śledź A, et al. Cardioneuroablation for management of cardioinhibitory vasovagal syncope and pacemaker complications. HeartRhythm Case Rep. 2020; 6(8): 531–534, doi: 10.1016/j.hrcr.2020.04.021, indexed in Pubmed: 32817835.
9. Tsun L, Chow LT, Chow SS, et al. Autonomic innervation of the human cardiac conduction system: changes from infancy to senility--an immunohistochemical and histochemical analysis. Anat Rec. 2001; 264(2): 169–182, doi: 10.1002/ar.1158, indexed in Pubmed: 11590594.
10. Coote JH. Myths and realities of the cardiac vagus. J Physiol. 2013; 591(17): 4073–4085, doi: 10.1113/jphysiol.2013.257758, indexed in Pubmed: 23878363.
11. A Study to Evaluate the Effect of Vagus Nerve Stimulation in Patients Undergoing VT Ablation ClinicalTrials.gov Identifier: NCT04359004.
12. Stec S, Jankowska-Polańska B, Jagielski D, et al. Rationale and design of SAN.OK_1 randomized controlled clinical trial and registry: Comparison of Early vs Late Permanent Pacemaker Implantation and Cardioneuroablation in Sinus Node Dysfunction. ClinicalTrials.gov Identifier: NCTO5196126.

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Angiotensin converting enzyme and sodium glucose cotransporter inhibitors alleviate inflammatory effects of SARS-CoV-2 in cardiomyocytes

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Coronavirus disease 2019 (COVID-19) patients frequently have cardiac involvement [1]. This is partly attributed to the abundant expression of angiotensin-converting enzyme 2 (ACE2), functional receptor of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in cardiomyocytes [2]. There are concerns regarding angiotensin-converting enzyme inhibitor (ACEi) use amid the pandemic as ACEi is postulated to upregulate ACE2 expression and increase susceptibility to SARS-CoV-2 myocardial damage [3]. Likewise, the use of sodium-glucose transport protein 2 inhibitors (SGLT2i) in diabetic COVID-19 patients is controversial. Diabetic societies recommend withholding SGLT2i if hospitalized for COVID-19 to reduce risk of diabetic ketoacidosis. In a stark contrast, investigators have been exploring the use of SGLT2i in COVID-19 patients, such as the Dapagliflozin in Respiratory Failure in Patients with COVID-19 (DARE-19) trial, owing to its potent cardiovascular protective effects [4]. To date, there is a lack of experimental data to guide ACEi and SGLT2i use among COVID-19 patients.

Recently, the present team [5] and others recapitulated myocardial damage of SARS-CoV-2 in induced-pluripotent stem cell-derived cardiomyocytes (iPSC-CM). SARS-CoV-2 causes myocardial damage by exerting direct cytopathogenic effects and inducing inflammation via cytokines/chemokines expression [5]. In the present study, an investigation of the effects of ACEi and SGLT2i pre-treatment on myocardial ACE2 expression, susceptibility to SARS-CoV-2 infection and cardiomyocytes viability using an iPSC-CM platform.

The study protocol was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (IRB-UW08-258 and UW 16-365 20-07-2016). Written informed consent was obtained from the participant. The iPSCs used were derived from a healthy Chinese volunteer. Detailed methods of iPSC generation, characterization, and *in vitro* cardiomyocyte differentiation used were previously reported by us [5, 6]. Approximately 3×10^4 and 1×10^4 iPSC-CM were plated into 24-well and 96-well culture dishes pre-coated with Matrigel plate

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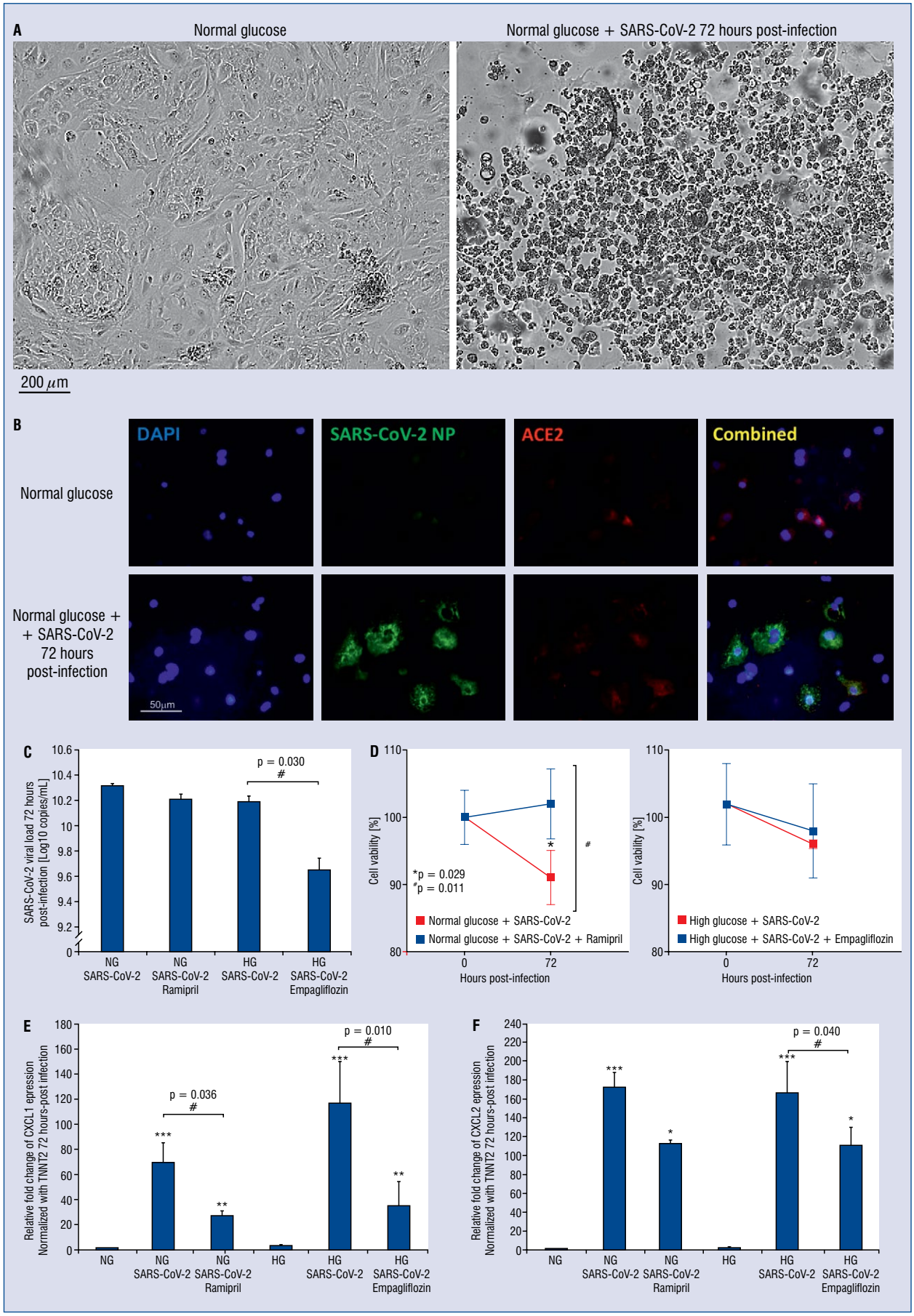
A
Normal glucose
Normal glucose + SARS-CoV-2 72 hours post-infection
200 μm
B
DAPI
SARS-CoV-2 NP
ACE2
Combined
Normal glucose
Normal glucose + + SARS-CoV-2 72 hours post-infection
50μm
C
SARS-CoV-2 viral load 72 hours post-infection [Log10 copies/mL]
p = 0.030
#
NG SARS-CoV-2
NG SARS-CoV-2 Ramipril
HG SARS-CoV-2
HG SARS-CoV-2 Empagliflozin
D
Cell vability [%]
*p = 0.029
#p = 0.011
Normal glucose + SARS-CoV-2
Normal glucose + SARS-CoV-2 + Ramipril
Hours post-infection
High glucose + SARS-CoV-2
High glucose + SARS-CoV-2 + Empagliflozin
E
Relative fold change of CXCL1 epression Normalized with TNNT2 72 hours-post infection
p = 0.036
p = 0.010
F
Relative fold change of CXCL2 epression Normalized with TNNT2 72 hours-post infection
p = 0.040

Figure 1. Effect of cardiometabolic drugs on induced-pluripotent stem cell-derived cardiomyocytes (iPSC-CM) infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); **A.** Brightfield microscopy with cytopathic changes of iPSC-CM including cell clumping and detachment from the culture dish at 72 hours post-infection (hpi); **B.** Immunofluorescence studies (blue: DAPI; green: SARS-CoV-2-NP, SARS-CoV-2 nucleocapsid protein; and red: angiotensin converting enzyme 2 [ACE2]) showing SARS-CoV-2 nucleocapsid proteins within iPSC-CM cytoplasm; **C.** Empagliflozin pre-treatment resulted in reduced supernatant viral load by 0.54 Log_{10} copies/mL at 72 hpi comparing to positive control ($^{\#}p = 0.030$). Data represent mean ± standard error of the mean from triplicate experiments. Comparisons between two groups were performed using the Student t test. Number sign ($^{\#}$) indicates statistical significance between infection group and infection group with cardiometabolic drug ($^{\#}p < 0.05$); HG — high glucose; NG — normal glucose; **D.** Cell viability reduced from 100 ± 4.05% to 91.0 ± 4.00% (*p = 0.029) at 72 hpi in positive control. Cell viability modestly improved by 12.1% ($^{\#}p = 0.011$) in the ramipril group. Data represent mean ± standard error of the mean from triplicate experiments. Comparisons between two groups were performed using the Student t test. Number sign ($^{\#}$) indicates statistical significance between infection group and infection group with cardiometabolic drug ($^{\#}p < 0.05$); **E.** Relative quantification of reverse transcription quantitative polymerase chain reaction products were assessed using the $2^{-\Delta\Delta Ct}$ method, using troponin T (TNNT2) as internal control, where $\Delta\Delta Ct = [(Ct_{target\ gene} - Ct_{TNNT2})$ Treatment group $- (Ct_{target\ gene} - Ct_{TNNT2})$ Control group]. SARS-CoV-2 infection upregulated C-X-C Motif Chemokine Ligand 1 (CXCL1) to 69.2-fold (***p < 0.001) and 117-fold (***p < 0.001) at 72 hpi in normal and high glucose conditions respectively. CXCL1 was downregulated to 27.0-fold ($^{\#}p = 0.036$) and 34.7-fold ($^{\#}p = 0.010$) by ramipril and empagliflozin, respectively. Data represent mean ± standard error of the mean from triplicate experiments. Comparisons between two groups were performed using the Student t test. Asterisk (*) indicates statistical significance between control group and infection or cardiometabolic drug group. Number sign ($^{\#}$) indicates statistical significance between infection group and infection group with cardiometabolic drug; ***p < 0.001; **p < 0.01; $^{\#}p < 0.05$; HG — high glucose; NG — normal glucose; **F.** SARS-CoV-2 infection upregulated C-X-C Motif Chemokine Ligand 2 (CXCL2) to 172-fold (***p < 0.001) and 166-fold (***p < 0.001) in normal and high glucose conditions, respectively. CXCL2 was downregulated to 110-fold ($^{\#}p = 0.040$) by empagliflozin. Data represent mean ± standard error of the mean from triplicate experiments. Comparisons between two groups were performed using the Student t test. Asterisk (*) indicates statistical significance between control group and infection or cardiometabolic drug group. Number sign ($^{\#}$) indicates statistical significance between the infection group and infection group with cardiometabolic drug; ***p < 0.001; *p < 0.05; $^{\#}p < 0.05$; HG — high glucose; NG — normal glucose.

(Thermo Scientific, USA). To evaluate the effects of cardiometabolic medications, iPSC-CM were pretreated for 7 days with ACEi ramipril (0.1 μM) (Cayman, USA), or SGLT2i empagliflozin (5 μM) (Selleckchem, USA). To recapitulate hyperglycemic state of diabetic patients, high glucose environment (22 mM glucose) was used for empagliflozin [6]. *In vitro* infection was performed by applying SARS-CoV-2 to iPSC-CM monolayers with multiplicity of infection of 0.1 and incubating at 37°C for 1 hour. Experiments involving live SARS-CoV-2 were performed in Biosafety Level-3 Facility.

Seventy-two hours post-infection (hpi), iPSC-CM ceased spontaneous beating and demonstrated cytopathogenic changes with cell clumping and detachment from culture dish (Fig. 1A, B). After ramipril pre-treatment, ACE2 mRNA expression assessed by reverse transcription quantitative polymerase chain reaction (RT-qPCR) in iPSC-CM was upregulated to 5.87-fold ($p < 0.001$). To assess supernatant viral load, RT-qPCR targeting SARS-CoV-2 using forward primer 5'-CGCATACAGTCTTRCAGGCT-3' and reverse primer 5'-GTGTGATGTTGAWATGACATGGTC-3' was performed (Fig. 1C). Despite an increased ACE2 expression after ramipril pre-treatment, iPSC-CM susceptibility to SARS-CoV-2 was not enhanced with no significant increase in SARS-CoV-2 RNA comparing to positive control. Cell viability was assessed using colorimetric-based Cell Counting Kit-8 (CCK-8; Dojindo Molecular Technologies, USA) (Fig. 1D). IPSC-CM viability was quantified using relative absorbance at 450 nm and the absorbance in normal glucose condition without infection or medication was taken to be 100%. Cell viability reduced from 100 ± 4.05% to 91.0 ± 4.00% ($p = 0.029$) at 72 hpi in positive control. Intriguingly, ramipril improved cell viability by 12.1% ($p = 0.011$) comparing to positive control albeit comparable viral load. Unlike ramipril, empagliflozin did not significantly affect ACE2 expression. Empagliflozin caused a modest reduction of supernatant SARS-CoV-2 viral load by 0.54 Log_{10} copies/mL ($p = 0.030$) and downregulated natriuretic peptide B (NPPB) mRNA expression from 3.21-fold to 1.96-fold ($p < 0.05$) comparing to positive control. Nonetheless, empagliflozin treatment did not affect iPSC-CM viability.

SARS-CoV-2 infection causes myocardial damage partly by upregulating expression of pro-inflammatory cytokine/chemokines, particularly

C-X-C Motif Chemokine Ligand 1 (CXCL1) and C-X-C Motif Chemokine Ligand 2 (CXCL2) [5]. Of note, the CXCL1-CXCR2 axis was known to mediate monocytic infiltration to the myocardium [7]. CXCL1 and CXCL2 mRNA expression in iPSC--CM increased to 69.2-fold ($p < 0.001$) and 172-fold ($p < 0.001$) in a normal glucose culture condition and 117-fold ($p < 0.001$) and 166-fold ($p < 0.001$) in a high glucose condition. Interestingly, ramipril attenuated SARS-CoV-2 induced CXCL1 expression to 27.0-fold ($p = 0.036$). Similarly, empaglifozin attenuated SARS-CoV-2 induced CXCL-1 and CXCL2 expression to 34.7-fold ($p = 0.010$) and 110-fold ($p = 0.040$) respectively (Fig. 1E, F).

In the present study, we exploited our recently established iPSC-CM platform to study the effects of ACEi and SGLT2i on ACE2 expression and SARS-CoV-2 susceptibility. We demonstrated that in concordance to previous animal models, ACEi treatment resulted in an upregulation of ACE2 expression in iPSC-CM. Counterintuitively, the ACEi-induced ACE2 upregulation in iPSC--CM did not lead to an increased susceptibility to SARS-CoV-2 infection. Plausibly, the abundance of ACE2 in iPSC-CM may have already been above the stoichiometry of entry for SARS-CoV-2 virus in baseline condition, thereby further increase in ACE2 expression with ramipril did not further increase SARS-CoV-2 cellular entry. In fact, ACEi treatment improved iPSC-CM survival upon SARS-CoV-2 infection and alleviated SARS-CoV-2 induced inflammatory response in iPSC-CM. This is in consistence with clinical observation that hospitalized patients taking ACEi appeared to have relative beneficial effects in terms of death or critical care unit admission [8]. One unexpected finding from our experiments was the potent anti-inflammatory effects of SGLT2i on SARS-CoV-2 infected myocardium. Pharmacological sodium-hydrogen exchanger isoform-1 (NHE-1) inhibition was shown to suppress nuclear factor kappa B (NF-κB) activity and proinflammatory response in endothelial cells stimulated by bacterial lipopolysaccharide [9]. As SGLT2i was shown to inhibit NHE-1 of cardiomyocytes [10], it is plausible that the marked downregulation of CXCL1 and CXCL2 were mediated through upstream suppression of NF-κB. Broadly speaking, the anti-inflammatory property of SGLT2i may also contribute to its potent effect against heart failure in diabetic patients, as diabetic cardiomyopathy is partly caused by myocardial inflammation. The current experiments had the following limitations: First, the experiments focused on the effects on the myocardium and its results cannot be directly extrapolated to other systems. Second, animal models will allow more holistic assessment of the systemic immune response.

Taken collectively, the results provided experimental evidence to support continuation of ACEi, and SGLT2i in stable diabetic patients amid the COVID-19 pandemic. The present findings also contributed to a better understanding of ACE2 physiology in human hearts and anti-inflammatory effects of SGLT2i.

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References

1. Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol. 2020; 5(7): 811–818, doi: 10.1001/jamacardio.2020.1017, indexed in Pubmed: 32219356.
2. Liu H, Gai S, Wang X, et al. Single-cell analysis of SARS-CoV-2 receptor ACE2 and spike protein priming expression of proteases in the human heart. Cardiovasc Res. 2020; 116(10): 1733––1741, doi: 10.1093/cvr/cvaa191, indexed in Pubmed: 32638018.
3. Zheng YY, Ma YT, Zhang JY, et al. COVID-19 and the cardiovascular system. Nat Rev Cardiol. 2020; 17(5): 259–260, doi: 10.1038/s41569-020-0360-5, indexed in Pubmed: 32139904.
4. Gager GM, Gelbenegger G, Jilma B, et al. Cardiovascular outcome in patients treated with SGLT2 inhibitors for heart failure: a meta-analysis. Front Cardiovasc Med. 2021; 8: 691907, doi: 10.3389/fcvm.2021.691907, indexed in Pubmed: 34336954.
5. Wong CK, Luk HKH, Lai WH, et al. Human-Induced pluripotent stem cell-derived cardiomyocytes platform to study SARS-CoV-2 related myocardial injury. Circ J. 2020; 84(11): 2027–2031, doi: 10.1253/circj.CJ-20-0881, indexed in Pubmed: 32981925.
6. Ng KM, Lau YM, Dhandhania V, et al. Empagliflozin ammeliorates high glucose induced-cardiac dysfuntion in human iPSC--derived cardiomyocytes. Sci Rep. 2018; 8(1): 14872, doi: 10.1038/s41598-018-33293-2, indexed in Pubmed: 30291295.
7. Wang L, Zhang YL, Lin QY, et al. CXCL1-CXCR2 axis mediates angiotensin II-induced cardiac hypertrophy and remodelling through regulation of monocyte infiltration. Eur Heart J. 2018; 39(20): 1818–1831, doi: 10.1093/eurheartj/ehy085, indexed in Pubmed: 29514257.
8. Bean DM, Kraljevic Z, Searle T, et al. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers are not associated with severe COVID-19 infection in a multi-site UK acute hospital trust. Eur J Heart Fail. 2020; 22(6): 967–974, doi: 10.1002/ejhf.1924, indexed in Pubmed: 32485082.
9. Németh ZH, Deitch EA, Lu Qi, et al. NHE blockade inhibits chemokine production and NF-kappaB activation in immunostimulated endothelial cells. Am J Physiol Cell Physiol. 2002; 283(2): C396–C403, doi: 10.1152/ajpcell.00491.2001, indexed in Pubmed: 12107048.
10. Uthman L, Baartscheer A, Bleijlevens B, et al. Class effects of SGLT2 inhibitors in mouse cardiomyocytes and hearts: inhibition of Na/H exchanger, lowering of cytosolic Na and vasodilation. Diabetologia. 2018; 61(3): 722–726, doi: 10.1007/s00125-017-4509-7, indexed in Pubmed: 29197997.

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RESEARCH LETTER

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Assessment of the physical performance in children with preexcitation syndrome, before and after catheter ablation of the accessory pathway: A pilot study

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Recently more interest has been given to the phenomenon of dyssynchrony of ventricular activation caused by the fusion of the intrinsic and antegrade conduction via the accessory pathway in patients with preexcitation syndrome. It has been noted that septal and right sided pathways were proven to have the main impact on the left ventricle dyssynchrony and causing dilated cardiomyopathy that can be reversible with either pharmacological or catheter ablation [1–9]. The aim of this study was to assess whether in children diagnosed with preexcitation syndrome, the key physical performance parameters assessed with the cardio-pulmonary exercise test (CPET) improves following successful catheter ablation of the accessory pathway.

The study group consisted of 14 children, 11 boys and 3 girls aged 8–16 years (12.7 mean), diagnosed with preexcitation syndrome, both symptomatic and asymptomatic patients, who were referred to our department for electrophysiologic (EP) study and ablation. All patients underwent routine assessment with 12-lead-electrocardiogram (ECG), 24-hour Holter ECG and echocardiography. Only patients with no associated cardiac anomalies were included into the study. A CPET according to the RAMP15 protocol was performed before and 3–4 months after the ablation.

Patients in the study group were examined using EPIQ ultrasound system (Philips). Standard protocol was used with routine measurements according to clinical practice and international guidelines.

The CPET was performed using the upright sitting cycle-ergometer according to the RAMP15 protocol. 12-lead-ECG was recorded and analyzed throughout the entire test and behavior of the delta wave was observed. Breath-by-breath measurement of the oxygen uptake (VO_2) and carbon dioxide (VCO_2) elimination was performed continuously together with respiratory exchange ratio (RER). To calculate the VO_2max, measurement at the VO_2 plateau during maximal exercise was used, alternatively the maximal VO_2 value at the peak exercise if the plateau was not observed. The oxygen pulse (O_2-pulse) was calculated by dividing VO_2 by heart rate measured at any point and then at the maximal exercise. Anaerobic threshold was calculated by the V-slope method. Workload expressed in Watts was recorded at the peak of exercise. Patients were verbally encouraged to continue the effort with voluntary termination at the patient's exhaustion.

Patients were qualified for the invasive treatment based on the clinical assessment and parent's/patient's decision only. All patients underwent invasive EP study and radiofrequency-ablation under general anaesthesia, using three-dimensional-mapping system (CARTO). Only patients with successful removal of the accessory pathway (AP) were included into the study.

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Table 1. Comparison of the cardio-pulmonary exercise test (CPET) and echocardiography results before and after the accessory pathway ablation.

	Group	M	SD	95% CI		t	p	Cohen's d
				LL	UL			
CPET parameters								
VO_2max [mL/kg/min]	Before	36.25	8.08	32.02	40.48	1.60	0.134	0.44
	After	38.45	7.61	34.46	42.44			
VO_2max [L/min]	Before	2.05	0.51	1.77	2.32	2.89	0.013*	0.84
	After	2.28	0.62	1.95	2.62			
RQ (RER)	Before	1.09	0.08	1.05	1.13	0.57	0.579	0.16
	After	1.10	0.09	1.05	1.15			
VE/VCO_2	Before	26.17	4.31	23.92	28.43	1.46	0.169	0.4
	After	27.14	3.73	25.18	29.09			
O_2 pulse [mL/beat]	Before	10.92	3.21	9.24	12.60	3.74	0.002*	1.04
	After	12.46	3.74	10.51	14.42			
Workload [watt]	Before	143.57	45.84	119.56	167.59	4.18	0.001*	1.16
	After	163.93	42.21	141.82	186.04			
VO_2/Work [mL/min/watt]	Before	11.17	1.46	10.40	11.94	0.60	0.558	0.17
	After	11.47	1.21	10.84	12.10			
Time [s]	Before	572.00	177.80	478.86	665.14	1.95	0.073	0.54
	After	621.07	166.37	533.93	708.22			
AT [mL/kg/min]	Before	18.12	4.39	15.63	20.60	0.70	0.501	0.21
	After	18.89	3.25	17.05	20.73			
AT [L/min]	Before	1.01	0.33	0.83	1.19	0.80	0.437	0.23
	After	1.06	0.24	0.94	1.19			
HR at peak effort [bpm]	Before	180.07	21.54	168.79	191.36	0.40	0.696	0.11
	After	182.14	9.69	177.06	187.22			
BP systolic at peak effort [mmHg]	Before	159.00	16.80	150.20	167.80	1.28	0.224	0.35
	After	165.43	16.69	156.69	174.17			
BP diastolic at peak effort [mmHg]	Before	70.23	19.22	59.78	80.68	–1.63	0.129	0.47
	After	58.23	13.58	50.85	65.61			
Echocardiography parameters								
RVIDd [mm]	Before	18.50	3.32	16.76	20.24	0.04	0.969	0.01
	After	18.53	3.49	16.70	20.36			
IVSd [mm]	Before	7.15	1.59	6.28	8.01	1.05	0.312	0.30
	After	7.42	1.68	6.50	8.33			
LVIDd [mm]	Before	47.80	4.87	45.25	50.35	–0.85	0.412	0.24
	After	47.25	4.43	44.93	49.57			
EF [%]	Before	70.84	4.78	68.33	73.34	–0.99	0.340	0.27
	After	69.21	3.51	67.37	71.05			
SF [%]	Before	39.15	2.85	37.60	40.70	–0.52	0.611	0.15

VO_2max — oxygen consumption at the peak of exercise; RQ (RER) — respiratory exchange ratio; VE — minute ventilation; VCO_2 — carbon dioxide output; AT — VO_2 at anaerobic threshold; HR — heart rate; BP — blood pressure; RVIDd — right ventricular internal dimension in diastole; IVSd — interventricular septal thickness at diastole; LVIDd — left ventricular internal dimension in diastole; EF — ejection fraction; SF — shortening fraction; n — count; M — mean; SD — standard deviation; 95% CI — 95% confidence interval; LL — lower limit; UL — upper limit; t — t-test statistic; p — p value; Cohen's d — effect size coefficient; *results with p value < 0.05

To examine the differences in the values of dependent variables between groups containing patients before and after ablation multiple t-Student tests for dependent samples were performed. Only complete cases for each continuous variable were chosen and then the normality assumption was checked using skewness values. For each group mean (M), standard deviation (SD), 95% confidence intervals (95% CI) with lower (LL) and upper (UL) limits were shown. As the effect size coefficient Cohen's d was used. The global significance level was $\alpha = 0.05$.

The echocardiography for all patients in the study group showed a normal heart structure, normal left ventricular size, and function within normal values. There were no statistically significant differences in echocardiographic measurements before and after the ablation procedure.

All patients both before and after the ablation achieved maximal effort, with RER ≥ 1.0 during the CPET with no differences regarding maximal heart rate (HR), systolic and diastolic, blood pressure, exercise time, anaerobic threshold, VO_2/work and VE/CO_2 ratios. After the ablation patients showed significantly higher values of O_2-pulse ($p = 0.002$), total VO_2max (L/min) with $p = 0.013$ and achieved higher workload during exercise ($p = 0.001$). The measurement of the VO_2max expressed in mL/kg/min did not differ significantly.

Results are shown in Table 1.

The present study shows that children with preexcitation syndrome improved the key parameters describing the physical performance following the successful catheter ablation of the accessory pathway. Following the ablation patients achieved higher VO_2max, O_2-pulse and workload during the exercise. The total VO_2 measurement improved however while expressed with relation to the body weight, failed to differ significantly. That could be an effect of a small study group, or body weight may play a role in VO_2 measurement. Exercise time was longer after the ablation, which correlates with higher workload, however it failed to differ statistically ($p = 0.07$; Cohen's $d = 0.54$), likely an effect of a small study group.

VO_2max is described by a Fick equation as a result of the cardiac output (CO) and maximal arterio-venous oxygen difference: $VO_2 = COx(a\text{-}v)O_2$. As the oxygen extraction is not affected in patients with cardiovascular problems, VO_2max mostly depends on the CO. O_2-pulse is the ratio between the VO_2 and HR, and it is a measure of the stroke volume (SV) during the exercise:

$$VO_2 = COx(a\text{-}v)O_2 = (SVxHR)x(a\text{-}v)O_2;$$
$$VO_2/HR = [SVxHRx(a\text{-}v)O_2]/HR = SVx(a\text{-}v)O_2.$$

In a recent study it was shown that in children with asymptomatic preexcitation, major physical performance parameters measured by the CPET (VO_2max, O_2-pulse) are diminished when compared to the healthy controls, and that effect was stronger in patients with persistent delta-wave throughout the exercise [10].

Multiple studies proved that mechanical dyssynchrony is present in patients with preexcitation and could even lead to dilated cardiomyopathy which resolves following successful ablation [1–9]. Therefore, a hypothesis postulated herein is that in the state of the physical activity the dyssynchronous activation of the cardiac muscle could be affecting the stroke volume and CO and contributing to the diminution of VO_2max and O_2-pulse. Successful removal of the AP should then restore cardiac synchrony and improve oxygen consumption during exercise. The current results seem to confirm this hypothesis.

Results of the study show that in children with preexcitation the key parameters improve after the successful ablation of the accessory pathway. Results are encouraging and further investigations are needed to fully explain the present findings.

Interpretation of the results must be careful as the study group is small and does not allow for more detailed analysis of the subgroups

Conflict of interest: None declared

References

1. Fazio G, Mongiovi' M, Sutera L, et al. Segmental dyskinesia in Wolff-Parkinson-White syndrome: a possible cause of dilatative cardiomyopathy. Int J Cardiol. 2008; 123(2): e31–e34, doi: 10.1016/j.ijcard.2006.11.109, indexed in Pubmed: 17292982.
2. Tomaske M, Janousek J, Rázek V, et al. Adverse effects of Wolff-Parkinson-White syndrome with right septal or posteroseptal accessory pathways on cardiac function. Europace. 2008; 10(2): 181–189, doi: 10.1093/europace/eun005, indexed in Pubmed: 18256123.
3. De Boeck BWL, Teske AJ, Leenders GE, et al. Detection and quantification by deformation imaging of the functional impact of septal compared to free wall preexcitation in the Wolff-Parkinson-White syndrome. Am J Cardiol. 2010; 106(4): 539–546.e2, doi: 10.1016/j.amjcard.2010.03.066, indexed in Pubmed: 20691313.
4. Kwon BoS, Bae EJ, Kim GiB, et al. Septal dyskinesia and global left ventricular dysfunction in pediatric Wolff-Parkinson-White syndrome with septal accessory pathway. J Cardiovasc Electrophysiol. 2010; 21(3): 290–295, doi: 10.1111/j.1540-8167.2009.01612.x, indexed in Pubmed: 19804548.

5. Udink ten Cate FEA, Kruessell MA, Wagner K, et al. Dilated cardiomyopathy in children with ventricular preexcitation: the location of the accessory pathway is predictive of this association. J Electrocardiol. 2010; 43(2): 146–154, doi: 10.1016/j.jelectrocard.2009.09.007, indexed in Pubmed: 19879594.
6. Dai CC, Guo BJ, Li WX, et al. Dyssynchronous ventricular contraction in Wolff-Parkinson-White syndrome: a risk factor for the development of dilated cardiomyopathy. Eur J Pediatr. 2013; 172(11): 1491–1500, doi: 10.1007/s00431-013-2070-z, indexed in Pubmed: 23812508.
7. Dai C, Guo B, Li W, et al. The effect of ventricular pre-excitation on ventricular wall motion and left ventricular systolic function. Europace. 2018; 20(7): 1175–1181, doi: 10.1093/europace/eux242, indexed in Pubmed: 29016834.
8. Lee HJ, Uhm JS, Hong YJ, et al. Altered myocardial characteristics of the preexcited segment in Wolff-Parkinson-White syndrome: A pilot study with cardiac magnetic resonance imaging. PLoS One. 2018; 13(6): e0198218, doi: 10.1371/journal.pone.0198218, indexed in Pubmed: 29856866.
9. Guo B, Dai C, Li Q, et al. Hazards of ventricular pre-excitation to left ventricular systolic function and ventricular wall motion in children: analysis of 25 cases. Cardiol Young. 2019; 29(3): 380–388, doi: 10.1017/S1047951118002500, indexed in Pubmed: 30767835.
10. Książczyk TM, Jaroń A, Pietrzak R, et al. Assessment of the physical performance in children with asymptomatic pre-excitation. Europace. 2022; 24(5): 855–859, doi: 10.1093/europace/euab171, indexed in Pubmed: 34648619.

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RESEARCH LETTER

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Severe hypocalcemia mimicking acute ST-segment elevation myocardial infarction: Paradigmatic case and review of literature

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A 65-year-old woman with a previous history of hypertension and hypercholesterolemia was admitted to the emergency department due to 2-week asthenia, diarrhoea and dizziness. Electrocardiogram (ECG) at admission showed ST-segment elevation in leads I, avL and V2 and depression in the inferior leads, suggestive of high lateral ST-segment elevation myocardial infarction (STEMI). QTc was 447 ms (Fig. 1A). She did not complain of chest pain or dyspnoea. Serum troponin levels were normal, and echocardiogram showed moderate systolic dysfunction with akinesia of medium segments of all cardiac walls. Laboratory evaluation evidenced severe hypocalcemia (6.1 mg/dL, normal 8.5–10.9 mg/dL) with low ionized calcium, corrected by serum albumin (2.6 mg/dL, normal 4.40–5.30 mg/dL). After calcium replenishment, ECG abnormalities reverted to normal (Fig. 1B) and echocardiogram demonstrated improvement of cardiac contractility. Deferred coronary angiography excluded significant epicardial coronary artery disease (Fig. 1C), as well as absence of endothelial dysfunction evaluated in the left anterior descending artery territory by acetylcholine provocation test and normal coronary flow reserve with mild elevation of the index of microcirculatory resistance (Fig. 1D). The patient was discharged after 1 week of hospitalization.

Electrolyte imbalances are a well-known cause of electrocardiographic abnormalities. In hypocalcemia, most frequent findings are ST segment and QTc prolongation, due to a reduction in phase two of the action potential. T wave may be flattened or inverted, but usually maintains its polarity. Although it has rarely been reported, hypocalcemia can induce ST segment elevation.

A literature review in Pubmed and Google Scholar databases regarding hypocalcemia as cause of STEMI was conducted. After evaluation by two independent investigators, 7 case reports were found.

Lehmann et al. [1] presented a case, in the year 2000, of a 24-year-old female presenting to the emergency department for loss of consciousness and seizures in the context of severe hypocalcemia due to hypoparathyroidism. ECG at admission showed ST segment elevation in I and aVL and depression in inferior and precordial leads, as well as QTc prolongation. Coronary angiography showed normal coronary arteries. After electrolyte supplementation, ECG changes reversed.

Similar cases have been reported subsequently and are described in Table 1, with no sex differences and a wide range of ages. In most of the cases (75%) ST-segment elevation is presented at lateral leads. Only Adeel et al. [2] described a case with ST elevation in inferior leads.

As it is known, the duration of the ST segment is inversely proportional to the plasmatic calcium concentration [3]. Consistent with that, corrected QT interval was prolonged in most of the patients, except for the one described by Kukla et al. [4], who presented with a shortened QT. Authors suggested the hypothesis of a coronary artery spasm as a possible cause. In the current patient, a vasoreactivity test was performed with increasing doses of acetylcholine, up to 100 μg, with no vasospastic response.

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Table 1. Summary of case reports about hypocalcemia mimicking ST-elevation.

Study	Age	Sex	Clinical presentation	ST segment elevation	T waves	QTc [ms]	Echocardiography	Coronary angiography	Other diagnostic tests	Cardiac enzymes
Lechmann et al. 2000	24	Female	Loss of consciousness, seizures	I, aVL	Positive	480	Moderate LV dysfunction Anterolateral impaired motion	No significant stenosis	—	Elevated
Ilveskoski et al. 2012	65	Male	Dyspnea, chest pain	I, aVL V1–V3	Inverted	578	Severe LV dysfunction Global	No significant stenosis No vasospasm		Plateau minimal elevation
Gómez-Domínguez et al. 2013	86	Female	Fatigue, chest pain, confusional state	V2–V4	Inverted	670	Severe LV dysfunction Global	No significant stenosis	—	Elevated
Kukla et al. 2016	50	Male	Chest pain, shortness of breath	I, aVL	Tall and peaked	320	Not performed	Not performed	—	Normal
Adeel et al. 2018	52	Male	Lethargy, weakness, diarrhea	II, III, aVF	Positive	481	Preserved LVEF No RWMA	Not performed	SPECT: absence of perfusion defects	Elevated
Pervaiz et al. 2019	57	Female	Clenching of the hands	I, aVL, V2–V6	Shallow inversion	587	Severe LV dysfunction Apical akinesia LV thrombus	Not performed	SPECT: absence of perfusion defects	—
Merlo et al. 2021	77	Female	Diarrhea, vomiting	I, aVL V2	Biphasic	600	Preserved LVEF No RWMA	No significant stenosis	—	Elevated

LV — left ventricle; LVEF — left ventricular ejection fraction; RWMA — regional wall motion abnormalities; SPECT — single photon emission computed tomography

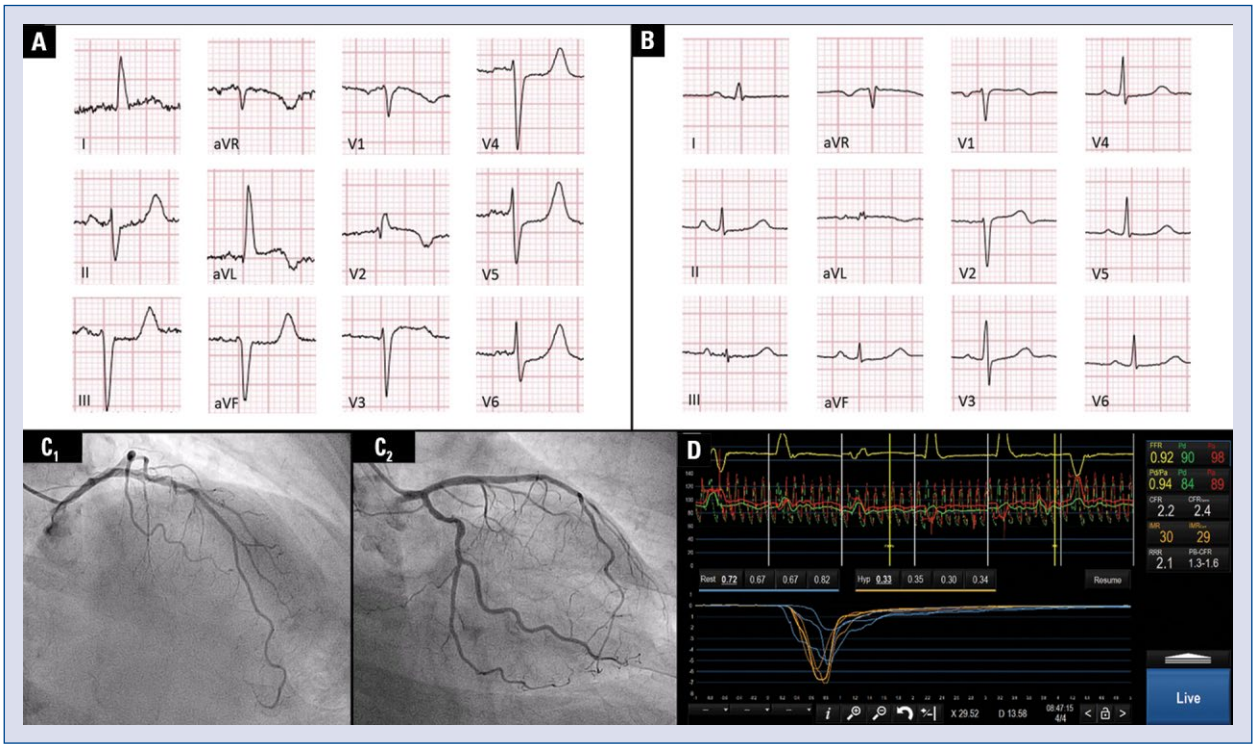

Figure 1. A. Electrocardiogram (ECG) at admission (25 mm/s): ST-segment elevation in I, aVL and V2 and depression in II, III and aVF. QTc 447 ms (Bazett's formula); **B.** ECG after electrolyte restocking, showing resolution of the abnormalities; **C.** Absence of significant epicardial coronary artery disease (C_1 = LCA: RAO Cranial; C_2 = LCA: RAO Caudal); **D.** Coronary physiological assessment: normal coronary flow reserve, mild elevation of index of microcirculatory resistance.

Very few cases have been reported in the literature hypothesizing a relationship between vasospasm and hypocalcemia [5, 6]. They presented patients with chest pain, ST segment changes and non-obstructive coronary arteries in the context of low calcium levels. Symptoms improved after calcium reposition so an assumption was made that hypocalcemia was related to a possible coronary spasm, however this was not proven with intracoronary physiology studies. Moreover, there is no clear physiopathological mechanism explaining this relationship.

After depolarization, calcium enters smooth muscle cells, triggering the opening of L-channels, promoting calcium interaction with calmodulin and subsequent activation of myosin. This mechanism explains why hypocalcemia can be related with vasodilation and hypotension, more than to vasospasm. It also explains the mechanism of action of calcium antagonists.

Left ventricular dysfunction was found in 4 of the cases. All of them had an angiography or perfusion imaging performed, showing the absence of coronary stenoses or myocardial perfusion defects.

Herein, is no certain explanation for the impairment of ventricular contractility, according to available research, calcium is a fundamental electrolyte participating in the generation of the action potential and cardiac muscle cell contraction. A severe reduction of its levels may have caused abnormalities in both electric and contractile activity, explaining those findings, as well as the absence of a correlation between regional wall motion abnormalities and ECG location of the ST elevation. Experimental studies suggest a correlation between depression of ventricular function and lower calcium concentrations [7]. The entry of calcium in the myocardial cells induces the release of calcium from the sarcoplasmic reticulum ("calcium-induced calcium release"), binds to troponin C and induces actin-myosin interaction. Hence, severe hypocalcemia could be a reversible cause of impaired myocardial contraction and heart failure. This has been described in literature as "hypocalcemic cardiomyopathy" [8]. Accordingly, transient left ventricular dysfunction has been described after blood transfusions with citrate, a calcium binding agent [9]. Other factors may play

a physiopathological role, like duration of the electrolyte imbalance or preexisting cardiac conditions.

All patients followed during hospitalization or at discharge showed improvement of ejection fraction after treatment of hypocalcemia. One patient died because of his critical condition at admission.

In conclusion, hypocalcemia can cause a "pseudo-STEMI" pattern, most frequently in lateral leads. Physiopathological mechanism remains unknown but significant coronary disease seems not to be the cause. Although it may present with elevated troponin and regional wall motion abnormalities, electrocardiographic changes and ventricular function may recover after electrolyte correction.

Conflict of interest: None declared

References

1. Lehmann G, Deisenhofer I, Ndrepepa G, et al. ECG changes in a 25-year-old woman with hypocalcemia due to hypoparathyroidism. Hypocalcemia mimicking acute myocardial infarction. Chest. 2000; 118(1): 260–262, doi: 10.1378/chest.118.1.260, indexed in Pubmed: 10893393.
2. Adeel MY, Clarke JRD, Shetty S, et al. Severe hypocalcemia mimicking acute inferior ST-segment elevation myocardial infarction. Oxf Med Case Reports. 2018; 2018(12): omy103, doi: 10.1093/omcr/omy103, indexed in Pubmed: 30487989.
3. Davis TM, Singh B, Choo KE, et al. Dynamic assessment of the electrocardiographic QT interval during citrate infusion in healthy volunteers. Br Heart J. 1995; 73(6): 523–526, doi: 10.1136/hrt.73.6.523, indexed in Pubmed: 7626350.
4. Kukla P, Kulik M, Jastrzębski M, et al. Severe hypocalcemia mimicking ST-segment elevation acute myocardial infarction. Ann Noninvasive Electrocardiol. 2017; 22(2), doi: 10.1111/anec.12401, indexed in Pubmed: 27604986.
5. Magnus PC, Missri J. Hypocalcemia-associated coronary vasospasm. Conn Med. 2005; 69(1): 3–7, indexed in Pubmed: 15736368.
6. Rasoul S, Dambrink JHE. Recurrent acute coronary syndrome due to coronary artery spasm in different coronary arteries. J Cardiol Cases. 2013; 8(3): 95–98, doi: 10.1016/j.jccase.2013.05.007, indexed in Pubmed: 30546754.
7. Lang RM, Fellner SK, Neumann A, et al. Left ventricular contractility varies directly with blood ionized calcium. Ann Intern Med. 1988; 108(4): 524–529, doi: 10.7326/0003-4819-108-4-524, indexed in Pubmed: 3248127.
8. Aguiar P, Cruz D, Ferro Rodrigues R, et al. Hypocalcemic cardiomyopathy. Rev Port Cardiol. 2013; 32(4): 331–335, doi: 10.1016/j.repc.2012.08.008, indexed in Pubmed: 23582987.
9. Gulati S, Bajpai A, Juneja R, et al. Hypocalcemic heart failure masquerading as dilated cardiomyopathy. Indian J Pediatr. 2001; 68(3): 287–290, doi: 10.1007/BF02723209, indexed in Pubmed: 11338230.

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Fulminant myocarditis and acute heart failure in the light of new American Heart Association 2020 guidelines. Mechanical cardiac support and endomyocardial biopsy. What should be first?

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Fulminant myocarditis is a rapidly progressive inflammatory process of the myocardium that may either end in spontaneous recovery or lead to hemodynamic instability, cardiogenic shock and arrhythmias resulting in a high risk of death [1, 2].

The 2020 American Heart Association (AHA) position paper summarises knowledge on fulminant myocarditis and highlights its diagnostic and therapeutic aspects [3]. Prompt initial assessment and seeking early signs of hemodynamic instability is extremely important in such cases. In the light of new AHA guidelines, presented herein is the history of a 27-year-old man diagnosed and treated successfully for fulminant myocarditis.

The patient, with no medical record, was admitted to Hospital with cardiogenic shock. The medical history revealed fever, weakness, vomiting and exercise intolerance for several days. Hypotonia with features of peripheral hypoperfusion was observed. Electrocardiogram showed sinus rhythm 120 bpm, right bundle branch block, ST-segment elevation in the precordial leads (Fig. 1A). Laboratory tests revealed: C-reactive protein 100 mg/L, procalcitonin 1.37 ng/mL, troponin T > 10000 ng/L, creatine kinase-MB 75 ng/L, N-terminal pro-B-type natriuretic peptide 16497 ng/L, lactates 4.1 mmol/L. In transthoracic echocardiography (TTE) a severe dysfunction of both ventricles with left ventricular (LV) ejection fraction (LVEF) 15%, LV end diastolic dimension 60 mm, LV outflow tract velocity time integral 8 cm and tricuspid annular plane systolic excursion 12 mm were found.

Immediate coronary angiography showed no significant stenoses. Based on the entire clinical picture a working diagnosis of fulminant myocarditis was made. Catecholamines were administered and an intra-aortic balloon pump (IABP) was introduced. Despite the treatment, cardiogenic shock persisted and the patient required mechanical circulatory support (MCS) with veno-arterial extracorporeal membrane oxygenation (VA-ECMO) (Fig. 1B). Moreover, mechanical ventilation and continuous renal replacement therapy were necessary due to multiorgan failure.

Unfortunately, the following TTE showed extensive right and LV failure with LV dilatation, LVEF decreased to 8%, with signs of echogenic blood and a lack of mobility of the aortic valve leaflets (Fig. 1C). The clinical picture reflected

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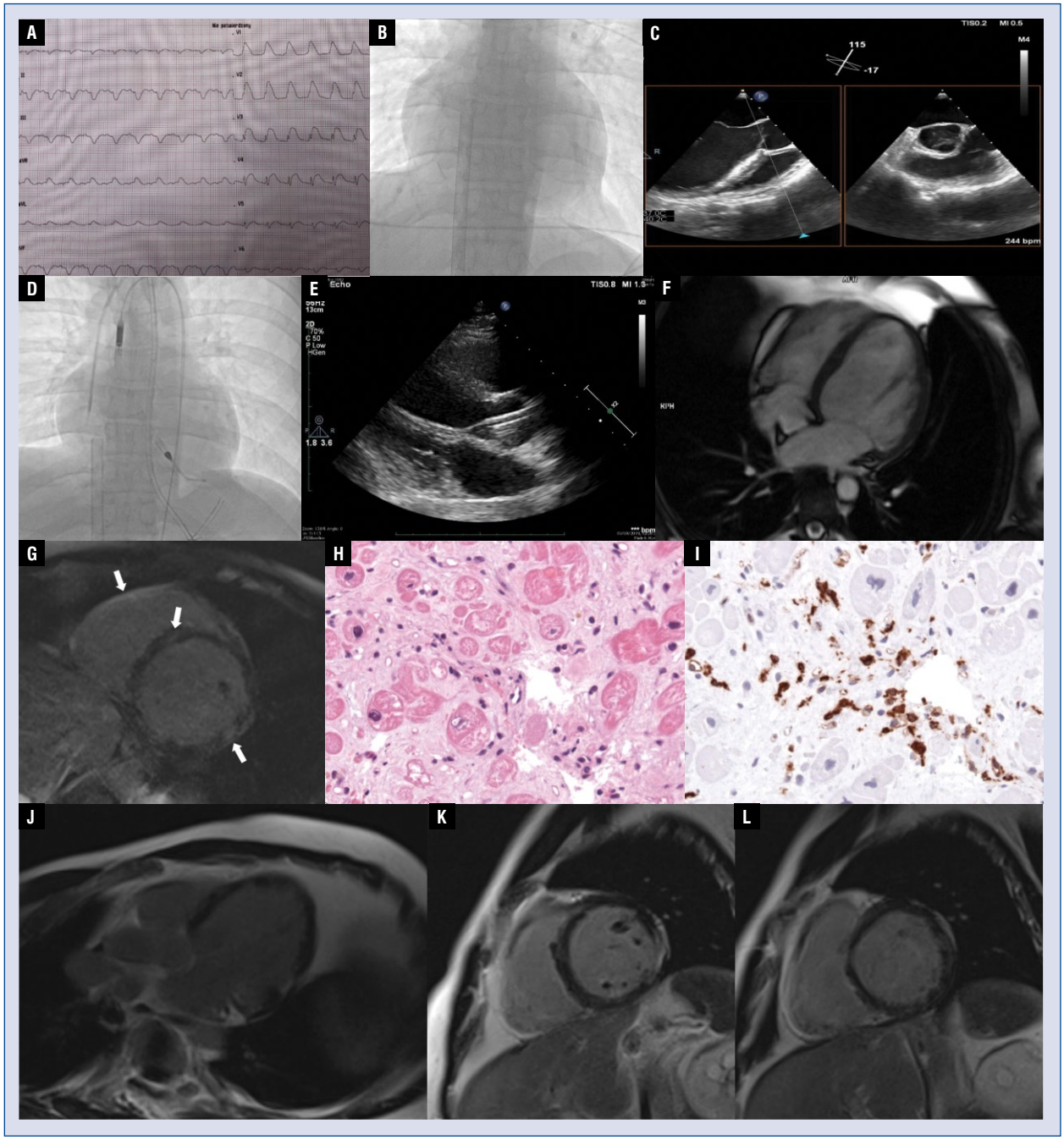

Figure 1. A. Electrocardiogram at admission; **B.** The implanted ECMO Cardiohelp, Maquet, Germany; **C.** Transthoracic echocardiography: left ventricle dilatation, presence of echogenic blood and lack of mobility of the aortic valve leaflets; **D.** Implanted Impella CP percutaneous intracardiac pump (Abiomed, Danvers MA) — angiographic image; **E.** Implanted Impella CP percutaneous intracardiac pump (Abiomed, Danvers MA) — echocardiographic image; **F, G.** Initial cardiac magnetic resonance (CMR): multiple, diffuse, intramuscular late gadolinium enhancement patterns in the myocardium of both ventricles (arrows); **H, I.** Endomyocardial biopsy: massive acute lymphocytic myocarditis, histological criteria — necrosis of adjacent muscle cells and a marked inflammatory infiltrate (Dallas criteria) as well as immunohistochemical criteria — an inflammatory infiltrate in the form of T lymphocytes at the amount of 46/mm^2; **J–L.** Follow up CMR.

a critical LV overload and therefore IABP was replaced with the Impella CP pump (Fig. 1D, E) to unload the LV.

During VA-ECMO, a hemostatic disturbance was observed with massive bleeding which required blood transfusions. In the following days

after the Impella CP implantation, TTE showed LVEF 30% and the patient's condition improved. Finally, it was possible to remove both, VA-ECMO and Impella CP.

Despite applied complex therapy, in the following days the serial TTE did not show any LVEF improvement. Short non-sustained ventricular tachycardias were observed. Therefore, the patient underwent cardiac magnetic resonance (CMR) that fulfilled the Lake Louis criteria, LVEF 23% (Fig. 1F, G).

Having immunosuppressive treatment in mind, endomyocardial biopsy (EMB) was performed, which revealed massive acute lymphocytic myocarditis (Fig. 1H, I). Simultaneously, virus infection was excluded in the myocardium by (RT-)PCRs, and therefore, steroid treatment could be initiated. Metyloprednizolon 500 mg/day i.v. for 7 days, then prednizon 65 mg/day p.o. for 4 weeks were administered. Then the dose was tapered-off every 5 days. Unfortunately, complex therapy (steroid and azathioprine) was not tolerated.

After 1 month of immunosuppressive therapy, the LV function improved. On the day of discharge, the patient's LVEF was 40% and his functional status was NYHA class II.

In a follow-up CMR performed 3 months after discharge Lake Louis criteria were not fulfilled, slight reduction of late gadolinium enchancement extend and LVEF 42% were observed (Fig. 1J–L).

Patients with fulminant myocarditis often require intensive care treatment with inotropic drugs and MCS. The latter usually allows achieving haemodynamic stabilisation. Recent data show that prolonged MCS has a positive effect on the cellular and molecular mechanisms responsible for myocardial remodeling, fibrosis, inflammation, and calcium metabolism, which increases the chance of recovery [4].

In the presented history, the IABP used in the first hours was ineffective and the patient required VA-ECMO [5]. The data indicate that the most commonly used MCS for fulminant myocarditis is VA-ECMO, which draws blood from the right atrium and pumps it into the aorta. At the same time, however, it increases the afterload of the damaged LV because it pumps blood in the opposite direction to the incoming blood flow from the heart. It puts additional strain on the LV and can lead to a dramatic reduction or even cessation of cardiac output with LV dilation. This condition generates excessive LV wall stress, impairs coronary flow and increases the risk of thrombus formation. In this situation rapid unloading of the LV is absolutely necessary. In our patient, the successive unloading was achieved by replacing IABP with the Impella CP which is a microaxial pump implanted percutaneously through the aortic valve into the LV. By pumping blood from the LV into the ascending aorta at a maximum rate of up to 4 L/min, it significantly reduces LV end-diastolic pressure and volume. The pump also allows for a reduction in VA-ECMO support, thus reducing the afterload. The combination of VA-ECMO with the Impella CP pump created a new name for this complex therapy — ECMELLA. According to the registry data, in patients treated this way, a significant reduction of in-hospital mortality and a higher rate of treatment success were observed [4, 6].

The AHA 2020 position statement emphasizes the importance of early imaging and invasive diagnosis. The timing of the latter, myocardial biopsy, depends on the anticoagulation used and the experience of the operator [3]. Performing EMB on admission was considered, however, due to the critical condition of the patient, massive multisite bleeding, complications related to VA-ECMO therapy, the EMB was performed after termination of MCS, during a stable period of the disease. Recent data showed a greater number of complications in EMB performed during MCS, albeit it led to histopathologic diagnosis. Researchers agree that the management of this patient population requires further refinement to improve procedural safety [7].

The presented report demonstrates that a patient suffering from fulminant myocarditis requires the cooperation of an interdisciplinary team. The main goal of treatment is the fastest possible stabilization of the cardiovascular system, therefore MCS should be the first procedure. MCS enables further diagnosis and adequate treatment. There is also evidence that it gives the inflamed myocardium a chance to regenerate. Taking in to consideration the benefits and risks, EMB should be performed as soon as possible, in order to initiate adequate treatment [8].

Conflict of interest: None declared

References

1. Gawor M. Postępowanie w zapaleniu mięśnia sercowego o piorunującym przebiegu. Medycyna po Dyplomie. 2020; 10: 31–39.
2. Rroku A, Kottwitz J, Heidecker B, et al. Update on myocarditis: what we know so far and where we may be heading. Eur Heart J Acute Cardiovasc Care. 2020 [Epub ahead of print]: 2048872620910109, doi: 10.1177/2048872620910109, indexed in Pubmed: 32319308.

3. Kociol RD, Cooper LT, Fang JC, et al. Recognition and initial management of fulminant myocarditis: a scientific statement from the American Heart Association. Circulation. 2020; 141(6): e69–e92, doi: 10.1161/CIR.0000000000000745, indexed in Pubmed: 31902242.
4. Tschöpe C, Van Linthout S, Klein O, et al. Mechanical unloading by fulminant myocarditis: LV-IMPELLA, ECMELLA, BI-PELLA, and PROPELLA concepts. J Cardiovasc Transl Res. 2019; 12(2): 116–123, doi: 10.1007/s12265-018-9820-2, indexed in Pubmed: 30084076.
5. Gawda R, Marszalski M, Sacha J, et al. Concomitant use of veno-arterial extracorporeal membrane oxygenation and Impella in the intensive care unit: a case report of fulminant myocarditis with multi-organ failure. Anaesthesiol Intensive Ther. 2020; 52(1): 63–66, doi: 10.5114/ait.2020.93233, indexed in Pubmed: 32200615.
6. Maniuc O, Salinger T, Anders F, et al. Impella CP use in patients with non-ischaemic cardiogenic shock. ESC Heart Fail. 2019; 6(4): 863–866, doi: 10.1002/ehf2.12446, indexed in Pubmed: 31095902.
7. van der Boon RMA, den Dekker WK, Meuwese CL, et al. Safety of endomyocardial biopsy in new-onset acute heart failure requiring veno-arterial extracorporeal membrane oxygenation. Circ Heart Fail. 2021; 14(8): e008387, doi: 10.1161/CIRCHEARTFAILURE.121.008387, indexed in Pubmed: 34344163.
8. Seferović PM, Tsutsui H, McNamara DM, et al. Heart Failure Association of the ESC, Heart Failure Society of America and Japanese Heart Failure Society Position statement on endomyocardial biopsy. Eur J Heart Fail. 2021; 23(6): 854–871, doi: 10.1002/ejhf.2190, indexed in Pubmed: 34010472.

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IMAGE IN CARDIOVASCULAR MEDICINE

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Neoatherosclerosis with silent plaque rupture in a saphenous vein graft causing no re-flow phenomenon assessed by optical coherence tomography and histopathology

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A 79-year-old man with a history of coronary artery bypass grafting 22 years earlier was hospitalized due to stable angina. A bare metal stent was implanted in his saphenous vein graft (SVG) 15 years ago and then, a drug-eluting stent was implanted for the in-stent restenosis 8 years ago. Coronary angiography revealed a severe in-stent restenosis in the SVG anastomosed to the right coronary artery (Fig. 1A). Optical coherence tomography (OCT) showed plaque fissure, cholesterol crystals, and low-intensity area without attenuation adjacent to the lipid-rich plaque (LRP), which suggested the intraplaque hemorrhage (IPH) (Fig. 1B, a, b). OCT also revealed the disrupted intimal flap within the stent (Fig. 1B, c) and mild to moderate stenosis with LRP outside the stent. Following balloon dilatation for the target lesion, no-reflow phenomenon occurred. The coronary flow resumed by aspiration thrombectomy and nitroprusside administration. Histopathological examination of the aspirated specimens showed that they were composed of atherosclerotic plaques with fibrin, cholesterol clefts and inflammatory cells including foam cells (Fig. 1C, 1D). Previous reports have shown that IPH is one of the factors contributing to coronary plaque destabilization and plaque progression, which might cause effort angina. This case showed for the first time an in-stent neoatherosclerosis with silent plaque rupture in SVG that caused no-reflow phenomenon detected with OCT and confirmed by histopathology. Observations suggested that the use of a distal protection device and the administration of vasodilators should be strongly considered when OCT identifies the characteristics of vulnerable plaque during percutaneous coronary intervention.

Conflict of interest: None declared

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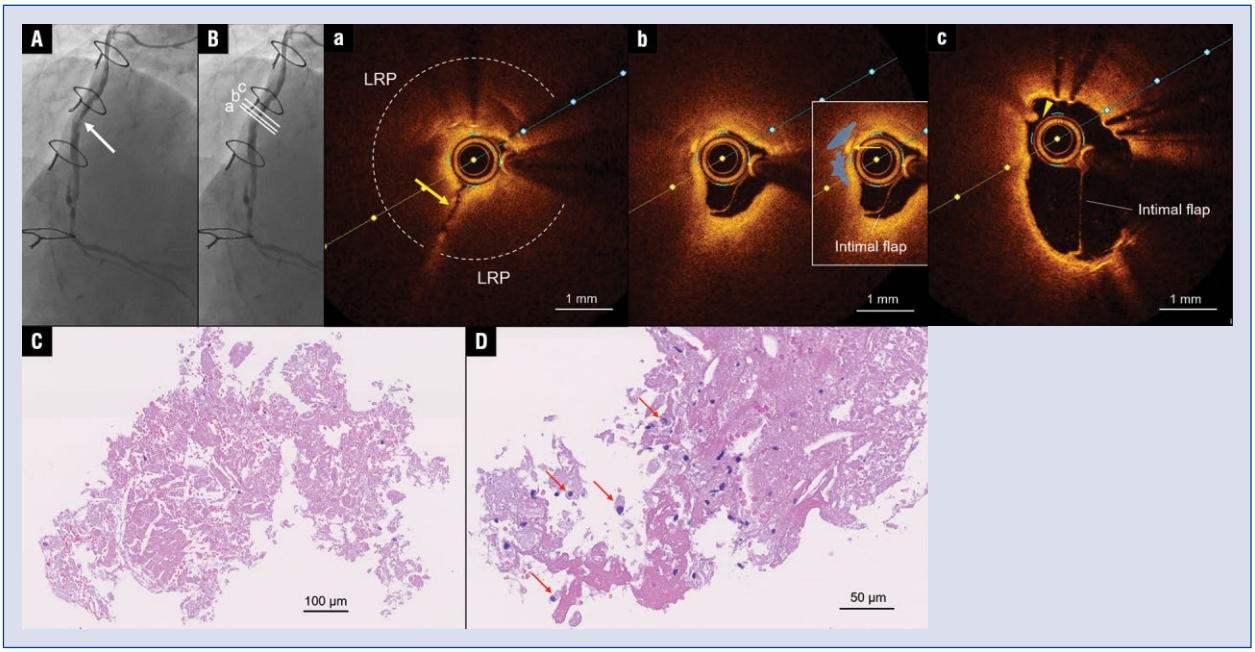

Figure 1. A. The initial coronary angiogram showing the in-stent restenosis in saphenous vein graft (white arrow). **B.** Optical coherence tomography images showing (**a**) plaque fissure (thick yellow arrow), lipid-rich plaque (LRP), (**b**) cholesterol crystals (thin yellow arrow), intraplaque hemorrhage (light blue area), and (**c**) disruption of the intimal flap (yellow arrowhead). **C, D.** Histopathology of aspirated specimens showing fibrin thrombi with cholesterol clefts and inflammatory cells including foam cells (red arrows).

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Simultaneous angiographic and instantaneous wave-free ratio co-registration assisted with intravascular ultrasound for optimal assessment of left main coronary artery ostial stenosis and optimization of the angioplasty effect

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Presented herein, is the case of a 58-year-old man with a prior history of ST-segment elevation myocardial infarction treated with fibrinolysis. Percutaneous coronary intervention (PCI) of circumflex artery (Cx) was performed in 2001, left descending coronary artery (LAD) in 2003, and again in 2012 as well as Cx and right coronary artery (RCA). PCI of the left-main coronary artery (LMCA) was performed in 2013.

The present angiography revealed 50% ostial in-stent re-stenosis of the LMCA (Fig. 1A). The good effect of PCI was maintained within the Cx, LAD and RCA. Fractional flow reserve (FFR) was 0.79 (intracoronary bolus of adenosine 200 μg) (Fig. 1B), while instantaneous wave free ratio (iFR) was 0.82 and pull-back demonstrated the main gradient drop in the ostial LMCA (Fig. 1C). Intravascular ultrasound (IVUS) was performed using the Verrata pressure guidewire (Philips Medical Systems, Best, Netherlands). Minimal lumen area (MLA) of the LMCA was 5.5 mm^2 (Fig. 1D). Co-registration of angiography and iFR assisted with manual IVUS pull-back made it possible to select stent length, despite the lack of mechanical IVUS pull-back. The 4.0 × 15 mm drug-eluting stent Ultimaster (Boston Scientific, MA, USA) was directly implanted at 20 atm. Optimization was performed with a 4.5 × 15 mm 25 atm non-compliant balloon using the proximal optimization technique. The control LMCA MLA was 9.3 mm^2 (Fig. 1E).

In conclusion, co-registration of coronary angiography, IVUS and iFR assisted with IVUS enables precise assessment of lesion morphology, its length and vessel width, as well as stenosis significance, especially in patients with ostial LMCA in-stent re-stenosis, where FFR assessment could be misleading (Fig. 1F).

Conflict of interest: None declared

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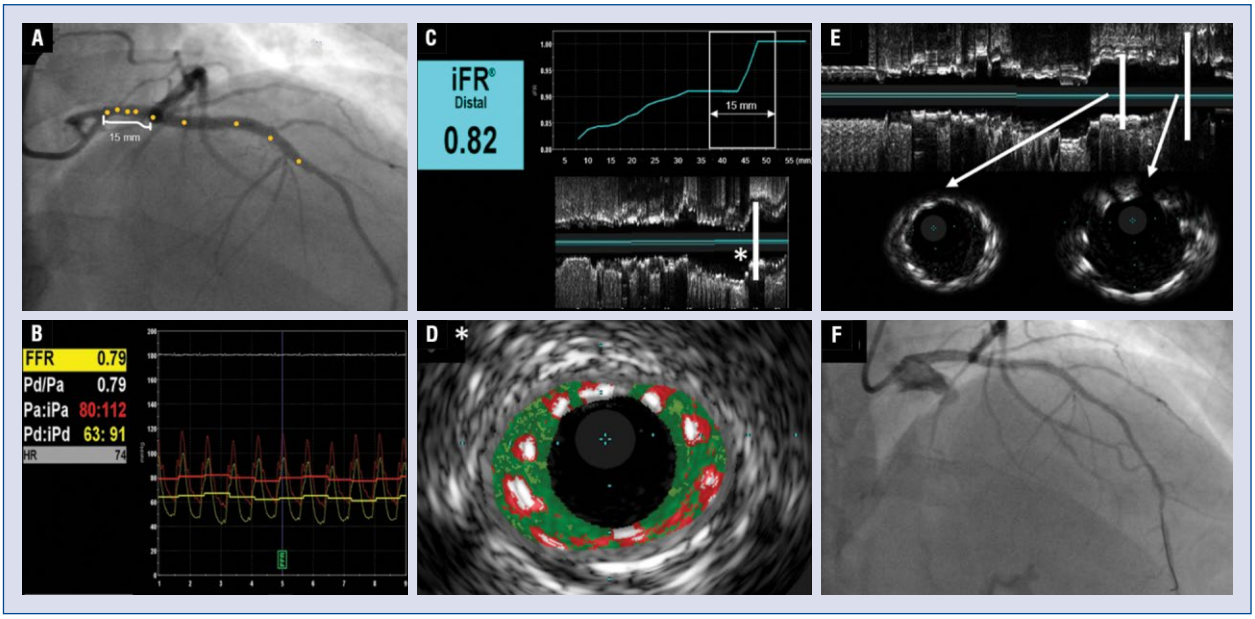

Figure 1. A. Coronary angiography — left coronary artery before percutaneous coronary intervention (PCI) with instantaneous wave free ratio (iFR) co-registration markers; **B.** Fractional flow reserve measurement before PCI; **C.** Instantaneous wave free ratio pull-back and parallel intravascular ultrasound (IVUS) longitudinal view before PCI; **D.** Transverse view of the stenosis presented in IVUS before PCI — virtual histology; **E.** Longitudinal and transverse views of the stented artery in IVUS after PCI; **F.** Coronary angiography — left coronary artery after PCI within the left main coronary artery. *A section of the artery with a significant drop in the iFR gradient.

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Extended emphysematous aortitis of the ascending aorta: An unusual fatal presentation of aortic valve endocarditis due to Clostridium Septicum

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A 58-year-old man was referred to our department for aortic valve endocarditis. Blood cultures were positive for Clostridium Septicum, a toxigenic germ. He had history of recurrent ileo-colic neoplasia in the context of familial Lynch syndrome.

Echocardiography revealed a severe aortic valve insufficiency related to a posterior cusp perforation and an 8-mm vegetation of the antero-right cusp (Fig. 1A). Thoracic angioscanner showed an extended aortitis of the ascending aorta: irregular hypodense parietal thickening (8 mm) beginning upstream of the coronary ostia and extending to the subclavian artery with the presence of gas gangrene (Fig. 1B). The evolution was a fast extension of intra-parietal gas gangrene images on another scanner performed 24 h apart (to anticipate the surgery procedure) (Fig. 1C).

The patient underwent emergent surgery because of refractory acute pulmonary edema on day 1. The procedure was minimal (isolated aortic valve replacement with bioprosthesis) because the aorta aspect was highly inflammatory with many areas of intimal necrosis.

He then received daily hyperbaric therapy and antibiotics (piperacillin/tazobactam and clindamycin). A third scanner performed at day 6 visualized 2 septic false aneurysms of the ascending aorta (Fig. 1D, E). The patient died on day 10 subsequent to cardiac tamponade probably related to aortic rupture.

Bacteremia due to Clostridium Septicum is generally associated with cecal carcinoma or hematologic malignancy. Although few cases of aortitis have been reported, combined aortic valve endocarditis and aortitis has been reported in only 3 cases so far and all were fatal despite adapted antibiotics and surgery.

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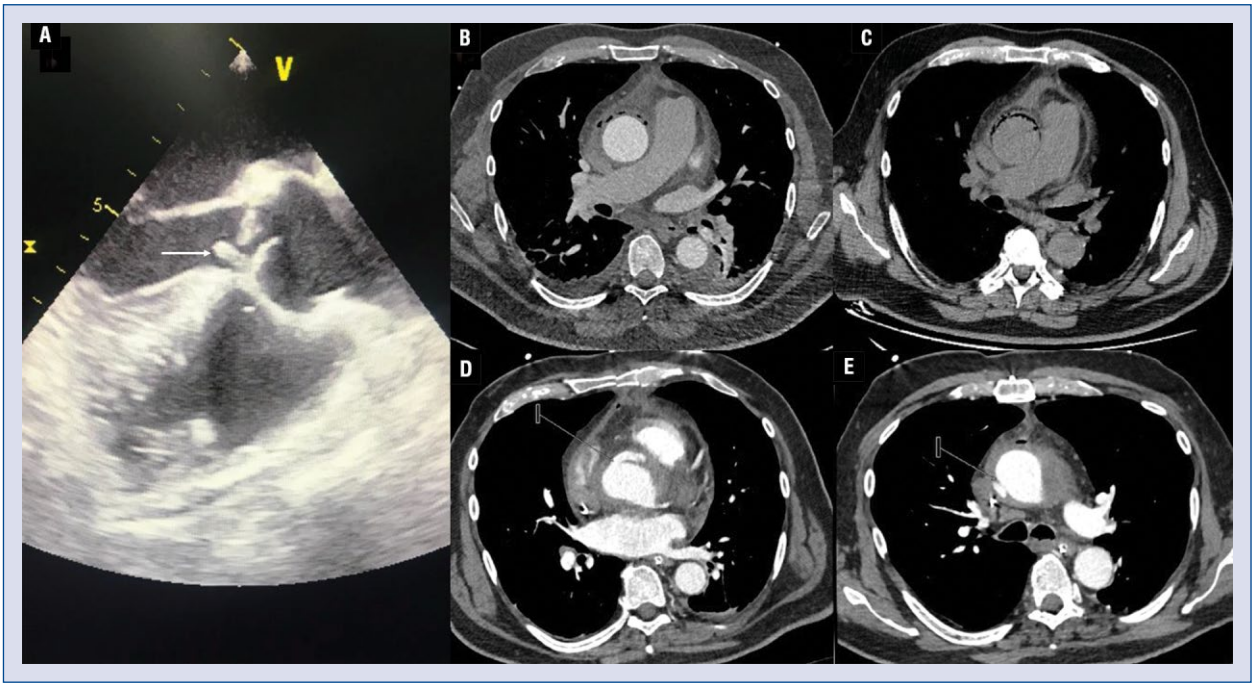

Figure 1. Extended emphysematous aortitis of the ascending aorta on thoracic angioscanner; **A.** Transoesophageal echocardiography showing an 8-mm vegetation of the antero-right cusp (indicated by the white arrow); **B.** Initial scanner showing irregular hypodense parietal thickening (8 mm) with the presence of gas gangrene; **C.** A second scan 24 h later showing a fast extension of the intra-parietal gas gangrene; **D, E.** A third scan at day 6 after surgery showing 2 septic false aneurysms of the ascending aorta (indicated by arrows).

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LETTER TO THE EDITOR

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Sutureless aortic bioprosthesis: Competitor or alternative for transcatheter aortic valve implantation? Single center experience with Perceval valves

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Currently, less invasive procedures draw a significant attention of valvular heart teams worldwide. Simultaneously, two concepts such as transcatheter aortic valve implantation (TAVI) and sutureless bioprosthesis have been developed. The latter one is represented by the Perceval prosthesis which cusps are made of bovine pericardium. This valve is mounted into a self-expanding nitinol stent, covered with a thin Carbofilm™ coating for biocompatibility improvement. The stent consists of two rings and nine connecting struts — inflow ring is located at the annulus level and outflow one at the sino-tubular junction. Struts support the valve and hold it in place with no need for sutures. After deployment the scaffold reaches the desired shape accommodating to the aortic root. Due to the absence of a suturing ring, the orifice area is maximized which provides optimized blood flow. The framework is smaller than conventional stented prostheses, which may help to achieve better hemodynamics and lower rate of patient-prosthesis mismatch (PPM). The purpose of the study was to collect the data regarding Perceval implantation outcome in a single-center all-comers registry. The study group comprised 50 patients (25 female, 25 male) with the mean age of 68.8 ± 10.3 years scheduled for Perceval implantation between 2013 and 2021. All operations were performed in the cardio-pulmonary bypass (CPB) from either full (n = 20) or upper ministernotomy (n = 30) (Table 1). After aortic annulus partial decalcification, the bioprostheses were deployed. The study was approved by our institutional committee. Patients' safety and Perceval performance were evaluated in in-hospital and follow-up observation. Adverse events were also recorded.

Data were reported as the means and standard deviations, or the medians with interquartile range (IQR), and discrete variables as counts or percentages. Kaplan-Meier method was applied to analyze probability of patients' survival. Statistical analysis was performed with use of JASP (2020, Version 0.13.1).

Implantation was technically successful in all patients. During in-hospital stay 6 patients died, including two within the first 30 days after surgery (1-month mortality rate 4%). Four of them (66.7%) were operated on urgently due to hemodynamic instability in a course of active endocarditis or prosthetic valve thrombosis. All patients completed follow-up period (median [IQR]) 23 (8, 38) months). Six-month, 1- and 3-year probability of survival stratified by means of Kaplan-Meier method were 0.88 ± 0.05, 0.85 ± 0.05 and 0.82 ± 0.06, respectively. Significant improvement in functional class at discharge was observed and persisted together

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Table 1. Clinical and procedural data (n = 50).

Male	25 (50%)
Age [years]	68.8 ± 10.3
EuroScore II [%]	4.1 ± 6.7
EuroScore II > 4%	10 (20%)
Active endocarditis	8 (16%)
Native valve	7 (14%)
Prosthetic valve	1 (2%)
Aortic stenosis pure or combined	41 (82%)
NYHA stages II–III	41 (82%)
NYHA stage IV	9 (18%)
Baseline PPG [mmHg]	88.8 ± 30.6
Baseline MPG [mmHg]	56.2 ± 18
Baseline LVEF [%]	58.3 ± 9.1
Size:	
S	3 (6%)
M	11 (22%)
L	18 (36%)
XL	18 (36%)
Surgical access:	
Ministernotomy	30 (60%)
Sternotomy	19 (38%)
Re-sternotomy	1 (2%)
Isolated AVR	41 (82%)
Isolated re-AVR	2 (4%)
Combined surgery (+CABG)	6 (12%)
Combined with other procedure	1 (2%)
Urgent or emergent surgery	10 (20%)
Cardiopulmonary bypass time [min]	72.3 ± 23.3
Cross-clamping time [min]	49.8 ± 12.7
30 days mortality	2 (4%)
3 months mortality	6 (12%)
All-cause long-term mortality	9 (18%)
Post-surgery AF	25 (50%)
Post-surgery permanent pacemaker implantation	3 (7%)
Post-surgery AKI	14 (33%)
Post-operative stay of survivors [days]	11.2 ± 8.6
Post-surgery new hemofiltration	3 (6%)
PPG [mmHg] — at discharge	23.9 ± 10.4
MPG [mmHg] — at discharge	13.5 ± 7.1
LVEF [%] — at discharge	56.7 ± 9.1
PPG [mmHg] — 3–12 months	20.7 ± 10
MPG [mmHg] — 3–12 months	11.8 ± 6.5
LVEF [%] — 3–12 months	59 ± 3.8
PPG [mmHg] — 1–7 years	24.5 ± 16
MPG [mmHg] — 1–7 years	13.7 ± 10.1
LVEF [%] — 1–7 years	58.6 ± 4.7

Continuous variables are presented as the means ± standard deviations whereas discrete one as numbers (n) with percentage (%); AF — atrial fibrillation; AKI — acute kidney injury; AVR — aortic valve replacement; BMI — body mass index; CABG — coronary artery bypass grafting; LVEF — left ventricular ejection fraction; MPG — mean pressure gradient; NYHA — New York Heart Association; PPG — peak pressure gradient

with good echocardiographic outcome in majority of patients in long term follow-up. One patient was diagnosed after 6 years with Perceval degeneration and underwent TAVI. One patient developed early mitral valve endocarditis without Perceval involvement and was re-operated.

Our single center experience with Perceval shows good procedural and clinical result, and low long-term mortality. Both 30-day and late survival in our group is comparable to previous reports and confirm safety and utility of Perceval prosthesis [1–8]. The first observation, by Shrestha et al. [7, 8] showed safety and efficacy of the Perceval in high-risk patients. In the largest prospective study performed in a cohort of 208 high-risk patients the reported in-hospital and 1-year mortality rates were 2.4% and 12.9%, respectively [2]. One of the main possible advantages of sutureless prostheses is the ease of implantation and consequently markedly reduced CPB and aortic cross-clamp (ACC) times. In the present study group prosthesis implantation was technically successful in all patients. However, regarding the aforementioned times, they were found to be relatively long. Of note, most of our procedures were carried out through ministernotomy. On the other hand, if we refer our CPB and ACC times to the previously reported upper ministernotomy surgical aortic valve replacement (SAVR) patients, they could be considered to be relatively short [9]. One of the most embarrassing issues after minimally invasive procedures is perivalvular leak (PVL). Perceval shows rate of PVL ranging from 1.6% to 15.8% [10]. We did not observe moderate or severe PVL and mild PVL was present in 3 patients.

Not uncommonly sutureless bioprostheses are compared to TAVI due to many technical and procedural similarities. They are both constructed on the nitinol cage with biological leaflets. There is no need for surgical suturing and the prostheses are anchored to the aortic root due to radial force. However, some specific conditions differ in these two types of procedures. Firstly, TAVI bioprosthesis is implanted into a calcified aortic valve, which is compressed towards the aortic sinus wall. Apart from the risk of PVL cerebral and peripheral embolism may occur. In the opposite, during Perceval implantation the calcified valve is completely removed and, if necessary, the annulus is decalcified. In TAVI patients, PVL results from preserved calcification, while in Perceval implantation from too excessive decalcification. TAVI is certainly contraindicated in active endocarditis, while currently Perceval not. Both sutureless bioprostheiss represent an

excellent solution for a wide variety of patients. While inoperable patients would benefit best from the TAVI procedure, Perceval is a valuable option for patients with an additional disease requiring simultaneous intervention. A significant group of patients with low to moderate perioperative risk may be treated alternatively with both procedures.

Based on experience of our center, patients were distinguished who particularly benefit from Perceval implantation such as subjects at borderline risk between SAVR and TAVI, with a suboptimal surgical anatomy (e.g. extensive calcifications infiltrating aortic annulus, small annulus) and with infective endocarditis. Moreover, patients with perioperative risk considered to be too high for SAVR, but still not relevant enough for TAVI, may be qualified for Perceval implantation. A second group of beneficiaries are those with very small and severely calcified annulus who may present with intraoperative problems in implantation of the mechanical valve or classic bioprosthesis which may be impossible without an additional annulus enlargement procedure or which may generate PPM. Finally, patients with active bacterial endocarditis may also benefit from Perceval implantation. The use of sutureless prosthesis enables minimizing the presence of artificial material in the infected field.

In conclusion, Perceval prosthesis is a safe and valuable option for patients with severe aortic stenosis. Particularly, patients at a borderline operative risk between SAVR and TAVI, with suboptimal surgical anatomy and infective endocarditis will benefit from Perceval implantation.

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References

1. Szecel D, Meuris B. Long-term outcome with sutureless valves: 12 years of Perceval experience. Ann Cardiothorac Surg. 2020; 9(4): 322–324, doi: 10.21037/acs.2020.04.03, indexed in Pubmed: 32832414.
2. Folliguet TA, Laborde F, Zannis K, et al. Sutureless perceval aortic valve replacement: results of two European centers. Ann Thorac Surg. 2012; 93(5): 1483–1488, doi: 10.1016/j.athoracsur.2012.01.071, indexed in Pubmed: 22541180.
3. Phan K, Tsai YC, Niranjan N, et al. Sutureless aortic valve replacement: a systematic review and meta-analysis. Ann Cardiothorac Surg. 2015; 4(2): 100–111, doi: 10.3978/j.issn.2225-319X.2014.06.01, indexed in Pubmed: 25870805.
4. Gersak B, Fischlein T, Folliguet TA, et al. Sutureless, rapid deployment valves and stented bioprosthesis in aortic valve replacement: recommendations of an International Expert Consensus Panel. Eur J Cardiothorac Surg. 2016; 49(3): 709–718, doi: 10.1093/ejcts/ezv369, indexed in Pubmed: 26516193.
5. Chauvette V, Mazine A, Bouchard D. Ten-year experience with the Perceval S sutureless prosthesis: lessons learned and future perspectives. J Vis Surg. 2018; 4: 87, doi: 10.21037/jovs.2018.03.10, indexed in Pubmed: 29963376.
6. Lorusso R, Folliguet T, Shrestha M, et al. Sutureless versus stented bioprostheses for aortic valve replacement: the randomized PERSIST-AVR study design. Thorac Cardiovasc Surg. 2020; 68(2): 114–123, doi: 10.1055/s-0038-1675847, indexed in Pubmed: 30497085.
7. Shrestha M, Khaladj N, Bara C, et al. A staged approach towards interventional aortic valve implantation with a sutureless valve: initial human implants. Thorac Cardiovasc Surg. 2008; 56(7): 398–400, doi: 10.1055/s-2008-1038722, indexed in Pubmed: 18810696.
8. Shrestha M, Folliguet T, Meuris B, et al. Sutureless Perceval S aortic valve replacement: a multicenter, prospective pilot trial. J Heart Valve Dis. 2009; 18(6): 698–702, indexed in Pubmed: 20099720.
9. Masuda T, Nakamura Y, Ito Y, et al. The learning curve of minimally invasive aortic valve replacement for aortic valve stenosis. Gen Thorac Cardiovasc Surg. 2020; 68(6): 565–570, doi: 10.1007/s11748-019-01234-z, indexed in Pubmed: 31659703.
10. D'Onofrio A, Messina A, Lorusso R, et al. Sutureless aortic valve replacement as an alternative treatment for patients belonging to the "gray zone" between transcatheter aortic valve implantation and conventional surgery: a propensity-matched, multicenter analysis. J Thorac Cardiovasc Surg. 2012; 144(5): 1010–1016, doi: 10.1016/j.jtcvs.2012.07.040, indexed in Pubmed: 22974713.