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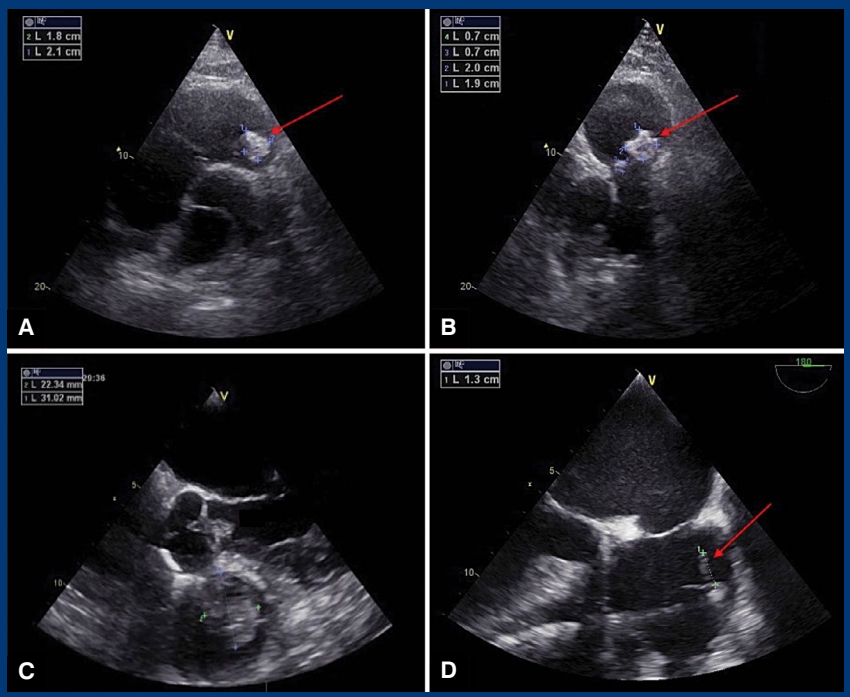

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Fourth universal definition of myocardial infarction. Selected messages from the European Society of Cardiology document and lessons learned from the new guidelines on ST-segment elevation myocardial infarction and non-ST-segment elevation-acute coronary syndrome

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**Equal contribution*

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Fourth universal definition of myocardial infarction: Key takeaways

The fourth universal definition of myocardial infarction (MI) [1] introduces several changes and new concepts of MI to enhance clinical practice. The most important of them being, in the opinion of the authors herein, the distinction between MI and myocardial injury as well as an emphasis on the utility of imaging techniques — cardiovascular magnetic resonance (CMR) in defining etiology of myocardial injury and coronary computed tomography angiography in the diagnosis of MI.

The clinical definition of MI specifies: **the presence of acute myocardial injury detected by abnormal cardiac biomarkers in the setting of evidence of acute myocardial ischemia [1].**

In clinical practice, cardiac troponin I and troponin T (the latter sometimes derives from skeletal muscles [2–4]) are recommended, especially in high-sensitivity cardiac troponin I (hs-cTn), mainly due to its specificity to the heart and sensitivity [5, 6]. Of note, for the first time, the acute myocardial injury was defined clearly as detection of elevated cardiac troponin values above the 99th percentile upper reference limit (URL) and occurrence of the rise and/or fall of focused cardiac troponin values [6]. Subsequently, without the concomitant rise and/or fall in the mentioned biomarker values, can only define chronic myocardial injury [7].

The authors emphasize the broad spectrum of clinical scenarios leading to myocardial injury, ranging from anemia, ventricular tachyarrhythmia, heart failure, kidney disease, and hypotensive shock to hypoxemia or other comorbidities (Fig. 1). However, without clinical evidence of acute ischemic myocardial injury, they should remain named "myocardial injury" in everyday practice.

For practical reasons, the authors emphasize the role of distinguishing between myocardial injury and infarction [1, 8]. The differences are presented in Figure 2.

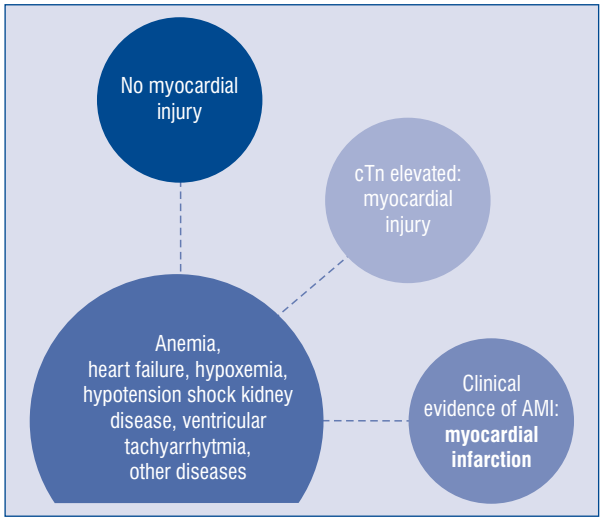

Figure 1. Spectrum of myocardial injury — from no injury to myocardial infarction; cTn — cardiac troponin; AMI — acute myocardial infarction.

Types of myocardial infarctions

The types of MIs were kept, and are presented clearly in Figure 2. Type 1 MI is defined as: the detection of a rise and/or fall of cTn with at least one value above the 99th percentile URL and with at least one of the following:

— symptoms of acute myocardial injury;
— new ischemic electrocardiography changes;
— development of pathological Q waves;
— imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology;
— identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy [1].

The criteria for type 2 MI do not include identification of coronary thrombus due to its mechanism — it develops secondarily to another illness or process. Possible mechanisms of imbalance between oxygen demand and oxygen supply can be fixed coronary atherosclerosis, coronary spasm, coronary embolism, coronary artery dissection, sustained tachyarrhythmia, severe bradyarrhythmia, severe hypertension, respiratory failure, shock, severe anemia or hypotension [8]. For the sake of patients, it is worth noticing that in this group, patient treatment should be based on restoration of the balance between oxygen demand and supply, through different interventions, concerning its primary cause, for instance heart-rate control, blood pressure-lowering or volume adjustment [8, 9].

Herein, the aim is to emphasize a fundamental issue concerning this document — differences between type 1 MI, type 2 MI, and non-ischemic myocardial injury.

Type 3 MI is very rare, constituting 3–4% of all MIs [10]. The authors highlight the difference between type 3 MI, it means death from probable cardiac reasons and sudden death from clearly non-cardiac causes (which is more

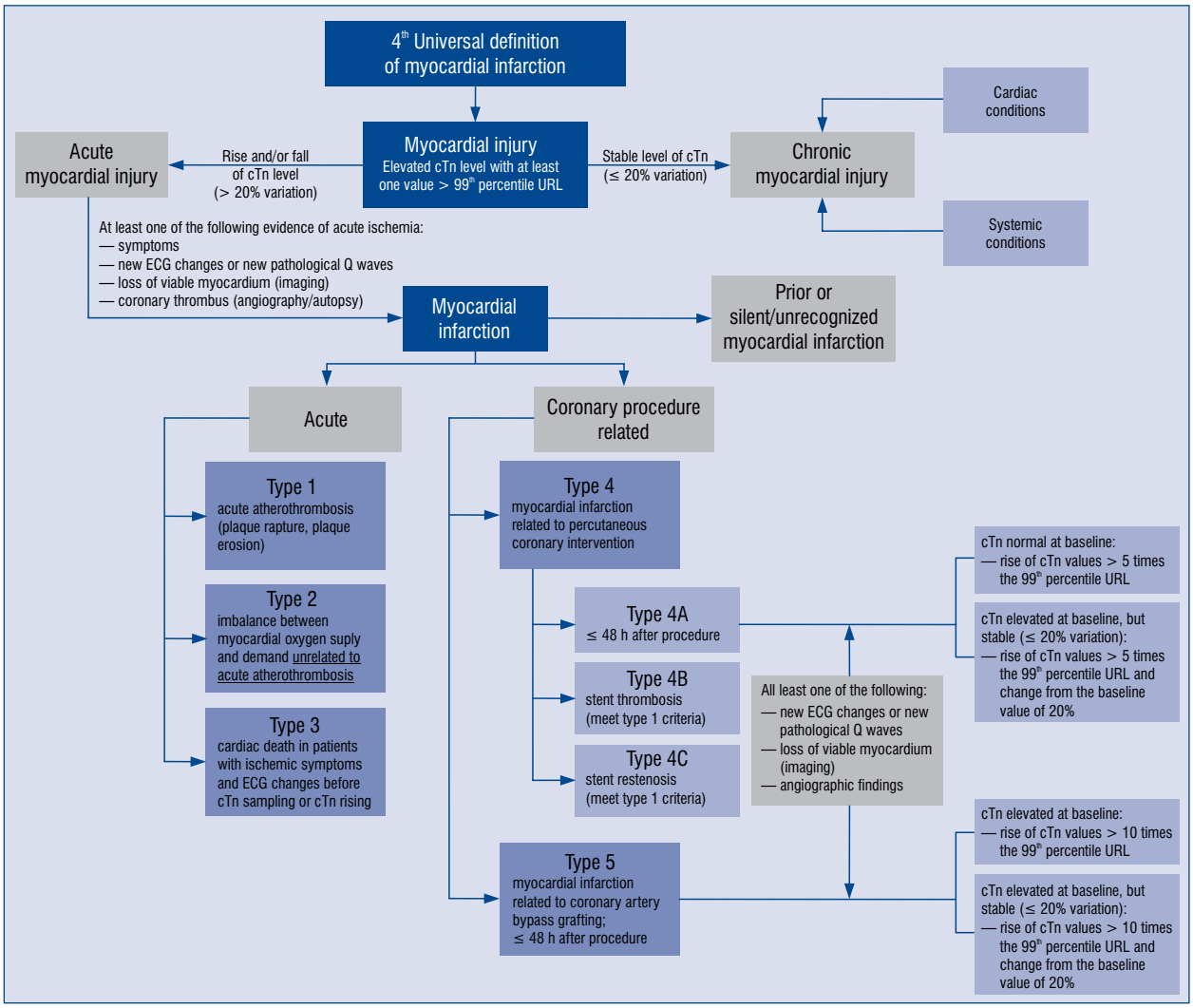

Figure 2. Scheme to distinguish myocardial injury and myocardial infarction and particular types of myocardial infarction; cTn — cardiac troponin; ECG — electrocardiogram; URL — upper reference limit.

frequent). Of note, when autopsy finds fresh or recent thrombus in the myocardial infarct-related artery, one should confirm type 1 MI instead of type 3 MI [11, 12].

The document clarifies the difference between periprocedural myocardial injury and MI, both percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). Consequently, it emphasizes the role of cardiac biomarkers' level and stability, before further evaluations and prior to regarding as a reference level for a particular patient. The situation in which an increased level of a cardiac biomarker is potentially the result of the MI and not the procedures mentioned above [13]. The diagnosis of a periprocedural myocardial injury requires:

— increase in cardiac biomarkers (cTn) level, when initially patient presents normal values or;
— increase in cardiac biomarkers (> 20%), when initially patient shows its values above the 99th percentile URL.

For periprocedural (≤ 48 h) MI related to the PCI (type 4a MI) and CABG (type 5 MI), five times and ten times increase in cTn value is required, respectively, if the patient presents normal initial values. These conditions are presented in Figure 3. In case of initial values of cTn above 99th percentile URL, a 20% rise is demanded, and the final value higher than five times 99th percentile URL or ten times 99th percentile URL in case of CABG. They must, of course, be accompanied by one of the known clinical criteria [1].

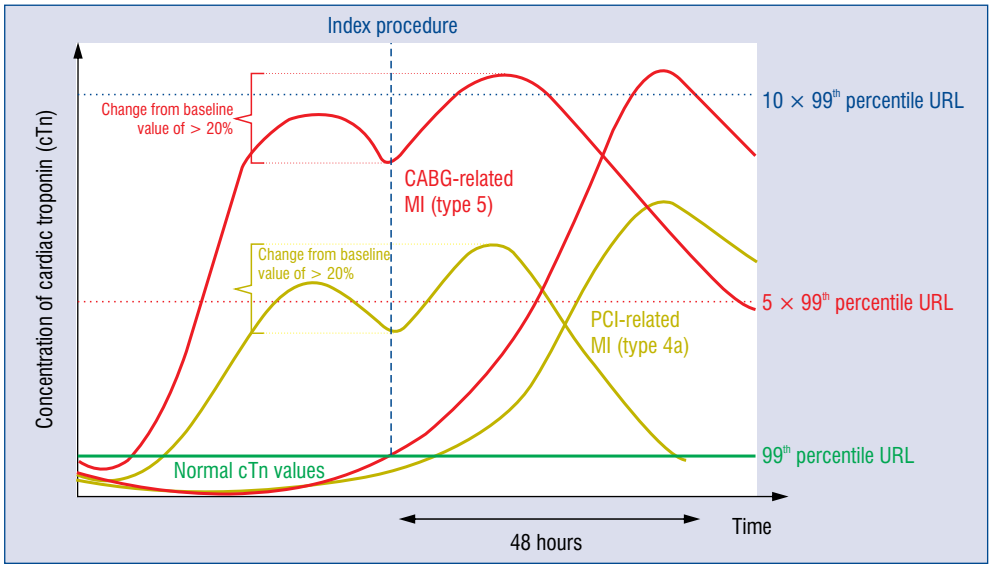

Figure 3. Concentration of cardiac troponin in different clinical scenarios relevant to revascularization procedures; cTn — cardiac troponin; CABG — coronary artery bypass grafting; PCI — percutaneous coronary intervention; URL — upper reference limit.

The definition of type 4c MI, connected with focal or diffuse restenosis after PCI, is based on a rise and/or fall of cTn values above the 99th percentile URL and definition based on the recognition of type 1 MI [1].

Myocardial injury and infarction associated with non-cardiac procedures

The occurrence of asymptomatic perioperative MI is strongly associated with 30-day mortality [14, 15]. Increased oxygen demand in the perioperative period and predominant etiology of myocardial ischemia are well recognized and the fact that about 35% of patients reveal hs-cTn level above the 99th percentile URL in post-operative blood samples [16, 17]. Therefore, increased vigilance is demanded in all high-risk individuals, and their baseline pre-operative value is necessary to collect.

Myocardial infarction with non-obstructive coronary arteries

The document also highlights the diagnosis of myocardial infarction with non-obstructive coronary arteries (MINOCA; ≤ 50% diameter stenosis in a major epicardiac vessel) [1]. The prevalence of MINOCA depends on sex (it occurs more frequently in women than men), the type of MI (it is more common in non-ST-segment elevation myocardial infarction [NSTEMI] than in ST-segment elevation myocardial infarction [STEMI]), and it concerns about 6–8% of patients with MI [18]. Multiple pathomechanisms underlie this condition and the heterogeneous group involves both coronary and non-coronary causes. The first authoritative international expert definition of MINOCA was published in the European Society of Cardiology working group position paper [18, 19]. Recently, the 2020 non-ST-segment elevation-acute coronary syndrome (NSTE-ACS) guidelines have maintained the approach to MINOCA as 'working diagnosis' [20] and the authors have proposed a clinical algorithm to aid in the diagnosis. The proposed 'traffic light' scheme includes different imaging tools such as echocardiography, cardiac ventriculography, CMR, intravascular imaging (intravascular ultrasonography [IVUS] or optical coherence tomography [OCT]) and intracoronary functional testing (acetylcholine or ergonovine). The most important recommendation seems to be to perform CMR in all MINOCA patients without an apparent underlying cause [20]. Patients with MINOCA can fulfil the criteria of MI type 1 and type 2 [21]. It should be stated that the current definition excludes Takotsubo syndrome (TTS) and myocarditis [20].

Takotsubo syndrome

According to available research, the authors underline for the first time, the relevance of TTS.

They focus on the discrepancy between the usually modest and transient increases in cTn values and the large territory of electrocardiography changes or left ventricle regional akinesis or hypokinesis including apical (82% of patients), mid-ventricular (14.6%), basal (2.2%), or focal (1.5%) territory. In TTS, the coronary arteries are usually angiographically intact while left ventriculography presents above mentioned regional wall motion abnormalities — in 10–15% of patients [1]. On the other hand, recently published analysis from the largest InterTAK Registry concludes that coronary artery disease may coexist in TTS patients, presents with the whole spectrum of coronary pathology including acute coronary occlusion, and is associated with adverse outcome [19]. Thus, the differential diagnosis with MI can be challenging [20, 21].

Consequently, unlike the previous attitude to TTS [19], the current guidelines classify it as 'other causes of myocardial injury' [1] or 'specific non-MINOCA status' [21]. However, TTS's diagnosis cannot be certainly stated in the acute phase because imaging follow-up is essential to prove the recovery of left ventricular function [21].

Spontaneous coronary dissection

Spontaneous coronary dissection (SCAD) leading to blood accumulation within the artery's false lumen with potential compression of the true lumen is an important non-atherosclerotic condition of MI [1]. It is triggered by vasa vasorum hemorrhage or intimal tear [21]. The NSTE-ACS guidelines specify three angiographic types of SCAD: type 1 with multiple radiolucent lumen, type 2 with long diffuse or smooth stenosis, and type 3 with focal or tubular stenosis [20]. The dissection coexisting with acute myocardial injury and evidence of ischemia is type 2 of MI. If coronary arteries are non-obstructive (stenosis < 50%) the criteria of MINOCA are fulfilled [1, 21]. SCAD can be missed on coronary computed tomography angiography, therefore OCT or IVUS are applicable in unclear clinical scenarios [21].

Cardiac magnetic resonance imaging

The accuracy of CMR provides an unequivocal assessment of the etiology of myocardial injury, allowing the repeated distinction between acute vs. chronic myocardial injury. It also identifies the presence and involvement of myocardial inflammation, thus providing a clear distinction between ischemic scar/fibrosis (extending from subendocardium to endocardium) and non-ischemic scar/fibrosis (subepicardial, mid-wall, insertion points) in myocardial injury (Fig. 4) [1].

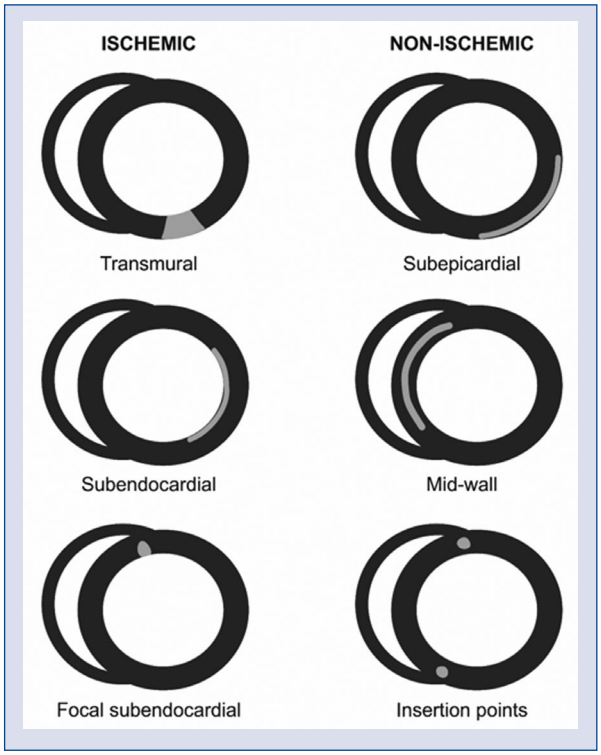

Figure 4. The different patterns of scarring in post-contrast cardiac magnetic resonance images — late-gadolinium enhancement.

COVID-19 and myocardial infarction

Since the initial outbreak of the novel coronavirus disease — severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)/coronavirus disease 2019 (COVID-19) — in December 2019, data from many countries (Italy, Spain, Switzerland, The United States of America) underline a dramatic drop in the number of ACS referrals to cardiovascular centers at the time of the COVID-19 outbreak, moreover reduction of PCI in STEMI patients was 38% [22–25]. In addition, Legutko et al. [26] and Siudak et al. [27] showed a greater decline in the number of procedures for NSTEMI, unstable angina or chronic coronary syndrome than in those for STEMI (19.2% vs. 16.2%). What is more, the decline of PCI procedures in NSTEMI after lockdown reached about 30% [27]. Of course, the obvious consequence of this situation is the staggering growth in MI complications, such as increased morbidity and mortality. Among the

mechanisms potentially decreasing admission to hospitals during the COVID-19 pandemic are: fear of contagion, relaxing lifestyle, decrease of air pollution, increase in pain threshold, which leads to a higher prevalence of silent or near silent MIs [28]. The need for urgent treatment according to the guidelines while maintaining the safety of medical personnel is necessary. Of note, invasive coronary angiography in acute ST-segment elevation coronary syndrome cannot be neglected, even in COVID-19 patients with myocarditis pretending to be ACS.

Key points from STEMI and NSTE-ACS guidelines

STEMI

— Some patients with coronary artery occlusion or global ischemia do not have typical ST-segment elevation in ECG. However, patients with clinical manifestation of ongoing myocardial ischemia and other ECG patterns (e.g., bundle branch block, ventricular pacing, hyperacute T-waves, isolated ST-segment depression in anterior leads, and/or universal ST-segment depression with ST-segment elevation in aVR) should be qualified for a primary PCI.
— Non-invasive imaging in STEMI patients plays a crucial role in the acute phase and during long-term management.
— The MINOCA coexisting with ST-segment elevation in ECG requires additional tests to diagnose the etiology and tailor proper management [29].

NSTE-ACS

— Myocyte injury is related to the release of troponin as intracellular protein into the systemic circulation and elevated troponin level is a marker of myocardial injury, not only a marker of MI. Troponin results should be interpreted in the clinical context.
— Patients with MINOCA can fulfil the criteria of MI type 1 and type 2 [21]. The 2020 NSTE-ACS guidelines have proposed a clinical algorithm to aid in the diagnosis of MINOCA, including different imaging tools such as echocardiography, cardiac ventriculography, CMR, intravascular imaging (IVUS or OCT) and intracoronary functional testing (acetylcholine or ergonovine). The most important recommendation seems to be to perform CMR in all MINOCA patients without an apparent underlying cause [20].
— hs-cTn assays have a higher negative predictive value for acute MI than standard troponin tests.
— Higher sensitivity and diagnostic accuracy for the diagnosis of MI enables shortening the time interval between the first and second hs-cTn assessment. The 0 h/1 h rule-in or rule-out algorithm first and 0 h/2 h second should be chosen. The cut-off values within both protocols are assay-specific and baseline level, acute change must be taken into account (1hΔ or 2hΔ). Additional blood draw after 3 h should be done if previous troponin assessment (0 h/1 h) is inconclusive and clinical status still suggests ACS. A rule-out 0 h/3 h protocol is still recommended but with the lower level of recommendation [20].

Conflict of interest: None declared

References

1. Thygesen K. 'Ten Commandments' for the Fourth Universal Definition of Myocardial Infarction 2018. Eur Heart J. 2019; 40(3): 226, doi: 10.1093/eurheartj/ehy856, indexed in Pubmed: 30649367.
2. Rittoo D, Jones A, Lecky B, et al. Elevation of cardiac troponin T, but not cardiac troponin I, in patients with neuromuscular diseases: implications for the diagnosis of myocardial infarction. J Am Coll Cardiol. 2014; 63(22): 2411–2420, doi: 10.1016/j.jacc.2014.03.027, indexed in Pubmed: 24747102.
3. Jaffe AS, Vasile VC, Milone M, et al. Diseased skeletal muscle: a noncardiac source of increased circulating concentrations of cardiac troponin T. J Am Coll Cardiol. 2011; 58(17): 1819–1824, doi: 10.1016/j.jacc.2011.08.026, indexed in Pubmed: 21962825.
4. Wens SCA, Schaaf GJ, Michels M, et al. Elevated plasma cardiac troponin T levels caused by skeletal muscle damage in pompe disease. Circ Cardiovasc Genet. 2016; 9(1): 6–13, doi: 10.1161/CIRCGENETICS.115.001322, indexed in Pubmed: 26787432.
5. Thygesen K, Mair J, Katus H, et al. Recommendations for the use of cardiac troponin measurement in acute cardiac care. Eur Heart J. 2010; 31(18): 2197–2204, doi: 10.1093/eurheartj/ehq251, indexed in Pubmed: 20685679.
6. Thygesen K, Mair J, Giannitsis E, et al. How to use high-sensitivity cardiac troponins in acute cardiac care. Eur Heart J. 2012; 33(18): 2252–2257, doi: 10.1093/eurheartj/ehs154, indexed in Pubmed: 22723599.
7. Sarkisian L, Saaby L, Poulsen T, et al. Prognostic impact of myocardial injury related to various cardiac and noncardiac conditions. Am J Med. 2016; 129(5): 506–514.e1, doi: 10.1016/j.amjmed.2015.12.009.
8. Januzzi JL, Sandoval Y. The many faces of type 2 myocardial infarction. J Am Coll Cardiol. 2017; 70(13): 1569–1572, doi: 10.1016/j.jacc.2017.07.784, indexed in Pubmed: 28935033.
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. Eur Heart J. 2015; 37(3): 267–315, doi: 10.1093/eurheartj/ehv320.
10. Jangaard N, Sarkisian L, Saaby L, et al. Incidence, frequency, and clinical characteristics of type 3 myocardial infarction in clinical

practice. Am J Med. 2017; 130(7): 862.e9-862.e14, doi: 10.1016/j.amjmed.2016.12.034, indexed in Pubmed: 28159605.
11. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. Eur Heart J. 2007; 28(20): 2525–2538, doi: 10.1093/eurheartj/ehm355, indexed in Pubmed: 17951287.
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. Rahimi K, Banning AP, Cheng ASH, et al. Prognostic value of coronary revascularisation-related myocardial injury: a cardiac magnetic resonance imaging study. Heart. 2009; 95(23): 1937–1943, doi: 10.1136/hrt.2009.173302, indexed in Pubmed: 19687014.
14. Devereaux PJ, Xavier D, Pogue J, et al. Characteristics and short-term prognosis of perioperative myocardial infarction in patients undergoing noncardiac surgery: a cohort study. Ann Intern Med. 2011; 154(8): 523–528, doi: 10.7326/0003-4819-154-8-201104190-00003, indexed in Pubmed: 21502650.
15. Devereaux PJ, Chan MTV, Alonso-Coello P, et al. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. JAMA. 2012; 307(21): 2295–2304, doi: 10.1001/jama.2012.5502, indexed in Pubmed: 22706835.
16. Kavsak PA, Walsh M, Srinathan S, et al. High sensitivity troponin T concentrations in patients undergoing noncardiac surgery: a prospective cohort study. Clin Biochem. 2011; 44(12): 1021–1024, doi: 10.1016/j.clinbiochem.2011.05.017, indexed in Pubmed: 21640092.
17. Duvall WL, Sealove B, Pungoti C, et al. Angiographic investigation of the pathophysiology of perioperative myocardial infarction. Catheter Cardiovasc Interv. 2012; 80(5): 768–776, doi: 10.1002/ccd.23446, indexed in Pubmed: 22419582.
18. Agewall S, Beltrame JF, Reynolds HR, et al. ESC working group position paper on myocardial infarction with non-obstructive coronary arteries. Eur Heart J. 2017; 38(3): 143–153, doi: 10.1093/eurheartj/ehw149, indexed in Pubmed: 28158518.
19. Napp LC, Cammann VL, Jaguszewski M, et al. Coexistence and outcome of coronary artery disease in Takotsubo syndrome. Eur Heart J. 2020; 41(34): 3255–3268, doi: 10.1093/eurheartj/ehaa210, indexed in Pubmed: 32484517.
20. Templin C, Ghadri JR, Diekmann J, et al. Clinical features and outcomes of takotsubo (stress) cardiomyopathy. N Engl J Med. 2015; 373(10): 929–938, doi: 10.1056/NEJMoa1406761, indexed in Pubmed: 26332547.
21. Collet JP, Thiele H. Lesson learnt from the new 2020 ESC guidelines on non-ST-segment elevation acute coronary syndrome: when clinical judgement precedes and overpasses weak recommendations. 2020 non-ST-segment elevation acute coronary syndrome guidelines on pre-treatment: primum non nocere! Eur Heart J. 2020 [Epub ahead of print], doi: 10.1093/eurheartj/ehaa861, indexed in Pubmed: 33205199.
22. Garcia S, Albaghdadi MS, Meraj PM, et al. Reduction in ST-segment elevation cardiac catheterization laboratory activations in the United States during COVID-19 pandemic. J Am Coll Cardiol. 2020; 75(22): 2871–2872, doi: 10.1016/j.jacc.2020.04.011, indexed in Pubmed: 32283124.
23. Rodriguez-Leor O, Cid-Alvarez B. STEMI care during COVID-19: losing sight of the forest for the trees. JACC Case Rep. 2020; 2(10): 1625–1627, doi: 10.1016/j.jaccas.2020.04.011.
24. Holy EW, Jakob P, Manka R, et al. Impact of a nationwide COVID-19 lockdown on acute coronary syndrome referrals. Cardiol J. 2020; 27(5): 633–635, doi: 10.5603/CJ.a2020.0091, indexed in Pubmed: 32643140.
25. Wańha W, Wybraniec M, Kapłon-Cieślicka A, et al. Myocardial infarction in the shadow of COVID-19. Cardiol J. 2020; 27(5): 478––480, doi: 10.5603/CJ.2020.0152, indexed in Pubmed: 33165896.
26. Legutko J, Niewiara Ł, Bartuś S, et al. Decline in the number of coronary angiography and percutaneous coronary intervention procedures in patients with acute myocardial infarction in Poland during the coronavirus disease 2019 pandemic. Kardiol Pol. 2020; 78(6): 574–576, doi: 10.33963/KP.15393, indexed in Pubmed: 32469190.
27. Siudak Z, Grygier M, Wojakowski W, et al. Clinical and procedural characteristics of COVID-19 patients treated with percutaneous coronary interventions. Catheter Cardiovasc Interv. 2020; 96(6): E568–E575, doi: 10.1002/ccd.29134, indexed in Pubmed: 32686899.
28. Niccoli G, Luescher TF, Crea F. Decreased myocardial infarction admissions during COVID times: what can we learn? Cardiovasc Res. 2020; 116(10): e126–e128, doi: 10.1093/cvr/cvaa146, indexed in Pubmed: 32463078.
29. 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.]. Kardiol Pol. 2018; 76(2): 229–313, doi: 10.5603/KP.2018.0041, indexed in Pubmed: 29457615.

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Underlying heart diseases and acute COVID-19 outcomes

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Abstract

Background: *The presence of any underlying heart condition could influence outcomes during the coronavirus disease 2019 (COVID-19).*

Methods: *The registry HOPE-COVID-19 (Health Outcome Predictive Evaluation for COVID-19, NCT04334291) is an international ambispective study, enrolling COVID-19 patients discharged from hospital, dead or alive.*

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Results: *HOPE enrolled 2798 patients from 35 centers in 7 countries. Median age was 67 years (IQR: 53.0–78.0), and most were male (59.5%). A relevant heart disease was present in 682 (24%) cases. These were older, more frequently male, with higher overall burden of cardiovascular risk factors (hypertension, dyslipidemia, diabetes mellitus, smoking habit, obesity) and other comorbidities such renal failure, lung, cerebrovascular disease and oncologic antecedents ($p < 0.01$, for all). The heart cohort received more corticoids (28.9% vs. 20.4%, $p < 0.001$), antibiotics, but less hydroxychloroquine, antivirals or tocilizumab. Considering the epidemiologic profile, a previous heart condition was independently related with short-term mortality in the Cox multivariate analysis (1.62; 95% CI 1.29–2.03; $p < 0.001$). Moreover, heart patients needed more respiratory, circulatory support, and presented more in-hospital events, such heart failure, renal failure, respiratory insufficiency, sepsis, systemic infammatory response syndrome and clinically relevant bleedings (all, $p < 0.001$), and mortality (39.7% vs. 15.5%; $p < 0.001$).*

Conclusions: *An underlying heart disease is an adverse prognostic factor for patients suffering COVID-19. Its presence could be related with different clinical drug management and would benefit from maintaining treatment with angiotensin converting enzyme inhibitors or angiotensin receptor blockers during in-hospital stay.*

Trial Numbers: NCT04334291/EUPAS34399. (Cardiol J 2021; 28, 2: 202–214)

Key words: COVID-19, mortality, cardiology, registry, prognosis, heart disease

Introduction

The recent outbreak of a zoonotic viral disease named coronavirus disease 2019 (COVID-19) [1] has been declared a pandemic by World Health Organization (WHO) [2]. With important morbimortality [3], some early-published data have already pointed-out previous or underlying heart conditions to be at higher risk for worse outcomes [4, 5]. Moreover, according to the American Centers for Disease Control and Prevention, elderly patients with comorbidities are at higher risk of becoming infected with COVID-19, especially those with coronary heart disease, hypertension, or diabetes [6]. In fact, some authors have suggested that the mortality rate of this respiratory-borne coronavirus or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) could be even higher in those with previous cardiovascular diseases than in patients with previous chronic respiratory diseases [7]. Furthermore, this is relevant since an important percentage of patients admitted for COVID-19 will present with an underlying cardiac problem. In a recent Chinese series, 25% had heart diseases, 44% had arrhythmias, and 58% had hypertension [8]. Additionally, there is preliminary evidence suggesting that the responsible virus affects primarily the cardiovascular system and the heart itself with direct myocardial injury among other deleterious mechanisms [9, 10].

Taken together, to sum up, there is growing evidence that underlying cardiovascular conditions lead to a higher likelihood of COVID-19 infection, more severe disease progression, and higher risk for mortality [11]. Moreover, the pandemic has posed a major impact in the treatment of regular heart diseases [12].

We analyze herein, the clinical profile, presentation and influence of previous treatments, primarily focusing on the mortality of patients with any underlying heart condition hospitalized because of COVID-19.

Methods

The present study was approved by the ethics committee of the promoting center, and was appraised and accepted by institutional board or local committees as well. Written informed consent was waived because of its anonymized observational design. All local principal researchers reviewed the draft and vouch for the accuracy and veracity of data. A complete list of hospitals, investigators, collaborators and definitions is available in the **Supplementary Appendix**.

Study design and participation criteria

The registry HOPE-COVID-19 (Health Outcome Predictive Evaluation for COVID-19, NCT04334291) is an international investigator-initiated study without conflicts of interest [13]. It was designed as an ambispective cohort, real life all-comers type, without any financial remuneration for researchers. Patients were eligible for enrollment when discharged after an in-hospital admission with a positive COVID-19 test or if their

attending physicians considered them highly likely to have presented the infection. Confirmed cases were those with positive throat swab samples tested using real-time reverse transcriptase–polymerase chain reaction assays according to the WHO recommendations. All decisions and clinical procedures were performed by the attending physician team independently of this study following the local regular practice and protocols. The data was collected in electronic format in a secure online database (www.HopeProjectMD.com). The information presented here correspond to the HOPE COVID-19 Registry with a cutoff performed on April 18th, 2020.

Definitions, objectives and study outcomes

A pragmatic definition of heart disease was adopted and divided into various groups according to the local research team, led by two experienced physicians. Any heart disease was considered when it was stated in the clinical history and/or the patient was receiving medication for that purpose. The following categories for the main heart problem of every patient were accepted: arrhythmias, coronary artery disease, heart failure or cardiomyopathy, heart valve disease, combined (when various of the former problems were present to a clinically relevant degree) and non-specified or other different from the mentioned groups (i.e. congenital heart disease). Study definitions are available in the appendix and online in the study webpage.

The objectives were:

— comparing the epidemiological and clinical profiles and management of COVID-19 patients with vs. without previous heart disease;
— determining the prognostic impact of an underlying heart disease on mortality;
— identifying independent predictors of mortality in the group with underlying heart disease.

The reference primary end-point was considered all-cause mortality. Other events were recorded as secondary end-points, such as invasive mechanical ventilation, non-invasive mechanical ventilation, prone, respiratory insufficiency, heart failure, renal failure, upper respiratory tract involvement, pneumonia, sepsis, systemic inflammatory response syndrome, clinically relevant bleeding, hemoptysis and embolic events. Events were allocated following local researcher criteria upon HOPE COVID-19 registry definitions.

Statistical analysis

Data are presented as mean ± standard deviation for continuous variables with a normal distribution, median (interquartile range [IQR]) for continuous variables with a non-normal distribution, and as frequency (%) for categorical variables. The Student t-test and the Mann-Whitney U-test were used to compare continuous variables with normal and non-normal distributions, when needed. The Chi-squared-test was used to compare categorical variables. Given the multiplicity of variables, only factors with $p < 0.05$ on the mentioned univariate analysis were entered into the Cox multivariate analysis. Mortality analysis was performed using the Kaplan-Meier estimates and log-rank tests to compare factors. Statistical analysis was completed with SPSS statistics v24.0 (SPSS, Inc., Chicago, IL, USA) in all analyses. All tests were two-sided, and a p-value less than 0.05 was considered statistically significant.

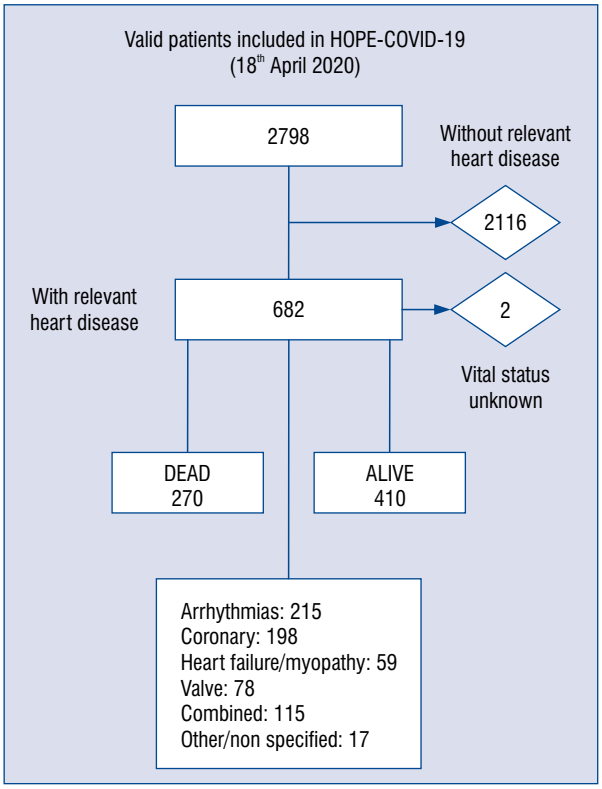


Figure 1. Study flow diagram.

Results

Finally, 2798 patients were enrolled in HOPE registry up to 18th April, 2020, from 35 centers in 25 cities and 7 countries (Canada, China, Cuba, Ecuador, Germany, Italy, and Spain) (Fig. 1).

Epidemiologic and clinical profiles

The median age was 67 years (IQR 53.0–78.0), and most were male (60%). The most frequent co-

morbidities were hypertension (49%) and dyslipidemia (35.1%). A relevant heart disease [13] was recorded in 682 (24%) cases. Further details are displayed, stratified by the presence of any heart disease or not, in Table 1. In the heart-disease cohort, deceased heart patients were older ($p < < 0.001$) and more frequently male (58.5% vs. 65.8%, $p = 0.001$), with a higher overall burden of cardiovascular risk factors (hypertension, dyslipemia, diabetes mellitus, smoking habit, obesity, $p < 0.01$ for all) and other comorbidities such as chronic renal failure, any lung disease, cerebrovascular disease and oncologic antecedent ($p < 0.01$, for all).

Regarding previous treatments, signs and symptoms, Table 1 displays the main findings, compared with patients without heart disease.

In addition, Table 2 presents the main analytic findings at the time of admission and in hospital management strategies. Chest X-ray exhibited any acute lung abnormality in more than 70%, mostly bilateral (57.6%). In this setting, heart patients needed more respiratory and circulatory support and presented higher in hospital events (Table 3). The specific drug most frequently used was hydroxychloroquine (72%), followed by antibiotics and any antiviral drug (mostly lopinavir/ritonavir). Nevertheless, the heart disease group received a different pattern of treatment, characterized by more systemic corticoids, antibiotics, but less hydroxychloroquine, antivirals or tocilizumab (Table 2).

Influence of a previous heart condition

Assessing the whole sample epidemiologic profile, gender (male), age (increasing) and the presence of hypertension, dyslipemia, diabetes mellitus, obesity (body mass index > 30), renal insufficiency, any lung disease, any heart disease, previous cerebrovascular condition, connective or liver disease, any cancer or immunosuppressive condition displayed a significantly higher mortality ($p < 0.01$ in all) in the univariate analysis.

Considering these variables in the multivariate assessment (Table 4), the following factors were considered independent risk factors: age, hypertension, chronic renal failure, any cancer and any heart disease (hazard ratio [HR] 1.62; 95% confidence interval [CI] 1.29–2.03).

Outcomes inside the heart disease cohort

Focusing on those with an underlying heart condition, these patients presented higher mortality (39.7% vs. 15.5%, non-adjusted odds ratio [OR] 3.58; 95% CI 2.95–4.34; $p < 0.001$; Figs. 2, 3). Heart patients, also, suffered more frequent in-hospital events, such as heart failure, acute renal failure, respiratory insufficiency, sepsis, systemic infammatory response syndrome and clinically relevant bleedings, (all, $p < 0.001$). Table 3 discusses this further and depicts the raw in-hospital events regarding the type of relevant heart condition group.

In the multivariate analysis for mortality, considering only the heart disease group, the following were included in the final model: age 70 years or more, hypertension, diabetes mellitus, chronic renal failure, use of oral anticoagulants, Vitamin D supplements, myalgia/arthralgia, O_2 saturation < 92%, decreased blood pressure, elevated D dimer, elevated C reactive protein, elevated lactate dehydrogenase (LDH), invasive mechanical ventilation, prone during admission, use of corticoids, hydroxychloroquine and angiotensin converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs) during admission. Tachypnea and use of high flow nasal cannulas were excluded for potential collinearity with other variables (O_2 saturation and mechanical ventilation). Of those, age (HR 4.3; 95% CI 2.23–8.28), hypertension (HR 1.7; 95% CI 1.01–2.89), O_2 saturation < 92% (HR 3.59; 95% CI 2.43–5.31), an elevated LDH (HR 1.66; 95% CI 1.01–2.73), the use of mechanical ventilation (HR 2.11; 95% CI 1.17–3.80) remained in the model as risk factors while the use of in hospital ACEIs/ARBS (HR 0.34; 95% CI 0.20–0.49) and hydroxychloroquine (HR 0.69; 95% CI 0.45–0.99) resulted as potential protective factors.

Discussion

The present study is a cohort study among patients with COVID-19 after discharge, reviewing the direct impact on mortality of previous heart diseases.

Regarding COVID-19, any kind of heart disease is probably a truly relevant condition. First, because compared to the general population, the incidence of cardio-cerebrovascular disease in patients with COVID-19 is much higher [14]. Second, because patients with hypertension, cardio-cerebrovascular diseases or diabetes are more likely to develop into severe/intensive care unit (ICU) cases or die after SARS-CoV-2 infection [5, 7, 14]. The overall proportion of hypertension, cardio-cerebrovascular problems and diabetes were about two-fold, three-fold and two-fold, respectively, higher in ICU/severe cases than in their non-ICU/severe counterparts [14]. In the present cohort, it was observed that outcomes of patients

Table 1. Clinical features, previous treatments and presentation symptoms before admission overall and stratified among patients with heart disease or without heart disease.

	All patients* N = 2798 No./total no. (%)	Heart disease**		P
		Absent (N = 2116) No./total no. (%)	Present (N = 682) No./total no. (%)	
Age [years]	/2788	/2109	/679	**< 0.001**
Median (IQR) [years]	67 (53.0–78.0)	63 (49–74)	75 (70–85)	
Distribution [years]:				
0–14	24 (0.9)	22 (1.0)	2 (0.3)	
15–49	540 (19.4)	514 (24.4)	26 (3.8)	
50–64	674 (24.2)	592 (28.1)	83 (12.2)	
≥ 65	1544 (55.5)	981 (46.5)	568 (83.7)	
Gender:	/2798			0.001
Female	1111 (39.7)	878 (41.5)	233 (34.2)	
Male	1687 (59.5)	1238 (58.5)	449 (65.8)	
Race:	/2798			**< 0.001**
Caucasian	2351 (84.0)	1743 (82.4)	608 (89.1)	
Latin	357 (12.8)	301 (14.2)	56 (8.2)	
Asian	34 (1.2)	32 (1.5)	2 (.3)	
Black	32(1.1)	21 (1.0)	11 (1.6)	
Other	24 (0.9)	19 (0.9)	45(0.3)	
Hypertension	/2784	/2106	/678	**< 0.001**
Yes	1370 (49.2)	1265 (60.1)	149 (22.0)	
Dyslipidemia	/2767	/2099	/668	**< 0.001**
Yes	971 (35.1)	602 (28.7)	369 (55.2)	
Diabetes mellitus (1 or 2)	/2677	/2039	/638	**< 0.001**
Yes	482 (18.0)	292 (14.3)	190 (29.8)	
Obesity (BMI > 30 kg/m^2)	/2023	/1527	/496	0.006
Yes	459 (22.7)	324 (21.2)	135 (27.2)	
CRI	/2681	/2045	/636	**< 0.001**
Yes	192 (7.2)	97 (4.7)	95 (14.9)	
Smoking habit:	/2494	/1887	/607	0.147
No	2321 (93.1)	1764 (93.5)	557 (91.8)	
Current	173 (6.9)	123 (6.5)	50 (8.2)	
Lung disease:				**< 0.001**
No	2266 (81.0)	171 (83.7)	495 (72.6)	
Asma	146 (5.2)	121 (5.7)	25 (3.7)	
COPD	197 (7.0)	108 (5.1)	89 (13.0)	
Interstitial	19 (0.7)	9 (0.4)	10 (1.5)	
Restrictive	23 (0.8)	13 (0.6)	10 (1.5)	
Other	147 (5.3)	94 (4.4)	53 (7.8)	
Any cancer	/2710	/2056	/654	**< 0.001**
Yes	367 (13.5)	240 (11.7)	127 (19.4)	
Any immunosuppressive disease	/2491	/1888	/603	0.060
Yes	195 (7.8)	137 (7.3)	58 (9.6)	

→

Table 1 (cont.). Clinical features, previous treatments and presentation symptoms before admission overall and stratified among patients with heart disease or without heart disease.

	All patients* N = 2798 No./total no. (%)	Heart disease**		P
		Absent (N = 2116) No./total no. (%)	Present (N = 682) No./total no. (%)	
Dependency level:				**< 0.001**
Not disclosed	53 (1.9)	38 (1.8)	15 (2.2)	
None	2397 (85.7)	1903 (89.9)	494 (72.4)	
Partially	249 (8.9)	115 (5.4)	134 (19.6)	
Totally	99 (3.5)	60 (2.8)	39 (5.7)	
Home oxygen therapy	/2762	/2089	/673	**< 0.001**
Yes	93 (3.4)	50 (2.4)	43 (6.4)	
ASA	/2747	/2076	/671	**< 0.001**
Yes	429 (15.6)	191 (9.2)	238 (35.5)	
Oral anticoagulation	/2732	/2064	/668	**< 0.001**
Yes	322 (11.8)	33 (1.6)	289 (43.3)	
ACEIs/ARBs	/2759	/2092	/667	**< 0.001**
Yes	979 (35.5)	596 (28.5)	383 (57.4)	
Beta-blockers	/2740	/2067	/673	**< 0.001**
Yes	483 (17.7)	129 (6.2)	354 (52.6)	
Inhaled beta agonist	2737	/2080	/657	**< 0.001**
Yes	289 (10.6)	169 (8.1)	120 (18.3)	
Inhaled corticoids	/2743	/2078	/665	**< 0.001**
Yes	241 (8.8)	150 (7.2)	91 (13.7)	
Vitamin D supplements	/2718	/2067	/651	**< 0.001**
Yes	287 (10.6)	165 (8.0)	122 (18.7)	
Tachypnea (> 22 bpm)	/2640	/2001	/639	**< 0.001**
Yes	666 (25.2)	443 (22.1)	223 (34.9)	
Hypo-anosmia	/2510	/1892	/618	**0.061**
Yes	176 (7.0)	143 (7.6)	33 (5.3)	
Dysgeusia	/2507	/1889	/618	**0.180**
Yes	198 (7.9)	157 (8.3)	41 (6.6)	
Sore throat	/2728	/260	/399	**0.005**
Yes	1889 (69.2)	158 (60.7)	257 (64.4)	
Fever	/2754	/2085	/669	**< 0.001**
Yes	2235 (81.2)	1735 (83.2)	500 (74.7)	
Cough	/2734	/2073	/661	**< 0.001**
Yes	1893 (69.2)	1477 (71.2)	416 (62.9)	
Diarrhea	/2632	/1992	/640	0.004
Yes	510 (19.4)	411 (20.6)	99 (15.5)	
Myalgia/arthralgia	/2651	/2009	/642	**< 0.001**
Yes	884 (33.3)	713 (35.5)	171 (26.6)	
O_2 saturation < 92%	/2699	/2043	/656	**< 0.001**
Yes	893 (33.1)	572 (28.0)	321 (48.9)	
Abnormal BP (SBP < 90/< 60 mmHg)	/2758	/2091	/667	**< 0.001**
Yes	109 (5.2)	109 (5.2)	81 (12.1)	

*Some data are missing at the time of interim analysis. Calculations and percentages are expressed upon the recorded data as are displayed in the table (recorded/total available).
**Comparisons and p values are applied to heart disease absence or presence.
ACEI/ARB — angiotensin converting enzyme inhibitors/angiotensin receptors blockers; ASA — acelylsalicylic acid; BMI — body mass index; BP — blood pressure; CRI — chronic renal insufficiency; COPD — chronic obstructive pulmonary disease; SBP — systolic blood pressure

Table 2. Relevant analytical results (early at admission) and in hospital management regarding the presence of heart disease or no presence of heart disease.

	All patients* N = 2798	Heart disease**		P
		Absent (N = 2116)	Present (N = 682)	
Elevated D dimer	/2394	/1825	/569	**0.001**
Yes	1538 (64.2)	1140 (62.5)	398 (69.9)	
Elevated procalcitonin	/2146	/1631	/515	**0.004**
Yes	527 (24.6)	376 (23.1)	151 (29.3)	
Elevated C reactive protein	/2724	/2059	/665	**< 0.001**
Yes	2456 (90.2)	1831 (88.9)	625 (94.0)	
Elevated troponin	/1325	/969	/356	**< 0.001**
Yes	222 (16.8)	119 (12.3)	103 (28.9)	
Elevated LDH	/2503	/1889	/614	**0.014**
Yes	1820 (72.7)	1350 (71.5)	470 (76.5)	
Elevated creatinine (> 1.5 mg/dL)	/2319	/1764	/555	**< 0.001**
Yes	375 (16.2)	223 (12.6)	152 (27.4)	
White count cell (≤ 4000/μL)	/2709	/2056	/653	**0.688**
Yes	462 (17.1)	354 (17.2)	108 (16.5)	
Lymphocytes count (≤ 1500/μL)	/2625	/2000	/625	**< 0.001**
Yes	1980 (75.4)	1474 (73.7)	506 (81.0)	
Hemoglobin levels (≤ 12 g/dL)	/2695	/2047	/648	**< 0.001**
Yes	681 (25.3)	427 (20.9)	254 (39.2)	
Platelet counts (≤ 150,000/μL)	/2701	/2053	/648	**< 0.001**
Yes	728 (27.0)	483 (23.5)	245 (37.8)	
MANAGEMENT				
High flow nasal cannula	/2686	/2026	/660	**< 0.001**
Yes	492 (18.3)	325 (16.0)	167 (25.3)	
Noninvasive mechanical ventilation	/2684	/2026	/658	**0.027**
Yes	390 (14.5)	277 (13.7)	113 (17.2)	
Invasive mechanical ventilation	/2646	/2008	/638	**0.927**
Yes	168 (6.3)	127 (6.3)	41 (6.4)	
Prone during admission	/2665	/2018	/647	**0.461**
Yes	246 (9.2)	191 (9.5)	55 (8.5)	
Circulatory/ECMO support	/948	/754	/194	**0.822**
Yes	4 (0.4)	3 (0.4)	1 (0.5)	
Use of corticoids	/2693	/2039	/654	**< 0.001**
Yes	604 (22.4)	415 (20.4)	189 (28.9)	
Use of hydroxichloroquine	/2728	/2067	/661	**0.001**
Yes	2306 (84.5)	1775 (85.9)	531 (80.3)	
Use of antivirals	/2726	/2066	/660	**< 0.001**
Yes	1795 (65.8)	1415 (68.5)	380 (57.6)	
Use of tocilizumab	/2681	/2036	/645	**0.012**
Yes	183 (6.8)	153 (7.5)	30 (4.7)	
Use of antibiotics	/2625	/1993	/632	**0.013**
Yes	1953 (74.4)	1459 (73.2)	494 (78.2)	
Use of ACEIs/ARBs during stay	/2598	/1981	/617	**< 0.001**
Yes	464 (17.9)	291 (14.7)	173 (28.0)	

*Some data are missing at the time of interim analysis. Calculations and percentages are expressed upon the recorded data as are displayed in the table (recorded/total available).
**Comparisons and p values are applied to heart disease absence or presence.
ACEI/ARB — angiotensin converting enzyme inhibitors/angiotensin receptors blockers; ECMO — extracorporeal membrane oxygenation; LDH — lactate dehydrogenase

Table 3. Events during in hospital stay, stratified by the presence of heart disease and type.

	Heart disease		P*	Odds ratio* (95% CI)	Type of heartdisease					
	Without	With			Arrhythmias	Coronary	Heart failure/ /myopathy	Valve	Combined	Non specified/ /other
Death	328 (15.5)	270 (39.7)	**< 0.001**	3.58 (2.95–4.34)	89 (41.6)	68 (34.3)	27 (45.8)	28 (36.4)	52 (45.2)	6 (35.3)
ICU admission	149 (7.0)	54 (7.9)	0.443	NS	12 (5.6)	19 (9.6)	6 (10.2)	9 (11.5)	6 (5.2)	2 (11.8)
Non-invasive mechanical ventilation	277 (13.7)	113 (17.2)	0.027	1.30 (1.03–1.66)	40 (19.5)	33 (17.2)	8 (14.3)	13 (17.1)	16 (14.2)	3 (18.8)
Invasive mechanical ventilation	127 (6.3)	41 (6.4)	0.927	NS	11 (5.5)	12 (6.5)	5 (9.4)	5 (7.0)	6 (5.4)	2 (12.5)
Heart failure	65 (3.2)	112 (17.2)	**< 0.001**	6.36 (4.61–8.76)	27 (13.5)	17 (9.1)	15 (26.3)	19 (24.7)	33 (29.2)	1 (6.3)
Acute renal failure	259 (12.6)	200 (30.3)	**< 0.001**	3.01 (2.4–3.72)	64 (31.5)	34 (17.8)	22 (37.9)	25 (32.5)	52 (45.6)	3 (18.8)
Respiratory insufficiency	879 (42.5)	431 (65.1)	**< 0.001**	2.52 (2.10–3.03)	136 (66.0)	118 (61.5)	42 (71.2)	49 (63.9)	76 (67.9)	10 (62.5)
Sepsis	226 (11.1)	130 (20.0)	**< 0.001**	2.00 (1.58–2.54)	48 (23.6)	33 (17.6)	8 (14.3)	15 (20.0)	24 (21.2)	2 (12.5)
SIRS	342 (17.0)	158 (24.5)	**< 0.001**	1.58 (1.28–1.96)	53 (10.6)	43 (8.6)	10 (2.0)	19 (3.8)	30 (26.5)	3 (20.0)
Embolic event	30 (1.5)	11 (1.7)	0.685	NS	12 (6.2)	6 (3.2)	2 (3.5)	3 (4.0)	4 (3.6)	0 (0.0)
Bleeding	28 (1.4)	27 (4.2)	**< 0.001**	3.12 (1.82–5.34)	3 (1.5)	3 (1.6)	0 (0.0)	2 (2.6)	3 (2.7)	0 (0.0)

*Comparing heart disease vs. none; ICU — intensive care unit; SIRS — systemic infammatory response syndrome; NS — non-significant

Table 4. Variables remaining in the model regarding mortality (multivariate analysis by Cox regression; backward: Wald)*.

Characteristic	Hazard ratio	95% confidence interval	P
Age 70 years or more	4.05	3.02–5.42	**< 0.001**
Hypertension	1.39	1.07–1.81	**0.013**
Any heart condition	1.62	1.29–2.03	**< 0.001**
Chronic renal failure	1.80	1.38–2.37	**< 0.001**
Any cancer	1.36	1.06–1.76	**0.016**
Any cerebrovascular condition	1.30	0.98–1.74	0.070

Variables included in the clinical model*: For modeling purposes, at this point only age, gender and relevant comorbidities were considered. Thus, those variables with p values< 0.05 regarding mortality were included in the multivariate analysis. The variables accepted were: age 70 years or more, gender, race, hypertension, dyslipemia, diabetes mellitus, obesity, chronic renal failure, any lung disease, cerebrovascular conditions, any heart disease, connective disease, any cancer, immunosuppressive condition, and any liver disease. The reference value was the absence of the precise condition. Previous medications were excluded for potential collinearity with the other mentioned variables (comorbidities)

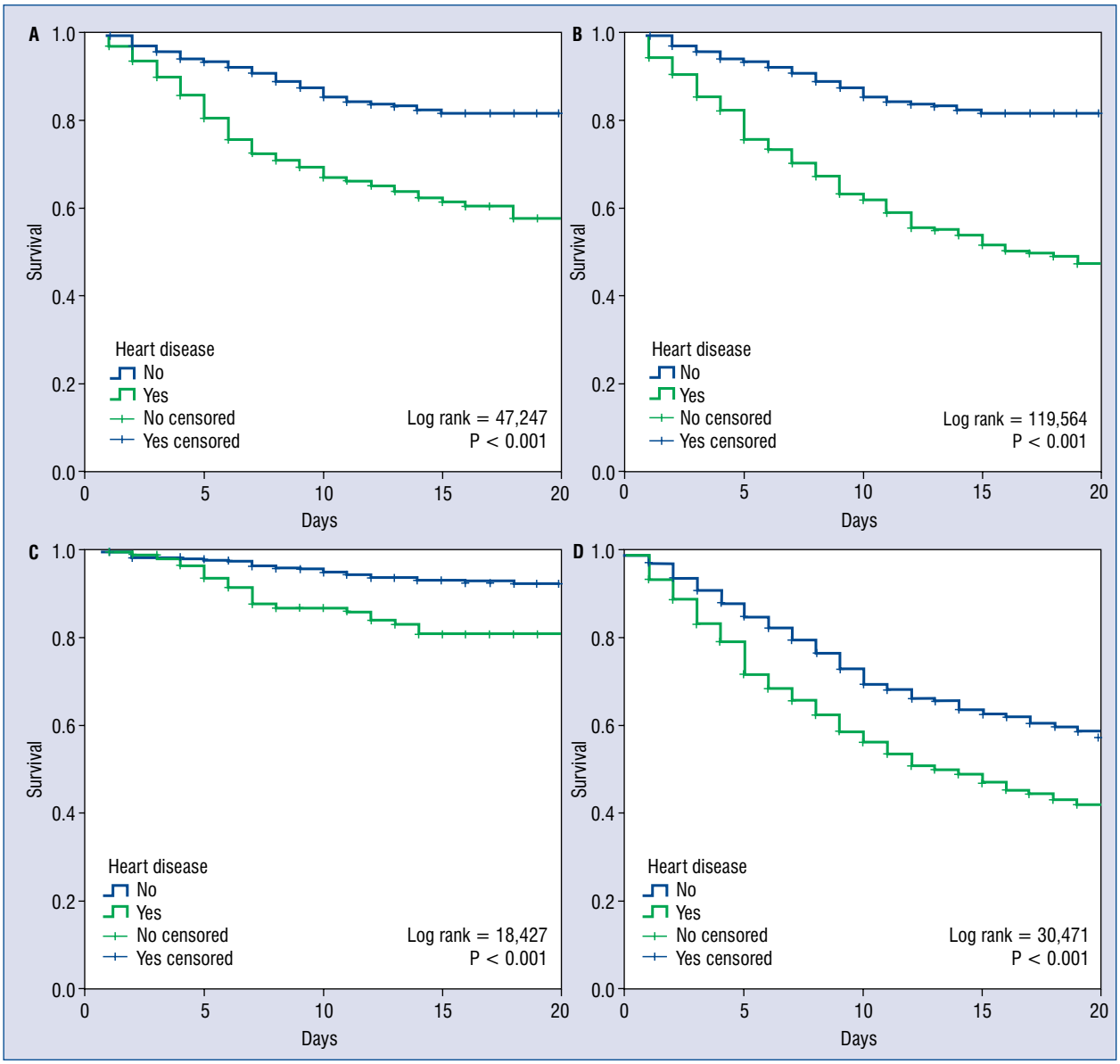
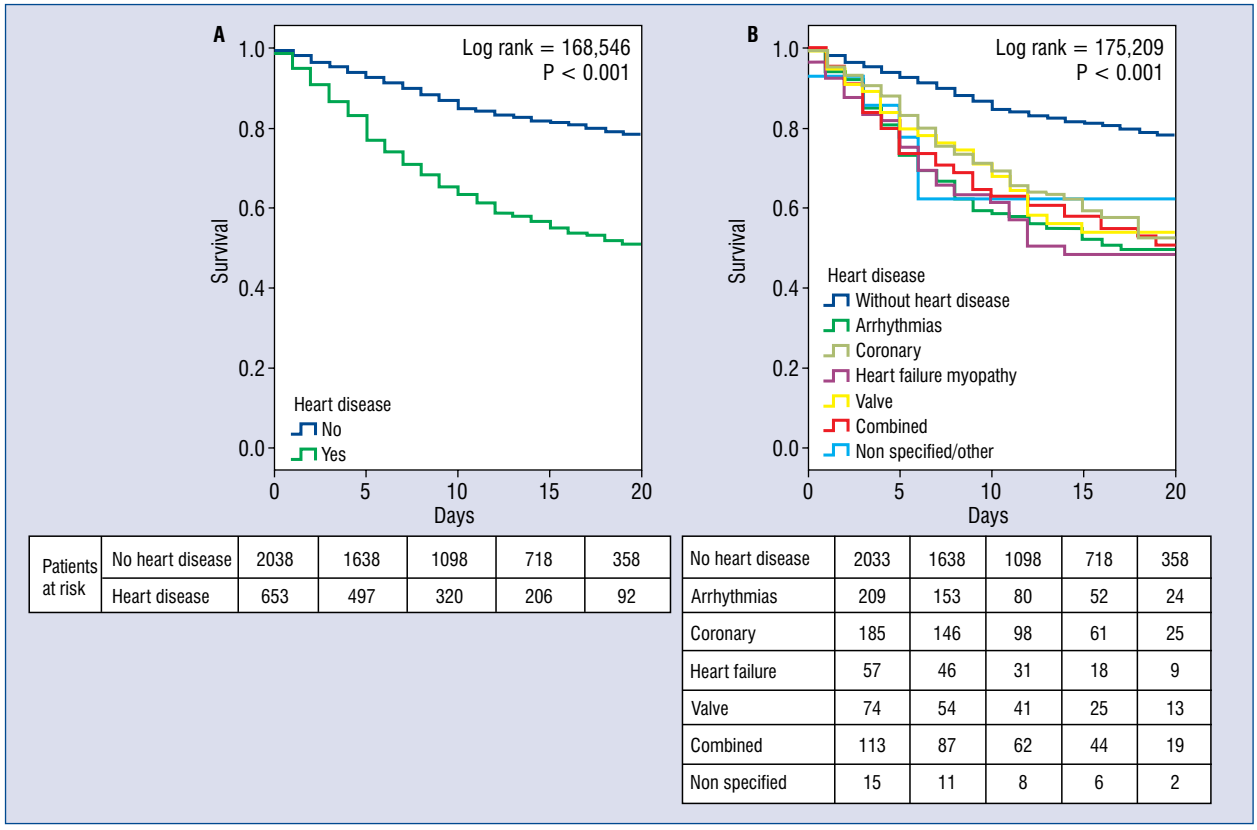


Figure 2. The Kaplan-Meier survival analysis stratifying for gender and age; T_0 = admission date; Considering only females (**A**) or males (**B**), less than 70 years old (**C**) and ≥ 70 years old (**D**).



Patients at risk						
	No heart disease	2038	1638	1098	718	358
	Heart disease	653	497	320	206	92

No heart disease	2033	1638	1098	718	358
Arrhythmias	209	153	80	52	24
Coronary	185	146	98	61	25
Heart failure	57	46	31	18	9
Valve	74	54	41	25	13
Combined	113	87	62	44	19
Non specified	15	11	8	6	2

Figure 3. Kaplan-Meier survival landmark analysis; T_0 = admission date; **A.** Assessing no heart disease vs. any type of heart condition; **B.** Same comparison but regarding type of heart diseases.

with any heart disease were clearly worse regarding mortality and other in-hospital complications. Overall, these findings suggest that preexisting heart problems marked a frailty point for COVID-19 patients warranting close surveillance, intensive management and were considered low threshold for admission.

On the other hand, at least 8.0% of COVID-19 patients suffered any kind of acute cardiac injury, but further analysis pointed out that the incidence of myocardial injury is much higher in ICU/severe patients, about 13-fold more than non-ICU/cardiac patients [9, 14].

Obviously, part of this frailty can be explained because of a different clinical profile (elderly, more cardiovascular risk factors, renal disease and other COVID-19 factors) among heart and no-heart disease cohort, but not entirely. Altogether, heart disease seems to be primarily a risk factor for bad prognosis in COVID-19 [15]. This way, usually cardiovascular involvement measured by troponin levels and cardiovascular complications are higher in heart disease patients, as we observed in HOPE.

This is expected because it has been reported that the COVID-19, which supposes a severe global aggression, could primarily involve the heart and cardiovascular systems. Several mechanisms are at play in this regard, either by direct or indirect mechanisms, in adults but also in infants [11, 15]. Anyway, elevated cardiac troponin seems to point toward a worse prognosis [16].

The viral (SARS-CoV-2) infection is prompted by the binding of the virus' spike protein to angiotensin-converting enzyme 2 (ACE2) [16]. The expression of this ACE2 in the heart has been described to be lower than that in other organs, such as the intestine and kidney, but higher than in the lung which serves as a main target organ of the virus, indicating a potential infection susceptibility of the human heart [17, 18]. In some specific circumstances, this heart susceptibility could be theoretically higher, since ACE2 expression has been reported to be significantly increased in patients with heart failure, post myocardial infarction and diabetes [18–20].

Some of the proposed pathophysiological mechanisms would be:

— Direct heart damage. Viral infection directly causes damage to cardiomyocyte. According to Oudit et al. [21], SARS-CoV viral RNA was detected in 35% of autopsied human heart samples from SARS-CoV infected patients during the past Toronto SARS outbreak. Of note, SARS-CoV and SARS-CoV-2 present high structural similarity between their receptor-binding domains [22]. Additionally, virus-infected cells can be injured, subsequently disturbing the micro-environment of the myocardium. SARS-CoV-2 infection in the human heart might attack pericytes as well, produce endothelial shedding and cause capillary dysfunction and induce micro-circulation disorders [15, 18]. In our series, the specific type of heart disease with higher mortality with frequent in-hospital complications was heart failure/myopathy suggesting that structurally weaker hearts could pose higher frailty.
— Hypoxia-induced myocardial injury. Because of lung pathology, pneumonia, respiratory distress syndrome, or the previously mentioned macro or micro vessel direct toxicity [15]. This condition, decreases the cell energy supply, leading to anaerobic fermentation, producing intracellular acidosis and oxygen free radicals to dismantle the phospholipid layer of the cell membrane. Moreover, hypoxia-induced influx of calcium also primes to injury and apoptosis of cardiac cells [15].
— Production of procoagulant factors predisposing to thrombosis, similar to the increase of myocardial infarctions reported after influenza infection [15, 23]. In fact, abnormal coagulation parameters and disseminated intravascular coagulation has been noted in COVID-19 [15] potentially contributing to damage the myocardium through thrombosis or ischemic events.
— Local inflammation. Although there are early reports of myocarditis [24], even fulminant, the exact mechanism is not clear, since lymphocyte infiltrates were not found in COVID-19 patients' autopsy [15, 25].
— Probably, a significant depletion and dysregulation of T cells can probably contribute to the cytokine storm (increased IL-2, IL-6, IL-10, GCSF, IFN-γ, MCP-1 and TNF-α) leading to the multiorgan damage setting depicted in COVID-19. Cardiac damage by this deleterious condition could be analogous to that reported in CAR-T (chimeric antigen receptor T cell therapies used in relapsing hematological malignancies).

Finally, last but not least, many specific drugs used for COVID-19 can cause cardiac side effects, arrhythmias or other cardiovascular disorders (hydroxychloroquine, antivirals, antibiotics, some immunomodulators). Different drug patterns were found when comparing patients with and without heart conditions. Therefore, during treatment of this condition, especially with the use of certain drugs, the risk of cardiac toxicity must be closely monitored, but to avoid depriving heart patients of potentially beneficial treatments. On the other side, special attention should be given to cardiovascular protective measures during management of COVID-19, since those patients have high risk of complications [13, 25–27]. In this aspect, the crucial role of ACEIs/ARBs needs to be taken into account [9, 10, 28, 29]. Despite under scientific review, preliminary data seem to warrant its maintenance in patients already on these meds at admission. Additionally, the present findings display a potential mortality benefit when maintaining these treatments in this setting (OR 0.34; 95% CI 0.20–0.49; $p < 0.001$; Table 4).

Limitations of the study

The main limitation is set by the study observational design and selecting only cases with higher risk profile or severe forms needing hospital admission. In addition, the definition of the variables, the specific type and degree of heart disease and the reporting for the events could present certain grade of variation among centers, countries and the precise moment in their pandemic curve. However, this would probably reflect the variation that medical practice has in real life. About the treatment applied, at all times it was decided by the attending physician. While these observations give us an overall idea of the treatment of the disease in this precise cohort, they do not produce information as robust as a clinical trial would do [30].

Thus, the only aim was to generate hypotheses; nevertheless, HOPE's present analysis probably reveals a pragmatic depiction of the outcomes and prognosis of patients with prevalent heart conditions who are admitted with COVID-19, a challenge for modern medicine [30, 31].

Conclusions

An underlying heart disease is an adverse prognostic factor for patients suffering COVID-19. Its presence could be related with varying clinical drug management and could benefit from main-

taining treatment with ACEIs or ARBs during in-hospital stay.

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HOPE COVID-19 Investigators, Scientific Committee And Collaborators: see **Supplementary Appendix**

Conflict of interest: None declared

References

1. WHO. WHO statement regarding cluster of pneumonia cases in Wuhan, China. https://www.who.int/china/news/detail/09-01-2020-who-statement-regarding-cluster-of-pneumonia-cases-in-wuhan-china (Accesed 3rd May 2020).
2. WHO. http://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/news/news/2020/3/who-announces-covid-19-outbreak-a-pandemic (Accesed 3rd May 2020).
3. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis. 2020; 20(5): 533–534, doi: 10.1016/S1473-3099(20)30120-1, indexed in Pubmed: 32087114.
4. Hulot JS. COVID-19 in patients with cardiovascular diseases. Arch Cardiovasc Dis. 2020; 113(4): 225–226, doi: 10.1016/j.acvd.2020.03.009, indexed in Pubmed: 32245656.
5. Shi S, Qin Mu, Shen Bo, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol. 2020; 5(7): 802–810, doi: 10.1001/jamacardio.2020.0950, indexed in Pubmed: 32211816.
6. Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID19). https://www.cdc.gov/coronavirus/2019ncov//needextraprecautions/peopleathigherrisk.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fspecific-groups% 2Fhigh-riskcomplications.html (Accessed 22 April 2020).
7. Madjid M, Solomon S, Vardeny O. Cardiac Implications of Novel Coronavirus (COVID-19). In: Committee ASaQ, editor. ACC Clinical Bulletin. USA: ACC; 2020.
8. Wang D, Hu Bo, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020; 323(11): 1061–1069, doi: 10.1001/jama.2020.1585, indexed in Pubmed: 32031570.
9. 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.
10. Bansal M. Cardiovascular disease and COVID-19. Diabetes Metab Syndr. 2020; 14(3): 247–250, doi: 10.1016/j.dsx.2020.03.013, indexed in Pubmed: 32247212.
11. Aghagoli G, Gallo Marin B, Soliman LB, et al. Cardiac involvement in COVID-19 patients: Risk factors, predictors, and complications: A review. J Card Surg. 2020; 35(6): 1302–1305, doi: 10.1111/jocs.14538, indexed in Pubmed: 32306491.
12. Holy EW, Jakob P, Manka R, et al. Impact of a nationwide COVID-19 lockdown on acute coronary syndrome referrals. Cardiol J. 2020; 27(5): 633–635, doi: 10.5603/CJ.a2020.0091, indexed in Pubmed: 32643140.
13. Núñez-Gil IJ, Estrada V, Fernández-Pérez C, et al. Health Outcome Predictive Evaluation for COVID 19 international registry (HOPE COVID-19), rationale and design. Contemp Clin Trials Commun. 2020; 20: 100654, doi: 10.1016/j.conctc.2020.100654, indexed in Pubmed: 32989425.
14. Li Bo, Yang J, Zhao F, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clin Res Cardiol. 2020; 109(5): 531–538, doi: 10.1007/s00392-020-01626-9, indexed in Pubmed: 32161990.
15. Zhu H, Rhee JW, Cheng P, et al. Correction to: cardiovascular complications in patients with COVID-19: consequences of viral toxicities and host immune response. Curr Cardiol Rep. 2020; 22(5): 36, doi: 10.1007/s11886-020-01302-4, indexed in Pubmed: 32405913.
16. Lorente-Ros A, Monteagudo Ruiz JM, Rincón LM, et al. Myocardial injury determination improves risk stratification and predicts mortality in COVID-19 patients. Cardiol J. 2020; 27(5): 489–496, doi: 10.5603/CJ.a2020.0089, indexed in Pubmed: 32589258.
17. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell. 2020; 181(2): 271–280.e8, doi: 10.1016/j.cell.2020.02.052, indexed in Pubmed: 32142651.
18. Chen Li, Hao G. The role of angiotensin-converting enzyme 2 in coronaviruses/influenza viruses and cardiovascular disease. Cardiovasc Res. 2020; 116(12): 1932–1936, doi: 10.1093/cvr/cvaa093, indexed in Pubmed: 32267499.
19. Burrell LM, Risvanis J, Kubota E, et al. Myocardial infarction increases ACE2 expression in rat and humans. Eur Heart J. 2005; 26(4): 369–75; discussion 322, doi: 10.1093/eurheartj/ehi114, indexed in Pubmed: 15671045.
20. Soro-Paavonen A, Gordin D, Forsblom C, et al. FinnDiane Study Group. Circulating ACE2 activity is increased in patients with type 1 diabetes and vascular complications. J Hypertens. 2012; 30(2): 375–383, doi: 10.1097/HJH.0b013e32834f04b6, indexed in Pubmed: 22179088.
21. Oudit GY, Kassiri Z, Jiang C, et al. SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. Eur J Clin Invest. 2009; 39(7): 618–625, doi: 10.1111/j.1365-2362.2009.02153.x, indexed in Pubmed: 19453650.
22. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020; 395(10224): 565–574, doi: 10.1016/s0140-6736(20)30251-8.
23. Waxman DA, Kanzaria HK, Schriger DL. Acute myocardial infarction after laboratory-confirmed influenza infection. N Engl J Med. 2018; 378(26): 2538–2539, doi: 10.1056/NEJMc1805679, indexed in Pubmed: 29952170.
24. Shi S, Qin Mu, Shen Bo, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan,

China. JAMA Cardiol. 2020; 5(7): 802–810, doi: 10.1001/jamacardio.2020.0950, indexed in Pubmed: 32211816.
25. Luo W, Hong Y, Gou J, et al. Clinical pathology of critical patient with coronavirus pneumonia (COVID-19). Pre-Prints. 2020: 1–14.
26. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020; 323(13): 1239–1242, doi: 10.1001/jama.2020.2648, indexed in Pubmed: 32091533.
27. Shi S, Qin Mu, Shen Bo, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol. 2020; 5(7): 802–810, doi: 10.1001/jamacardio.2020.0950, indexed in Pubmed: 32211816.
28. Duffy EY, Cainzos-Achirica M, Michos ED. Primary and secondary prevention of cardiovascular disease in the era of the coronavirus pandemic. Circulation. 2020; 141(24): 1943–1945, doi: 10.1161/CIRCULATIONAHA.120.047194, indexed in Pubmed: 32310675.
29. Huang Z, Jiang Y, Chen J, et al. Inhibitors of the renin-angiotensin system: The potential role in the pathogenesis of COVID-19. Cardiol J. 2020; 27(2): 171–174, doi: 10.5603/CJ.a2020.0056, indexed in Pubmed: 32286678.
30. Kowalik MM, Trzonkowski P, Łasińska-Kowara M, et al. COVID-19 — Toward a comprehensive understanding of the disease. Cardiol J. 2020; 27(2): 99–114, doi: 10.5603/CJ.a2020.0065, indexed in Pubmed: 32378729.
31. Dzieciatkowski T, Szarpak L, Filipiak KJ, et al. COVID-19 challenge for modern medicine. Cardiol J. 2020; 27(2): 175–183, doi: 10.5603/CJ.a2020.0055, indexed in Pubmed: 32286679.

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Single-center five-year outcomes after interventional edge-to-edge repair of the mitral valve

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Abstract

Background: *The MitraClip procedure was established as a therapeutic alternative to mitral valve surgery for symptomatic patients with severe mitral regurgitation (MR) at prohibitive surgical risk. In this study, the aim was to evaluate 5-year outcomes after MitraClip.*

Methods: *Consecutive patients undergoing the MitraClip system were prospectively included. All patients underwent clinical follow-up and transthoracic echocardiography.*

Results: *Two hundred sixty-five patients (age: 81.4 ± 8.1 years, 46.7% female, logistic EuroSCORE: 19.7 ± 16.7%) with symptomatic MR (60.5% secondary MR [sMR]). Although high procedural success of 91.3% was found, patients with primary MR (pMR) had a higher rate of procedural failure (sMR: 3.1%, pMR: 8.6%; p = 0.04). Five years after the MitraClip procedure, the majority of patients presented with reduced symptoms and improved functional capacity (functional NYHA class: p = 0.0001; 6 minutes walking test: p = 0.04). Sustained MR reduction (≤ grade 2) was found in 74% of patients, and right ventricular (RV) function was significantly increased (p = 0.03). Systolic pulmonary artery pressure (sPAP) was significantly reduced during follow-up only in sMR patients (p = 0.05, p = 0.3). Despite a pronounced clinical and echocardiographical amelioration and low interventional failure, 5-year mortality was significantly higher in patients with sMR (p = 0.05). The baseline level of creatinine (HR: 0.695), sPAP (HR: 0.96) and mean mitral valve gradient (MVG) (HR: 0.82) were found to be independent predictors for poor functional outcome and mortality.*

Conclusions: *Transcatheter mitral valve repair with the MitraClip system showed low complication rates and sustained MR reduction with improved RV function and sPAP 5 years after the procedure was found in all patients, predominantly in patients with sMR. Despite pronounced functional amelioration with low procedure failure, sMR patients had higher 5-year mortality and worse outcomes. Baseline creatinine, MVG, and sPAP were found to be independent predictors of poor functional outcomes and 5-year mortality.* (Cardiol J 2021; 28, 2: 215–222)

Key words: MitraClip, transcatheter mitral valve repair, long-term outcomes, mitral regurgitation

Introduction

Mitral regurgitation (MR) is the second most frequent valve disease, with an increasing prevalence in elderly (> 75 years) patients, and is related to reduced functional capacity and impaired quality of life. Transcatheter mitral valve repair (TMVR) with the MitraClip system (Abbot Vascular, Inc.,

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Santa Clara, California) is a therapeutic alternative to mitral valve (MV) surgery in symptomatic patients with moderate to severe MR at prohibitive surgical risk [1–3]. TMVR with the MitraClip procedure can be successfully performed in patients with secondary MR (sMR) and primary MR (pMR) if mitral valve (MV) anatomy is suitable [4]. Its clinical efficacy and safety have been proven in a large number of patients [4–6].

Acute procedural success rates are reported to be up to 99% and are followed by symptomatic improvement in about 80% of cases [7].

A high baseline systolic pulmonary artery pressure (sPAP), an elevated baseline mitral valve mean gradient (MVG), concomitant chronic kidney disease, anemia, peripheral artery disease, and tricuspid regurgitation have been previously reported as independent predictors of poor short-term outcomes after MitraClip procedures [8, 9, 10].

Although more than 70,000 patients have undergone MitraClip procedures to date, data on long-term outcome and durability of MR reduction are limited, and parameters predicting adverse long-term outcomes are not well defined.

The objectives of the present study were to evaluate functional and echocardiographic long-term outcomes 5 years subsequent to transcatheter edge-to-edge mitral valve repair with the MitraClip procedure in a single high-volume center and assess predictors of poor outcomes.

Methods

Patients and endpoints

In this single-center study, consecutive patients undergoing TMVR with the MitraClip system were prospectively included. From February 2011 to February 2014 symptomatic (New York Heart Association [NYHA] functional class > II), and surgical high-risk patients with moderate-to-severe MR were evaluated for TMVR. All patients underwent TMVR following heart team judgement according to surgical high-risk (logistic EuroSCORE II > 10%).

All patients underwent clinical and echocardiographic examinations before and 5 years after the MitraClip procedure.

According to Mitral Valve Academic Research Consortium (MVARC) definitions, the primary endpoint was defined as all-cause mortality [11]. The secondary endpoint was an improvement in functional capacity: NYHA functional class at follow-up was < II; 25% amelioration in exercise capacity (six minute walk test [6MWT]).

The study was authorized by the local ethics committee and in accordance with the Declaration of Helsinki. All patients signed written, informed consent before study inclusion.

Echocardiography and follow-up assessment

Echocardiographic assessment before and after TMVR was done following current recommendations and guidelines which included a comprehensive echocardiography [4, 12]. The severity of MR was graded using the radius of proximal isovelocity surface area (PISA radius), effective regurgitant orifice area (EROA), as well as vena contracta (VC) width and regurgitant volume. EROA and regurgitation volume were calculated using the semi-quantitative PISA-method [13]. The echocardiographic studies were performed with a commercially available echocardiographic system (iE 33, Philips Medical Systems, Andover, Massachusetts) and echocardiography probes (X5-1, X7-2t) allowing acquisition of two- (2D) and three-dimensional (3D) data sets. sPAP was estimated from Doppler-based tricuspid regurgitation systolic peak velocity according to use of the modified Bernoulli equation (Delta-pressure: 4 × velocity) to approximate differences of pressure between the right ventricle and the right atrium.

The echocardiographer who performed follow-up evaluation was blinded to procedural outcomes and patient characteristics. Trained personnel carried out clinical follow-up evaluation, unattended by the interventionalists or procedural echocardiographer.

Interventional edge-to-edge repair of MR

Procedural details of TMVR with the MitraClip system have been described previously [14, 15]. During the MitraClip procedure, acute changes of MR severity were assessed by intraprocedural transesophageal echocardiography as supposed by Armstrong and Foster [16], and Wunderlich and Siegel [17]. Acute procedural success was defined as a reduction of MR by at least one grade having a residual MR < 2+. The number of clips required for procedural success was left to the discretion of the treating physician. Before the clip release, echocardiography was performed to exclude clinically relevant MV stenosis (mean MVG > 5 mmHg).

Statistical analysis

Normal distribution of continuous variables was examined using the Kolmogorov–Smirnov test. Continuous data were expressed as mean values ±

Table 1. Baseline demographical characteristics.

	All patients (n = 265)	sMR (n = 160)	pMR (n = 105)	P
Gender (female)	46.7%	40.9%	56.7%	0.1
Age [years]	81.4 ± 8.1	79.1 ± 8.7	84.6 ± 5.7	0.1
BMI [kg/m^2]	25.4 ± 4.2	26 ± 4.6	24.5 ± 3.4	0.1
Logistic EuroSCORE [%]	19.7 ± 16.7	21.4 ± 17.5	16.9 ± 15.2	0.3
NYHA ≥ II	100%	100%	100%	1
NYHA III	68.1%	55.8%	86.2%	
NYHA IV	31.9%	44.2%	13.8%	0.06
Chronic heart failure	70.7%	81.4%	66.7%	0.1
Coronary heart diesease	71.4%	75.9%	65%	0.3
Arterial hypertension	66.7%	70.5%	61.3%	0.3
History of stroke	4%	2.3%	6.5%	0.4
Peripheral artery diesease	10.7%	11.4%	9.7%	0.6
Diabetes mellitus	34.7%	45.5%	29.4%	0.09
Hyperlipidemia	36%	45.5%	31.6%	0.1
Nicotine	24%	25%	22.6%	0.5
Creatinine [mg/dL]	1.5 ± 0.8	1.6 ± 0.9	1.4 ± 0.7	0.2

sMR — secondary mitral regurgitation; pMR — primary mitral regurgitation; BMI — body mass index; NYHA — New York Heart Association functional classification

standard deviation. The Student two-sample t-test or the Mann-Whitney-U test was performed to compare continuous variables. The Fisher exact test or χ^2 test was used to compare categorical data. Two-tailed p-values were considered to be significant if ranging below 0.05. Univariate analysis was performed to assess the impact of etiology of MR on clinical outcomes. The predictors of 5-year mortality were estimated employing the Cox proportional regression analysis. Survival and cumulative incidence of re-do in groups were compared using the Log-rank test and were estimated with the Kaplan-Meier curve. The regression and receiver operating characteristic (ROC) analysis were performed to determine independent predictors with cut-off values of functional outcomes and mortality.

Statistics were performed using SPSS for Windows (PASW statistic, Version 20.0.0.0, SPSS Inc., Chicago, Illinois, USA).

Results

Baseline data and procedural outcomes

Two hundred sixty-five consecutive, surgical high-risk patients (81.4 ± 8.1 years, 46.7% female, Logistic EuroSCORE: 19.7 ± 6.7%, 60.5% sMR) underwent TMVR with the MitraClip system, and the majority of patients (88%, n = 233) completed a 5-year follow-up including physical, laboratory and echocardiographical examinations. Patients lost to follow-up (n = 32) were contacted concerning quality of life, complaints and hospitalization via telephone.

The baseline characteristics are presented in Table 1. There were no differences between groups in demographic baseline characteristics. However, at baseline, patients with sMR presented worse functional capacity (6MWT: 253.3 ± 107.7 m vs. 267.1 ± 160.2 m; p = 0.2; NYHA > III: 44.2% vs. 13.8%; p = 0.06) compared to patients with pMR.

The procedure was successfully performed in 242 (91.3%) patients with implantation of more than one clip in 32% of cases. Six MitraClip procedures were aborted due to relevant MV stenosis (MVG > 5 mmHg) after the clip closure. Four of those patients were treated for pMR. 13 procedures were aborted due to irreducible MR.

Of note, there was no procedural-related mortality, 10 (23.8%) patients had minor bleeding, and one patient had pericardial tamponade, which could be effectively treated with pericardiocentesis. All acute complications could be successfully managed before discharge. Overall, interventional failure rates were low, however, patients with pMR showed statistically significant higher interventional failure rates (pMR: 8.6%, sMR: 3.1%; p = 0.04).

Table 2. Baseline echocardiographical characteristics.

	All patients (n=265)	sMR (n = 160)	pMR (n = 105)	P
LVEDV [mL]	154.4 ± 59	165.3 ± 62.6	135.8 ± 49.2	0.03
LVESV [mL]	87.3 ± 52.4	106.4 ± 53.3	59.3 ± 36.6	0.0001
LVEF [%]	46.3 ± 17.4	38.3 ± 14.1	58.1 ± 15	0.0001
sPAP [mmHg]	47.5 ± 15	46.2 ± 15.7	50 ± 14	0.4
MV gradient [mmHg]	1.6 ± 0.9	1.4 ± 0.8	1.8 ± 1	0.03
Severity of MR	3.2 ± 0.4	3.1 ± 0.3	3.4 ± 0.5	0.1
MR grade III	79.7%	90.9%	63.3%	0.02
MR grade IV	18.9%	6.8%	36.7%	0.03
E/A ratio	2.4 ± 1	2.6 ± 1.2	2.2 ± 0.8	0.2
PISA radius [cm]	0.9 ± 0.2	0.8 ± 0.2	0.9 ± 0.3	0.2
VC width [cm]	1.4 ± 4.4	1.5 ± 5.3	1.2 ± 2.3	0.7
EROA [cm^2]	0.6 ± 0.3	0.5 ± 0.1	0.6 ± 0.4	0.3
Regurgitation volume [mL]	54.4 ± 16	53.2 ± 16	56.3 ± 16.2	0.4
Tricuspid regurgitation	2.1 ± 0.8	2.1 ± 0.8	2 ± 0.8	0.6
TAPSE [cm]	1.8 ± 0.4	1.7 ± 0.4	2 ± 0.2	0.09

sMR — secondary mitral regurgitation; pMR — primary mitral regurgitation; LVEDV — left ventricular end-diastolic volume; LVESV — left ventricular end-systolic volume; LVEF — left ventricular ejection fraction; sPAP — systolic pulmonary artery pressure; MV — mitral valve: MR — mitral regurgitation; PISA — proximal isovelocity surface area; VC — vena contracta; EROA — effective regurgitant orifice area; TAPSE — tricuspid annular systolic excursion

During 5-year follow-up three patients underwent surgery for recurrent MR (pMR: 1.9%, sMR: 0.6%; p = 0.3), 16 patients required a second clipping (sMR: 6.8%, pMR: 4.7%, p = 0.5) and four patients were treated with additional catheter-based approaches (Carillon®, Cardiac Dimension, Kirkland, The USA; Cardioband®, Edwards Lifesciences, United Kingdom) due to recurrent severe MR and decompensated heart failure (sMR: 1.8%, pMR: 0.9%, p = 0.6) (**Suppl. Fig. 4**).

Echocardiographic measures at baseline and five-year follow-up

Concerning baseline echocardiographic characteristics, there were no significant differences in MR defining parameters and sPAP between sMR and pMR. Patients with sMR had larger baseline left ventricle (LV) volumes (LVEDV: 165.3 ± 62.6 mL, 135.8 ± 49.2 mL; p = 0.03; LVESV: 106.4 ± ± 53.3 mL, 59.3 ± 36.6 mL; p = 0.001) and significantly impaired baseline LV systolic function (38.3 ± ± 14.1%, 58.1 ± 15%; p = 0.0001). Patients with sMR showed impaired right ventricle (RV) function at baseline as well (TAPSE: 1.7 ± 0.4 cm, 2 ± 0.2 cm; p = 0.09) (Table 2).

At 5-year follow-up a sustained reduction of MR (MR ≤ 2) was found in 74% of patients (sMR: 77%, pMR: 71.5%; p = 0.9) (Fig. 1). There were no significant changes in LV volumes ($LVEDV_{sMR}$: 162.4 ± ± 56.7 mL, 154.5 ± 66.9 mL; p = 0.5; $LVEDV_{pMR}$: 127.8 ± 47.3 mL, 116.6 ± 26.4 mL; p = 0.3; $LVESV_{sMR}$: 105.2 ± 45.5 mL, 99.6 ± 57.8 mL; p = 0.6; $LVESV_{pMR}$: 56.2 ± 34.5 mL, 51.6 ± 20.2 mL; p = 0.5). Left ventricular ejection fraction (LVEF) was not significantly changed 5 years after the MitraClip procedure (EF_{sMR} 36.9 ± 12.6%, 38.7 ± ± 13.6%, p = 0.5; EF_{pMR} 58.1 ± 12.2%, 58.4 ± 9.7%, p = 0.9). In sMR patients, sPAP was significantly reduced at follow-up (50 ± 17.4 mmHg, 39.3 ±

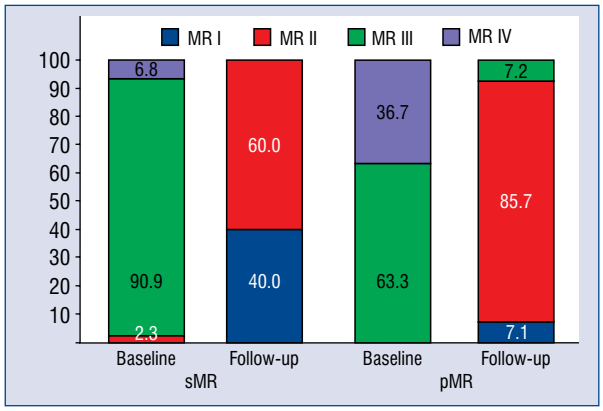

Figure 1. Reduction of mitral regurgitation (MR) at 5-year follow-up; pMR — primary mitral regurgitation; sMR — secondary mitral regurgitation.

Table 3. Echocardiographical and clinical outcomes at follow-up.

	Baseline	Follow-up	P
LVEDV [mL]	150 ± 55.5	140.9 ± 58.4	0.3
sMR	162.4 ± 56.7	154.5 ± 66.9	0.5
pMR	127.8 ± 47.3	116.5 ± 26.4	0.3
LVESV [mL]	87.6 ± 47.7	82.4 ± 52.8	0.4
sMR	105.2 ± 45.5	99.6 ± 57.8	0.6
pMR	56.2 ± 34.5	51.6 ± 20.2	0.5
LVEF [%]	44.5 ± 16.1	45.8 ± 15.5	0.5
sMR	36.9 ± 12.6	38.7 ± 13.6	0.5
pMR	58.1 ± 12.2	58.4 ± 9.7	0.9
IVSDD [cm]	1.2 ± 0.3	1 ± 0.2	0.04
sMR	1.2 ± 0.3	1 ± 0.2	0.04
pMR	1.3 ± 0.3	1.2 ± 0.3	0.3
MR	3.1 ± 0.4	1.7 ± 0.5	0.0001
sMR	3 ± 0.3	1.6 ± 0.5	0.0001
pMR	3.4 ± 0.5	2 ± 0.4	0.0001
MR ≤ II [%]	0	97.4	0.0001
sMR	0	100	0.0001
pMR	0	92.9	0.0001
MR > II [%]	100	2.6	0.0001
sMR	100	0	0.0001
pMR	100	7.1	0.0001
Mitral gradient [mmHg]	1.4 ± 0.8	3.5 ± 2.9	0.0001
sMR	1.4 ± 0.8	2.8 ± 1.3	0.0001
pMR	1.5 ± 0.9	4.8 ± 4.5	0.02
TAPSE [cm]	1.8 ± 0.3	1.9 ± 0.4	0.008
sMR	1.7 ± 0.4	1.9 ± 0.4	0.03
pMR	2 ± 0.2	2.1 ± 0.4	0.5
sPAP [mmHg]	49.7 ± 17.3	40.7 ± 17.5	0.02
sMR	50 ± 17.4	39.3 ± 17.3	0.05
pMR	49.4 ± 18.3	41.6 ± 18.7	0.3
NYHA functional class	3.4 ± 0.5	2.2 ± 0.9	0.0001
sMR	3.5 ± 0.5	2.1 ± 0.9	0.0001
pMR	3.2 ± 0.4	2.2 ± 1	0.004
6MWT [m]	243.8 ± 121.3	298.1 ± 118.6	0.04
sMR	235.3 ± 107.7	305.3 ± 123.1	0.03
pMR	267.1 ± 160.2	278.6 ± 111.9	0.8
NT-proBNP [pg/mL]	5987.3 ± 9989.3	4614.7 ± 5596.6	0.5
sMR	3844.7 ± 3099.4	4581.1 ± 4356.1	0.2
pMR	10510.6 ± 16770.4	4685.8 ± 7939.8	0.4

sMR — secondary mitral regurgitation; pMR — primary mitral regurgitation; LVEDV — left ventricular end-diastolic volume; LVESV — left ventricular end-systolic volume; LVEF — left ventricular ejection fraction; IVSDD — diastolic interventricular septum diameter; MR — mitral regurgitation; TAPSE — tricuspid annular systolic excursion; sPAP — systolic pulmonary artery pressure; NYHA — New York Heart Association; 6MWT — six minutes walking test; NTpro-BNP — N-terminal pro-B-type natriuretic peptide

± 17.3 mmHg, p = 0.05), however, not significantly in pMR patients (49.4 ± 18.3 mmHg; 41.6 ± 18.7 mmHg, p = 0.3) (Table 3). RV function increased significantly just in patients with sMR (1.7 ± 0.4 cm, 1.9 ± 0.4 cm, p = 0.03; 2 ± 0.2 cm, 2.1 ± 0.4 cm, p = 0.5). MVG significantly increased after

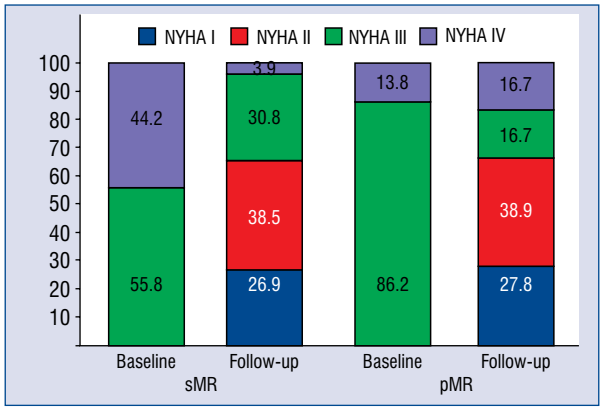

Figure 2. Changes in functional New York Heart Association (NYHA) class; pMR — primary mitral regurgitation; sMR — secondary mitral regurgitation.

MitraClip procedures (1.4 ± 0.8 mmHg, 3.5 ± 2.9 mmHg; p = 0.001) without incidence of clinically relevant MV stenosis.

Clinical outcomes and predictors of outcome

At 5-year follow-up the majority of patients (65.4%) presented with improved heart failure related symptoms (functional NYHA class ≤ II) and improved exercise tolerance (6MWT: 243.8 ± 121.3 m, 298.1 ± 118.6 m; p = 0.04). The functional capacity at follow-up did not differ between the groups (NYHA > II: sMR 34.6%, pMR 33.3%; p = 0.6). However, functional amelioration was more pronounced in sMR patients as assessed by functional NYHA class (sMR: 3.5 ± 0.5, 2.1 ± 0.9, p = 0.0001; pMR: 3.2 ± 0.4, 2.2 ± 1; p = 0.04) (Fig. 2) and 6MWT (sMR: 235.3 ± 107.7 m, 305.3 ± ±123.1 m; p = 0.03; pMR: 267.1 ± 160.2 m, 278.6 ± ± 111.9 m; p = 0.8). Decreased levels of N-terminal pro-B-type natriuretic peptide were documented in both groups (sMR: 7635.3 ± 13639.8 pg/mL, 3943.4 ± ± 4190.5 pg/mL; p = 0.01; pMR: 7157.2 ± 10920 pg/mL, 4313.7 ± 7574.8 pg/mL; p = 0.02) (Table 3).

All-cause mortality was 16% at 5-year follow-up and was significantly higher in patients with sMR (sMR: 19%, pMR: 10%; p = 0.05) (**Suppl. Table 1, Suppl. Fig. 3**).

According to the ROC analysis baseline sPAP > 45 mmHg, baseline MVG > 1.5 mmHg and baseline level of creatinine > 2 mg/dL were found to be independent predictors for all-cause mortality at 5-year follow-up. Furthermore, baseline level of creatinine (cut-off value: 1.33 mg/dL; HR: 0.695), baseline sPAP (cut-off value: 50 mmHg; HR: 0.96) and baseline MVG (cut-off value: 1.4 mmHg; HR: 0.82) were used as independent predictors for poor functional outcomes at 5-year follow-up (**Suppl. Figs. 1, 2**).

Discussion

The main findings of the present study are as follows: (1) Acute procedural failure was higher in pMR patients. (2) A majority of patients (74%) showed sustained MR reduction, increased RV function and reduced sPAP at 5-year follow-up. (3) Despite pronounced clinical and echocardiographic amelioration at follow-up and lower interventional failure rates, all-cause 5-year mortality was significantly higher in sMR patients. Baseline levels of creatinine > 2 mg/dL, MVG > 1.5 mmHg and sPAP > 50 mmHg were independent predictors of the 5-year mortality and poor functional outcomes.

Survival and re-intervention rates

Mortality after TMVR with the MitraClip device has been evaluated previously in different studies. Toggweiler et al. [18] found in 75 patients, a patient mortality of 4% at 30 days, 9% at 1 year and 25% (sMR 28%, pMR 18%) at 2 years after the MitraClip procedure. Comparable data were presented in 304 patients by Capodanno et al. [19] (4% at 30 days, 11% at 1-year, and 19% at 2-years). The EVEREST II study found a 20% 5-year mortality without statistical difference between MR etiologies [20].

In line with those studies, sustained MR reduction was found with improved functional capacity and quality of life 5 years after the MitraClip procedure. Although patients in the present study were considerably older (mean age: 81 years), they had more often sMR and in higher baseline NYHA functional classes, long-term mortality rates (16%) were comparable to the cited studies. In contrast to EVEREST II, higher mortality in patients with sMR was found despite noticeable improvement of functional capacity at follow-up. Of note, in the early EVEREST studies, echocardiographic feasibility criterias were far more restrictive, and the majority of patients were treated for pMR, which might account for different acute and long-term procedural success rates.

Higher all-cause mortality at follow-up in sMR patients was found, and might be explained by the advanced age of sMR patients, a more impaired baseline LV and RV function compared to pMR patients. Similar findings were presented in the

COAPT (Cardiovascular Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial. In this trial, Stone et al. [21] found 29.1% 2-year mortality in 302 patients with sMR despite being younger patients, was relevantly higher than the present collective. This might be explained through the present findings "predictors of mortality" such as impaired baseline renal function (creatinine clearance < 51 mL/min), advanced systolic heart failure (LVEF 31%), and elevated RV systolic pressure (> 44 mmHg).

Buzzatti et al. [22] showed higher 5-year mortality (about 50%) with good mid-term results including reduction of MR and improved symptoms in 339 patients with relevant MR. In line with current results, they found pronouncedly worse outcomes and higher mortality in patients with secondary MR associated with worse LV remodelling and function.

Predictors of adverse outcome

Azzalini et al. [23] showed that an impaired LV function was associated with increased mortality in 77 patients with sMR 1 year after the MitraClip procedure. This finding is in line with the present data. A higher 5-year mortality in sMR patients with reduced baseline LV function was found (EF < 40%) compared to pMR patients with a baseline LVEF > 55%.

Another independent marker for secondary endpoint was the baseline level of creatinine (> 2 mg/dL) in the current study. This finding is supported by a study from Ohno et al. [24]. They found a significant adverse effect of concomitant chronic kidney disease on MR reduction, functional capacity (NYHA functional class), survival and frequency of re-repair in 214 patients with severe MR one year after the MitraClip procedure.

Toggweiler et al. [18] (baseline MVG > 3 mmHg) and Neuss et al. [9] (post-procedural MVG > 5 mmHg) showed a devastating impact of higher MVG on clinical outcomes and procedural success. In concordance with those results, baseline MVG (> 1.5 mmHg) as an independent predictor for both primary and secondary endpoints at 5-year follow-up was found in the present study.

Moreover, Matsumoto et al. [10] found that pre-existing pulmonary hypertension was a strong predictor of higher all-cause mortality 12 months after the MitraClip procedure. The association between worse outcomes and advanced heart disease and symptoms have been presented by Buzzatti et al. [22] in more than 300 patients with relevant MR at 5-year follow-up. The cited study validates present findings; elevated baseline sPAP values are an independent predictor of (> 45 mmHg) adverse outcomes and (> 50 mmHg) all-cause mortality at 5-year follow-up.

Limitations of the study

This single-center retrospective study has several limitations. Data was reported from a single-center experience, and all echocardiographic analyses were not verified by an independent core lab. Furthermore, the 5-year follow-up was sufficiently completed in 233 (88%) patients. Because of this, the present results should be proven in multi-center studies with a larger patient collective.

Conclusions

Transcatheter mitral valve repair with the MitraClip procedure was found to be safe, lead to sustained MR reduction, and increase RV function during 5 years subsequent to the procedure. Despite pronounced functional and echocardiographical amelioration and lower procedural failure, sMR patients showed a higher all-cause mortality at 5-year follow-up compared to patients with pMR. Elevated baseline creatinine, baseline levels of MVG and baseline sPAP were associated with poor functional outcome and high all-cause mortality 5-year after MitraClip.

Conflict of interest: None declared

References

1. Baldus S, Schillinger W, Franzen O, et al. MitraClip therapy in daily clinical practice: initial results from the German transcatheter mitral valve interventions (TRAMI) registry. Eur J Heart Fail. 2012; 14(9): 1050–1055, doi: 10.1093/eurjhf/hfs079, indexed in Pubmed: 22685268.
2. Franzen O, van der Heyden J, Baldus S, et al. MitraClip® therapy in patients with end-stage systolic heart failure. Eur J Heart Fail. 2011; 13(5): 569–576, doi: 10.1093/eurjhf/hfr029, indexed in Pubmed: 21471146.
3. Garatti A, Castelvecchio S, Bandera F, et al. Mitraclip procedure as a bridge therapy in a patient with heart failure listed for heart transplantation. Ann Thorac Surg. 2015; 99(5): 1796–1799, doi: 10.1016/j.athoracsur.2014.07.079, indexed in Pubmed: 25952210.
4. Silvestry FE, Rodriguez LL, Herrmann HC, et al. Echocardiographic guidance and assessment of percutaneous repair for mitral regurgitation with the Evalve MitraClip: lessons learned from EVEREST I. J Am Soc Echocardiogr. 2007; 20(10): 1131–1140, doi: 10.1016/j.echo.2007.02.003, indexed in Pubmed: 17570634.
5. Feldman T, Kar S, Rinaldi M, et al. Percutaneous mitral repair with the MitraClip system: safety and midterm durability in the initial EVEREST (Endovascular Valve Edge-to-Edge REpair Study) cohort. J Am Coll Cardiol. 2009; 54(8): 686–694, doi: 10.1016/j.jacc.2009.03.077, indexed in Pubmed: 19679246.

6. Mauri L, Garg P, Massaro JM, et al. The EVEREST II Trial: design and rationale for a randomized study of the evalve mitraclip system compared with mitral valve surgery for mitral regurgitation. Am Heart J. 2010; 160(1): 23–29, doi: 10.1016/j.ahj.2010.04.009, indexed in Pubmed: 20598968.
7. Mauri L, Foster E, Glower DD, et al. 4-year results of a randomized controlled trial of percutaneous repair versus surgery for mitral regurgitation. J Am Coll Cardiol. 2013; 62(4): 317–328, doi: 10.1016/j.jacc.2013.04.030, indexed in Pubmed: 23665364.
8. Puls M, Lubos E, Boekstegers P, et al. One-year outcomes and predictors of mortality after MitraClip therapy in contemporary clinical practice: results from the German transcatheter mitral valve interventions registry. Eur Heart J. 2016; 37(8): 703–712, doi: 10.1093/eurheartj/ehv627, indexed in Pubmed: 26614824.
9. Neuss M, Schau T, Isotani A, et al. Elevated mitral valve pressure gradient after mitraclip implantation deteriorates long-term outcome in patients with severe mitral regurgitation and severe heart failure. JACC Cardiovasc Interv. 2017; 10(9): 931–939, doi: 10.1016/j.jcin.2016.12.280, indexed in Pubmed: 28473116.
10. Matsumoto T, Nakamura M, Yeow WL, et al. Impact of pulmonary hypertension on outcomes in patients with functional mitral regurgitation undergoing percutaneous edge-to-edge repair. Am J Cardiol. 2014; 114(11): 1735–1739, doi: 10.1016/j.amjcard.2014.08.044, indexed in Pubmed: 25306555.
11. Stone GW, Adams DH, Abraham WT, et al. Clinical Trial Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and Replacement: Part 1: Clinical Trial Design Principles: A Consensus Document From the Mitral Valve Academic Research Consortium. J Am Coll Cardiol. 2015; 66(3): 278–307, doi: 10.1016/j.jacc.2015.05.046, indexed in Pubmed: 26184622.
12. Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr. 2003; 16(7): 777–802, doi: 10.1016/S0894-7317(03)00335-3, indexed in Pubmed: 12835667.
13. Ashikhmina E, Shook D, Cobey F, et al. Three-dimensional versus two-dimensional echocardiographic assessment of functional mitral regurgitation proximal isovelocity surface area. Anesth Analg. 2015; 120(3): 534–542, doi: 10.1213/ANE.0000000000000409, indexed in Pubmed: 25166465.
14. Sherif MA, Paranskaya L, Yuecel S, et al. MitraClip step by step; how to simplify the procedure. Neth Heart J. 2017; 25(2): 125–130, doi: 10.1007/s12471-016-0930-7, indexed in Pubmed: 27933588.
15. Thornton T, McDermott L. MitraClip® system design and history of development. Percutaneous Mitral Leaflet Repair. 2013: 36–44, doi: 10.3109/9781841849669-8.
16. Armstrong EJ, Foster E. Echocardiographic evaluation for mitral regurgitation grading and patient selection. Percutaneous Mitral Leaflet Repair: MitraClip Therapy for Mitral Regurgitation, vol. 17. First Informa Healthcare. 2012 : 73–79.
17. Wunderlich NC, Siegel RJ. Peri-interventional echo assessment for the MitraClip procedure. Eur Heart J Cardiovasc Imaging. 2013; 14(10): 935–949, doi: 10.1093/ehjci/jet060, indexed in Pubmed: 24062377.
18. Toggweiler S, Zuber M, Sürder D, et al. Two-year outcomes after percutaneous mitral valve repair with the MitraClip system: durability of the procedure and predictors of outcome. Open Heart. 2014; 1(1): e000056, doi: 10.1136/openhrt-2014-000056, indexed in Pubmed: 25332799.
19. Capodanno D, Adamo M, Barbanti M, et al. Predictors of clinical outcomes after edge-to-edge percutaneous mitral valve repair. Am Heart J. 2015; 170(1): 187–195, doi: 10.1016/j.ahj.2015.04.010, indexed in Pubmed: 26093881.
20. Feldman T, Kar S, Elmariah S, et al. Randomized comparison of percutaneous repair and surgery for mitral regurgitation: 5-year results of EVEREST II. J Am Coll Cardiol. 2015; 66(25): 2844–2854, doi: 10.1016/j.jacc.2015.10.018, indexed in Pubmed: 26718672.
21. Stone G, Lindenfeld J, Abraham W, et al. Transcatheter mitral-valve repair in patients with heart failure. New Engl J Med. 2018; 379(24): 2307–2318, doi: 10.1056/nejmoa1806640.
22. Buzzatti N, Denti P, Scarfò IS, et al. Mid-term outcomes (up to 5 years) of percutaneous edge-to-edge mitral repair in the real-world according to regurgitation mechanism: A single-center experience. Catheter Cardiovasc Interv. 2018 [Epub ahead of print], doi: 10.1002/ccd.28029, indexed in Pubmed: 30592134.
23. Azzalini L, Millán X, Khan R, et al. Impact of left ventricular function on clinical outcomes of functional mitral regurgitation patients undergoing transcatheter mitral valve repair. Catheter Cardiovasc Interv. 2016; 88(7): 1124–1133, doi: 10.1002/ccd.26460, indexed in Pubmed: 26891711.
24. Ohno Y, Attizzani GF, Capodanno D, et al. Impact of chronic kidney disease on outcomes after percutaneous mitral valve repair with the MitraClip system: insights from the GRASP registry. EuroIntervention. 2016; 11(14): e1649–e1657, doi: 10.4244/EIJV11I14A316, indexed in Pubmed: 27056125.

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Efficacy and safety of drug-eluting stents in elderly patients: A meta-analysis of randomized trials

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Abstract

Background: *Current guidelines recommend newer generation drug-eluting stents (DES) over bare-metal stents (BMS) in patients with ischemic heart disease. However, there is no age-specific recommendation in elderly patients.*

Methods: *Meta-analysis was performed of 6 randomized studies enrolling 5,042 elderly patients who underwent percutaneous coronary intervention (PCI) with stent implantation (DES, n = 2,579; BMS, n = 2,463).*

Results: *Combined data indicated a significant reduction in major adverse cardiovascular events (MACEs) with use of DES (odds ratio [OR] 0.56, 95% confidence interval [CI] 0.44–0.71, p < 0.001). Moreover, use of DES was associated with a significantly lower incidence of myocardial infarction (OR 0.54, 95% CI 0.36–0.81, p = 0.003) and repeat revascularization (OR 0.44, 95% CI 0.31–0.62, p < 0.001), was compared to that with the use of BMS. Stent thrombosis and bleeding complication rates were not significantly different between groups. In a subgroup meta-analysis, short duration (1 or 6 months) dual antiplatelet therapy (DAPT) was associated with a significantly lower MACE rate (OR 0.49, 95% CI 0.34–0.80; p = 0.003) in elderly patients who underwent PCI with everolimus-eluting stent implantation, compared with that using long duration DAPT.*

Conclusions: *This meta-analysis provides clinically relevant evidence that DES rather than BMS should be selected for elderly patients.* (Cardiol J 2021; 28, 2: 223–234)

Key words: drug-eluting stent, bare-metal stent, elderly, clinical trials, clinical research

Introduction

The introduction of drug-eluting stents (DES) and advanced pharmacotherapy resulted in a significant reduction in restenosis rates [1–5]. This improvement, however, increased the prevalence of bleeding complications due to use of DES and longer duration of dual antiplatelet therapy (DAPT), compared to that using bare-metal stents (BMS) [6]. Long duration of DAPT after DES deployment was associated with higher risk of major bleeding complications despite the beneficial effects of novel platforms, especially in vulnerable populations such as patients over 75 years old [7].

Until recently, guidelines have not provided evidence-based recommendations for treatment of elderly patients [8]. Recently, the SYNERGY II Everolimus eluting stent in patients older than

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75 years, undergoing coronary revascularization associated with a short DAPT (SENIOR) trial demonstrated that use of DES rather than BMS in patients older than 75 years results in lower adverse clinical event rates at 1 year [9]. These observations were also previously seen in the Xience or Vision Stents for the Management of Angina in the Elderly (XIMA) trial, which demonstrated a reduction in myocardial infarction (MI) and in-stent restenosis in the DES group without an increase in bleeding [10]. The superiority of DES in the SENIOR trial was mainly due to a reduction of target lesion revascularization (TLR), but there were no significant differences between all-cause death, MI, and stroke. Therefore, it is unclear whether the clinical benefits of DES were overestimated [11]. Herein, a meta-analysis was performed of randomized studies aiming to assess the benefits and risks associated with DES vs. BMS use for percutaneous coronary intervention (PCI) in elderly patients.

Methods

This study was designed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [12]. A comprehensive MEDLINE, EMBASE, and Cochrane database search was conducted until September 6, 2018, using the following medical subject headings alone and in different combinations: "drug-eluting stent(s)", "DES", "bare-metal stent(s)", "BMS", "coronary artery disease" and "elderly patients". Randomized studies that evaluated elderly patients undergoing PCI and reported on clinical outcomes with follow-up time ≥ 12 months were included. Conventionally, "elderly" has been defined as a chronological age of ≥ 65 years. In the present study however, elderly patients were defined as > 70 years old. Only full articles in peer-reviewed journals were considered.

Two investigators (SAB, YK) extracted baseline study characteristics, clinical outcomes, and DAPT duration of interest from the retrieved studies. Any divergences were resolved by consensus. The number of events associated with clinical outcomes was tabulated for the longest follow-up available.

The primary endpoint was major adverse cardiovascular events (MACEs), defined as a composite of cardiac death, MI, and repeat revascularization, including TLR and target vessel revascularization (TVR). Secondary endpoints were individual components of MACE, definite/probable stent thrombosis, as defined by the Academic Research Consortium, and bleeding complications according to both Thrombolysis in Myocardial Infarction and Bleeding Academic Research Consortium classifications [13, 14]. Subgroup meta-analysis of DES implantation with short (1 or 6 months) vs. long (> 12 months) DAPT duration was performed to determine MACE, stent thrombosis, and bleeding complication rates. Moreover, a meta-regression analysis was performed to identify moderators in a linear relationship among baseline characteristics according to the percentage of hypertension, diabetes mellitus, dyslipidemia, and acute coronary syndrome (ACS). The SENIOR trial was included in the short DAPT group, while the XIMA, Basel Stent Kosten Effektivitäts Trial-PROspective Validation Examination (BASKET-PROVE), and Everolimus-Eluting Stents Versus Bare-Metal Stents in ST-Segment Elevation Myocardial Infarction (EXAMINATION) trials were included in the long DAPT group.

Quality assessment was performed for both study groups. The risk of bias was assessed of each study with the Cochrane tool and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tool [15, 16] was used to assess quality as high, moderate, low, or very low. Most clinical trials showed low evidence of bias with the Cochrane tool. In addition, the level of evidence was strong for primary outcomes assessed with the GRADE tool.

Statistical analysis

The number of patients, events, means, standard deviations (SDs), and percentages were abstracted. Estimates were calculated with a random effects model and confirmed with a fixed effects model and was expressed as odds ratios (ORs). A p-value ≤ 0.05 (2-tailed) indicated statistical significance. The random effects model was prioritized over the fixed effects model and sensitivity analysis was conducted to identify sources of inconsistency. The I^2 statistic was used for evaluation of heterogeneity between studies with values of < 30%, 30% to 60%, and > 60%, corresponding to low, moderate, and high degrees of heterogeneity, respectively [17]. Publication bias was assessed using both the Egger and Begg's tests. A p-value < 0.05 indicated evidence of bias [18]. All data analyses were performed using R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria). This study was registered with PROSPERO, number CRD42019112969.

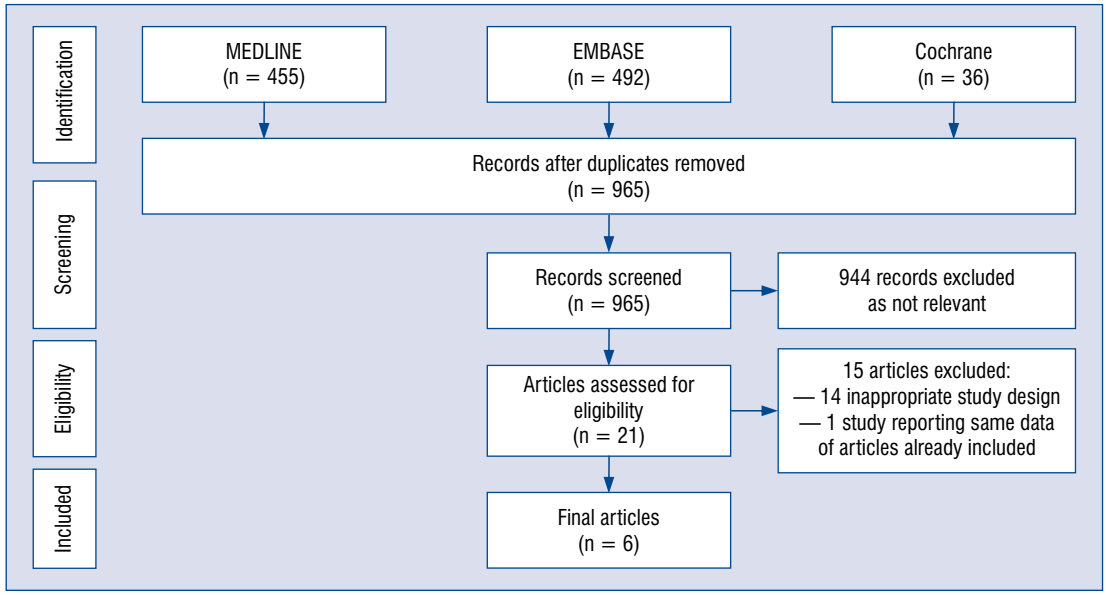

Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow chart for the trial selection process.

Results

The flow chart of the study selection process is shown in Figure 1. Six multi-center randomized controlled trials enrolling 5,042 elderly patients with coronary artery disease (CAD), who underwent PCI with either DES (n = 2,579) or BMS (n = 2,463) implantation were included [9, 10, 19–22]. The study design and characteristics of the trials involved are shown in Table 1. When studies reported results from both unmatched and matched populations, data regarding the matched subgroup were considered. The mean follow-up completion for all trials was relevant, with an overall rate of 98%. The recommended DAPT duration varied between trials (1–12 months), but was the same in both the DES and BMS groups, except in the XIMA trial (1 month of DAPT for patients receiving BMS and 12 months for patients receiving DES).

During long-term follow-up (range 1–2 years), combined data indicated a significant reduction in MACE with DES use (OR 0.56, 95% confidence interval [CI] 0.44–0.71, $p < 0.001$, Fig. 2A). There was no significant difference in stent thrombosis between groups (OR 0.68, 95% CI 0.40–1.14, $p = 0.142$, Fig. 2B). Bleeding complication rates were similar for both groups (OR 0.96, 95% CI 0.78–1.18, $p = 0.686$, Fig. 2C). In addition, the risk of cardiac death did not differ between the groups (OR 0.81, 95% CI 0.65–1.02, $p = 0.075$, Fig. 3A). However, use of DES rather than BMS was associated with a significantly lower incidence of MI (OR 0.54, 95% CI 0.36–0.81, $p = 0.003$, Fig. 3B) and repeat revascularization (OR 0.44, 95% CI 0.31–0.62, $p < 0.001$, Fig. 3C). The funnel plots and the Egger and Begg tests did not suggest any significant publication bias (Fig. 4).

In elderly patients who underwent PCI with everolimus-eluting stent (EES) implantation, subgroup meta-analysis showed a significant decrease in MACE in the short DAPT (1 or 6 months) group (OR 0.49, 95% CI 0.34–0.80; $p = 0.003$), without statistical heterogeneity ($I^2 = 23.7\%$; $p = 0.08$; Fig. 5A). However, there were no significant differences in stent thrombosis and bleeding complication rates according to DAPT duration (Fig. 5B, C). Subgroup analysis showed a significant decrease in MACE with all DES types, including EESs, biolimus-eluting stents, and zotarolimus-eluting stents (ZESs). Moreover, use of a ZES was associated with a significantly lower incidence of definite/probable stent thrombosis (OR 0.40, 95% CI 0.20–0.83; Fig. 6).

Discussion

The main findings of the present study were as follows: 1) DES deployment was associated with significant reduction in MACE, MI, and repeat revascularization in elderly patients; 2) DES implantation was associated with the risk of stent thrombosis and bleeding complications similar to that of BMS implantation; 3) In subgroup meta-

Table 1. Randomized controlled trials design characteristics of included studies.

Study	Year	Design	DES device	Control device	Follow-up (months)	Total patients (DES/BMS)	Follow-up completion	Recommended duration of DAPT	Primary outcome
SENIOR trial [9]	2018	Multicenter randomized	Everolimus (synergy II)	BMS (Omega or Rebel)	12	596/604	98%	Stable: 1 month ACS: 6 months	All death, MI, TLR, or stroke
LEADERS FREE sub-study [19]	2017	Multicenter randomized	Biolimus (biofreedom)	BMS (Gazelle)	12	789/775	97%	1 month (all group)	Cardiac death, MI, TLR, stent thrombosis, or bleeding (BARC 3–5)
ZEUS sub-study [20]	2016	Multicenter randomized	Zotarolimus (endeavor)	BMS (Skylor, Vision, etc)	12	424/404	100%	1 month (all group)	All death, MI, or TVR
BASKET-PROVE sub-study [21]	2015	Multicenter randomized	Everolimus (Xiencce) + Sirolimus (Cypher)	BMS (Vision)	24	258/147	96%	12 months (all group)	Cardiac death or MI
EXAMINATION sub-study [22]	2015	Multicenter randomized	Everolimus (Xience)	BMS (Vision)	12	113/132	97%	12 months (all group)	All death, MI or repeat revascularization
XIMA trial [10]	2014	Multicenter randomized	Everolimus (Xience)	BMS (Vision)	12	399/401	100%	BMS: 1 month DES: 12 months	All death, MI, CVA, TVR, or bleeding (TIMI major)

ACS — acute coronary syndrome; BARC — Bleeding Academic Research Consortium; BASKET-PROVE — Basel Stent Kosten Effektivitäts Trial–Prospective Validation Examination; BMS — bare metal stent; CVA — cerebrovascular accident; EXAMINATION — Everolimus-Eluting Stents vs Bare-Metal Stents in ST-Segment Elevation Myocardial Infarction; LEADERS FREE — prospective, double-blind, randomized comparison of the Biofreedom Biolimus A9 Drug-Coated Stent vs the Gazelle Bare-Metal Stent in patients at high bleeding risk; MI — myocardial infarction; SENIOR — drug-eluting stents in elderly patients with coronary artery disease; TIMI — Thrombolysis In Myocardial Infarction; TLR — target lesion revascularization; TVR — target-vessel revascularization; XIMA — Xience or Vision Stents for the Management of Angina in the Elderly; ZEUS — Zotarolimus-Eluting vs Bare Metal Stents in Uncertain Drug-Eluting Stent Candidates

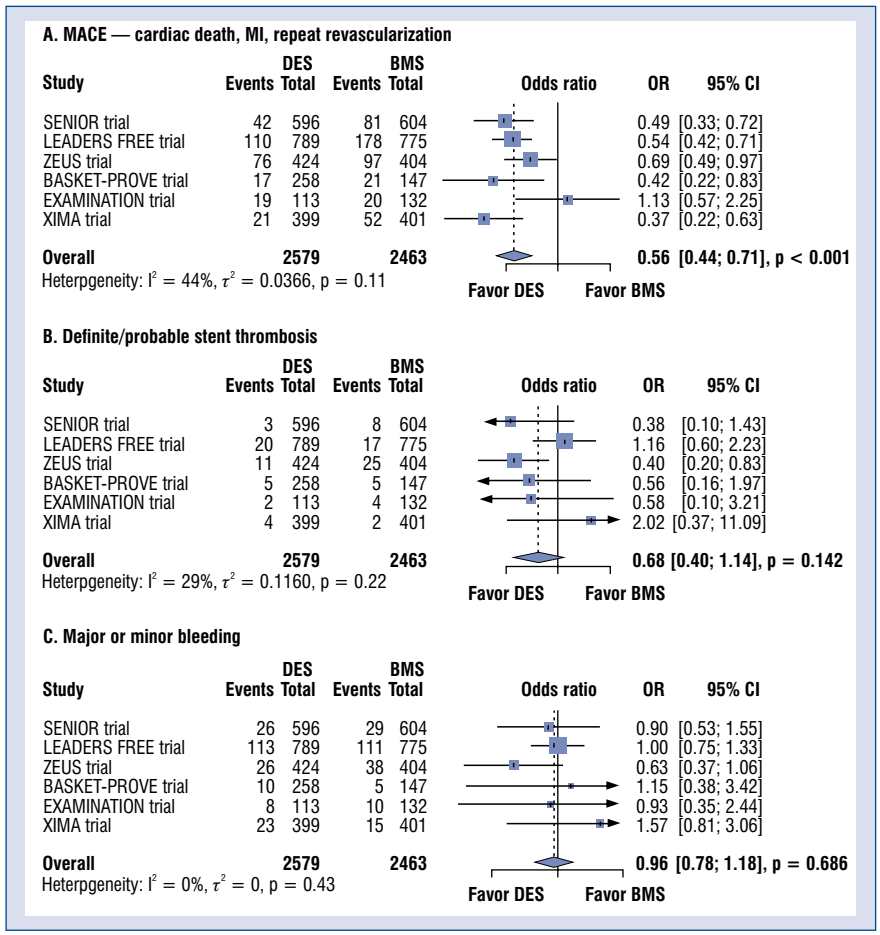

Figure 2. Forest plot for the risk of major adverse cardiovascular event (MACE; **A**), definite/probable stent thrombosis (**B**), and bleeding (**C**) in elderly patients treated with drug-eluting stents (DES) versus bare-metal stents (BMS); MI — myocardial infarction; CI — confidencial interval.

analysis, clinical outcomes were similar for short and long DAPT duration in elderly patients who underwent PCI with EES implantation.

Current guidelines recommend stenting with the newer generation of DES rather than BMS in patients with ischemic heart disease including ST--segment elevation myocardial infarction (STEMI), because of better efficacy and safety profiles [23, 24]. Moreover, guidelines support DES as the preferred treatment option regardless of DAPT duration in patients with high bleeding risk [25]. Nevertheless, age-specific recommendations in elderly patients are not available; thus, BMS has been the preferred option in elderly patients due to shorter DAPT duration [8].

As shown in Table 2, the results of 6 randomized trials, including 4 studies involving patients older than 80 years of age on average, can be seen as appropriate evidence to determine PCI strategy in elderly patients. However, differences in the definitions of primary and secondary outcomes make it difficult to comprehensively assess the benefits of DES in the treatment of elderly patients. The beneficial effects of DES on all-cause death have only been reported in a sub-study of the BASKET-PROVE trial [21]. Furthermore, the cardiac death rate was comparable to that in 6 of the studies included. In contrast to the other 4 randomized studies, the SENIOR trial and sub-study of the EXAMINATION trial did not show a difference in the risk of MI in both the DES and BMS groups [9, 22]. Particularly in the sub-study of the EXAMINATION trial for STEMI patients, DES use did not show any benefits over BMS use in patients over 75 years old [22]. In meta-analysis, DES use was associated with a significant reduction in redefined MACE, including cardiac death, MI, and repeat revascularization. Except for the sub-study of the EXAMINATION trial, the studies included showed benefits of DES use for MACE in

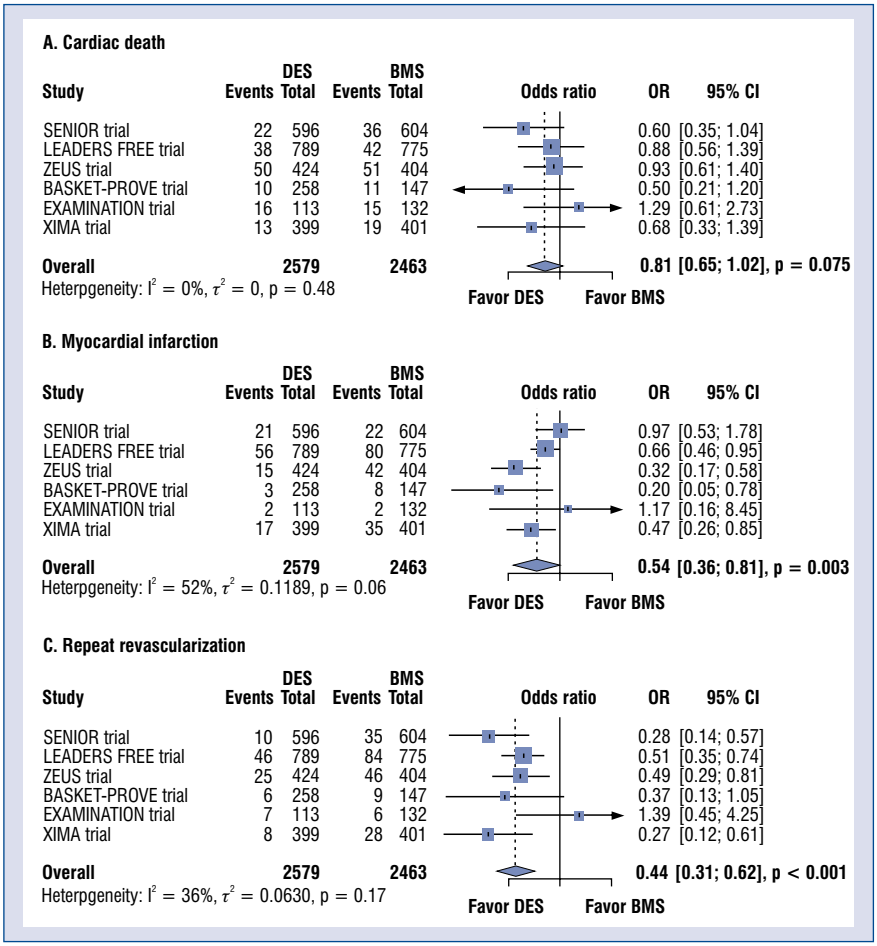

Figure 3. Forest plot for the risk of cardiac death (**A**), myocardial infarction (**B**), and repeat revascularization (**C**) in elderly patients treated with drug-eluting stents (DES) versus bare-metal stents (BMS); CI — confidencial interval.

elderly patients. Furthermore, our pooled analysis demonstrated that PCI with DES implantation was apparently superior to BMS use in terms of MI and repeat revascularization. The Norwegian Coronary Stent Trial (NORSTENT), a large randomized trial comparing long-term outcomes after DES (n = 4,504) vs. BMS use (n = 4,509), reported results similar to those in the present study, with a significantly lower rate of repeat revascularization at 6 years in the group receiving DES [26]. However, NORSTENT enrolled relatively younger patients, and did not show the benefits of DES use for MI compared with the findings in the present study. Although it is difficult to compare the outcomes of MI between the NORSTENT and the present study, the differences may reflect the significant benefit of DES for elderly patients who tend to have more extensive and complex lesions. The risk of stent thrombosis and bleeding complications with use of DES was comparable to that of BMS in the 6 trials included and the NORSTENT. This tendency was also observed in the meta-analysis. Therefore, when considering efficacy and safety, DES use should be considered in elderly patients, as described in the current guidelines.

The scoring systems used to determine DAPT duration include the DAPT score and PREdicting bleeding Complications in patients undergoing Stent implantation and subsequent Dual Anti Platelet Therapy (PRECISE-DAPT) [27, 28]. In both scoring models, age has been used to assess bleeding and ischemic risk since post-PCI bleeding complications were associated with a significant increase in adverse clinical outcomes in patients older than 75 years of age [29]. However, the usefulness of these scores for improving outcomes remains unclear, due to the lack of evidence in the setting of randomized controlled trials. According to current guidelines, short DAPT duration should be considered in patients with high bleeding risk

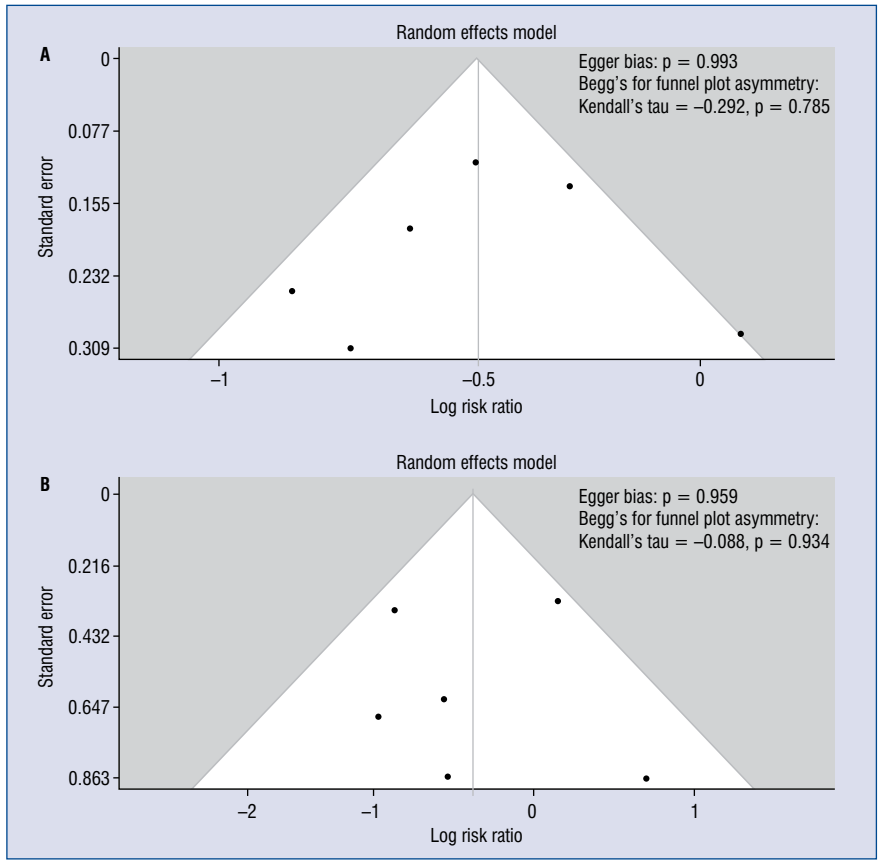

Figure 4. Funnel plot. **A.** Funnel plot for major adverse cardiovascular events (MACE); **B.** Funnel plot for definite/ /probable stent thrombosis.

(PRECISE-DAPT score ≥ 25), with 3 months of DAPT for stable CAD and 6 months of DAPT for ACS [25]. The current subgroup meta-analysis in elderly patients who underwent PCI with EES implantation showed no significant differences between use of short DAPT duration and long DAPT duration in stent thrombosis and bleeding complications, as shown in Figure 5. Moreover, short DAPT duration was associated with a significantly lower incidence of MACE, compared with using long DAPT duration. Therefore, short DAPT duration is as safe as long DAPT duration in elderly patients who undergo PCI with EES implantation.

Limitations of the study

There were several limitations in this study. First, there was considerable heterogeneity between studies, which was particularly evident when comparing studies using different designs. Second, the definition of MACE was different in each study. Therefore, MACE was redefined to reduce confounders. Third, the definition of elderly varies from 65 to 75 years of age, but the present study defined elderly to be > 70 years of age, since there have been few randomized controlled trials in those aged ≥ 75 years. Fourth, differences in DAPT duration according to DES or BMS use were reported in only 1 of the 6 trials included (XIMA trial: 1 month of DAPT for patients receiving BMS and 12 months for those receiving DES), which could affect outcomes. Fifth, there are two types of EES, durable polymer EES (XIENCE™, Abbott Vascular, Santa Clara, CA, USA) and bioabsorbable polymer EES (SYNERGY™, Boston Scientific, Marlborough, MA, USA). Bioabsorbable polymer (BP)-DES implantation was reported to have better endothelial healing and conjugate protein expression than durable polymer-DES implantation [30]. Unique characteristics of BP-DES might affect the results of short and long DAPT duration on subgroup analysis. However, subgroup analysis included bioabsorbable or durable polymer EES. In addition, the proportion of ACS patients could not be assessed in the short and long DAPT duration groups and the comparison of DAPT duration was not randomly allocated between studies. Thus, a careful interpretation of subgroup analysis of DAPT duration is necessary.

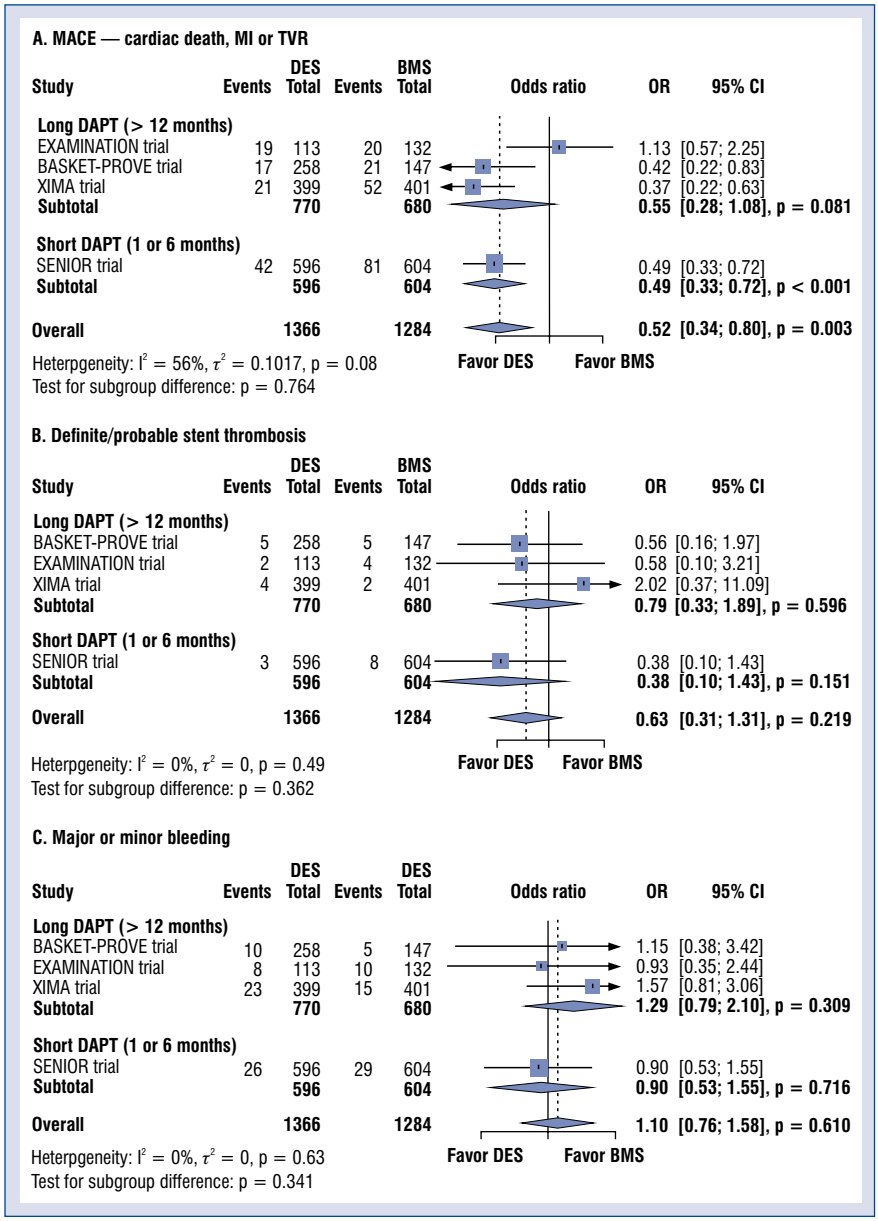

Figure 5. A–C. Subgroup meta-analysis of the effect of short (≤ 1 or 6 months) versus long (> 12 months) dual antiplatelet therapy (DAPT) duration in elderly patients who underwent percutaneous coronary intervention (PCI) with everolimus-eluting stent (EES) implantation. DES — drug-eluting stents; BMS — bare-metal stents; CI — confidence interval; MACE — major adverse cardiovascular events; MI — myocardial infarction; TVR — target vessel revascularization.

Conclusions

This meta-analysis builds upon recent evidence to support the efficacy and safety of DES use, and provides clinically relevant evidence that DES rather than BMS should be selected for treatment of elderly patients. Furthermore, short DAPT duration should be considered when PCI with EES implantation is performed in elderly patients.

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Conflict of interest: None declared

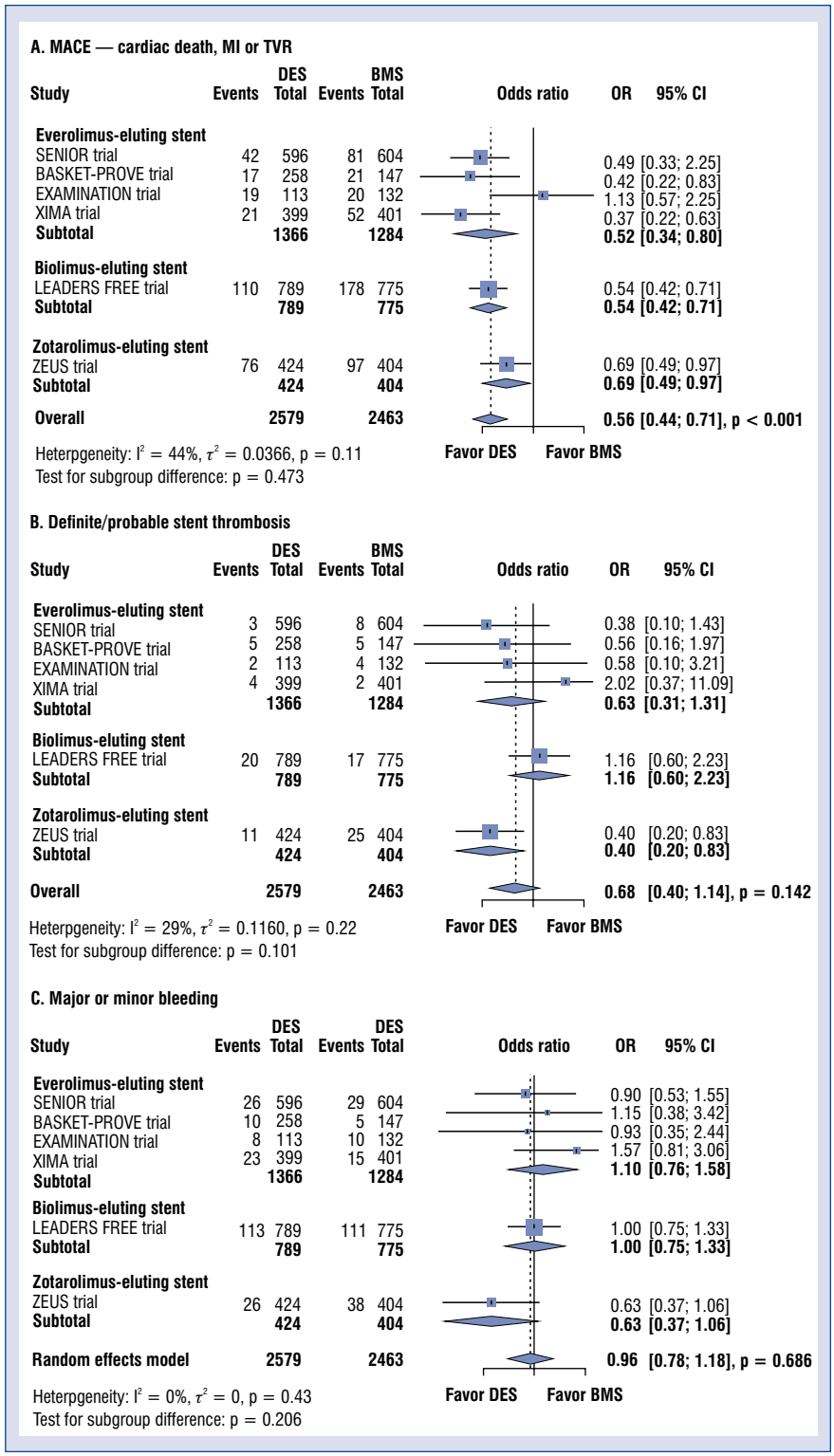

Figure 6. A–C. Subgroup meta-analysis of the effect according to drug-eluting stents (DES) type. BMS — bare-metal stents; MACE — major adverse cardiovascular events; MI — myocardial infarction; TVR — target vessel revascularization; CI — confidence interval.

Table 2. Baseline characteristics of individuals enrolled in the clinical trials.

Variable	SENIOR trial [9]		LEADERS FREE sub-study [19]		ZEUS sub-study [20]		BASKET-PROVE sub-study [21]		EXAMINATION sub-study [22]		XIMA trial [10]	
	DES	BMS	DES	BMS	DES	BMS	DES	BMS	DES	BMS	DES	BMS
Numbers of patients	1,200 (596 vs. 604)		1,564 (789 vs. 775)		828 (424 vs. 404)		405 (258 vs. 147)		245 (113 vs. 132)		800 (399 vs. 401)	
Age (years)	81.4 ± 4.3	81.4 ± 4.2	81.3 ± 4.3	81.3 ± 4.3	80.4	80.5	79.1 ± 3.4	79.1 ± 3.6	≥ 75 years		83.6 ± 3.2	83.4 ± 3.1
Men	368 (62%)	379 (63%)	504 (63.9%)	492 (63.5%)	274 (61.6%)	259 (64.1%)	130 (50.4%)	93 (63.3%)	72 (63.7%)	87 (64.9%)	245 (61.1%)	237 (59.1%)
Body mass index	26.3 ± 4.3	25.9 ± 3.9	26.9 ± 4.3	26.5 ± 4.0	26 [24-29]	26 [24-29]	–	–	27.4 ± 3.77	27.6 ± 3.85	–	–
Diabetes mellitus	158 (27%)	157 (26%)	248 (31.4%)	214 (27.6%)	137 (32.3%)	117 (29%)	41 (15.9%)	21 (14.3%)	27 (23.6%)	33 (25%)	103 (25.6%)	97 (24.2%)
Hypertension	427 (72%)	488 (81%)	615 (77.9%)	618 (79.8%)	344 (81.1%)	336 (83.2%)	194 (75.2%)	102 (69.4%)	71 (62.8%)	94 (71.2%)	301 (75.1%)	311 (77.6%)
Dyslipidemia	311 (52%)	320 (53%)	474 (60.1%)	458 (59.1%)	191 (45%)	193 (47.8%)	145 (56.2%)	84 (57.1%)	38 (33.6%)	43 (32.6%)	231 (57.6%)	212 (52.9%)
Smoker	43 (7%)	38 (6%)	–	–	44 (10.4%)	45 (11.1%)	31 (12.2%)	21 (14.3%)	–	–	20 (5%)	16 (4%)
Previous stroke	39 (7%)	48 (8%)	80 (10.1%)	66 (8.5%)	32 (7.5%)	34 (8.4%)	15 (5.8%)	11 (7.5%)	5 (4.4%)	7 (5.3%)	31 (7.8%)	43 (10.7%)
Previous MI	109 (18%)	80 (13%)	155 (19.7%)	154 (19.9%)	117 (27.6%)	114 (28.2%)	45 (17.4%)	26 (17.0%)	5 (4.4%)	10 (7.6%)	119 (29.8%)	86 (21.5%)
Previous PCI	139 (23%)	143 (24%)	172 (21.8%)	164 (21.1%)	90 (21.2%)	83 (20.5%)	31 (12.0%)	19 (12.9%)	3 (2.7%)	6 (4.5%)	51 (12.8%)	41 (10.2%)
Previous CABG	36 (6%)	42 (7%)	69 (8.8%)	68 (8.8%)	39 (9.2%)	38 (9.4%)	10 (3.9%)	6 (4.1%)	5 (4.4%)	2 (5.3%)	28 (7%)	17 (4.2%)
Clinical indication:												
Stable angina	201 (34%)	215 (36%)	556 (70.5%)	546 (70.5%)	147 (34.7%)	140 (34.7%)	89 (34.5%)	55 (37.4%)	–	–	256 (32%)	
UAP/NSTEMI	209 (37%)	208 (35%)	233 (29.5%)	229 (29.5%)	212 (50%)	199 (50.0%)	95 (36.8%)	50 (34.0%)	–	–	144 (18%)	
STEMI	65 (11%)	62 (10%)			65 (15.3%)	62 (15.3%)	74 (28.7%)	42 (28.6%)	113 (100%)	132 (100%)	400 (50%)	
Multivessel CAD	202 (34%)	183 (31%)	503 (63.7%)	494 (63.8%)	285 (67.2%)	176 (68.3%)	131 (50.8%)	78 (53.1%)	18 (15.9%)	19 (14.4%)	150 (37.4%)	158 (39.5%)
Treated coronary artery:												
LAD	320 (54%)	313 (52%)	–	–	234 (55.2%)	196 (48.5%)	144 (55.8%)	82 (55.8%)	50 (44.2%)	50 (37.8%)	243 (60.7%)	253 (63%)
LCX	177 (30%)	159 (27%)	–	–	141 (33.3%)	155 (38.4%)	59 (22.9%)	41 (27.9%)	15 (13.2%)	16 (12.1%)	127 (31.7%)	120 (30%)
RCA	213 (36%)	227 (38%)	–	–	162 (38.2%)	161 (39.9%)	109 (42.3%)	58 (39.5%)	46 (40.7%)	64 (48.4%)	153 (38.1%)	142 (35.3%)
Left main	23 (4%)	8 (1%)	–	–	26 (6.1%)	27 (6.7%)	3 (1.2%)	3 (2.0%)	1 (0.01%)	1 (0.01%)	30 (7.6%)	33 (8.3%)

BMS — bare-metal stents; CABG — coronary artery bypass surgery; CAD — coronary artery disease; DES — drug-eluting stents; LAD — left anterior descending artery; LCX — left circumflex artery; MI — myocardial infarction; NSTEMI — non-ST-segment elevation myocardial infarction; PCI — percutaneous coronary intervention; RCA — right coronary artery; STEMI — ST-segment elevation myocardial infarction; UAP — unstable angina pectoris; rest abbreviations — see Table 1.

References

1. Menichelli M, Parma A, Pucci E, et al. Randomized trial of Sirolimus-Eluting Stent Versus Bare-Metal Stent in Acute Myocardial Infarction (SESAMI). J Am Coll Cardiol. 2007; 49(19): 1924–1930, doi: 10.1016/j.jacc.2007.01.081, indexed in Pubmed: 17498576.
2. Spaulding C, Henry P, Teiger E, et al. TYPHOON Investigators. Sirolimus-eluting versus uncoated stents in acute myocardial infarction. N Engl J Med. 2006; 355(11): 1093–1104, doi: 10.1056/NEJMoa062006, indexed in Pubmed: 16971716.
3. Laarman GJ, Suttorp MJ, Dirksen MT, et al. Paclitaxel-eluting versus uncoated stents in primary percutaneous coronary intervention. N Engl J Med. 2006; 355(11): 1105–1113, doi: 10.1056/NEJMoa062598, indexed in Pubmed: 16971717.
4. Stettler C, Wandel S, Allemann S, et al. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. Lancet. 2007; 370(9591): 937–948, doi: 10.1016/S0140-6736(07)61444-5, indexed in Pubmed: 17869634.
5. Horst B, Rihal CS, Holmes DR, et al. Comparison of drug-eluting and bare-metal stents for stable coronary artery disease. JACC Cardiovasc Interv. 2009; 2(4): 321–328, doi: 10.1016/j.jcin.2008.11.010, indexed in Pubmed: 19463444.
6. Cassese S, Byrne RA, Tada T, et al. Clinical impact of extended dual antiplatelet therapy after percutaneous coronary interventions in the drug-eluting stent era: a meta-analysis of randomized trials. Eur Heart J. 2012; 33(24): 3078–3087, doi: 10.1093/eurheartj/ehs318, indexed in Pubmed: 23091199.
7. Gerber RT, Arri SS, Mohamed MO, et al. Age is not a bar to PCI: Insights from the long-term outcomes from off-site PCI in a real-world setting. J Interv Cardiol. 2017; 30(4): 347–355, doi: 10.1111/joic.12400, indexed in Pubmed: 28670721.
8. Rich MW, Chyun DA, Skolnick AH, et al. Knowledge Gaps in Cardiovascular Care of the Older Adult Population: A Scientific Statement From the American Heart Association, American College of Cardiology, and American Geriatrics Society. J Am Coll Cardiol. 2016; 67(20): 2419–2440, doi: 10.1016/j.jacc.2016.03.004, indexed in Pubmed: 27079335.
9. Varenne O, Cook S, Sideris G, et al. Drug-eluting stents in elderly patients with coronary artery disease (SENIOR): a randomised single-blind trial. Lancet. 2018; 391(10115): 41–50, doi: 10.1016/S0140-6736(17)32713-7, indexed in Pubmed: 29102362.
10. de Belder A, de la Torre Hernandez JM, Lopez-Palop R, et al. A prospective randomized trial of everolimus-eluting stents versus bare-metal stents in octogenarians: the XIMA Trial (Xience or Vision Stents for the Management of Angina in the Elderly). J Am Coll Cardiol. 2014; 63(14): 1371–1375, doi: 10.1016/j.jacc.2013.10.053, indexed in Pubmed: 24216285.
11. Leidi F, Schiavon R. Drug-eluting stents vs. bare metal stents in elderly patients. Intern Emerg Med. 2018; 13(5): 773–774, doi: 10.1007/s11739-018-1839-5, indexed in Pubmed: 29594816.
12. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009; 339: b2535–b2535, doi: 10.1136/bmj.b2535.
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. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation. 2011; 123(23): 2736–2747, doi: 10.1161/CIRCULATIONAHA.110.009449, indexed in Pubmed: 21670242.
15. 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.
16. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. BMJ. 2004; 328(7454): 1490, doi: 10.1136/bmj.328.7454.1490, indexed in Pubmed: 15205295.
17. Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ. 2003; 327(7414): 557–560, doi: 10.1136/bmj.327.7414.557, indexed in Pubmed: 12958120.
18. 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.
19. Morice MC, Talwar S, Gaemperli O, et al. Drug-coated versus bare-metal stents for elderly patients: A predefined sub-study of the LEADERS FREE trial. Int J Cardiol. 2017; 243: 110–115, doi: 10.1016/j.ijcard.2017.04.079, indexed in Pubmed: 28579168.
20. Ariotti S, Adamo M, Costa F, et al. Is Bare-Metal Stent Implantation Still Justifiable in High Bleeding Risk Patients Undergoing Percutaneous Coronary Intervention?: A Pre-Specified Analysis From the ZEUS Trial. JACC Cardiovasc Interv. 2016; 9(5): 426–436, doi: 10.1016/j.jcin.2015.11.015, indexed in Pubmed: 26965932.
21. Kurz DJ, Bernheim AM, Tüller D, et al. Improved outcomes of elderly patients treated with drug-eluting versus bare metal stents in large coronary arteries: results from the BAsel Stent Kosten-Effektivitäts Trial PROspective Validation Examination randomized trial. Am Heart J. 2015; 170(4): 787–795.e1, doi: 10.1016/j.ahj.2015.07.009, indexed in Pubmed: 26386803.
22. Ielasi A, Brugaletta S, Silvestro A, et al. Everolimus-eluting stent versus bare-metal stent in elderly (≥75 years) versus non-elderly (<75 years) patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention: insights from the examination trial. Int J Cardiol. 2015; 179: 73–78, doi: 10.1016/j.ijcard.2014.10.038, indexed in Pubmed: 25464418.
23. 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.
24. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. Considerations for the choice between coronary artery bypass grafting and percutaneous coronary intervention as revascularization strategies in major categories of patients with stable multivessel coronary artery disease: an accompanying article of the task force of the 2018 ESC/EACTS guidelines on myocardial revascularization. Eur Heart J. 2019; 40(2): 204–212, doi: 10.1093/eurheartj/ehy532, indexed in Pubmed: 30165435.
25. 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.

26. Bønaa KH, Mannsverk J, Wiseth R, et al. Drug-eluting or bare-metal stents for coronary artery disease. N Engl J Med. 2016; 375(13): 1242–1252, doi: 10.1056/NEJMoa1607991, indexed in Pubmed: 27572953.
27. Yeh RW, Secemsky EA, Kereiakes DJ, et al. Development and Validation of a Prediction Rule for Benefit and Harm of Dual Antiplatelet Therapy Beyond 1 Year After Percutaneous Coronary Intervention. JAMA. 2016; 315(16): 1735–1749, doi: 10.1001/jama.2016.3775, indexed in Pubmed: 27022822.
28. Costa F, van Klaveren D, James S, et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. Lancet. 2017; 389(10073): 1025––1034, doi: 10.1016/S0140-6736(17)30397-5, indexed in Pubmed: 28290994.
29. Ndrepepa G, Neumann FJ, Schulz S, et al. Incidence and prognostic value of bleeding after percutaneous coronary intervention in patients older than 75 years of age. Catheter Cardiovasc Interv. 2014; 83(2): 182–189, doi: 10.1002/ccd.25189, indexed in Pubmed: 24030753.
30. Mori H, Cheng Qi, Lutter C, et al. Endothelial barrier protein expression in Biodegradable polymer sirolimus-eluting versus durable polymer everolimus-eluting metallic stents. JACC Cardiovasc Interv. 2017; 10(23): 2375–2387, doi: 10.1016/j.jcin.2017.06.059, indexed in Pubmed: 29102583.

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Biodegradable polymer-coated thin strut sirolimus--eluting stent versus durable polymer-coated everolimus-eluting stent in the diabetic population

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Abstract

Background: *The number of patients with diabetes mellitus (DM) presenting with coronary artery disease is increasing and accounts for more than 30% of patients undergoing percutaneous coronary interventions (PCI). The biodegradable polymer drug-eluting stents were developed to improve vascular healing. It was sought herein, to determine 1-year clinical follow-up in patients with DM treated with the thin strut biodegradable polymer-coated sirolimus-eluting stent (BP-SES) versus durable coating everolimus-eluting stent (DP-EES).*

Methods: *Patients were retrospectively analyzed with DM were treated with either a BP-SES (ALEX™, Balton, Poland, n = 670) or a DP-EES (XIENCE™, Abbott, USA, n = 884) with available 1 year clinical follow-up using propensity score matching. Outcomes included target vessel revascularization (TVR) as efficacy outcome and all-cause death, myocardial infarction, and definite/probable stent thrombosis as safety outcomes.*

Results: *After propensity score matching 527 patients treated with BP-SES and 527 patients treated with DP-EES were selected. Procedural and clinical characteristics were similar between both groups. In-hospital mortality was 3.23% in BP-SES vs. 2.09% in DP-EES group (p = 0.25). One-year follow-up demonstrated comparable efficacy outcome TVR (BP-SES 6.64% vs. DP-EES 5.88%; p = 0.611), as well as similar safety outcomes of all-cause death (BP-SES 10.06% vs. DP-EES 7.59%; p = 0.158), myocardial infarction (BP-SES 7.959% vs. DP-EES 6.83%; p = 0.813), and definite/probable stent thrombosis (BP-SES 1.14% vs. DP-EES 0.76%; p = 0.525).*

Conclusions: *The thin-strut biodegradable polymer coated, sirolimus-eluting stent demonstrated comparable clinical outcomes at 1-year after implantation to DP-EES. These data support the relative safety and efficacy of BP-SES in diabetic patients undergoing PCI.* (Cardiol J 2021; 28, 2: 235–243)

Key words: drug-eluting stents, percutaneous coronary intervention, diabetes mellitus

Introduction

The number of patients with diabetes mellitus (DM) presenting with coronary artery disease (CAD) is increasing and accounts for more than 30% of patients undergoing percutaneous coronary interventions (PCI) [1]. The pathophysiology associated with diabetic vasculopathy is multifactorial

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and includes endothelial dysfunction, non-enzymatic glycation end products, circulating free fatty acids, increased systemic inflammation, diabetic autonomic neuropathy, and the vascular effects of hyperinsulinemia [2, 3]. Randomized clinical trials, have demonstrated higher efficacy of coronary artery bypass grafting (CABG) when compared with PCI in DM population especially in patients with multivessel disease and complex coronary anatomy [4]. Nevertheless, advances in the drug eluting stents (DES) technology, have made stents a viable and less invasive alternative therapy when compared to CABG for patients with less complex anatomy. Second-generation DES reduced rates of stent thrombosis (ST) with preserved low restenosis rates when compared to first-generation DES [5–7]. However, very late ST and neoatherosclerosis have been recently observed also with second-generation DES [8–10]. To address the limitations of the durable polymer DES, new platforms that make use of biodegradable polymers have been developed. The safety and effectiveness of biodegradable polymer coated DES (BP-DES) over first-generation DES has been previously demonstrated in reducing the risk of very late ST and restenosis [11–13]. However, patients with DM constitute a challenging subset, with poorer outcomes after PCI in comparison with non-diabetics. These patients often present with unfavorable coronary anatomy with small and diffusely diseased vessels and multi-vessel involvement [14].

In the present study, it was sought to determine the 1-year clinical follow-up of patients treated with the thin strut BP-coated sirolimus-eluting stent (BP-SES) versus durable coating everolimus-eluting stent (DP-EES) in an all-comers DM population.

Methods

Study design

The interventional cardiology network registry is a prospective, observational registry which includes all patients treated with PCI in 4 Polish interventional cardiology centers in Poland. A retrospective screening of unselected patients (n = = 21,400) treated with PCI between 2010 and 2016 was undertaken. All consecutive patients included were previously diagnosed with DM who underwent single or multi-vessel revascularization with either BP-SES (ALEX, Balton, Warsaw, Poland) or DP-EES (XIENCE, Abbott Vascular, Santa Clara, CA, USA) during the index procedure following acute coronary syndrome or stable angina presentation. Follow-up data for patients treated in years 2015–2016 is currently not available. Therefore, for final analysis only patients treated between 2010 and 2014 were selected, due to availability of 1-year follow-up data for all the patients. Due to observational nature of the study and lack of any interference in diagnostic and therapeutic decision-making process no permission was required from the Institutional Review Board and Bioethics Committee.

Stent system description

The BP-SES used in this study is a Conformité Européenne (CE)-approved balloon expandable cobalt-chromium stent with a 71 microns strut thickness covered with a biodegradable copolymer of poly-lactic and glycolic acid together with sirolimus. In a previously published study, BP-SES demonstrated comparable safety and efficacy in all-comers and acute myocardial infarction (MI) patient population when compared to the benchmark balloon-expandable cobalt-chromium DP--EES [15, 16]. DP-EES was previously granted the specific indication for DM patients from the Food and Drug Administration of the United States and CE mark from the European Commission. DP-EES has a strut thickness of 81 microns. Everolimus is blended in a non-erodible polymer coated over another non-erodible polymer primer layer.

Study population

The demographic, clinical and angiographic data collected in the course of the index hospitalization were retrieved from a prospectively recorded Institutional Electronic Database. Follow-up data, including exact dates of death, MI and repeat revascularization were obtained from the health insurer (National Health Fund) database. Detailed angiographic data for repeat revascularization were obtained from the medical centers that performed the procedures.

All patients underwent coronary angiography with following or postponed PCI using standard devices. All interventional strategies, including the use of stents, choice of stent type and periprocedural antithrombin and antiplatelet therapy, were at the discretion of the attending physicians. Pharmacological treatments recommended by the European Society of Cardiology were introduced before and after the intervention unless contraindicated.

Ethics approval and consent to participate

Due to the observational nature of this study and lack of any interference in a diagnostic and therapeutic decision-making process no permission

was required from the Institutional Review Board and Bioethics Committee.

Definitions and endpoints

The efficacy outcome was defined as target vessel revascularization (TVR). The safety outcomes included separate endpoints of death, MI, and definite or probable ST. MI was defined as an ischemic event that fulfilled the European Society of Cardiology/American College of Cardiology criteria for MI and was clinically distinct from the index event at the time of first hospitalization [17]. TVR was defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel including ischemia-driven and symptomatic-driven intervention. ST was considered as acute (0–24 h), subacute (> 24 h to 30 days) or late (> 31 days) and was defined as either definitive or probable according to the Academic Research Consortium [18].

Statistical analysis

Categorical variables are presented as percentages and were compared using the χ^2 test, whereas continuous variables are displayed as means ± standard deviation and were compared using the Student t-test. A propensity score method was used to match the BP-SES and DP-EES groups for all baseline clinical characteristics and angiographic parameters listed in Tables 1 and 2. The area under curve for logistic model was 0.708 (95% confidence interval 0.686–0.731); $p < 0.0001$. The greedy matching algorithm, available in NCSS, was used with the distance calculation option set to "Mahalanobis Distance within Propensity Score Calipers (no matching outside caliper)" and caliper to 0.2*Sigma. Cumulative event rates in 1-year follow-up were analyzed with the Kaplan-Meier method and compared with the log-rank test. All tests were 2-tailed, and a p-value < 0.05 was considered to indicate statistical significance. Statistics were calculated with STATISTICA 12 (Statsoft, Tulsa, Oklahoma, USA) and NCSS 12 Statistical Software (NCSS, LLC. Kaysville, Utah, USA).

Results

Baseline demographic characteristics

A total of 670 BP-SES and 884 DP-EES patients were found to be eligible for matching. Patients in BP-SES group were older than in DP-EES group (respectively: 68.78 ± 9.14 vs. 67.75 ± 9.60; $p = 0.031$). Previous MI and PCI procedures were less common in the BP-SES group when compared to DP-EES (respectively: 31.34% vs. 37.22%; $p = 0.016$, 22.69% vs. 30.20%; $p < 0.001$). Cardiogenic shock at admission occurred more often in BP-SES than in DP-EES group (respectively: 3.28% vs. 1.36%; $p = 0.010$)

Following propensity score analysis and matching, 527 pairs were selected for further analysis with a mean age of 68.41 ± 9.13 years in BP-SES group and 68.21 ± 9.34 in DP-EES group. There were no relevant differences found in baseline characteristics following matching. The proportions of patients with ST-segment elevation MI (BP-SES 10.63% vs. DP-EES 10.63%) and non-ST segment elevation MI (BP-SES 30.17% vs. DP-EES 28.08%) unstable (BP-SES 38.9% vs. DP-EES 37.57%) and stable angina (BP-SES 24.29% vs. DP-EES 23.52%) were comparable between matched groups. An overview of the unmatched and matched baseline characteristics is presented in Table 1.

Patients angiographic and procedural characteristics

Before propensity score matching, there were significant differences between BP-SES and DP--EES in angiographic and procedural characteristics. Left main CAD occurred less frequently in the BP--SES group when compared to the DP-SES group. The rate of multi-vessel PCI was lower in BP-DES compared to DP-EES. The proportion of direct stenting rate was similar in both studied groups. Also, number of stents implanted per patient was similar between the groups.

After propensity score matching angiographic and procedural characteristics such as a multivessel CAD, left main CAD and targeted vessels were comparable between studied groups. There was no difference in single-vessel intervention rates. There was no difference in the number and length of stents implanted per patient. Angiographic and procedural characteristics, before and after propensity score matching, are summarized in Table 2.

Clinical outcomes in matched cohorts

In-hospital (BP-SES 3.23% vs. DP-EES 2.09%; $p = 0.250$) and 30-day mortality (BP-SES 4.55% vs. DP-EES 2.47%; $p = 0.066$) was comparable in the matched groups. The efficacy outcome of TVR rates at 12 months did not differ significantly between BP-SES and DP-EES (respectively: 6.64% vs. 5.88%; $p = 0.611$). There was also no difference in safety endpoints between the matched groups regarding death, MI, and definite/probable ST (Fig. 1).

Table 1. Baseline characteristics.

	Unmatched			Matched		
	BP-SES (n = 670)	DP-EES (n = 884)	P	BP-SES (n = 527)	DP-EES (n = 527)	P
Age [years]	68.78 ± 9.14	67.75 ± 9.60	0.031	68.41 ± 9.13	68.21 ± 9.34	0.711
Female	49.10%	45.02%	0.110	47.06%	48.96%	0.538
Previous MI	31.34%	37.22%	0.016	32.26%	34.91%	0.361
Previous PCI	22.69%	30.20%	0.001	24.67%	26.19%	0.571
Previous bypass surgery	10.30%	10.86%	0.722	10.06%	10.82%	0.687
Previous stroke	5.82%	4.86%	0.403	4.93%	4.93%	1.000
Hypertension	90.15%	89.48%	0.666	89.94%	89.75%	0.919
Hypercholesterolemia	40.60%	42.76%	0.392	40.04%	42.31%	0.453
Smoking	14.33%	11.65%	0.118	13.28%	13.09%	0.927
Obesity	45.97%	44.34%	0.523	45.73%	45.35%	0.902
Chronic heart failure	26.42%	26.58%	0.942	26.38%	27.51%	0.677
Chronic renal failure	13.58%	14.14%	0.753	12.71%	12.33%	0.852
Cardiogenic shock	3.28%	1.36%	0.010	2.09%	1.71%	0.652
Indication for procedure:						
STEMI	11.04%	9.05%	0.192	10.63%	10.63%	1.000
NSTEMI	29.10%	11.04%	0.156	28.08%	30.17%	0.456
Unstable angina	37.46%	37.22	0.921	38.90%	37.57%	0.657
Stable CAD	23.30%	24.03%	0.738	24.29%	23.52%	0.773

MI — myocardial infarction; PCI — percutaneous coronary intervention; STEMI — ST-segment elevation myocardial infarction; NSTEMI — non-ST-segment elevation myocardial infarction; CAD — coronary artery disease

Table 2. Angiographic and procedural characteristics.

	Unmatched			Matched		
	BP-SES (n = 670)	DP-EES (n = 884)	P	BP-SES (n = 527)	DP-EES (n = 527)	P
Multi-vessel CAD	66.87%	70.14%	0.169	66.22%	67.36%	0.695
LM CAD	4.03%	7.13%	0.001	3.98%	3.98%	1.000
Target vessel:						
LM	1.04%	5.88%	< 0.001	1.33%	0.57%	0.204
LAD	38.66%	51.36%	< 0.001	42.31%	44.40%	0.494
Cx	23.88%	12.56%	< 0.001	19.76%	21.26%	0.490
RCA	32.24%	26.92%	0.022	32.26%	29.79%	0.387
Bypass	4.18%	3.28%	0.351	4.36%	3.98%	0.758
Single vessel PCI	85.67%	77.04%	< 0.001	85.01%	85.39%	0.543
Bifurcation PCI	6.72%	17.53%	< 0.001	7.40%	7.21%	0.906
Stents used per patient	1.45 ± 0.82	1.46 ± 0.75	0.847	1.42 ± 0.77	1.41 ± 0.73	0.890
Total length of stents	26.39 ± 16.94	30.61 ± 17.67	< 0.001	26.85 ± 16.75	26.84 ± 15.28	0.991
Maximal implantation pressure	14.67 ± 2.23	14.64 ± 2.79	0.854	14.68 ± 2.24	14.64 ± 2.72	0.823
Direct stent implantation	40.00%	35.52%	0.071	37.76%	38.33%	0.849
Post dilatation	22.54%	23.08%	0.802	21.82%	18.79%	0.221
Thrombectomy	4.18%	3.96%	0.828	3.23%	4.36%	0.333
Procedural glycoprotein IIb/IIIa inhibitor	5.07%	5.54%	0.684	4.36%	4.36%	1.000

CAD — coronary artery disease; LM — left main; LAD — left anterior descending; Cx — circumflex; RCA — right coronary artery; PCI — percutaneous coronary intervention

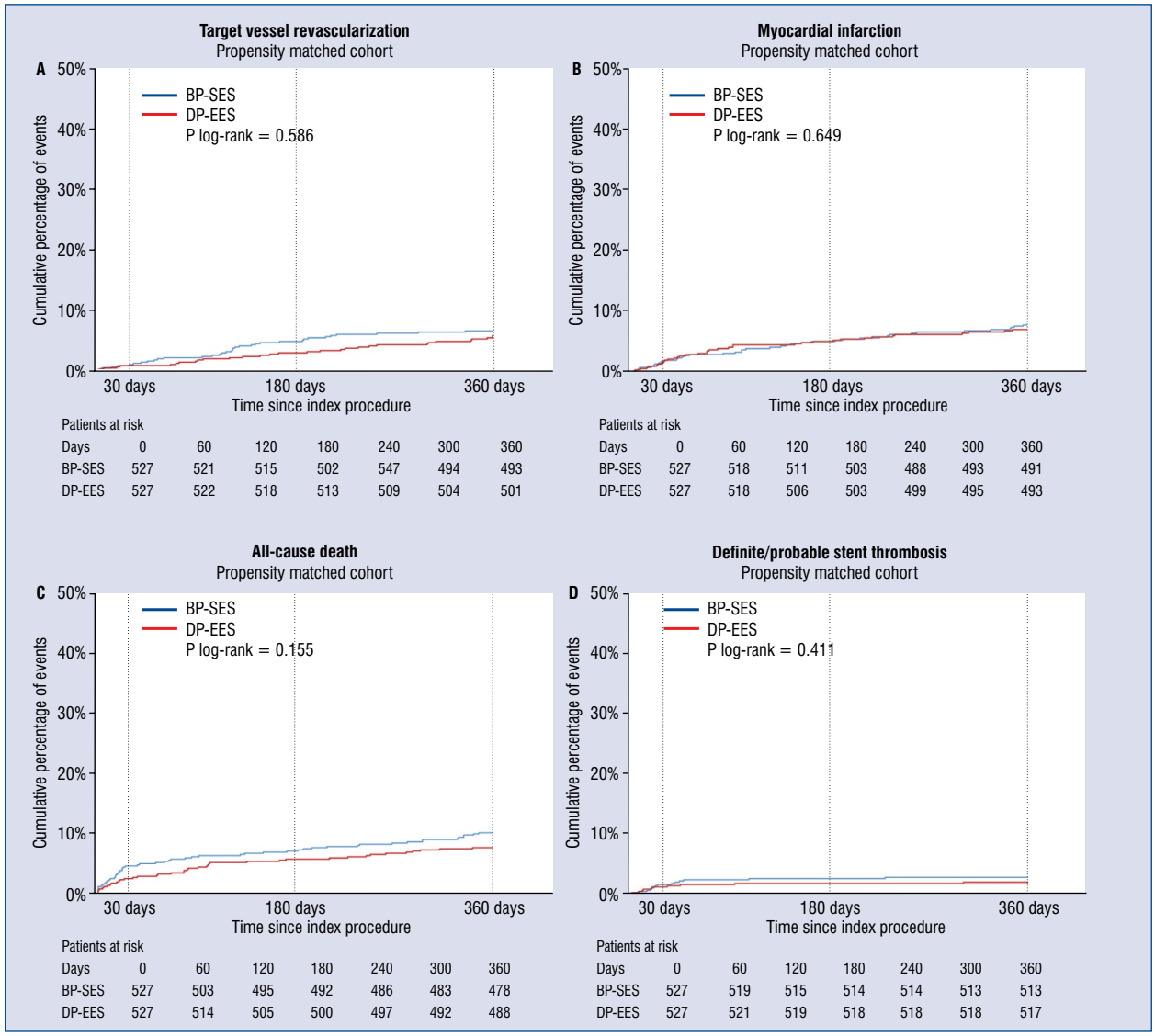

Figure 1. One-year Kaplan-Meier events rates. Kaplan-Meier curves show the cumulative incidence of target vessel revascularization (**A**); myocardial infarction (**B**); all-cause death (**C**); and definite/probable stent thrombosis (**D**).

All-cause mortality at 1 year was similar in both groups (BP-SES 10.06% vs. DP-EES 7.59%; p = 0.158). MI rates were comparable in both groups (BP-SES 7.59% vs. DP-EES 6.83%; p = 0.633). The cumulative rates of definite/probable ST were relatively low with no significant difference between the matched groups (BP-SES 2.66% vs. DP-SES 1.90%; p = 0.408). Also, there was no difference in acute (BP-SES 0.00% vs. DP-SES 0.19%; p = 0.317), subacute (BP-SES 1.52% vs. DP-SES 0.95%; p = = 0.402) and late (BP-SES 1.14% vs. DP-SES 0.76%; p = 0.525) definite/probable ST. In summary, no significant differences were found in terms of clinical outcomes after 1 year. Detailed follow-up results are presented in Table 3.

Discussion

The present study describes a direct comparison of the clinical outcomes of thin strut biodegradable polymer coated sirolimus-eluting stent against benchmark non-erodible polymer coated everolimus-eluting stent in the DM patients. The major finding of this investigation in a propensity-matched cohort is comparable 1-year clinical outcomes for the BP-SES when compared with DP-EES, with reasonable event rates, demonstrating similar safety and efficacy of the devices in the DM patient population.

Coronary artery disease remains the most important cause of morbidity and mortality among

Table 3. Clinical outcomes at 30 days, 6 months, and 12 months in a propensity matched cohort.

	BP-SES (n = 527)	DP-EES (n = 527)	P
30 days			
Target vessel revascularization	6 (1.14%)	5 (0.95%)	0.762
Myocardial infarction	9 (1.71%)	9 (1.71%)	1.000
All cause death	24 (4.55%)	13 (2.47%)	0.066
6 months			
Target vessel revascularization	26 (4.93%)	16 (3.04%)	0.115
Myocardial infarction	26 (4.93%)	26 (4.93%)	1.000
All cause death	37 (7.02%)	30 (5.69%)	0.377
12 months			
Target vessel revascularization	35 (6.64%)	31 (5.88%)	0.611
Myocardial infarction	40 (7.59%)	36 (6.83%)	0.633
All cause death (n)	53 (10.06%)	40 (7.59%)	0.158
Definite/probable stent thrombosis			
Acute (0–1 days)	0 (0.00%)	1 (0.19%)	0.317
Subacute (2–30 days)	8 (1.52%)	5 (0.95%)	0.402
Late (31–365 days)	6 (1.14%)	4 (0.76%)	0.525

patients with DM. It is estimated that ≈75% of patients with diabetes will die from cardiovascular causes [19]. DM patients often present with unfavorable coronary anatomy with small and diffusely diseased vessels and multi-vessel involvement when compared to non-diabetics [14]. Hyperglycemia and associated metabolic disarrangements enhance the development, progression, and instability of atherosclerotic plaque [2]. The diabetic vasculopathy pathophysiology is multifactorial and includes vascular effects of hyperinsulinemia, non-enzymatic glycation end products, endothelial dysfunction, circulating free fatty acids, diabetic autonomic neuropathy, and increased systemic inflammation [2]. Despite similar initial angioplasty success rates, DM patients have higher restenosis rates and worse long-term outcomes. Also, in a DM population, acute coronary syndrome is more frequent and has a higher risk of complications [20]. Although DES implantation reduces neointimal hyperplasia and TVR rates in these patients, diabetes remains a risk factor for restenosis and adverse events after PCI [21, 22]. The increase in oxidative and inflammatory mediators in diabetic patients promotes atherosclerosis [19]. Rapamycin and its analogs (like sirolimus and everolimus) are mTOR complex inhibitor agents. In animal models, the enhancement of the extracellular signal response kinase (ERK) pathway produces a relative resistance to mTOR inhibitors. Therefore, the demonstration of an enhanced activity of the ERK pathway in diabetic vasculature provides an alternative pathway, not affected by limus analogues, for proliferation of vascular smooth muscle cells. This potentially explains the reduction in the long-term effectivity of limus eluting stents in DM [23].

Higher adverse events rate etiology in DM patients seems to be multifactorial and due to patient-related and stent-related causes [24]. In the present study, propensity matched analysis was performed, therefore most of the patients related variables were controlled and equally distributed. Regarding the possible stent-related causes there are different characteristics of tested devices that could impact outcomes between BP-SES and DP-EES, such as the thinner strut thickness (71 μm vs. 81 μm), the presence of biodegradable polymer, and the limus analogue used (sirolimus vs. everolimus). Although polymer provides a reservoir for programmed drug release, it has no function when drug release is completed, and it may affect late and very late safety and efficacy of DES. In fact, durable polymers may be associated with inflammation, neoatherosclerosis and incomplete stent endothelialization which may contribute to the risk of adverse events also observed with new durable polymers DES [25, 26]. However, recent reports demonstrated similar clinical outcomes after implantation of BP-DES when compared to second generation durable polymer coated

stents despite their theoretical advantages. In a large meta-analysis, treatment with BP-DES significantly reduced late lumen loss and late stent thrombosis rates, without clear benefits on harder endpoints compared to durable polymer DP-DES [27]. Herein, it was speculated that, in the pro-inflammatory milieu typical of DM patients, the presence of biodegradable polymer and thinner struts could be important factors that could affect long-term outcomes after BP-SES implantation when compared to DP-EES [28].

A previously published study demonstrated favorable safety and efficacy of DP-EES in a diabetic population [29]. Clinical events in the present study was numerically higher in the BP-SES group when compared to the DP-EES group, however the differences were not statically significant. Therefore, BP-SES demonstrated no-inferior outcomes to DP-EES in a diabetic population. There was no significant difference in TVR rates between the BP--SES and DP-EES groups (respectively: 6.64% vs. 5.88%; p = 0.611). The current study also showed that treatment with BP-SES was not associated with significantly increased mortality (respectively: 10.06% vs. 7.59%; p = 0.158) and MI rates (respectively: 7.59% vs. 6.83%; p = 0.634) when compared to DP-EES. Furthermore, no significant differences were found in terms of definite and probable stent thrombosis (BP-SES 2.66% vs. DP-SES 1.90%; p = 0.408). The 12-month rates of ST found in this study are slightly higher than in randomized trials comparing biodegradable and durable polymer coated DES. However, it needs to be emphasized that the mentioned difference is probably attributed exclusively to a diabetic population and a high proportion of patients with acute coronary syndromes which are included in present study [30].

It has been previously postulated that longer follow-up is required to demonstrate risk reduction of adverse events in favor of BP-DES compared with DP-DES [31]. For example, 5-year results in the LEADERS trial showed BP-DES was associated with a significant reduction in very late, (> 1 year), definite stent thrombosis [32]. Therefore, follow-up beyond 1 year is required to clarify the potential benefit of BP-SES over DP-EES on clinical outcomes in the DM population.

Taking into consideration the above observations, in a propensity-matched cohort, the opinion reached was that BP-SES included in the present study displays a similar efficacy profile as benchmark DP-EES, without compromising safety, which is of utmost importance among DM patients treated in routine clinical practice.

Limitations of the study

First, the current study is limited by its observational nature and patients were not enrolled in a randomized fashion. Thus, any findings should be confirmed by prospective and sufficiently powered clinical trials. Nevertheless, more challenging patients are often excluded from randomized controlled trials. For such reasons, observational studies can be used as complementary forms of research in real-world populations [33]. An attempted to minimize the selection bias on whether to implant BP-SES or DP-EES by using a propensity score matching for a wide range of variables was undertaken. However, not all differences between the groups could be addressed. For example, matching by coronary lesion complexity according to the American College of Cardiology/American Heart Association classification was not performed.

Second, no routine angiographic surveillance was scheduled, and thus no conclusions regarding potential restenosis could be made. Also, no intravascular imaging data was collected. Adequate DAPT is one of the most important factors preventing stent thrombosis. However, data on antiplatelet drug compliance during follow-up was not available.

Third, only patients treated between 2010 and 2014 were evaluated due to lack of currently available follow-up for 546 patients treated in the years 2015–2016.

Fourth, optimal medical therapy could have impacted clinical outcomes, especially in terms of ST and cardiac death, but unfortunately no specific analysis was performed because data from therapy at follow-up was not available.

Finally, the present study is limited to 1 year of follow-up, while theoretical differential clinical outcomes between the compared technologies might have been observed during long-term follow-up.

Conclusions

This is the first competitive evaluation of BP-SES vs. DP-EES in DM population. It provides evidence for the safety and efficacy of BP-SES. The 12-month outcomes for BP-SES were similar to DP-EES. These findings should be verified in a prospective, randomized trial.

Conflict of interest: None declared

References

1. Centers for Disease Control and Prevention. National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the

United States, 2014. Atlanta, GA: US Department of Health and Human Services; 2014.
2. Orasanu G, Plutzky J. The pathologic continuum of diabetic vascular disease. J Am Coll Cardiol. 2009; 53(5 Suppl): S35–S42, doi: 10.1016/j.jacc.2008.09.055, indexed in Pubmed: 19179216.
3. Rask-Madsen C, King GL. Mechanisms of Disease: endothelial dysfunction in insulin resistance and diabetes. Nat Clin Pract Endocrinol Metab. 2007; 3(1): 46–56, doi: 10.1038/ncpendmet0366, indexed in Pubmed: 17179929.
4. Farkouh M, Domanski M, Sleeper L, et al. Strategies for Multivessel Revascularization in Patients with Diabetes. N Engl J Med. 2012; 367(25): 2375–2384, doi: 10.1056/nejmoa1211585.
5. Räber L, Magro M, Stefanini GG, et al. Very late coronary stent thrombosis of a newer-generation everolimus-eluting stent compared with early-generation drug-eluting stents: a prospective cohort study. Circulation. 2012; 125(9): 1110–1121, doi: 10.1161/CIRCULATIONAHA.111.058560, indexed in Pubmed: 22302840.
6. Stefanini GG, Windecker S. Stent thrombosis: no longer an issue with newer-generation drug-eluting stents? Circ Cardiovasc Interv. 2012; 5(3): 332–335, doi: 10.1161/CIRCINTERVENTIONS.112.970970, indexed in Pubmed: 22715449.
7. Dores H, Raposo L, Campante Teles R, et al. Stent thrombosis with second- versus first-generation drug-eluting stents in real-world percutaneous coronary intervention: analysis of 3806 consecutive procedures from a large-volume single-center prospective registry. J Invasive Cardiol. 2013; 25(7): 330–336, indexed in Pubmed: 23813060.
8. Naidu SS, Krucoff MW, Rutledge DR, et al. Contemporary incidence and predictors of stent thrombosis and other major adverse cardiac events in the year after XIENCE V implantation: results from the 8,061-patient XIENCE V United States study. JACC Cardiovasc Interv. 2012; 5(6): 626–635, doi: 10.1016/j.jcin.2012.02.014, indexed in Pubmed: 22721657.
9. Nakazawa G, Otsuka F, Nakano M, et al. The pathology of neoatherosclerosis in human coronary implants bare-metal and drug-eluting stents. J Am Coll Cardiol. 2011; 57(11): 1314–1322, doi: 10.1016/j.jacc.2011.01.011, indexed in Pubmed: 21376502.
10. Park SJ, Kang SJ, Virmani R, et al. In-stent neoatherosclerosis: a final common pathway of late stent failure. J Am Coll Cardiol. 2012; 59(23): 2051–2057, doi: 10.1016/j.jacc.2011.10.909, indexed in Pubmed: 22651862.
11. Räber L, Kelbæk H, Ostojic M, et al. Effect of biolimus-eluting stents with biodegradable polymer vs bare-metal stents on cardiovascular events among patients with acute myocardial infarction: the COMFORTABLE AMI randomized trial. JAMA. 2012; 308(8): 777–787, doi: 10.1001/jama.2012.10065, indexed in Pubmed: 22910755.
12. Stefanini GG, Byrne RA, Serruys PW, et al. Biodegradable polymer drug-eluting stents reduce the risk of stent thrombosis at 4 years in patients undergoing percutaneous coronary intervention: a pooled analysis of individual patient data from the ISAR-TEST 3, ISAR-TEST 4, and LEADERS randomized trials. Eur Heart J. 2012; 33(10): 1214–1222, doi: 10.1093/eurheartj/ehs086, indexed in Pubmed: 22447805.
13. Palmerini T, Biondi-Zoccai G, Della Riva D, et al. Clinical outcomes with bioabsorbable polymer- versus durable polymer-based drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. J Am Coll Cardiol. 2014; 63(4): 299–307, doi: 10.1016/j.jacc.2013.09.061, indexed in Pubmed: 24211507.
14. Kip KE, Faxon DP, Detre KM, et al. Coronary angioplasty in diabetic patients. The National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry. Circulation. 1996; 94(8): 1818–1825, doi: 10.1161/01.cir.94.8.1818, indexed in Pubmed: 8873655.
15. Gasior P, Gierlotka M, Szczurek-Katanski K, et al. Bioresorbable polymer-coated thin strut sirolimus-eluting stent vs durable polymer-coated everolimus-eluting stent in daily clinical practice: Propensity matched one-year results from interventional cardiology network registry. Catheter Cardiovasc Interv. 2019; 93(7): E362–E368, doi: 10.1002/ccd.27919, indexed in Pubmed: 30298545.
16. Gąsior P, Gierlotka M, Szczurek-Katanski K, et al. Safety and efficacy of biodegradable polymer-coated thin strut sirolimus-eluting stent vs. durable polymer-coated everolimus-eluting stent in patients with acute myocardial infarction. Postepy Kardiol Interwencyjnej. 2018; 14(4): 347–355, doi: 10.5114/aic.2018.79194, indexed in Pubmed: 30603024.
17. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Eur Heart J. 2012; 33(20): 2551–2567.
18. 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.
19. Preis SR, Hwang SJ, Coady S, et al. Trends in all-cause and cardiovascular disease mortality among women and men with and without diabetes mellitus in the Framingham Heart Study, 1950 to 2005. Circulation. 2009; 119(13): 1728–1735, doi: 10.1161/CIRCULATIONAHA.108.829176, indexed in Pubmed: 19307472.
20. Fang J, Alderman MH. Impact of the increasing burden of diabetes on acute myocardial infarction in New York City: 1990-2000. Diabetes. 2006; 55(3): 768–773, doi: 10.2337/diabetes.55.03.06.db05-1196, indexed in Pubmed: 16505241.
21. Flaherty JD, Davidson CJ. Diabetes and coronary revascularization. JAMA. 2005; 293(12): 1501–1508, doi: 10.1001/jama.293.12.1501, indexed in Pubmed: 15784875.
22. Sabaté M, Jiménez-Quevedo P, Angiolillo DJ, et al. Randomized comparison of sirolimus-eluting stent versus standard stent for percutaneous coronary revascularization in diabetic patients: the diabetes and sirolimus-eluting stent (DIABETES) trial. Circulation. 2005; 112(14): 2175–2183, doi: 10.1161/CIRCULATIONAHA.105.562421, indexed in Pubmed: 16203930.
23. Woods TC. Dysregulation of the mammalian target of rapamycin and p27Kip1 promotes intimal hyperplasia in diabetes mellitus. Pharmaceuticals (Basel). 2013; 6(6): 716–727, doi: 10.3390/ph6060716, indexed in Pubmed: 24276258.
24. Dangas GD, Claessen BE, Caixeta A, et al. In-stent restenosis in the drug-eluting stent era. J Am Coll Cardiol. 2010; 56(23): 1897–1907, doi: 10.1016/j.jacc.2010.07.028, indexed in Pubmed: 21109112.
25. Nakazawa G, Nakano M, Otsuka F, et al. Evaluation of polymer-based comparator drug-eluting stents using a rabbit model of iliac artery atherosclerosis. Circ Cardiovasc Interv. 2011; 4(1): 38–46, doi: 10.1161/CIRCINTERVENTIONS.110.957654, indexed in Pubmed: 21205943.
26. Kang SJ, Lee CW, Song H, et al. OCT analysis in patients with very late stent thrombosis. JACC Cardiovasc Imaging. 2013; 6(6): 695–703, doi: 10.1016/j.jcmg.2013.02.006, indexed in Pubmed: 23643282.

27. Lupi A, Gabrio Secco G, Rognoni A, et al. Meta-analysis of bioabsorbable versus durable polymer drug-eluting stents in 20,005 patients with coronary artery disease: an update. Catheter Cardiovasc Interv. 2014; 83(6): E193–E206, doi: 10.1002/ccd.25416, indexed in Pubmed: 24478247.
28. Endothelial dysfunction in diabetes mellitus. Vasc Health Risk Manag. 2007; 3(6): 853–876.
29. Kaul U, Bhagwat A, Pinto B, et al. Paclitaxel-eluting stents versus everolimus-eluting coronary stents in a diabetic population: two-year follow-up of the TUXEDO-India trial. EuroIntervention. 2017; 13(10): 1194–1201, doi: 10.4244/EIJ-D-17-00333, indexed in Pubmed: 28741578.
30. Christiansen EH, Jensen LO, Thayssen P, et al. Biolimus-eluting biodegradable polymer-coated stent versus durable polymer-coated sirolimus-eluting stent in unselected patients receiving percutaneous coronary intervention (SORT OUT V): a randomised non-inferiority trial. Lancet. 2013; 381(9867): 661–669, doi: 10.1016/S0140-6736(12)61962-X, indexed in Pubmed: 23374649.
31. Stefanini GG, Byrne RA, Serruys PW, et al. Biodegradable polymer drug-eluting stents reduce the risk of stent thrombosis at 4 years in patients undergoing percutaneous coronary intervention: a pooled analysis of individual patient data from the ISAR-TEST 3, ISAR-TEST 4, and LEADERS randomized trials. Eur Heart J. 2012; 33(10): 1214–1222, doi: 10.1093/eurheartj/ehs086, indexed in Pubmed: 22447805.
32. Serruys PW, Farooq V, Kalesan B, et al. Improved safety and reduction in stent thrombosis associated with biodegradable polymer-based biolimus-eluting stents versus durable polymer-based sirolimus-eluting stents in patients with coronary artery disease: final 5-year report of the LEADERS (Limus Eluted From A Durable Versus ERodable Stent Coating) randomized, noninferiority trial. JACC Cardiovasc Interv. 2013; 6(8): 777–789, doi: 10.1016/j.jcin.2013.04.011, indexed in Pubmed: 23968698.
33. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. N Engl J Med. 2000; 342(25): 1887–1892, doi: 10.1056/NEJM200006223422507, indexed in Pubmed: 10861325.

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Lack of prognostic significance for major adverse cardiac events of soluble suppression of tumorigenicity 2 levels in patients with ST-segment elevation myocardial infarction

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Abstract

Background: *Elevation of soluble suppression of tumorigenicity 2 (sST2) is associated with cardiac fibrosis and hypertrophy. Under investigation herein, was whether sST2 level is associated with major adverse cardiac events (MACE) and left ventricular (LV) remodeling after primary percutaneous coronary intervention (PCI) in patients with acute ST-segment elevation myocardial infarction (STEMI).*

Methods: *In total, this study included 184 patients who underwent successful primary PCI. A subsequent guideline-based medical follow-up was included (61.4 ± 11.8 years old, 85% male, 21% with Killip class ≥ I). sST2 concentration correlations with echocardiographic, angiographic, laboratory parameters, and clinical outcomes in STEMI patients were evaluated.*

Results: *The median sST2 level was 60.3 ng/mL; 6 (3.2%) deaths occurred within 1 year. The sST2 level correlated with LV ejection fraction (LVEF) changes from baseline to 6 months ($r = -0.273$; $p = 0.006$) after adjustment for echocardiographic parameters including wall motions score index (WMSI). Recovery of LVEF at 6 months was highest in the tertile 1 group (Δ6 months – baseline LVEF; tertile 1, $p = 0.001$; tertile 2, $p = 0.319$; tertile 3, $p = 0.205$). The decrease in WMSI at 6 months was greater in the tertiles 1 and 2 groups than in the tertile 3 group (Δ6 months – baseline WMSI; tertile 1, $p = 0.001$; tertile 2, $p = 0.013$; tertile 3, $p = 0.055$). There was no association between sST2 levels and short-term (log rank $p = 0.598$) and long-term ($p = 0.596$) MACE.*

Conclusions: *sST2 concentration have predictive value for LV remodeling on echocardiography in patients with STEMI who underwent primary PCI. However, sST2 concentration was not associated with short-term and long-term MACE.* (Cardiol J 2021; 28, 2: 244–254)

Key words: suppression of tumorigenicity 2 protein, myocardial infarction, left ventricular remodeling

Introduction

Acute ST-segment elevation myocardial infarction (STEMI) makes a significant contribution to morbidity and mortality in many parts of the world [1–4]. It is well known that early diagnosis and proper management, especially delay from the onset of symptoms to revascularization are important for long-term prognosis [5, 6]. Timely diagnosis allows physicians to stratify their patients by risk, and consequently provides them with the opportunity to select appropriate treatments. Biomarkers have been used to assist with timely diagnosis and to predict precise short- or long-term prognosis in

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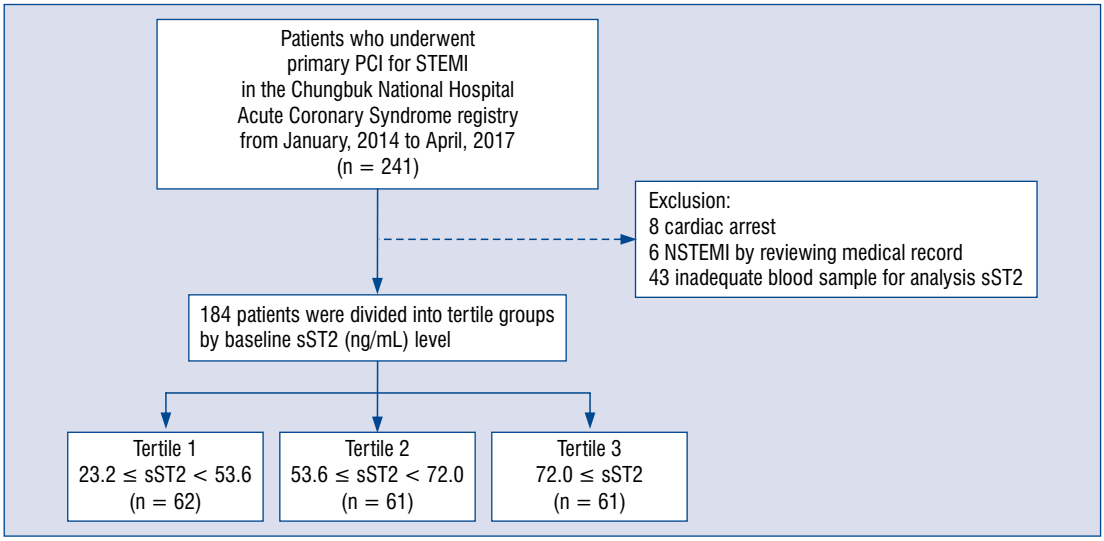

Figure 1. Study flow chart of patient enrolment; NSTEMI — non-ST-segment elevation myocardial infarction; STEMI — ST-segment elevation myocardial infarction; PCI — percutaneous coronary intervention.

STEMI patients. As a result, cardiac biomarkers, such as creatine phosphokinase (CPK), creatinine kinase-myocardial band (CK-MB), cardiac specific troponins, and natriuretic peptides, are widely used to diagnose and predict prognosis in patients with STEMI [7–9]. Circulating soluble suppression of tumorigenicity 2 (sST2) is a known biomarker of cardiac remodeling and inflammation, especially in heart failure (HF) patients. It is thought to act as a decoy receptor for interleukin-33, rendering it unavailable to membrane-bound ST2 receptors that medicate anti-inflammatory and anti-fibrotic effects [10–12]. Several studies have reported that increased sST2 in the initial phase of STEMI is closely related to adverse outcomes, both in the short- and long-term [13–16]. However, current guidelines do not recommend the examination of sST2 as a biomarker in the treatment for STEMI. Therefore, under investigation herein, are the associations between the concentration of sST2 and the clinical and echocardiographic outcome. Its performance was compared to established risk predictors such as the Killip classification, Thrombolysis in Myocardial Infarction (TIMI) risk score, and the Canadian acute coronary syndrome (CACS) score.

Methods

Study design and population

The study was a single center, retrospective, observational study. The study population consisted of 184 patients who underwent successful primary percutaneous coronary intervention (PCI) for STEMI from January 2014 to April 2017 at the Chungbuk National University Hospital, Republic of Korea. In total, 184 patients were included. Figure 1 shows the study flow chart. Written informed consent was obtained from all patients, and exclusion criteria were as follows: (1) end-stage renal disease requiring dialysis; (2) life expectancy < 12 months; (3) pre-hospital or pre-PCI cardiac arrest; (4) prior coronary artery bypass graft surgery; (5) known malignancy or inflammatory disease. The study complied with the Declaration of Helsinki and was approved by the institutional review board (IRB) of Chungbuk National University Hospital (CBNUH 2018-07-013).

Laboratory assays

All plasma samples were collected before primary PCI with arterial access. The plasma samples were stored in plastic cryovials at –80°C at the Chungnbuk National University Hospital Brach Bank of the Korean Biobank Network until required for analysis. The sST2 concentration in blood specimens was measured using an enzyme-linked immunosorbent assay kit (ELISA) (Elabscience Biotechnology, China) [17]; calibration and standardization were performed according to the manufacturer instructions. Intra-assay and inter-assay coefficients of variance were reported as < 2.5% and < 4.0%, respectively [18]. To examine a dose-response relationship between sST2 and outcomes, tertiles of sST2 were analyzed and defined as tertile 1: 0 < 53.6 ng/mL, tertile 2: 53.6 ≤ sST2 < 72.0 (ng/mL), and tertile 3: sST2 ≥ 72.0 (ng/mL).

Initial treatment strategies

The initial treatments in hospitalized patients with STEMI were administration of loading doses for dual antiplatelet agents and primary PCI that was performed after intravenous administration of 7,000 IU of heparin. Second generation drug-eluting stents were implanted in all patients, and the decision on whether to use intravascular imaging modalities, an intra-aortic balloon pump, thrombectomy devices, or extracorporeal membrane oxygenation devices was made by the operator.

Time for revascularization was determined in three ways: (1) time from symptom onset to balloon inflation, (2) time from symptom onset to medical contact, and (3) time from medical contact to balloon inflation. All patients received standard medical treatment with revascularization at the discretion of the attending physician.

Echocardiographic measurement

All patients underwent transthoracic echocardiography (IE33, Philips Medical System, Andover, MA, USA; Vivid 7, GE Vingmed Ultrasound, Horten, Norway; SC2000, Siemens, Erlangen, Germany) within 12 hours of the index procedure. The left ventricular (LV) systolic function (LV ejection fraction [LVEF]), LV internal dimension at diastole (LVIDd), ratio of the early diastolic peak mitral inflow velocity to early diastolic mitral annular velocity (E/E'), left atrial volume index (LAVI), and wall motion score index (WMSI) were obtained according to the American Society of Echocardiography guidelines [19]. Follow-up echocardiography was performed 6 months after discharge at outpatient clinics. ΔLVEF, ΔLVIDd, ΔE/E', ΔLAVI, and ΔWMSI were defined by subtracting the baseline echocardiographic parameters from the echocardiographic performed 6 months after discharge from initial hospitalization.

Follow-up and endpoint

Standard medications, including dual antiplatelet agents, beta-blockers, renin–angiotensin–aldosterone system inhibitors, statins, and nitrates, were provided by responsible physicians according to the guidelines. The primary endpoint was major adverse cardiac event (MACE) at 1 year; this comprised of occurrence of cardiovascular death, non-fatal myocardial infarction (MI), and non-fatal stroke. The secondary endpoint was differences in echocardiographic parameters indicating LV remodeling between baseline and 6-month follow-up. The endpoints were obtained by reviewing electronic hospital medical records.

Statistical analysis

Demographic, clinical, echocardiographic, and laboratory variables were described as means and standard deviation (SD) in normally distributed variables, and variables with a non-normal distribution were described as medians and interquartile range (IQR). The analysis of variance was used to compare normally distributed variables, and the Kruskal-Wallis test was used to compare continuous variables in a state of non-normality. Categorical variables were compared using the χ^2 test or the Fisher exact test. Univariable Pearson and Spearman correlation and partial correlation were used to evaluate the magnitude and significance of relationships among continuous variables.

The Wilcoxon signed rank test was used to compare changes in echocardiographic parameters by time within groups. Multiple Cox proportional hazard analyses were performed in an effort to identify independent predictors of 1-year MACE after primary PCI. Variables were retained and entered into a multivariable model if their univariable p value was < 0.05.

The Kaplan-Meier method was used to estimate event-free survival, and differences between the curves were compared using the log-rank test.

Analyses were performed using SPSS 25.0 (SPSS Inc, Chicago, IL, USA), and SAS 9.4 (SAS Institute Inc, Cary, NC, USA). P-values (two-tailed) < 0.05 were considered to indicate statistical significance.

Results

Patient characteristics related to sST2 tertile

In total, 184 subjects, who were followed up 1 year after successful primary PCI for STEMI, were evaluated in this study. The mean age of the subjects was 61.4 ± 11.8 years, and 15% were female. In addition, 57% had a culprit lesion in the left anterior descending artery, the median (IQR) symptom to door time was 120 (53, 267) min, the door to balloon time was 39 (30, 50) min, 21% were Killip classification ≥ 2, 54% were TIMI risk score > 4, 17% were CACS score > 1, and 100% presented with STEMI. The median sST2 concentration was 60.3 ng/mL (25^{th}, 75^{th} percentile: 48.7, 77.3 ng/mL, respectively; range: 23.2–197.5 ng/mL). Of these, 62 (33.6%) patients were included in tertile 1, 61 (33.2%) patients were included in tertile 2, and 61 (33.2%) patients were included in tertile 3. The baseline characteristics of patients stratified by sST2 concentration are shown in Table 1. Higher sST2 concentration showed an association

Table 1. Baseline characteristics according to sST2 tertile in patients with ST-segment elevation myocardial infarction.

Variables	Overall (n = 184)	sST2 [ng/mL]			P
		Tertile 1 23.2 ≤ sST2 < 53.6 (n = 62)	Tertile 2 53.6 ≤ sST2 < 72.0 (n = 61)	Tertile 3 72.0 ≤ sST2 (n = 61)	
Age [years]	61.4 ± 11.8	58.4 ± 9.8	63.0 ± 12.7	62.5 ± 12.3	0.058
Body weight [kg]	67.8 ± 12.4	68.8 ± 11.8	66.6 ± 13.0	68.5 ± 12.2	0.554
Female	28 (15%)	9 (15%)	8 (13%)	11 (18%)	0.763
Baseline HR [bpm]	76 ± 20	75 ± 20	76 ± 18	77 ± 22	0.910
Baseline SBP [mmHg]	130 (110, 145)	130 (110, 149)	130 (110, 140)	130 (109, 146)	0.885
Baseline DBP [mmHg]	80 (70, 90)	80 (70, 90)	79 (70, 90)	80 (70, 90)	0.597
Symptom to door time [min]	120 (53, 267)	117 (40, 280)	120 (58, 201)	120 (49, 342)	0.876
Symptom to balloon time [min]	160 (88, 300)	162 (87, 315)	168 (87, 248)	160 (93, 380)	0.911
Door to balloon time [min]	39 (30, 50)	40 (30, 52)	37 (28, 50)	40 (33, 50)	0.343
Prior angina	8 (4%)	3 (5%)	2 (3%)	3 (5%)	1.000
Smoking	127 (69.0%)	39 (63%)	44 (72%)	44 (72%)	0.462
Hypertension	101 (55%)	28 (45%)	34 (56%)	39 (64%)	0.111
Diabetes	59 (32%)	17 (28%)	18 (30%)	24 (39%)	0.332
Culprit lesion:					0.660
LAD	105 (57%)	37 (60%)	38 (62%)	30 (49%)	
LCX	20 (11%)	6 (10%)	6 (10%)	8 (13%)	
RCA	59 (32%)	19 (31%)	17 (28%)	23 (38%)	
Killip class > I	38 (21%)	10 (16%)	10 (16%)	18 (30%)	0.125
TIMI risk score > 4	99 (54%)	27 (44%)	35 (57%)	37 (61%)	0.131
CACS risk score > 1	25 (17%)	7 (11%)	11 (18%)	14 (23%)	0.226
Medication:					
ASA	184 (100%)	62 (100%)	61 (100%)	61 (100%)	1.000
P2Y12 inhibitors*	175 (95%)	60 (97%)	56 (92%)	59 (97%)	0.474
Beta-blocker	159 (86%)	56 (90%)	49 (80%)	54 (89%)	0.221
ACEI or ARB	149 (81%)	51 (82%)	50 (82%)	48 (79%)	0.892
Statin	170 (93%)	58 (94%)	56 (92%)	56 (93%)	0.939
Laboratory findings:					
Initial CPK [IU/L]	132 (85, 256)	135 (89, 259)	130 (85, 256)	129 (78, 258)	0.937
Peak CPK [IU/L]	1895 (769, 3757)	1594 (602, 3882)	1888 (684, 3713)	1927 (905, 3846)	0.657
Initial CK-MB [ng/mL]	3.3 (1.8, 10.9)	2.7 (1.7, 7.2)	3.2 (1.7, 10.9)	3.7 (1.8, 14.8)	0.661
Peak CK-MB [ng/mL]	184.8 (62.3, 300.0)	157.4 (60.0, 300.0)	190.5 (61.0, 300.0)	188.5 (66.7, 300.0)	0.719
Peak CK-MB > 300	62 (34%)	20 (32%)	21 (34%)	21 (35%)	0.942
Initial troponin-T [ng/mL]	0.03 (0.01, 0.13)	0.02 (0.01, 0.07)	0.02 (0.01, 0.11)	0.04 (0.01, 0.21)	0.273
Peak troponin-T [ng/mL]	2.74 (0.96, 6.01)	1.42 (0.44, 5.89)	3.77 (1.12, 6.75)	2.92 (0.76, 5.89)	0.117
Peak troponin-T > 10	23 (13%)	7 (11%)	10 (16%)	6 (10%)	0.569
Initial pro-BNP [pg/mL]†	90.4 (33.6, 394.8)	57.5 (24.9, 212.0)	59.9 (17.9, 335.6)	172.4 (36.8, 926.9)	0.339
Initial hs-CRP [mg/L]	0.16 (0.10, 0.29)	0.16 (0.10, 0.29)	0.16 (0.11, 0.41)	0.17 (0.11, 0.27)	0.728
Initial WBC [/uL]	11290 (8830, 13700)	11065 (8618, 14090)	11500 (9065, 13090)	10630 (9060, 13695)	0.825
Initial eosinophil [/uL]	11 (4, 20)	13 (4, 24)	10 (4, 20)	10 (3, 20)	0.524

→

Table 1 (cont.). Baseline characteristics according to sST2 tertile in patients with ST-segment elevation myocardial infarction.

Variables	Overall (n = 184)	sST2 [ng/mL]			P
		Tertile 1 23.2 ≤ sST2 < 53.6 (n = 62)	Tertile 2 53.6 ≤ sST2 < 72.0 (n = 61)	Tertile 3 72.0 ≤ sST2 (n = 61)	
Major cardiac event (30 days):					
Cardiac death	6 (3%)	2 (3%)	3 (5%)	1 (2%)	0.702
Heart failure	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1.000
Major cardiac event (1 year):					
Cardiac death	6 (3%)	2 (3%)	3 (5%)	1 (2%)	0.702
Heart failure	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1.000

*Ticagrelor 124 (71%), prasugrel 17 (10%), clopidogrel 39 (19%)
†pro-BNP level was obtained in 19 subjects
Data are presented as number (%) and mean (standard deviation) or median (interquartile).
Non-parametric continuous variables, which were evaluated by the Kolmogorov-Smimov method, were analyzed by the Kruskal-Wallis test.
sST2 — soluble suppression of tumorigenicity 2; HR — heart rate; SBP — systolic blood pressure; DBP — diastolic blood pressure; LAD — left anterior descending artery; LCX — left circumflex artery; RCA — right coronary artery; TIMI — Thrombolysis in Myocardial Infarction; CACS — Canadian acute coronary syndrome; ASA — acetylsalicylic acid; ACEI — angiotensin-converting enzyme inhibitor; ARB — angiotensin receptor blocker; CPK — creatine phosphokinase; CK-MB — creatine kinase myocardial bound; BNP — B-type natriuretic peptide; hs-CRP — high sensitivity C-reactive protein; WBC — white blood cell

with trends for old age, hypertension, higher Killip classification, TIMI risk score, and CACS score, although these were not statistically significant. Furthermore, the sST2 level was not associated with age, body weight, sex, smoking, prior angina, diabetes, culprit lesion, and time from symptom onset to initiation of primary PCI. The levels of initial and peak CPK, CK-MB, and cardiac specific troponin were not significantly higher in the higher sST2 tertile groups compared to tertile 1. Inflammatory biomarkers, including high sensitivity C-reactive protein (hs-CRP), white blood cell (WBC) and eosinophil count, were not significantly different among three groups of sST2 concentration. There were no differences in the short- and long-term MACEs based on sST2 concentration.

sST2 and echocardiographic angiographic data

A summary of the echocardiographic data is provided in Tables 2 and 3. When categorized by sST2 concentration, there were no significant differences in the baseline and follow-up in terms of LVEF, LVIDd, E/E', LAVI, and WMSI among the sST2 tertile groups (Table 2). However, in terms of changes in echocardiographic parameters, a lower sST2 concentration was associated with ΔLVEF (absolute percent point difference of LVEF at 6 month vs. baseline; tertile 1, 7.3 [–0.8, 15.8], p = 0.001; tertile 2, 1.3 [–4.3, 9.1], p = 0.319; tertile 3, 1.7 [–8.1, 10.1], p = 0.205) and ΔWMSI (absolute numeric difference of WMSI at 6 month vs. baseline; tertile 1, –0.1 [–0.2, 0], p = 0.001; tertile 2, –0.1 [–0.2, 0.1], p = 0.013; tertile 3, 0 [–0.3, 0], p = 0.055; Table 3 and Fig. 2).

sST2 levels in relation to other biomarkers and risk stratification strategies

A significant univariate association was found only between baseline sST2 concentration and ΔLVEF (r = –0.232, p = 0.018). The baseline troponin-T level was not statistically significant but showed a correlation tendency with baseline sST2 concentration (r = 0.144, p = 0.051). Following adjustment for the relevant variables, partial correlation analysis showed a constant association between sST2 concentration and ΔLVEF (r = –0.273, p = 0.006; adjusted by ΔLVIDd, ΔE/E', ΔLAVI, and ΔWMSI).

According to categories in the known risk stratification strategies, including Killip classification, TIMI risk score, and CACS score, there were no significant differences between risk scores (Fig. 3). In the linear regression model, no significant associations were found between sST2 and known risk stratification strategies (sST2 and Killip classification, β = 0.005, p = 0.320; sST2 and TIMI risk score, β = 0.008, p = 0.220; sST2 and CACS score, β = 0.008, p = 0.222). However, there were significant associations among risk stratification strategies (TIMI risk score and Killip classification, β = 0.382, p < 0.001; CACS score and Killip clas-

Table 2. Echocardiographic parameters according to sST2 tertile in patients with ST-segment elevation myocardial infarction.

Variables	sST2 [ng/mL]			P
	Tertile 1 23.2 ≤ sST2 < 53.6	Tertile 2 53.6 ≤ sST2 < 72.0	Tertile 3 72.0 ≤ sST2 < 197.5	
Baseline (n = 181)				
LVEF [%]	58 (46, 66)	62 (56, 69)	58 (52, 66)	0.241
LVIDd [mm]	50 (47, 52)	51 (46, 54)	50 (46, 54)	0.687
E/E′	10.3 (8.1, 12.6)	10.4 (8.5, 13.9)	11.7 (8.8, 16.2)	0.319
LAVI [mL/m^2]	27.9 (25.5, 33.3)	30.5 (26.1, 39.0)	29.7 (24.5, 36.5)	0.178
WMSI	1.4 (1.1, 1.8)	1.4 (1.1, 1.6)	1.4 (1.1, 1.7)	0.498
6-month follow-up (n = 103)				
LVEF (%]	63 (56, 70)	64 (58, 72)	61 (53, 69)	0.676
LVIDd [mm]	51 (48, 54)	51 (48, 55)	51 (47, 54)	0.841
E/E′	9.3 (7.7, 11.8)	9.9 (8.5, 14.0)	9.6 (8.4, 11.2)	0.564
LAVI [mL/m^2]	28.3 (25.3, 32.6)	31.0 (26.9, 35.7)	29.2 (24.6, 36.8)	0.459
WMSI	1.2 (1.0, 1.6)	1.2 (1.0, 1.4)	1.3 (1.0, 1.7)	0.714

Data are presented as number (%) and mean (standard deviation) or median (interquartile). Non-parametric continuous variables, which were evaluated by the Kolmogorov-Smimov method, were analyzed by the Kruskal-Wallis test. LVEF — left ventricular ejection fraction; LVIDd — left ventricular internal dimension, diastolic; LAVI — left atrial volume index; WMSI — wall motions score index

Table 3. Comparisons of serial changes in echocardiographic parameters after 6 months compared to baseline.

	Δ 6 month — baseline	P
Tertile 1 (n = 34)		
LVEF [%]	7.3 (–0.8, 15.8)	0.001
LVIDd [mm]	0 (–1.3, 3.5)	0.309
E/E′	–0.7 (–2.4, 1.8)	0.487
LAVI [mL/m^2]	1.2 (–4.9, 7.1)	0.260
WMSI	–0.1 (–0.2, 0)	0.001
Tertile 2 (n = 33)		
LVEF [%]	1.3 (–4.3, 9.1)	0.319
LVIDd [mm]	–0.5 (–3.2, 2.9)	0.894
E/E′	0.5 (–2.1, 2.8)	0.889
LAVI [mL/m^2]	1.2 (–5.9, 5.6)	0.407
WMSI	–0.1 (–0.2, 0.1)	0.013
Tertile 3 (n = 36)		
LVEF [%]	1.7 (–8.1, 10.1)	0.205
LVIDd [mm]	1.2 (–1.2, 3.8)	0.067
E/E′	–1.0 (–2.9, 1.0)	0.090
LAVI [mL/m^2]	–0.6 (–5.3, 7.8)	0.972
WMSI	0 (–0.3, 0)	0.055

Data are presented as median (interquartile) and were analyzed through Wilcoxon signed rank sum test. LVEF — left ventricular ejection fraction; LVIDd — left ventricular internal dimension, diastolic; LAVI — left atrial volume index; WMSI — wall motions score index

sification, $\beta = 0.605$, $p < 0.001$; TIMI risk score and CACS score, $\beta = 0.658$, $p < 0.001$).

Association between adverse outcomes and sST2 concentration

Over the course of 1 year following the index PCI, 6 MACE occurred (6 cardiovascular deaths), with an event rate of 3%, and all events occurred within 30 days. Cox regression analysis was used to identify independent predictors for MACE after primary PCI, and the results are shown in Table 4. Baseline systolic blood pressure, symptom to door time, symptom to balloon time, TIMI risk score, and CACS score were independently associated with 1-year MACE by univariate analysis. After adjusting these variables, baseline systolic blood pressure (HR 0.97 [0.94–0.99], $p = 0.011$) was found to independently predict 1-year MACE in this registry. sST2 concentration was not shown to be associated with both short- and long-term outcomes by survival analysis (Fig. 4).

Discussion

Main findings

The current study sought to explore the relationship among pre-procedural serum sST2 concentration and clinical, echocardiographic, and laboratory results in patients with STEMI. The

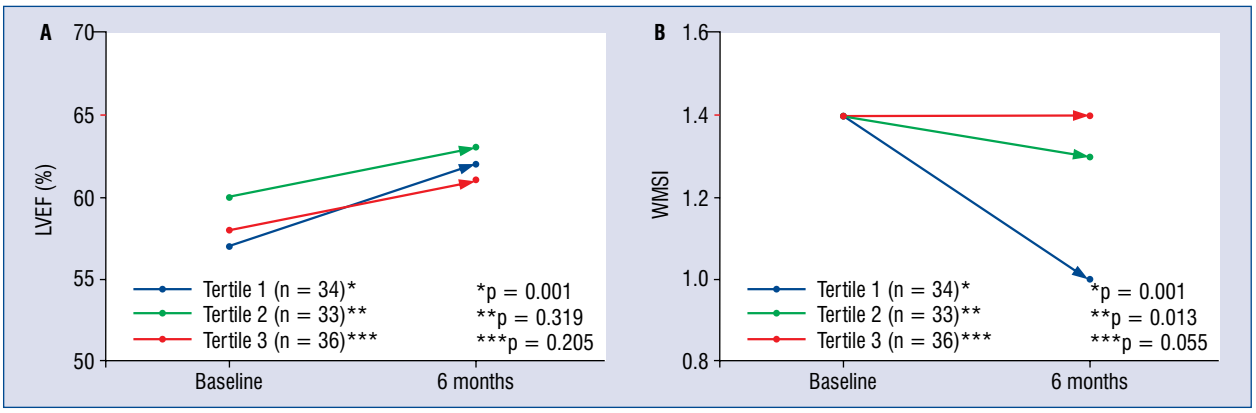

Figure 2. Time-dependent changes in left ventricular ejection fraction (LVEF; **A**) and wall motions score index (WMSI; **B**) by sST2 tertile groups.

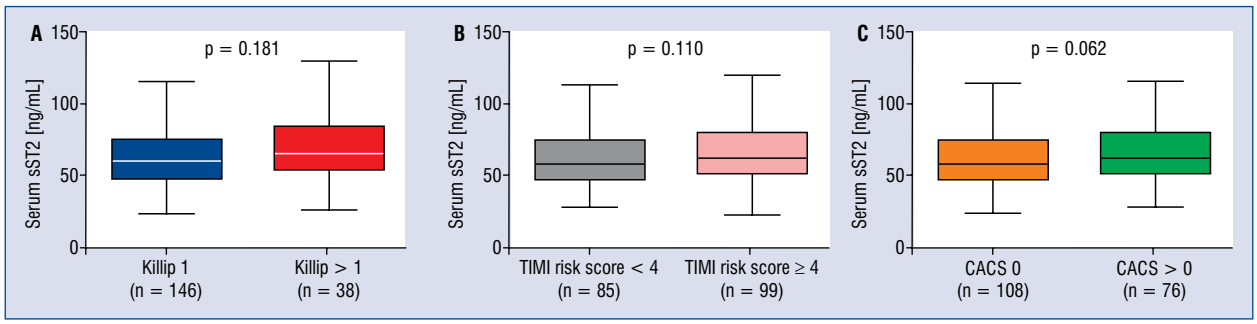

Figure 3. Comparison of sST2 level for Killip, TIMI risk score, CACS score classification in patients with ST-segment elevation myocardial infarction; **A.** Killip classification 1 vs. > 1; **B.** TIMI risk score < 4 vs. ≥ 4; **C.** CACS score 0 vs. > 0; TIMI — thrombolysis in myocardial infarction; CACS — Canadian acute coronary syndrome.

results demonstrated that an elevated concentration of sST2 was a negative predictor of improvement in LV systolic function 6 months after index primary PCI and lower sST2 tertile groups were associated with a significant improvement in WMSI at 6 months. However, a higher sST2 level was not shown to be a predictor of adverse cardiovascular outcomes, independent of traditional risk stratification strategies, including the TIMI risk score, Killip classification, and CACS score for STEMI. Furthermore, the sST2 level was not associated with other biomarkers, including peak CPK, CK-MB, and cardiac specific troponin, and was not shown to be associated with other risk stratification strategies. The location of culprit lesions was not associated with serum sST2 concentration. there was no statistical association found between the serum sST2 concentration and adverse cardiovascular outcomes after primary PCI in this single registry.

sST2 and cardiovascular disease

It is known that ST2, an interleukin-1 receptor family member, is basally expressed by cardiomyocytes [20]. ST2 consists of membrane and soluble forms, and an increase in soluble ST2 has been shown to negatively impact the cardioprotective effect, which in turn, can lead to myocardial remodeling and fibrosis [21, 22]. This finding raised the possibility that the concentration of sST2 may be of predictive value in cardiovascular disease. Indeed, preclinical studies have shown upregulation of sST2 in cardiomyocytes in models of MI [23], while clinical studies have demonstrated the association between a higher sST2 concentration and adverse cardiovascular outcomes in patients with STEMI [13–16, 24]. Furthermore, several studies have demonstrated that short-term changes in sST2 concentration were prognostic of mortality in severe HF [25] among dyspneic patients with

Table 4. Cox regression analysis for predictors of 1-year major adverse cardiac events.

	Univariable analysis		Multivariable model 1*	
	Unadjusted HR (95% CI)	P	Adjusted HR (95% CI)	P
Age	1.03 (0.96–1.11)	0.364		
Female	2.27 (0.50–14.9)	0.247		
Smoking	0.45 (0.09–2.23)	0.328		
Hypertension	4.26 (0.50–36.4)	0.186		
Diabetes	1.09 (0.20–5.92)	0.925		
Baseline SBP	0.97 (0.95–0.99)	0.001	0.97 (0.94–0.99)	0.011
Symptom to door time	1.00 (1.00–1.00)	0.035	1.00 (1.00–1.00)	0.022
Symptom to balloon time	1.00 (1.00–1.00)	0.036		
Door to balloon time	1.00 (0.95–1.06)	0.974		
LAD vs. non-LAD lesion	1.53 (0.28–8.34)	0.624		
Killip classification	1.61 (0.90–2.89)	0.111		
TIMI risk score	1.56 (1.12–2.16)	0.009	1.27 (0.68–2.37)	0.451
CACS score	2.73 (1.27–5.89)	0.010	0.85 (0.16–4.36)	0.840
Peak CPK	1.00 (1.00–1.00)	0.351		
Peak CK-MB	1.00 (0.99–1.01)	0.978		
Peak troponin T	1.30 (1.02–1.65)	0.170		
sST2	0.99 (0.95–1.02)	0.439		
Tertile by sST2:				
Tertile 2 vs. 1	1.53 (0.26–9.12)	0.644		
Tertile 3 vs. 1	0.51 (0.05–5.60)	0.580		

*Model 1: Adjusted for the baseline SBP, symptom to door time, TIMI risk score, and CACS score. The pro-BNP was not included in the analysis due to the small number of subjects. CI — confidence interval, HR — hazard ratio; rest abbreviations are defined in Tables 1 and 2.

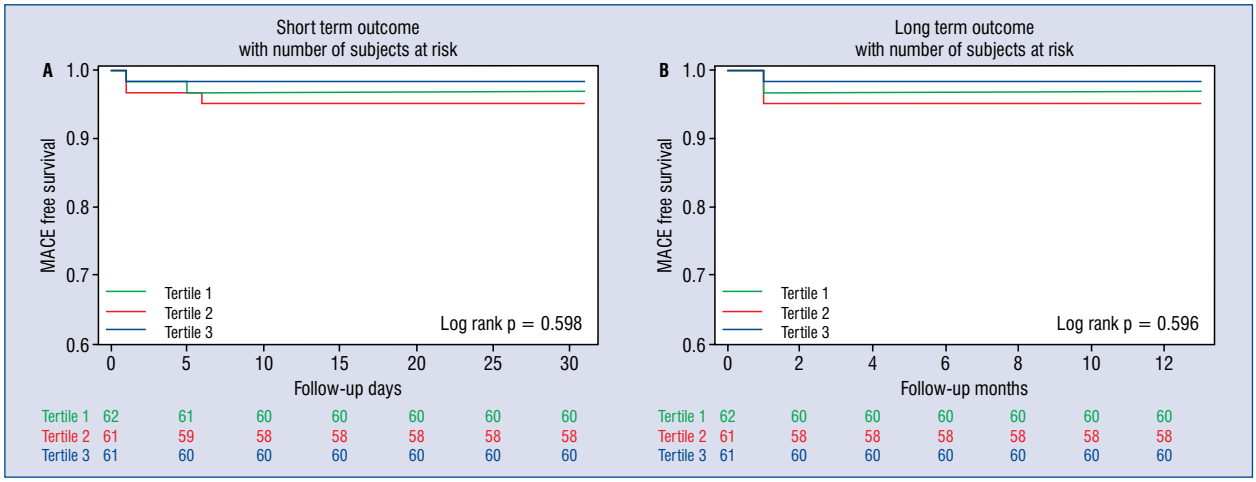

Figure 4. Cumulative incidence of major cardiac adverse events (MACE) during 30 days (**A**) and 1-year (**B**) by sST2 tertile in patients with ST-segment elevation myocardial infarction.

and without acute HF [26]. Many further reports corroborated the prognostic power of sST2 in multiple acute and chronic cardiovascular settings [27, 28].

sST2 as a predictor of 30-day and 1-year MACE after primary PCI

Two reports on data derived from three randomized clinical trials in patients with STEMI

provide data on the predictive value of serum sST2 concentration for adverse outcome up to 30-days after MI, while further studies reported on prognostic implications up to a median follow-up period of 20 months [13, 29, 30]. Shimpo et al. [29] showed that an ascending quartile of serum sST2 concentration significantly corresponded to increasing time from symptom onset, higher heart rates, higher cardiac troponin-I, higher B-type natriuretic peptide (BNP), higher CRP, higher creatinine, and an increasing likelihood of an anterior location of the MI. However, in the present study, the sST2 level was not correlated with other biomarkers, culprit lesion of MI, and time from symptom onset to door/balloon. Sabatine et al. [13] revealed that sST2 and NT-proBNP were found to have complementary roles in STEMI compared to the TIMI risk score. Dhillon et al. [30] also demonstrated a correlation between sST2 and the Global Registry of Acute Coronary Events (GRACE) risk score. However, in the current study, the proBNP level was collected in only 19 subjects and performing a correlation analysis between sST2 and proBNP was not possible. Furthermore, sST2 concentration was not associated with risk stratification strategies including TIMI risk score, Killip classification, and CACS score.

Although a small number of subjects have been included, contrary to prior studies in STEMI [13, 15, 16], the present results did not provide a prognostic power of serum sST2 concentration for adverse cardiovascular outcomes. One possible argument for this discrepancy is that restoration time of flow from symptoms onset affect to myocardial damage which is related to increased biomechanical strain that causes higher sST2 levels. Severe myocardial damage and remodeling is expected in a relatively long term from symptom onset. Previous studies have revealed the time from symptom onset to lytic therapy 2.4 ± 1.3 h to 4.2 ± 3.0 h [13], and 2.8 ± 1.6 to 4.0 ± 1.9 [29]. Analysis of serial measurements of serum sST2 in 228 patients showed an increase sST2 with time especially after 3 h, with a peak level at 12 h for most patients [29]. It was identified herein, that the time from symptom to PCI (median; 2.7–2.8 h) was revealed to be relatively less than in previous studies. This indicates that, perhaps the impact of serum sST2 level would not have been strong in this study.

sST2 and LV remodeling

While data related to circulating sST2 concentration to cardiac function and structure are variable and sparse, some reports have shown a weak inverse relationship between sST2 level and various cardiovascular disease cohorts [31]. Weir et al. [32] analyzed the relationship between sST2 and serial change in LV function after acute MI measured by cardiac magnetic resonance imaging, NT-proBNP, norepinephrine, and aldosterone at baseline and at 12- and 24-week follow-up. It was demonstrated that sST2 had a significant inverse correlation with the change in LVEF between baseline and 6-month follow-up. In addition, the LV end-diastolic volume index was correlated with changes in sST2 concentration. An inverse correlation was demonstrated between the serial change in LVEF, WMSI by transthoracic echocardiography, and baseline sST2 tertile. Furthermore, the LVEF was significantly increased after 6 months in tertile 1, and WMSI was significantly improved after 6 months in tertiles 1 and 2. The serum sST2 concentration after STEMI was related to mid-term changes in LV function and remodeling.

Limitations of the study

The present study should be interpreted in the context of its limitations. First, the present study is observational and was a relatively small single--center retrospective study. The treatment groups may have been confounded by selection bias. Nevertheless, the cohort registry was homogenous, and all study populations included STEMI patients who underwent primary PCI and were managed using the same protocol. Secondly, the blood for sST2 measurements was taken at the presentation of STEMI, and the follow-up sST2 values were not examined. Third, 93%, 86%, and 81% of patients not 100% took statin, beta-blocker, and angiotensin converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) during in-hospital day due to elevated liver enzyme in the case of statin, marked sinus bradycardia even if there were no symptoms in the case of beta-blocker, and suspected acute kidney injury or electrolyte imbalance, such as hyperkalemia in the case of ACEI or ARB. However, most of these drugs were administered unless there was a specific contraindication during outpatient clinic term. Fourth, the time from the first symptom onset to hospital or PCI was quite short compared to that of the Korea Acute Myocardial Infarction Registry (KAMIR), which is the nationwide, prospective, multicenter registry of Korean patients with acute MI (symptom onset to balloon time; median 220 min at 2014; 210 min at 2015; 200 min at 2016; and 212 min at 2017) [3]. Differences were found, including short-and long-term MACE, in this registry compared to

the KAMIR data. Although it is considered possible that a relatively short reperfusion time from symptom onset may have affected the outcome, this could not be determined in this study.

Finally, most previous studies of sST2 in cardiac disease applied different assays than those used in the current study; this limits the transferability of the present results to findings of previous investigations.

Conclusions

In conclusion, lower values of sST2, obtained at the time of presentation at hospital in patients with STEMI resulted in less damaged myocardium and improved LV systolic function in the mid-term which is associated with a lesser likelihood of LV remodeling. However, higher values of sST2 were not associated with either short- or long-term MACE. Data herein, provides valuable information on clinical outcomes and the structural association with sST2 concentration.

Conflict of interest: None declared

References

1. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. Circulation. 2016; 133(4): e38–360, doi: 10.1161/CIR.0000000000000350, indexed in Pubmed: 26673558.
2. Ibanez B, James S, Agewall S, et al. ESC Scientific Document Group. 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.
3. 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.
4. Sim DS, Jeong MHo. Differences in the Korea Acute Myocardial Infarction Registry Compared with Western Registries. Korean Circ J. 2017; 47(6): 811–822, doi: 10.4070/kcj.2017.0027, indexed in Pubmed: 29035427.
5. Menees DS, Peterson ED, Wang Y, et al. Door-to-balloon time and mortality among patients undergoing primary PCI. N Engl J Med. 2013; 369(10): 901–909, doi: 10.1056/NEJMoa1208200, indexed in Pubmed: 24004117.
6. Afilalo J, Piazza N, Tremblay S, et al. Symptom-to-door time in ST segment elevation myocardial infarction: overemphasized or overlooked? Results from the AMI-McGill study. Can J Cardiol. 2008; 24(3): 213–216, doi: 10.1016/s0828-282x(08)70587-7, indexed in Pubmed: 18340392.
7. Lindahl B, Toss H, Siegbahn A, et al. Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. FRISC Study Group. Fragmin during Instability in Coronary Artery Disease. N Engl J Med. 2000; 343(16): 1139–1147, doi: 10.1056/NEJM200010193431602, indexed in Pubmed: 11036119.
8. Chan D, Ng LL. Biomarkers in acute myocardial infarction. BMC Med. 2010; 8: 34, doi: 10.1186/1741-7015-8-34, indexed in Pubmed: 20529285.
9. Vieira C, Nabais S, Ramos V, et al. Multimarker approach with cystatin C, N-terminal pro-brain natriuretic peptide, C-reactive protein and red blood cell distribution width in risk stratification of patients with acute coronary syndromes. Rev Port Cardiol. 2014; 33: 127–36.
10. Sanada S, Hakuno D, Higgins LJ, et al. IL-33 and ST2 comprise a critical biomechanically induced and cardioprotective signaling system. J Clin Invest. 2007; 117(6): 1538–1549, doi: 10.1172/JCI30634, indexed in Pubmed: 17492053.
11. Turnquist HR, Zhao Z, Rosborough BR, et al. IL-33 expands suppressive CD11b+ Gr-1(int) and regulatory T cells, including ST2L+ Foxp3+ cells, and mediates regulatory T cell-dependent promotion of cardiac allograft survival. J Immunol. 2011; 187(9): 4598–4610, doi: 10.4049/jimmunol.1100519, indexed in Pubmed: 21949025.
12. Seki K, Sanada S, Kudinova AY, et al. Interleukin-33 prevents apoptosis and improves survival after experimental myocardial infarction through ST2 signaling. Circ Heart Fail. 2009; 2(6): 684–691, doi: 10.1161/CIRCHEARTFAILURE.109.873240, indexed in Pubmed: 19919994.
13. Sabatine MS, Morrow DA, Higgins LJ, et al. Complementary roles for biomarkers of biomechanical strain ST2 and N-terminal prohormone B-type natriuretic peptide in patients with ST-elevation myocardial infarction. Circulation. 2008; 117(15): 1936–1944, doi: 10.1161/CIRCULATIONAHA.107.728022, indexed in Pubmed: 18378613.
14. Kohli P, Bonaca MP, Kakkar R, et al. Role of ST2 in non-ST-elevation acute coronary syndrome in the MERLIN-TIMI 36 trial. Clin Chem. 2012; 58(1): 257–266, doi: 10.1373/clinchem.2011.173369, indexed in Pubmed: 22096031.
15. Yu J, Oh PC, Kim M, et al. Improved early risk stratification of patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention using a combination of serum soluble ST2 and NT-proBNP. PLoS One. 2017; 12(8): e0182829, doi: 10.1371/journal.pone.0182829, indexed in Pubmed: 28796845.
16. Jenkins WS, Roger VL, Jaffe AS, et al. Prognostic Value of Soluble ST2 After Myocardial Infarction: A Community Perspective. Am J Med. 2017; 130(9): 1112.e9–1112.e15, doi: 10.1016/j.amjmed.2017.02.034, indexed in Pubmed: 28344136.
17. Kuroiwa K, Li H, Tago K, et al. Construction of ELISA system to quantify human ST2 protein in sera of patients. Hybridoma. 2000; 19(2): 151–159, doi: 10.1089/02724570050031194, indexed in Pubmed: 10868795.
18. Dieplinger B, Januzzi JL, Steinmair M, et al. Analytical and clinical evaluation of a novel high-sensitivity assay for measurement of soluble ST2 in human plasma--the Presage ST2 assay. Clin Chim Acta. 2009; 409(1-2): 33–40, doi: 10.1016/j.cca.2009.08.010, indexed in Pubmed: 19699192.
19. Mitchell C, Rahko PS, Blauwet LA, et al. Guidelines for Performing a Comprehensive Transthoracic Echocardiographic Examination in Adults: Recommendations from the American Society of Echocardiography. J Am Soc Echocardiogr. 2019; 32(1): 1–64, doi: 10.1016/j.echo.2018.06.004, indexed in Pubmed: 30282592.

20. Weinberg E, Shimpo M, Keulenaer GDe, et al. Expression and Regulation of ST2, an Interleukin-1 Receptor Family Member, in Cardiomyocytes and Myocardial Infarction. Circulation. 2002; 106(23): 2961–2966, doi: 10.1161/01.cir.0000038705.69871.d9.
21. Pascual-Figal DA, Januzzi JL. The biology of ST2: the International ST2 Consensus Panel. Am J Cardiol. 2015; 115(7 Suppl): 3B–7B, doi: 10.1016/j.amjcard.2015.01.034, indexed in Pubmed: 25665766.
22. Vasile VC, Jaffe AS. Emerging biomarkers for acute heart conditions. Curr Opin Cardiol. 2014; 29(4): 312–318, doi: 10.1097/HCO.0000000000000077, indexed in Pubmed: 24806784.
23. Kakkar R, Lee RT. The IL-33/ST2 pathway: therapeutic target and novel biomarker. Nat Rev Drug Discov. 2008; 7(10): 827–840, doi: 10.1038/nrd2660, indexed in Pubmed: 18827826.
24. Eggers KM, Armstrong PW, Califf RM, et al. ST2 and mortality in non-ST-segment elevation acute coronary syndrome. Am Heart J. 2010; 159(5): 788–794, doi: 10.1016/j.ahj.2010.02.022, indexed in Pubmed: 20435187.
25. Weinberg EO, Shimpo M, Hurwitz S, et al. Identification of serum soluble ST2 receptor as a novel heart failure biomarker. Circulation. 2003; 107(5): 721–726, doi: 10.1161/01.cir.0000047274.66749.fe, indexed in Pubmed: 12578875.
26. Januzzi JL, Peacock WF, Maisel AS, et al. Measurement of the interleukin family member ST2 in patients with acute dyspnea: results from the PRIDE (Pro-Brain Natriuretic Peptide Investigation of Dyspnea in the Emergency Department) study. J Am Coll Cardiol. 2007; 50(7): 607–613, doi: 10.1016/j.jacc.2007.05.014, indexed in Pubmed: 17692745.
27. Richards AM, Di Somma S, Mueller T. ST2 in stable and unstable ischemic heart diseases. Am J Cardiol. 2015; 115(7 Suppl): 48B–58B, doi: 10.1016/j.amjcard.2015.01.041, indexed in Pubmed: 25678392.
28. Januzzi JL, Pascual-Figal D, Daniels LB. ST2 testing for chronic heart failure therapy monitoring: the International ST2 Consensus Panel. Am J Cardiol. 2015; 115(7 Suppl): 70B–75B, doi: 10.1016/j.amjcard.2015.01.044, indexed in Pubmed: 25670638.
29. Shimpo M, Morrow DA, Weinberg EO, et al. Serum levels of the interleukin-1 receptor family member ST2 predict mortality and clinical outcome in acute myocardial infarction. Circulation. 2004; 109(18): 2186–2190, doi: 10.1161/01.CIR.0000127958.21003.5A, indexed in Pubmed: 15117853.
30. Dhillon OS, Narayan HK, Khan SQ, et al. Pre-discharge risk stratification in unselected STEMI: is there a role for ST2 or its natural ligand IL-33 when compared with contemporary risk markers? Int J Cardiol. 2013; 167(5): 2182–2188, doi: 10.1016/j.ijcard.2012.05.073, indexed in Pubmed: 22835988.
31. Okar S, Kaypakli O, Şahin DY, et al. Fibrosis Marker Soluble ST2 Predicts Atrial Fibrillation Recurrence after Cryoballoon Catheter Ablation of Nonvalvular Paroxysmal Atrial Fibrillation. Korean Circ J. 2018; 48(10): 920–929, doi: 10.4070/kcj.2018.0047, indexed in Pubmed: 30238709.
32. Weir RAP, Miller AM, Murphy GEJ, et al. Serum soluble ST2: a potential novel mediator in left ventricular and infarct remodeling after acute myocardial infarction. J Am Coll Cardiol. 2010; 55(3): 243–250, doi: 10.1016/j.jacc.2009.08.047, indexed in Pubmed: 20117403.

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Erythrocyte transfusion limits the role of elevated red cell distribution width on predicting cardiac surgery associated acute kidney injury

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Abstract

Background: *Acute kidney injury (AKI) is one of the more serious complications after cardiac surgery. Elevated red cell distribution width (RDW) was reported as a predictor for cardiac surgery associated acute kidney injury (CSAKI). However, the increment of RDW by erythrocyte transfusion makes its prognostic role doubtful. The aim of this study is to elucidate the impact of erythrocyte transfusion on the prognostic role of elevated RDW for predicting CSAKI.*

Methods: *A total of 3207 eligible patients who underwent cardiac surgery during 2016–2017 were enrolled. Changes of RDW was defined as the difference between preoperative RDW and RDW measured 24 h after cardiac surgery. The primary outcome was CSAKI which was defined by the Kidney Disease: Improving Global Outcomes Definition and Staging (KDIGO) criteria. Univariate and multivariate analysis were performed to identify predictors for CSAKI.*

Results: *The incidence of CSAKI was 38.07% and the mortality was 1.18%. CSAKI patients had higher elevated RDW than those without CSAKI (0.65% vs. 0.39%, $p < 0.001$). Multivariate regression showed that male, age, New York Heat Association classification 3–4, elevated RDW, estimated glomerular filtration rate < 60 mL/min/1.73 m^2, cardiopulmonary bypass time > 120 min and erythrocyte transfusion were associated with CSAKI. Subgroup analysis showed elevated RDW was an independent predictor for CSAKI in the non-transfused subset (adjusted odds ratio: 1.616, $p < 0.001$) whereas no significant association between elevated RDW and CSAKI was found in the transfused patients (odds ratio: 1.040, $p = 0.497$).*

Conclusions: *Elevated RDW is one of the independent predictors of CSAKI in the absence of erythrocyte transfusion, which limits the prognostic role of the former on predicting CSAKI.* (Cardiol J 2021; 28, 2: 255–261)

Key words: red cell distribution width, erythrocyte transfusion, cardiac surgery, acute kidney injury

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Introduction

Acute kidney injury (AKI) is one of the prevalent and severe complications after cardiac surgery. The mortality of patients who develop cardiac surgery associated acute kidney injury (CSAKI) or severe AKI with renal replacement therapy (RRT) required remains high [1]. The diagnosis of AKI is mainly based on serum creatine and urine output, whereas these functional markers are insufficient to predict AKI at an earlier stage. Therefore, new biomarkers have been studied for diagnosing AKI earlier [2–5]. Although new biomarkers for predicting AKI have been developed, they are expensive, and restrain the prevalence of utilization in developing countries like India, Brazil and the Chinese mainland, where cardiac surgery is booming and AKI incidence is high.

Red cell distribution width (RDW) is recognized as an index of erythrocyte volume variability and is routinely reported as a part of a complete blood cell count. Recently, its role of predicting CSAKI has been revealed [6, 7]. RDW is reported associating with inflammation or ischemia reperfusion injury [8, 9], and is likely to elevate after cardiac surgery, especially surgery with cardiopulmonary bypass (CPB) [10]. Accordingly, postoperative elevated RDW is potentially associated with the oxidative stress and inflammation during operation and early phase of the postoperative period.

Meanwhile, erythrocyte transfusion is performed widely in cardiac surgery and reported as a potentially modifiable risk factor for CSAKI [11]. Recent evidence suggests that RDW increases after erythrocyte transfusion [12]. However, little is known about whether the increment of RDW by transfusion will influence its value for predicting CSAKI.

The purpose of the present study is to validate the role of elevated RDW predicting CSAKI and analyze whether or not its prognostic role is confounded by erythrocyte transfusion.

Methods

Patient sample

This study was approved by the ethical board of Zhongshan Hospital, Fudan University (Approval Number B2017–039). Informed consent was obtained from all participants. Data from consecutive patients aged 18 years or older who underwent valve and/or coronary artery bypass grafting (CABG) surgery from January 2016 to December 2017 were included in this single-center cohort study. To reduce the confounding effect of acute life-threatening blood loss, patients who received plasma, platelet or more than four units of erythrocytes on the day of surgery were excluded. Other exclusion criteria were: transfusion of red blood cell (RBC) during the 28 days before enrollment, urgent surgery, preoperative mechanical ventilation or tracheotomy, preoperative defibrillator or ventricular assist devices, preoperative RRT, preoperative liver dysfunction, or sepsis.

Data collection

All perioperative data were prospectively collected and extracted retrospectively from the database of Zhongshan Hospital cardiac surgery. All data were checked twice by professional personnel before input into the database. Demographic and procedure-related variables known to be associated with AKI were included in this study after a literature review. They included gender, age, comorbidities, contrast media exposure history, preoperative cardiac function status (New York heart association [NYHA] classification), baseline estimated glomerular filtration rate (eGFR, calculated with CKD-EPI formulae [13]), surgical type, CPB duration, and erythrocyte transfusion amount on the day of surgery. Each unit of erythrocyte contains 300 mL. Full blood counts were measured from BD EDTA-K2 samples using a Sysmex XN9000 electronic counter. Both preoperative and post-operative RDW were collected and changes of RDW was defined as the difference between preoperative RDW and RDW measured 24 h after cardiac surgery. The reference range of RDW value was 11.0–16.0% in this hospital. If there were more than one cardiac surgery procedures performed during a single hospitalization, only the data on the first surgery was included in the analysis.

The primary end-point was postoperative AKI. AKI was defined according to the KDIGO guideline [14] as any of the following: increase in SCr by ≥ 0.3 mg/dL ($\geq 26.5\ \mu$mol/L) within 48 h; or increase in SCr to ≥ 1.5 times the baseline that is known or presumed to have occurred within the prior 7 days or urine volume < 0.5 mL/kg/h for 6 h.

Statistical analyses

Statistical analyses were performed by SPSS statistics for Windows (Version 25.0. IBM Corp, Armonk, NY). Continuous variables were expressed as the mean ± standard deviation (SD) and analyzed by unpaired t-tests, with the Welch adjustment when necessary. Continuous variables that violated the normality assumption were expressed

as median and 25th to 75th percentiles and analyzed by the Mann-Whitney U test. Categorical variables were expressed as absolute (n) and relative (%) frequency and were analyzed by the Pearson 2-test or the Fisher exact test whenever appropriate. A significant level was considered $p < 0.05$.

Univariate analyses were performed to identify a potential association with CSAKI and those with $p < 0.05$ were entered into multivariate regression analysis to identify independent risk factors for both end-points. An adjusted logistic regression model was developed with variables that showed $p < 0.05$ in univariate analysis.

Subgroup analysis was performed to elucidate the impact of erythrocyte transfusion on the prognostic role of elevated RDW for CSAKI. Patients were classified into two groups according to whether receiving transfusions or not. Multivariable regressions were performed to identify the predictive role of elevated RDW for CSAKI in both subsets.

Results

Baseline characteristics

A total of 3207 eligible patients who underwent cardiac surgery during 2016–2017 were enrolled in this cohort study. Characteristics of patients are presented in Table 1. The CSAKI rate in the entire cohort was 38.07% (1221/3207). Among AKI patients, the incidence of stage 1, 2 and 3 were 72.9% (890/1221), 17.5% (214/1221) and 9.6% (117/1221). Male, elder, and those who had more comorbidities such as hypertension and impaired preoperative cardiac and renal function were likely to develop CSAKI. Those patients who underwent complex surgery with multiple procedures or CPB were more inclined to develop CSAKI as well. However, patients in the present study were classified as undergoing valve surgery and no significant relation was found between the occurrence of CSAKI and multidirectional surgery types. The postoperative RDW and elevated RDW were higher in patients who developed CSAKI. Moreover, AKI patients received more RBC transfusions. The in-hospital mortality (2.8 vs. 0.2%, $p < 0.001$) and length of stay (14 vs. 13%, $p < 0.001$) of CSAKI patients were significantly higher as well (Table 1). The magnitude of elevated RDW were higher in patients who received RBC transfusions, regardless of the occurrence of AKI. However, no significant trend of elevated RDW between different RBC transfusion groups was found (Fig. 1).

Predictors for CSAKI

Univariate analysis was performed to identify potential risk factors associated with CSAKI from the variables that showed a p value < 0.05 in Table 1. Male gender (odds ratio [OR]:1.596, 95% CI 1.375–1.852), age (per year) (OR: 1.030, 95% CI 1.024–1.037), preoperative hypertension (OR: 1.288, 95% CI 1.108–1.497), NYHA classification 3–4 (OR: 1.407, 95% CI 1.215–1.629), preoperative eGFR < 60 mL/min/1.73 m^2 (OR: 2.399, 95% CI 1.851–3.108), complex procedure (OR: 2.752, 95% CI 2.001–3.784), CPB time > 120 min (OR: 2.134, 95% CI 1.752–2.599), erythrocyte transfusion (per unit) (OR: 1.340, 95% CI 1.243–1.445) and elevated RDW (OR: 1.335, 95% CI 1.232–1.447) were identified as potential predictors for CSAKI (Table 2).

Multivariate regression was developed with variables that showed a $p < 0.05$ in the univariate analysis. Male gender (OR: 2.127, 95% CI 1.759–2.571), age (per year) (OR: 1.033, 95% CI 1.024–1.042), NYHA classification 3–4 (OR: 1.214, 95% CI 1.002–1.471), preoperative eGFR < 60 mL/ /min/1.73 m^2 (OR: 1.602, 95% CI 1.124–2.284), CPB time > 120 min (OR: 1.919, 95% CI 1.553–2.372), erythrocyte transfusion (per unit) (OR: 1.167, 95% CI 1.056–1.289) and elevated RDW (OR: 1.108, 95% CI 1.005–1.222) were identified as independent predictors for CSAKI (Table 2).

Subgroup analysis

Patients were classified into two groups by whether they received transfusions or not. The CSAKI rate of the transfused patients was higher than the non-transfused (46.9% vs. 33.8%, $p < 0.001$).

Multivariate regression was performed in both subgroups and showed elevated RDW was associated with CSAKI (OR: 1.613, $p < 0.001$) in the non-transfused group whereas no significance between the elevated RDW and CSAKI ($p = 0.497$) was found in the transfused subgroup (Table 3).

The proportion of valve surgery is higher in Chinese patients undergoing heart surgery. A subgroup analysis was performed of patients undergoing valve surgery finding no significant correlation between e-RDW and CSAKI in patients undergoing blood transfusion, while increased e-RDW was a risk factor for CSAKI in non-transfused patients (OR: 1.877) (Table 4).

Discussion

The current study found that patients who developed CSAKI were more male, elderly and

Table 1. Perioperative patient characteristics of the study population.

Characteristics	Without AKI (n = 1986)	AKI (n = 1221)	P
Demographic data			
Male	1121 (56.4%)	823 (67.4%)	< 0.001
Age [years]	55.21 ± 12.68	59.22 ± 10.92	< 0.001
Medical history			
Hypertension	619 (31.2%)	450 (36.9%)	< 0.001
Diabetes mellitus	214 (10.8%)	148 (12.1%)	0.244
NYHA classification 3–4	1108 (55.8%)	781 (64.0%)	< 0.001
Laboratory index			
Hemoglobin [g/L]	133.54 ± 14.98	134 ± 15.99	0.419
Albumin [g/L]	39.83 ± 3.10	39.62 ± 3.21	0.071
Pre-op RDW [%]	13.43 ± 1.32	13.48 ± 1.28	0.187
Post-op RDW [%]	13.79 ± 1.60	14.13 ± 1.55	< 0.001
Elevated RDW [%]	0.39 ± 0.22	0.65 ± 0.23	< 0.001
Kidney function			
Serum creatinine [μmol/L]	76.84 ± 19.31	84.83 ± 31	< 0.001
eGFR [mL/min/1.73 m^2]	90.99 ± 21.42	84.86 ± 22.98	< 0.001
Procedure			
Isolated valve	1271 (64.0%)	717 (58.7%)	0.003
Single valve surgery:			
AVR	374 (18.83%)	158 (12.94%)	0.106
MVP	187 (9.41%)	120 (9.82%)	0.981
MVR	148 (7.45%)	146 (11.95%)	0.225
Double valve surgery:			
AVR+MVP	11 (0.56%)	35 (2.86%)	0.078
DVR	146 (7.35%)	69 (5.65%)	0.498
MVR+TVP	157 (7.90%)	65 (5.32%)	0.497
Triple valve surgery:			
AVR+MVR+TVP	110 (5.53%)	104 (8.50%)	0.355
Others*	138 (6.94%)	20 (1.63%)	0.588
Minimal invasive valve surgery	128 (6.44%)	72 (5.89%)	0.974
Isolated CABG	650 (32.7%)	400 (32.8%)	0.986
Valve and CABG	65 (3.3%)	104 (8.5%)	< 0.001
CPB time [min]	93.61 ± 30.58	110.82 ± 36.39	< 0.001
Erythrocyte transfusion**			
0 U	1427 (71.9%)	728 (59.6%)	< 0.001
1 U	397 (20.0%)	303 (24.8%)	0.001
2 U	39 (2.0%)	52 (4.3%)	< 0.001
3 U	107 (5.4%)	105 (8.6%)	< 0.001
4 U	16 (0.8%)	33 (2.7%)	< 0.001
Prognosis			
In-hospital mortality	4 (0.2%)	34 (2.8%)	< 0.001
Length of hospital stay	13 (10–16)	14 (11–18)	< 0.001

The values are expressed as the median (interquartile range) and mean ± standard deviation or number (percentage). P-values are the results of unpaired t-test or Mann–Whitney U test for continuous variables, and χ^2 test or Fisher's exact test for categorical variables.
*Other procedures include tricuspid valve surgery, repairment of paraprosthetic regurgitation.
**The amount of erythrocyte transfusion refers to the total amount of erythrocyte transfusion for each patient received on the day of surgery.
AKI — acute kidney injury; AVR — aortic valve replacement; CABG — coronary artery bypass grafting; CPB — cardiopulmonary bypass; DVR — aortic valve replacement and mitral valve replacement; eGFR — estimated glomerular filtration rate, calculated by CKD-EPI formulae; MVP — mitral valve plasty; MVR — mitral valve replacement; NYHA — New York Heart Association; RDW — red cell distribution width; TVP — tricuspid valve plasty

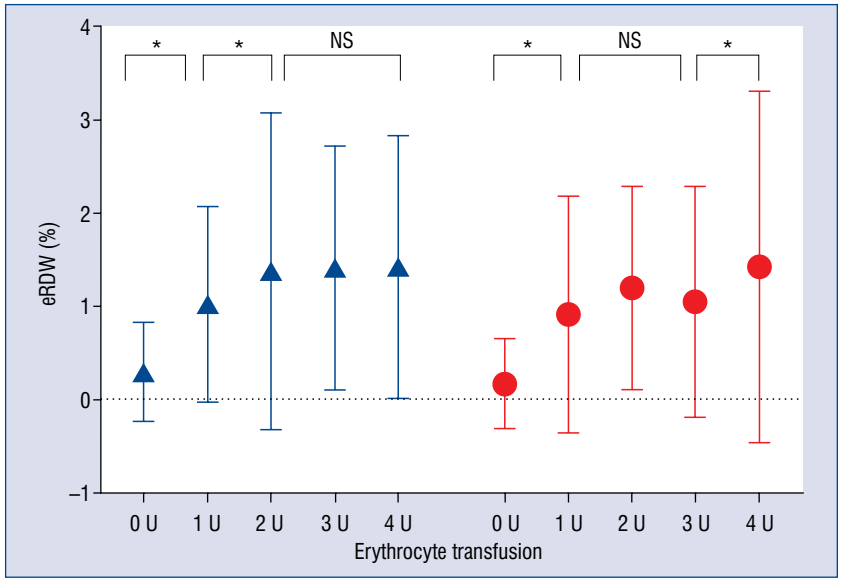

Figure 1. The magnitude of elevated red cell distribution width (eRDW) between different transfusion amount in both acute kidney injury (AKI) and non-AKI subgroups; *p < 0.001; NS — not significant; ▲ — AKI; ● — NONAKI.

Table 2. Analysis of risk factors for CSAKI in entire cohort.

Variables	Unadjusted			Adjusted		
	OR	95% CI	P	OR	95% CI	P
Male	1.596	1.375–1.852	< 0.001	2.127	1.759–2.571	< 0.001
Age [years]	1.030	1.024–1.037	< 0.001	1.033	1.024–1.042	< 0.001
Hypertension	1.288	1.108–1.497	< 0.001			
NYHA classification 3–4	1.407	1.215–1.629	< 0.001	1.214	1.002–1.471	0.048
Elevated RDW (%)	1.335	1.232–1.447	< 0.001	1.108	1.005–1.222	0.039
eGFR < 60 mL/min/1.73 m^2	2.399	1.851–3.108	< 0.001	1.602	1.124–2.284	0.009
Valve + CABG	2.752	2.001–3.784	< 0.001			
CPB time > 120 min	2.134	1.752–2.599	< 0.001	1.919	1.553–2.372	< 0.001
Erythrocyte transfusion [U]*	1.340	1.243–1.445	< 0.001	1.167	1.056–1.289	0.002

*The amount of erythrocyte transfusion refers to the total amount of erythrocyte transfusion for each patient received on the day of surgery. CABG —coronary artery bypass grafting; CI — confidence interval; CSAKI — cardiac surgery associated acute kidney injury; CPB — cardiopulmonary bypass; eGFR — estimated glomerular filtration rate, calculated by CKD-EPI formulae; NYHA — New York Heart Association; OR — odds ratio; RDW — red cell distribution width

Table 3. Subgroup analysis of risk factors for CSAKI.

Variables	Transfusion			Non-transfusion		
	OR	95% CI	P	OR	95% CI	P
Male	2.130	1.582–2.866	< 0.001	2.216	1.722–2.850	< 0.001
Age [years]	1.030	1.016–1.044	< 0.001	1.035	1.024–1.047	< 0.001
eGFR < 60 mL/min/1.73 m^2	1.888	1.165–3.060	0.01			
CPB time > 120 min	2.251	1.631–3.107	< 0.001	1.675	1.257–2.232	< 0.001
NYHA classification 3–4	1.384	1.004–1.909	0.047			
Erythrocyte transfusion [U]*	1.198	1.028–1.391	0.021			
Elevated RDW	1.040	0.928–1.167	0.497 (NS)	1.613	1.277–2.037	< 0.001

*The amount of erythrocyte transfusion refers to the total amount of erythrocyte transfusion for each patient received on the day of surgery. CI — confidence interval; CSAKI — cardiac surgery associated acute kidney injury; CPB — cardiopulmonary bypass; eGFR — estimated glomerular filtration rate, calculated by CKD-EPI formulae; NYHA — New York Heart Association; OR — odds ratio; RDW — red cell distribution width; NS — not significant

Table 4. Subgroup analysis of risk factors for CSAKI in patients underwent valve surgery.

Variables	Transfusion			Non-transfusion		
	OR	95% CI	P	OR	95% CI	P
Male	1.035	1.020–1.051	< 0.001	1.037	1.025–1.048	< 0.001
Age [years]	1.873	1.355–2.587	< 0.001	2.194	1.703–2.826	< 0.001
NYHA classification 3–4	1.430	1.009–2.026	0.045	1.386	1.079–1.781	0.011
Erythrocyte transfusion [U]*	1.194	1.006–1.417	0.042			
Elevated RDW			0.314 (NS)	1.877	1.470–2.397	< 0.001

*The amount of erythrocyte transfusion refers to the total amount of erythrocyte transfusion for each patient received on the day of surgery.
CI — confidence interval; CSAKI — cardiac surgery associated acute kidney injury; NYHA — New York Heart Association; OR — odds ratio; RDW — red cell distribution width; NS — not significant

had more comorbidities. The magnitude of elevated RDW and erythrocyte transfusion were significantly higher in those who developed CSAKI as well. In the entire cohort and non-transfused subgroup, the elevated RDW was identified as independent predictor for CSAKI whereas a similar association was not validated in the transfused subgroup.

Although extensive research has been carried out on the prognostic role of RDW, no single study exists which reports transfusion data or includes transfusion patients [9, 15–17]. According to available research, this is the first study describing the effect of transfusion on the prognostic role of RDW in cardiac surgery patients.

Elevated RDW may indicate several pathogeneses during perioperative phases. First, elevated RDW was reported to be associated with systemic inflammatory response and proinflammatory cytokines during CPB surgery [8, 9]. Second, RDW increases when the number of erythrocytes in which hemoglobin is incompletely saturated with oxygen [18]. Finally, an increase of RDW reflects the increase in variation of erythrocyte size caused by oxidative stress [19].

Recent evidence has shown a relationship between RDW and AKI or its outcome [6, 7, 16]. In a previous study, the elevated RDW was indicated as an independent prognostic factor for severity and poor prognosis of CSAKI [7]. However, transfusion characteristics were not reported. The results in the current study showed a consistent interpretation of elevated RDW associating with CSAKI in the entire cohort and non-transfused patients whereas a similar association was not validated in patients receiving erythrocyte transfusion. One possible explanation was that the role of elevated RDW indicating intraoperative inflammatory response and oxidative stress was predominant in non-transfused patients whereas an identical role was inferior as elevated RDW can be attributed to erythrocyte transfusion, which was reported as another predictor for CSAKI [11].

A prior study noted the incremental effect of erythrocyte transfusion on RDW [12]. This elevated RDW was detectable immediately after transfusion and reached its highest value at 24 h after RBC transfusion. In the current study, the change of RDW was defined as the difference between RDW measured 24 h after cardiac surgery and preoperative RDW. If a patient received multiple numbers of RBC transfusion within the observation period, the cumulative increment of RDW by RBC transfusion will confound its prognostic role. In the transfused subgroup, each unit of erythrocyte transfusion increased 19.8% the risk of CSAKI. Accordingly, the analogous spectrum of ORs (1.08–1.26) for each unit of transfusion were reported in several studies indicating a solid association between erythrocyte transfusion and AKI [20–23].

Limitations of the study

There were several limitations in this study. First, it was a single-center retrospective study. Second, hematopoietic factors were not available in the study population, as it was not routinely tested in the cardiac surgery population. Finally, inflammatory cytokines and biomarkers were not measured in the present study. Therefore, the potential association between the severity of inflammation or oxidative stress and elevated RDW was not quantizable.

Conclusions

In summary, the current study indicated that elevated RDW was associated with the onset of CSAKI in non-transfused cardiac surgery patients. A similar prognostic role of RDW was not valid in

transfused patients due to the increment effect of transfusion on RDW. This confounding influence shall be considered in further studies evaluating the role of RDW.

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References

1. Fuhrman DY, Kellum JA. Epidemiology and pathophysiology of cardiac surgery-associated acute kidney injury. Curr Opin Anaesthesiol. 2017; 30(1): 60–65, doi: 10.1097/ACO.0000000000000412, indexed in Pubmed: 27820742.
2. Albert C, Haase M, Albert A, et al. Urinary biomarkers may complement the cleveland score for prediction of adverse kidney events after cardiac surgery: a pilot study. Ann Lab Med. 2020; 40(2): 131–141, doi: 10.3343/alm.2020.40.2.131, indexed in Pubmed: 31650729.
3. Kellum JA, Chawla LS. Cell-cycle arrest and acute kidney injury: the light and the dark sides. Nephrol Dial Transplant. 2016; 31(1): 16–22, doi: 10.1093/ndt/gfv130, indexed in Pubmed: 26044835.
4. Koyner JL, Zarbock A, Basu RK, et al. The impact of biomarkers of acute kidney injury on individual patient care. Nephrol Dial Transplant. 2020; 35(8): 1295–1305, doi: 10.1093/ndt/gfz188, indexed in Pubmed: 31725154.
5. Srisawat N, Kellum J. The role of biomarkers in acute kidney injury. Critical Care Clinics. 2020; 36(1): 125–140, doi: 10.1016/j.ccc.2019.08.010.
6. Duchnowski P, Hryniewiecki T, Kuśmierczyk M, et al. Anisocytosis predicts postoperative renal replacement therapy in patients undergoing heart valve surgery. Cardiol J. 2019 [Epub ahead of print], doi: 10.5603/CJ.a2019.0020, indexed in Pubmed: 30799549.
7. Zou Z, Zhuang Y, Liu L, et al. Role of elevated red cell distribution width on acute kidney injury patients after cardiac surgery. BMC Cardiovasc Disord. 2018; 18(1): 166.
8. Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation. 2003; 107(3): 499–511, doi: 10.1161/01.cir.0000052939.59093.45, indexed in Pubmed: 12551878.
9. 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.
10. Christen S, Finckh B, Lykkesfeldt J, et al. Oxidative stress precedes peak systemic inflammatory response in pediatric patients undergoing cardiopulmonary bypass operation. Free Radic Biol Med. 2005; 38(10): 1323–1332, doi: 10.1016/j.freeradbiomed.2005.01.016, indexed in Pubmed: 15855050.
11. Karkouti K. Transfusion and risk of acute kidney injury in cardiac surgery. Br J Anaesth. 2012; 109 Suppl 1: i29–i38, doi: 10.1093/bja/aes422, indexed in Pubmed: 23242748.
12. Spadaro S, Taccone FS, Fogagnolo A, et al. The effects of blood transfusion on red blood cell distribution width in critically ill patients: a pilot study. Transfusion. 2018; 58(8): 1863–1869.
13. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009; 150(9): 604–612, doi: 10.7326/0003-4819-150-9-200905050-00006, indexed in Pubmed: 19414839.
14. Kellum JA, Lameire N. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). Crit Care. 2013; 17(1): 204, doi: 10.1186/cc11454, indexed in Pubmed: 23394211.
15. Patel HH, Patel HR, Higgins JM. Modulation of red blood cell population dynamics is a fundamental homeostatic response to disease. Am J Hematol. 2015; 90(5): 422–428.
16. Oh HJ, Park JT, Kim JK, et al. Red blood cell distribution width is an independent predictor of mortality in acute kidney injury patients treated with continuous renal replacement therapy. Nephrol Dial Transplant. 2012; 27(2): 589–594, doi: 10.1093/ndt/gfr307, indexed in Pubmed: 21712489.
17. Hunziker S, Celi LA, Lee J, et al. Red cell distribution width improves the simplified acute physiology score for risk prediction in unselected critically ill patients. Crit Care. 2012; 16(3): R89, doi: 10.1186/cc11351, indexed in Pubmed: 22607685.
18. Nishiyama Y, Niiyama H, Harada H, et al. Effect of exercise training on red blood cell distribution width as a marker of impaired exercise tolerance in patients with coronary artery disease. Int Heart J. 2016; 57(5): 553–557, doi: 10.1536/ihj.16-015, indexed in Pubmed: 27581674.
19. 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.
20. Hajjar LA, Vincent JL, Galas FR, et al. Transfusion requirements after cardiac surgery: the TRACS randomized controlled trial. JAMA. 2010; 304(14): 1559–1567, doi: 10.1001/jama.2010.1446, indexed in Pubmed: 20940381.
21. Jiang W, Teng J, Xu J, et al. Dynamic predictive scores for cardiac surgery: associated acute kidney injury. J Am Heart Assoc. 2016; 5(8), doi: 10.1161/JAHA.116.003754, indexed in Pubmed: 27491837.
22. Karkouti K, Wijeysundera DN, Yau TM, et al. Acute kidney injury after cardiac surgery: focus on modifiable risk factors. Circulation. 2009; 119(4): 495–502, doi: 10.1161/CIRCULATIONAHA.108.786913, indexed in Pubmed: 19153273.
23. Parolari A, Pesce LL, Pacini D, et al. Risk factors for perioperative acute kidney injury after adult cardiac surgery: role of perioperative management. Ann Thorac Surg. 2012; 93(2): 584–591, doi: 10.1016/j.athoracsur.2011.09.073, indexed in Pubmed: 22269725.

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Vitamin D deficiency and anemia is highly prevalent and dependent on the etiology of heart failure: A pilot study

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Abstract

Background: *Anemia and vitamin D deficiency are common factors in chronic heart failure (CHF). The aim of this study was to assess vitamin D levels as well as its binding protein and anemia in relation to a cause of CHF: coronary heart disease, valvular disease and cardiomyopathy.*

Methods: *One hundred and sixteen consecutive patients (36 females and 80 males) with CHF were admitted for percutaneous coronary interventions (PCI). Hemoglobin concentration, serum creatinine, B-type natriuretic peptide (BNP), 25-hydroxyvitamin D [25(OH)D] and its binding protein-VDBP were measured.*

Results: *The prevalence of anemia was 22%. BNP was the highest in the group with coronary artery disease. Ejection fraction was the lowest in cardiomyopathy group. 25(OH)D was lowest in valvular disease group, significantly lower than in the coronary artery group. A similar pattern of change showed vitamin D binding protein. The prevalence of vitamin D deficiency (level below 20 ng/mL) in the whole group was 95%, in 49% of the patients 25(OH)D was below 10 ng/mL. In univariate analysis 25(OH)D correlated with hemoglobin, red blood cell count, hematocrit, mean corpuscular volume and BNP in patients with CHF in the whole group. In multiple regression analysis, predictors of 25(OH)D were estimated, glomerular filtration rate, BNP and valvular disease.*

Conclusions: *25(OH)D deficiency is common in CHF patients. Valvular disease is associated the most severe vitamin D deficiency and worsened kidney function. A higher prevalence of anemia in CHF due to coronary heart disease may be associated with wider use of angiotensin converting enzyme inhibitors and acetylsalicylic acid. Heart and kidney function are predictors of 25(OH)D level in the patients of this study.* (Cardiol J 2021; 28, 2: 262–270)

Key words: vitamin D deficiency, anemia, heart failure

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Introduction

Heart failure (HF) is a common clinical syndrome caused by a variety of cardiac diseases [1]. HF prevalence has been increasing recently due to an aging population and prolongation of life by modern therapeutic innovations. Despite improvements in therapy, the mortality rate in patients with HF has remained unacceptably high [1]. In the 1970s, hypertension and coronary disease, particularly myocardial infarction (MI), were the primary causes of HF in the United States and Europe [1–3]. However, coronary artery disease (CAD) and diabetes mellitus have become increasingly responsible for HF while hypertension and valve disease have become less common because of improvements in diagnosis and therapy [4–7]. Risk factors for HF include coronary heart disease, cigarette smoking, hypertension, obesity, diabetes, and valvular heart disease [5, 8]. Vitamin D deficiency and anemia are frequent findings in HF [1–4]. It was previously shown that the prevalence of anemia in a cohort undergoing percutaneous coronary intervention (PCI) was 21% and related to the New York Heart Association (NYHA) class [9].

Taking all these data into consideration, including fact that studies on anemia and 25-hydroxyvitamin D [25(OH)D] in HF are scarce and equivocal, this cross-sectional study was designed to investigate: a) the prevalence of anemia and vitamin D deficiency in patients with HF due to CAD, cardiomyopathy or valvular disease undergoing PCIs; b) relation between 25(OH)D, its binding protein and anemia in these three subpopulations.

Methods

The study was performed on 116 consecutive patients: 36 females and 80 males with chronic HF with reduced ejection fraction admitted to the Department of Invasive Cardiology for PCIs. The criteria for patients with HF to be included in the study were according to the European Society of Cardiology (ESC) guidelines from 2016 [10]: 1) age ≥ 18 years; 2) documented history of HF of ≥ 6 months; 3) left ventricular ejection fraction (LVEF) ≤ 40% as assessed by echocardiography (performed at the beginning of the study, using the Simpson planimetric method); 4) clinical stability and unchanged medications for ≥ 1 month prior to the study. Patients were divided into three subgroups: group I — patients with chronic HF due to CAD (n = 40); group II — patients with HF due to cardiomyopathy (n = 31); and group III — patients with HF due to valvular disease without signs or symptoms of CAD (n = 45).

Exclusion criteria included: 1) acute coronary syndrome or coronary revascularization within 3 months before the study; 2) unplanned hospitalization due to HF deterioration or any other cardiovascular reason within 1 month before the study; 3) any acute or chronic illness that might influence iron metabolism (including malignancy, infection, chronic kidney disease [CKD] requiring renal replacement therapy, and hematological diseases); 4) any anemia and/or iron deficiency treatment either at the beginning or during 12 months prior to the study. The study protocol was approved by the local ethics committee and all subjects gave informed written consent. The study was conducted in accordance with the Declaration of Helsinki. In all patients, venous blood samples were taken in the morning following an overnight fast and after lying supine at rest for at least 15 min. Hematological parameters were assessed from fresh venous blood sampled with ethylenediaminetetraacetic acid (EDTA). Biochemical parameters were assessed in clotted samples. After centrifuging, serum was collected and frozen at –80°C until laboratory analysis.

The following blood biomarkers were measured directly: hemoglobin concentration, serum creatinine, B-type natriuretic peptide (BNP) were assayed by standard laboratory methods in the central laboratory at the University Hospital. Estimated glomerular filtration rate (eGFR) was assessed using Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) [11]. Creatinine clearance was estimated using the Cockcroft-Gault formula (creatinine clearance = (140 – age) × body weight/serum creatinine × 72 if female × 0.85) [12]. 25(OH)D was assayed using commercially available kits from Gentaur, Kampenhout, Belgium and its binding protein (VDBP) using assays from R&D, Minneapolis, MN, USA. Kidney function was assessed either by serum creatinine or creatinine clearance according to Cockcroft-Gault formula.

Anemia was defined according to the World Health Organization (WHO) criteria, i.e., hemoglobin below 12 g/dL in females and 13 g/dL in males [13]. According to the WHO, vitamin D insufficiency is defined as serum 25(OH)D below 20 ng/mL (50 nmoL/L) [14]. However, Holick [15] defined vitamin D deficiency as serum 25(OH)D level below 20 ng/mL and vitamin D insufficiency as less than 30 ng/mL (75 nmoL/L). The rationale to change the definition was based on the finding that serum

parathyroid hormone, which correlated negatively with serum 25(OH)D, declined as serum 25(OH)D raised and achieved a plateau at a serum 25(OH)D of approximately 30 ng/mL (75 nmoL/L) [16, 17].

Statistical analysis

The statistical significance of differences between the groups was tested using either analysis of variance with F statistics, the Student t test, or χ^2 test, where appropriate. The associations between variables were assessed using the univariate Pearson correlation coefficients or the Spearman rank correlation coefficients. A value of $p < 0.05$ was considered statistically significant. The multiple regression analysis was used to determine independent factors affecting the dependent variables. Factors showing linear correlation with 25(OH)D ($p < 0.1$) were included in the analysis. All statistical analyses were performed using Statistica 13.1.

Results

According to the definition, the prevalence of anemia in the studied cohort was 22% (18% in females and 25% in males). In NYHA class I prevalence of anemia was 11%, in class II — 22%, in class III — 23%, and 31% in class IV ($p < 0.01$ for trend). Baseline clinical and biochemical characteristics of the population studied is presented in Table 1. The group with cardiomyopathy was significantly younger than the two other groups. The degree of HF is reflected by NYHA class (median value was 2 in all groups) and did not differ between groups studied, however BNP was the highest in the group with CAD and LVEF was the lowest in the cardiomyopathy group. Kidney function assessed either by serum creatinine or creatinine clearance according to the Cockcroft-Gault formula, which included body weight, which were similar, whereas eGFR was significantly higher in the cardiomyopathy group when compared to the valvular disease group. 25(OH)D was lowest in valvular disease and cardiomyopathy group, significantly lower than in the coronary artery group. VDBP was significantly lower in group III relative to group I. When the definition of Holick was adopted [15], the prevalence of vitamin D deficiency in the whole group was 95%, only 6 patients had vitamin levels higher than 20 ng/mL, all of them in group I. Serum 25(OH)D below 10 ng/mL was found in 49% of the patients studied, 40% in group I, 45% in group II and 60% in group III, respectively. When patients were classified as anemic/non-anemic it was found that in group I, serum iron was lower in anemic relative to non-anemic patients (39 ± 17 vs. $80 \pm \pm 33$ μg/dL, $p < 0.01$), as well as eGFR by CKD-EPI (69 ± 33 vs. 86 ± 31 mL/min/1.73 m^2, $p < 0.05$). In group II in anemic patients eGFR by CKD-EPI was lower relative to non-anemic patients (69 ± 33 vs. 93 ± 37 mL/min/1.73 m^2, $p < 0.05$). In group III, NYHA class was higher in anemic patients when compared to their non-anemic counterparts (3 ± 1 vs. 2 ± 0.5, $p < 0.05$). In univariate analysis vitamin D correlated with hemoglobin ($r = 0.61$, $p < 0.01$; Fig. 1), red blood cell count ($r = 0.42$, $p < 0.05$), hematocrit ($r = 0.44$, $p < 0.01$), mean corpuscular volume (MCV; $r = 0.25$, $p < 0.05$) and BNP ($r = 0.30$, $p < 0.01$; Fig. 2) in patients with HF (in the whole group). Vitamin D binding protein was related to age ($r = 0.21$, $p < 0.05$; Fig. 3). In the multivariable-adjusted logistic regression analyses on the etiology of HF, predictors of 25(OH)D were eGFR ($r = 0.38$, $p = 0.004$), BNP ($r = 0.41$, $p = 0.003$) and valvular etiology ($r = 0.29$, $p = 0.005$), adjusted R^2 was 45%, F (4,53), $p < 0.001$, SE = 6.82.

Discussion

In the present study, 25(OH)D concentration was assessed together with its binding protein in patients with HF referred for coronary angiography. The main finding in the current study was a high prevalence of vitamin D deficiency (almost 100% in the whole group) and an especially profound vitamin D deficiency (< 10 ng/mL) in HF patients. 25(OH)D was lowest in patients with HF due to valvular disease, significantly lower than in patients with CAD. In the present study, all patients had 25(OH)D lower than 30 ng/mL. Almost 50% of the population studied had 25(OH)D lower than 10 ng/mL. It was also found that VDBP was lowest in the valvular disease group relative to the coronary artery group. Measurements were done in the winter time. 25(OH)D levels in 24 heathy age and sex matched volunteers were also assessed and it was found that 8 of them had 25(OH)D levels below 20 ng/mL, but higher than 10 ng/mL. Mean level was 22 ± 7 ng/mL, and the VDBP level was 337 ± 55 μg/mL. It was highly significant, above ($p < 0.001$) than in the studied population. As reported in the literature, the bone-centric guidelines recommend a target 25(OH)D concentration of 20 ng/mL (50 nmol/L), and age-dependent daily vitamin D doses of 400–800 IU. The guidelines focused on pleiotropic effects of vitamin D recommend a target 25(OH)D concentration of 30 ng/mL (75 nmol/L), and age, body weight, disease status,

Table 1. Clinical and biochemical characteristics of groups studied.

	Group I Coronary heart disease	Group II Cardio-myopathy	Group III Valvular disease	P
Age [years]	68 ± 11	61 ± 10	67 ± 10	I vs. II: p < 0.01 II vs. III: p < 0.01
Anemic patients	29%	20%	21%	I vs. II: p < 0.05
Hemoglobin [g/dL]	13 ± 12	14 ± 2	13 ± 2	NS
Hematocrit [%]	40 ± 5	42 ± 5	40 ± 5	NS
Erythrocyte count [$\times 10^{12}/\mu L$]	4.5 ± 0.5	4.7 ± 0.5	4.5 ± 0.6	NS
MCV [fL]	89 ± 5	90 ± 5	89 ± 4	NS
Iron [μg/dL]	65 ± 33	88 ± 33	89 ± 44	I vs. II: p < 0.01 I vs. III: p < 0.001
Ferritin [ng/mL]	167 (79;246)	175 (113; 276)	115 (75;193)	II vs. III: p < 0.05
Transferrin saturation [%]	23 ± 12	29 ± 13	28 ± 14	I vs. II: p < 0.05 I vs. III: p < 0.05
Functional iron deficiency	7%	8%	11%	NS
Absolute iron deficiency	5%	6%	9%	NS
Vitamin D [ng/mL]	13 ± 6	10 ± 5	10 ± 3	I vs. II: p < 0.05 I vs. III: p < 0.05
Vitamin D binding protein [μg/mL]	281 ± 106	262 ± 51	245 ± 81	I vs. III: p < 0.05
Vitamin D deficiency	85%	100%	100%	I vs. II: p < 0.05 I vs. III: p < 0.05
Creatinine [mg/dL]	1.0 ± 0.3	1.0 ± 0.2	1.0 ± 0.3	NS
Creatinine clearance [mL/min]	70 ± 22	72 ± 21	67 ± 17	NS
eGFR by CKD-EPI [mL/min/1.72 m^2]	81 ± 31	88 ± 34	71 ± 21	II vs. III: p < 0.05
CKD prevalence	27%	30%	25%	NS
Ejection fraction [%]	29 ± 8	24 ± 7	40 ± 16	I vs. II: p < 0.05 I vs. III: p < 0.01 II vs. III: p < 0.01
BNP [pg/mL]	328 (210; 723)	263 (125; 599)	227 (81; 466)	I vs. III: p < 0.05
Hypertension	61%	57%	61%	NS
Diabetes	32%	19%	28%	NS
Atrial fibrillation	23%	33%	38%	NS
ACEI	94%	97%	76%	I vs. III: p < 0.001 II vs. III: p < 0.001
ASA	94%	64%	55%	I vs. II: p < 0.001 I vs. III: p < 0.001
Thienopyridines	60%	24%	22%	I vs. II: p < 0.001 I vs. III: p < 0.001
Anticoagulants	11%	33%	31%	I vs. II: p < 0.01 I vs. III: p < 0.001
Diuretics	79%	87%	67%	I vs. III: p < 0.05 II vs. III: p < 0.001

Data given are percentages, means ± standard deviation or median and interquartile ranges. ACEI — angiotensin converting enzyme inhibitors; ASA — acetylsalicylic acid; BNP — B-type natriuretic peptide; CKD — chronic kidney diseaese; CKD-EPI — Chronic Kidney Disease Epidemiology Collaboration equation; eGFR — estimated glomerular filtration rate; MCV — mean corpuscular volume

and ethnicity-dependent vitamin D doses ranging between 400 and 2000 IU/day [18, 19].

Kolaszko et al. [20] assessed 25(OH)D levels in patients hospitalized in the cardiology ward with regard to a presence or absence of HF. It was found that these groups did not differ with regard to 25(OH)D levels. In addition, 25(OH)D levels were similar in patients with or without CAD,

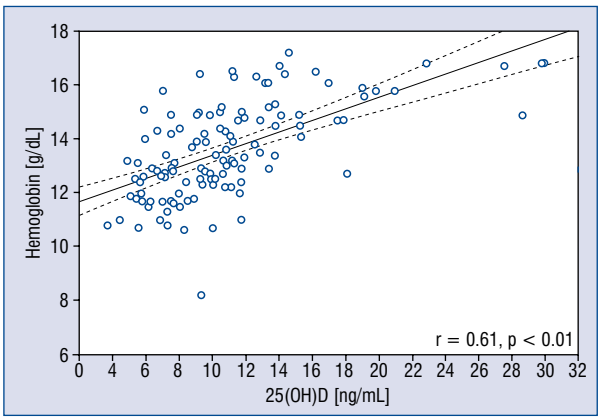

Figure 1. Correlation between hemoglobin and 25(OH)D in heart failure patients.

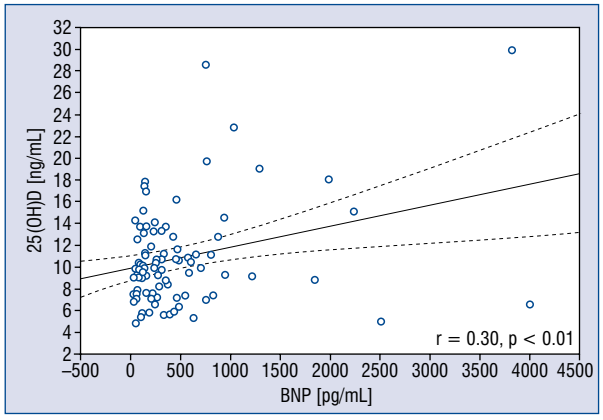

Figure 2. Correlation between B-type natriuretic peptide (BNP) and 25(OH)D in heart failure patients.

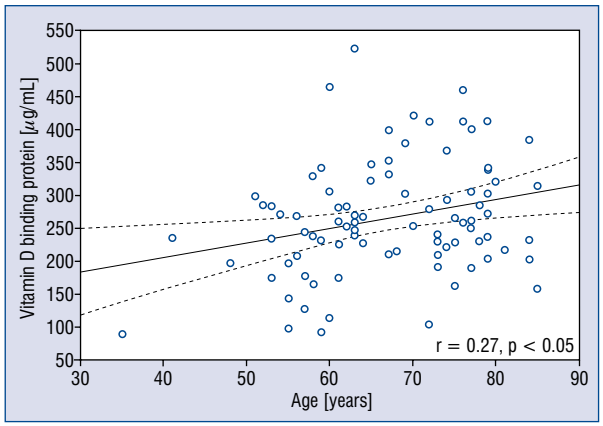

Figure 3. Correlation between vitamin D binding protein and age in heart failure patients.

however, the prevalence of vitamin D deficiency or insufficiency was not reported. The mean level of 25(OH)D in the present study was 12 ± 5 ng/mL in HF and samples were taken in the winter time, similar to the paper by Kolaszko et al. [20]. Being fully aware of seasonal variations [21] data was not collected on dietary supplements of vitamins and other nutrients as well as medications affecting bone health (i.e. steroids). The population herein was slightly older than those studied by Kolaszko et al. [20]. Moreover, 25(OH)D was assessed and its binding protein in HF patients of three different etiologies, while in previous studies etiology was not taken into account. Renal function as reflected by eGFR was comparable to the Kolaszko et al. [20] study. Polat et al. [22] reported that lowered 25(OH)D concentration in HF due to cardiomyopathy was related to severity of the disease. In the present study, there was no correlation between LVEF and 25(OH)D in any group studied.

In the Pandey et al. [23] study more than 90% of HF patients with preserved ejection fraction had 25(OH)D insufficiency, and 30% were deficient. It was also associated with exercise intolerance as reflected by lower peak VO_2 and 6-minute walk distance in HF with preserved ejection fraction. Saponaro et al. [24] evaluated the levels of vitamin D in patients with HF and were compared to a control group to assess the effects of vitamin D on HF outcome. They reported that patients with HF had statistically lower 25(OH)D levels ($p < 0.001$) and a statistically higher prevalence of vitamin D insufficiency (61.1% vs. 39.5%, $p < 0.001$) and deficiency (24.7% vs. 6.6%, $p < 0.001$), relative to the healthy controls. In addition, a significant inverse relationship was observed between baseline 25(OH)D and risk of HF-related death, having a hazard ratio of 0.59 (95% confidence interval 0.37–0.92, $p = 0.02$), and was confirmed in a multivariate adjusted analysis. In corroboration with this study, Walker et al. [25] in a prospective cohort study of 1802 patients with chronic HF and LVEF ≤ 45% found that sepsis was the major cause of death in their study. As sepsis death was independently associated with lower log serum vitamin D than non-sepsis death, and vitamin D supplementation was suggested to possibly be one of the targeted preventative strategies.

Pludowski et al. [26] evaluated the 25(OH)D concentration in a representative group of 5775 adult volunteers in 22 Polish cities. Conducted

in late winter, mean and median concentration of 25(OH)D were 18 ± 10 ng/mL and 16 ng/mL, respectively. In the whole group (spring and winter measurements) serum 25(OH)D levels lower than 20 ng/mL were found in 66%. Also reported, 16% of the participants had surprisingly low levels of 25(OH)D i.e. below 10 ng/mL. In the current study, 49% of the participants had 25(OH)D lower than 10 ng/mL. In the study performed in northern Poland on 448 adults from February to mid-April, the mean 25(OH)D level was 14 ± 7 ng/mL years and 84% had a concentration of less than 20 ng/mL (< 50 nmol/L) [27]. Similar data came from a study on 274 elderly (mean age 69 years) postmenopausal women living in Warsaw [28]. The mean 25(OH)D level was 14 ng/mL (winter time) and 83% had 25(OH)D deficiency. A debate continues on the lower limit of normal for 25(OH)D levels, which depends upon geographic location and sunlight exposure of the reference population. Moreover, there is no consensus on optimal 25(OH)D concentration for skeletal or extraskeletal health. The Institute of Medicine concluded that a serum 25(OH)D concentration of 20 ng/mL (50 nmol/L) is sufficient for most individuals [29], but other experts (Endocrine Society, National Osteoporosis Foundation [NOF], International Osteoporosis Foundation [IOF], American Geriatrics Society [AGS]) suggest that a minimum level of 30 ng/mL (75 nmol/L) is necessary in older adults to minimize the risk of falls and fractures [30–32]. Zhang et al. [33]. reported a plateau above 20 ng/mL for incidence, but much higher for mortality. In the Moli-sani study vitamin D deficiency was associated, independently of known HF risk factors, with an increased risk of hospitalization for HF in an Italian adult population [34].

In the present study, a vast majority of patients had vitamin D deficiency, could not be solely ascribed to impaired kidney function. Other causes of 25(OH)D deficiency include: decreased intake or absorption, reduced sun exposure, increased hepatic catabolism, decreased endogenous synthesis (via decreased 25-hydroxylation in the liver or 1-hydroxylation in the kidney), or end-organ resistance to 25(OH)D. Winter levels of 25(OH)D mainly depend on food intake and previous liver storage. Dietary assessment was not performed in the present population studied. As cutaneous vitamin D production and vitamin D stores decline with age [35], this explanation may also be considered, at least partially. In addition to reduced endogenous production, vitamin D intake is often low in older subjects. It has been also reported that in hospitalized patients, 25(OH)D deficiency defined as level < 15 ng/mL) was found in 57%, of whom 22% were considered severely deficient (serum concentration of 25(OH)D < 8 ng/mL) [36]. As shown, predictors of vitamin D deficiency were inadequate vitamin D intake, winter season, and housebound status. As vitamin D deficiency may be dependent, in part, upon the age of patients on hospital wards [37, 38], it should be stressed that in a subgroup of patients < 65 years without known risk factors, vitamin D deficiency was still detected in 42% [35] of them. As it has been reported previously [39], vitamin D deficiency predisposes up-regulation of renin–angiotensin–aldosterone (RAA) system, causes left ventricle hypertrophy and vascular smooth muscle cell hypertrophy as well.

Anemia was found in 22% of patients studied. Its prevalence rose significantly with NYHA class (from 11% in class I to 31% in class IV). A subclinical inflammatory state was reported, as reflected by elevated levels of cytokines, hemodilution, dietary deficiencies including iron and other microelements, the use of medications affecting RAA system, CKD, poor nutrition and decreased bone marrow perfusion may all contribute to the development of anemia in HF [40–42]. Inflammatory cytokines or high sensitivity C-reactive protein were not studied in the present patients, however, CKD was present in 25–30% of patients as well as iron deficiency (both absolute and functional) was diagnosed in 12–20% depending on the HF etiology, in addition a vast majority of the patients were treated with drugs affecting the RAA system, and as well as acetylsalicylic acid (ASA) and anticoagulants. Therefore, the high prevalence of anemia in the studied group appears to be multifactorial with an important role of CKD as a subclinical inflammatory state and iron deficiency. In addition, therapy of chronic HF with the RAA system blockade and use of other drugs potentially contributed as anticoagulant to the presence of anemia in this population. Higher prevalence of anemia of valvular origin of chronic HF might be associated with a higher prevalence of impaired kidney function as reflected by lower eGFR and creatinine clearance, higher prevalence of iron deficiency (both absolute and functional).

As reviewed previously, angiotensin converting enzyme inhibitors (ACEI)/angiotensin II receptor blockers (ARB) can decrease hemoglobin levels by 0.2–0.3 g/dL [43]. ACEI declined vascular resistance in efferent arterioles in glomeruli, increased oxygenation in the peritubular region and thereby lowered the signal for synthesis of erythropoietin.

The tetrapetide N-acetyl-Ser–Asp–Lys–Pro (Ac-SDKP) named goralatide or seraspenide, a normal inhibitor of entry for pluripotent cells into the S-phase, is metabolized by ACE. During therapy with ACEI, Ac-SDKP can accumulate and cause a decline in erythropoiesis [44].

Findings in the present study show a correlation between 25(OH)D and anemia in patients with HF. It may be due to the fact, that patients with worse kidney function and anemia had a lower 25(OH)D. In other studies associations were found in patients scheduled for cardiac surgery and coronary angiography [45–47]. However, in the randomized controlled trials two studies reported no effect of vitamin D in anemia [48, 49], while two others performed in CKD showed a beneficial effect of vitamin D on the dose of erythropoietin stimulating agents [50, 51]. In Effect of Vitamin D on Mortality in Heart Failure (EVITA) trial vitamin D supplementation had no effect on anemia prevalence in advanced HF patients [52]. In the EVITA trial prevalence of anemia was 17% in the treatment group and 11% in the placebo group, whereas at termination of the study, the prevalence was much higher, reaching 32% in both groups. No data on iron status were provided. In the current study, prevalence of iron deficiency (absolute and functional) was close to 20%. However, no correlations were found between iron parameters, 25(OH)D and its binding protein. It was assumed that there may simply be no causal relationship between anemia, iron status and 25(OH)D in HF. It is well established that vitamin D deficiency is highly prevalent in patients with CKD undergoing renal replacement therapy [53]. This supports the findings that kidney function was a predictor of 25(OH)D in HF. As shown previously, prevalence of CKD was high in patients undergoing PCI despite normal serum creatinine, particularly in higher NYHA class [53, 54]. It corroborates with the present study that BNP was also a predictor of 25(OH)D in HF patients.

Limitations of the study

This study has several strengths and, on the other hand, several limitations. As all patients underwent coronary angiography, we were able to divide the cohort with regard to the etiology of HF. Moreover, vitamin D binding protein as well as detailed iron status data was also assessed. A limitation could be a lack of assessment of parathyroid hormone, calcium, phosphate and cross-sectional design. Other limitations include retrospective data analysis, and no advanced statistical approach to analyze independent associations.

Conclusions

Vitamin D deficiency is very common in HF patients, predominantly in valvular disease. Higher prevalence of anemia in HF due to CAD may be associated with wider ACEI and ASA use relative to other etiologies. Correlation between anemia and 25(OH)D are of interest but require further study to elucidate possible pathogenetic mechanism(s) and also do not provide a rationale for vitamin supplementation. However, heart and kidney function are predictors of 25(OH)D level.

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References

1. Ho KK, Pinsky JL, Kannel WB, et al. The epidemiology of heart failure: the Framingham Study. J Am Coll Cardiol. 1993; 22(4 Suppl A): 6A–613A, indexed in Pubmed: 8376698.
2. Levy D, Larson MG, Vasan RS, et al. The progression from hypertension to congestive heart failure. JAMA. 1996; 275(20): 1557–1562, indexed in Pubmed: 8622246.
3. Tomaszuk-Kazberuk A, Sobkowicz B, Kaminski K, et al. Myocardial perfusion assessed by contrast echocardiography correlates with angiographic perfusion parameters in patients with a first acute myocardial infarction successfully treated with angioplasty. Can J Cardiol. 2008; 24(8): 633–639, indexed in Pubmed: 18685744.
4. Kannel WB, Ho K, Thom T. Changing epidemiological features of cardiac failure. Br Heart J. 1994; 72(2 Suppl): S3–S9, indexed in Pubmed: 7946754.
5. He J, Ogden LG, Bazzano LA, et al. Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. Arch Intern Med. 2001; 161(7): 996–1002, indexed in Pubmed: 11295963.
6. Gheorghiade M, Bonow RO. Chronic heart failure in the United States: a manifestation of coronary artery disease. Circulation. 1998; 97(3): 282–289, indexed in Pubmed: 9462531.
7. Michniewicz E, Mlodawska E, Lopatowska P, et al. Patients with atrial fibrillation and coronary artery disease — Double trouble. Adv Med Sci. 2018; 63(1): 30–35, doi: 10.1016/j.advms.2017.06.005, indexed in Pubmed: 28818746.
8. Baldasseroni S, Opasich C, Gorini M, et al. Left bundle-branch block is associated with increased 1-year sudden and total mortality rate in 5517 outpatients with congestive heart failure: a report from the Italian network on congestive heart failure. Am Heart J. 2002; 143(3): 398–405, indexed in Pubmed: 11868043.
9. Malyszko J, Bachorzewska-Gajewska H, Malyszko J, et al. Prevalence of chronic kidney disease and anemia in patients with coronary artery disease with normal serum creatinine undergo-

ing percutaneous coronary interventions: relation to New York Heart Association class. Isr Med Assoc J. 2010; 12(8): 489–493, indexed in Pubmed: 21337818.
10. Ponikowski P, Voors AA, Anker SD, et al. Authors/Task Force Members, Document Reviewers. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2016; 18(8): 891–975, doi:10.1002/ejhf.592, indexed in Pubmed: 27207191.
11. Stevens PE, Levin A. Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Ann Intern Med. 2013; 158(11): 825–830, doi: 10.7326/0003-4819-158-11-201306040-00007, indexed in Pubmed: 23732715.
12. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976; 16(1): 31–41, doi: 10.1159/000180580, indexed in Pubmed: 1244564.
13. World Health Organization. Nutritional anaemias: Report of a WHO Scientific Group. World Health Organ Tech Rep Ser. 1968; 405: 5–37.
14. WHO Scientific Group on the Prevention and Management of Osteoporosis 2003 Prevention and management of osteoporosis: report of a WHO scientific group. Geneva: World Health Organization.
15. Holick MF. Vitamin D deficiency. N Engl J Med. 2007; 357(3): 266–281, doi: 10.1056/NEJMra070553, indexed in Pubmed: 17634462.
16. http://books.nap.edu/openbook.php?record_id=13050 (Accessed on April 28, 2018).
16. Food and Nutrition Board of the Institute of Medicine. Vitamin D. In: Dietary reference intakes for calcium, hoshorus, magnesium, vitamin D, fluoride. National Academies Press, Washington, DC 1997: 250.
17. Pludowski P, Holick MF, Grant WB, et al. Vitamin D supplementation guidelines. J Steroid Biochem Mol Biol. 2018; 175: 125–135, doi:10.1016/j.jsbmb.2017.01.021, indexed in Pubmed: 28216084.
18. Spedding S, Vanlint S, Morris H, et al. Does vitamin D sufficiency equate to a single serum 25-hydroxyvitamin D level or are different levels required for non-skeletal diseases? Nutrients. 2013; 5(12): 5127–5139, doi: 10.3390/nu5125127, indexed in Pubmed: 24352091.
19. Kolaszko A, Nowalany-Kozielska E, Ceranowicz P, et al. The Role of Parathyroid Hormone and Vitamin D Serum Concentrations in Patients with Cardiovascular Diseases. Dis Markers. 2018; 2018: 5287573, doi: 10.1155/2018/5287573, indexed in Pubmed: 29599854.
20. Dopico XC, Evangelou M, Ferreira RC, et al. Widespread seasonal gene expression reveals annual differences in human immunity and physiology. Nat Commun. 2015; 6: 7000, doi: 10.1038/ncomms8000, indexed in Pubmed: 25965853.
21. Polat V, Bozcali E, Uygun T, et al. Low vitamin D status associated with dilated cardiomyopathy. Int J Clin Exp Med. 2015; 8(1): 1356–1362, indexed in Pubmed: 25785137.
22. Pandey A, Kitzman DW, Houston DK, et al. Vitamin D Status and Exercise Capacity in Older Patients with Heart Failure with Preserved Ejection Fraction. Am J Med. 2018; 131(12): 1515.e11–1515.e19, doi: 10.1016/j.amjmed.2018.07.009, indexed in Pubmed: 30076811.
23. Saponaro F, Saba A, Frascarelli S, et al. Vitamin D measurement and effect on outcome in a cohort of patients with heart failure. Endocr Connect. 2018 [Epub ahead of print]; 7(9): 957–964, doi: 10.1530/EC-18-0207, indexed in Pubmed: 30049838.
24. Walker AMN, Drozd M, Hall M, et al. Prevalence and Predictors of Sepsis Death in Patients With Chronic Heart Failure and Reduced Left Ventricular Ejection Fraction. J Am Heart Assoc. 2018; 7(20): e009684, doi: 10.1161/JAHA.118.009684, indexed in Pubmed: 30371261.
25. Płudowski P, Ducki C, Konstantynowicz J, et al. Vitamin D status in Poland. Pol Arch Med Wewn. 2016; 126(7-8): 530–539, doi: 10.20452/pamw.3479, indexed in Pubmed: 27509842.
26. Kmieć P, Żmijewski M, Waszak P, et al. Vitamin D deficiency during winter months among an adult, predominantly urban, population in Northern Poland. Endokrynol Pol. 2014; 65(2): 105–113, doi: 10.5603/EP.2014.0015, indexed in Pubmed: 24802733.
27. Napiórkowska L, Budlewski T, Jakubas-Kwiatkowska W, et al. Prevalence of low serum vitamin D concentration in an urban population of elderly women in Poland. Pol Arch Med Wewn. 2009; 119(11): 699–703, indexed in Pubmed: 19920793.
28. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Endocrine Society. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011; 96(7): 1911–1930, doi: 10.1210/jc.2011-0385, indexed in Pubmed: 21646368.
29. Vieth R. What is the optimal vitamin D status for health? Prog Biophys Mol Biol. 2006; 92(1): 26–32, doi: 10.1016/j.pbiomolbio.2006.02.003, indexed in Pubmed: 16766239.
30. Dawson-Hughes B, Mithal A, Bonjour JP, et al. IOF position statement: vitamin D recommendations for older adults. Osteoporos Int. 2010; 21(7): 1151–1154, doi: 10.1007/s00198-010-1285-3, indexed in Pubmed: 20422154.
31. American Geriatrics Society Workgroup on Vitamin D Supplementation for Older Adults. Recommendations abstracted from the American Geriatrics Society Consensus Statement on vitamin D for Prevention of Falls and Their Consequences. J Am Geriatr Soc. 2014; 62(1): 147–152, doi:10.1111/jgs.12631, indexed in Pubmed: 24350602.
32. Zhang R, Li B, Gao X, et al. Serum 25-hydroxyvitamin D and the risk of cardiovascular disease: dose-response meta-analysis of prospective studies. Am J Clin Nutr. 2017; 105(4): 810–819, doi: 10.3945/ajcn.116.140392, indexed in Pubmed: 28251933.
33. Costanzo S, De Curtis A, Di Castelnuovo A, et al. Moli-sani Study Investigators. Serum vitamin D deficiency and risk of hospitalization for heart failure: Prospective results from the Moli-sani study. Nutr Metab Cardiovasc Dis. 2018; 28(3): 298–307, doi: 10.1016/j.numecd.2017.11.008, indexed in Pubmed: 29331539.
34. Tsai KS, Wahner HW, Offord KP, et al. Effect of aging on vitamin D stores and bone density in women. Calcif Tissue Int. 1987; 40(5): 241–243, indexed in Pubmed: 3107776.
35. Thomas MK, Lloyd-Jones DM, Thadhani RI, et al. Hypovitaminosis D in medical inpatients. N Engl J Med. 1998; 338(12): 777–783, doi:10.1056/NEJM199803193381201, indexed in Pubmed: 9504937.
36. Perin A, Zanatta E, Pigatto E, et al. Hypovitaminosis D in an hospitalized old population of Western Friuli. Reumatismo. 2012; 64(3): 166–171, doi:10.4081/reumatismo.2012.166, indexed in Pubmed: 22842300.
37. Ramel A, Jonsson PV, Bjornsson S, et al. Vitamin D deficiency and nutritional status in elderly hospitalized subjects in Iceland. Public Health Nutr. 2009; 12(7): 1001–1005, doi: 10.1017/S1368980008004527, indexed in Pubmed: 19144240.

38. Zittermann A. Vitamin D and disease prevention with special reference to cardiovascular disease. Prog Biophys Mol Biol. 2006; 92(1): 39–48, doi:10.1016/j.pbiomolbio.2006.02.001, indexed in Pubmed: 16600341.
39. Anand IS, Gupta P. Anemia and iron deficiency in heart failure: current concepts and emerging therapies. Circulation. 2018; 138(1): 80–98, doi:10.1161/CIRCULATIONAHA.118.030099, indexed in Pubmed: 29967232.
40. Sîrbu O, Floria M, Dascalita P, et al. Anemia in heart failure - from guidelines to controversies and challenges. Anatol J Cardiol. 2018; 20(1): 52–59, doi:10.14744/AnatolJCardiol.2018.08634, indexed in Pubmed: 29952364.
41. Tomaszuk-Kazberuk A, Bolińska S, Młodawska E, et al. Does admission anaemia still predict mortality six years after myocardial infarction? Kardiol Pol. 2014; 72(6): 488–493, doi: 10.5603/KP.a2014.0046, indexed in Pubmed: 24526561.
42. Malyszko J, Oberbauer R, Watschinger B. Anemia and erythrocytosis in patients after kidney transplantation. Transpl Int. 2012; 25(10): 1013–1023, doi: 10.1111/j.1432-2277.2012.01513.x, indexed in Pubmed: 22716097.
43. Stigant CE, Cohen J, Vivera M, et al. ACE inhibitors and angiotensin II antagonists in renal transplantation: an analysis of safety and efficacy. Am J Kidney Dis. 2000; 35(1): 58–63, doi: 10.1016/S0272-6386(00)70302-7, indexed in Pubmed: 10620545.
44. Ernst JB, Zittermann A, Pilz S, et al. Independent associations of vitamin D metabolites with anemia in patients referred to coronary angiography: the LURIC study. Eur J Nutr. 2017; 56(3): 1017–1024, doi: 10.1007/s00394-015-1149-x, indexed in Pubmed: 26746220.
45. Ernst JB, Becker T, Kuhn J, et al. Independent association of circulating vitamin D metabolites with anemia risk in patients scheduled for cardiac surgery. PLoS One. 2015; 10(4): e0124751, doi: 10.1371/journal.pone.0124751, indexed in Pubmed: 25885271.
46. Zittermann A, Kuhn J, Dreier J, et al. Association of 25-hydroxyvitamin D with anemia risk in patients scheduled for cardiac surgery. Int J Lab Hematol. 2014; 36(1): 29–36, doi: 10.1111/ijlh.12112, indexed in Pubmed: 23710993.
47. Sooragonda B, Bhadada SK, Shah VN, et al. Effect of vitamin D replacement on hemoglobin concentration in subjects with concurrent iron-deficiency anemia and vitamin D deficiency: a randomized, single-blinded, placebo-controlled trial. Acta Haematol. 2015; 133(1): 31–35, doi:10.1159/000357104, indexed in Pubmed: 25012612.
48. Madar AA, Stene LC, Meyer HE, et al. Effect of vitamin D3 supplementation on iron status: a randomized, double-blind, placebo-controlled trial among ethnic minorities living in Norway. Nutr J. 2016; 15(1): 74, doi: 10.1186/s12937-016-0192-7, indexed in Pubmed: 27506667.
49. Rianthavorn P, Boonyapapong P. Ergocalciferol decreases erythropoietin resistance in children with chronic kidney disease stage 5. Pediatr Nephrol. 2013; 28(8): 1261–1266, doi: 10.1007/s00467-013-2431-x, indexed in Pubmed: 23420502.
50. Naini AE, Hedaiati ZP, Gholami D, et al. The effect of Vitamin D administration on treatment of anemia in end-stage renal disease patients with Vitamin D deficiency on hemodialysis: A placebo-controlled, double-blind clinical trial. J Res Med Sci. 2015; 20(8): 745–750, doi: 10.4103/1735-1995.168375, indexed in Pubmed: 26664421.
51. Ernst JB, Prokop S, Fuchs U, et al. Randomized supplementation of 4000 IU vitamin D daily vs placebo on the prevalence of anemia in advanced heart failure: the EVITA trial. Nutr J. 2017; 16(1): 49, doi: 10.1186/s12937-017-0270-5, indexed in Pubmed: 28835271.
52. Malyszko J, Koc-Zorawska E, Kozminski P, et al. Underrecognition and Underestimation of Disturbances in Calcium-Phosphate Balance in Kidney Transplant Recipients. Transplant Proc. 2018; 50(6): 1790–1793, doi: 10.1016/j.transproceed.2018.02.155, indexed in Pubmed: 30056901.
53. Tomaszuk-Kazberuk A, Bachorzewska-Gajewska H, Malyszko J, et al. Impact of diabetes mellitus on survival in patients with end-stage renal disease: a three-year follow-up. Kidney Blood Press Res. 2011; 34(2): 83–86, doi: 10.1159/000323894, indexed in Pubmed: 21266825.

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Carotid intima–media thickness (IMT) in patients with severe familial and non-familial hypercholesterolemia: The effect of measurement site on the IMT correlation with traditional cardiovascular risk factors and calcium scores

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Abstract

Background: *The carotid intima–media thickness (IMT) measurement may be carried out proximally (pIMT) or distally (dIMT) in relation to the bulb of the common carotid artery which has significant implications on the results and correlation with risk factors. The aim of the study was to compare the pIMT and dIMT in patients with familial hypercholesterolemia confirmed by genetic testing (FH group) and patients with severe non-familial hypercholesterolemia, with negative results of genetic testing (NFH group) and to determine the correlation of results with traditional atherosclerotic risk factors and calcium scores.*

Methods: *A total of 86 FH and 50 NFH patients underwent pIMT and dIMT measurements of both carotid arteries as well as computed tomography (CT) with coronary and thoracic aorta calcium scoring.*

Results: *The meanpIMT of both right and left common carotid artery were significantly higher in patients with FH compared to the NFH group (meanpRIMT 0.721 ± 0.152 vs. 0.644 ± 0.156, $p < 0.01$, meanpLIMT 0.758 ± 0.173 vs. 0.670 ± 0.110, $p < 0.01$). Patient age, pre-treatment low-density lipoprotein (LDL) cholesterol levels (LDLmax) at baseline and systolic blood pressure were independent predictors of pIMT increases in both carotid arteries. Smoking history, age and LDLmax were independent predictors of dIMT increase. There was a significant correlation between the calcium scores of the ascending aorta, coronary artery and aortic valve and all IMT parameters.*

Conclusions: *The IMT measured proximally better between patients with familial and non-familial hypercholesterolemia. The association between IMT and traditional cardiovascular risk factors varies between measurement sites. IMT values correlate CT calcium scores in all patients with hypercholesterolaemia regardless of genetic etiology.* (Cardiol J 2021; 28, 2: 271–278)

Key words: atherosclerosis, familial hypercholesterolemia, intima–media thickness, calcium scores, multidetector computed tomography

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Introduction

Familial hypercholesterolemia (FH) is an inherited genetic condition characterized by elevated low-density lipoprotein (LDL) levels and an associated increased risk of atherosclerosis. The carotid intima–media thickness (IMT) measurement is an established method for indirect atherosclerosis risk assessment. The computed tomography (CT)-based calcium score measurement is another method which directly indicates the severity of atherosclerosis. The IMT is also associated with atherosclerosis-independent processes such as intimal hyperplasia. However, all known risk factors for atherosclerosis accelerate its thickening. There is a well-established correlation between increased IMT and a higher cardiovascular risk of both cerebrovascular and cardiac events [1, 2]. Nevertheless, current guidelines on the prevention of cardiovascular diseases do not recommend routine IMT measurement [3]. The IMT offers fairly low test repeatability, which is considered its significant methodological disadvantage. Furthermore, different researchers use different IMT measurement techniques, which makes it difficult to compare their findings [4]. The IMT measurement in patients with FH, as a high-risk group, is performed in order to determine the long-term effect of cholesterol-lowering treatments. It is also used for children and young adults in order to identify particular high-risk patients early in life [5–7]. The IMT measurement may be carried out proximally — just below the bulb (pIMT) of the common carotid artery (CCA), or slightly lower, distally, in the area where the lines demarcating the contour of the intima–media complex run parallel (dIMT). The former method has been the predominant approach in many previous studies and clinical trials [8–10]. However, today, the latter method is more often preferred [11]. The results of the measurement performed using both methods in the same group of patients differ significantly from each other and correlate with different risk factors [12]. However, it seems that the measurement taken just below the bulb, which is the usual location of early atherosclerotic plaque, may better reflect the atherosclerotic tendency compared to the distal measurement.

The aim of this study was to compare the pIMT and dIMT in patients with FH confirmed by genetic testing (FH group) and patients with severe non-familial hypercholesterolemia, with negative results of genetic testing (NFH group) and to determine the correlation of results with traditional atherosclerotic risk factors and CT-based calcium scores.

Methods

The study group was selected from 156 consecutive patients with suspected FH, with a minimum score of 3 on the Dutch Lipid Clinic Network diagnostic criteria, and a positive result of genetic testing for FH. The inclusion and exclusion criteria have been previously reported elsewhere [13]. Additionally, 3 patients with known p.(Gly20Arg) gene polymorphism, which is currently considered a polymorphic variant likely associated with a milder FH phenotype, were not included in the IMT analysis. After the exclusion criteria were applied, 86 patients with FH were enrolled (35 male [M], 51 female [F], mean age 49.8 ± 11.6). The control group consisted of 50 patients (23 M, 27 F, mean age 51.5 ± 9.9) diagnosed with severe hypercholesterolemia around the same period and with a negative genetic test result. No participant had a history of previous cardiovascular episodes. All patients had an ultrasound scan of both carotid arteries and IMT measurements were performed. The IMT was measured proximally and distally along the carotid artery, with each measurement covering a 1 cm-long segment [12]. All scans were taken using a GE Vivid E9 ultrasound scanner and 4.5–12 MHz linear probe (GE 11L). The scanning depth was optimised at 3–5 cm. All scans were digitally recorded alongside the electrocardiogram (ECG) reading. The semi-automatic measurement was taken along the 1 cm distal wall segment at the peak of the ECG R-wave using an EchoPAC Clinical Workstation (GE) with dedicated software. The first measurement was taken where the common carotid artery begins to widen, forming a bulb (pIMT). The second measurement was taken where the lines demarcating the inner and outer contour of the IMT complex begin to run parallel (dIMT, Fig. 1). The mean IMT (meanIMT) for a given segment and the maximum value for the left and right carotid artery (maxIMT) were then computed. All measurements were performed twice and then averaged. In order to estimate the repeatability of IMT measurements, intra- and interobserver variability analysis was also performed on 50 patients from the NFH group, with measurements taken independently by an experienced cardiologist and radiologist. All participants also underwent an ECG-gated cardiac CT with calcium score assessment of coronary arteries, aortic valve and aorta in line with the method previously reported elsewhere [13, 14]. The study protocol was approved by the local ethics committee.

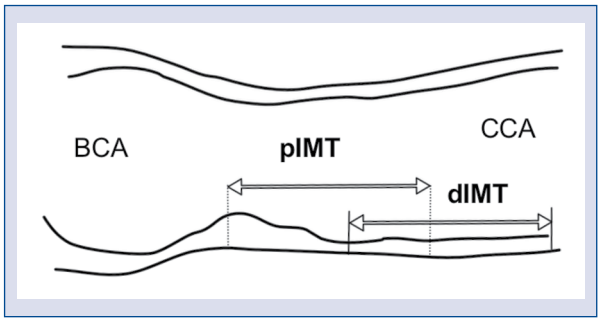

Figure 1. Principles of proximal (pIMT) and distal (dIMT) intima–media thickness measurements. Location determined relative to the common carotid artery (CCA) bulb; BCA — bulb of the carotid artery.

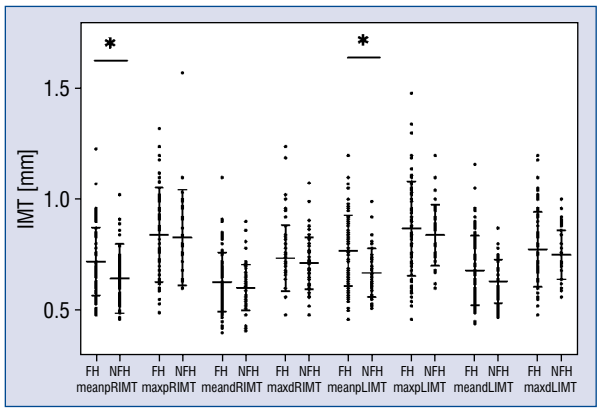

Figure 2. The intima–media thickness of the left and right carotid arteries measured near the bulb (pIMT) and below the bulb (dIMT) in the familial hypercholesterolemia (FH) and non-familial hypercholesterolemia (NFH) groups. *p < 0.01, there were no significant differences in remaining subgroups; IMT — intima–media thickness; RIMT — right carotid artery IMT; LIMT — left carotid artery IMT; meanpIMT — mean proximal IMT; maxpIMT — maximum proximal IMT; meandIMT — mean distal IMT; maxdIMT — maximum distal IMT; pIMT — proximal IMT; dIMT — distal IMT.

Statistical analysis

The IMT results were presented graphically including mean and standard deviations. The normality of distribution assumption was assessed using the Kolmogorov-Smirnov test. The differences between means were assessed using the student T-test or Mann-Whitney U-test for normally and non-normally distributed variables, respectively. The correlations between the IMT and aortic calcium scores were determined using the Spearman rank correlation coefficient. The associations between IMT and traditional cardiovascular risk factors were determined using the multiple linear regression model. All analyses were carried out using SPSS Statistics software. The results were considered significant for $p < 0.05$.

Results

The detailed clinical and genetic characteristics of the study group have been previously reported elsewhere [13]. No statistical differences in age, body mass index (BMI), blood pressure, history of diabetes (3% vs. 10%), smoking (33% vs. 42%) and pretreatment high-density lipoprotein cholesterol (HDLmax) or triglycerides levels (TG) between the FH and NFH groups were found. The FH group however had higher pretreatment total cholesterol (TCmax, 9.4 ± 2.2 vs. 8.1 ± 1.5, $p < 0.001$) and low-density lipoprotein cholesterol levels (LDLmax, 7.1 ± 1.7 vs. 5.1 ± 1.1, $p < 0.001$). The percentage of patients on statin treatment during inclusion to the study also did not significantly differ between the groups (53.4% vs. 40%). Figure 2 presents the dIMT and pIMT measurement results. The meanpIMT of both right and left CCA were significantly higher in patients with FH compared to the NFH group. The maxpIMT, meandIMT, and maxdIMT values were higher in the FH group, although the differences were not significant. The results of multiple linear regression including the IMT parameters and traditional cardiovascular risk factors are shown in Tables 1 and 2. The analysis included the risk factors which did not correlate significantly with each other and correlated with the IMT parameters in a univariate linear regression model. The results of the analysis were presented separately for the right and left carotid artery. Age, pre-treatment cholesterol levels (LDLmax) and systolic blood pressure (SBP) were independent predictors of mean pIMT increase in both carotid arteries. Maximum pIMT values did not correlate significantly with traditional risk factors, except for age. Smoking history, except for the meandLIMT, age and LDLmax were independent predictors of mean and maximum dIMT increase in both carotid arteries. There was no significant correlation between the IMT parameters and diastolic blood pressure, HDLmax and TGmax levels.

The correlations between the IMT parameters and the calcium scores of the aortic valve, ascending aorta, descending aorta and coronary arteries were also evaluated. The results are shown in Table 3. Although it was not high, there was a significant correlation between the calcium scores of the

Table 1. Results of multivariate regression analysis of the right carotid artery intima–media thickness (IMT) with selected traditional risk factors.

	meanpRIMT		maxpRIMT		meandRIMT		maxdRIMT	
R^2 model P	**0.245** **< 0.001**		**0.175** **< 0.01**		**0.306** **< 0.001**		**0.276** **< 0.001**	
Variable	**Coeff.**	**P**	**Coeff.**	**P**	**Coeff.**	**P**	**Coeff.**	**P**
Age	**0.004**	**< 0.001**	**0.005**	**< 0.01**	**0.004**	**< 0.001**	**0.004**	**< 0.001**
Sex	0.024	NS	0.025	NS	0.025	NS	0.030	NS
SBP	**0.002**	**< 0.05**	0.0003	NS	0.001	NS	0.001	NS
LDLmax	**0.001**	**< 0.01**	0.001	0.07	**0.0004**	**< 0.01**	**0.0004**	**< 0.05**
BMI	0.001	NS	0.09	0.07	0.005	0.08	0.005	0.09
Smoking	0.04	NS	0.07	0.07	**0.046**	**< 0.05**	**0.062**	**0.01**

SBP — systolic blood pressure; LDLmax — maximum value of low-density lipoprotein cholesterol (before treatment); BMI — body mass index; RIMT — right carotid artery IMT; LIMT — left carotid artery IMT; meanpIMT — mean proximal IMT, maxpIMT — maximum proximal IMT; meandIMT — mean distal IMT; maxdIMT — maximum distal IMT; NS — non significant

Table 2. Results of multivariate regression analysis including the left carotid artery intima–media thickness (IMT) and selected traditional risk factors.

	meanpLIMT		maxpLIMT		meandLIMT		maxdLIMT	
R^2 model P	**0.19** **< 0.01**		0.07 NS		**0.25** **< 0.001**		**0.255** **< 0.001**	
Variable	**Coeff.**	**P**	**Coeff.**	**P**	**Coeff.**	**P**	**Coeff.**	**P**
Age	**0.003**	**< 0.05**	0.003	NS	**0.004**	**< 0.001**	**0.004**	**< 0.01**
Sex	0.011	NS	0.048	NS	0.041	NS	0.037	NS
SBP	**0.002**	**< 0.05**	0.0004	NS	0.001	NS	0.002	0.07
LDLmax	**0.001**	**< 0.05**	0.0004	NS	**0.001**	**< 0.01**	**0.001**	**< 0.05**
BMI	0.002	NS	–0.0001	NS	0.005	NS	0.003	NS
Smoking	0.047	NS	0.041	NS	0.026	NS	**0.058**	**< 0.05**

SBP — systolic blood pressure; LDLmax — maximum value of low-density lipoprotein cholesterol (before treatment); BMI — body mass index; RIMT — right carotid artery IMT; LIMT — left carotid artery IMT; meanpIMT — mean proximal IMT, maxpIMT — maximum proximal IMT; meandIMT — mean distal IMT; maxdIMT — maximum distal IMT; NS — non significant

Table 3. Correlation between intima–media thickness (IMT) and calcium scores (Spearman's rank correlation coefficient).

	CCS	TCSasc	TCSdsc	AVCS
meanpRIMT	0.42**	0.38**	0.28**	0.29**
maxpRIMT	0.19*	0.27**	0.17	0.24**
meandRIMT	038**	0.32**	0.28**	0.26**
maxdRIMT	0.36**	0.30**	0.27**	0.23**
meanpLIMT	0.35	0.39**	0.28**	0.30**
maxpLIMT	0.21*	0.36**	0.21*	0.22*
meandLIMT	0.29**	0.38	0.13	0.30**
maxdLIMT	0.33**	0.34	0.19*	0.21*

*p < 0.05, **p < 0.01; CCS — coronary calcium score; TCasc — ascending aorta calcium score; TCdsc — descending aorta calcium score; AVCS — aortic valve calcium score; RIMT — right carotid artery IMT; LIMT — left carotid artery IMT; meanpIMT — mean proximal IMT; maxpIMT — maximum proximal IMT; meandIMT — mean distal IMT; maxdIMT — maximum distal IMT

Table 4. Intraobserver and interobserver variability (defined by intra-class coefficient).

	Intraobserver variability	Interobserver variability	P
meanpIMT	96.2	92.9	< 0.001
maxpIMT	94.8	90.8	< 0.001
meandIMT	94.9	91.9	< 0.001
maxdIMT	93	87.1	< 0.001

IMT — intima–media thickness; meanpIMT — mean proximal IMT; maxpIMT — maximum proximal IMT; meandIMT — mean distal IMT; maxdIMT — maximum distal IMT

ascending aorta, coronary artery and aortic valve and all IMT parameters. There was a significant correlation between the calcium score of the descending aorta and most IMT parameters, except for the maxpRIMT and meandLIMT. The strongest correlation was shown between the calcium scores and the meanpIMT of both carotid arteries. On the other hand, there was a higher correlation between the IMT parameters and the calcium scores of the coronary arteries and ascending aorta, but lower correlation between the IMT and the calcium score of the descending aorta.

In order to estimate the repeatability of IMT measurements, intra- and interobserver variability analysis was also performed on 50 patients from the NFH group. The results are shown in Table 4. There was a high intra- and interobserver agreement for all analyzed variables, and were higher for the meanIMT than the maxIMT.

Discussion

A host of studies discuss IMT measurements of patients with hypercholesterolemia. The present study focused on two aspects of IMT measurement, which to date have been rarely discussed. The effect of the measurement site on the IMT values in patients with familial and non-familial severe hypercholesterolemia was assessed. The average values of distal IMT measurements obtained in both subgroups in the current study exceeds the 75th percentile of the normal range as defined in the literature [15]. This corresponds to an increased cardiovascular risk, even though enrolled participants had no history of previous cardiovascular incidents. Furthermore, half of the participants (49.6%) had been treated with statins prior to enrolment. Naturally, statin treatment affected the IMT results. However, the percentage of patients on statins in both groups was comparable.

The meanpIMT values in both carotid arteries were significantly higher in the FH than in the NFH group. Although the values of the remaining IMT parameters were higher in the FH group, the between-group differences were not significant. The TCmax and LDLmax levels were also higher in the FH group, which explains the differences in the meanpIMT. However, the difference in the dIMT was not significant and can be explained by the fact that dispersion of the meandIMT values were lower than those of the meanpIMT values. As a result, it is more difficult to demonstrate measurement site-related differences between two groups of the same size. It should also be noted that as a result of statin treatment administered to some participants, the total cholesterol year score, which reflects the lifetime cumulative total cholesterol, was only slightly (and borderline significantly) higher in the FH group [13]. In patients with hypercholesterolemia from both FH and NFH groups, IMT measured proximally to the bulb (pIMT) was higher than IMT measured distally from the bulb (dIMT). Furthermore, pIMT differed significantly between FH and NFH groups. Willekes et al. [16] also found that IMT increases as the distance shortens between the measurement site and the bulb. Studies of cadavers have shown that atherosclerotic plaque in the bulb precedes the onset of atherosclerotic plaque in the common carotid arteries by about three decades [12]. This can be partly explained by the weaker shear stress near the bulb [17], which facilitates lipid penetration into the vascular endothelium [18]. Thus, pIMT is likely to reflect early stages of atherosclerosis earlier than dIMT in patients with hypercholesterolemia. The present findings of higher IMT in the left carotid artery compared to the right carotid artery has been previously described in several studies [19].

In the current analysis, in most cases, there was a significant correlation between IMT parameters and calcium scores, with higher coefficients seen for pIMT than dIMT. This association between IMT and coronary calcium scores has been previously reported in studies carried out in differ-

ent populations. Arad et al. [20] found a correlation between IMT, coronary calcium scores and the presence of the most hemodynamically significant coronary angiography-confirmed lesion in patients aged 50–75 with coronary artery disease (CAD). Davis et al. [21] also found a strong correlation between IMT and coronary calcium scores in an asymptomatic group of 182 men and 136 women aged 33–42 years, after adjustment for sex and age. Cohen et al. [22] demonstrated a similar correlation in their sample of 150 patients. In their study, CT calcium scoring and IMT thickness measurement were carried out in 61% of study participants either as a part of cardiovascular prevention or in order to determine the severity of their atherosclerosis. Interestingly, unlike the present study, the highest correlation was found between the calcium scores and the maximum rather than mean IMT. However, their IMT calculation was based on the IMT values measured in the CCA, the bulb and internal carotid artery. In the current study, a significant, but not high, correlation between IMT and calcium scores of not only the coronary arteries but also the aortic valve and the ascending aorta was found. Additionally, there was a significant correlation between the majority of the calculated IMT parameters and descending aorta calcium score, although the correlation coefficient was the lowest. This finding is in line with the Framingham offspring study by Kathiresan et al. [23], who found low correlations between the presence of atherosclerotic plaque in the carotid and coronary arteries, and the aorta. Some authors emphasize that IMT and calcium scores represent different stages of vascular wall degeneration. Furthermore, the presence of calcifications, especially in older aged patients, may not closely correlate with traditional risk factors, such as cholesterol levels, hypertension, diabetes, obesity or history of smoking, whereas these correlations are shown for IMT. Therefore, IMT measurement is believed to be a more sensitive indicator of early atherosclerotic changes [24] whilst calcium scores reflect locally advanced atherosclerosis [21].

Also under analysis herein, was the correlation between traditional risk factors and IMT parameters measured proximally and distally from the carotid artery bulb. Multiple linear regression analysis showed that age, SPB and LDLmax were independent predictors of the mean IMT increase for measurements taken proximally to the bulb, whereas age was the only independent predictor of the maximum pIMT. It has been emphasized that the maximum IMT, being less repeatable than the mean IMT, may reflect more advanced atherosclerotic stages with focal thickening of plaque or represent a sampling error [11]. When measured distally from the bulb, the mean and maximum IMT were similarly predicted by the same independent traditional factors, including age, LDLmax, and smoking history. The similarities between both distal IMT (meandIMT and maxdIMT) parameters can be explained by the fact that these are measured along an even, parallel segment of the carotid artery, therefore both measurements would not differ significantly, unlike meanpIMT and maxpIMT which were measured along an uneven carotid artery segment, which makes measurements significantly discrepant. Age and LDLmax were independent predictors for all meanIMT parameters. The SBP predicted a higher meanpIMT in the present study, whereas positive smoking history predicted a higher value of most distal IMT measurements. The literature data evaluating the effect of IMT measurement site on its correlation with traditional risk factors for atherosclerosis is significantly limited. Polak et al. [12] measured IMT in randomly chosen Caucasian individuals from the MESA study population and found distal IMT to be lower, but correlated better with cardiovascular risk factors than proximal IMT. In another study, the same authors assessed the IMT measurement site as a predictor of CAD and its effect on the correlation with traditional risk factors [12]. Measurements were taken in 279 randomly chosen Caucasian individuals without a history of previous cardiovascular incidents from the MESA study population. The dIMT better predicted CAD than pIMT. However, diagnosis was only made in 11 patients during the study and therefore, the robustness of the analysis was significantly affected by the low CAD incidence.

Limitations of the study

Although an increased IMT is generally considered to reflect early atherosclerotic changes, this consideration may not always be true. The IMT is also a measure of smooth muscle hypertrophy reflecting normal aging and the differentiation of those two processes is limited. The main limitation of this single-center study is the relatively small number of patients. Small numbers might have overfitted the multivariable analysis. Nevertheless, the present analysis met all necessary requirements of multivariate logistic regression. Moreover, many of patients with severe hypercholesterolemia enrolled in the study were treated

over a long period with statins which could have affected the natural history of IMT increase.

Conclusions

The IMT measured at the carotid artery bulb is higher than the IMT value measured further from the bulb and better differentiates between patients with FH and NFH. The association between IMT and traditional cardiovascular risk factors varies between measurement sites, which additionally indicates differences in the mechanism of IMT increase depending on the distance from the bulb. The IMT values correlated with coronary, aortic valve and aortic calcium scores in all patients with hypercholesterolemia regardless of genetic etiology.

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Conflict of interest: None declared

References

1. O'Leary DH, Polak JF, Kronmal RA, et al. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. N Engl J Med. 1999; 340(1): 14–22, doi: 10.1056/NEJM199901073400103, indexed in Pubmed: 9878640.
2. Chambless LE, Heiss G, Folsom AR, et al. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987-1993. Am J Epidemiol. 1997; 146(6): 483–494, doi: 10.1093/oxfordjournals.aje.a009302, indexed in Pubmed: 9290509.
3. Piepoli MF, Hoes AW, Brotons C, 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.
4. Lorenz MW, Markus HS, Bots ML, et al. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. Circulation. 2007; 115(4): 459–467, doi: 10.1161/CIRCULATIONAHA.106.628875, indexed in Pubmed: 17242284.
5. Lavrencic A, Kosmina B, Keber I, et al. Carotid intima-media thickness in young patients with familial hypercholesterolaemia. Heart. 1996; 76(4): 321–325, doi: 10.1136/hrt.76.4.321, indexed in Pubmed: 8983678.
6. Kusters D, Wiegman A, Kastelein J, et al. Carotid intima-media thickness in children with familial hypercholesterolemia. Circ Res. 2014; 114(2): 307–310, doi: 10.1161/circresaha.114.301430.
7. Wiegman A, de Groot E, Hutten BA, et al. Arterial intima-media thickness in children heterozygous for familial hypercholesterolaemia. Lancet. 2004; 363(9406): 369–370, doi: 10.1016/S0140-6736(04)15467-6, indexed in Pubmed: 15070569.
8. Kornet L, Lambregts J, Hoeks AP, et al. Differences in near-wall shear rate in the carotid artery within subjects are associated with different intima-media thicknesses. Arterioscler Thromb Vasc Biol. 1998; 18(12): 1877–1884, doi: 10.1161/01.atv.18.12.1877, indexed in Pubmed: 9848879.
9. Iglesias del Sol A, Bots ML, Grobbee DE, et al. Carotid intima-media thickness at different sites: relation to incident myocardial infarction; The Rotterdam Study. Eur Heart J. 2002; 23(12): 934–940, doi: 10.1053/euhj.2001.2965, indexed in Pubmed: 12069447.
10. Hollander M, Hak AE, Koudstaal PJ, et al. Comparison between measures of atherosclerosis and risk of stroke: the Rotterdam Study. Stroke. 2003; 34(10): 2367–2372, doi: 10.1161/01.STR.0000091393.32060.0E, indexed in Pubmed: 12958327.
11. Iana Simova,. Intima-media thickness: Appropriate evaluation and proper measurement, described. E-journal of the ESC Council for Cardiology Practice 2015; Vol. 13, N° 21.
12. Polak JF, Post WS, Carr JJ, et al. Associations of common carotid intima-media thickness with coronary heart disease risk factors and events vary with distance from the carotid bulb. J Am Soc Echocardiogr. 2014; 27(9): 991–997, doi: 10.1016/j.echo.2014.04.019, indexed in Pubmed: 24944141.
13. Galaska R, Kulawiak-Galaska D, Wegrzyn A, et al. Assessment of Subclinical Atherosclerosis Using Computed Tomography Calcium Scores in Patients with Familial and Nonfamilial Hypercholesterolemia. J Atheroscler Thromb. 2016; 23(5): 588–595, doi: 10.5551/jat.31161, indexed in Pubmed: 26666465.
14. Gałąska R, Kulawiak-Gałąska D, Chmara M, et al. Aortic valve calcium score in hypercholesterolemic patients with and without low-density lipoprotein receptor gene mutation. PLoS One. 2018; 13(12): e0209229, doi: 10.1371/journal.pone.0209229, indexed in Pubmed: 30592719.
15. Stein JH, Korcarz CE, Hurst RT, et al. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. J Am Soc Echocardiogr. 2008; 21(2): 93–111; quiz 189, doi: 10.1016/j.echo.2007.11.011, indexed in Pubmed: 18261694.
16. Willekes C, Brands PJ, Willigers JM, et al. Assessment of local differences in intima-media thickness in the human common carotid artery. J Vasc Res. 1999; 36(3): 222–228, doi: 10.1159/000025645, indexed in Pubmed: 10393508.
17. Kornet L, Lambregts J, Hoeks AP, et al. Differences in near-wall shear rate in the carotid artery within subjects are associated with different intima-media thicknesses. Arterioscler Thromb Vasc Biol. 1998; 18(12): 1877–1884, doi: 10.1161/01.atv.18.12.1877, indexed in Pubmed: 9848879.
18. Nerem RM. Vascular fluid mechanics, the arterial wall, and atherosclerosis. J Biomech Eng. 1992; 114(3): 274–282, doi: 10.1115/1.2891384, indexed in Pubmed: 1522720.
19. Sun Yu, Lin CH, Lu CJ, et al. Carotid atherosclerosis, intima media thickness and risk factors: an analysis of 1781 asymptomatic

subjects in Taiwan. Atherosclerosis. 2002; 164(1): 89–94, doi: 10.1016/s0021-9150(02)00017-5.

20. Arad Y, Spadaro LA, Roth M, et al. Correlations between vascular calcification and atherosclerosis: a comparative electron beam CT study of the coronary and carotid arteries. J Comput Assist Tomogr. 1998; 22(2): 207–211, doi: 10.1097/00004728-199803000-00008, indexed in Pubmed: 9530380.
21. Davis PH, Dawson JD, Mahoney LT, et al. Increased carotid intimal-medial thickness and coronary calcification are related in young and middle-aged adults. The Muscatine study. Circulation. 1999; 100(8): 838–842, doi: 10.1161/01.cir.100.8.838, indexed in Pubmed: 10458720.
22. Cohen GI, Aboufakher R, Bess R, et al. Relationship between carotid disease on ultrasound and coronary disease on CT angiography. JACC Cardiovasc Imaging. 2013; 6(11): 1160–1167, doi: 10.1016/j.jcmg.2013.06.007, indexed in Pubmed: 24229768.
23. Kathiresan S, Larson MG, Keyes MJ, et al. Assessment by cardiovascular magnetic resonance, electron beam computed tomography, and carotid ultrasonography of the distribution of subclinical atherosclerosis across Framingham risk strata. Am J Cardiol. 2007; 99(3): 310–314, doi: 10.1016/j.amjcard.2006.08.028, indexed in Pubmed: 17261388.
24. Wolski C, Rotkiewicz A, Grzelak P, et al. Comparison of tomographic coronary artery calcification index (calcium score) and ultrasonographic measurement of intima-media complex thickness in diabetic subjects. Pol J Radiol. 2011; 76(4): 15–20, indexed in Pubmed: 22802849.

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Systematic review and meta-analysis appraising efficacy and safety of adrenaline for adult cardiopulmonary resuscitation

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Abstract

Background: *There is a beneficial effect of adrenaline during adult cardiopulmonary resuscitation (CPR) from cardiac arrest but there is also uncertainty about its safety and effectiveness. The aim of this study was to evaluate the use of adrenaline versus non-adrenaline CPR.*

Methods: *PubMed, ScienceDirect, Embase, CENTRAL (Cochrane Central Register of Controlled Trials) and Google Scholar databases were searched from their inception up to 1st July 2020. Two reviewers independently assessed eligibility and risk of bias, with conflicts resolved by a third reviewer. Risk ratio (RR) or mean difference of groups were calculated using fixed or random-effect models.*

Results: *Nineteen trials were identified. The use of adrenaline during CPR was associated with a significantly higher percentage of return of spontaneous circulation (ROSC) compared to non-adrenaline treatment (20.9% vs. 5.9%; RR = 1.87; 95% confidence interval [CI] 1.37–2.55; p < 0.001). The use of adrenaline in CPR was associated with ROSC at 19.4% and for non-adrenaline treatment — 4.3% (RR = 3.23; 95% CI 1.89–5.53; p < 0.001). Survival to discharge (or 30-day survival) when using adrenaline was 6.8% compared to non-adrenaline treatment (5.5%; RR = 0.99; 95% CI 0.76–1.30; p = 0.97). However, the use of adrenaline was associated with a worse neurological outcome (1.6% vs. 2.2%; RR = 0.57; 95% CI 0.42–0.78; p < 0.001).*

Conclusions: *This review suggests that resuscitation with adrenaline is associated with the ROSC and survival to hospital discharge, but no higher effectiveness was observed at discharge with favorable neurological outcome. The analysis showed higher effectiveness of ROSC and survival to hospital discharge in non-shockable rhythms. But more multicenter randomized controlled trials are needed in the future.* (Cardiol J 2021; 28, 2: 279–292)

Key words: adrenaline, epinephrine, cardiac arrest, cardiopulmonary resuscitation, outcome, return of spontaneous circulation, meta-analysis, systematic review

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Introduction

Sudden cardiac arrest (SCA) is a challenge for medical personnel, especially in the context of emergency medical teams, where there are a limited number of personnel in the resuscitation team [1, 2]. Adrenaline has been a key component of advanced life support algorithms for many years. Adrenaline is a catecholamine, showing sympathomimetic activity dependent on direct or indirect stimulation of $\alpha 1$, $\alpha 2$, $\beta 1$, $\beta 2$ receptors. For cardiopulmonary resuscitation (CPR), the effect on $\alpha 1$ receptors is significant due to vasoconstriction. This increases the aortic diastolic pressure, which increases coronary perfusion pressure and cerebral perfusion pressure. As numerous studies indicate, coronary perfusion pressure is closely correlated with the survival of cardiac arrest [3, 4]. It is recommended by both the European Resuscitation Council (ERC) [5], as well as the American Heart Association (AHA) [6]. The use of adrenaline during CPR does not have the highest class of recommendations. Although adrenaline can improve global cerebral and coronary blood flow, due to its vascular contraction, the microcirculatory flow may be reduced [7, 8]. There is a consistent pattern in studies that suggests that adrenaline can initially resume heart function and increase chances of survival, but can generally increase brain injury [9].

The objective herein, was to compare the survival to hospital discharge rates in patients with cardiac arrest treated with and without adrenaline. In this meta-analysis, we hypothesized that adrenaline confirms benefit over placebo or non-adrenaline treatment under adult CPR as seen by the rate of return of spontaneous circulation (ROSC) and survival to hospital discharge.

Methods

This systematic review and meta-analysis were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for conducting and reporting results [10] and The Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines [11] for observational studies. The systematic review protocol has not been registered. Ethical approval was not required for this meta-analysis.

Literature search strategy and inclusion criteria

An electronic database search without language restrictions was performed in a standardized, unblinded manner by two independent reviewers (K.L. and M.C.). Inter-reviewer disagreements were resolved by consultation of the third author (J.S.). The search strategy was first applied to PubMed, Web of Science, Embase, ScienceDirect, the Cochrane Central Register of Controlled Trials (CENTRAL) databases from their inception, to July 1, 2020. In addition to these sources, manual searches in Google and Google Scholar, and web pages of reliable organizations (gray literature) were conducted. An additional manual cross-reference and related-article search was conducted to identify articles that were not found through prior searches.

Inclusive criteria: (a) Research types: randomized controlled trials, quasi-randomized trials, observational studies; (b) Research subjects: human studies involved adult patients with cardiac arrest were included in our meta-analysis. Studies which were preprint were also included. Case--control studies, non-trials conducted on simulated models, editorials, reviews, guidelines, meta--analysis and theoretical models were excluded from the review.

The following search terms were used: "adrenaline" OR "epinephrine" AND "cardiac arrest" OR "heart arrest" OR "circulation arrest" OR "circulatory arrest" OR "induced heart arrest" OR "heart stand still" OR "cardiac ventric* fibrillation" OR "heart ventric* fibrillation" OR "pulseless ventric* tachycardia" OR "asysto*" OR "pulseless electrical activity".

Data extraction

Two independent reviewers conducted the data extraction and checked by each other (K.L. and J.S.). A third reviewer (L.S.) was available to resolve cases for which eligibility was unclear. For each study, a record of the first author, publication time, sample size, country, research type, the primary and secondary measures; inclusion and exclusion criteria; and study quality was included.

Outcomes

The primary outcome of the current meta--analysis was survival to discharge, defined as the rate of survival to hospital discharge or survival at 30 days. The secondary outcome was the ROSC and survival to discharge with favorable neurological outcome defined as a score of 3 or less on the modified Rankin scale [12] or 14 or 15 points in Glasgow Coma Scale [13].

Quality assessment of included studies

Quality assessment was performed by two reviewers (K.S. and K.J.F.). Inter-reviewer disa-

greements were resolved by consultation (J.S.). For quality assessment of randomized controlled trials (RCTs), the Cochrane Collaboration risk assessment tool for RCTs was used. Studies were graded as "low risk", "high risk" or "unclear" for: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. The review authors' judgments about each risk of bias item are provided in the **Supplementary Digital File 1**. The Newcastle-Ottawa quality assessment scale was used to appraise the outcome of interest for the cohort study. The modified Newcastle-Ottawa scale was used for the cross-sectional study [14] and is shown in **Supplementary Digital File 1**.

Statistical analysis

All statistical analyses were performed with Review Manager Software 5.4 (The Cochrane Collaboration, Oxford, Copenhagen, Denmark) to carry out the single-arm meta-analysis. Outcomes were summarized using the Mantel-Haenszel risk ratios (RRs) or mean differences with a 95% confidence interval (CI). 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. [15]. Heterogeneity was quantitatively evaluated by I^2 statistic (no heterogeneity, I^2 = 0–25%; moderate heterogeneity, I^2 = 25–50%; large heterogeneity, I^2 = 50–75%; extreme heterogeneity, I^2 = 75–100%). The random-effects model was used for $I^2 > 50\%$; otherwise, the fixed effects model was employed. All statistical tests were two-sided and were considered when $p < 0.05$.

Results

The systematic literature search identified 1282 relevant publications. After the review of titles and abstracts, 45 studies were selected as being potentially eligible for inclusion into this systematic review. After reading the full-text articles, 5 RCTs (published between 1995 and 2018) including 4951 participants [16–20] and 14 nonrandomized trials (published between 1994 and 2016) including 91,537 participants [13, 21–33] were finally included (Fig. 1). Other information was listed in the Tables 1 and 2 of characteristics of included studies.

Return of spontaneous circulation

Twelve studies reported ROSC [13, 16–18, 20–22, 24–28]. Polled analysis showed that the use of adrenaline during CPR was associated with a significantly higher percentage of ROSC compared to non-adrenaline treatment (20.9% vs. 5.9%; RR = 1.87; 95% CI 1.37–2.55; $p < 0.001$; Fig. 2). The above trend was reflected in both RCTs (35.9% vs. 12.8%; RR = 2.28; 95% CI 1.49–3.49; $p < 0.001$) and observational studies (19.9% vs. 5.8%; RR = 1.70; 95% CI 1.15–2.53; $p = 0.009$).

The incidence of ROSC for shockable rhythms for adrenaline use was 24.0% and 28.1% for non-adrenaline use (RR = 0.86; 95% CI 0.77–0.96; $p = 0.007$). For non-shockable rhythms, the reverse trend was observed (Fig. 3). The use of adrenaline in the CPR process was associated with ROSC at 19.4% and for non-adrenaline treatment — 4.3% (RR = 3.23; 95% CI 1.89–5.53; $p < 0.001$).

Survival to discharge

Survival to discharge (or 30 day survival) using adrenaline was 6.8% compared to the non-adrenaline treatment (5.5%; RR = 0.99; 95% CI 0.76–1.30; $p = 0.97$; Fig. 4) [16–18, 20–24, 26–33].

In the case of non-shockable rhythms, the use of adrenaline compared to non-adrenaline treatment was associated with higher survival to hospital discharge rate (3.9% vs. 2.9%, respectively; RR = 1.16; 95% CI 0.86–1.55; $p = 0.32$; Fig. 5) [17, 21, 22, 24, 28–30, 33]. For shockable rhythms, higher survival to discharge was observed in the non-adrenaline group compared to the adrenaline group (27.1% vs. 15.7%, respectively; RR = 0.63; 95% CI 0.56–0.70; $p < 0.001$) [17, 21, 22, 28, 29, 33].

Survival to discharge with favorable neurological outcome

Ten studies [13, 16, 17, 20–22, 24, 26–28] reported survival to discharge with a favorable neurological outcome and indicated that the use of adrenaline was associated with worse outcome (1.6% vs. 2.2%; RR = 0.57; 95% CI 0.42–0.78; $p < 0.001$).

In randomized clinical trials [16, 17, 20], the use of adrenaline was associated with a slightly higher percentage of patients with survival and favorable neurological outcome compared to the non-adrenaline group (2.9% vs. 2.4%; RR = 1.21; 95% CI 0.95–1.54; $p = 0.13$). The opposite trend was observed for observational studies (**Suppl. Digital File 1**) [13, 21, 22, 24, 26–28].

The analysis in subgroups concerning the type of rhythm showed that in cases of shockable

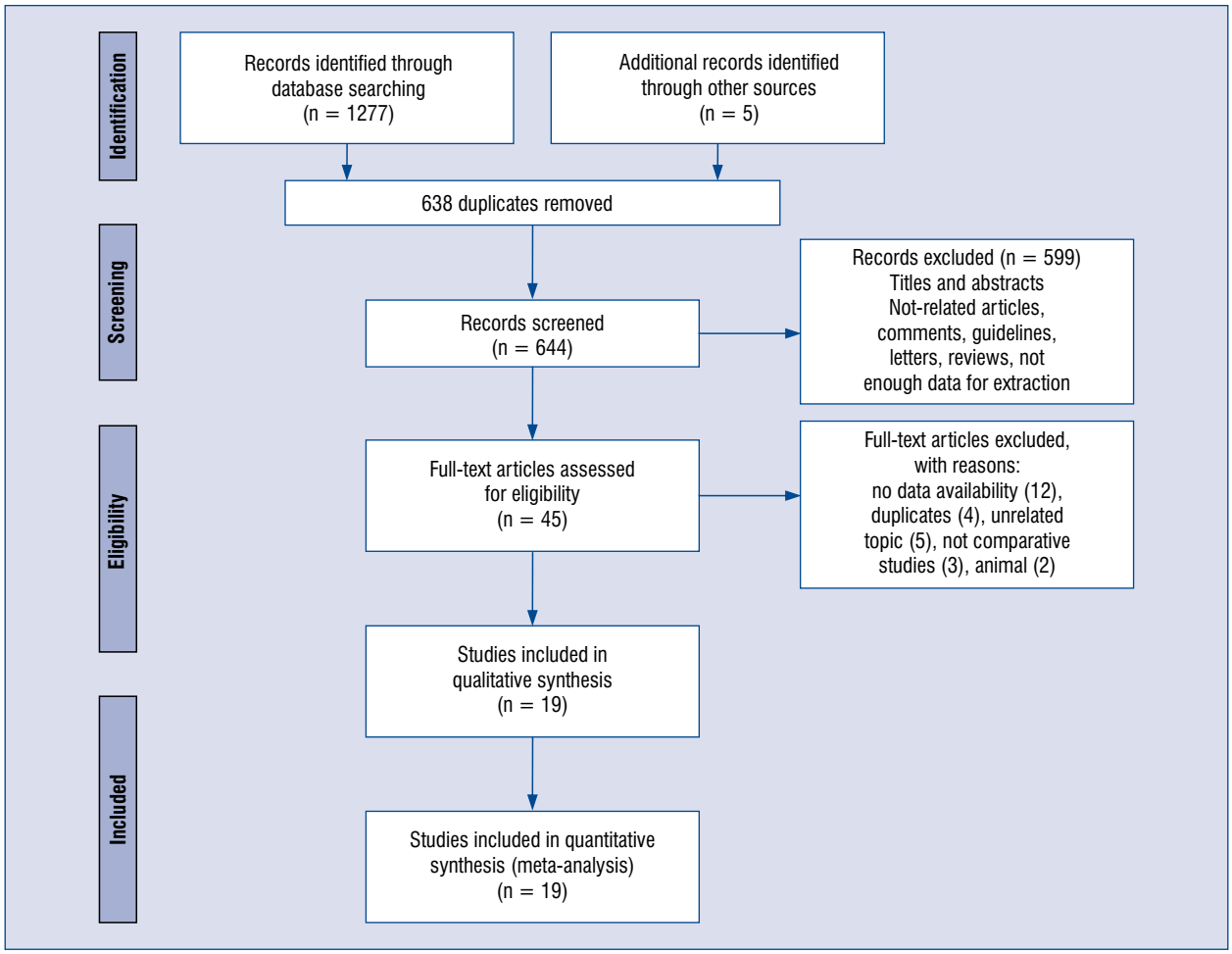

Figure 1. Flow diagram showing stages of database searching and study selection.

rhythms, the use of adrenaline was associated with statistically significant worse prognosis (survival to discharge with the favorable neurological outcome) than the non-adrenaline group (7.4% vs. 19.1%, respectively; RR = 0.40; 95% CI 0.35–0.45; p < < 0.001; **Suppl. Digital File 1**) [21, 22, 24, 28, 33]. For non-adrenaline rhythms the outcome was comparable and was 0.8% vs. 0.9%, respectively (RR = = 0.94; 95% CI 0.16–5.50; p = 0.94) [21, 22, 28, 33].

Long-period outcome

Two studies reported 3-month survival rates [16, 20]. Higher survival rates were observed for adrenaline (3.7%), while for non-adrenaline treatment the survival rate was 2.8% (RR = 1.34; 95% CI 1.06–1.68; p = 0.01). One study, Perkins et al. [16] reported good neurological outcome at 3 months. Better results were obtained with adrenaline compared to the non-adrenaline group (2.1% vs. 1.6%; RR = 1.30; 95% CI 0.94–1.80; p = 0.11).

Quality of evidence

The risk of bias in the included RCTs as well as nonrandomized studies is summarized in **Supplementary Digital File 1**. Only four studies were randomized controlled trials. The risk of bias was assessed as low or moderate in most of the studies.

Discussion

The main finding was as follows: (1) the use of adrenaline increased the chances of ROSC; (2) adrenaline was associated with increased survival to hospital discharge rate, however, survival to discharge with favorable neurological outcome was better in the non-adrenaline group.

Studies published in recent years on the use of adrenaline in SCA are extremely important because of the large number of participants and also because of their randomized nature with

Table 1. Baseline demographic data of the studies when available.

Study	Country	Setting	Type of subject	Adrenaline group			Non-adrenaline group			Adrenaline: non-adrenaline ratio parameters			
				N	Age	Males	N	Age	Males	Initials cardiac rhythm (n)	Cardiac cause (%)	Witnessed by bystander (%)	Bystander CPR (%)
Randomized controlled trials													
Perkins et al. 2018	UK	OHCA	M	4015	69.7 ± 16.6	2609 (65.0%)	3999	69.8 ± 16.4	2584 (64.6%)	VF (716:684) pVT (25:20) PEA (955:937) AS (3149:2135:2194	91.1:92.3	50.1:49.2	59.3:58.7
Jacobs et al. 2011	Australia	OHCA	M	272	64.3 ± 17.5	193 (71.0%)	262	64.9 ± 17.4	196 (74.8%)	VF/pVT (119:126) PEA (91:70) AS (62:66)	90.4:92.4	44.1:52.7	52.9:49.2
Nordseth et al. 2012	Norway	OHCA	NT	101	65.5 ± 12.7	63 (62.4%)	73	66.8 ± 11.5	48 (65.8%)	PEA (101:73)	51.5:63.9	50.5:65.8	38.6:42.5
Woodhouse et al. 1995	Australia	OHCA/IHCA	NT	145	68 ± 13	NA	100	67 ± 14	NA	VF (88:39)	NA	NA	NA
Olasveengen et al. 2009	Norway	OHCA	NT	418	64 ± 18	302 (72.2%)	433	64 ± 17	303 (70.0%)	VF/pVT (144:142) PEA (82:63) AS (192:228)	71.8:70.4	67.7:63.0	62.4:63.3
Observational stidues													
Fukuda et al. 2016	Japan	OHCA	M	33328	74.1 ± 15.2	20750 (62.3%)	33400	74.2 ± 15.2	20750 (62.1%)	VF (3934:3951) pVT (86:69) PEA (11171:11201) AS (18209:18179)	61.8:61.9	56.9:57.1	47.0:46.8
Gato et al. 2013	Japan	OHCA	M	23676	73.3 ± 15.3	14886 (62.9%)	185901	74.0 ± 16.2	105898 (56.7%)	VF (3077:12037) pVT (59:319) PEA (7460:34153) AS (13080:139392)	NA	55.0:33.2	48.3:45.3
Naset et al. 2013	Norway	OHCA	NT	119	69 ± 61.8	94 (79.0%)	104	66 ± 53.8	81 (77.9%)	VF/pVT (93:94) PEA (13:5) AS (13:5)	84.0:88.5	78.2:71.2	73.9:67.3
Machida et al. 2012	Japan	OHCA	NT	49	63 ± 18	33 (67.3%)	443	64 ± 18	291 (65.7%)	VF/pVT (12:63) PEA (15:124) AS (22:255)	44.9:33.2	53.0:31.8	51.0:53.3
Dumas et al. 2014	France	OHCA	NT	228	58.0 ± 16	172 (75.4%)	228	58.1 ± 17	170 (74.6%)	VF/pVT (142:142)	NA	92.1:93.9	55.3:54.8
Fukuda et al. 2015	Japan	OHCA	M	770	NA	NA	6301	NA	NA	VF/pVT (554:291)	NA	NA	NA
Hagihara et al. 2012	Japan	OHCA	NT	13401	72.4 ± 15.5	8480 (63.3%)	13401	72.4 ± 15.7	8427 (62.9%)	NA	60.0:59.6	57.7:58.7	NA
Hayashi et al. 2012	Japan	OHCA	NT	1013	72.1 ± 15.0	660 (65.2%)	2148	73.9 ± 15.2	1243 (57.9%)	VF (205:301)	72.8:64.7	100:100	41.1:41.8

Table 1 (cont.). Baseline demographic data of the studies when available.

Study	Country	Setting	Type of subject	Adrenaline group			Non-adrenaline group			Adrenaline: non-adrenaline ratio parameters			
				N	Age	Males	N	Age	Males	Initials cardiac rhythm (n)	Cardiac cause (%)	Witnessed by bystander (%)	Bystander CPR (%)
Hayashi et al. 2012	Japan	OHCA	NT	1013	72.1 ± 15.0	660 (65.2%)	2148	73.9 ± 15.2	1243 (57.9%)	VF (205:301)	72.8:64.7	100:100	41.1:41.8
Herlitz et al. 1995 (VF)	Sweden	OHCA	M	417	60 ± 15	NA	786	61.8 ± 13.8	NA	VF (417:786)	NA	20.1:10.9	5.0:2.4
Herlitz et al. 1994 (AS)	Sweden	OHCA	M	344	NA	NA	NA	NA	NA	AS (344:878)	NA	NA	NA
Herlitz et al. 1995 (PEA)	Sweden	OHCA	M	45	NA	NA	NA	NA	NA	PEA (37:711)	NA	NA	NA
Kaji et al. 2014	USA	OHCA	NT	160	65.5 ± 3.7	79 (49.4%)	24	60.3 ± 4	18 (75.0%)	VF/pVT (48:18)	NA	73.1:95.8	41.9:70.8
Holmberg et al. 2002	Sweden	OHCA	M	4566	NA	3648 (67.5%)	6207	68.5	5034 (81.1%)	VF (2329:3780)	NA	70.0:64.4	34.6:30.5
Nakahara et al. 2013	Japan	OHCA	NT	13421	NA	8856 (65.9%)	82658	NA	50605 (61.2%)	VF/pVT (2464:12479) PEA/AS (10957:70179)	NA	NA	48.2:46.6

NA — not available; OHCA — out-of-hospital cardiac arrest; IHCA — in-hospital cardiac arrest; Type of subject: M — mixed; NT — non-trauma; AS — asystole; PEA — pulseses electrical activity; VF — ventricular fibrillation; pVT — pulsetess ventricular tachycardia

Table 2. Description of studies included in the analysis.

Study	Inclusion criteria	Exclusion criteria	Primary outcome	Survival to hospital discharge/30 days			
				Adrenaline group	Non-adrenaline group	Odds ratio (95% CI)	
						Unadjusted	Adjusted
Perkins et al. 2018	Adult patients who had sustained an out-of-hospital cardiac arrest for which advanced life support was provided by trial-trained paramedics	Known or apparent pregnancy, an age of less than 16 years, cardiac arrest from anaphylaxis or asthma, or the administration of epinephrine before the arrival of the trial-trained paramedic	Survival at 30 days	130/4012 (3.2%)	94/3995 (2.4%)	1.39 (1.06–1.82)	1.47 (1.09–1.97)
Jacobs et al. 2011	All adult, non-traumatic OHCA patients were randomized to receive advanced life support with (IV) or without (no IV) administration of IV drugs	ROSC before the EMS personnel had time to administer drugs	Survival to hospital discharge	11/272 (4.0%)	5/262 (1.9%)	2.17 (0.74–6.32)	NA
Nordseth et al. 2012	NA	NA	Survival to hospital discharge	1/101 (1.0%)	4/73 (5.5%)	0.17 (0.02–1.58)	NA

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Table 2 (cont.). Description of studies included in the analysis.

Study	Inclusion criteria	Exclusion criteria	Primary outcome	Survival to hospital discharge/30 days			
				Adrenaline group	Non--adrenaline group	Odds ratio (95% CI)	
						Unadjusted	Adjusted
Woodhouse et al. 1995	Patients with OHCA and IHCA	NA	ROSC, discharge from hospital rates and favorable rhythm changes	3/145 (2.1%)	NA	NA	NA
Fukuda et al. 2016	All patients with OHCA (defined as pulselessness, apnea, and unresponsiveness)	Patients with a delay in treatment (the time from call to contact with patient or epinephrine administration > 60 min and the time from contact with patient to hospital arrival > 120 min). In addition, patients with missing, in-complete, inconsistent, or unknown data on time, first documented rhythm, etiology of cardiac arrest, or prehospital advanced life support were excluded	Favorable neurological status at 1 month after OHCA	1759/33400 (5.3%)	2184/33400 (6.5%)	1.12 (0.83–1.51)	NA
Gato et al. 2013	All patients with OHCA	Arrest after EMS arrival; No resuscitation cases; Age < 18 years-old or unknown; Initial cardiac rhythm unknown	Survival at one month	1277/20676 (6.2%)	7157/185901 (3.8%)	1.42 (1.34–1.51)	NA
Naset et al. 2013	All adult, non-traumatic OHCA patients were randomized to receive advanced life-support with (IV) or without (no IV) administration of IV drugs	ROSC before the EMS personnel had time to administer drugs	Effects of adrenaline on cardiac rhythms and rhythm transitions	14/119 (11.7%)	21/104 (20.2%)	0.53 (0.25–1.10)	NA
Machida et al. 2012	Patients who experienced OHCA	Age younger than 18 years	Survival to hospital discharge	8/49 (16.3%)	64/443 (14.4%)	1.16 (0.52–2.58)	
Olasveengen et al. 2009	All patients older than 18 years with nontraumatic OHCA	(1) Cardiac arrest witnessed by ambulance crew because these patients almost always have an intravenous needle in place at the time of the cardiac arrest, (2) Resuscitation initiated or interrupted by physicians outside of the ambulance team, or (3) Cardiac arrest induced by asthma or anaphylactic shock	Survival to hospital discharge	44/418 (10.5%)	40/433 (9.2%)	1.16 (0.74–1.81)	NA

Table 2 (cont.). Description of studies included in the analysis.

Study	Inclusion criteria	Exclusion criteria	Primary outcome	Survival to hospital discharge/30 days			
				Adrenaline group	Non--adrenaline group	Odds ratio (95% CI)	
						Unadjusted	Adjusted
Dumas et al. 2014	Patients who experienced nontraumatic OHCA, achieved ROSC, and were subsequently admitted to a large Parisian cardiac arrest--receiving hospital	NA	Favorable neurological outcome at discharge, defined as a CPC of 1 or 2	NA	NA	NA	NA
Fukuda et al. 2015	Adults aged 18 years or older with OHCA caused by respiratory disease and for whom resuscitation was attempted by EMS personnel with subsequent transport to medical institutions	Patients were excluded from the analysis if data on the onset date, call receipt time, hospital arrival time, airway management status, or the usage status of a public access AED were missing or unknown. Patients who were provided only AED or ventilation by a bystander	Favorable neurological outcome 1 month after cardiac arrest, defined a priori as a Glasgow--Pittsburgh cerebral performance category 1 (good performance) or 2 (moderate disability)	51/770 (6.6%)	376/6301 (6.0%)	0.37 (0.13–0.85)	NA
Hagihara et al. 2012	Patients aged 18 years or older had an OHCA before arrival of EMS personnel	NA	Return of spontaneous circulation before hospital arrival	687/13471 (5.1%)	944/13486 (7.0%)	0.71 (0.64–0.79)	0.60 (0.49–0.74)
Hayashi et al. 2012	The non-traumatic bystander witnessed OHCA patients aged 18 years	Shock-responding VF arrests	Neurologically intact 1-month survival as defined by CPC categories 1 or 2	137/1013 (13.5%)	258/2148 (12.0%)	1.15 (0.92–1.43)	NA
Herlitz et al. 1995 (a)	Patients with out-of-hospital cardiac arrest found in VF	Patients with PEA, asystole	NA	12/417 (2.9%)	19/786 (2.4%)	1.2 (0.57–2.49)	NA
Herlitz et al. 1994	Patients with out-of-hospital cardiac arrest found in asystole	Patients with PEA, VF and VT	NA	7/344 (2.0%)	13/878 (1.5%)	1.38 (0.55–3.49)	NA
Herlitz et al. 1995 (b)	Patients with out-of-hospital cardiac arrest found in PEA	Patients with asystole, VF and VT	NA	41/276 (14.9%)	55/472 (11.7%)	1.32 (0.86–2.04)	NA
Kaji et al. 2014	Adult patients aged 18 years or older with OHCA	Age < 18 years, patients with traumatic arrest, and those with an arrest related to a definite respiratory cause, a drug overdose, strangulation, electrocution, or drowning	Survival to hospital discharge with favorable neurologic outcome, defined as a GCS of 14 or 15	56/160 (35.0%)	19/24 (79.2%)	0.1 (0.1–0.4)	NA
Holmberg et al. 2002	All out-of-hospital cardiac arrests where patients	NA	Survival at one month	156/4566 (3.4%)	388/6207 (6.3%)	0.53 (0.44–0.64)	NA

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Table 2 (cont.). Description of studies included in the analysis.

Study	Inclusion criteria	Exclusion criteria	Primary outcome	Survival to hospital discharge/30 days			
				Adrenaline group	Non-adrenaline group	Odds ratio (95% CI)	
						Unadjusted	Adjusted
Nakahara et al. 2013	Patients aged 15–94 who had an out of hospital cardiac arrest witnessed by a bystander	Cases with no witness, patients who arrested after the arrival of EMS (as we focused on cardiac arrest in situations without medical personnel), those who were given adrenaline after return of spontaneous circulation (re-arrest cases), those in whom arrest was attributable to external causes (such as trauma, drowning, poisoning, and asphyxia), and those with missing, contradictory, or outlying data (such as negative or long (> 2 h) response interval). Patients those who were transported by ambulance without an emergency lifesaving technician or by ambulance with doctors	Overall survival and neurologically intact survival with the Glasgow-Pittsburgh cerebral performance category score 1–2 at 1 month or at discharge	834/13421 (6.2%)	6557/82658 (7.9%)	0.77 (0.71–0.83)	NA

AED — automated external defibrillator; CPC — Cerebral Performance Cate score; EMS — emergency medical service; GCS — Glasgow Coma Scale; IHCA — in-hospital cardiac arrest; IV — intravascular; OHCA — out-of-hospital cardiac arrest; PEA — pulseless electrical activity; ROSC — return of spontaneous circulation; VF — ventricular fibrillation; VT — ventricular tachycardia

a double-blinded placebo. The data obtained in this meta-analysis again indicates the need to consider the usefulness of routine adrenaline administration in SCA. While the use of adrenaline has been shown to increase the ROSC and survival to hospital discharge, it does not affect the favorable neurological outcome. The results suggest considering routine adrenaline use in case of out-of-hospital SCA.

Return of spontaneous circulation is one of the basic outcomes of resuscitation, especially in the prehospital setting [34]. Pooled analysis showed that the use of adrenaline increases the chance of ROSC, which was evident in both RCTs and observational studies. It was apparent that administration of adrenaline for shockable rhythms was associated with a lower incidence of ROSC. It should be noted, however, that adrenaline is administered according to the guidelines only after ineffective defibrillation, not from the initiation of CPR procedures. In the case of non-shockable rhythms, the difference in ROSC was very significant, ROSC was 19.4% for adrenaline and 4.3% for non-adrenaline treatment.

Another important element is survival to discharge, where, as in the case of ROSC, it was observed that for non-shockable rhythms, the use of adrenaline compared to non-adrenaline treatment was associated with higher survival to hospital discharge rate, however, these differences were not statistically significant. Again, as for ROSC for shockable rhythms, higher survival to discharge was observed in the non-adrenaline group.

Survival to discharge with the favorable neurological outcome is essential for the functioning of the patient after the SCA incident with a satisfactory quality of life. In the case of shockable rhythms, the use of adrenaline was associated with a statistically significantly worse prognosis.

The administration of adrenaline in SCA is one of the key elements of resuscitation, especially in cases of non-shockable rhythms [5, 6]. However, it should be noted that there are many milestones in the history of the development of guidelines for resuscitation and many changes have been milestones, including the issue of ratio of chest compressions to the number of breaths, the use of defibrillation, including automated external defibrillator, and improved quality of chest compressions or airway management, where supraglottic airway devices were introduced and less emphasis on the need for endotracheal intubation.

There were also changes in pharmacotherapy in sudden cardiac arrest; over the years, the adrenaline dose was changed, and the rule was introduced

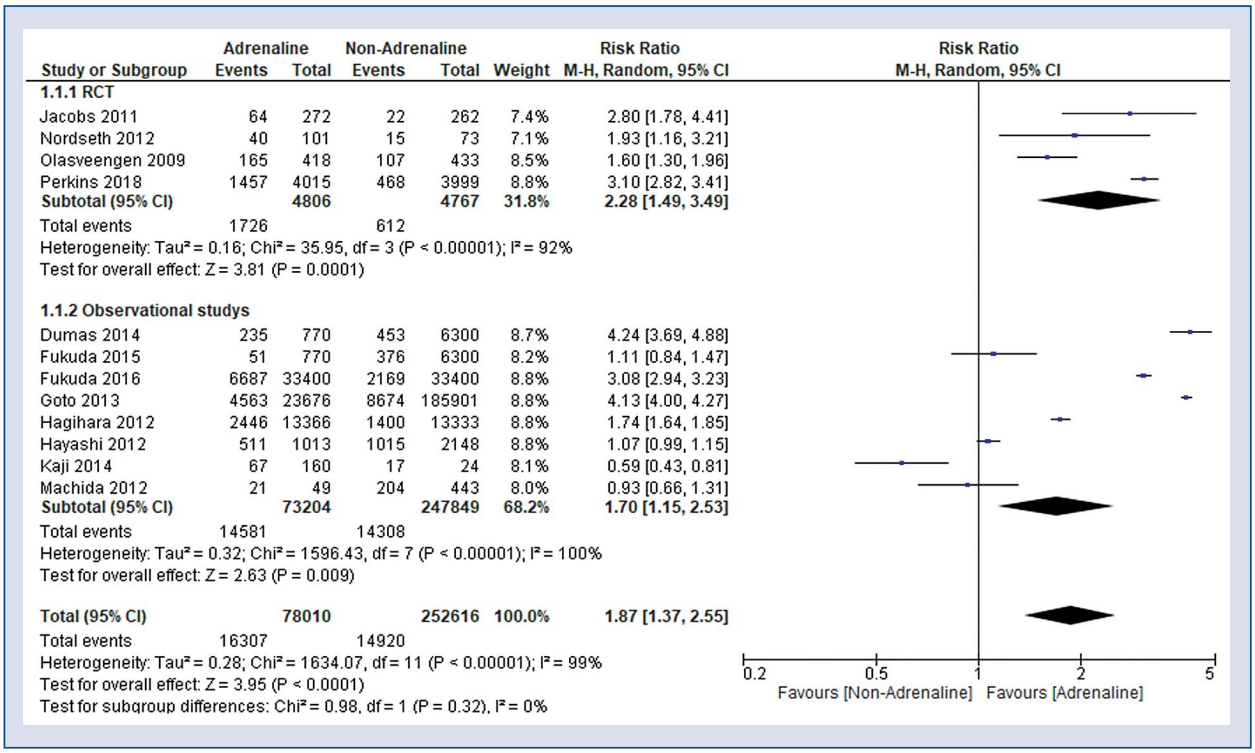

Figure 2. Forest plot of return of spontaneous circulation in adrenaline vs. non-adrenaline groups. The center of each square represents the relative risk for individual trials, and the corresponding horizontal line stands for a 95% confidence interval (CI). The diamonds represent pooled results; RCT — randomized controlled trial.

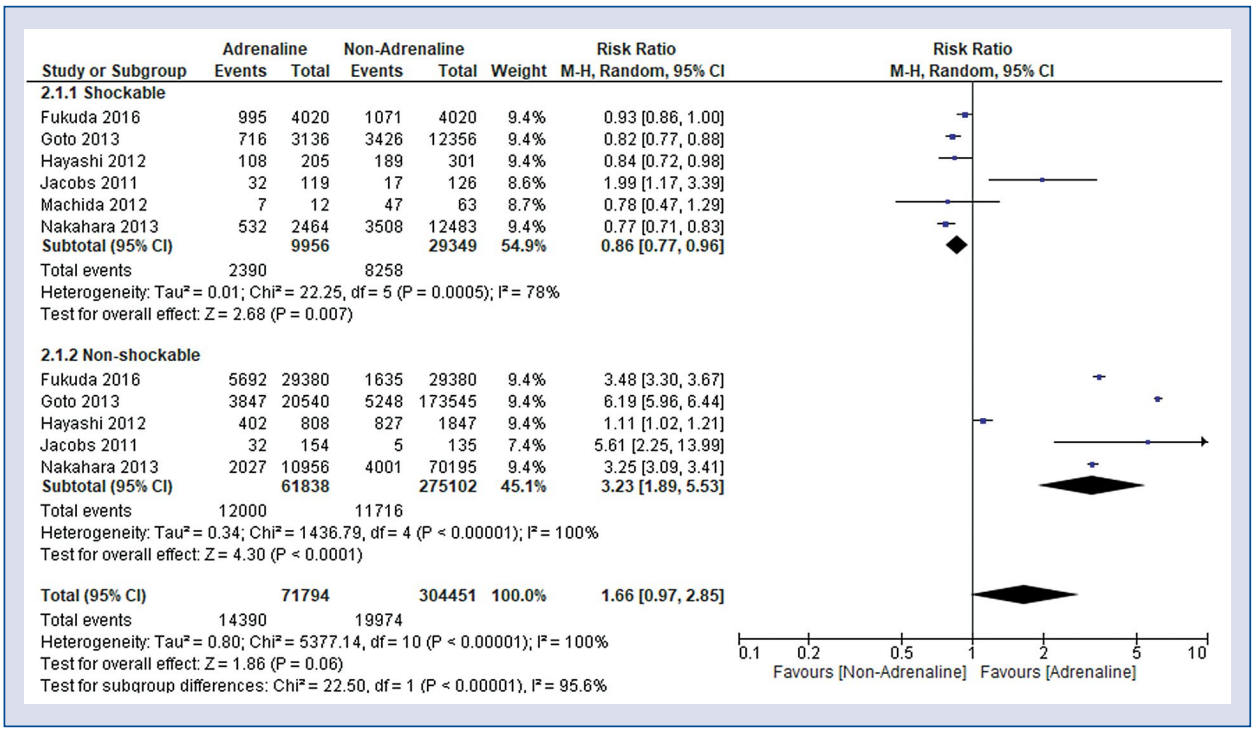

Figure 3. Forest plot of return of spontaneous circulation by type of rhythm in adrenaline vs. non-adrenaline groups. The center of each square represents the relative risk for individual trials, and the corresponding horizontal line stands for a 95% confidence interval (CI). The diamonds represent pooled results.

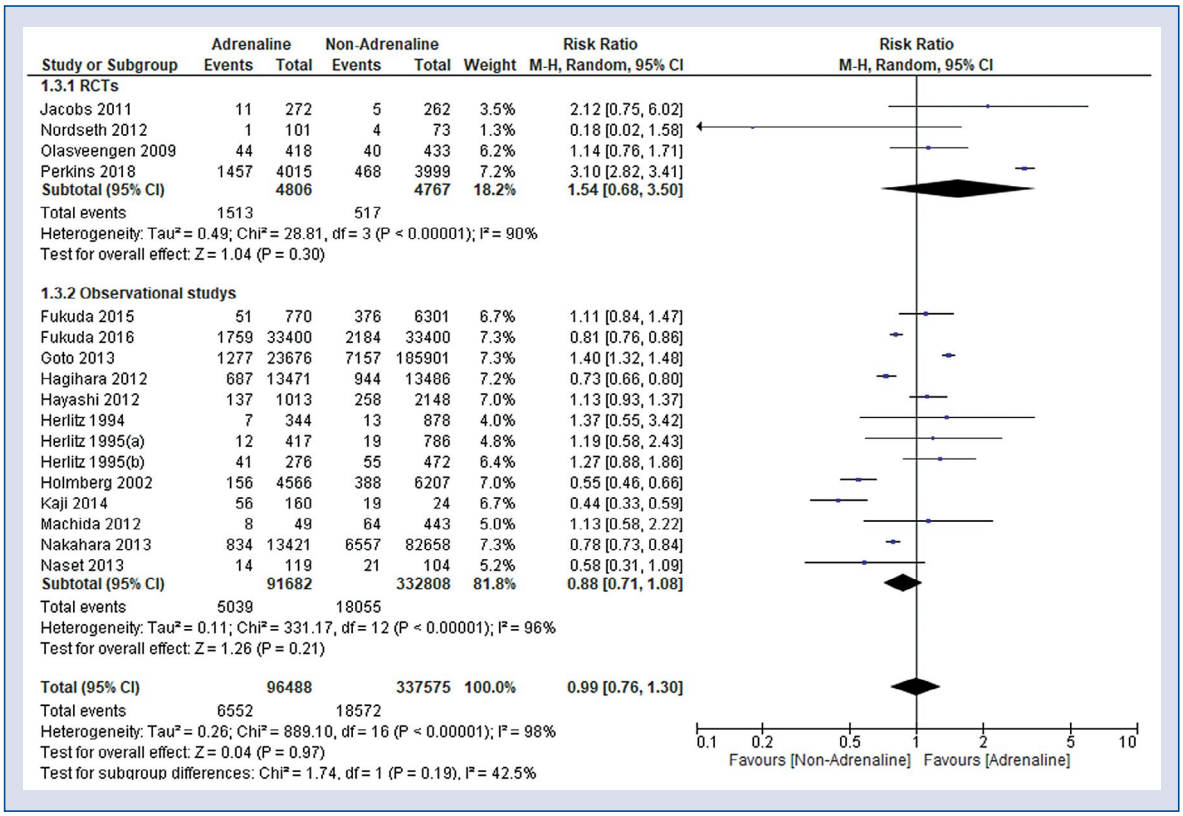

Figure 4. Forest plot of survival to hospital discharge in adrenaline vs. non-adrenaline groups. The center of each square represents the relative risk for individual trials, and the corresponding horizontal line stands for a 95% confidence interval (CI). The diamonds represent pooled results; RCTs — randomized controlled trials.

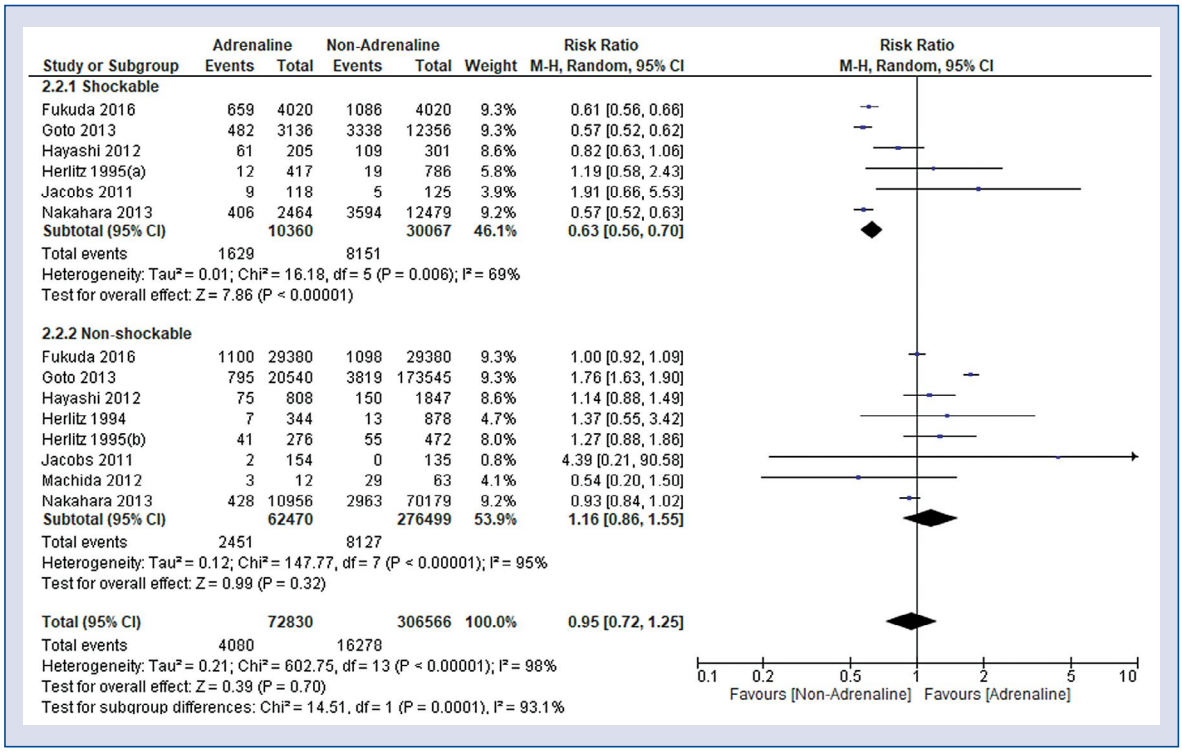

Figure 5. Forest plot of survival to hospital discharge by type of rhythm in adrenaline vs. non-adrenaline groups. The center of each square represents the relative risk for individual trials, and the corresponding horizontal line stands for a 95% confidence interval (CI). The diamonds represent pooled results.

that for non-shockable rhythms adrenaline is not administered immediately after SCA recognition. Perhaps the next stage will be the re-analysis of indications for adrenaline administration in SCA at the pre-hospital and hospital stages for shockable and non-shockable rhythms.

Changes in the guidelines and recommendations for resuscitation must be based on further scientific evidence based on high quality randomized clinical trials conducted in both hospital and out-of-hospital settings [35]. Although achieving ROSC is a key task of the resuscitation team, the patient's survival with a favorable neurological outcome is the most important goal and outcome. Both AHA and ERC guidelines are based on the analysis of scientific evidence and the most important are randomized double-blind clinical trials and meta-analyses including pooled data on large patient groups.

The advantage of the meta-analysis is the rigorous application of rules and criteria used in meta-analyses and a thorough search of available databases, as well as references in publications and manual searches in Google and Google Scholar, and the web pages of reliable organizations (gray literature) and analyses of the results obtained as well as following PRISMA statement for conducting and reporting results and The MOOSE guidelines for observational studies.

Limitations of the study

The results reported in the present systematic review and meta-analysis are subject to several limitations. First, only four studies included in the meta-analysis were randomized controlled trials. Some outcome measures were not uniformly reported across studies and, therefore, were difficult to combine in a meta-analysis. The studies analyzed differed significantly in terms of the number of participants. Another limitation relates to the inclusion of research only in the context of out-of--hospital cardiac arrest. The results of adrenaline administration during CPR in hospital conditions may be different. Therefore, further analyses are planned for in-hospital cardiac arrest. When analyzing the results obtained in this article, all the limitations typical for meta-analyses, including the risk of bias and heterogeneous studies, should also be considered.

Return of spontaneous circulation and the neurological outcome are significantly influenced by the quality of resuscitation, especially the quality of chest compressions [1, 36–38]. Unfortunately, the analyzed studies did not routinely use devices and methods to monitor the quality of chest compression, and chest compression depth and rate, as well as full chest recoil, which has a significant impact on the overall quality of CPR and the overall outcome of the rescue procedure. High-quality chest compressions consist of achieving the correct recommended compression depth, compressions rate, correct chest recoil, minimizing interruptions in chest compressions, as well as the highest possible percentage of correct compressions concerning all compressions carried out with the correct compression site [39–41]. The lack of chest compression quality measurement may affect the results [1], but this effect is reduced by the randomized nature of the double-blinded studies.

The results obtained underline the need for further research on the use of vasopressors in the course of CPR. Another factor to be taken into account is the need to establish a vascular access (intravenous or intraosseous) for the administration of drugs, which may cause difficulties during resuscitation [42]. If the routine supply of adrenaline during CPR is discontinued, this may result in a lack of immediate need for intravascular access and may further increase the focus on high-quality chest compression, electrotherapy and ventilation and the elimination of potentially reversible causes [5].

Conclusions

The present meta-analysis demonstrates that resuscitation with adrenaline is associated with the ROSC and survival to hospital discharge, but no higher effectiveness was noted for discharge with favorable neurological outcome. The analysis showed higher effectiveness of ROSC and survival to hospital discharge in non-shockable rhythms. But more multicenter RCTs are needed in the future.

Acknowledgements

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Conflict of interest: None declared

References

1. Majer J, Jaguszewski MJ, Frass M, et al. Does the use of cardiopulmonary resuscitation feedback devices improve the quality of chest compressions performed by doctors? A prospective, randomized, cross-over simulation study. Cardiol J. 2019; 26(5): 529–535, doi: 10.5603/CJ.a2018.0091, indexed in Pubmed: 30155865.

2. Malysz M, Kacprzak P. Is low voltage ventricular fibrillation still a diagnostic problem? Disaster Emerg Med J. 2019; 4(1): 31–32, doi: 10.5603/demj.2019.0007.
3. Rojas-Salvador C, Moore JC, Salverda B, et al. Effect of controlled sequential elevation timing of the head and thorax during cardiopulmonary resuscitation on cerebral perfusion pressures in a porcine model of cardiac arrest. Resuscitation. 2020; 149: 162–169, doi: 10.1016/j.resuscitation.2019.12.011, indexed in Pubmed: 31972229.
4. Segal N, Metzger AK, Moore JC, et al. Correlation of end tidal carbon dioxide, amplitude spectrum area, and coronary perfusion pressure in a porcine model of cardiac arrest. Physiol Rep. 2017; 5(17): e13401, doi: 10.14814/phy2.13401, indexed in Pubmed: 28899911.
5. Soar J, Nolan JP, Böttiger BW, et al. European Resuscitation Council Guidelines for Resuscitation 2015: Section 3. Adult advanced life support. Resuscitation. 2015; 95: 100–147, doi: 10.1016/j.resuscitation.2015.07.016, indexed in Pubmed: 26477701.
6. Link MS, Berkow LC, Kudenchuk PJ, et al. Part 7: Adult Advanced Cardiovascular Life Support: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2015; 132(18 Suppl 2): S444–S464, doi: 10.1161/CIR.0000000000000261, indexed in Pubmed: 26472995.
7. Krejci V, Hiltebrand LB, Sigurdsson GH. Effects of epinephrine, norepinephrine, and phenylephrine on microcirculatory blood flow in the gastrointestinal tract in sepsis. Crit Care Med. 2006; 34(5): 1456–1463, doi: 10.1097/01.CCM.0000215834.48023.57, indexed in Pubmed: 16557162.
8. 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.
9. Ng KT, Teoh WY. The effect of prehospital epinephrine in out-of-hospital cardiac arrest: a systematic review and meta-analysis. Prehosp Disaster Med. 2019; 34(5): 532–539, doi: 10.1017/S1049023X19004758, indexed in Pubmed: 31455452.
10. Moher D, Shamseer L, Clarke M, et al. PRISMA-P Group. 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.
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. Haywood K, Whitehead L, Nadkarni VM, et al. COSCA (Core Outcome Set for Cardiac Arrest) in Adults: An Advisory Statement From the International Liaison Committee on Resuscitation. Circulation. 2018; 137(22): e783–e801, doi: 10.1161/CIR.0000000000000562, indexed in Pubmed: 29700122.
13. Kaji AH, Hanif AM, Bosson N, et al. Predictors of neurologic outcome in patients resuscitated from out-of-hospital cardiac arrest using classification and regression tree analysis. Am J Cardiol. 2014; 114(7): 1024–1028, doi: 10.1016/j.amjcard.2014.06.031, indexed in Pubmed: 25118118.
14. Wells GA, Shea B, O'Connell D, et al: The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. The Ottawa Hospital Research Institute. 2014. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed May 10, 2020).
15. 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.
16. Perkins GD, Ji C, Deakin CD, et al. A randomized trial of epinephrine in out-of-hospital cardiac arrest. N Engl J Med. 2018; 379(8): 711–721, doi: 10.1056/NEJMoa1806842, indexed in Pubmed: 30021076.
17. Jacobs IG, Finn JC, Jelinek GA, et al. Effect of adrenaline on survival in out-of-hospital cardiac arrest: A randomised double-blind placebo-controlled trial. Resuscitation. 2011; 82(9): 1138–1143, doi: 10.1016/j.resuscitation.2011.06.029, indexed in Pubmed: 21745533.
18. Nordseth T, Olasveengen TM, Kvaløy JT, et al. Dynamic effects of adrenaline (epinephrine) in out-of-hospital cardiac arrest with initial pulseless electrical activity (PEA). Resuscitation. 2012; 83(8): 946–952, doi: 10.1016/j.resuscitation.2012.02.031, indexed in Pubmed: 22429969.
19. Woodhouse SP, Cox S, Boyd P, et al. High dose and standard dose adrenaline do not alter survival, compared with placebo, in cardiac arrest. Resuscitation. 1995; 30(3): 243–249, doi: 10.1016/0300-9572(95)00890-x.
20. Olasveengen TM, Sunde K, Brunborg C, et al. Intravenous drug administration during out-of-hospital cardiac arrest: a randomized trial. JAMA. 2009; 302(20): 2222–2229, doi: 10.1001/jama.2009.1729, indexed in Pubmed: 19934423.
21. Fukuda T, Ohashi-Fukuda N, Matsubara T, et al. Effect of prehospital epinephrine on out-of-hospital cardiac arrest: a report from the national out-of-hospital cardiac arrest data registry in Japan, 2011-2012. Eur J Clin Pharmacol. 2016; 72(10): 1255–1264, doi: 10.1007/s00228-016-2093-2, indexed in Pubmed: 27411936.
22. Goto Y, Maeda T, Goto Y. Effects of prehospital epinephrine during out-of-hospital cardiac arrest with initial non-shockable rhythm: an observational cohort study. Crit Care. 2013; 17(5): R188, doi: 10.1186/cc12872, indexed in Pubmed: 24004456.
23. Neset A, Nordseth T, Kramer-Johansen Jo, et al. Effects of adrenaline on rhythm transitions in out-of-hospital cardiac arrest. Acta Anaesthesiol Scand. 2013; 57(10): 1260–1267, doi: 10.1111/aas.12184, indexed in Pubmed: 24032427.
24. Machida M, Miura SI, Matsuo K, et al. Effect of intravenous adrenaline before arrival at the hospital in out-of-hospital cardiac arrest. J Cardiol. 2012; 60(6): 503–507, doi: 10.1016/j.jjcc.2012.07.001, indexed in Pubmed: 22890074.
25. Dumas F, Bougouin W, Geri G, et al. Is epinephrine during cardiac arrest associated with worse outcomes in resuscitated patients? J Am Coll Cardiol. 2014; 64(22): 2360–2367, doi: 10.1016/j.jacc.2014.09.036, indexed in Pubmed: 25465423.
26. Fukuda T, Fukuda-Ohashi N, Doi K, et al. Effective pre-hospital care for out-of-hospital cardiac arrest caused by respiratory disease. Heart Lung Circ. 2015; 24(3): 241–249, doi: 10.1016/j.hlc.2014.09.004, indexed in Pubmed: 25445432.
27. Hagihara A, Hasegawa M, Abe T, et al. Prehospital epinephrine use and survival among patients with out-of-hospital cardiac arrest. JAMA. 2012; 307(11): 1161–1168, doi: 10.1001/jama.2012.294, indexed in Pubmed: 22436956.
28. Hayashi Y, Iwami T, Kitamura T, et al. Impact of early intravenous epinephrine administration on outcomes following out-of-hospital cardiac arrest. Circ J. 2012; 76(7): 1639–1645, doi: 10.1253/circj.cj-11-1433, indexed in Pubmed: 22481099.

29. Herlitz J, Ekström L, Wennerblom B, et al. Adrenaline in out-of-hospital ventricular fibrillation. Does it make any difference? Resuscitation. 1995; 29(3): 195–201, doi: 10.1016/0300-9572(94)00851-6.
30. Herlitz J, Ekström L, Wennerblom B, et al. Predictors of early and late survival after out-of-hospital cardiac arrest in which asystole was the first recorded arrhythmia on scene. Resuscitation. 1994; 28(1): 27–36, doi: 10.1016/0300-9572(94)90051-5.
31. Herlitz J, Ekström L, Wennerblom B, et al. Survival among patients with out-of-hospital cardiac arrest found in electromechanical dissociation. Resuscitation. 1995; 29(2): 97–106, doi: 10.1016/0300-9572(94)00821-v.
32. Holmberg M, Holmberg S, Herlitz J. Low chance of survival among patients requiring adrenaline (epinephrine) or intubation after out-of-hospital cardiac arrest in Sweden. Resuscitation. 2002; 54(1): 37–45, doi: 10.1016/s0300-9572(02)00048-5.
33. Nakahara S, Tomio J, Takahashi H, et al. Evaluation of pre-hospital administration of adrenaline (epinephrine) by emergency medical services for patients with out of hospital cardiac arrest in Japan: controlled propensity matched retrospective cohort study. BMJ. 2013; 347: f6829, doi: 10.1136/bmj.f6829, indexed in Pubmed: 24326886.
34. Robak O, Pruc M, Malysz M, et al. Pre-filled syringes with adrenaline during cardiopulmonary resuscitation in nonshockable rhythms. Pilot randomised crossover simulation study. Disaster Emerg Med J. 2020; 5(2): 79–84, doi: 10.5603/demj.a2020.0025.
35. Blanco J, Madziala M, Szalast P. Which chest compression technique is more fatiguing for rescuer? Disaster Emerg Med J. 2018; 3(4): 150–151, doi: 10.5603/demj.2018.0031.
36. Malysz M, Dabrowski M, Böttiger BW, et al. Resuscitation of the patient with suspected/confirmed COVID-19 when wearing personal protective equipment: A randomized multicenter crossover simulation trial. Cardiol J. 2020; 27(5): 497–506, doi: 10.5603/CJ.a2020.0068, indexed in Pubmed: 32419128.
37. Kłosiewicz T, Puślecki M, Zalewski R, et al. Assessment of Chest Compression Quality — a systematic review. Disaster Emerg Med J. 2020; 5(1): 49–56, doi: 10.5603/demj.a2020.0010.
38. Majer J, Kaminska H, Wieczorek W, et al. Impact of a CPRrmeter feedback device on chest compression quality performed by nurses — a randomized crossover study. Disaster Emerg Med J. 2018; 3(1): 36–37, doi: 10.5603/demj.2018.0008.
39. Kramer-Johansen Jo, Edelson DP, Losert H, et al. Uniform reporting of measured quality of cardiopulmonary resuscitation (CPR). Resuscitation. 2007; 74(3): 406–417, doi: 10.1016/j.resuscitation.2007.01.024, indexed in Pubmed: 17391831.
40. Sutton RM, Wolfe H, Nishisaki A, et al. Pushing harder, pushing faster, minimizing interruptions… but falling short of 2010 cardiopulmonary resuscitation targets during in-hospital pediatric and adolescent resuscitation. Resuscitation. 2013; 84(12): 1680–1684, doi: 10.1016/j.resuscitation.2013.07.029, indexed in Pubmed: 23954664.
41. Smereka J, Iskrzycki Ł, Makomaska-Szaroszyk E, et al. The effect of chest compression frequency on the quality of resuscitation by lifeguards. A prospective randomized crossover multicenter simulation trial. Cardiol J. 2019; 26(6): 769–776, doi: 10.5603/CJ.a2018.0121, indexed in Pubmed: 30338845.
42. Nolan JP, Deakin CD, Ji C, et al. Intraosseous versus intravenous administration of adrenaline in patients with out-of-hospital cardiac arrest: a secondary analysis of the PARAMEDIC2 placebo-controlled trial. Intensive Care Med. 2020; 46(5): 954–962, doi: 10.1007/s00134-019-05920-7, indexed in Pubmed: 32002593.

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Mild therapeutic hypothermia after out-of-hospital cardiac arrest: What does really matter?

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Abstract

Background: *Mild therapeutic hypothermia (MTH) is a recommended treatment of comatose patients after out-of-hospital cardiac arrest (OHCA). The aim of the study was to examine determinants of clinical outcome in OHCA survivors treated with MTH and variables associated with MTH induction time.*

Methods: *Presented herein is an analysis of combined results from a retrospective and a prospective observational study which included 90 OHCA survivors treated with MTH from January 2010 to March 2018. Multivariate regression analysis was performed to determine variables associated with poor neurologic outcome (Cerebral Performance Category 3–5), mortality, and prolonged induction time.*

Results: *At hospital discharge, 59 (65.6%) patients were alive, of whom 36 (61%) had a good neurologic outcome. Older patients (odds ratio [OR] 1.07, 95% confidence interval [CI] 1.03–1.12) with lower Glasgow Coma Scale (GCS) (OR 0.49, 95% CI 0.30–0.80) were at higher risk of poor neurological outcome. The predictors of in-hospital death included: older age (OR 1.08, 95% CI 1.02–1.13), lower GCS score (OR 0.47, 95% CI 0.25–0.85), presence of cardiogenic shock (OR 3.43, 95% CI 1.11–10.53), and higher doses of adrenaline (OR 1.27, 95% CI 1.04–1.56). Longer induction was associated with shorter cardio-pulmonary resuscitation (CPR) (unstandardized coefficient –3.95, 95% CI –7.09 to –0.81) and lower lactate level (unstandardized coefficient –18.55, 95% CI –36.10 to –1.01).*

Conclusions: *Unfavorable neurologic outcome in OHCA patients treated with MTH is associated with age and lower GCS score. Risk factors for in-hospital mortality include age, high-dose adrenaline administration, lower GCS score and presence of cardiogenic shock. CPR duration and lactate level were predictive of prolonged MTH induction time.* (Cardiol J 2021; 28, 2: 293–301)

Key words: mild therapeutic hypothermia, targeted temperature management, out-of-hospital cardiac arrest

Introduction

Out-of-hospital cardiac arrest (OHCA) is still burdened with high risk of death. Among those who experience OHCA only around 30% survive before hospital admission [1] and 10% until hospital discharge [2]. The risk of OHCA occurrence is greater among the population of older men [3]. Even in survivors, brain damage leads to impaired neurological function and their ability to live an independent life is often limited [4]. Current guidelines recommend targeted temperature management (TTM) for the treatment of comatose patients after OHCA [5, 6], however the results presented in the literature regarding cardiac arrest patients with non-shakable rhythms are inconclusive [7]. TTM is a term most commonly understood as maintenance of the body's core temperature between 32°C and 36°C and therefore covers a wider range than mild therapeutic hypothermia (MTH),

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defined as temperature control between 32°C and 34°C. While favorable clinical outcome of MTH was proven in several clinical studies [8–10], the impact of maintaining patient temperatures at 34–36°C remains less clear. A randomized study by Nielsen et al. [11] suggests equivalent results in patients treated with TTM at 33°C and 36°C. Significant variability in clinical outcome among subjects treated with TTM raises questions regarding determinants of treatment success [12]. Despite the use of pre-specified programmed pattern of cooling, several studies reported that patients with poor neurological outcome had significantly shorter time required to achieve the target temperature (TT) than patients with good outcome [13–15]. These results raises the question about the causes of this phenomenon. Herein is hypothesized that a more severe ischemic insult may result in greater brain damage leading to impaired thermoregulatory control. According to this assumption, individuals with better post-OHCA neurologic function preserve their thermoregulation ability, which in turn results in longer induction time of MTH. However, the question as to whether length of MTH induction is an indicator of brain damage severity and what are the predictors associated with prolonged MTH induction remains unanswered.

Therefore, in this study possible determinants of clinical outcome in OHCA survivors treated with MTH were examined, including the induction time. Variables associated with the duration of MTH induction were also evaluated.

Methods

Study design and TTM protocol

This study combines results of a retrospective observational single-center analysis performed at the Department of Cardiology and Internal Medicine of the University Hospital No. 1 in Bydgoszcz, Poland from January 2010 to December 2016 and a prospective, observational, multicenter study [16] performed from January 2017 to March 2018 including OHCA survivors treated with MTH. The study comprised all consecutive adult subjects treated with MTH (using invasive intravascular cooling with TT of 33°C) for non-traumatic OHCA regardless of initial rhythm, who achieved a return of spontaneous circulation (ROSC). The Utstein-style guidelines for reporting OHCA were implemented in the study [17].

According to local protocol, patients were considered for MTH if they remained comatose after return of ROSC. Cooling was initiated as soon as possible with ice packs, intravenous administration of cold normal saline (0.9% solution of sodium chloride at the temperature of 4°C), and Intravascular Temperature Management™ CoolGard 3000® (Zoll Circulation Inc. USA). MTH was considered effective when patient core temperature decreased below 34°C, with TT of 33.0 ± 0.2°C, and was maintained for at least 12 h with an optimal duration of 24 h. The rewarming phase was conducted in an actively controlled manner at a rate of 0.3°C per hour. Urine bladder temperature measurements were used to automatically guide changes in patient core temperature. All patients were mechanically ventilated, sedated with continuous intravenous infusion of propofol and fentanyl and were treated according to current European Society of Cardiology guidelines. More detailed information regarding MTH protocol has been previously described [10].

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by the Ethics Committee of The Nicolaus Copernicus University in Torun, Collegium Medicum in Bydgoszcz (approval reference number KB 615/2015). The prospective part of this study is a sub-study of the Mild Therapeutic Hypothermia for Patients With Acute Coronary Syndrome and Cardiac Arrest Treated With Percutaneous Coronary Intervention (UNICORN) study (ClinicalTrials.gov Identifier: NCT02611934), which was supported by "Diamentowy Grant" financed by the Ministry of Science and Higher Education of the Republic of Poland from research funds for the years 2015–2018.

Data collection

Data were obtained from hospital records and included: age, sex, comorbidities, first monitored rhythm, bystander basic life support (BLS), total dose of adrenaline (epinephrine) used by emergency medical service (EMS) during cardiopulmonary resuscitation (CPR), etiology of cardiac arrest, Glasgow Coma Scale (GCS) score on admission, blood pH on admission, blood lactate level on admission, left ventricular ejection fraction on admission, presence of cardiogenic shock, and initial temperature measured in the urinary bladder (recorded at the initiation of intravascular cooling). Time intervals used for the analysis included: time in cardiac arrest (time from the onset of OHCA to ROSC), CPR duration (time from the beginning of CPR by EMS to ROSC), pre-induction (time from ROSC to initiation of intravascular cooling), induction (time from initiation of intravascular cooling to arrival at TT of 33.0 ± 0.2°C), maintenance (time

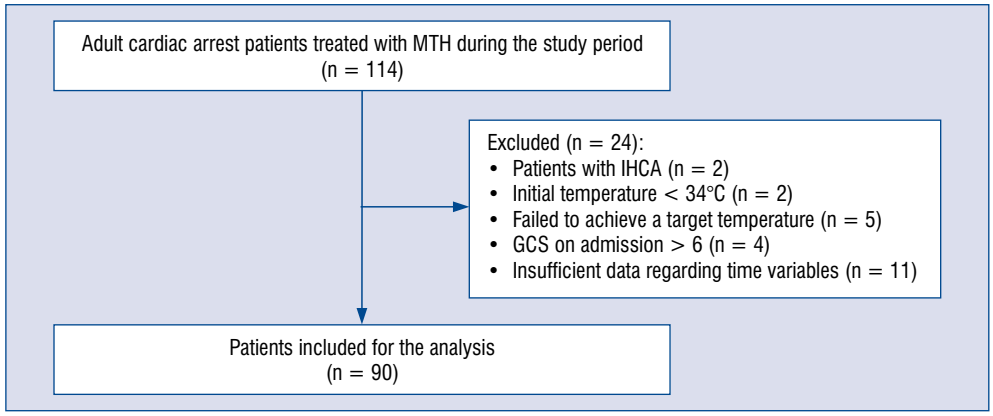

Figure 1. Numbers of patients initially screened, those excluded from the study and finally those who were included for analysis; GCS — Glasgow Coma Scale; IHCA — in-hospital cardiac arrest; MTH — mild therapeutic hypothermia.

from arrival at TT to initiation of active rewarming). Neurologic outcome was assessed using the Glasgow–Pittsburgh Cerebral Performance Categories (CPC) at hospital discharge and recorded as CPC 1 (good performance), CPC 2 (moderate disability), CPC 3 (severe disability), CPC 4 (vegetative state), or CPC 5 (brain death or death) [18]. Good neurological outcome was defined as CPC 1–2 and poor neurologic outcome was CPC 3–5 at the time of hospital discharge.

Statistical analysis

Continuous variables were presented as means with standard deviation or medians with interquartile range according to the distribution. Categorical variables were described as frequencies and percentages. Normality of the distribution was examined with the Shapiro-Wilk test. The Student T-test or Mann-Whitney test were used for comparison of continuous variables based on distribution normality. Categorical variables were compared using the χ^2 or Fisher's exact test, as appropriate. Univariate logistic regression analysis was performed to determine variables associated with poor neurologic outcome and in-hospital mortality. In order to identify variables affecting MTH induction time, univariate linear regression analysis was conducted. All variables significant at $p \leq 0.1$ in the univariate analysis were entered into multivariate regression models. Stepwise regression with backward elimination was performed to find the best possible fitting of each model. All statistical analysis was performed with IBM SPSS Statistics version 23. A two-sided significance level of $p < 0.05$ was applied for statistical significance.

Results

Population characteristics and final outcome

A total of 114 adult cardiac arrest patients were treated with MTH during the study period. Twenty-four patients were excluded from analysis (Fig. 1) and data on the remaining 90 patients were further investigated. At hospital discharge, 59 (65.56%) patients were alive, of whom 36 (61.02%) had a good neurologic outcome. Their clinical characteristics stratified by outcomes is shown in Table 1. The study group consisted mainly of men (n = 72, 80%). Mean age was 61.8 ± 12.5 years. In the majority of patients (n = 79, 87.8%), the initial recorded rhythm was shockable. Patients with good neurologic outcome were younger than those with poor outcome (56.4 ± 12.1 vs. 65.3 ± 11.5, p = 0.001), had a higher incidence of shockable initial rhythm (100% vs. 79.6%, p = 0.003) and a higher GCS score on admission (4.0 [4.0–5.0] vs. 3.5 [3.0– 4.0], p = 0.004).

Survivors, as compared with non-survivors, were younger (59.3 ± 12.1 vs. 66.5 ± 12.0, p = 0.009), more likely to have shockable initial rhythm (93.2% vs. 77.4%, p = 0.04) and less likely to present with cardiogenic shock (45.8% vs. 71.0%, p = 0.02). They also required smaller amounts of adrenaline during CPR (2.0 mg [1.0–5.0] vs. 4.0 mg [2.75–7.0], p = 0.006) and had a higher GCS score on admission (4.0 [3.0–5.0] vs. 3.0 [3.0–4.0], p = 0.004] (Table 1).

According to the univariate analysis, lower admission GCS score, older age and shorter MTH induction time were associated with poor neuro-

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Table 1. Baseline characteristics of study group with stratification by outcome.

	Total	Good neurologic outcome	Poor neurologic outcome	P	Survivor	Nonsurvivor	P
Age [years] (n = 90)	61.76 ± 12.47	56.44 ± 12.09	65.53 ± 11.53	**0.001**	59.25 ± 12.05	66.52 ± 12.04	**0.009**
Male (n = 90)	72 (80.0%)	31 (86.1%)	41 (75.9%)	0.24	45 (76.3%)	27 (87.1%)	0.22
Initial shockable rhythm (n = 90)	79 (87.8%)	36 (100%)	43 (79.6%)	**0.003**	55 (93.2%)	24 (77.4%)	**0.04**
Bystender BLS (n = 88)	49 (54.4%)	23 (65.7%)	26 (49.1%)	0.12	36 (63.2%)	13 (41.9%)	0.06
Adrenaline [mg] (n = 83)	3.0 (1.0–5.0)	2.0 (1.0–5.0)	3.5 (1.75–5.25)	0.16	2.0 (1.0–5.0)	4.0 (2.75–7.0)	**0.006**
Ischemic etiology (n = 90)	76 (84.4%)	28 (77.8%)	48 (88.9%)	0.79	49 (83.1%)	27 (87.1%)	0.88
pH (n = 90)	7.252 ± 0.111	7.264 ± 0.093	7.245 ± 0.120	0.4	7.260 ± 0.095	7.238 ± 0.137	0.43
Lactate [mmol/L] (n = 72)	2.8 (1.88–5.5)	2.74 (1.6–4.18)	3.0 (2.1–6.59)	0.11	2.74 (1.78–5.37)	3.8 (2.2–7.8)	0.18
EF [%] (n = 87)	35.0 (25.0–40.0)	34.0 (25.0–40.0)	35.0 (24.0–40.0)	0.81	35.0 (27.0–40.0)	35.0 (20.0–40.0)	0.24
GCS on admission (n = 90)	4.0 (3.0–5.0)	4.0 (4.0–5.0)	3.5 (3.0–4.0)	**0.004**	4.0 (3.0–5.0)	3.0 (3.0–4.0)	**0.004**
Cardiogenic shock (n = 90)	49 (54.4%)	18 (50%)	31 (57.4%)	0.5	27 (45.8%)	22 (71.0%)	**0.02**
Initial temperature [°C] (n = 72)	36.25 ± 1.05	36.48 ± 1.01	36.12 ± 1.06	0.16	36.41 ± 1.02	35.99 ± 1.07	0.11
Hypertension (n = 90)	39 (43.3%)	15 (41.7%)	24 (44.4%)	0.79	25 (42.4%)	14 (45.2%)	0.8
Diabetes mellitus (n = 90)	29 (32.2%)	12 (33.3%)	17 (31.5%)	0.85	20 (33.9%)	9 (29.0%)	0.1
Previous stroke (n = 90)	6 (6.7%)	1 (2.8%)	5 (9.3%)	0.4	4 (6.8%)	2 (6.5%)	0.24
Previous ACS (n = 90)	26 (28.9%)	10 (27.8%)	16 (29.6%)	0.85	14 (23.7%)	12 (38.7%)	0.38

ACS — acute coronary syndrome; BLS — basic life support; EF — ejection fraction; GCS — Glasgow Coma Scale

logical outcome (CPC 3–5) at hospital discharge (Table 2). As a result of stepwise regression with backward elimination, two parameters — lactate level and MTH induction time — were excluded from the equation. The best fitted multiple regression model revealed that older patients (odds ratio [OR] 1.07, 95% confidence interval [CI] 1.03–1.12, p = 0.001) and those with a lower GCS score on admission (OR 0.49, 95% CI 0.30–0.80, p = 0.004) were at higher risk of poor neurological outcome.

Analogous analysis was conducted to determine risk factors of non-survival. In the univariate analysis, older age, higher adrenaline dosage during CPR, lower admission GCS score and presence of cardiogenic shock were associated with higher in-hospital mortality (Table 2). For multivariate analysis two new variables were added, i.e. CPR duration and bystander BLS. Eventually, stepwise regression revealed older age (OR 1.08, 95% CI 1.02–1.13, p = 0.006), lower GCS score (OR 0.47, 95% CI 0.25–0.85, p = 0.01), presence of cardiogenic shock (OR 3.43, 95% CI 1.11–10.53, p = 0.03), and higher doses of adrenaline during CPR (OR 1.27, 95% CI 1.04–1.56, p = 0.02) to be risk factors of in-hospital death.

Determinants of the duration of MTH induction

Patients who recovered with a CPC of 1 or 2, had a significantly longer median induction time than patients with a CPC of 3–5 (325.0 min [230.0–615.0] vs. 260.0 min [180.0–360.0], p = 0.04; Table 3). According to univariate analysis, lower lactate level, higher GCS score on admission, higher initial body temperature, shorter time in cardiac arrest and shorter CPR duration were significantly associated with the duration of MTH induction (Table 4). As a potential confounder, initial temperature was excluded from further analysis. According to multivariate analysis, longer duration of MTH induction was independently associated with shorter CPR duration [unstandardized coefficient –3.95, 95% CI –7.09 to –0.81, p = 0.01) and lower lactate level (unstandardized coefficient –18.55, 95% CI –36.10 to –1.01, p = 0.04).

Discussion

No differences were found regarding MTH induction time in terms of OHCA survival, however patients with poor neurologic outcome had significantly shorter MTH induction time than patients with a good outcome. Older age and lower GCS score on admission were also identified as independent predictors of worse neurologic outcome as well as older age, higher adrenaline dosage during CPR, lower baseline GCS score and presence of cardiogenic shock as independent risk factors of mortality. CPR duration and lactate concentration were independently associated with the duration of MTH induction.

Previous studies delivered inconsistent results regarding the relationship between MTH induction time and neurologic outcome. Nielsen et al. [19] reported that neither time to initiation of TTM, time to achieve TT, duration of TTM nor rewarming time were associated with neurologic outcome. An analysis of 588 patients conducted by Haugk et al. [13] indicated that patients with favorable outcome had both longer — time from ROSC to TT as well as induction time, with no difference in time from ROSC to initiation of cooling. They also performed a multivariate regression analysis and found 86% higher odds of a good neurologic outcome with an increase in each tertile (< 120 min, 120–220 min, and > 220 min) of time to TT (adjusted OR 1.86, p = 0.04). The median time needed to achieve TT, despite numerical difference, was not associated with overall survival (202 min for survivors vs. 158 min for non-survivors, p = 0.57). Several procedure-related differences between the studies and within particular studies should be underlined. In the study by Haugk et al. [13], TT was defined as less than 34°C and different cooling methods including endovascular, head cooling, surface (ice, water, air), nasopharyngeal, intravenous, and mixed were applied. Perman et al. [14] analyzed 321 patients from various centers and categorized them by induction time (< 120 min, 120–300 min, > 300 min). The authors reported that age, shockable initial rhythm, time in cardiac arrest and induction time > 300 min were associated with a higher probability of a favorable neurologic outcome. In contrast to this, other publications showed rapid TT achievement to be associated with better neurologic results [20–23]. However, all those studies defined time to TT as the period from the onset of cardiac arrest to arrival at a temperature of 33°C or < 34°C, therefore it was equivalent to three different time intervals used in the current study (time in cardiac arrest, pre-induction and induction). In each of these time periods patients are affected by various conditions potentially determining outcome, thus we believe that the analysis should be conducted separately for each of these time intervals. Shorter time in cardiac arrest [19, 24] and sooner initiation of

Table 2. Univariate and multivariate regression analysis for poor neurologic outcome and non-survival.

	Poor neurologic outcome				Non-survival			
	Univariate analysis		Multivariable analysis		Univariate analysis		Multivariable analysis	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Age (n = 90)	1.07 (1.02–1.11)	0.002	1.09 (1.03–1.15)	0.002	1.05 (1.01–1.10)	0.01	1.08 (1.02–1.14)	0.007
Male (n = 90)	0.51 (0.16–1.58)	0.24	–	–	2.1 (0.63–7.04)	0.23	–	–
Bystender BLS (n = 88)	0.50 (0.21–1.21)	0.13	–	–	0.42 (0.17–1.03)	0.06	0.57 (0.19–1.78)	0.34
Adrenaline (n = 83)	1.13 (0.96–1.33)	0.16	–	–	1.25 (1.06–1.49)	0.01	1.24 (1.00–1.55)	0.049
Ischemic etiology (n = 90)	2.29 (0.72–7.27)	0.79	–	–	1.38 (0.39–4.81)	0.88	–	–
pH (n = 90)	0.20 (0.004–10.53)	0.43	–	–	0.17 (0.003–8.60)	0.38	–	–
Lactate (n=72)	1.17 (0.97–1.41)	0.1	1.19 (0.96–1.49)	0.12	1.12 (0.95–1.32)	0.17	–	–
EF (n = 87)	0.99 (0.94–1.03)	0.56	–	–	0.96 (0.92–1.01)	0.11	–	–
GCS on admission (n = 90)	0.55 (0.36–0.85)	0.007	0.61 (0.34–1.01)	0.099	0.52 (0.31–0.86)	0.01	0.51 (0.27–0.96)	0.04
Cardiogenic shock (n = 90)	1.35 (0.58–3.15)	0.5	–	–	2.90 (1.14–7.34)	0.03	3.61 (1.15–11.36)	0.03
Initial temperature (n = 72)	0.72 (0.45–1.15)	0.17	–	–	0.67 (0.41–1.09)	0,103	–	–
Hypertension (n = 90)	1.12 (0.48–2.63)	0.79	–	–	1.12 (0.47–2.69)	0.8	–	–
Diabetes mellitus (n = 90)	0.92 (0.37–2.26)	0.85	–	–	0.79 (0.31–2.05)	0.64	–	–
Previous stroke (n = 90)	3.57 (0.40–31.93)	0.26	–	–	0.95 (0.16–5.49)	0.95	–	–
Previous ACS (n = 90)	1.10 (0.43–2.79)	0.85	–	–	2.03 (0.79–5.19)	0.14	–	–
Time in cardiac arrest (n = 90)	1.01 (0.98–1.04)	0.54	–	–	1.02 (0.99–1.04)	0.2	–	–
CPR duration (n=90)	1.02 (0.99–1.04)	0.29	–	–	1.03 (0.998–1.05)	0.08	1.01 (0.97–1.05)	0.63
Pre-induction time (n = 79)	1.00 (0.997–1.01)	0.42	–	–	0.999 (0.998–1.001)	0.91	–	–
Induction time (n = 85)	0.997 (0.995–0.999)	0.02	0.999 (0.996–1.002)	0.4	0.998 (0.996–1.001)	0.17	–	–

ACS — acute coronary syndrome; BLS — basic life support; CI — confidence interval; CPR — cardio-pulmonary resuscitation; EF — ejection fraction; GCS — Glasgow Coma Scale; OR — odds ratio

Table 3. Time intervals and final outcome.

	Total	Good neurologic outcome	Poor neurologic outcome	P	Survivor	Nonsurvivor	P
Time in CA [min] (n = 87)	28.0 (20.0–40.0)	30,0 (20.0–40.0)	27.0 (20.0–38.0)	0.85	25.0 (20.0–38.75)	30.0 (23.0–40.0)	0.21
CPR duration [min] (n = 90)	15.5 (10.0–25.25)	15.0 (8.5–25.0)	16.5 (11.75–30.0)	0.35	15.0 (10.0–25.0)	20.0 (15.0–35.0)	0.06
Pre-induction time [min] (n = 79)	185.0 (144.0–255.0)	165.0 (136.25–275.0)	205.0 (150.0–250.0)	0.2	185.0 (145.0–260.0)	205.5 (141.0–251.25)	0.95
Induction time [min] (n = 85)	290.0 (180.0–420.0)	325.0 (230.0–615.0)	260.0 (180.0–360.0)	**0.04**	300.0 (230.0–457.5)	240.0 (180.0–370.0)	0.09
Maintenance time [min] (n = 85)	1420.0 (1240.0–1450.0)	1380.0 (1200.0–1440.0)	1432.5 (1282.5–1471.25)	0.16	1420.0 (1253.0–1440.0)	1415.0 (1155.0–1480.0)	0.96

CA — cardiac arrest; CPR — cardio-pulmonary resuscitation

Table 4. Univariate and multivariate regression analysis for mild therapeutic hypothermia (MTH) induction time.

	Univariate analysis		Multivariable analysis	
	Unstandardised coefficient (95% CI)	P	Unstandardised coefficient (95% CI)	P
Age (n = 90)	–2.49 (–6.39 to 1.42)	0.21	–	–
Male (n = 90)	–7.65 (–129.93 to 114.63)	0.9	–	–
Initial shockable rhythm (n = 90)	81,27 (–69.47 to 232,0)	0.29	–	–
Bystender BLS (n = 88)	31.92 (–67.54 to 131.38)	0.53	–	–
Adrenaline (n = 83)	–9.362 (–26.98 to 8.26)	0.29	–	–
Ischemic etiology (n = 90)	–13.97 (–148.9 to 120.967)	0.62	–	–
pH (n = 90)	124.76 (–319.6 to 569.13)	0.58	–	–
Lactate (n = 72)	–20.38 (–38.56 to –2.2)	0.03	–16.2 (–34.49 to 2.1)	0.08
EF (n = 87)	0.964 (–4.307 to 6.235)	0.72	–	–
GCS on admission (n = 90)	47.87 (1.63 to 94.11)	0.04	25.77 (–27.31 to 78.87)	0.34
Cardiogenic shock (n = 90)	–40.06 (–137.89–57.78)	0.42	–	–
Initial temperature (n = 72)	116.75 (73.17 to 160.33)	<0.001	–	–
Hypertension (n = 90)	52.69 (–45.36 to 150.73)	0.29	–	–
Diabetes mellitus (n = 90)	85.84 (–17.14 to 188.82)	0.101	–	–
Previous stroke (n = 90)	–116.04 (–310.5 to 78.43)	0.24	–	–
Previous ACS (n = 90)	47.31 (–60.12 to 78.43)	0.38	–	–
Time in cardiac arrest (n = 90)	–3.35 (–6.25 to –0.45)	0.02	3.31 (–4.48 to 11.01)	0.4
CPR duration (n = 90)	–4.23 (–7.05 to –1.4)	0.004	–6.75 (–14.62 to 1.11)	0.09
Pre-induction time (n = 79)	0.17 (–0.42 to 0.762)	0.56	–	–

ACS — acute coronary syndrome; BLS — basic life support; CI — confidence interval; CPR — cardio-pulmonary resuscitation; EF — ejection fraction; GCS — Glasgow Coma Scale

MTH [25] were associated with better neurologic outcome. Lee et al. [15] analyzed 515 patients treated with MTH in terms of time intervals and neurologic outcome. Despite a significant difference in the induction time between the groups with favorable and unfavorable outcome and no difference in the pre-induction time, regression analysis revealed the opposite results. No association between induction time and outcome were found while elongation of pre-induction by each 30 min increased the odds for poor outcome by 11%. In the present study, induction time was also found to be significantly longer in patients with good neurologic outcome when compared with the poor outcome group. Subsequent univariate analysis revealed an association between MTH induction time and neurological outcome, however, similar to the results presented by Lee et al. [15], the finding was not confirmed in the multivariate model. Unlike the analysis by Haugk et al. [13] and Perman et al. [14], the induction time was not categorized to avoid a possible bias resulting from switching from a continuous to categorical variable. In the current study, older age and lower GCS score on admission were the only independent risk factors of poor neurologic outcome, these observations are consistent with previous studies [15, 19]. The phenomenon of shorter induction time in patients with unfavorable outcome was suspected to be a result of more severe initial brain injury, impaired thermoregulation, and greater vulnerability to cooling [14]. A study evaluating heat generation in patients treated with MTH after cardiac arrest revealed an association between greater heat production and better baseline health status, reduced ischemic injury and improved neurologic outcome [26]. A study published by Leão et al. [27] showed that, apart from shorter induction time, patients with unfavorable neurologic outcome had a higher incidence of hypoxic-ischemic brain injury on magnetic resonance imagining and a higher concentration of neuron specific enolase. The present results are consistent with these studies [14, 15, 19, 26, 27] and might indirectly support the

hypothesis that shorter induction time in patients with unfavorable neurological outcome is related to more severe brain injury, since the initial neurologic condition reflected by GCS on admission was a strong outcome predictor. Furthermore, an association between longer MTH induction time and higher GCS score was found in univariate analysis, however results were not confirmed in the multivariate model. The differences between the studies regarding time intervals could result from the implementation of various definitions, different methods of cooling [28] and temperature measurement [29], and heterogeneity of the study populations (inclusion of patients regardless of the etiology and place of cardiac arrest or the type of the initial rhythm).

There were no differences in time intervals between survivors and non-survivors in the present study. Similar results were presented by Haugk et al. [13]. The current study found that older age, higher doses of adrenaline during CPR, lower GCS score on admission and presence of cardiogenic shock were predictors of in-hospital mortality. Lee et al. [15] also reported lower initial GCS scores along with non-shockable rhythm, longer time in cardiac arrest and a higher Sequential Organ Failure Assessment (SOFA) score were independent risk factors for mortality, while no association was found between other time variables (pre-induction and induction) and odds for survival. In contrast to previous results, Leão et al. [27] showed a correlation between higher mortality at 6 months after cardiac arrest and shorter time to TT.

Addressing the multiple inconsistencies regarding time intervals in TTM and particularly the MTH induction time, the predictors were determined for delayed achievement of TT. In univariate regression analysis, longer MTH induction time was associated with lower lactate level, higher GCS score on admission, shorter time in cardiac arrest, and shorter CPR duration. According to the multivariate analysis, only shorter CPR duration and lower lactate level on admission were associated with prolonged induction time. The role of initial temperature in patients treated with MTH was raised in some previous studies, linking lower initial temperature with in-hospital [30] and long-term [31] mortality. This parameter however, was excluded from analysis as a potential confounder.

Limitations of the study

One of the main limitations of the present study is its partly retrospective and observational nature. Furthermore, only a relatively small group of patients were analyzed. Another limitation was the difficulty in precisely determining all essential time points.

Conclusions

Favorable neurologic outcome (CPC 1–2) in OHCA patients treated with MTH is associated with younger age and higher GCS score upon admission. The risk factors for increased in-hospital mortality in this population included older age, higher doses of adrenaline during CPR, lower GCS score on admission and presence of cardiogenic shock. Neither the induction nor pre-induction time was an independent risk factor for neurologic outcome or overall survival. CPR duration and lactate level on admission were predictors for prolonged induction time.

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Conflict of interest: None declared

References

1. 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. 2018 [Epub ahead of print], doi: 10.5603/CJ.a2018.0140, indexed in Pubmed: 30444257.
2. Atwood C, Eisenberg MS, Herlitz J, et al. Incidence of EMS-treated out-of-hospital cardiac arrest in Europe. Resuscitation. 2005; 67(1): 75–80, doi: 10.1016/j.resuscitation.2005.03.021, indexed in Pubmed: 16199289.
3. 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. 2018 [Epub ahead of print], doi: 10.5603/CJ.a2018.0025, indexed in Pubmed: 29611174.
4. Pusswald G, Fertl E, Faltl M, et al. Neurological rehabilitation of severely disabled cardiac arrest survivors. Part II. Life situation of patients and families after treatment. Resuscitation. 2000; 47(3): 241–248, indexed in Pubmed: 11114453.
5. Donnino MW, Andersen LW, Berg KM, et al. Temperature Management After Cardiac Arrest: An Advisory Statement by the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. Circulation. 2015; 132(25): 2448–2456, doi: 10.1161/CIR.0000000000000313, indexed in Pubmed: 26434495.

6. 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.
7. 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.
8. 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.
9. 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.
10. 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.
11. 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.
12. 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. 2016; 1(4): 115–119, doi: 10.5603/mrj.2016.0021.
13. Haugk M, Testori C, Sterz F, et al. Relationship between time to target temperature and outcome in patients treated with therapeutic hypothermia after cardiac arrest. Crit Care. 2011; 15(2): R101, doi: 10.1186/cc10116, indexed in Pubmed: 21439038.
14. Perman SM, Ellenberg JH, Grossestreuer AV, et al. Shorter time to target temperature is associated with poor neurologic outcome in post-arrest patients treated with targeted temperature management. Resuscitation. 2015; 88: 114–119, doi: 10.1016/j.resuscitation.2014.10.018, indexed in Pubmed: 25447429.
15. Lee BK, Jeung KW, Jung YH, et al. Relationship between timing of cooling and outcomes in adult comatose cardiac arrest patients treated with targeted temperature management. Resuscitation. 2017; 113: 135–141, doi: 10.1016/j.resuscitation.2016.12.002, indexed in Pubmed: 27987398.
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. Perkins G, Jacobs I, Nadkarni V, et al. Cardiac Arrest and Cardiopulmonary Resuscitation Outcome Reports: Update of the Utstein Resuscitation Registry Templates for Out-of-Hospital Cardiac Arrest. Resuscitation. 2015; 96: 328–340, doi: 10.1016/j.resuscitation.2014.11.002.
18. Booth CM, Boone RH, Tomlinson G, et al. Is this patient dead, vegetative, or severely neurologically impaired? Assessing outcome for comatose survivors of cardiac arrest. JAMA. 2004; 291(7): 870–879, doi: 10.1001/jama.291.7.870, indexed in Pubmed: 14970067.
19. Nielsen N, Hovdenes J, Nilsson F, et al. Hypothermia Network. Outcome, timing and adverse events in therapeutic hypothermia after out-of-hospital cardiac arrest. Acta Anaesthesiol Scand. 2009; 53(7): 926–934, doi: 10.1111/j.1399-6576.2009.02021.x, indexed in Pubmed: 19549271.
20. Chiota NA, Freeman WD, Barrett K. Earlier Hypothermia Attainment is Associated with Improved Outcomes after Cardiac Arrest. J Vasc Interv Neurol. 2011; 4(1): 14–17, indexed in Pubmed: 22518262.
21. Sendelbach S, Hearst MO, Johnson PJo, et al. Effects of variation in temperature management on cerebral performance category scores in patients who received therapeutic hypothermia post cardiac arrest. Resuscitation. 2012; 83(7): 829–834, doi: 10.1016/j.resuscitation.2011.12.026, indexed in Pubmed: 22230942.
22. Wolff B, Machill K, Schumacher D, et al. Early achievement of mild therapeutic hypothermia and the neurologic outcome after cardiac arrest. Int J Cardiol. 2009; 133(2): 223–228, doi: 10.1016/j.ijcard.2007.12.039, indexed in Pubmed: 18353458.
23. Schock RB, Janata A, Peacock WF, et al. Time to Cooling Is Associated with Resuscitation Outcomes. Ther Hypothermia Temp Manag. 2016; 6(4): 208–217, doi: 10.1089/ther.2016.0026, indexed in Pubmed: 27906641.
24. Kim WY, Ahn S, Hong JS, et al. The impact of downtime on neurologic intact survival in patients with targeted temperature management after out-of-hospital cardiac arrest: National multicenter cohort study. Resuscitation. 2016; 105: 203–208, doi: 10.1016/j.resuscitation.2016.03.020, indexed in Pubmed: 27060537.
25. Italian Cooling Experience (ICE) Study Group. Early- versus late-initiation of therapeutic hypothermia after cardiac arrest: preliminary observations from the experience of 17 Italian intensive care units. Resuscitation. 2012; 83(7): 823–828, doi: 10.1016/j.resuscitation.2011.12.002, indexed in Pubmed: 22155700.
26. Murnin MR, Sonder P, Janssens GN, et al. Determinants of heat generation in patients treated with therapeutic hypothermia following cardiac arrest. J Am Heart Assoc. 2014; 3(3): e000580, doi: 10.1161/JAHA.113.000580, indexed in Pubmed: 24780205.
27. Leão RN, Ávila P, Cavaco R, et al. Therapeutic hypothermia after cardiac arrest: outcome predictors. Rev Bras Ter Intensiva. 2015; 27(4): 322–332, doi: 10.5935/0103-507X.20150056, indexed in Pubmed: 26761469.
28. 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.
29. 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. 2018 [Epub ahead of print], doi: 10.5603/CJ.a2018.0115, indexed in Pubmed: 30246234.
30. Benz-Woerner J, Delodder F, Benz R, et al. Body temperature regulation and outcome after cardiac arrest and therapeutic hypothermia. Resuscitation. 2012; 83(3): 338–342, doi: 10.1016/j.resuscitation.2011.10.026, indexed in Pubmed: 22079947.
31. Hovdenes J, Røysland K, Nielsen N, et al. A low body temperature on arrival at hospital following out-of-hospital-cardiac-arrest is associated with increased mortality in the TTM-study. Resuscitation. 2016; 107: 102–106, doi: 10.1016/j.resuscitation.2016.08.011, indexed in Pubmed: 27565034.

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Poor long-term outcome in acute coronary syndrome in a real-life setting: Ten-year outcome of the TACOS study

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Abstract

Background: *Long-term outcome of the three categories of acute coronary syndrome (ACS) in real-life patient cohorts is not well known. The objective of this study was to survey the 10-year outcome of an ACS patient cohort admitted to a university hospital and to explore factors affecting the outcome.*

Methods: *A total of 1188 consecutive patients (median age 73 years) with ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI) or unstable angina pectoris (UA) in 2002–2003 were included and followed up for ≥ 10 years.*

Results: *Mortality for STEMI, NSTEMI and UA patients during the follow-up period was 52.5%, 69.9% and 41.0% ($p < 0.001$), respectively. In multivariable Cox regression analysis, only age and creatinine level at admission were independently associated with patient outcome in all the three ACS categories when analyzed separately.*

Conclusions: *All the three ACS categories proved to have high mortality rates during long-term follow-up in a real-life patient cohort. NSTEMI patients had worse outcome than STEMI and UA patients during the whole follow-up period. Our study results indicate clear differences in the prognostic significance of various demographic and therapeutic parameters within the three ACS categories.* (Cardiol J 2021; 28, 2: 302–311)

Key words: acute coronary syndrome, myocardial infarction, prognosis, unstable angina

Introduction

Acute coronary syndromes (ACS) represent a spectrum of clinical events ranging from unstable angina pectoris (UA) to non-ST-segment elevation (NSTEMI) and ST-segment elevation myocardial infarction (STEMI). Despite the fact that ischemic heart disease remains the leading cause of death globally [1], data on long-term mortality, especially beyond the first few years, is scarce.

Elderly patients are underrepresented or even excluded in clinical trials. As many as 50% of real-world acute myocardial infarction (MI) patients may not be represented in randomized clinical tri-

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als [2]. On the other hand, the general population is aging, elderly individuals comprise the fastest growing segment of the population worldwide, and coronary artery disease is common in the elderly [3, 4]. Older MI patients are less likely to receive evidence-based care than younger patients [5].

Studies have shown that UA patients have better short-term outcome than patients with acute MI, but long-term outcome may not differ greatly [6]. According to randomized clinical trials, NSTEMI patients have better outcome than STEMI patients during the first few weeks after the acute event, but they are at higher risk for adverse outcome over the long-term [7].

In a prospective observational study, we previously reported 10-month outcome data of consecutive ACS patients (n = 1188) treated in a university hospital [8]. The aim of the present study was to establish the 10-year outcome data of all the three clinical entities of ACS in the same patient cohort. We also studied the effect of baseline clinical factors and data collected during the initial hospital stay on patient outcome.

Methods

Study population

Details of the patient selection have been described elsewhere [8]. Briefly, the Tampere Acute COronary Study (TACOS) study cohort consisted of 1188 ACS patients admitted to Tampere University hospital from the city of Tampere and 11 neighboring municipalities, a region of 340,000 inhabitants. From January 1st 2002 to March 31st 2003 all patients admitted to the emergency department presenting with acute MI as verified by an elevated blood troponin I (cTnI > 0.2 μg/L) value were recruited. In addition, from September 1st 2002 to March 31st 2003 all consecutive troponin-negative patients with UA were also recruited. Patients who died in or were discharged from the emergency department were not included. The complete study population consisted of 343 (29%) patients with STEMI, 655 (55%) with NSTEMI and 190 (16%) with UA.

The study complies with the Declaration of Helsinki. The Ethics Committee of the Pirkanmaa Hospital District approved the study protocol (Permission R02100). All subjects gave their written informed consent for participation.

ACS categories

All patients had symptoms and/or clinical signs suggestive of ACS. Patients with STEMI had elevated troponin levels (> 0.2 μg/L) and their electrocardiogram (ECG) fulfilled the predefined criteria for STEMI: ST-segment elevation in ≥ 2 adjacent leads, in leads V_1–V_6 ≥ 1.5 mm (≥ 2 mm in at least one lead), in leads II, III, aVF, and I and aVL ≥ 1 mm.

Also, in NSTEMI patients, the troponin values were elevated, but the ECG did not fulfil the criteria for STEMI. UA patients showed no elevation in a minimum of two cTnI levels 6–12 h apart.

Follow-up

Data was collected by a study nurse and two of the investigators (ME and KJN). The follow-up was set to begin at the moment of the ECG recording used for analysis, and it ended at death or at the end of follow-up — March 31st 2013. Mortality was gathered by linking the personal identity code from the TACOS study to the Causes of Death register, maintained by Statistics Finland, which records 100% of deaths of Finnish citizens at home and nearly 100% abroad. Follow-up was complete with 716 deaths and 472 patients alive at the end of the follow up. When comparing mortality to literature, exact 10-year mortality was used.

Statistical analysis

Categorical variables were expressed as numbers of patients or percentages and continuous variables as means or medians followed by quartiles (Q_1–Q_3). Fisher's exact test was used for categorical variables and the Mann-Whitney U or Kruskal-Wallis test for numerical variables. A two-tailed p-value of < 0.05 was considered statistically significant. Kaplan-Meier curves were used to present the unadjusted survival data. Cox regression analysis was used to identify the baseline and in-hospital prognostic variables concerning mortality at follow-up. Cox univariate and multivariable regression analyses including all the variables were presented. Troponin I values were used only for the STEMI and NSTEMI categories due to immeasurable low (< 0.2 μg/L) values in UA patients. To utilize the power of the wide study population, the variables previous smoking and coronary angiography were not included in the final model because of lack of data in a significant proportion of patients. Mortality rates at pre-specified points in time were calculated by dividing the amount of cumulative events before the time point by the number of patients at risk at the beginning of the follow-up. All calculations were performed with the SPSS 22.0 statistical package.

Results

Baseline characteristics and in-hospital data of the study patients were reported previously [9]. The median age of patients at study inclusion was 73 years (63–80 years) and the male/female ratio was 58%/42%. The NSTEMI patients were older (median age 75 years) than the STEMI (69 years) and UA (68 years) patients. The relative proportion of female patients was higher in the NSTEMI than in the STEMI and UA categories (46%, 36%, and 37%, respectively; $p = 0.003$). There were no significant differences in the rate of hypertension (50–55%, $p = 0.297$) or diabetes (22–29%, $p = 0.065$) between the three groups. The rate of diuretic usage at admission was highest in the NSTEMI category (42%, 19%, and 32%, respectively; $p < 0.001$).

The median survival times for the STEMI and NSTEMI categories were 9.7 years and 4.7 years. The mean survival times were 7.3 (95% confidence interval [CI] 6.8–7.7), 5.4 (95% CI 5.0–5.7) and 7.7 (95% CI 7.2–8.3) for STEMI, NSTEMI and UA categories, respectively ($p < 0.001$). The 5-year mortality rates were 32.4%, 51.3%, and 25.3% ($p < 0.001$), while the 10-year mortality rates were 52.5%, 69.9%, and 41.0% ($p < 0.001$) for the STEMI, NSTEMI and UA categories, respectively (Fig. 1). Among all deaths, 73.9%, 72.5% and 57.7% were due to cardiovascular causes for the STEMI, NSTEMI and UA patient categories, respectively ($p = 0.019$).

Variables predicting outcome at follow-up according to Cox univariate and multivariable regression analyses are presented in Table 1. Age, male gender, active smoking, diabetes, higher creatinine level, STEMI and NSTEMI ACS categories were independent predictors of worse outcome, while bypass surgery and hypertension were associated with better outcome. Diuretic use both at hospital arrival and discharge was associated with worse outcome, while statin use at discharge was associated with better outcome (Table 2).

When multivariable Cox regression analysis was performed separately for the ACS categories, only age and creatinine level at admission proved to be independent outcome predictors for all three categories (Table 3). Active smoking was an indicator of worse outcome in both STEMI and NSTEMI categories. Diuretic use at discharge had a strong negative impact on outcome both in NSTEMI and UA patients (Table 2). In NSTEMI, which was the largest patient category, invasive treatment and beta-blocker use at discharge were associated with better outcome.

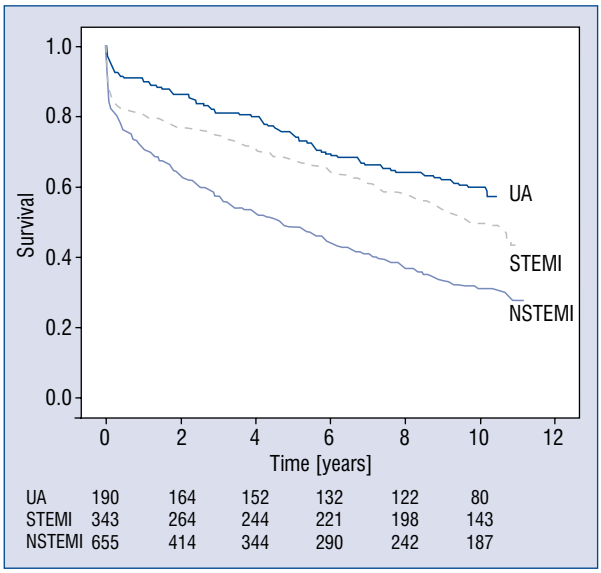

Figure 1. Kaplan-Meier estimates of survival and the number at risk at different time points in the three acute coronary syndrome categories. The y axis shows the proportion of patients alive at different time points (1.0 = 100%); abbreviations — see text.

Discussion

The present all-comers' study showed that: 1) all 3 patient categories of ACS have poor long-term outcome, 2) NSTEMI patients have the worst outcome, 3) the survival curves of STEMI and NSTEMI patients stay clearly separated for a follow-up period of ≥ 10 years, 4) UA patients have better outcome than MI patients also in the long term, and 5) factors affecting outcome differ between the three ACS categories.

Randomized clinical trials and the real-life setting in ACS: "Two different worlds"

In general, there is limited data on patient outcome in ACS beyond the first few years [9]. Especially, there is very little long-term mortality data from complete ACS cohorts, which include STEMI, NSTEMI and UA patients. Existing data shows wide variation in mortality reflecting distinct differences between randomized controlled trials with pre-specified exclusion criteria and "real-life" populations, which include consecutive patients independently of co-morbidities, ethnicity, age and gender. In randomized controlled trials of invasively treated STEMI patients, the 5-year mortality rate in STEMI may be as low as 10% [10]. The Global Registry of Acute Coronary Events (GRACE) study is widely acknowledged and has had significant im-

Table 1. Prognostic factors related to mortality according to univariate and multivariable Cox regression analyses.

	Median (IQR) or %	Valid cases	Univariate			Multivariable		
			Hazard ratio	95% CI	P	Hazard ratio	95% CI	P
Age	73 (63–80)	1188	1.075	1.067–1.084	< 0.001	1.056	1.044–1.069	< 0.001
Male gender	58	1188	0.689	0.595–0.798	< 0.001	1.283	1.060–1.552	0.011
Active smoking	19	1081	0.647	0.517–0.810	< 0.001	1.590	1.218–2.076	0.001
Ex-smoker	45	849	1.013	0.849–1.208	0.885	Not in the final model[¤]		
Hypertension	54	1179	1.147	0.989–1.331	0.070	0.763	0.621–0.938	0.010
Diabetes:								
No diabetes	74	1184	1					
Diabetes mellitus type 1	1	1184	1.925	0.995–3.722	0.052	2.811	1.284–6.154	0.010
Diabetes mellitus type 2	25	1184	1.744	1.487–2.045	< 0.001	1.287	1.067–1.552	0.008
Previous MI	24	1172	1.472	1.251–1.733	< 0.001	0.950	0.768-1.176	0.639
Plasma creatinine [/10 μmol/L]*	8.7 (7.2–10.9)	1186	1.050	1.040–1.060	< 0.001	1.023	1.008–1.039	0.003
cTnI [/10 μmol/L]*	0.47 (0.06-2.6)	1188	1.000	0.099–1.010	0.979	1.005	1.000–1.011	0.060
C-reactive protein [/10 mg/L]*[#]	1.2 (0.34–5.69)	1173	1.040[#]	1.030–1.049[#]	< 0.001	1.006	0.994–1.019	0.306
Systolic blood pressure	145 (125–167)	1187	0.996	0.994–0.999	0.003	0.998	0.994–1.002	0.297
Diastolic blood pressure	80 (69–91)	1187	0.989	0.984–0.993	< 0.001	1.002	0.996–1.009	0.476
PCI[a]	15	1188	0.426	0.328–0.553	< 0.001	0.680	0.453–1.020	0.063
CABG	9	1188	0.554	0.413–0.742	< 0.001	0.532	0.383–0.738	< 0.001
Category of ACS:		1188						
UAP	16		1					
STEMI	29		1.372	1.051–1.790	0.020	1.699	1.216–2.374	0.002
NSTEMI	55		2.264	1.780–2.880	< 0.001	1.810	1.352–2.422	< 0.001
CAG data available:		560				Not in the final model[¤]		
< 50% stenosis	12		1		1			
1-vessel disease	29		1.014	0.623–1.649	0.956			
2-vessel disease	24		1.121	0.682–1.844	0.652			
3-vessel disease	27		1.899	1.194–3.021	0.007			
Left main disease[b]	8		3.133	1.818–5.397	< 0.001			

IQR — interquartile range; CI — confidence interval; MI — myocardial infarction; cTnI — cardiac troponin I; PCI — percutaneous coronary invention; CABG — coronary artery bypass surgery; ACS — acute coronary syndrome; UA — unstable angina pectoris; STEMI — ST-segment elevation myocardial infarction; NSTEMI — non-ST-segment elevation myocardial infarction; CAG — coronary angiography
*Values at admission, for cTNI and C-reactive protein highest of two values 6–12 h apart
[¤]To utilize the power of the wide study population, ex-smoking and CAG were not included in the final model because of lack of data in a significant proportion of patients
[#]For plasma creatinine, cTnI and C-reactive protein, hazard ratio and CI were calculated using values per 10 mg/L
[a]Primary PCI was not standard therapy in STEMI patients
[b]Either isolated or in association with 1-, 2- or 3-vessel disease

Table 2. Prognostic factors related to mortality according to univariate and multivariable Cox regression analyses

	Median (IQR) or %	Valid cases	Univariate			Multivariable		
			Hazard ratio	95% CI	P	Hazard ratio	95% CI	P
Medication at admission:								
ASA	45	1184	1.110	0.958–1.286	0.165	0.968	0.785–1.193	0.758
Beta-blocker	50	1186	1.283	1.108–1.487	0.001	1.078	0.874–1.329	0.485
Nitrate	48	1186	1.603	1.383–1.859	< 0.001	1.014	0.816–1.260	0.900
Calcium-antagonist	21	1186	1.228	1.032–1.461	0.021	1.141	0.903–1.442	0.270
Diuretic	34	1186	3.161	2.721–3.672	< 0.001	1.718	1.392–2.121	< 0.001
Statin	22	1187	0.747	0.621–0.900	0.002	1.279	0.982–1.665	0.068
ACE-inhibitor	45	1185	1.520	1.286–1.797	< 0.001	0.964	0.764–1.218	0.761
AT2-inhibitor	7	1186	0.963	0.720–1.287	0.798	1.306	0.824–2.071	0.256
Digitalis	12	1187	2.566	2.112–3.116	< 0.001	1.100	0.823–1.469	0.520
Warfarin	45	1187	2.053	1.682–2.505	< 0.001	1.004	0.714–1.411	0.983
Clopidogrel	1	1186	0.370	0.139–0.989	0.047	0.575	0.203–1.627	0.297
Medication at discharge:								
Aspirin	88	1188	0.490	0.401–0.599	< 0.001	0.880	0.656–1.180	0.392
Beta-blocker	93	1188	0.742	0.562–0.979	0.035	0.691	0.475–1.004	0.053
Nitrate	72	1188	1.317	1.108–1.564	0.002	1.005	0.810–1.246	0.967
Calcium-antagonist	18	1188	1.160	0.966–1.393	0.113	0.960	0.751–1.226	0.741
Diuretic	50	1188	3.273	2.751–3.893	< 0.001	1.702	1.349–2.147	<0.001
Statin	34	1188	0.381	0.328–0.442	< 0.001	0.710	0.573–0.880	0.002
ACE-inhibitor	47	1188	1.193	1.031–1.382	0.018	1.020	0.839–1.242	0.841
AT2-inhibitor	8	1188	0.906	0.683–1.202	0.493	0.778	0.501–1.208	0.263
Digitalis	16	1188	2.515	2.110–2.997	< 0.001	1.147	0.8721.509	0.327
Warfarin	24	1188	1.337	1.136–1.574	< 0.001	1.052	0.822–1.345	0.688
Clopidogrel	20	1188	0.490	0.396–0.605	< 0.001	0.927	0.661–1.300	0.662

IQR — interquartile range; CI — confidence interval; ASA — acetylsalicylic acid; ACE — angiotensin-converting enzyme; AT2 — angiotensin II

pact on risk stratification in ACS [11]. In the "long-term" GRACE study (GRACE UK-Belgian), 5-year mortality of STEMI and NSTEMI patients was 19% and 22%, respectively [9]. These figures are in strong contrast with the corresponding mortality figures of 32.4%, and 51.3% in the present study. The 2002 New Zealand ACS Audit Group carried out a comprehensive collection of data from all ACS patients admitted to a New Zealand hospital over a 14-day period in May 2002, and found mortality rates close to those of the present study in STEMI patients (34%), while the mortality rate (33%) for NSTEMI patients was between that reported in the GRACE UK-Belgian study and the present study [12]. Differences in patient age is probably an important explanatory factor for the observed variation in mortality rates; age at study inclusion was 65/72/69 years for STEMI and 67/73/75 years for NSTEMI in GRACE, New Zealand ACS and TACOS, respectively. Also, a retrospective "real life" analysis of 2,763 consecutive ACS patients found much higher mortality at long-term (median 8.2 years) in patients > 65 years (69.7%) compared with those ≤ 65 years (18.6%) [13].

When comparing longer outcome in STEMI patients, the 10-year mortality rates in the New Zealand ACS audit study (48%) and the present study (52.5%) are comparable. In NSTEMI patients, higher 10-year mortality rates were found: 51% and 69.9%, probably not entirely explained by the 2-year age difference at study inclusion.

A recent meta-analysis of 8 randomized non-ST-segment elevation ACS (NSTE-ACS; NSTEMI and UA together) trials included 6,657 patients [14]. At a mean of 10.3 year follow-up, the risk of all-cause mortality was 28.5%. Again, this is certainly much

Table 3. Characteristics significant in at least one of the three acute coronary syndrome categories retained in the final multivariate Cox regression model.

Characteristic	Hazard ratio	95% CI	P
STEMI category			
Age	1.067	1.044–1.091	< 0.001
Male gender	1.141	0.744–1.748	0.546
Active smoking	2.017	1.237–3.289	0.005
Hypertension	0.832	0.568–1.220	0.346
Diabetes:			
No diabetes			
Diabetes mellitus type 1	7.949	1.609–39.264	0.011
Diabetes mellitus type 2	1.509	1.020–2.233	0.040
Previous MI	0.658	0.413–1.048	0.078
Plasma creatinine [/10 μmol/L]	1.092	1.032–1.155	0.002
C-reactive protein [/10 mg/L]	1.029	1.004–1.055	0.022
cTnI [/10μmol/L]	1.005	0.999–1.012	0.114
Medication at admission:			
Diuretic	1.357	0.881–2.089	0.166
ACE-inhibitor	0.625	0.375–1.041	0.071
Warfarin	0.638	0.311–1.307	0.219
PTCA	0.813	0.505–1.309	0.394
CABG	0.822	0.416–1.623	0.572
Medication at discharge:			
Beta-blocker	0.841	0.355–1.994	0.695
Diuretic	1.137	0.768–1.682	0.521
Statin	0.573	0.386–0.853	0.006
Digitalis	2.111	1.136–3.925	0.018
NSTEMI category			
Age	1.044	1.029–1.060	< 0.001
Male gender	1.121	0.892–1.410	0.328
Active smoking	1.537	1.091–2.165	0.014
Hypertension	0.753	0.593–0.955	0.019
Diabetes:			
No diabetes			
Diabetes mellitus type 1	1.774	0.637–4.939	0.272
Diabetes mellitus type 2	1.144	0.911–1.436	0.247
Previous MI	1.066	0.842–1.351	0.595
Plasma creatinine [/10 μmol/L]	1.037	1.020–1.055	< 0.001
C-reactive protein [/10 mg/L]	0.999	0.985–1.013	0.874
cTnI [/10μmol/L]	1.035	1.014–1.058	0.001
Medication at admission:			
Diuretic	1.827	1.411–2.366	< 0.001
ACE-inhibitor	1.104	0.864–1.412	0.429
Warfarin	1.370	1.003–1.870	0.048
PTCA	0.569	0.374–0.864	0.008
CABG	0.456	0.310–0.673	< 0.001
Medication at discharge:			
Beta-blocker	0.554	0.352–0.872	0.011
Diuretic	2.104	1.547–2.862	< 0.001
Statin	0.795	0.629–1.005	0.055
Digitalis	1.250	0.951–1.642	0.109

→

Table 3 (cont.). Characteristics significant in at least one of the three acute coronary syndrome categories retained in the final multivariate Cox regression model.

Characteristic	Hazard ratio	95% CI	P
UAP category			
Age	1.117	1.073–1.164	< 0.001
Male gender	3.400	1.625–7.113	0.001
Active smoking	1.995	0.614–6.481	0.251
Hypertension	1.003	0.558–1.805	0.992
Diabetes:			
No diabetes			
Diabetes mellitus type 1	131.881	0.882–19712.989	0.056
Diabetes mellitus type 2	2.103	1.173–3.770	0.013
Previous MI	0.696	0.361–1.345	0.281
Plasma creatinine [/10 μmol/L]	0.946	0.905–0.989	0.015
C-reactive protein [/10 mg/L]	1.221	1.102–1.352	< 0.001
Medication at admission:			
Diuretic	0.683	0.296–1.577	0.372
ACE-inhibitor	1.354	0.704–2.606	0.364
Warfarin	0.700	0.342–1.429	0.327
PTCA	0.028	0.000–4.118	0.160
CABG	0.222	0.047–1.039	0.056
Medication at discharge:			
Beta-blocker	1.281	0.571–2.874	0.548
Diuretic	4.807	1.937–11.931	0.001
Statin	1.131	0.610–2.099	0.695
Digitalis	0.907	0.432–1.900	0.795

ACE — angiotensin-converting enzyme; CABG — coronary artery bypass surgery; CI — confidence interval; cTnI — cardiac troponin I; MI — myocardial infarction; NSTEMI — non-ST-segment elevation myocardial infarction; PTCA — percutaneous transluminal coronary angioplasty; STEMI — ST-segment elevation myocardial infarction; UAP — unstable angina pectoris

lower than in both NSTEMI (69.9%) and UA (41%) in the present study. However, the mean age of the NSTE-ACS patients in the meta-analysis was ~76 at the end of 10.3-year follow-up, while in the present study, the median age at study inclusion in NSTEMI patients was 75 years (68 years for UA) [8].

STEMI/NSTEMI comparison

Clinical trial evidence is limited with regard to the efficacy and hazards of pharmacological and invasive management of NSTE-ACS in the elderly. According to Alexander et al. [15], the age gap between trials and community populations begins at age 75 and widens with age. Studies have shown that long-term outcome in NSTEMI patients is not improving, and this has been attributed to the fact that they have a more complex phenotype [16]. Compared with STEMI patients, those with NSTEMI tend to be older and have more comorbidity. In the Worcester Heart Attack Study (WHAS) with a population 3,762 patients, post-discharge death rates in a sub-cohort with longer follow-up, 5-year death rates for STEMI (mean age for all patients 65.5 years) and NSTEMI (mean age for all patients 72.6 years) were 30.2% and 52.4%, which are in the same range as in the present study: 32.4% for STEMI, 51.3% for NSTEMI [17].

Regarding STEMI, the introduction of primary percutaneous coronary intervention (PCI) programs and improvements in coronary interventions and medical therapy have resulted in definite improvement in patient outcome [18, 19]. However, patients > 75 years of age are underrepresented in randomized clinical STEMI trials; age over 75 or 80 years was a typicalexclusion criteria in many trials [20]. Therefore, limited data is available for guidance on the best management of this growing subset of patients, although registry data seems

to support the superiority of primary PCI over conservative treatment also in the elderly [21]. The Florence Acute Myocardial Infarction Registry (AMI-Florence) was a population-based prospective observational registry, where the baseline data were collected in 2000–2001 (2002–2003 in our study) [21]. In STEMI patients (n = 875), the 8-year mortality rate was 49%, comparable to 42.3% in the present study. In AMI-Florence, primary PCI was performed in 50% of the STEMI patients admitted within 24 h, whereas in the current study 24% had PCI during the index hospital admission, while 57% received fibrinolytic therapy [8].

Unstable angina pectoris

Existing data on the long-term outcome of UA is scarce mainly due to the fact that researchers tend to combine NSTEMI and UA into NSTE-ACS [22]. It was previously reported that UA patients (median age at study inclusion 68 years) had low in-hospital mortality (2.6%), but at 10 months, the mortality rate had increased to 12% [8]. With longer follow-up, 5- and 10-year mortality rates of UA patients clearly increased to 25.3% and 41%, respectively. The corresponding mortality rate at 10 years in the New Zealand ACS Audit trial was 32% [12]. In the GRACE UK-Belgian study, 5-year mortality rate in UA was 18% [9]. With the introduction of the sensitive troponins to detect myocardial injury, it is probable that a considerable proportion of the UA patients in the present study would be classified as NSTEMI using today's diagnostic methods [23].

Predictors of mortality

When analyzing all patients together in the present study, the well-established cardiovascular risk factors retained their statistical significance as independent outcome predictors in the multivariable analyses. However, only age and renal dysfunction (higher creatinine levels), which are well documented risk factors, showed negative prognostic impact uniformly in all three ACS categories. For example, active smoking affected outcome only in STEMI and NSTEMI patients, while male gender was associated with inferior outcome only in UA patients. Previous study evidence for a gender difference in mortality in ACS patients is conflicting. In a major systematic review, Buchholz et al. [24] found considerable heterogeneity of study results when analyzing 26 studies reporting mortality at 5 to 9 years. Most studies reported clear attenuation of study results after covariates other than age were introduced in the analyses.

The fact that diuretic use had the strongest impact on the outcome of patients in the NSTEMI category is not surprising, as these patients were older and probably had more co-morbidity, such as heart failure. In the PRAIS-UK registry, which dealt with NSTEMI patients treated in the late 1990's, history of heart failure was a predictor of inferior outcome during 10-year follow-up [25].

Herein, there is no definite explanation for the protective effect on outcome of hypertension in the NSTEMI patients, other than possible positive effects on use of hypertensive medication on ventricular remodeling. Hypertension could also maintain circulation of the kidneys longer in the severely ill, hypovolemic patients and hence, a delayed progression of kidney failure.

Limitations of the study

This study has clear limitations; those related to data collection and patient classification were described previously [8]. The follow-up of UA patients was shorter than in the STEMI and NSTEMI groups. The categorization of those with left bundle branch block as NSTEMI or UA patients could increase the risk of random error. However, only 9% of left bundle branch block patients were treated with fibrinolytic therapy, which supports the decision for this classification.

There are two additional limitations typical for outcome studies with long follow-up in patients with cardiovascular diseases. The first limitation is the low rate of invasive procedures [17]. Especially in STEMI, the rate of invasive procedures during the index hospital stay in the present study was lower than what is typical for Western countries today. Yet, most (55%) patients in the examined cohort had NSTE-ACS, where the rate of invasive procedures did not increase as much as in the treatment of STEMI [26]. In addition, in the NSTEMI category, the median age at study inclusion was 75 years, and older patients tend to have lower rates of invasive procedures [27]. Also, the use of medical therapy is known to improve outcome, such as statins, were not at the level that is expected in patient care today. Because of these limitations, the study results do not necessarily reflect the outcome of ACS patients treated according to a modern standard. Another general limitation of studies with long-term follow-up is the fact that changes in patient medication and new coronary interventions are difficult or impossible to control for.

Conclusions

All three ACS categories herein proved to have high mortality rates during long-term follow-up in a real-life patient cohort. NSTEMI patients had worse outcomes than STEMI and UA patients during the whole follow-up period. The present study results also indicates considerable differences in the prognostic significance of various demographic and therapeutic parameters within the three ACS categories.

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References

1. World Health Oranization. The top 10 causes of death. 2017. http://www.who.int/mediacentre/factsheets/fs310/en/ (accessed 25 Jan 2018).
2. Zeymer U, Senges J. Why do we need prospective registries in patients with acute myocardial infarction? Eur Heart J. 2003; 24(18): 1611–1612, indexed in Pubmed: 14499222.
3. Fach A, Bünger S, Zabrocki R, et al. Comparison of Outcomes of Patients With ST-Segment Elevation Myocardial Infarction Treated by Primary Percutaneous Coronary Intervention Analyzed by Age Groups (<75, 75 to 85, and >85 Years); (Results from the Bremen STEMI Registry). Am J Cardiol. 2015; 116(12): 1802–1809, doi: 10.1016/j.amjcard.2015.09.022, indexed in Pubmed: 26602071.
4. Bromage DI, Jones DA, Rathod KS, et al. Outcome of 1051 Octogenarian Patients With ST-Segment Elevation Myocardial Infarction Treated With Primary Percutaneous Coronary Intervention: Observational Cohort From the London Heart Attack Group. J Am Heart Assoc. 2016; 5(6), doi: 10.1161/JAHA.115.003027, indexed in Pubmed: 27353606.
5. Nauta ST, Deckers JW, Akkerhuis KM, et al. Age-dependent care and long-term (20 year) mortality of 14,434 myocardial infarction patients: changes from 1985 to 2008. Int J Cardiol. 2013; 167(3): 693–697, doi: 10.1016/j.ijcard.2012.03.064, indexed in Pubmed: 22465352.
6. Capewell S, Murphy NF, MacIntyre K, et al. Short-term and long-term outcomes in 133,429 emergency patients admitted with angina or myocardial infarction in Scotland, 1990-2000: population-based cohort study. Heart. 2006; 92(11): 1563–1570, doi: 10.1136/hrt.2005.085399, indexed in Pubmed: 16775090.
7. Cox DA, Stone GW, Grines CL, et al. Comparative early and late outcomes after primary percutaneous coronary intervention in ST-segment elevation and non-ST-segment elevation acute myocardial infarction (from the CADILLAC trial). Am J Cardiol. 2006; 98(3): 331–337, doi: 10.1016/j.amjcard.2006.01.102, indexed in Pubmed: 16860018.
8. Nikus KC, Eskola MJ, Virtanen VK, et al. Mortality of patients with acute coronary syndromes still remains high: a follow-up study of 1188 consecutive patients admitted to a university hospital. Ann Med. 2007; 39(1): 63–71, doi: 10.1080/08037060600997534, indexed in Pubmed: 17364452.
9. Fox KAA, Carruthers KF, Dunbar DR, et al. Underestimated and under-recognized: the late consequences of acute coronary syndrome (GRACE UK-Belgian Study). Eur Heart J. 2010; 31(22): 2755–2764, doi: 10.1093/eurheartj/ehq326, indexed in Pubmed: 20805110.
10. Moscarella E, Spitaleri G, Brugaletta S, et al. Impact of body mass index on 5-year clinical outcomes in patients with ST-segment elevation myocardial infarction after everolimus-eluting or bare-metal stent implantation. Am J Cardiol. 2017; 120(9): 1460–1466, doi: 10.1016/j.amjcard.2017.07.040, indexed in Pubmed: 28864322.
11. Fox KAA, Eagle KA, Gore JM, et al. GRACE and GRACE2 Investigators. The Global Registry of Acute Coronary Events, 1999 to 2009--GRACE. Heart. 2010; 96(14): 1095–1101, doi: 10.1136/hrt.2009.190827, indexed in Pubmed: 20511625.
12. Ellis CJ, Gamble GD, Williams MJA, et al. Regional Cardiac Society NZ ACS Audit Group. All-Cause Mortality Following an Acute Coronary Syndrome: 12-Year Follow-Up of the Comprehensive 2002 New Zealand Acute Coronary Syndrome Audit. Heart Lung Circ. 2019; 28(2): 245–256, doi: 10.1016/j.hlc.2017.10.015, indexed in Pubmed: 29150157.
13. Plakht Y, Shiyovich A, Gilutz H. Predictors of long-term (10-year) mortality postmyocardial infarction: age-related differences. Soroka Acute Myocardial Infarction (SAMI) Project. J Cardiol. 2015; 65(3): 216–223, doi: 10.1016/j.jjcc.2014.06.001, indexed in Pubmed: 24994020.
14. 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.
15. Alexander KP, Newby LK, Cannon CP, et al. American Heart Association Council on Clinical Cardiology, Society of Geriatric Cardiology. Acute coronary care in the elderly, part I: Non-ST-segment-elevation acute coronary syndromes: a scientific statement for healthcare professionals from the American Heart Association Council on Clinical Cardiology: in collaboration with the Society of Geriatric Cardiology. Circulation. 2007; 115(19): 2549–2569, doi: 10.1161/CIRCULATIONAHA.107.182615, indexed in Pubmed: 17502590.
16. Cohen M. Long-term outcomes in high-risk patients with non-ST-segment elevation myocardial infarction. J Thromb Thrombolysis. 2016; 41(3): 464–474, doi: 10.1007/s11239-015-1227-1, indexed in Pubmed: 26001907.
17. Darling CE, Fisher KA, McManus DD, et al. Survival after hospital discharge for ST-segment elevation and non-ST-segment elevation acute myocardial infarction: a population-based study. Clin Epidemiol. 2013; 5: 229–236, doi: 10.2147/CLEP.S45646, indexed in Pubmed: 23901296.
18. Radovanovic D, Nallamothu BK, Seifert B, et al. Temporal trends in treatment of ST-elevation myocardial infarction among men and women in Switzerland between 1997 and 2011. Eur Heart J Acute Cardiovasc Care. 2012; 1(3): 183–191, doi: 10.1177/2048872612454021, indexed in Pubmed: 24062906.

19. Rogers WJ, Frederick PD, Stoehr E, et al. Trends in presenting characteristics and hospital mortality among patients with ST elevation and non-ST elevation myocardial infarction in the National Registry of Myocardial Infarction from 1990 to 2006. Am Heart J. 2008; 156(6): 1026–1034, doi: 10.1016/j.ahj.2008.07.030, indexed in Pubmed: 19032996.
20. Helft G, Georges JL, Mouranche X, et al. Outcomes of primary percutaneous coronary interventions in nonagenarians with acute myocardial infarction. Int J Cardiol. 2015; 192: 24–29, doi: 10.1016/j.ijcard.2015.04.227, indexed in Pubmed: 25985011.
21. Barchielli A, Santoro GM, Balzi D, et al. Long-term prognosis after primary PCI in unselected patients with ST-elevation myocardial infarction. J Cardiovasc Med (Hagerstown). 2012; 13(12): 819–827, doi: 10.2459/JCM.0b013e328356a29c, indexed in Pubmed: 22772599.
22. 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.
23. 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.
24. Bucholz EM, Butala NM, Rathore SS, et al. Sex differences in long-term mortality after myocardial infarction: a systematic review. Circulation. 2014; 130(9): 757–767, doi: 10.1161/CIRCULATIONAHA.114.009480, indexed in Pubmed: 25052403.
25. Erdem G, Bakhai A, Taneja AK, et al. Rates and causes of death from non-ST elevation acute coronary syndromes: ten year follow-up of the PRAIS-UK registry. Int J Cardiol. 2013; 168(1): 490–494, doi: 10.1016/j.ijcard.2012.09.160, indexed in Pubmed: 23138011.
26. Prami T, Khanfir H, Deleskog A, et al. Clinical factors associated with initiation of and persistence with ADP receptor-inhibiting oral antiplatelet treatment after acute coronary syndrome: a nationwide cohort study from Finland. BMJ Open. 2016; 6(11): e012604, doi: 10.1136/bmjopen-2016-012604, indexed in Pubmed: 27881527.
27. Hvelplund A, Galatius S, Madsen M, et al. Significance of the invasive strategy after acute myocardial infarction on prognosis and secondary preventive medication: a nationwide study of 6364 women and 11,915 men. J Invasive Cardiol. 2012; 24(1): 19–24, indexed in Pubmed: 22210585.

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Nutritional risk index is a better predictor of early mortality than conventional nutritional markers after transcatheter aortic valve replacement: A prospective cohort study

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Abstract

Background: *Nutritional risk index (NRI) has been shown to better predict survival than body mass index (BMI) or albumin after several cardiovascular interventions. Under assessment herein is whether NRI can have higher predictive value than conventional parameters for short-term survival after transcatheter aortic valve replacement (TAVR).*

Methods: *A prospective cohort study was performed. In-hospital, 1-month and 3-month survival was evaluated. Since most patients undergoing TAVR are over 65, the NRI definition for a geriatric population (GNRI) was used. The impact of baseline BMI, albumin levels, and GNRI on in-hospital and short-term survival was assessed.*

Results: *One hundred fifty two patients aged 82 ± 5.4 were included. In-hospital, 1-month, and 3-month mortality was 5.3%, 5.9%, and 9.2%, respectively. Mean GNRI was 112.7 ± 11.9, and was significantly lower in patients who died in-hospital (101.0 ± 8.8 vs. 113.3 ± 11.7), at 30 days (103.4 ± ± 10.9 vs. 113.3 ± 11.7), and at 90 days (104.0 ± 9.6 vs. 113.6 ± 11.8) than in survivors (all, $p < 0.05$). Three-month mortality in patients with no nutritional risk was 6.8% (9/132) vs. 25% (5/20) in patients with malnutrition ($p = 0.022$). In univariate analysis, GNRI predicted in-hospital, 30-day, and 90-day mortality (all, $p < 0.05$). Predictive value remained significant after adjusting for age, EuroSCORE II, and STS-Score ($p < 0.05$). Based on receiver operating curves, GNRI (AUC: 0.73) showed a better discrimination for 3-month mortality than albumin (0.69), weight (0.67) or BMI (0.62). The optimal cut-off value was 109.8.*

Conclusions: *The geriatric nutritional risk index predicts short-term mortality after TAVR and has a higher discriminating ability than other commonly used nutritional variables. It is a simple parameter that identifies those patients who could benefit from pre-procedural nutritional therapy.* (Cardiol J 2021; 28, 2: 312–320)

Key words: aortic valve stenosis, body mass index, transcatheter aortic valve replacement, hypoalbuminemia

Introduction

Malnutrition is frequent in elderly patients and has been shown to affect survival in several cardiovascular diseases, such as chronic heart failure [1] or coronary artery disease [2]. Transcatheter aortic valve replacement (TAVR) is mainly performed in high-risk patients, the vast majority of which

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are geriatric patients. In such patients, nutritional status could be a useful prognostic factor to be considered before any planned TAVR. Nutritional status in patients undergoing TAVR has been evaluated in several ways, including body mass index (BMI) and laboratory parameters such as albumin levels. Higher BMI and higher albumin levels have been previously associated with more favorable outcomes after TAVR [3]. Regarding albumin, low baseline levels have been shown to predict in-hospital, 30-day and long-term mortality [3, 4]. Furthermore, a meta-analysis has shown BMI, as a continuous variable, to be associated with a better early prognosis after TAVR [5]. The nutritional risk index (NRI), originally described by Buzby et al. [6], is a simple tool that combines both clinical and laboratory parameters. Since its introduction, it has been applied in several medical specialties, mainly in the field of oncology [7, 8]. NRI has been recently shown to have a better prognostic value than both BMI and albumin in several cardiovascular diseases and procedures, including acute or chronic heart failure [1, 9], heart transplants [10], coronary artery disease [2] or percutaneous coronary interventions [11]. NRI is not only an easy tool to assess nutritional status, but it does not require any complex or additional test to those performed routinely on admission. The geriatric nutritional risk index (GNRI) is a version of the NRI adapted for elderly patients; thus, it could be particularly useful for the population usually undergoing TAVR. The present study sought to elucidate the impact of nutritional status, measured with both GNRI and conventional parameters, on clinical outcomes and particularly short-term survival after TAVR.

Methods

Study population

A prospective, observational, cohort study was performed in patients undergoing TAVR with a new generation valve prosthesis using a transfemoral access from July 2016 to September 2017 in the documented center. Consecutive patients with symptomatic severe aortic stenosis having a prohibiting risk for surgical aortic valve replacement were included, as assessed by a multidisciplinary Heart Team. Patients with an isolated or combined severe aortic regurgitation and patients requiring a valve-in-valve procedure were also included.

Procedures

Pre-procedural baseline demographic, clinical and laboratory characteristics were assessed and baseline nutritional data, including serum albumin and BMI, were obtained. New York Health Association (NYHA) class was assessed, and EuroSCORE II and STS scores were documented.

After a Heart Team decision, TAVR procedures were carried out according to standard techniques. The choice of prosthesis was left to operator discretion. Use of local anesthesia and conscious sedation was the aim for all patients. Procedural details were also recorded.

In-hospital survival was evaluated and at follow-up to assess vital status, which was performed at 1 and 3 months through outpatient visits and/or with telephone interviews by a physician.

Nutritional assessment based on GNRI

Since most patients undergoing TAVR are older than 65, the NRI definition adapted to an old population was used, as described by Bouillanne et al. [12]: **Geriatric (G) NRI = (1.489) × Albumin (g/L) + [(41.7 × (present weight/ideal weight)]**.

In order to be consistent with GNRI use, patients under 65 years were excluded from the analysis. Ideal weight (WLo) was calculated according to Lorentz equations [12]:

WLo (kg) in men: (Height – 100) – [(Height – 150)/4]
WLo (kg) in women: (Height – 100) – [(Height – 150)/2.5]

Based on this definition, patients were divided into four grades of nutrition-related risk, as suggested in the literature [12]: GNRI > 98 (no risk), GNRI 92 to ≤ 98 (low risk), GNRI 82 to < 92 (moderate risk), and GNRI < 82 (major risk). Due to the low number of malnourished individuals, for inferential categorical analyses, all patients with some degree of malnutrition were combined into one category (GNRI ≤ 98) and those without malnutrition into another one (GNRI > 98).

Outcomes

The primary endpoint of this study was overall mortality at 3 months. Secondary endpoints included in-hospital and 1-month mortality. Exploratory variables were length of stay in hospital, and NYHA improvement at 3 months after TAVR.

Statistical analysis

Categorical variables were described with frequencies and percentages, and continuous variables were reported with mean ± standard deviation (SD) if normally distributed or median (range) if not normally distributed. The Fisher test or χ^2 was used to compare categorical variables. The Student

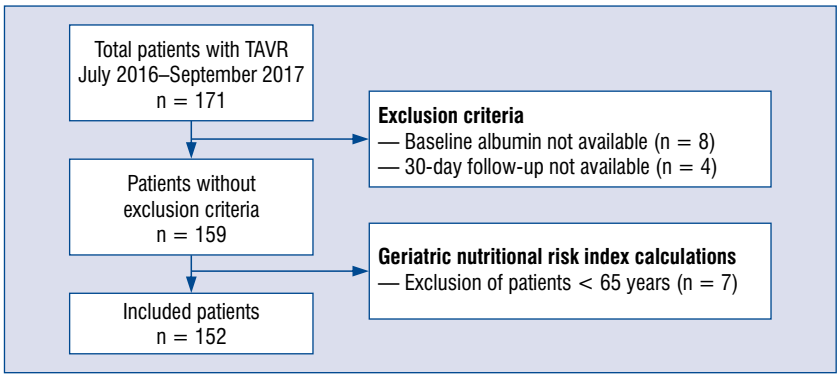

Figure 1. Flowchart of the study population; TAVR — transcatheter aortic valve replacement.

t-test was used to compare means and the Mann-Whitney U test was used to compare medians. Primary and secondary endpoints were assessed hierarchically in the following pre-specified order: 3-month, 1-month, and in-hospital mortality. All other endpoints were considered exploratory, and no adjustments were made for multiplicity of tests. Survival prediction was evaluated by means of a logistic regression (adjusted by potential confounding factors). Statistical significance was based on a p-value < 0.05. Receiver operating curves (ROC) were created to assess sensitivity and specificity of the GNRI in predicting survival, as well as those for individual components of the index. The best cut-off value was decided using the highest value of the Youden index. SPSS statistical software package version 24.0 was used for all analyses.

All patients gave signed and informed consent prior to intervention and the study was performed under the protocol, which was approved by the local ethics committee (296/16).

Results

Study population

Out of 171 patients who underwent TAVR between July 2016 and September 2017, 8 patients were excluded from the analysis due to unavailable baseline albumin levels and 4 patients were excluded due to missing follow-up data. In order to be consistent with GNRI use, 7 patients under 65 years were excluded from the analysis. A flow-chart of patient exclusion in the present study population is shown in Figure 1.

Baseline and procedural characteristics

Transcatheter aortic valve replacement was performed in 152 patients using various new generation prostheses including Portico valve (St. Jude Medical) (n = 91), Sapien 3 valve (Edwards Lifesciences) (n = 20), Evolut R valve (Medtronic) (n = 20), and Symetis valve (Boston Scientific) (n = 21).

Overall mean ± SD age was 82 ± 5.4 years, and 41.4% of patients were female. EuroSCORE II and STS score were 5.3 ± 6 and 4.0 ± 2.8, respectively.

Baseline and procedural characteristics of the whole population and in patients with and without malnutrition are shown in Table 1. Most patients had hypertension (93%), and other common comorbidities were coronary artery disease (58%), diabetes (35%), and most patients had some degree of chronic renal failure. No significant differences were shown between groups except regarding nutritional parameters, including weight, albumin and GNRI. Both EuroSCORE II and STS scores differed significantly between groups as expected.

Nutritional results

Overall baseline mean GNRI value was 112.7 ± ± 11.9, median BMI was 26.9 (16.4–41.7) kg/m^2, and median albumin level was 4.2 (2.5–5) g/dL. Based on GNRI values, 86.8% of patients had no nutritional risk (GNRI > 98), 9.9% had low risk (GNRI 92 to ≤ 98), 3.3% had moderate risk (GNRI 82 to < 92), and no patients were at major risk (GNRI < 82) prior to intervention, with median GNRI values being 115.6 ± 9.8, 95.3 ± 1.8, and 88.1 ± 1.8, respectively. Mean BMI and albumin values varied within categories but did not show a clear tendency.

Mean age was 81.6 ± 5.4 years in no risk patients, 83.7 ± 4.1 years in low risk patients, and 86.2 ± 6.9 years in patients at moderate risk.

Table 1. Baseline and procedural characteristics of the population according to geriatric nutritional risk index (GNRI).

	Overall population (n = 152)	Patients with no nutritional risk (GNRI > 98) (n = 132)	Patients with nutritional risk (GNRI ≤ 98) (n = 20)	P
Baseline characteristics				
Age [years]	82 ± 5.4	81.6 ± 5.4	84.4 ± 4.9	**0.032**
Sex (female)	41.4% (n = 63)	41.7% (n = 55)	40% (n = 8)	0.888
Weight [kg]	77.0 ± 14.0	79.0 ± 13.6	63.9 ± 8.9	**0.0001**
Ideal weight [kg]	62.2 ± 7.4	62.0 ± 7.3	63.4 ± 8.3	0.442
Height [cm]	167.1 ± 9.6	166.9 ± 9.5	168.7 ± 10.7	0.427
BMI [kg/m^2]	26.9 (16.4–41.7)	27.5 (19.5–41.7)	21.9 (16.4–31.1)	**0.0001**
Albumin [g/dL]	4.2 (2.5–5)	4.2 (2.6–5)	3.5 (2.5–4.4)	**0.0001**
GNRI	112.7 ± 11.9	115.6 ± 9.8	93.5 ± 3.6	**0.0001**
Frailty	68.4% (n = 104)	67.4% (n = 89)	75% (n = 15)	0.611
Chronic renal failure	96.7% (n = 147)	96.2% (n = 127)	100% (n = 20)	0.999
Carotid occlusive disease	18.4% (n = 28)	17.4% (n = 23)	25% (n = 5)	0.535
Peripheral artery disease	15.1% (n = 23)	15.9% (n = 21)	10% (n = 2)	0.740
Previous cardiac surgery	13.2% (n = 20)	11.4% (n = 15)	25% (n = 5)	0.146
Previous MI	10.5% (n = 16)	9.1% (n = 12)	20% (n = 4)	0.230
Previous stroke	13.8% (n = 21)	13.6 (n = 18)	15% (n = 3)	0.999
Previous TIA	2% (n = 3)	2.3% (n = 3)	0% (n = 0)	0.999
Coronary artery disease	57.9% (n = 88)	56.8% (n = 75)	65% (n = 13)	
Porcelain aorta	17.1% (n = 26)	18.9% (n = 25)	5% (n = 1)	0.200
COPD	15.8% (n = 24)	15.2% (n = 20)	20% (n = 4)	0.525
Diabetes	34.9% (n = 53)	34.1% (n = 45)	40% (n = 8)	0.621
Hypertension	92.8% (n = 141)	92.4% (n = 122)	95% (n = 19)	0.999
EuroSCORE II	5.4 ± 6.1	4.8 ± 4.8	9.4 ± 10.5	**0.002**
STS score	4.1 ± 2.8	3.6 ± 1.8	7.2 ± 5.1	**0.0001**
Procedural characteristics				
Type of valve:				
Portico	59.9% (n = 91)	59.1% (n = 78)	65% (n = 13)	
Evolut	13.2% (n = 20)	12.9% (n = 17)	15% (n = 3)	
Symetis	13.8% (n = 21)	13.6% (n = 18)	15% (n = 3)	
Sapien 3	13.2% (n = 20)	14.4% (n = 19)	5% (n = 1)	
Contrast dye [mL] (n = 150)	140 (10–550)	150 (10–550)	125 (50–240)	0.249
Fluoroscopy time [min] (n = 149)	18.4 (7.9–230)	18.4 (7.9–230)	18.4 (8.0–47.0)	0.802
Simultaneous PCI (n = 150)	2.7% (n = 4)	3.1% (n = 4)	0% (n = 0)	0.999

Bold figures show significant differences; BMI — body mass index; COPD — chronic obstructive pulmonary disease; MI — myocardial infarction; PCI — percutaneous coronary intervention; TIA — transient ischemic attack

Lower GNRI values (thus, more severe malnutrition) were associated with older age; however, this did not reach statistical significance.

Clinical outcomes and survival

Overall mortality was 5.3% in-hospital, 5.9% at 1 month, and 9.2% at 3 month follow up. Causes of 3-month mortality were the following: cardiovascular (3 refractory cardiogenic shock, and 1 electromechanical dissociation), non-cardiovascular (4 life-threatening bleeding, 1 life-threatening cerebrovascular accident, 1 critical limb ischemia, 1 acute kidney failure, 2 multi-organ failure syndrome), and 1 unknown cause.

Table 2. Baseline characteristics of the population according to short-term survival.

	Patients with survival at 3-months (n = 138)	Patients who died at 3-months (n = 14)	P
Baseline characteristics			
Age [years]	82 ± 5.3	81.8 ± 6.9	0.919
Sex (female)	39.9% (n = 55)	57.1% (n = 8)	0.259
Weight [kg]	77.8 ± 13.9	69.14 ± 13.5	**0.027**
Ideal weight [kg]	62.4 ± 7.3	60.1 ± 8.3	0.282
Height [cm]	167.4 ± 9.5	164.5 ± 10.6	0.291
BMI [kg/m^2]	27.2 (18.1–41.7)	25.1 (16.4–37.4)	0.133
Albumin [g/dL]	4.2 (2.7–5)	3.7 (2.5–4.8)	**0.018**
GNRI	113.6 ± 11.8	104 ± 9.6	**0.004**
Frailty	66.7% (n = 92)	85.7% (n = 12)	0.227
Chronic renal failure	96.4% (n = 133)	100% (n = 14)	0.999
Carotid occlusive disease	18.1% (n = 25)	21.4% (n = 3)	0.723
Peripheral artery disease	15.9% (n = 22)	7.1% (n = 1)	0.696
Previous cardiac surgery	14.5% (n = 20)	0% (n = 0)	0.217
Previous MI	10.1% (n = 14)	14.3% (n = 2)	0.644
Previous stroke	13.8% (n = 19)	14.3% (n = 2)	0.999
Previous TIA	1.4% (n = 2)	7.1% (n = 1)	0.253
Coronary artery disease	60% (n = 80)	57.1% (n = 8)	
Porcelain aorta	18.1% (n = 25)	7.1% (n = 1)	0.466
COPD	15.2% (n = 21)	21.4% (n = 3)	0.465
Diabetes	35.5% (n = 49)	28.6% (n = 4)	0.772
Hypertension	93.5% (n = 129)	85.7% (n = 12)	0.268
EuroSCORE II	5.5 ± 6.2	4.3 ± 4.5	0.482
STS score	4.0 ± 2.7	4.6 ± 3.1	0.486
Procedural characteristics			
Type of valve:			
Portico	71.4%	84.6%	
Evolut	12.5%	7.7%	
Symetis	0%	7.7%	
Sapien 3	16.1%	0%	
Contrast dye [mL] (n = 150)	140 (10–550)	185 (110–270)	0.096
Fluoroscopy time [min] (n = 149)	18.1 (7.9–230)	20.6 (12.7–47)	0.138
Simultaneous PCI (n = 150)	2.2% (n = 3)	7.7% (n = 1)	0.327

Bold figures show significant differences; BMI — body mass index; COPD — chronic obstructive pulmonary disease; MI — myocardial infarction; PCI — percutaneous coronary intervention; TIA — transient ischemic attack

Three-month mortality in patients with no nutritional risk was 6.8% (9/132) vs. 25% (5/20) in patients with some degree of malnutrition according to GNRI ($p = 0.022$, the Fisher test). Mortality at 1-month and in-hospital also showed a similar trend: 4.5% (6/132) in well-nourished patients vs. 15% (3/20) in malnourished patients at 1 month, and 3.8% (5/132) in well-nourished patients vs. 15% (3/20) in malnourished patients in-hospital, with differences not reaching statistical significance.

Mean GNRI values were significantly lower in patients who died in-hospital (101.0 ± 8.8 vs. 113.3 ± ± 11.7), at 30 days (103.4 ± 10.9 vs. 113.3 ± 11.7), and at 90 days (104.0 ± 9.6 vs. 113.6 ± 11.8) than in those who survived (two-sample Student t-test, all, $p < 0.05$). Results were also significant for baseline albumin levels when comparing patients

who died within 3 months after the intervention vs. those who survived: 3.7 (2.5–4.8) vs. 4.2 (2.7–5) ($p = 0.018$, Mann-Whitney U Test), respectively. BMI showed a numerical difference but did not reach statistical significance. Further details are shown in Table 2.

In univariate analysis, GNRI significantly predicted in-hospital, 30-day and 90-day mortality (all, $p < 0.05$). Predictive capacity of GNRI remained significant in multivariate analysis after adjusting for potential confounders including age, and pre-interventional risk-scores (EuroSCORE II and STS-Score) ($p < 0.05$, logistic regression). No other baseline characteristics were significant independent predictors in univariate analysis. Albumin level was also significantly predictive, and BMI was numerically higher in patients who survived.

In order to investigate if the predictive value of GNRI was mainly driven by results in patients with high vs. low general clinical risk, some post hoc exploratory analyses in subgroups of patients were performed as defined by EuroSCORE/STS risk level. The overall trend was confirmed in all subgroups. In patients with an intermediate/ /high EuroSCORE II risk (n = 55), mortality rates were 2.44% in patients with no nutritional risk vs. 21.43% in patients with some degree of nutritional risk ($p < 0.05$). In patients with a low EuroSCORE II risk (n = 97), mortality rates were 8.80% vs. 33.30%, respectively ($p = 0.11$). In patients with an intermediate/high STS risk (n = 54), mortality rates were 8.80% in patients with no nutritional risk vs. 33.30% in patients with some degree of nutritional risk ($p = 0.34$). In patients with a low STS risk (n = 98), mortality rates were 9.76% vs. 23.08%, respectively ($p = 0.08$). In regression analyses the GNRI predictive capacity reached significance in the STS high/intermediate group ($p < 0.05$) and the EuroSCORE low-risk group ($p = 0.01$).

According to ROC, GNRI showed a better discrimination for 3-month mortality than its individual components (3-month: area under curve [AUC] GNRI: 0.73 vs. AUC albumin: 0.69 vs. AUC weight: 0.67) or BMI (AUC BMI: 0.62). Similar results were found for in-hospital and 1-month mortality. ROC for GNRI and 3-month mortality is shown in Figure 2. The optimal GNRI cut-off in the present series was 109.8.

In a subgroup analysis based on the traditional BMI classification, patients with underweight (BMI < 20 kg/m^2) showed a numerically higher mortality than normal weight, overweight, and obese patients, with the difference not reaching statistical

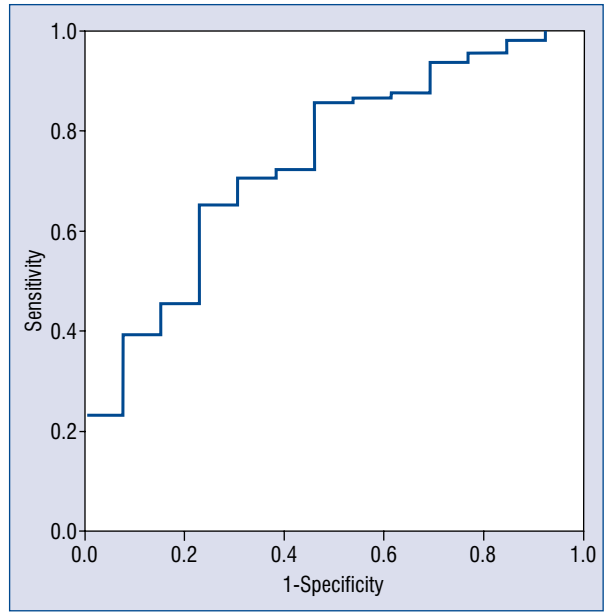

Figure 2. Receiver operating curve for geriatric nutrition risk index and 3-month mortality; area under the curve: 0.74; 95% confidence interval: 0.60–0.88; $p < 0.005$.

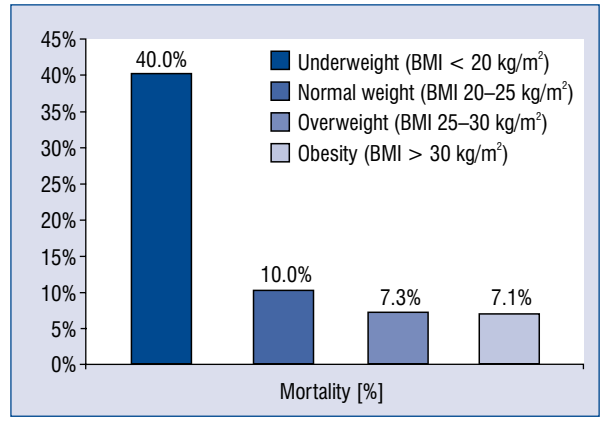

Figure 3. Relationship between 3-month mortality and body mass index (BMI) classification.

significance. Detailed mortality percentages are shown in Figure 3.

The NYHA class change at 3 months after TAVR could be assessed in 118 patients. An improvement of at least one level was shown in most of them (84.7%). Such an improvement was observed in 86.6% of patients with no nutrition risk vs. 69.2% of patients with some degree of nutritional risk (p = NS).

No significant differences in median length of stay in hospital were observed between different

nutritional status groups (9 days in patients with no degree of malnutrition vs. 10 days in patients with some degree of malnutrition).

Discussion

Overall outcomes in the current TAVR population are in line with those previously described in the literature, with short-term mortality and in-hospital complications according to Valve Academic Research Consortium-2 criteria being similar to those reported for all new generation valves [13–15].

According to available research, this is the first prospective cohort study on the predictive value of GNRI in TAVR patients in a European population, in which an improved predictive value of GNRI as compared to commonly used nutritional parameters is shown and a practical clinical threshold is estimated. Differences between patients who died and survivors at 90 days were significant regarding GNRI, weight and albumin, but not regarding BMI. The overall GNRI predictive value is supported by the uniform trend observed in exploratory analyses in all risk level subgroups defined by EuroSCORE and STS scores. Specifically, the significant predictive value of GNRI in some subgroups suggests a potential added value of GNRI to predict futility of TAVR.

Geriatric nutritional risk index showed a higher discrimination in prediction of short-term mortality than its individual parameters or BMI, as shown by ROC-curves. A preliminary GNRI cut-off value of 109.8 is suggested; further studies in larger populations are warranted to confirm its clinical value. The trend to a less common NYHA improvement in patients with some degree of nutritional risk is consistent with the overall negative impact of poor nutrition on clinical outcomes.

Data analysis has recently appeared from a Japanese registry which has also suggested that GNRI has a prognostic value in TAVR [16]. Patient details were based on registry records and information on deaths were obtained from the treating hospital or by calling family members. Although no comparison of its predictive value with other nutritional markers were reported, a significantly increased mortality rate was also found in patients with lower GNRI values.

In the present cohort, no patients with a very high-risk malnutrition were identified, but several showed some extent of malnutrition. A possible explanation is that patients with severe malnutrition or who are frail may have been excluded for TAVR screening due to the presumed futility of the intervention.

The present results are in line with previously published studies showing a good predictive value of pre-operative GNRI in other cardiovascular therapies such as heart failure [17], heart transplant [10] or more recently percutaneous coronary intervention [11]. Other reports have shown low GNRI to delay rehabilitation after cardiac surgery in elderly patients [18], which remains to be studied after TAVR.

Several studies have shown that low levels of pre-procedural albumin are associated with short-term and mid-term mortality [3, 4, 19]. These results have been confirmed in the present study. However, the GNRI (combining both albumin and other body mass parameters) showed an even better discrimination capacity in predicting short-term mortality after TAVR than pre-procedural albumin.

Body mass index as a continuous variable has previously been shown to be associated with a better short-term prognosis after TAVR [5]. Continuous BMI data in the current study did not significantly predict mortality, probably due to the low number of events. However, median BMI was lower in patients not surviving at 3 months. When categorizing patients according to BMI values, underweight patients (BMI < 20 kg/m^2) showed a numerically higher mortality (40%) than all groups with a higher BMI (7.1–10%), with the difference not reaching statistical significance. However, this association has been significant in other studies with a long-term follow-up [20].

The interpretation of BMI as a risk factor suggesting malnutrition in patients undergoing TAVR is complicated by the so-called "obesity paradox" resulting in a better survival in several cardiovascular interventions including TAVR [21, 22]. Previous studies have shown that overweight and obese patients undergoing TAVR show better outcomes than those with a low BMI [23]. A recent meta-analysis showed better short- and long-term survival in obese patients (BMI > 30 kg/m^2) compared to patients of normal weight [20]. The finding of GNRI being better than BMI and albumin in predicting in-hospital/short-term survival in TAVR, even after adjusting for potential confounders, could reflect an immediate negative effect of malnutrition rather than a favorable effect of overweight/obesity.

Several nutritional tools have been used in TAVR to assess nutritional status such as grip strength, gait speed, bioimpedance analysis, or nutritional questionnaires (e.g. Mini Nutritional

Assessment [MNA]) [24, 25]. The main limitation of GNRI is that it is mainly based on albumin, a biochemical marker that can be affected by other co-morbidities, such as hepatic cirrhosis; moreover, inflammatory disorders are known to result in a catabolic state and a reduced liver synthesis of albumin. The major strength of GNRI is that it is practical, since it only involves one calculation including the routinely measured BMI and albumin levels on admission, and no extra equipment or measuring devices are required. The need for a formula to estimate GNRI could certainly be a practical drawback. However, an online calculator is available at http://touchcalc.com/calculators/gnri. Routine recording of pre-interventional GNRI is not only easy to perform, but it provides a useful nutritional assessment tool to identify those patients at risk of malnutrition. GNRI is suggested to be helpful to classify patients regarding their short-term mortality risk. This might help to decide which patients could benefit from a nutritional intervention prior to TAVR.

Malnutrition is frequent in elderly patients undergoing TAVR and it should not be overlooked when stratifying patients. Therefore, measuring baseline GNRI values and assessing the improvement of such index prior to TAVR could be useful in protecting this vulnerable group of patients. As already proven in other heart diseases (e.g. heart failure) [26], GNRI is a modifiable factor, both in terms of pre-interventional albumin levels and pre-interventional BMI (i.e. weight), and a strategy to improve nutritional status before an intervention such as TAVR should be considered. Further randomized trials are warranted to test this hypothesis, and to assess the practicality and time needed to improve nutritional status in such patients.

Previous studies in TAVR have shown that some parameters besides the conventional risk scores (EuroSCORE II and STS score) offer prognostic information; that is diabetes mellitus, mobility and nutritional status measured with questionnaires [25]. Other studies have suggested adding baseline albumin levels to risk stratification factors before TAVR [4, 27]. If the present results are confirmed by further studies, GNRI could be considered in risk scores, for it has a stronger prognostic discriminating ability than the nutritional parameters already included in such scores and other specific measurements such as albumin.

Being a single-center investigation with a limited sample size are limitations in the present study; however, the results are consistent and strongly significant. Some other limitations must also be acknowledged. Firstly, as in any observational study, although an adjustment was used for the imbalance in major baseline characteristics, confounding factors due to unmeasured variables cannot be excluded. Secondly, this is the first study from a single center; further studies will be needed at a multicenter level for these findings to be extrapolated to a wider population. Thirdly, cause of death was not always available because some of the follow-up data on vital status were obtained from a family member who was not aware of the exact cause of death. Therefore, data on specific causes of death should be interpreted with caution. Fourthly, long-term survival was not analyzed in this study; however, GNRI showed a strong association with survival in the short-term.

Conclusions

Geriatric nutritional risk index predicts short-term mortality in patients undergoing TAVR and appears to have a higher discriminating ability than other commonly used nutritional variables, such as serum albumin and BMI. It is a simple and easy to calculate parameter, and its routine use could be useful in identifying those patients who could benefit from nutritional therapy prior to intervention. Further prospective, multicenter studies with a longer follow-up, as well as randomized trials using an established GNRI threshold, and GNRI improvement prior to TAVR are needed to confirm this relationship in the long-term.

Conflict of interest: Mariuca Vasa-Nicotera is proctor for Abbott and Medtronic, Stephan Fichtlscherer and Thomas Walther are proctors and report consultancy activities for Abbott and Edwards Lifesciences. All other authors have no conflicts of interest related to the subject of the article.

References

1. Sargento L, Vicente Simões A, Rodrigues J, et al. Geriatric nutritional risk index as a nutritional and survival risk assessment tool in stable outpatients with systolic heart failure. Nutr Metab Cardiovasc Dis. 2017; 27(5): 430–437, doi: 10.1016/j.numecd.2017.02.003, indexed in Pubmed: 28438373.
2. Kunimura A, Ishii H, Uetani T, et al. Impact of Geriatric Nutritional Risk Index on cardiovascular outcomes in patients with stable coronary artery disease. J Cardiol. 2017; 69(1): 383–388, doi: 10.1016/j.jjcc.2016.09.004, indexed in Pubmed: 27727086.
3. Koifman E, Magalhaes MA, Ben-Dor I, et al. Impact of pre-procedural serum albumin levels on outcome of patients undergoing transcatheter aortic valve replacement. Am J Cardiol. 2015; 115(9): 1260–1264, doi: 10.1016/j.amjcard.2015.02.009, indexed in Pubmed: 25759105.

4. Yamamoto M, Shimura T, Kano S, et al. Prognostic Value of Hypoalbuminemia After Transcatheter Aortic Valve Implantation (from the Japanese Multicenter OCEAN-TAVI Registry). Am J Cardiol. 2017; 119(5): 770–777, doi: 10.1016/j.amjcard.2016.11.019, indexed in Pubmed: 28017301.
5. Takagi H, Umemoto T. ALICE (All-Literature Investigation of Cardiovascular Evidence) Group. „Obesity paradox" in transcatheter aortic valve implantation. J Cardiovasc Surg (Torino). 2017; 58(1): 113–120, doi: 10.23736/S0021-9509.16.09233-8, indexed in Pubmed: 26939045.
6. Buzby GP, Williford WO, Peterson OL, et al. A randomized clinical trial of total parenteral nutrition in malnourished surgical patients: the rationale and impact of previous clinical trials and pilot study on protocol design. Am J Clin Nutr. 1988; 47(2 Suppl): 357–365, doi: 10.1093/ajcn/47.2.357, indexed in Pubmed: 3124597.
7. Bo Y, Wang K, Liu Y, et al. The geriatric nutritional risk index predicts survival in elderly esophageal squamous cell carcinoma patients with radiotherapy. PLoS One. 2016; 11(5): e0155903, doi: 10.1371/journal.pone.0155903, indexed in Pubmed: 27196126.
8. Shoji F, Matsubara T, Kozuma Y, et al. Preoperative Geriatric Nutritional Risk Index: A predictive and prognostic factor in patients with pathological stage I non-small cell lung cancer. Surg Oncol. 2017; 26(4): 483–488, doi: 10.1016/j.suronc.2017.09.006, indexed in Pubmed: 29113668.
9. La Rovere MT, Maestri R, Olmetti F, et al. Additional predictive value of nutritional status in the prognostic assessment of heart failure patients. Nutr Metab Cardiovasc Dis. 2017; 27(3): 274–280, doi: 10.1016/j.numecd.2016.09.009, indexed in Pubmed: 27914696.
10. Barge-Caballero E, García-López F, Marzoa-Rivas R, et al. Prognostic value of the nutritional risk index in heart transplant recipients. Rev Esp Cardiol (Engl Ed). 2017; 70(8): 639–645, doi: 10.1016/j.rec.2017.01.005, indexed in Pubmed: 28209304.
11. Wada H, Dohi T, Miyauchi K, et al. Prognostic impact of the geriatric nutritional risk index on long-term outcomes in patients who underwent percutaneous coronary intervention. Am J Cardiol. 2017; 119(11): 1740–1745, doi: 10.1016/j.amjcard.2017.02.051, indexed in Pubmed: 28388993.
12. Bouillanne O, Morineau G, Dupont C, et al. Geriatric Nutritional Risk Index: a new index for evaluating at-risk elderly medical patients. Am J Clin Nutr. 2005; 82(4): 777–783, doi: 10.1093/ajcn/82.4.777.
13. Eggebrecht H, Mehta RH. Transcatheter aortic valve implantation (TAVI) in Germany 2008-2014: on its way to standard therapy for aortic valve stenosis in the elderly? EuroIntervention. 2016; 11(9): 1029–1033, doi: 10.4244/EIJY15M09_11, indexed in Pubmed: 26384006.
14. Jakobsen L, Terkelsen CJ, Søndergaard L, et al. Short- and long-term mortality and stroke risk after transcatheter aortic valve implantation. Am J Cardiol. 2018; 121(1): 78–85, doi: 10.1016/j.amjcard.2017.09.014, indexed in Pubmed: 29103605.
15. Mas-Peiro S, Vasa-Nicotera M, Weiler H, et al. Thirty-day outcomes in 100 consecutive patients undergoing transfemoral aortic valve replacement with the portico valve on an all-comer basis. J Invasive Cardiol. 2017; 29(12): 431–436, indexed in Pubmed: 29207365.
16. Shibata K, Yamamoto M, Kano S, et al. Importance of Geriatric Nutritional Risk Index assessment in patients undergoing transcatheter aortic valve replacement. Am Heart J. 2018; 202: 68–75, doi: 10.1016/j.ahj.2018.04.021, indexed in Pubmed: 29883896.
17. Minamisawa M, Miura T, Motoki H, et al. Geriatric nutritional risk index predicts cardiovascular events in patients at risk for heart failure. Circ J. 2018; 82(6): 1614–1622, doi: 10.1253/circj.CJ-17-0255, indexed in Pubmed: 29212959.
18. Ogawa M, Izawa KP, Satomi-Kobayashi S, et al. Poor preoperative nutritional status is an important predictor of the retardation of rehabilitation after cardiac surgery in elderly cardiac patients. Aging Clin Exp Res. 2017; 29(2): 283–290, doi: 10.1007/s40520-016-0552-3, indexed in Pubmed: 26980452.
19. Bogdan A, Barbash IM, Segev A, et al. Albumin correlates with all-cause mortality in elderly patients undergoing transcatheter aortic valve implantation. EuroIntervention. 2016; 12(8): e1057–e1064, doi: 10.4244/EIJY15M10_09, indexed in Pubmed: 27159658.
20. Sannino A, Schiattarella GG, Toscano E, et al. Meta-Analysis of Effect of Body Mass Index on Outcomes After Transcatheter Aortic Valve Implantation. Am J Cardiol. 2017; 119(2): 308–316, doi: 10.1016/j.amjcard.2016.09.031, indexed in Pubmed: 27839771.
21. Bundhun PK, Li N, Chen MH. Does an obesity paradox really exist after cardiovascular intervention?: a systematic review and meta-analysis of randomized controlled trials and observational studies. Medicine (Baltimore). 2015; 94(44): e1910, doi: 10.1097/MD.0000000000001910, indexed in Pubmed: 26554791.
22. Konigstein M, Havakuk O, Arbel Y, et al. The obesity paradox in patients undergoing transcatheter aortic valve implantation. Clin Cardiol. 2015; 38(2): 76–81, doi: 10.1002/clc.22355, indexed in Pubmed: 25649013.
23. Abawi M, Rozemeijer R, Agostoni P, et al. Effect of body mass index on clinical outcome and all-cause mortality in patients undergoing transcatheter aortic valve implantation. Neth Heart J. 2017; 25(9): 498–509, doi: 10.1007/s12471-017-1003-2, indexed in Pubmed: 28536936.
24. Shimura T, Yamamoto M, Kano S, et al. Impact of frailty markers on outcomes after transcatheter aortic valve replacement: insights from a Japanese multicenter registry. Ann Cardiothorac Surg. 2017; 6(5): 532–537, doi: 10.21037/acs.2017.09.06, indexed in Pubmed: 29062750.
25. Eichler S, Salzwedel A, Harnath A, et al. Nutrition and mobility predict all-cause mortality in patients 12 months after transcatheter aortic valve implantation. Clin Res Cardiol. 2018; 107(4): 304–311, doi: 10.1007/s00392-017-1183-1, indexed in Pubmed: 29164390.
26. Bourdel-Marchasson I, Emeriau JP. Nutritional strategy in the management of heart failure in adults. Am J Cardiovasc Drugs. 2001; 1(5): 363–373, doi: 10.2165/00129784-200101050-00006, indexed in Pubmed: 14728018.
27. Grossman Y, Barbash IM, Fefer P, et al. Addition of albumin to traditional risk score improved prediction of mortality in individuals undergoing transcatheter aortic valve replacement. J Am Geriatr Soc. 2017; 65(11): 2413–2417, doi: 10.1111/jgs.15070, indexed in Pubmed: 28941287.

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Local fluid dynamics in patients with bifurcated coronary lesions undergoing percutaneous coronary interventions

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Abstract

Although the coronary arteries are uniformly exposed to systemic cardiovascular risk factors, atherosclerosis development has a non-random distribution, which follows the local mechanical stresses including flow-related hemodynamic forces. Among these, wall shear stress plays an essential role and it represents the major flow-related factor affecting the distribution of atherosclerosis in coronary bifurcations. Furthermore, an emerging body of evidence suggests that hemodynamic factors such as low and oscillating wall shear stress may facilitate the development of in-stent restenosis and stent thrombosis after successful drug-eluting stent implantation. Drug-eluting stent implantation represents the gold standard for bifurcation interventions. In this specific setting of interventions on bifurcated lesions, the impact of fluid dynamics is expected to play a major role and constitutes substantial opportunity for future technical improvement. In the present review, available data is summarized regarding the role of local fluid dynamics in the clinical outcome of patients with bifurcated lesions. (Cardiol J 2021; 28, 2: 321–329)

Key words: fluid dynamics, wall shear stress, coronary bifurcation lesions, percutaneous coronary intervention, bifurcation stenting, in-stent restenosis and thrombosis

Coronary bifurcation lesions: Complex structure

The epicardial coronary artery tree is an extremely complex vascular structure characterized by a high number of arterial branching points where complex hemodynamic local conditions of blood flow facilitates atherogenesis. A bifurcation coronary lesion is a lesion occurring at, or adjacent to, a significant division of a major epicardial coronary artery [1]. Coronary bifurcation anatomy may basically be regarded as a complex vessel/function

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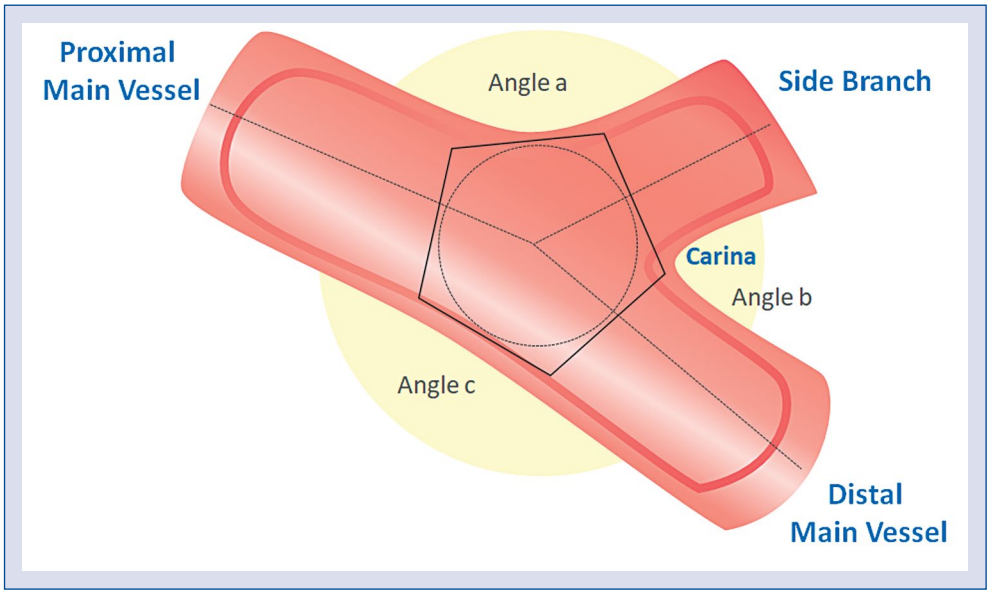

Figure 1. An idealized coronary artery bifurcation. The bifurcation anatomy is usually best described by the three segments model comprised of the proximal main vessel (MV), the distal MV and side branch (SB). The area comprised of the ideal interception between MV and SB is commonly identified as the polygon of confluence.

structure where three different vessel segments, namely proximal main vessel (MV), distal MV, and side branch (SB), are interpolated through the bifurcation core segment where the distinction between MV and SB is merely virtual (Fig. 1) [1]. The area comprised by the ideal interception between MV and SB is commonly identified as the polygon of confluence (Fig. 1). The carina represents the point at which the proximal MV divides into distal MV and SB, and has the critical functional role of splitting the antegrade flow ("flow divider") (Fig. 1). Three angles (a, b, c) allows describing of the spatial orientation between the three bifurcation segments (Fig. 1).

Coronary bifurcations represent the target lesion in 15–20% of all percutaneous coronary interventions (PCI) and, due to their specific anatomic-functional features, remain a daily challenge in contemporary interventional cardiology practice [1]. Drug-eluting stent (DES) implantation early has become the gold standard for bifurcation PCI [2], but the search for the best implantation technique is an evolving field. Bifurcation PCI is associated with higher procedural complications and clinical adverse event risks [1, 3]. Local biomechanics, and fluid shear stresses in particular, appear to be implicated in the development of both in-stent restenosis (ISR) and stent thrombosis (ST) which usually explains the occurrence of adverse clinical events in PCI patients [4].

The purpose of this review is to summarize the available data regarding the role of local fluid dynamics in clinical outcomes of stented bifurcations.

Fluid dynamics at the level of coronary bifurcations

Atherosclerosis has a non-random distribution that reflects the local effect of flow-related biomechanical forces. In particular, atherosclerotic plaques usually develop in arterial segments where blood flow perturbations occur, including the ostia of branches, the inner side of curvatures and major bifurcations [5].

Among different coronary hemodynamic measures, shear stress (SS) is defined as the tangential stress derived from the friction of adjacent layers of blood flowing parallel to each other in the vessel path. The wall shear stress (WSS) is the shear stress acting on the luminal surface of the arterial wall and has a recognized impact on vessel wall biology [5]. Low WSS modulates endothelial gene expression through complex mechanoreception and mechanotransduction processes [5, 6], which includes endothelial cell dysfunction causing an increased uptake of lipoproteins, up-regulation of leukocyte adhesion molecules, and leukocyte endothelial transmigration [7, 8]. Generally, the magnitude of WSS varies within a range of 1–7 Pa [5, 9]. Low (< 0.4–0.5 Pa or < 4–5 dyne/cm^2) and

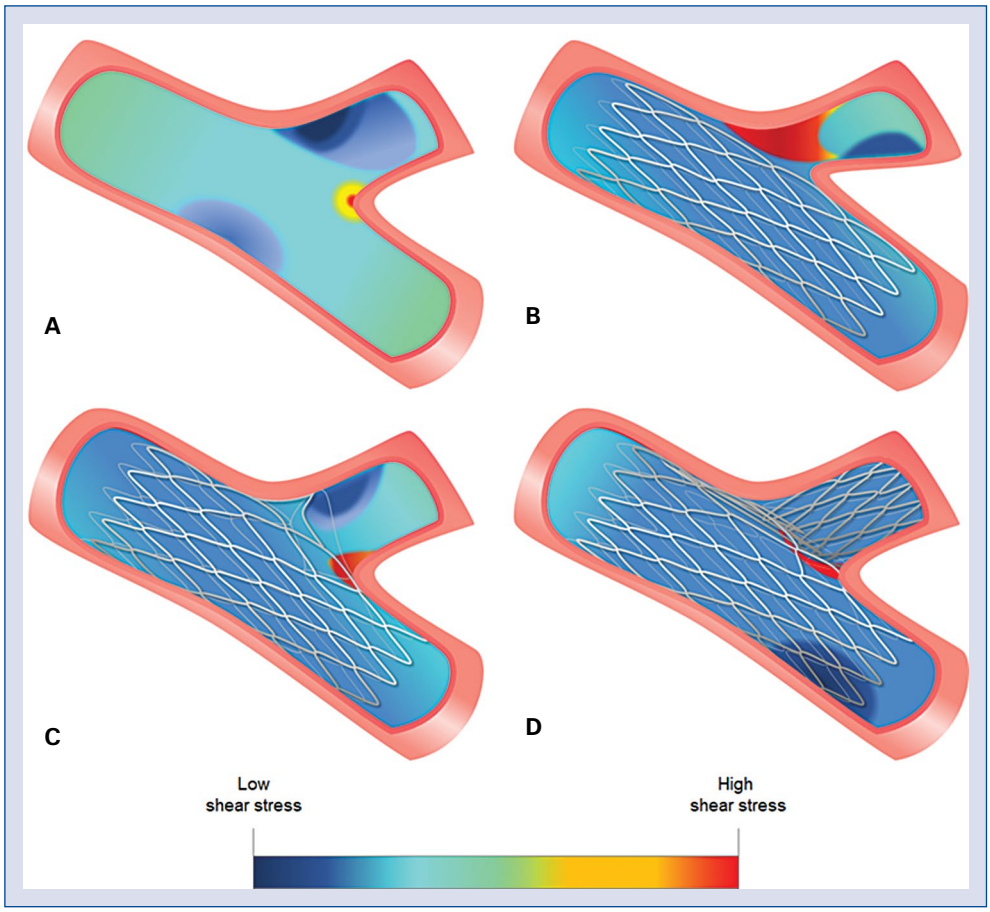

Figure 2. Theoretical local shear stress (SS) distribution in an idealized coronary artery bifurcation before and after stent implantation; **A.** Before stenting (low SS values are present at the level of lateral walls of the main vessel (MV) and the proximal side branch (SB), while high SS values are at the level of the carina and at the internal walls of the distal MV and SB); **B.** After stent implantation in the MV without intervention on the SB; **C.** After MV stenting followed by kissing balloon inflation with short balloons selected in order to avoid proximal MV overstretch; **D.** After the double stenting technique.

oscillatory WSS is considered pro-atherogenic, whereas higher WSS, ranging between 1 and 7 Pa, is considered athero-protective [6, 9]. High WSS (> 7 Pa) has pro-thrombotic potential [5, 9].

A bifurcation divides the blood flow and modifies the blood flow velocity profile. As explained by Finet et al. [10], a bifurcation causes incoming blood flow to deviate from its initial streamline in the mother vessel with a skewed velocity profile, where higher speeds are on the internal parts of the SB in continuity with the carina and low and oscillatory WSS in the arterial walls facing the carina. Such a disturbed laminar flow creates areas with reversed flow (i.e., flow separation, recirculation and reattachment to forward flow) or circumferential swirling, which promotes atherogenesis [11].

In summary, as shown in Figure 2A, low and oscillatory SS areas are typically located at the lateral walls of the MV and SB, while carina is characterized by high SS. Both low and oscillatory WSS constitute a pro-atherogenic local factor contributing to initiation and progression of atherosclerosis [12]. Furthermore, it has been noted that the location of focal elevated WSS can be often matched with the plaque rupture site [13]. Therefore, the relationship between WSS and atherosclerosis is reciprocal, since plaque formation leads to blood flow perturbation, which results in local SS alteration. WSS inhomogeneity tends to increase with an increase of the bifurcation angle and SB diameter. In particular, a wide angle between MV and SB intensifies flow perturbations, increases the spatial WSS variations in the bifurcation region and low WSS in the lateral walls: the higher the angle and diameter the lower the WSS. The aforementioned may promote atherosclerosis development [11, 14].

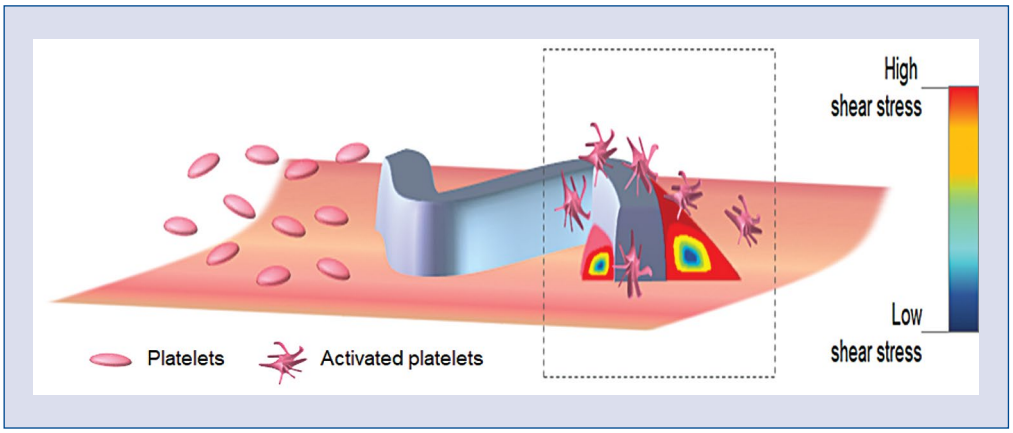

Figure 3. Local shear stress distribution around the stent struts and their possible interactions with circulating platelets. Regions of low shear stress are localized around stent struts and are associated with stagnation flow and boundary layer separation immediately upstream and downstream of the struts.

Table 1. Key hemodynamic parameters assessed in coronary stenting procedures [5, 6, 9, 17–20].

	Relevant values/thresholds identified in biological studies	Main biological effects in stented regions
Time-averaged wall shear stress (TAWSS)	**Low TAWSS:** < 0.4 Pa	Low TAWSS associated with an increased risk of neointima hyperplasia and inflammation
	High TAWSS: > 20–25 Pa	High TAWSS associated with fibrin deposition and stent struts uncoverage
Oscillatory shear index (OSI)	**High OSI:** > 0.2	High OSI associated with an increased risk of neointima hyperplasia, inflammation, thrombosis
Relative residence time (RRT)	**High RRT:** > 4.17 Pa^{-1}	High RRT associated with neointima hyperplasia and thrombus formation

Local flow modifications after stent implantation

Drug-eluting stent implantation, as with any current stenting procedure, affects the regional arterial geometry, and consequently alters local flow conditions. These flow changes are represented by low WSS, flow recirculation, blood flow separation created by stent struts, and prolonged particulate residence time.

The idealized local flow perturbation at the stent strut/vessel wall level is depicted in Figure 3. These stent-induced disturbances of blood flow contribute to complex spatiotemporal alterations in WSS, which lead to increased thrombogenicity around the stent struts and changes in endothelial phenotype that promote inflammatory cell migration [15]. Simulations of blood flow in the vicinity of stent struts in vessel models determine the effect of model strut geometries upon the generation of prothrombotic conditions that are mediated by flow perturbations [16]. Furthermore, changes in local WSS distribution are responsible for the vascular smooth muscle cells proliferative and migratory responses that lead to neointimal hyperplasia and restenosis [17].

The major hemodynamic parameters that have been assessed at stented coronary bifurcations through computational fluid dynamics simulations are: time-averaged wall shear stress (TAWSS), oscillatory shear index (OSI) and relative residence time (RRT) (Table 1). TAWSS expresses the frictional force per unit area that is exerted by the blood flowing to the vascular wall due to viscous properties of blood averaged in a cardiac cycle [18]. OSI is a dimensionless parameter that accounts for the degree of deviation of WSS from the antegrade flow direction [18–20], used to identify regions on

the vessel wall subjected to highly oscillating wall shear stress directions during the cardiac cycle. RRT is an index of flow derived from TAWSS and OSI that measures how long the particles stay near the wall of the vessel [18]. High values of RRT indicate that residence time of particles near the wall is prolonged [21] with the possibility of inducing ISR [19]. Furthermore, thrombus formation is enhanced at areas of slow and reversed flow characterized by high OSI and high RRT [18].

The insertion of a stent in bifurcation affects local fluid dynamics. Indeed, stent architecture and stent strut profile have a significant impact on fluid dynamics and drug transport in the arterial wall. In particular, increasing strut thickness and number of stent struts resulted in an increase of area exposed to low WSS [17]. This has recently been confirmed by a biomechanical analysis, whose results corroborate the findings of the large-scale ISAR STEREO clinical trials and highlight the crucial role of strut thickness in coronary stent design [22]. Moreover, streamlined stent structure profiles (e.g. elliptical and tear-drop) exhibit better hemodynamic performance compared to the standard square or circular profiles since the streamlined ones have smaller recirculation zones and a lower percentage of inter-strut area where the WSS level is decreased [8]. In cases of stent malapposition, or incomplete stent apposition, stent struts resulted in separation from the intimal surface of the arterial wall with evidence of blood behind the strut. Malapposed stent struts disrupt the laminar flow and can generate regions of high shear stress, which are known to facilitate the development of stent thrombosis [8].

Flow modifications after stenting in bifurcations

The complex local flow microenvironment generated during PCI with stent implantation at the level of coronary bifurcations may also influence ISR, ST and clinical outcomes [23]. In bifurcation stenting, there is an increased rate of restenosis and a higher risk of late stent thrombosis. In DES most of the thrombi originate at the flow divider sites where uncovered struts are more frequently observed [12], while ISR has been shown to be associated with low WSS [8, 17].

Pathologic studies have shown that eccentric neointimal hyperplasia occurs predominantly at the lateral wall of the stented MV of a coronary bifurcation, with concomitant adhesion and accumulation of leukocytes, whereas the carina is almost completely free of leukocytes [24].

Yazdani et al. [7], using *in vitro* experimental bifurcation models, demonstrated that deployment of stents can alter boundary layer separation of the lateral walls and can produce flow disturbances (vortical structures) at the carina. Regions of boundary layer separation were associated with low WSS, poor mass transfer of blood flow and an increase in residence time of circulating blood elements. Furthermore, the development of vortical structures can prolong and alter areas with low WSS and can influence drug deposition, arterial healing post-stenting, and local fibrin and platelet deposition.

In cases of DES, recirculation zones with reduced flow and low WSS prolongs residence time and increases local concentration of the eluted compound. In such regions with decelerated flow, the locally augmented anti-proliferative drug effect might thereby antagonize the pro-restenotic effect of low WSS per se [8]. Consequently, this inflammatory response at the lateral walls suggests that there is a specific link among local low WSS, inflammation and focal ISR.

Moreover, stent complications such as malapposition, under-expansion, edge dissections and intra-stent tissue prolapse are often detected in patients successfully treated by bifurcation stenting [25]. Such "imperfections" may theoretically contribute to less optimal stenting outcomes in bifurcation interventions. For example, implantation of two overlapping stents substantially reduces WSS downstream of the junction as compared with a single longer stent, likely indicating a region prone to re-narrowing at the overlap zone [8].

Impact of stenting techniques on bifurcation fluid dynamics

Percutaneous coronary intervention procedures for coronary bifurcations can utilize different technique for stenting [26]. The simplest stent technique is the provisional SB stenting technique, which uses one stent in the MV, eventually followed by further interventions (like ballooning and/or stenting) in the SB. Conversely, double stenting techniques comprise many different techniques involving the use of stents in both the MV and the SB [26].

Despite numerous clinical and computational studies, the effect of each stent implantation method on the coronary artery hemodynamic is not well understood. To date, studies on bifurcation stinting fluid dynamics have been conducted by *in vitro* bench testing and computational simulations.

Computational fluid dynamics (CFD) is a powerful emerging tool since it offers the possibility to investigate local hemodynamics of non-stented and stented coronary artery bifurcations at a level of detail not easily accessed with experimental techniques [27, 28]. Computer simulations can assess the local hemodynamic microenvironment in bifurcations, pre- and post-stenting, providing an insight into the role of local hemodynamic stresses on neointimal hyperplasia and stent thrombosis [4].

Fluid dynamics in provisional technique

In coronary bifurcations, MV stenting restores main lumen and creates side-cell strut jailing at the level of SB ostium. This implies a peculiar pattern of flow in the coronary bifurcation characterized by a pronounced velocity jet in the SB with vortices extending from jailed struts into the SB and causing eccentric areas of low velocity on the main lateral wall away from the carina and in the SB distal to the carina (Fig. 2B).

Side branch ballooning is able to reduce (if present), ostial SB residual stenosis and remove stent struts from the SB ostium. According to computer simulations, this creates a more concentric region of low velocity in the MV distal to the carina and an area of low velocity in the SB lateral wall [29]. However, the total area of the luminal surface exposed to low TAWSS is essentially the same before and after SB balloon angioplasty [29]. In other words, although post-stenting SB angioplasty provides an excellent result in terms of SB patency (from a fluid dynamics perspective), there are only modest differences especially in the MV, indicating that a potential for MV ISR or ST may be unchanged.

Interestingly, the course of time may play an important role in flow alterations after bifurcation stenting. Zhang et al. [30] observed that both the reduction of WSS in the lateral wall of MV and an increase of WSS in SB would predict no restenosis 8 months after stenting of true bifurcation lesions by the provisional SB technique with SB ballooning. Over time, flow tends to return to its original pattern before PCI with high WSS in the internal wall and low WSS in the lateral wall. Yet, proliferation inhibition related to DES implantation may be sufficient to prevent the development of significant restenosis.

Another important issue is related to the technique for SB ballooning. Typically, kissing balloon inflation is commonly selected since it prevents major MV stent distortion [31]. Yet, it is now known that kissing balloon inflation has different consequences according to the stent's side-cells that are crossed with the wire and the balloon [32, 33].

In summary, the pattern of stent strut removal (and consequently the turbulence generated by the presence of residual jailing struts) may differ during kissing balloon inflation practice making its influence on SB flow somewhat unpredictable. Another important issue related with kissing ballooning is represented by its potential to induce MV overstretch. A CFD study documented that after kissing balloon inflation, a wider region characterized by low WSS in the proximal part of the MV was induced [34]. As a consequence of such proximal MV overstretch, the percentage of lumen area of the stented region exposed to WSS lower than 0.5 Pa was 79.0% after kissing as compared to 62.3% before the kissing balloon [34].

In conclusion, kissing balloon inflation (when performed after distal SB rewiring) may restore a better SB flow (with reduced accelerations and recirculation related with SB ostial stenosis and jailing stent struts) but has marginal or even adverse impact on MV shear stress (Fig. 2C).

Fluid dynamics in two-stent techniques

Double stenting specific techniques have been developed with the aim of improving the angiographic result in both the MV and the SB. However, the double stenting technique failed to show improved outcomes in clinical trials and hence these techniques are not recommended for unselected bifurcated coronary lesions [35]. The search for technical refinements in double stenting is ongoing and technical innovations may offer promising results [36]. All double stenting techniques have the potential for stent malapposition areas, which may influence local fluid dynamics. In a bench test study comparing different double stenting techniques, the crush technique resulted in a higher risk of malapposition than either the culotte or T-/TAP technique [37].

Due to different areas of double layers of struts and malapposed stent struts, each double stenting technique has a distinct impact on the flow patterns. Nevertheless, all double-stenting techniques failed to improve the fluid dynamics result over provisional. According to Raben et al. [38], double-stented cases (culotte, crush and T-stenting technique with high protrusion) showed a detrimental influence of multiple metallic layers on WSS. In particular, low flow regions protruding toward the centerline of the MV and following the distal surface of the SB stent were observed. In the double-stented models, the simultaneous presence of two devices led to the creation of a metallic carina between the SB and the distal part of the

MV, in addition to the presence of a larger number of stent struts at the flow divider. The disturbance created by this geometry led to low velocity and WSS as well as high shear stress in and around the region of the flow divider and in the proximal MV (Fig. 2D). Unapposed struts in the neocarina cause severe flow disturbances with a high shear rate that may increase the risk of platelet adhesion and stent thrombosis [37].

In a study by Brindise et al. [39], three different stenting techniques were compared in four compliant coronary artery models with a 60° bifurcation: provisional, crush and culotte technique. Overall, the culotte technique resulted in minimal stent induced flow disturbances as compared with the crush technique. Moreover, the culotte technique mitigated detrimental effects induced by a high bifurcation angle.

These observations, however, have not been confirmed by any further studies. In the study by Katritsis et al. [18], the crush technique with the use of a thin-strut stent resulted in improved hemodynamics compared with culotte or T-stenting, which had the most favourable fluid dynamics. Furthermore, the "nano-crush" and modified T techniques seem to restore the most physiologic fluid dynamic patterns (with the lowest values of WSS) with the addition of a final proximal optimization technique appears to be a favourable step [40].

Finally, it has been noted that SB stent length, in a setting of double stenting techniques, may have impact on local fluid dynamics during double stenting techniques. A longer SB stent adversely affects the hemodynamics of the SB by inducing lower WSS and higher OSI in the SB [41].

In summary, the double stenting technique is expected to induce blood flow perturbations which are not completely predictable and probably depend from the type and length of selected stents, specific sequence for their implantation and final result achieved. These issues, which are well recognized in experimental setting, are expected to be even more pronounced in clinical practice. This is because stent/vessel interactions, during each technical step of the complex sequences needed for double stenting, are not entirely predictable in clinical settings.

Conclusions and future perspectives

Coronary bifurcations represent common target lesions in contemporary PCI practice. DES improved clinical results of PCI on bifurcated lesions but they still represent a technical challenge graved by higher clinical risks. As a consequence, interventional management of bifurcation lesions is an evolving field [4]. Fluid-dynamic perturbations are known to be increased at the level of stents implanted at bifurcated lesions and have, theoretically, potential impact on stent healing.

Currently, the possibility to create highly accurate three-dimensional geometrical models of coronary bifurcations that include a precise fidelity of stent geometry has become a reality [28]. The application of CFD simulation algorithms to such reconstructions allows the collecting of detailed flow-related hemodynamic force evaluation and local microenvironment assessment following bifurcation stenting. Post-PCI fluid dynamics is dependent on a series of factors including stent selection, stent implantation technique, and bifurcation geometry. CFD from patient-specific models may represent a powerful tool in calculating local fluid dynamics quantity, such as WSS, to guide and optimize PCI strategies in order to predict adverse events and improve clinical outcomes. Therefore, effort should be made to optimize stent deployment and stent/scaffold design to ensure an optimal hemodynamic profile and reduce the risk of complications after PCI. Integration of this data and analysis may help improve the identification of both "tailored" PCI strategies and device improvements. In particular, CFD simulations can theoretically be used as a tool to guide both bifurcation stenting strategy and selection of the stenting technique with optimal post-PCI flow conditions in this challenging setting. In conclusion, patient-level CFD modeling has the potential to recover a critical role for the future improvement of bifurcation PCI and the integration of this tool with others to assess hemodynamic parameters which could guide future coronary bifurcation treatment.

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References

1. Lassen JF, Burzotta F, Banning AP, et al. Percutaneous coronary intervention for the left main stem and other bifurcation lesions: 12th consensus document from the European Bifurcation Club. EuroIntervention. 2018; 13(13): 1540–1553, doi: 10.4244/EIJ-D-17-00622, indexed in Pubmed: 29061550.
2. Sawaya FJ, Lefèvre T, Chevalier B, et al. Contemporary approach to coronary bifurcation lesion treatment. JACC Cardiovasc Interv. 2016; 9(18): 1861–1878, doi: 10.1016/j.jcin.2016.06.056, indexed in Pubmed: 27659563.

3. Park TK, Park YH, Song YB, et al. Long-Term clinical outcomes of true and non-true bifurcation lesions according to medina classification- results from the COBIS (COronary Bifurcation Stent) II registry. Circ J. 2015; 79(9): 1954–1962, doi: 10.1253/circj.CJ-15-0264, indexed in Pubmed: 26134457.
4. Antoniadis AP, Mortier P, Kassab G, et al. Biomechanical modeling to improve coronary artery bifurcation stenting: expert review document on techniques and clinical implementation. JACC Cardiovasc Interv. 2015; 8(10): 1281–1296, doi: 10.1016/j.jcin.2015.06.015, indexed in Pubmed: 26315731.
5. Chatzizisis YS, Coskun AU, Jonas M, et al. Role of endothelial shear stress in the natural history of coronary atherosclerosis and vascular remodeling: molecular, cellular, and vascular behavior. J Am Coll Cardiol. 2007; 49(25): 2379–2393, doi: 10.1016/j.jacc.2007.02.059, indexed in Pubmed: 17599600.
6. Morbiducci U, Kok AM, Kwak BR, et al. Atherosclerosis at arterial bifurcations: evidence for the role of haemodynamics and geometry. Thromb Haemost. 2016; 115(3): 484–492, doi: 10.1160/TH15-07-0597, indexed in Pubmed: 26740210.
7. Yazdani SK, Nakano M, Otsuka F, et al. Atheroma and coronary bifurcations: before and after stenting. EuroIntervention. 2010; 6 Suppl J: J24–J30, doi: 10.4244/EIJV6SUPJA5, indexed in Pubmed: 21930487.
8. Koskinas KC, Chatzizisis YS, Antoniadis AP, et al. Role of endothelial shear stress in stent restenosis and thrombosis: pathophysiologic mechanisms and implications for clinical translation. J Am Coll Cardiol. 2012; 59(15): 1337–1349, doi: 10.1016/j.jacc.2011.10.903, indexed in Pubmed: 22480478.
9. Malek AM, Alper SL, Izumo S. Hemodynamic shear stress and its role in atherosclerosis. JAMA. 1999; 282(21): 2035–2042, doi: 10.1001/jama.282.21.2035, indexed in Pubmed: 10591386.
10. Finet G, Huo Y, Rioufol G, et al. Structure-function relation in the coronary artery tree: from fluid dynamics to arterial bifurcations. EuroIntervention. 2010; 6 (Suppl J): J10–J15, doi: 10.4244/EIJV6SUPJA3, indexed in Pubmed: 21930472.
11. Giannoglou GD, Antoniadis AP, Koskinas KC, et al. Flow and atherosclerosis in coronary bifurcations. EuroIntervention. 2010; 6 (Suppl J): J16–J23, doi: 10.4244/EIJV6SUPJA4, indexed in Pubmed: 21930484.
12. Antoniadis AP, Giannopoulos AA, Wentzel JJ, et al. Impact of local flow haemodynamics on atherosclerosis in coronary artery bifurcations. EuroIntervention. 2015; 11 (Suppl V): V18–V22, doi: 10.4244/EIJV11SVA4, indexed in Pubmed: 25983161.
13. Fukumoto Y, Hiro T, Fujii T, et al. Localized elevation of shear stress is related to coronary plaque rupture: a 3-dimensional intravascular ultrasound study with in-vivo color mapping of shear stress distribution. J Am Coll Cardiol. 2008; 51(6): 645–650, doi: 10.1016/j.jacc.2007.10.030, indexed in Pubmed: 18261684.
14. Huo Y, Finet G, Lefevre T, et al. Which diameter and angle rule provides optimal flow patterns in a coronary bifurcation? J Biomech. 2012; 45(7): 1273–1279, doi: 10.1016/j.jbiomech.2012.01.033, indexed in Pubmed: 22365499.
15. Otsuka F, Finn AV, Yazdani SK, et al. The importance of the endothelium in atherothrombosis and coronary stenting. Nat Rev Cardiol. 2012; 9(8): 439–453, doi: 10.1038/nrcardio.2012.64, indexed in Pubmed: 22614618.
16. Jiménez JM, Prasad V, Yu MD, et al. Macro- and microscale variables regulate stent haemodynamics, fibrin deposition and thrombomodulin expression. J R Soc Interface. 2014; 11(94): 20131079, doi: 10.1098/rsif.2013.1079, indexed in Pubmed: 24554575.
17. Wentzel JJ, Gijsen FJH, Schuurbiers JCH, et al. The influence of shear stress on in-stent restenosis and thrombosis. EuroIntervention. 2008; 4 (Suppl C): C27–C32, indexed in Pubmed: 19202688.
18. Katritsis DG, Theodorakakos A, Pantos I, et al. Flow patterns at stented coronary bifurcations: computational fluid dynamics analysis. Circ Cardiovasc Interv. 2012; 5(4): 530–539, doi: 10.1161/CIRCINTERVENTIONS.112.968347, indexed in Pubmed: 22763345.
19. Chiastra C, Morlacchi S, Gallo D, et al. Computational fluid dynamic simulations of image-based stented coronary bifurcation models. J R Soc Interface. 2013; 10(84): 20130193, doi: 10.1098/rsif.2013.0193, indexed in Pubmed: 23676893.
20. Chiastra C, Gallo D, Tasso P, et al. Healthy and diseased coronary bifurcation geometries influence near-wall and intravascular flow: A computational exploration of the hemodynamic risk. J Biomech. 2017; 58: 79–88, doi: 10.1016/j.jbiomech.2017.04.016, indexed in Pubmed: 28457603.
21. Pinto SIS, Campos JB. Numerical study of wall shear stress-based descriptors in the human left coronary artery. Comput Methods Biomech Biomed Engin. 2016; 19(13): 1443–1455, doi: 10.1080/10255842.2016.1149575, indexed in Pubmed: 26883291.
22. Martin D, Boyle F. Sequential structural and fluid dynamics analysis of balloon-expandable coronary stents: a multivariable statistical analysis. Cardiovasc Eng Technol. 2015; 6(3): 314–328, doi: 10.1007/s13239-015-0219-9, indexed in Pubmed: 26577363.
23. Van der Heiden K, Gijsen FJH, Narracott A, et al. The effects of stenting on shear stress: relevance to endothelial injury and repair. Cardiovasc Res. 2013; 99(2): 269–275, doi: 10.1093/cvr/cvt090, indexed in Pubmed: 23592806.
24. Richter Y, Groothuis A, Seifert P, et al. Dynamic flow alterations dictate leukocyte adhesion and response to endovascular interventions. J Clin Invest. 2004; 113(11): 1607–1614, doi: 10.1172/JCI21007, indexed in Pubmed: 15173887.
25. Burzotta F, Talarico GP, Trani C, et al. Frequency-domain optical coherence tomography findings in patients with bifurcated lesions undergoing provisional stenting. Eur Heart J Cardiovasc Imaging. 2014; 15(5): 547–555, doi: 10.1093/ehjci/jet231, indexed in Pubmed: 24255135.
26. Louvard Y, Thomas M, Dzavik V, et al. Classification of coronary artery bifurcation lesions and treatments: time for a consensus! Catheter Cardiovasc Interv. 2008; 71(2): 175–183, doi: 10.1002/ccd.21314, indexed in Pubmed: 17985377.
27. Migliavacca F, Chiastra C, Chatzizisis YS, et al. Virtual bench testing to study coronary bifurcation stenting. EuroIntervention. 2015; 11 (Suppl V): V31–V34, doi: 10.4244/EIJV11SVA7, indexed in Pubmed: 25983167.
28. Chiastra C, Migliori S, Burzotta F, et al. Patient-Specific modeling of stented coronary arteries reconstructed from optical coherence tomography: towards a widespread clinical use of fluid dynamics analyses. J Cardiovasc Transl Res. 2018; 11(2): 156–172, doi: 10.1007/s12265-017-9777-6, indexed in Pubmed: 29282628.
29. Williams AR, Koo BK, Gundert TJ, et al. Local hemodynamic changes caused by main branch stent implantation and subsequent virtual side branch balloon angioplasty in a representative coronary bifurcation. J Appl Physiol (1985). 2010; 109(2): 532–540, doi: 10.1152/japplphysiol.00086.2010, indexed in Pubmed: 20507966.
30. Zhang JJ, Zhang JJ, Chen SL, et al. Contradictory shear stress distribution prevents restenosis after provisional stenting for

bifurcation lesions. J Interv Cardiol. 2010; 23(4): 319–329, doi: 10.1111/j.1540-8183.2010.00572.x, indexed in Pubmed: 20642478.
31. Sgueglia GA, Chevalier B. Kissing balloon inflation in percutaneous coronary interventions. JACC Cardiovasc Interv. 2012; 5(8): 803–811, doi: 10.1016/j.jcin.2012.06.005, indexed in Pubmed: 22917451.
32. Burzotta F, Trani C. In bifurcation PCI, as in everyday life, the consequences of kissing may not always be the same. EuroIntervention. 2016; 11(11): e1209–e1213, doi: 10.4244/EIJV11I11A240, indexed in Pubmed: 26865437.
33. Chiastra C, Morlacchi S, Pereira S, et al. Computational fluid dynamics of stented coronary bifurcations studied with a hybrid discretization method. Eur J Mech - B/Fluids. 2012; 35: 76–84, doi: 10.1016/j.euromechflu.2012.01.011.
34. Morlacchi S, Chiastra C, Gastaldi D, et al. Sequential structural and fluid dynamic numerical simulations of a stented bifurcated coronary artery. J Biomech Eng. 2011; 133(12): 121010, doi: 10.1115/1.4005476, indexed in Pubmed: 22206427.
35. Katritsis DG, Siontis GCM, Ioannidis JPA. Double versus single stenting for coronary bifurcation lesions: a meta-analysis. Circ Cardiovasc Interv. 2009; 2(5): 409–415, doi: 10.1161/CIRCINTERVENTIONS.109.868091, indexed in Pubmed: 20031750.
36. Chen SL, Zhang JJ, Han Y, et al. Double kissing crush versus provisional stenting for left main distal bifurcation lesions: DKCRUSH-V randomized trial. J Am Coll Cardiol. 2017; 70(21): 2605–2617, doi: 10.1016/j.jacc.2017.09.1066, indexed in Pubmed: 29096915.
37. Foin N, Alegria-Barrero E, Torii R, et al. Crush, culotte, T and protrusion: which 2-stent technique for treatment of true bifurcation lesions? - insights from in vitro experiments and microcomputed tomography. Circ J. 2013; 77(1): 73–80, doi: 10.1253/circj.cj-12-0272, indexed in Pubmed: 23006784.
38. Raben JS, Morlacchi S, Burzotta F, et al. Local blood flow patterns in stented coronary bifurcations: an experimental and numerical study. J Appl Biomater Funct Mater. 2015; 13(2): e116–e126, doi: 10.5301/jabfm.5000217, indexed in Pubmed: 25589159.
39. Brindise MC, Chiastra C, Burzotta F, et al. Hemodynamics of Stent Implantation Procedures in Coronary Bifurcations: An In Vitro Study. Ann Biomed Eng. 2017; 45(3): 542–553, doi: 10.1007/s10439-016-1699-y, indexed in Pubmed: 27460012.
40. Rigatelli G, Zuin M, Dell'Avvocata F, et al. Evaluation of coronary flow conditions in complex coronary artery bifurcations stenting using computational fluid dynamics: Impact of final proximal optimization technique on different double-stent techniques. Cardiovasc Revasc Med. 2017; 18(4): 233–240, doi: 10.1016/j.carrev.2017.01.002, indexed in Pubmed: 28108202.
41. Chen HY, Koo BK, Kassab GS. Impact of bifurcation dual stenting on endothelial shear stress. J Appl Physiol (1985). 2015; 119(6): 627–632, doi: 10.1152/japplphysiol.00082.2015, indexed in Pubmed: 26183473.

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Epilepsy and hypertension: The possible link for sudden unexpected death in epilepsy?

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Abstract

Epilepsy affects about 50 million people worldwide. Sudden unexpected death in epilepsy (SUDEP) is the main cause of death in epilepsy accounting for up to 17% of all deaths in epileptic patients, and therefore remains a major public health problem. SUDEP likely arises from a combination and interaction of multiple risk factors (such as being male, drug resistance, frequent generalized tonic-clonic seizures) making risk prediction and mitigation challenging. While there is a general understanding of the physiopathology of SUDEP, mechanistic hypotheses linking risk factors with a risk of SUDEP are still lacking. Identifying cross-talk between biological systems implicated in SUDEP may facilitate the development of improved models for SUDEP risk assessment, treatment and clinical management. In this review, the aim was to explore an overlap between the pathophysiology of hypertension, cardiovascular disease and epilepsy, and discuss its implication for SUDEP. Presented herein, evidence in literature in support of a cross-talk between the renin–angiotensin system (RAS) and sympathetic nervous system, both known to be involved in the development of hypertension and cardiovascular disease, and as one of the underlying mechanisms of SUDEP. This article also provides a brief description of local RAS in brain neuroinflammation and the role of centrally acting RAS inhibitors in epileptic seizure alleviation.
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Key words: hypertension, epilepsy, SUDEP, cardiovascular diseases, renin–angiotensin system, neuroinflammation

Introduction

Epilepsy with its comorbidities such as depression and anxiety significantly affect quality of life. Importantly, mortality rates in epileptics are greatly higher than that of the general population [1], and sudden unexpected death in epilepsy (SUDEP), known as a seizure related event, is the main cause of death in those patients. The etiology of SUDEP remains unclear. Effective seizure control was shown to be a preventive strategy for premature death in epilepsy [2], however, approximately 30% of patients do not respond to treatment with common anticonvulsants [3].

Epileptic seizures result from uncontrollable neuronal excitation in the brain; therefore, epilepsy is considered to be a neuronal disease. However, recent investigations indicate that the model of epileptogenesis could be more complex. The evidence that seizure increases levels of inflammatory mediators in brain suggests that cytokines and prostaglandins could be therapeutic targets for new antiepileptic drugs [4]. Experimental studies on animal models of epilepsy showed that local renin–angiotensin system (RAS) in the brain is involved in neuroinflammation and administration of common antihypertensive drugs, such as angiotensin II receptor blocker (ARB) that crosses the

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brain barrier, reduces blood pressure and attenuated neuronal injury [3, 5].

In the current literature a few review papers targeting the possible pathophysiology mechanism of SUDEP, but no one has confronted hypertension with epilepsy. Some interesting original articles present studies conducted on animal models with hypertension and epilepsy, suggesting the overlap between hypertension and epilepsy pathophysiology.

The aim of this review is to present pathophysiological and clinical aspects of hypertension, cardiovascular diseases (CVD) and epilepsy and to explore the possibility that these disorders are related to each other.

This review advances the hypothesis that components of RAS in association with sympathetic activity may play a crucial role in the patomechanism of SUDEP. Evidence in the literature is presented that shows RAS inhibitors may be used to potentially alleviate epileptic seizures and build a hypothesis that targeting RAS may also reduce the risk of SUDEP.

Epilepsy and SUDEP

Epilepsy is a neurological disease characterized by recurrent seizures resulting from abnormal excessive or synchronous activity in brain [6]. An imbalance between excitation and inhibition in the brain, the basis of this phenomenon, results from alterations at many levels of brain functioning, neuronal circuits, and genetic predisposition [7]. Epilepsy diagnosis requires the presence of at least one unprovoked seizure in a patient who has other factors associated with high recurrence risk of latter seizures [1, 6]. Depending on the character of the onset, seizures are classified as focal or generalized, with motor or nonmotor onset [8]. Status epilepticus (SE) is defined as 5 min of ongoing seizure activity to diagnose convulsive SE (bilateral tonic-clonic SE) and 10 min for focal or absence SE [9].

Every hundredth person suffers from epilepsy and in about one-third of those patients, refractory epilepsy is recognized [7]. Importantly, the risk of premature death in patients with epilepsy is about 2–3 times higher than the general population [1].

Sudden unexpected death in eplilepsy accounts for up to 17% of deaths in patients with epilepsy [10]. SUDEP is defined as a sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death in patients with epilepsy, with or without evidence of a seizure excluding documented status epilepticus, in which postmortem examination does not reveal a toxicological or anatomical cause of death [11]. SUDEP incidence is estimated to be from 0.3 to 6 persons per 1000 adult person-years [2]; however, SUDEP may be under-diagnosed due to the fact that the 10th revision of International Classification of Disease does not include term SUDEP as a cause of death [1, 10].

There are still limited tools to stratify individual risk for SUDEP [12]. A number of risk factors have been reported to be associated with SUDEP, including general tonic-clonic seizures and poor seizure control, young onset and long duration of epilepsy, and young age [11]. It is estimated that young adults (aged 20–45 years) have 27.5 higher risk of SUDEP than the general population [13]. The reasons for the increased incidence of SUDEP in early adulthood are unknown, therefore a better understanding of underlying pathophysiology is crucial for treatment and SUDEP prevention [10].

Pathomechanism of SUDEP: Sympathetic system and heart

Sudden unexpected death in epilepsy is proposed to result from the accumulation of disturbances in numerous biological systems such as the cardiac, respiratory, and nervous systems [11]. MORTEMUS study suggested that impaired respiratory function may play a crucial role in this condition based on the fact that terminal apnea always preluded terminal asystole in epileptic patients who died unexpectedly [14]. In addition, the brainstem arousal system dysfunction and dysregulation in the neurotransmitter and neuromodulator system are mechanisms that presumably take part in the pathogenesis of SUDEP [12].

Seizure affects cardiac function which may lead to Takotsubo syndrome, cardiomyocyte injury, arterial hypertension and probably even premature death in epileptic patients [15]. Clinical data suggest that there is a resemblance between SUDEP and sudden cardiac deaths such as both unexpected events are characterized by abrupt loss of consciousness [16]. Sudden cardiac deaths occur mostly in the morning when the patient is awake, while SUDEP mostly when patient is asleep in a prone position [12]. Ruthirago at al. [10] suggested that some cases of SUDEP could be misinterpreted as sudden cardiac deaths, cardiorespiratory failure or sudden infant death syndrome, especially in patients without prior diagnosis of epilepsy.

Seizures affect central autonomic system and as a result may alter pulmonary and cardiovascular functions which are linked with the risk of

SUDEP [17]. Refractory epilepsy is accompanied by increased sympathetic tone and reactivity and decreased parasympathetic tone and reactivity [15]. More than 90% cases of seizure are associated with increased heart rate, suggesting that cardiac dysfunction is strongly related to chronic, refractory epilepsy [18]. According to Powell et al. [19], chronic epilepsy contributes to channelopathy, that can result in fatal arrhythmias. Electrocardiographic abnormalities, including repolarization alteration, are found in individuals with a long history of epilepsy. ST segment depression was described to occur during and just after the seizure. QT lengthening was also observed in an association with electroencephalographic discharges, especially in those patients who have later died from SUDEP [20].

Importantly, anticonvulsants may also trigger SUDEP by facilitating the occurrence of severe cardiac arrhythmias via altering cardiac conduction and the length of QT interval. Interestingly, an abrupt antiepileptic drugs withdrawal results in increased sympathetic tone and therefore could create conditions for sudden, unexpected death [3, 11, 21].

Prevalence of hypertension with the focus on young population

Hypertension affects 30–45% adults worldwide [22]. The incidence of arterial hypertension is projected to increase by 15–20% by 2025 as a consequence of an aging population and the obesity epidemic [22].

The prevalence of hypertension in a group of adults aged 18–39 is 7.3%, the majority are men. This group of patients is less likely to have controlled hypertension than those aged 60 and over [23]. Clinical data demonstrated that young adults with documented elevated blood pressure have slower rates of antihypertensive medication initiation than older patients. Importantly, uncontrolled hypertension, both in young and older populations, increases the risk of future cardiovascular events [24].

Hypertension mediated organ damage: The role of RAS and sympathetic system

Untreated or poorly controlled hypertension is associated with structural and/or functional changes in heart, blood vessels, brain, eyes and kidneys, which are markers of asymptomatic CVD [22]. The role of systemic RAS is classically recognized in the regulation of cardiovascular homeostasis. RAS plays a critical role in the pathophysiology of hypertension, and therefore in the development of hypertension-related target organ damage [25]. A growing body of evidence shows that circulating RAS does not act independently, but in cooperation with local RAS in different tissues and organs [26]. The extent of local RAS contribution to cardiovascular complications remains unknown [26].

The activated RAS is associated with the altered expression and distribution of its components, with the main focus on angiotensin II (Ang II) and its receptor angiotensin II type 1 receptor (AT1), the strongest element of RAS [26]. Overactivity of AT1 receptor has been demonstrated to be associated with vascular remodeling, endothelial dysfunction and accelerated arterial stiffening [27]. Conversely, angiotensin-converting enzyme inhibitors (ACEI) and AT1 receptor blockers have been shown to prevent tissue damage. Conceivably, the beneficial effect of ACEI and AT1 receptors may be attributed to both systemic and local RAS blockage/ /inhibition [25].

An overactive sympathetic nervous system (SNS) is characteristic for CVD including hypertension and hypertension-related organ damage, such as left ventricular hypertrophy, renal dysfunction or arteriolar remodeling [28]. Many studies suggest that the RAS might be a link between sympathetic nervous system activity and hypertension [29].

It has been shown that SNS affects the release of renin from the kidneys. Ang II, a crucial effector of RAS which acts by binding to AT1 receptors on sympathetic nerve endings, induces SNS activity by enhancing norepinephrine release [26]. Taken altogether, it suggests that inhibition of RAS contributes to decreased SNS activity and alleviated organ complications.

Hypertension and epilepsy

According to the study presented by Wilner et al. [30], on a group of patients older than 19 years with epilepsy, hypertension was the most common comorbid condition. This observation suggests that hypertension may play an important role in epilepsy.

The association between hypertension and epilepsy seems to be bidirectional. The cerebral damage resulting from high blood pressure could lower seizure threshold and therefore cause epilepsy [31]. Thus, chronic hypertension contributes to late onset of seizure [32]. On the other hand, seizure onset is connected with increased sympathetic tone. That could lead by itself to increased blood pressure. Hypertension as a frequent, sometimes severe comorbid condition, and may be complicated

by posterior reversible encephalopathy syndrome in some cases [20].

Brain RAS and neuroinflammation

The brain RAS is involved in body water balance, maintenance of blood pressure, cyclicity of reproductive hormones and sexual behaviors, and regulation of releasing pituitary gland hormones [33]. A growing body of evidence suggests the role of neuroinflammation in the pathology of epilepsy, as it has been shown, is the association with the occurrence of seizure and generation of pathological lesions after seizure [34]. According to Sun et al. [5], the expression of Ang II peptide substantially increased in activated microglia after seizure. Ang II and its AT1 receptor amplify neuroinflammatory reaction, that in turn contribute to neurodegeneration. Subsequently, the inhibition of AT1 receptor may result in reduced inflammatory response and decreased levels of oxidative stress. In epilepsy RAS inhibitors may act as anti-inflammatory and neuroprotective agents. Experimental studies have also shown that blockade of AT1 receptor reduced the infarct volume after ischemia in rats. The neuroinflammation in the hippocampus is strongly associated with activated microglia and cognitive impairment in epileptic patients [5, 35, 36]. Interestingly, it has been reported that ACEI can attenuate neuroinflammation and prevent neuronal loss in the hippocampus during epilepsy [37]. Contrary to Ang II, the axis Ang 1-7/Mas receptor is involved in attenuation of the inflammatory process. Anti-inflammatory action can also exist in the brain and may play an important role in epilepsy [38].

RAS inhibitors alleviate epileptic seizure

Hippocampus is recruited in the most common type of epilepsy — temporal lobe epilepsy [34]. Rat epilepsy models showed that seizures were associated with increased expression of ACE and AT1 receptor in the temporal lobe epilepsy. In turn, treatment with ACEI substantially reduced limbic and tonic-clonic seizure severity without affecting blood pressure [3, 31, 39]. ARB treatment was associated with not only seizure suppression, but also systolic blood pressure reduction [3].

Other studies have revealed that pilocarpine-induced acute and silent phase of experimental status epilepticus was associated with a high concentration of Ang 1-7 peptides. This observation was attributed to the response to injury and the anti-inflammatory effects of Ang 1-7. The chronic period (which started with the first spontaneous seizure, after the acute and silent phase) was associated with higher levels of Ang II peptides contrary to the acute and silent phase, which was accompanied with its lower concentrations. The expression of tonin mRNA, element of local RAS, an alternative pathway to Ang II generation from angiotensinogen, were significantly increased [40].

Angiotensin II receptor blockers have been shown to affect transforming growth factor (TGF)-beta signaling pathway. This cytokine is associated with vascular injury in the brain e.g. after stroke and trauma, and thus may play a crucial role in epileptogenesis. Losartan effectively blocked TGF-beta activation in the brain and in this way acted as antiepileptic drug in the animal model of acquired epilepsy [39]. The potential neuroprotective effects of RAS targeted drugs were demonstrated by a study showing that administration of losartan (ARB) led to essential delays in the occurrence of seizure, shorten seizure duration and frequency in the animal model of epilepsy [31]. There is a need for further investigation on this underlying mechanism.

Conclusions

A better understanding of SUDEP is needed to develop effective prevention strategies. In this review, compelling evidence is presented describing the link between hypertension, brain RAS, sympathetic system and epilepsy. Based on evidence from literature it is hypothesized that targeting RAS may be an effective strategy to reduce epileptic seizure in humans and potentially reduce the risk of SUDEP.

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References

1. Zhuo L, Zhang Y, Zielke HR, et al. Sudden unexpected death in epilepsy: Evaluation of forensic autopsy cases. Forensic Sci Int. 2012; 223(1-3): 171–175, doi: 10.1016/j.forsciint.2012.08.024, indexed in Pubmed: 22999232.
2. Manolis TA, Manolis AA, Melita H, et al. Sudden unexpected death in epilepsy: The neuro-cardio-respiratory connection. Seizure. 2019; 64: 65–73, doi: 10.1016/j.seizure.2018.12.007, indexed in Pubmed: 30566897.

3. Pereira MG, Becari C, Oliveira JAC, et al. Inhibition of the renin-angiotensin system prevents seizures in a rat model of epilepsy. Clin Sci (Lond). 2010; 119(11): 477–482, doi: 10.1042/CS20100053, indexed in Pubmed: 20533906.
4. Shimada T, Takemiya T, Sugiura H, et al. Role of inflammatory mediators in the pathogenesis of epilepsy. Mediators Inflamm. 2014; 2014: 901902, doi: 10.1155/2014/901902, indexed in Pubmed: 25197169.
5. Sun H, Wu H, Yu X, et al. Angiotensin II and its receptor in activated microglia enhanced neuronal loss and cognitive impairment following pilocarpine-induced status epilepticus. Mol Cell Neurosci. 2015; 65: 58–67, doi: 10.1016/j.mcn.2015.02.014, indexed in Pubmed: 25724109.
6. Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia. 2014; 55(4): 475–482, doi: 10.1111/epi.12550, indexed in Pubmed: 24730690.
7. Stafstrom C, Carmant L, et al. Seizures and epilepsy: An overview for neuroscientists. Cold Spring Harb Perspect Med. 2015; 5(6): 1–18.
8. Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: position paper of the ILAE Commission for Classification and Terminology. Zeitschrift fur Epileptol. 2018; 31(4): 272–281.
9. Leitinger M, Trinka E, Giovannini G, et al. Epidemiology of status epilepticus in adults: A population-based study on incidence, causes, and outcomes. Epilepsia. 2019; 60(1): 53–62, doi: 10.1111/epi.14607, indexed in Pubmed: 30478910.
10. Ruthirago D, Julayanont P, Karukote A, et al. Sudden unexpected death in epilepsy: ongoing challenges in finding mechanisms and prevention. Int J Neurosci. 2018; 128(11): 1052–1060, doi: 10.1080/00207454.2018.1466780, indexed in Pubmed: 29667458.
11. Surges R, Thijs RD, Tan HL, et al. Sudden unexpected death in epilepsy: risk factors and potential pathomechanisms. Nat Rev Neurol. 2009; 5(9): 492–504, doi: 10.1038/nrneurol.2009.118, indexed in Pubmed: 19668244.
12. Devinsky O, Hesdorffer DC, Thurman DJ, et al. Sudden unexpected death in epilepsy: epidemiology, mechanisms, and prevention. Lancet Neurol. 2016; 15(10): 1075–1088, doi: 10.1016/S1474-4422(16)30158-2, indexed in Pubmed: 27571159.
13. Holst AG, Winkel BoG, Risgaard B, et al. Epilepsy and risk of death and sudden unexpected death in the young: a nationwide study. Epilepsia. 2013; 54(9): 1613–1620, doi: 10.1111/epi.12328, indexed in Pubmed: 23895621.
14. Ryvlin P, Nashef L, Lhatoo SD, et al. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study. Lancet Neurol. 2013; 12(10): 966–977, doi: 10.1016/S1474-4422(13)70214-X, indexed in Pubmed: 24012372.
15. Finsterer J, Wahbi K. CNS-disease affecting the heart: brain-heart disorders. J Neurol Sci. 2014; 345(1-2): 8–14, doi: 10.1016/j.jns.2014.07.003, indexed in Pubmed: 25034054.
16. Priori SG, Aliot E, Blømstrom-Lundqvist C, et al. Task Force on Sudden Cardiac Death of the European Society of Cardiology. Eur Heart J. 2001; 22(16): 1374–1450, doi: 10.1053/euhj.2001.2824, indexed in Pubmed: 11482917.
17. Devinsky O. Effects of seizures on autonomic and cardiovascular function. Epilepsy Curr . 2004; 4(2): x43–46, doi: 10.1111/j.1535-7597.2004.42001.x.
18. Ravindran K, Powell KL, Todaro M, et al. The pathophysiology of cardiac dysfunction in epilepsy. Epilepsy Res. 2016; 127: 19–29, doi: 10.1016/j.eplepsyres.2016.08.007, indexed in Pubmed: 27544485.
19. Powell KL, Jones NC, Kennard JT, et al. HCN channelopathy and cardiac electrophysiologic dysfunction in genetic and acquired rat epilepsy models. Epilepsia. 2014; 55(4): 609–620, doi: 10.1111/epi.12563, indexed in Pubmed: 24592881.
20. Stöllberger C, Finsterer J. Cardiorespiratory findings in sudden unexplained/unexpected death in epilepsy (SUDEP). Epilepsy Res. 2004; 59(1): 51–60, doi: 10.1016/j.eplepsyres.2004.03.008, indexed in Pubmed: 15135167.
21. Elger CE, Schmidt D. Modern management of epilepsy: a practical approach. Epilepsy Behav. 2008; 12(4): 501–539, doi: 10.1016/j.yebeh.2008.01.003, indexed in Pubmed: 18314396.
22. Williams B, Mancia G, Spiering W, et al. 2018 ESC / ESH Guidelines for the management of arterial hypertension. ; 2018: 1–98.
23. Yoon SS, Carroll MD, Fryar CD. Hypertension prevalence and control among adults: United States, 2011-2014. NCHS Data Brief. 2015; 220: 1–8, indexed in Pubmed: 26633197.
24. De Venecia T, Lu M, Figueredo VM. Hypertension in young adults. Postgrad Med. 2016; 128(2): 201–207, doi: 10.1080/00325481.2016.1147927, indexed in Pubmed: 26821528.
25. Iwanami J, Mogi M, Iwai M, et al. Inhibition of the renin-angiotensin system and target organ protection. Hypertens Res. 2009; 32(4): 229–237, doi: 10.1038/hr.2009.5, indexed in Pubmed: 19262496.
26. Stupin A, Drenjancevic I, Rasic L, et al. A cross-talk between the renin-angiotensin and adrenergic systems in cardiovascular health and disease. Southeast Eur Med J. 2017; 1(1): 90–107.
27. Neves MF, Cunha AR, Cunha MR, et al. The role of renin-angiotensin-aldosterone system and its new components in arterial stiffness and vascular aging. High Blood Press Cardiovasc Prev. 2018; 25(2): 137–145, doi: 10.1007/s40292-018-0252-5, indexed in Pubmed: 29476451.
28. Grassi G, Allyn M, Murray E, et al. The Sympathetic Nervous System alteration in human hypertension. 2016; 116(6): 976–90.
29. Tsuda K. Renin-Angiotensin system and sympathetic neurotransmitter release in the central nervous system of hypertension. Int J Hypertens. 2012; 2012: 474870, doi: 10.1155/2012/474870, indexed in Pubmed: 23227311.
30. Wilner AN, Sharma BK, Soucy A, et al. Common comorbidities in women and men with epilepsy and the relationship between number of comorbidities and health plan paid costs in 2010. Epilepsy Behav. 2014; 32: 15–20, doi: 10.1016/j.yebeh.2013.12.032, indexed in Pubmed: 24463303.
31. Tchekalarova JD, Ivanova N, Atanasova D, et al. Long-term treatment with losartan attenuates seizure activity and neuronal damage without affecting behavioral changes in a model of co-morbid hypertension and epilepsy. Cell Mol Neurobiol. 2016; 36(6): 927–941, doi: 10.1007/s10571-015-0278-3, indexed in Pubmed: 26464042.
32. Tchekalarova J, Loyens E, Smolders I. Effects of AT1 receptor antagonism on kainate-induced seizures and concomitant changes in hippocampal extracellular noradrenaline, serotonin, and dopamine levels in Wistar-Kyoto and spontaneously hypertensive rats. Epilepsy Behav. 2015; 46: 66–71, doi: 10.1016/j.yebeh.2015.03.021, indexed in Pubmed: 25922088.

33. McKinley MJ, Albiston AL, Allen AM, et al. The brain renin-angiotensin system: location and physiological roles. Int J Biochem Cell Biol. 2003; 35(6): 901–918, doi: 10.1016/s1357-2725(02)00306-0, indexed in Pubmed: 12676175.
34. Pereira MG, Souza LL, Becari C, et al. Angiotensin II-independent angiotensin-(1-7) formation in rat hippocampus: involvement of thimet oligopeptidase. Hypertension. 2013; 62(5): 879–885, doi: 10.1161/HYPERTENSIONAHA.113.01613, indexed in Pubmed: 24041943.
35. Wright JW, Harding JW. The brain renin-angiotensin system: a diversity of functions and implications for CNS diseases. Pflugers Arch. 2013; 465(1): 133–151, doi: 10.1007/s00424-012-1102-2, indexed in Pubmed: 22535332.
36. Saavedra JM, Sánchez-Lemus E, Benicky J. Blockade of brain angiotensin II AT1 receptors ameliorates stress, anxiety, brain inflammation and ischemia: Therapeutic implications. Psychoneuroendocrinology. 2011; 36(1): 1–18, doi: 10.1016/j.psyneuen.2010.10.001, indexed in Pubmed: 21035950.
37. De Bundel D, Smolders I, Vanderheyden P, et al. Ang II and Ang IV: unraveling the mechanism of action on synaptic plasticity, memory, and epilepsy. CNS Neurosci Ther. 2008; 14(4): 315–339, doi: 10.1111/j.1755-5949.2008.00057.x, indexed in Pubmed: 19040556.
38. Ibrahim MA, Koorbanally NA, Islam MS. In vitro anti-oxidative activities of the various parts of Parkia biglobosa and GC-MS analysis of extracts with high activity. Afr J Tradit Complement Altern Med [Internet]. Afr J Tradit Complement Altern Med. 2013; 10(5): 283–291.
39. Bar-Klein G, Cacheaux LP, Kamintsky L, et al. Losartan prevents acquired epilepsy via TGF-β signaling suppression. Ann Neurol. 2014; 75(6): 864–875, doi: 10.1002/ana.24147, indexed in Pubmed: 24659129.
40. Gouveia TL, Frangiotti MI, de Brito JM, et al. The levels of renin--angiotensin related components are modified in the hippocampus of rats submitted to pilocarpine model of epilepsy. Neurochem Int. 2012; 61(1): 54–62, doi: 10.1016/j.neuint.2012.04.012, indexed in Pubmed: 22542773.

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Boosting telemedicine through remote monitoring of cardiac electronic devices during the Italian COVID-19 outbreak

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Remote monitoring of cardiac implantable electronic devices (CIEDs) affords an alternative to the one-on-one interaction required in traditional outpatient visits, and provides access to complete information on device performance [1]. The principal purposes of remote monitoring are: to reduce face-to-face hospital visits; ensure continuous follow-up and early detection of device malfunctions and subsequent clinical problems; and provide superior information processing [2].

On 31 December 2019, China reported a cluster of pneumonia cases with unknown etiology to the World Health Organization (WHO), the causative pathogen later being identified as a novel coronavirus (SARS-CoV-2) [3]. On 11 March 2020, WHO declared the pandemic phase of the outbreak [4].

On 20 February 2020, a male admitted to hospital in Codogno (Lombardy, Italy) was confirmed as the first Italian citizen with COVID-19 [5–7]. The following day, a second outbreak was detected, in the Veneto region (Padua). The Government quarantined these two "red" areas by closing schools and commercial activities, and cancelling events. Our public hospital is located west of Vò Euganeo and east of Codogno; i.e., between the two outbreaks.

COVID-19 patients at highest risk for more severe complications and death include people aged > 60 years and people with comorbidities. Mortality increases with age, with the highest rate among individuals over 80 years of age. Furthermore, mortality is higher among males compared with females. Patients with CIEDs followed by our clinical center are of advanced age (mean age 78.5 ± ± 10.6 years), with more than half (53.8%) 80 years of age or older (Table 1); most have cardiovascular disease; and there was a higher prevalence of men (62.7%; n = 570). Because the duration of this medical emergency was unknown and the above mentioned clinic population was largely at higher risk of serious consequences from COVID-19 (Table 1), the aim was to check cardiac devices of patients using a home-monitoring system as much as was feasible, thereby reducing outpatient visits and decreasing infection risk for these fragile patients. While the Government was gradually extending restrictions outside of the two red areas, our unit quickly established a new procedure optimizing the management of CIED follow-ups.

Overall, the remote monitoring system covered 909 CIEDs including 678 pacemakers (PMs), 198 implantable cardioverter-defibrillators (ICDs) and 33 loop recorders. The following measures were introduced: first, patients previously refusing device remote monitoring were contacted and strongly encouraged to accept this system. Should they accept, the telemonitoring system was dispatched and activated through a phone-mediated technical support system. Second, all devices without auto-thresholds (i.e., patients without PM-dependency) were exclusively checked through remote monitoring. Third, the new procedure required a mandatory attempt to solve all device alarms via phone communication.

From 3 February to the day preceding the Italian outbreak, 40 patients had CIED monitoring transmissions checked remotely (26 PMs and

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Table 1. Cardiovascular risk factors and comorbidities in the patients overall and comparison between the two samples evaluated between February 3rd and March 9th.

	Overall patients with cardiac electronic devices (n = 909)	People evaluated from February 3rd to February 20th (n = 88)	People evaluated from February 21st to March 9th (n = 91)	P
Age [years]	78.5 ± 10.6	80.3 ± 13.2	79.4 ± 12.8	0.6
Age ≥ 80 year-old	489 (54%)	45	40	0.4
Males	570 (63%)	55	59	0.7
Hypertension	511 (56%)	48	54	0.5
Diabetes mellitus	68 (7%)	4	4	0.6
Dyslipidemia	288 (32%)	25	28	0.7
Coronary artery disease	212 (23%)	22	21	0.9
Dilatative cardiomyopathy	85 (9%)	10	12	0.8
Valvular disease	34 (4%)	3	1	0.4
Atrial fibrillation	373 (41%)	25	30	0.5
Chronic heart failure	139 (15%)	15	21	0.4
Chronic kidney disease*	177 (19%)	17	16	0.8
COPD	55 (6%)	3	5	0.7

*Glomerular filtration rate < 50 mL/min/m^2; COPD — chronic obstructive pulmonary disease

Table 2. Patients with cardiac implantable electronic devices managed via face-to-face outpatient visits or remote monitoring during two equivalent time frames: before and after 20 February 2020 (Day 0 of the Italian COVID-19 outbreak).

	Before Day 0 (n = 84)	After Day 0 (n = 83)	Difference, N (% change)
Outpatient visits	44 (52.4%)	25 (30.1%)	–19 (–43.2%)
Remote monitoring	40 (47.6%)	58 (69.9%)	+18 (+45.0%)

14 ICDs), whereas 44 underwent checks face-to--face (Table 2). Among these face-to-face checks, 17 were for clinical evaluation of the device pocket/ /wound after PM/ICD implantation/replacement, 9 were electronic checks for devices unsuited to home monitoring, 4 were checks of remaining battery life, 4 were in patients who had previously refused home monitoring, 6 in patients with suspected device malfunctioning, and 4 for ICDs without an auto-threshold. In the same period, 4 alerts were received: 2 in patients with new-onset atrial fibrillation (AF) and 2 in patients with abnormal sensing of the ventricular lead. These patients were all managed through in-hospital consultations.

In an equivalent time frame following the COVID-19 outbreak, from 21 February (when the new procedure was activated) and up to 9 March, the total CIED transmissions checked remotely was 58 (40 PMs and 18 ICDs) and the number of face-to-face outpatient visits was 25, including 15 clinical evaluations of the wound/pocket after device implantation/replacement and 10 checks of old PMs without a remote monitoring option (Table 2). In-office checks were avoided in 9 patients (5 received the remote monitoring device at home, 4 had ICDs without an auto-threshold). During this period, 8 non-urgent alerts were received: 2 sinus pauses detected by loop recorders (these were already known about; no intervention needed), 1 inappropriate shock (the patient was instructed by phone to increase their beta-blocker dose), 2 cases of a low percentage of biventricular stimulation in cardiac resynchronization devices (no intervention required; these patients were already waiting for atrioventricular node ablation), 1 case of low sensing of the ventricular lead (we knew of this; the patient was in follow-up), and 2 new cases of AF. Among the 2 latter patients, one needed urgent evaluation for initiation of oral anticoagulation and the other, who had a dual-chamber PM and a history of recurrent episodes of AF, required pharmacotherapy modification; their prescription

was electronically sent to the pharmacy, avoiding travel to the hospital. Actually 5 out of 8 non-urgent alerts were "already-known" problems, therefore they were more easily managed through phone calls, thus avoiding in-office checks.

In summary, the application of the new procedure following the Italian COVID-19 outbreak resulted in a robust 43.2% decrease in the need for outpatient checks conducted face-to-face. Notably, all the alerts except one were managed through phone communication. At the same time, remote monitoring increased markedly, by 45%.

Although comprising a small sample of patients and of short duration, this study demonstrates that a simple modified approach might be helpful for reducing in-office checks in patients with CIEDs, preserving the safety and efficiency of the whole monitoring system. This appears important in the current COVID-19 pandemic emergency, where reducing the number of new cases per unit of time is essential. Minimizing travel and hospital/ /outpatient clinic admissions for patients may markedly reduce the spread of COVID-19, especially if adopted by all hospitals for a prolonged duration, particularly those with high patient volumes. Furthermore, remote monitoring could be highly valuable for patient management and follow-up, in general. It reduces the number of face-to-face visits required — saving patients' time and expense — and, thanks to continuous follow-up and early detection of device malfunctions, improves safety and quality of life.

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References

1. Hernández-Madrid A, Lewalter T, Proclemer A, et al. Remote monitoring of cardiac implantable electronic devices in Europe: results of the European Heart Rhythm Association survey. Europace. 2014; 16(1): 129–132, doi: 10.1093/europace/eut414, indexed in Pubmed: 24344325.
2. Zanotto G, Melissano D, Baccillieri S, et al. Intrahospital organizational model of remote monitoring data sharing, for a global management of patients with cardiac implantable electronic devices: a document of the Italian Association of Arrhythmology and Cardiac Pacing. J Cardiovasc Med (Hagerstown). 2020; 21(3): 171–181, doi: 10.2459/JCM.0000000000000912, indexed in Pubmed: 32004241.
3. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese center for disease control and prevention. JAMA. 2020; 323(13): 1239–1242, doi: 10.1001/jama.2020.2648, indexed in Pubmed: 32091533.
4. World Health Organization. Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020 (Accessed 08 May 2020).
5. Spina S, Marrazzo F, Migliari M, et al. The response of Milan's Emergency Medical System to the COVID-19 outbreak in Italy. Lancet. 2020; 395(10227): e49–e50, doi: 10.1016/s0140-6736(20)30493-1.
6. Carinci F. Covid-19: preparedness, decentralisation, and the hunt for patient zero. BMJ. 2020; 368: bmj.m799, doi: 10.1136/bmj.m799, indexed in Pubmed: 32111645.
7. Grasselli G, Pesenti A, Cecconi M. Critical care utilization for the COVID-19 outbreak in lombardy, italy: early experience and forecast during an emergency response. JAMA. 2020; 323(16): 1545–1546, doi: 10.1001/jama.2020.4031, indexed in Pubmed: 32167538.

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Cardiovascular comorbidity and death from COVID-19: Prevalence and differential characteristics

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Coronavirus disease (COVID-19), caused by SARS-CoV-2, originated as a global pandemic and has had a major impact on Europe. Spain, with more than 1,600,000 confirmed cases and a fatality rate of approximately 2.75%, is one of the most affected countries to date [1]. A high prevalence of cardiovascular (CV) comorbidity, consisting mostly of coronary artery disease (CAD) and arrhythmias, has been reported among the deceased [2, 3].

Additionally, a wide variety of CV manifestations has been described in COVID-19 patients, either as a result of the invasion of endothelial cells and myocardiocytes (carriers of the ACE receptor on their membrane) by the SARS-CoV-2, as a consequence of the cytokine storm [2] or due to impaired microcirculatory function [4].

The purpose herein, is to describe the prevalence of CV comorbidity in the patients who died on the hospital wards of a Spanish tertiary hospital and to examine the differences in baseline characteristics, laboratory findings, days until death and treatment received compared to those who died without these comorbidities.

All patients infected with SARS-CoV-2 who died in the hospital wards between March 9 and April 16, 2020, were consecutively included. Those who died in the intensive care unit were excluded on the grounds that their evolution and potential causes of morbidity and death might be different. Clinical and analytical variables were collected. Myocardial injury, measured as maximum elevation of troponin I, was analyzed. A patient who suffered an acute coronary syndrome with ST-segment elevation due to late thrombosis from a previously implanted stent was excluded from the analysis for this variable. The CURB-65 scale was used to stratify the risk at admission [5].

A total of 324 deceased patients were included, with an age of 81 ± 10 years, 44% of them were women, and a high prevalence of hypertension (78%), dyslipidemia (58%) and diabetes (34%). Sixty-two (19%) had a history of atrial fibrillation (AF) and 40 (12%) of previous CAD.

Patients with AF vs. patients without AF were older (85 ± 6 vs. 81 ± 10 years, $p = 0.0006$). They presented with a higher prevalence of hypertension (90% vs. 75%, $p = 0.012$) and chronic kidney disease (53% vs. 37%, $p = 0.022$) (Table 1).

Patients with CAD vs. patients without CAD, in turn, exhibited a higher prevalence of hypertension (95% vs. 76%, $p = 0.006$), dyslipidemia (83% vs. 54%, $p = 0.001$) and ventricular systolic dysfunction (55% vs. 23%, $p < 0.001$). No differences were found in the presence of other comorbidities.

Most patients (88%) had a CURB-65 score of 2 or higher on admission, with no differences noted between those with and without CV comorbidity.

Fifty-two percent of the patients who presented with maximum troponin values above the limit of normality (0.05 ng/mL) and 22% presented values higher than 5 times that limit. No differences were found in the presence of troponin elevation or in its quantitative value in patients with AF or CAD.

D-dimer elevation was present in 77% of patients, being less frequent in those with AF (80% vs. 63%, $p = 0.016$), irrespective of the anticoagulation received. No differences were found regarding the presence of lymphopenia, lactate dehydrogenase or ferritin elevation.

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Table 1. Differences in baseline characteristics, laboratory findings and treatment received in patients with and without cardiovascular comorbidity.

	Patients with AF	Patients without AF	P	Patients with CAD	Patients without CAD	P
N (n, %)	62 (19%)	262 (81%)		40 (12%)	284 (88%)	
Sex (female)	24 (38%)	119 (45%)	0.341	9 (23%)	134 (47%)	0.003
Age (years)	85 ± 6	81 ± 10	0.0006	83 ± 7	81 ± 10	0.4351
Hypertension	56 (90%)	198 (75%)	0.012	38 (95%)	216 (76%)	0.006
Dyslipemia	33 (53%)	154 (59%)	0.421	33 (83%)	154 (54%)	0.001
Mellitus diabetes	22 (35%)	89 (34%)	0.852	14 (35%)	97 (34%)	0.916
Chronic renal failure	33 (53%)	97 (37%)	0.022	21 (53%)	109 (38%)	0.088
Chronic pulmonary disease	21 (34%)	77 (29%)	0.474	12 (30%)	86 (30%)	0.971
Left ventricular systolic dysfunction	19 (31%)	69 (26%)	0.514	22 (55%)	66 (23%)	< 0.001
CURB-65 ≥ 2	56 (95%)	218 (86%)	0.06	36 (95%)	238 (87%)	0.162
Maximum troponin during admission	0.06 [0.03–0.20]	0.06 [0.02–0.23]	0.953	0.06 [0.03–0.20]	0.06 [0.02–0.23]	0.806
Troponin I elevation	14 (63%)	91 (51%)	0.179	14 (63%)	91 (51%)	0.246
D-dimer elevation	27 (63%)	173 (80%)	0.016	24 (77%)	176 (77%)	0.944
LDH elevation	52 (96%)	238 (100%)	0.13	35 (97%)	255 (99%)	0.264
Ferritin elevation	32 (82%)	169 (85%)	0.702	25 (86%)	176 (84%)	0.741
Lymphopenia	53 (91%)	198 (80%)	0.053	34 (89%)	217 (81%)	0.215
Treatment:						
Hydroxych:oroquine	36 (58%)	179 (69%)	0.124	24 (60%)	191 (67%)	0.355
Antiretroviral drugs	28 (45%)	100 (38%)	0.305	14 (35%)	114 (40%)	0.533
Corticosteroids	19 (31%)	123 (47%)	0.02	18 (45%)	124 (44%)	0.873
Biological drugs (tocilizumab or interferon)	9 (15%)	51 (19%)	0.389	7 (18%)	53 (19%)	0.893
Anticoagulation			< 0.001			0.021
No anticoagulation	16 (26%)	76 (29%)		14 (35%)	78 (28%)	
Anticoagulation at prophylactic dose	8 (13%)	153 (58%)		12 (30%)	149 (52%)	
Anticoagulation at full dose	38 (61%)	33 (13%)		14 (35%)	57 (20%)	

All data are expressed as mean ± standard deviation, number (%) or median [interquartile range]; AF — atrial fibrillation; CAD — coronary artery disease; LDH — lactate dehydrogenase

Regarding treatment, patients with AF more frequently received anticoagulation at full doses compared to patients without AF (61% vs. 13%, $p < 0.001$). However, the proportion of patients within this group without full-dose anticoagulation (39%) is noteworthy. These numbers were thought to be either a result of potential drug interactions of oral anticoagulants or the critical clinical status or may be a combination of both. Furthermore, patients with AF received corticosteroids less frequently (31% vs. 47%, $p = 0.02$). There were no significant differences in the use of antiretroviral drugs or hydroxychloroquine in any of the groups.

No differences were noted regarding the number of days from admission to death, nor in the analysis of cumulative survival (Log rank $p = 0.5$ for cumulative survival of patients with AF vs. patients without AF; and Log rank $p = 0.358$ for cumulative survival of patients with CAD vs. patients without CAD).

The prevalence of AF and CAD amongst those who died in the hospital wards in our center was lower than that reported in Italy by the Istituto Superiore di Sanità (30% CAD and 24.5% AF among the deceased) [6], despite the fact that the presented population is slightly older (81 ± 10 vs. 79.5 ± 8.1 years).

Although CAD or AF patients had more comorbidities and AF patients received less corticosteroids, their risk stratification on admission and the time from symptoms onset to death were similar.

The percentage of patients in the present study sample showed troponin elevation reached 52%, much higher than the usual 8–12% amongst patients diagnosed with COVID-19 [7]. This higher frequency of troponin I elevation in the sample of deceased patients (compared to the general COVID-19 population with different outcomes), together with the absence of differences between the groups with and without CV comorbidity, seems to indicate that the development of myocardial insult depends fundamentally on the severity of the disease and not on the baseline characteristics of the patient, as it has been suggested in another series [8].

Due to the work overload caused by the pandemic, echocardiograms were not performed during the admission of most of the patients with myocardial injury defined as elevation of biomarkers. However, it would be interesting to know if this troponin elevation corresponded to impaired ventricular function, as had been described to be the case in sepsis [9].

Given the high prevalence of CV comorbidity in patients who develop severe forms of COVID-19, further research is needed on the management and prognosis of this population. Likewise, given the high incidence of myocardial insult amongst those with severe forms of the disease, the pathophysiological substrate of myocardial damage and the potential benefit of cardioprotective strategies should be studied.

Conflict of interest: None declared

References

1. Ministerio de Sanidad, Consumo y Bienestar Social. Actualización nº 258. Enfermedad por el coronavirus (COVID-19). 2020. https://www.mscbs.gob.es/en/profesionales/saludPublica/ccayes/alertasActual/nCov-China/documentos/Actualizacion_135_COVID-19.pdf (Accessed November 26th 2020).
2. European Society of Cardiology. ESC guidance for the diagnosis and management of CV disease during the COVID-19 pandemic. 2020. https://www.escardio.org/Education/COVID-19-and-Cardiology/ESC-COVID-19-Guidance (Accessed November 26th 2020).
3. Kowalik MM, Trzonkowski P, Łasińska-Kowara M, et al. COVID-19 — Toward a comprehensive understanding of the disease. Cardiol J. 2020; 27(2): 99–114, doi: 10.5603/CJ.a2020.0065, indexed in Pubmed: 32378729.
4. Gąsecka A, Filipiak KJ, Jaguszewski MJ. Impaired microcirculation function in COVID-19 and implications for potential therapies. Cardiol J. 2020; 27(5): 485–488, doi: 10.5603/CJ.2020.0154, indexed in Pubmed: 33165898.
5. Lim WS, Baudouin SV, George RC, et al. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. Thorax. 2009; 64 Suppl 3: iii1–ii55, doi: 10.1136/thx.2009.121434, indexed in Pubmed: 19783532.
6. Onder G, Rezza G, Brusaferro S. Case-Fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA. 2020; 323(18): 1775–1776, doi: 10.1001/jama.2020.4683, indexed in Pubmed: 32203977.
7. Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. Clin Chem Lab Med. 2020; 58(7): 1131–1134, doi: 10.1515/cclm-2020-0198, indexed in Pubmed: 32119647.
8. Lorente-Ros A, Monteagudo Ruiz JM, Rincón LM, et al. Myocardial injury determination improves risk stratification and predicts mortality in COVID-19 patients. Cardiol J. 2020; 27(5): 489–496, doi: 10.5603/CJ.a2020.0089, indexed in Pubmed: 32589258.
9. Kim JS, Kim M, Kim YJ, et al. Troponin testing for assessing sepsis-induced myocardial dysfunction in patients with septic shock. J Clin Med. 2019; 8(2), doi: 10.3390/jcm8020239, indexed in Pubmed: 30759844.

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RESEARCH LETTER

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Pulmonary artery and left atrial appendage anatomical relationship using electrocardiogram--gated computed tomography: An important aspect of left atrial appendage occlusion

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Atrial fibrillation (AF) is an important cause of morbidity and mortality worldwide. The Framingham study and other studies have demonstrated a fivefold increase in overall stroke risk associated with AF [1]. Vitamin K antagonists have been shown to reduce stroke or systemic thromboembolism by 64% and all-cause mortality by 26%. The newer non-vitamin K antagonist oral anticoagulants give an additional reduction effect with better adherence observed. Unfortunately, chronic anticoagulation is associated with a significant risk of major bleeding. Patients who have contraindications to anticoagulant treatment may derive benefit from left atrial appendage (LAA) occlusion. Transcatheter LAA closure has emerged as a potential alternative to oral anticoagulation in AF patients and contraindications for long-term oral anticoagulation. In recent years, it has been reported in the literature a few cases of pulmonary artery (PA) wall perforation leading to cardiac tamponade and even death following by an appendage closure using Amplatzer Cardiac Plug (ACP) or Amplatzer Amulet Occluder (AAO) [2, 3]. One of those reports revealed a close anatomical relationship between LAA and PA as the most likely explanation for this complication, based on the preprocedural cardiac computed tomography (CT) examination [4]. The aim of the present study was to assess the anatomical relationship and the distance between LAA and PA by means of electrocardiogram (ECG)-gated CT.

Data of consecutive 55 patients (mean age 63.1 ± 10.7; 30 females, 25 males), referred to coronary CT angiography were analysed. Only CT examinations comprising an entire cardiac cycle analysis were included in the study. All patients were in sinus rhythm after having fasted for 3 hours prior to the CT scan. The CT was performed during inspiration, scanning from the aortic arch to the diaphragm using a 128-row dual source CT scanner (Siemens Somatom Flash) with ECG gating. A retrospective ECG-triggered scan protocol with temporal resolution of 75 ms was used. For all patients, 80 mL of nonionic contrast medium was injected at rate of 6 mL/min using a triphasic injection protocol. The region of interest was set in the ascendens aorta to ensure adequate opacification of the left cardiac chambers. Images were reconstructed with a slice thickness of 0.6 mm both during ventricular systole and diastole. Analysis was performed using axial source images and multi-planar reformats. The following measurements were taken: the minimal distance from the LAA to the PA (minD), the distance form LAA ostium to the location of the closest proximity of LAA and PA (depth_minD), distance from the LAA to the PA measured at 10 mm (D10) and 15 mm (D15) from the LAA

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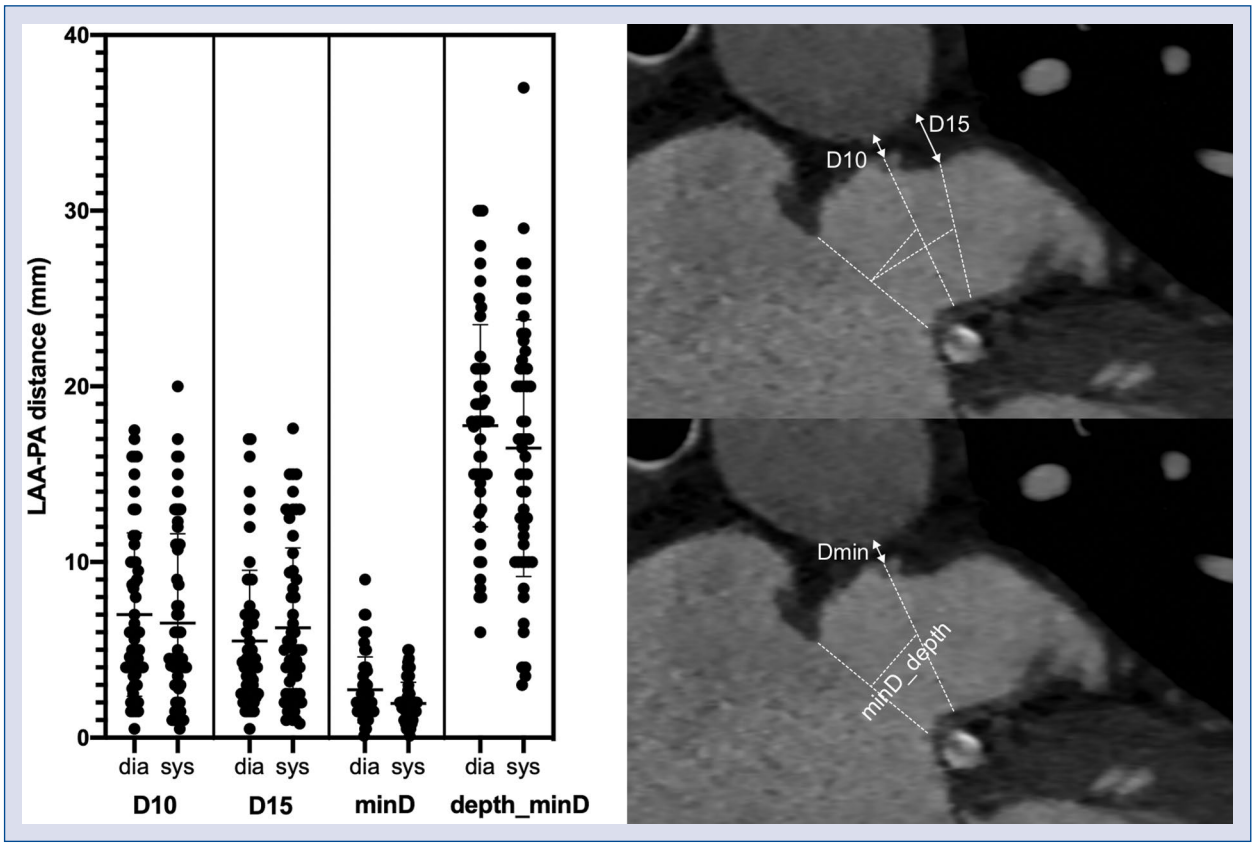

Figure 1. The distance from left atrial appendage (LAA) to the pulmonary artery (PA); D10 — the distance from the LAA to the PA measured at 10 mm from the LAA ostium; D15 — the distance from the LAA to the PA measured at 15 mm from the LAA ostium; minD — the minimal distance from the LAA to the PA; depth-minD — the distance form LAA ostium to the location of the closest proximity of LAA; dia — ventricular diastole; sys — ventricular systole.

ostium. The distance 10 mm and 15 mm were chosen as markers of a potential landing zone for LAA occluder devices. All measurements were averaged and taken by an experienced in cardiac CT radiologist and cardiologist blinded to patient clinical data. They were analysed separately during ventricular diastole and systole.

The results are presented in the Figure 1 as a scatter plot with marked mean value and standard deviation. Direct contact of proximal LAA and PA defined as the distance between their lumens < 1 mm was observed in 8 (14.5%) patients and varied from 2 (3.6%) in ventricular diastole up to 6 (10.9%) in ventricular systole in a potential landing zone.

There are several case reports describing PA perforation following LAA closure, and majority of them concerned the older ACP device. In those situations, there were suggestions that small anchors used for device stabilization in some situations may have had a higher risk of extending through the LAA wall and damaging the PA wall. In the newer AAO, some parts of the plug were redesigned including stabilizing anchors [5]. What is interesting, time from plug implantation to pulmonary perforation varied from 3 hours [6] till 6 months after the procedure [7], what brings potential risk to the patient of having cardiac tamponade out of the hospital. The current analysis of cardiac anatomy based on CT examinations, confirmed close proximity of the pulmonary trunk and potential landing zone for occluder devices in LAA in a significant number of patients. Direct contact of proximal LAA and PA defined as the distance between their lumens < 1 mm was observed in 8 (14.5%) patients. It was significantly lower when compared with results of Halkin et al. [6]. Halkin et al. [6] found direct contact between LAA and PA in 28% of patients qualified to pulmonary vein isolation and with AF. The analysis was performed during ventricular diastole [6]. In present study patients were in sinus rhythm, but patients with sinus rhythm with a history of paroxysmal AF

represent a significant number of patients referred to LAA occlusion. Good contractility of the LAA as the result of underlying sinus rhythm may play an important role in facilitating PA perforation in those patients [8]. Previous research has shown that LAA size significantly depends on loading conditions of the LA [9]. Therefore, the present results could be underestimated when compared with real-life conditions, due to the study group fasting for 3 hours prior to the CT scan. Analysis herein, underlines the importance of careful assessment of the anatomical relationships between LAA and surroundings structures before implantation of the device. Avoiding excessive oversizing seems to be an important part of the preprocedural planning in patients with direct contact between the atrial appendage and the PA. In selected patients the choice of a different closure device with smaller anchors may be the proper option [10]. Cardiac CT is an optimal method to achieve the abovementioned goals.

In conclusion, close proximity between the PA and a proximal part of the LAA occurs in a significant percentage of patients. Cardiac CT can be used to optimize risk assessment, procedure planning and device selection performed before LAA occlusion in relation to the probability of a potential PA injury.

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References

1. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke. 1991; 22(8): 983–988, doi: 10.1161/01.str.22.8.983, indexed in Pubmed: 1866765.
2. Zwirner J, Bayer R, Hädrich C, et al. Pulmonary artery perforation and coronary air embolism-two fatal outcomes in percutaneous left atrial appendage occlusion. Int J Legal Med. 2017; 131(1): 191–197, doi: 10.1007/s00414-016-1486-1, indexed in Pubmed: 27815629.
3. Suwalski G, Wojnowski A, Mizerski J, et al. Delayed pulmonary artery perforation with left atrial appendage occluder hooks. Ann Thorac Surg. 2016; 101(2): e37–e39, doi: 10.1016/j.athoracsur.2015.09.026, indexed in Pubmed: 26777968.
4. Hanazawa K, Brunelli M, Saenger J, et al. Close proximity between pulmonary artery and left atrial appendage leading to perforation of the artery, tamponade and death after appendage closure using cardiac plug device. Int J Cardiol. 2014; 175(2): e35–e36, doi: 10.1016/j.ijcard.2014.04.260, indexed in Pubmed: 24838059.
5. Grygier M, Wojakowski W, Smolka G, et al. [Left atrial appendage occlusion: consensus document of Association of Cardiovascular Interventions and Heart Rhythm Section of Polish Cardiac Society]. Kardiol Pol. 2018; 76(3): 677–697, doi: 10.5603/KP.a2018.0057, indexed in Pubmed: 29441512.
6. Halkin A, Cohen C, Rosso R, et al. Left atrial appendage and pulmonary artery anatomic relationship by cardiac-gated computed tomography: Implications for late pulmonary artery perforation by left atrial appendage closure devices. Heart Rhythm. 2016; 13(10): 2064–2069, doi: 10.1016/j.hrthm.2016.07.015, indexed in Pubmed: 27430898.
7. Wang E, Lin WW, Xu XF, et al. Delayed presentation of pulmonary artery perforation by an Amulet left atrial appendage closure device. BMJ Case Rep. 2018; 2018, doi: 10.1136/bcr-2018-227098, indexed in Pubmed: 30391926.
8. Chun KR, Bordignon S, Urban V, et al. Left atrial appendage closure followed by 6 weeks of antithrombotic therapy: a prospective single-center experience. Heart Rhythm. 2013; 10(12): 1792–1799, doi: 10.1016/j.hrthm.2013.08.025, indexed in Pubmed: 23973952.
9. Korsholm K, Berti S, Iriart X, et al. Expert recommendations on cardiac computed tomography for planning transcatheter left atrial appendage occlusion. JACC Cardiovasc Interv. 2020; 13(3): 277–292, doi: 10.1016/j.jcin.2019.08.054, indexed in Pubmed: 31678086.
10. Asmarats L, Rodés-Cabau J. A look at current and emerging nonpharmacologic stroke prevention therapies. Spectrum Devices Percutaneous Left Atrial Appendage Occlusion. 2018; 12(3): 34–39.

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IMAGE IN CARDIOVASCULAR MEDICINE

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Pulmonary valve and atrial lead infective endocarditis: A successful non-surgical treatment of significant vegetation with pulmonary complications

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A 64-year-old male with congestive heart failure and an implantable cardioverter-defibrillator in place with a 3-month history of febrile, fatigue, cough, and weight loss was referred with a suspicion of cardiac device-related infective endocarditis which was confirmed with a blood culture (*Streptococcus gallolyticus*).

Transthoracic echocardiography (TTE) and transesophageal echocardiography showed reduced left ventricular ejection fraction (25%), moderate tricuspid regurgitation with no features of vegetation, floating masses on the pulmonary valve (PV) causing functional PV stenosis with severe regurgitation (Vmax 2.1 m/s, PHT 228 ms; Fig. 1A, B), and an oscillating mass on the atrial lead (Fig. 1C). Cardiac computed tomography (CT) revealed a widening of the pulmonary trunk with emboli at the bifurcation. The patient received empirical (vancomycin, gentamicin) and subsequently targeted (vancomycin, ciprofloxacin) antibiotic therapy, followed by hardware removal with transvenous lead extraction (Libertor locking stylet and Byrd Sheath; Cook Vacsular Inc, USA; Fig. 1E). The patient had not qualified for PV surgery due to high procedural risk.

After 3 weeks, peripheral pulmonary embolism was still observed in an angio-CT, along with lesions suspected for malignancy in both lungs (Fig. 1F), which was excluded by high-resolution CT and bronchofiberoscopy. At 3-month followup there was no fever, inflammatory markers were low, pulmonary lesions were resolved and TTE showed stable PV vegetation size.

We described a rare case of lead-related infective endocarditis with co-existing PV vegetations and no tricuspid valve involvement. Complete hardware removal and antimicrobial therapy turned out to be a sufficient treatment option. Large vegetations with numerous pulmonary emboli can be effectively treated non-surgically if a patient is hemodynamically stable.

Conflict of interest: None declared

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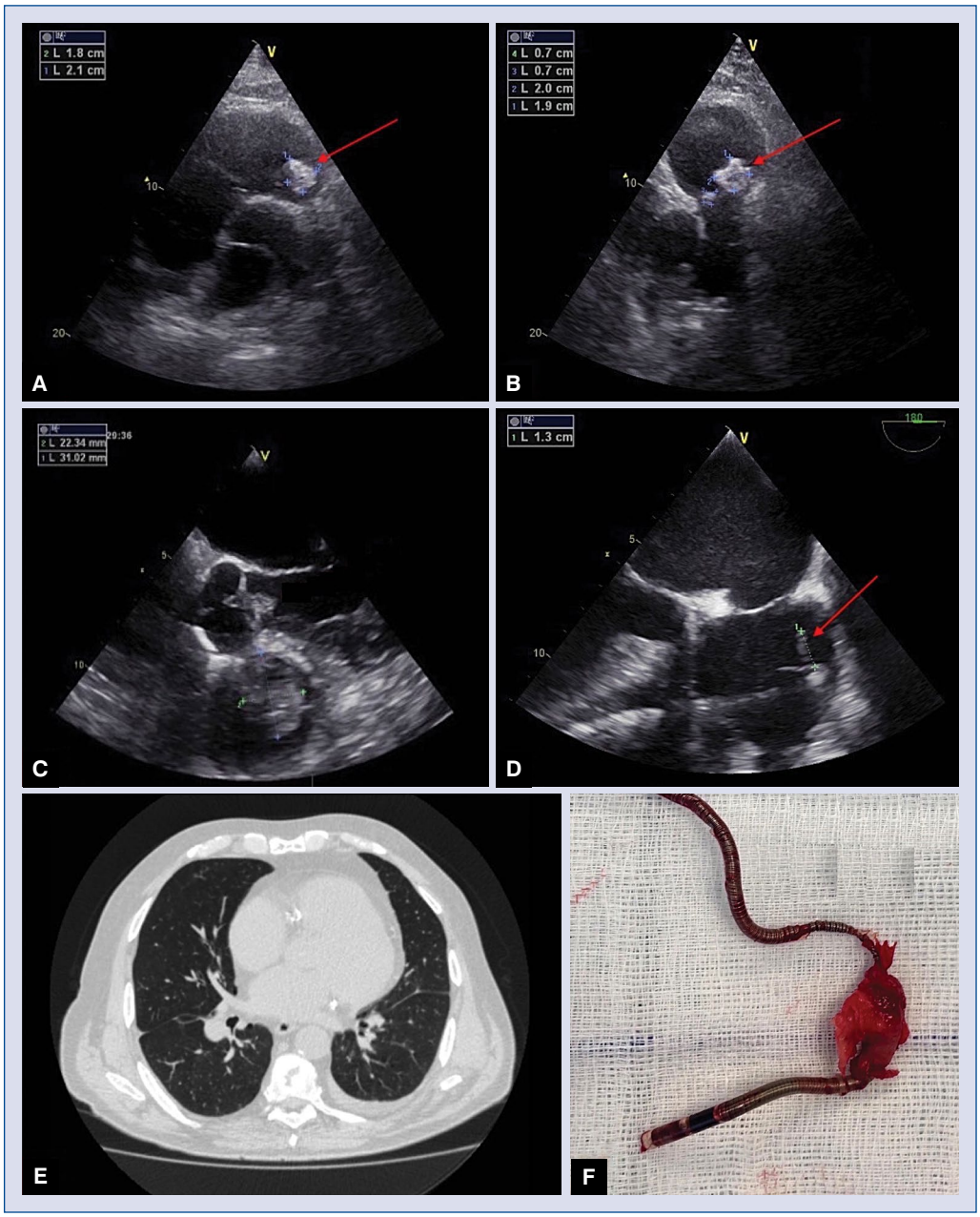

Figure 1. A. Two-dimensional transthoracic echocardiography (2D TTE) parasternal short-axis view at the level of the great vessels: vegetation is visible at the pulmonary artery valve (main pulmonary artery focused projection); **B.** 2D TTE focused on the pulmonary valve; **C.** Large vegetation (22 × 31 mm in size) in right ventricular outflow tract seen in transesophageal echocardiography (TEE); **D.** TEE showing atrial lead vegetation; **E.** Computed tomography scan showing multiple bilateral lung opacities mimicking malignancy that turned out to be inflammatory; **F.** Atrial lead vegetation (intraoperative photography).

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IMAGE IN CARDIOVASCULAR MEDICINE

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Bail-out use of Wiggle wire for stuck wire in dissection lumen under optical frequency domain imaging

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An 80-year-old woman with cerebral infarction complained of chest pain at rest. Coronary angiography (CAG) revealed severe stenosis in the proximal-mid right coronary artery (RCA) (Fig. 1A). The RCA lesion was then dilated with a cutting balloon (2.75/10 mm) at 12 atm (Fig. 1B). After predilation, optical frequency domain imaging (OFDI) was attempted; however, we could not cross the OFDI catheter through the lesion. After rechecking the CAG findings in detail, we recognized the wire was running outside the RCA curve (Fig. 1C, D). Several attempts were made to advance another guidewire along the inner side of the RCA curve; however, the second guidewire tended to pass through the same route as the first guidewire. We then managed to advance a crooked guidewire (Wiggle, Abbott Vascular) with a double-lumen catheter backup into the distal RCA, and ascertained the Wiggle wire located at the lesser-curvature side on fluoroscopy (Fig. 1E, F). Subsequent OFDI through the Wiggle wire confirmed the Wiggle wire in the true lumen and the first wire in the dissection lumen (Fig. 1G–I). In addition, there was a calcified flap (white arrow, Fig. 1I) at the proximal entry of the dissection lumen, which might interfere with the OFDI catheter crossing through the first wire. A drug-eluting stent (3.0/40 mm) was implanted through the Wiggle wire without difficulty (Fig. 1J). After postdilations, repeat OFDI depicted full expansion of the stent despite residual dissection lumen (Fig. 1K), and final CAG showed an acceptable result (Fig. 1L).

Conflict of interest: None declared

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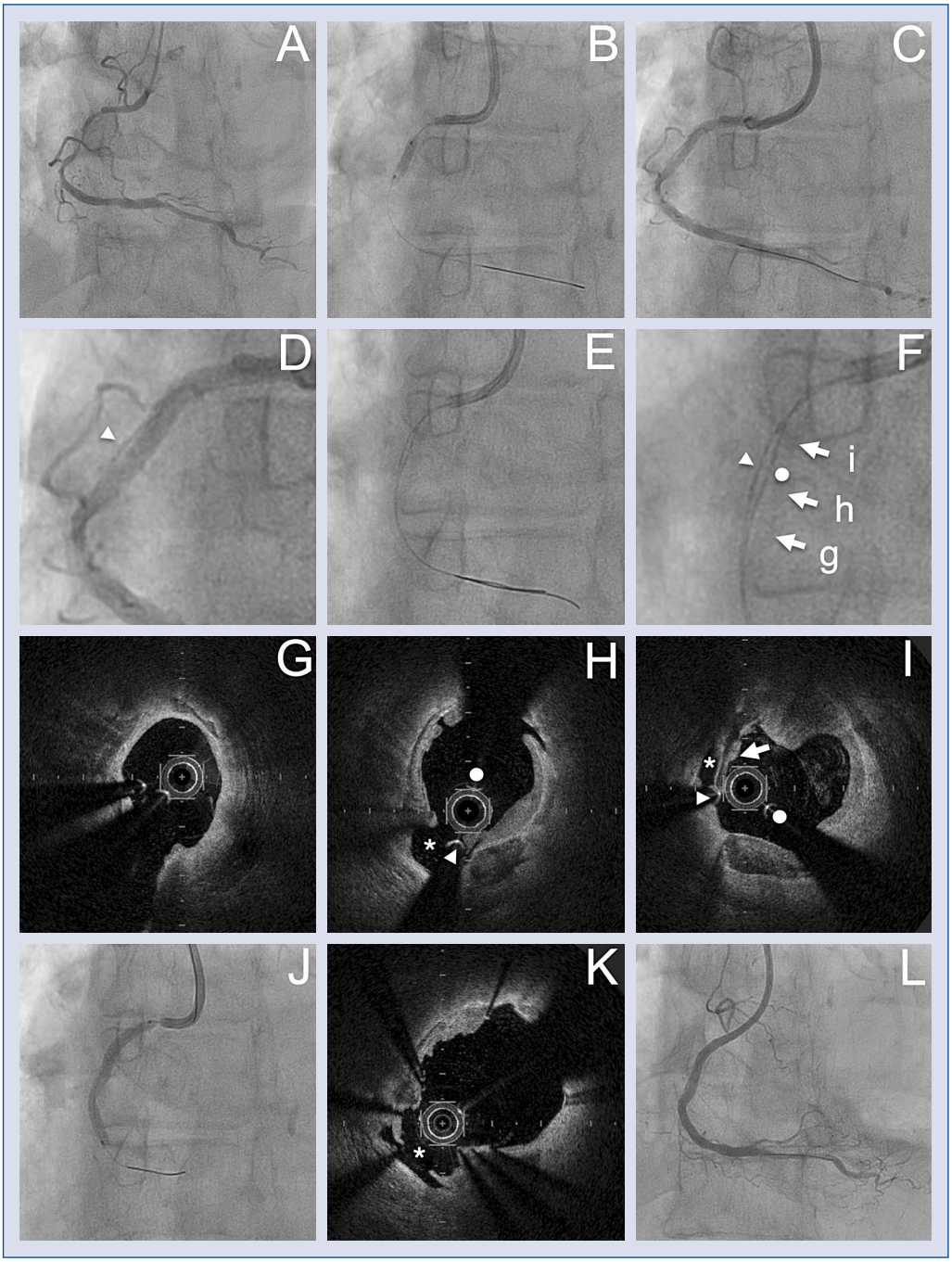

Figure 1. A. Coronary angiography (CAG; left anterior oblique view) showed a significant stenosis in the proximal--mid right coronary artery (RCA); **B.** Predilation with a cutting balloon; **C, D** (magnified image). CAG after predilations depicted the first wire (white arrowhead) located at the outer side of the RCA curve; **E, F** (magnified image). The Wiggle wire (white circle) positioned at the inner side compared with the first wire (white arrowhead) on fluoroscopy. Optical frequency domain imaging (OFDI) images after crossing the Wiggle wire (panels G–I corresponding to arrows in panel F) confirmed the Wiggle wire (white circle) and the first wire (white arrowhead) located in the true lumen and in the dissection lumen (white asterisk), respectively; **G.** Bifurcation of the right ventricular branch; **H.** Mid part of the dissection lumen; **I.** Calcified flap (white arrow) at proximal entry site of the dissection lumen; **J.** Implantation of a drug-eluting stent; **K.** Optimal stent expansion/apposition and residual dissection lumen (white asterisk) on final OFDI; **L.** Final CAG.

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IMAGE IN CARDIOVASCULAR MEDICINE

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Multiple embolic events and ruption of the central venous catheter in a patient with atrial fibrillation

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A 46-year-old male with a previous history of persistent atrial fibrillation was hospitalized due to signs of intestinal occlusion. An urgent computed tomography (CT) angiography demonstrated superior mesenteric artery occlusion. Due to signs of intestine gangrenous subtotal a small intestine resection was made. On account of short bowel syndrome, a central venous catheter for parenteral nutrition was placed. After discharge the patient decided to discontinue antithrombotic treatment and after a few weeks presented with ischemic stroke with left-sided hemiplegia.

After 2 months the patient was admitted to hospital due to symptoms of acute lower left limb ischemia. An extremity CT angiography revealed complete occlusion of the left superficial femoral artery and popliteal artery (Fig. 1A). A chest X-ray and CT performed during qualification for surgery revealed the presence of a fractured fragment of a central venous catheter in the right atrium (Fig. 1C, D). Using the right femoral vein approach, a fragment of the catheter was removed from the right atrium (Fig. 1E, F). Subsequently, percutaneous tromboaspiration of the thrombus from the left femoral artery, intraarterial fibrinolysis, and percutaneous transluminal angioplasty of the left popliteal artery were performed (Fig. 1B).

The incidence of cerebral embolism among patients with atrial fibrillation is 1.92/100 person-years and the incidence of systemic embolic events is 0.23/100 person-years (58% in the lower extremities, 31% in the visceral-mesenteric system, 11% in the upper extremities). Reported herein, is a rare case of 3 subsequent embolic events (cerebral, mesenteric and lower extremities arteries) during 3 months.

Conflict of interest: None declared

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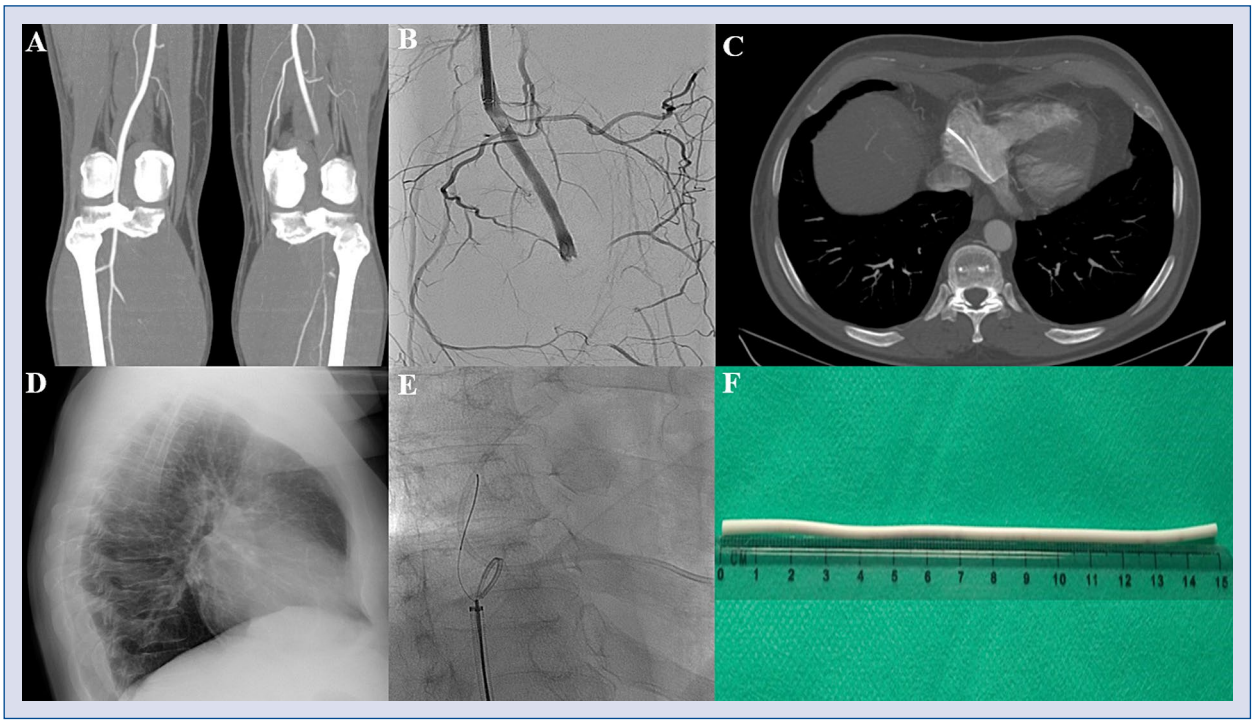

Figure 1. A. Computed tomography angiography — complete occlusion of the left popliteal artery; **B.** Angiography--complete occlusion of the left popliteal artery; **C.** Chest computed tomography-fractured fragment of a central venous catheter in the right atrium; **D.** Chest X-ray-fractured fragment of a central venous catheter in the right atrium; **E.** Removal of the fragment of the central venous catheter; **F.** Removed fragment of the central venous catheter.

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Walking on a thin line between potent platelet inhibition for myocardial infarction and risk of hemorrhagic complications. Tirofiban induced subconjunctival hemorrhage

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Tirofiban, an antagonist of the glycoprotein IIb/IIIa receptor, is indicated for the treatment of acute coronary syndrome (ACS), in combination with heparin. Tirofiban has been shown to decrease the rate of death in myocardial infarction and refractory ischemia patients.

Herein is presented the case of a 41-year-old active smoker, transferred to our hospital for anterior ST-segment elevation myocardial infarction (Fig. 1A). Loading doses of acetylsalicylic acid (500 mg), prasugrel (60 mg) and 5000 UI of heparin were administered during transfer. Coronary angiogram demonstrated plaque rupture in the proximal left anterior descending artery (LAD) (Fig. 1B), associated with heavy thrombus burden visualized on optical coherence tomography (Fig. 1C). A high dose bolus of tirofiban (25 μg/kg) followed by a continuous infusion (0.1 μg/kg/min) was administered and percutaneous coronary intervention of LAD was performed with two drug eluting stents (Fig. 1D). Three hours after initiation of tirofiban administration, the patient developed bilateral severe subconjunctival hemorrhage (Fig. 1E) associated with blurred vision, prompting interruption of tirofiban perfusion. In this setting, de-escalation of P2Y12 inhibitor therapy was performed, prasugrel was switched for clopidogrel. The patient thrombocyte count was within normal range. Cardiac and ophthalmologic clinical evolution were favorable. According to available research, this is the first report of severe subconjunctival hemorrhage occurring as a complication of tirofiban administration.

Potent platelet inhibition for patients presenting ACS has consistently been associated with a reduction of major adverse cardiac events. According to the most recent European Society of Cardiology revascularization guidelines, dual antiplatelet therapy associating acetylsalicylic acid and ticagrelor or prasugrel is recommended for patients presenting ACS. Glycoprotein IIb/IIIa inhibitors can be used as an adjunctive therapy during percutaneous coronary intervention in cases of high thrombus burden. Hemorrhagic complications need to be addressed with caution, justifying individualized tailored antiplatelet therapy adaptations when warranted.

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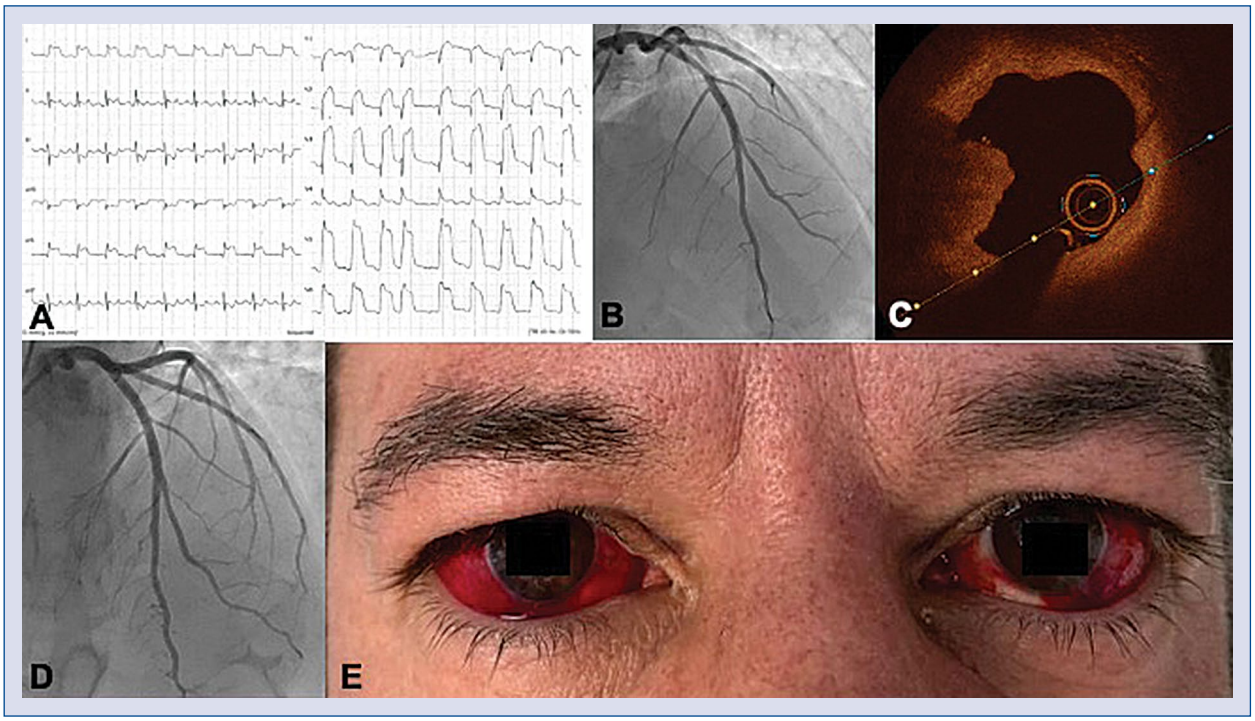

Figure 1. A. Admission electrocardiogram demonstrating anterior ST-segment elevation myocardial infarction; **B.** Coronary angiogram demonstrating a hazy lesion in the proximal left anterior descending artery (LAD); **C.** Intracoronary imaging by means of optical coherence tomography, demonstrating plaque rupture on the level of the proximal LAD; **D.** Coronary angiogram after percutaneous coronary intervention of the LAD with two drug eluting stents; **E.** Bilateral severe subconjunctival hemorrhage, developed 3 hours after initiation of tirofiban administration.

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LETTER TO THE EDITOR

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Post-COVID-19 heart syndrome

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This paper was guest edited by Prof. Anna Tomaszuk-Kazberuk

To date, 92,111,432 of coronavirus disease 2019 (COVID-19), cases were confirmed worldwide and the number of asymptomatic patients remains largely unknown. There are emerging retrospective data implying that the COVID-19 infection has long-term complications, although there is still a paucity of large, prospective trials to investigate the true prevalence of these complications. Besides lung inflammation, myocardial injury is a typical COVID-19-related phenomenon, present in 20–30% of patients and contributing to 40% of deaths [1]. However, myocardial injury in the course of COVID-19 may be even more prevalent [2].

An autopsy study including 39 patients who had died due to COVID-19 showed features of myocardial abnormalities in patients, in whom the cardiac complications had not previously been diagnosed [3]. Histopathologic evaluation of the myocardium did not fulfil the criteria of acute myocarditis, but in 62% patients (24/39) the presence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was confirmed within the myocardium. Among them, 67% of patients (16/24) demonstrated evidence of myocardial virus replication, as defined by a virus load above 1,000 virus copies per μg RNA. In addition, the cytokine response panel consisting of 6 proinflammatory genes was increased in those 16 patients, compared with patients without SARS-CoV-2 in the heart, but this had not (yet) been associated with an influx of inflammatory cells. As assessed using in situ hybridization, interstitial cells and infiltrating macrophages, but not cardiomyocytes were the most probable virus localization within the myocardium [3].

The silent but progressive myocardial injury in the course of COVID-19 might contribute to the development of heart failure and other cardiovascular complications following virtual recovery. This hypothesis is confirmed by the results of another study, where the authors performed cardiac magnetic resonance in 100 COVID-19 convalescents at 2 to 3 months following the acute phase of the disease [4]. Persistent cardiac involvement was observed in 78 (78%) patients and ongoing myocardial inflammation in 60 (60%) patients, which was independent of the severity and overall course of the acute disease and the time from the original diagnosis. Moreover, increased troponin concentration was demonstrated in 76 (76%) of patients without any clinically overt signs and symptoms of myocardial dysfunction.

In another study including 139 healthcare workers with confirmed past SARS-CoV-2 infec-

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tion, cardiac magnetic resonance features of myocarditis were observed in 37% of the participants at a median of 10 weeks after infection [5]. Importantly, only half of the participants had symptoms of COVID-19, demonstrating that cardiac sequelae might be associated with an altered or delayed immune response, and that even asymptomatic patients and/or patients not aware of the infection may suffer from serious cardiovascular complication in the longer perspective.

The long-term health consequences of COVID-19 were also evaluated in 1733 patients with COVID-19 in Wuhan, China [6]. Six months following hospital discharge, the main persisting symptoms were fatigue or muscle weakness (1038/1655, 63%), sleep difficulties (437/1655, 26%) and anxiety or depression (367/1733, 23%). In addition, 76% of patients (1265/1655) declared at least one persisting symptom. In addition, 13% (107/822) participants without acute kidney injury and with normal estimated glomerular filtration rate (eGFR more than 90 mL/min/1.73 m^2) in the acute phase had eGFR less than 90 mL/min/1.73 m^2 at follow-up, implying the COVID-19-induced kidney injury [6]. Although cardiovascular imaging was not a part of this study, it is likely that at least a part of patients who reported the fatigue and muscle weakness might have developed cardiac dysfunction.

Altogether, emerging results from the hitherto studies indicate that SARS-CoV-2 infection may be associated with the long-term extrapulmonary organ manifestations, with cardiac involvement being one of the most prevalent. The long-term impact of COVID-19-associated cardiac dysfunction remains unknown. Hence, it is relevant to evaluate the presence of the potential myocardial damage in patients with a history of SARS-CoV-2 infection, even if the course was asymptomatic. Moreover, it is crucial to focus on the group of patients who were not aware of the infection, as the post-COVID-19 heart syndrome might be the first indicator of past infection [7]. In the societal perspective, there is a risk that SARS-CoV-2 might further increase the cardiovascular morbidity and mortality [8]. Further long-term studies are required to determine the incidence and clinical course of myocardial damage caused by COVID-19 in order to implement a routine cardiac imaging screening that allows for the treatment of post-COVID-19 heart syndrome.

Conflict of interest: None declared

References

1. Akhmerov A, Marbán E. COVID-19 and the Heart. Circ Res. 2020; 126(10): 1443–1455, doi: 10.1161/CIRCRESAHA.120.317055, indexed in Pubmed: 32252591.
2. Gąsecka A, Filipiak KJ, Jaguszewski MJ. Impaired microcirculation function in COVID-19 and implications for potential therapies. Cardiol J. 2020; 27(5): 485–488, doi: 10.5603/CJ.2020.0154, indexed in Pubmed: 33165898.
3. Lindner D, Fitzek A, Bräuninger H, et al. Association of cardiac infection with SARS-CoV-2 in confirmed COVID-19 autopsy cases. JAMA Cardiol. 2020; 5(11): 1281–1285, doi: 10.1001/jamacardio.2020.3551, indexed in Pubmed: 32730555.
4. Puntmann VO, Carerj ML, Wieters I, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). JAMA Cardiol. 2020; 5(11): 1265–1273, doi: 10.1001/jamacardio.2020.3557, indexed in Pubmed: 32730619.
5. Eiros R, Barreiro-Perez M, Martin-Garcia A, et al. Pericarditis and myocarditis long after SARS-CoV-2 infection: a cross-sectional descriptive study in health-care workers. , doi: 10.1101/2020.07.12.20151316.
6. Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet. 2021; 397(10270): 220–232, doi: 10.1016/s0140-6736(20)32656-8.
7. Lorente-Ros A, Monteagudo Ruiz JM, Rincón LM, et al. Myocardial injury determination improves risk stratification and predicts mortality in COVID-19 patients. Cardiol J. 2020; 27(5): 489–496, doi: 10.5603/CJ.a2020.0089, indexed in Pubmed: 32589258.
8. Li G, Saguner AM, An J, et al. Cardiovascular disease during the COVID-19 pandemic: Think ahead, protect hearts, reduce mortality. Cardiol J. 2020; 27(5): 616–624, doi: 10.5603/CJ.a2020.0101, indexed in Pubmed: 32789839.