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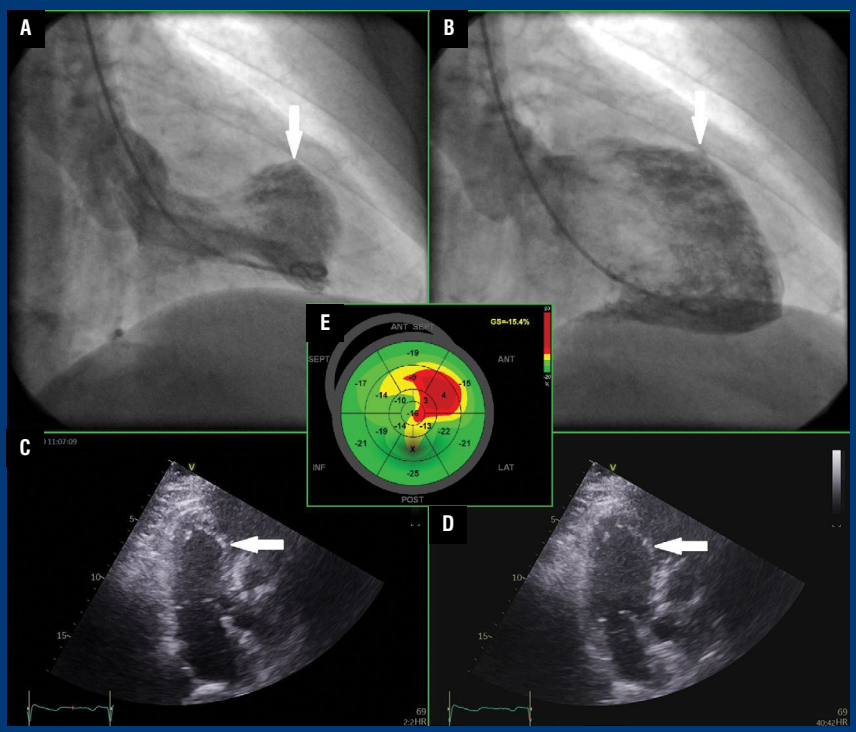

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Characteristics and outcomes of in-hospital cardiac arrest in COVID-19. A systematic review and meta-analysis

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Abstract

Background: *The purpose herein, was to perform a systematic review of interventional outcome studies in patients with in-hospital cardiac arrest before and during the coronavirus disease 2019 (COVID-19) pandemic period.*

Methods: *A meta-analysis was performed of publications meeting the following PICOS criteria: (1) participants, patients > 18 years of age with cardiac arrest due to any causes; (2) intervention, cardiac arrest in COVID-19 period; (3) comparison, cardiac arrest in pre-COVID-19 period; (4) outcomes, detailed information for survival; (5) study design, randomized controlled trials, quasi-randomized or observational studies comparing cardiac arrest in COVID-19 and pre-COVID-19 period for their effects in patients with cardiac arrest.*

Results: *Survival to hospital discharge for the pre-pandemic and pandemic period was reported in 3 studies (n =1432 patients) and was similar in the pre-pandemic vs. the pandemic period, 35.6% vs. 32.1%, respectively (odds ratio [OR] 1.72; 95% confidence interval [CI] 0.81–3.65; p = 0.16; I^2 = 72%). Return of spontaneous circulation was reported by all 4 studies and were also similar in the pre and during COVID-19 periods, 51.9% vs. 48.7% (OR 1.27; 95% CI 0.78–2.07; p = 0.33; I^2 = 71%), respectively. Pooled analysis of cardiac arrest recurrence was also similar, 24.9% and 17.9% (OR 1.60; 95% CI 0.99–2.57; p = 0.06; I^2 = 32%) in the pre and during COVID-19 cohorts. Survival with Cerebral Performance Category 1 or 2 was higher in pre vs. during pandemic groups (27.3 vs. 9.1%; OR 3.75; 95% CI 1.26–11.20; p = 0.02). Finally, overall mortality was similar in the pre vs. pandemic groups, 65.9% and 67.2%, respectively (OR 0.67; 95% CI 0.33–1.34; p = 0.25; I^2 = 76%).*

Conclusions: *Compared to the pre-pandemic period, in hospital cardiac arrest in COVID-19 patients was numerically higher but had statistically similar outcomes.* (Cardiol J 2021; 28, 4: 503–508)

Key words: coronavirus disease 2019, SARS-CoV-2, pandemic, in-hospital cardiac arrest, cardiopulmonary resuscitation, outcome

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Introduction

In December 2019 the coronavirus disease (COVID-19) emerged in Wuhan, China and spread rapidly throughout the world causing a pandemic [1]. As of March 2021, there were over 126 million confirmed cases and over 2.7 million deaths worldwide [2].

Clinically, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for COVID-19, manifests with wide variability ranging from being asymptomatic to severe respiratory failure and death. An estimated 14% of patients with COVID-19 require hospitalization, with 2% requiring intensive care [3]. While coexisting conditions, such as, hypertension, diabetes, cardiovascular disease, obesity, chronic obstructive pulmonary disease and chronic renal failure have been associated with poor prognosis [4], respiratory failure is the leading cause of admission to the intensive care unit (ICU) [5]. Further, studies show that the mortality rate in the ICU can be greater than 35% [6], and the leading cause of such high mortality is in-hospital cardiac arrest (IHCA) [7].

To understand the role of COVID-19 on outcomes of IHCA, we designed a systematic review of studies in adults during versus pre-pandemic periods of patients who suffered from cardiac arrest.

Methods

The study was performed following the recommendation Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for reporting systematic reviews and meta-analyses [8]. Before starting the study, there was agreement on the analysis methods and the inclusion and exclusion criteria to be used. Because of its nature, this study was exempt from an institutional board review.

Inclusion and exclusion criteria

Studies included in this meta-analysis met the following PICOS criteria: (1) Participants: patients > 18 years of age with cardiac arrest due to any causes, (2) Intervention: cardiac arrest in COVID-19 period, (3) Comparison: cardiac arrest in pre-COVID-19 period, (4) Outcomes: detailed information for survival, (5) Study design: randomized controlled trials, quasi-randomized or observational studies comparing cardiac arrest during and before the COVID-19 period for their effects in patients with cardiac arrest. Studies were excluded if they were reviews, case reports, conference or poster abstracts, or articles not containing original data.

Search strategy

A computerized search of the Medline (PubMed), Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, Web of Science was performed from inception to February 2nd, 2021. Titles and abstracts were screened by two authors independently (A.G. and M.P.). All retrieved articles were reviewed by two authors (J.S. and M.C.). Any disagreement was resolved through consensus or, if necessary, by discussion with a third author (L.S.).

The search was performed using the following terms: "cardiac arrest" OR "CA" OR "heart arrest" OR "circulation arrest" OR "cardiopulmonary resuscitation" OR "CPR" OR "in-hospital cardiac arrest" OR "IHCA" OR "return of spontaneous circulation" OR "ROSC" OR "cardiac ventric* fibrillation" OR "heart ventric* fibrillation" OR "pulseless ventric* tachycardia" OR "asysto*" OR "pulseless electrical activity" OR "PEA" AND "SARS-CoV-2" OR "COVID-19". Bibliographies of retrieved articles were manually checked for additional references to identify all eligible studies and achieve minimal publication bias. Only full articles in the English language were considered. All references were saved in an EndNote (EndNote, Inc., Philadelphia, PA, USA) library that was used to identify duplicates.

Data extraction

Information was recorded on study characteristics and demographics such as authors, publication year, inclusion and exclusion criteria, primary outcome, findings, as well as per group sample size and outcomes. Two reviewers (A.G., M.J.J.) independently abstracted data, which a third investigator (L.S.) independently verified. Authors of articles were contacted when data were missing or were reported in a format that did not allow statistical analysis. Care was taken to avoid inclusion of data from duplicate publications. In the case of suspected data discrepancies, the relevant author was contacted directly. Moreover, each reviewer performed independent data abstraction, using a standardized predefined data collection form.

Quality assessment

Two investigators (A.G. and L.S.) independently extracted individual study data and evaluated the studies for risk of bias. Any disagreements were discussed and resolved in a consensus meeting

with the third reviewer (M.J.J.). The ROBINS-I tool (Risk of Bias in Non-randomized Studies — of Interventions) was used to assess the quality of studies [9]. Robvis application was used to for visualize risk-of-bias assessments [10]. The scale has seven main domains (confounding, participant selection, classification of interventions, deviation from interventions, missing data, outcome measurement, and selection of reported results) and assigns one point for each of four judgements, which are rated as critical, serious, moderate or low (**Suppl. Fig. S3 and Fig. S4**).

Outcomes

The following outcomes were evaluated in the analysis, based on the consensus among content experts in our group with regard to important outcomes. The primary outcome was survival to hospital discharge, or 30 days (SHD), whichever came first. Secondary outcomes were return of spontaneous circulation (ROSC), recurrence of cardiac arrest, survival with favorable neurologic status (defined as a survival with Cerebral Performance Category [CPC] 1 or 2), and overall mortality.

Statistical analysis

Statistical analysis was performed using Review Manager software (v.5.4, Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark). The Mantel-Haenszel method was used to analyze dichotomous outcomes, and results are reported as odds ratios (ORs) with 95% confidence interval (CI). Continuous outcome differences were analyzed using an inverse variance model with a 95% CI, and values are reported as mean difference. 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. [11].

All p values were two-tailed and considered significant if < 0.05. Heterogeneity was quantified in each analysis by the tau-squared and I-squared statistics. Heterogeneity was detected with the chi-squared test with n – 1 degree of freedom, which was expressed as I^2. Values of $I^2 > 50\%$ and $> 75\%$ were considered to indicate moderate and significant heterogeneity among studies, respectively.

Results

Study characteristics

A total of 4 studies [12–15], reporting on 1609 patients (n = 788 pre and n = 821 pandemic patients), met all inclusion/exclusion criteria (Table 1;

Table 1. Characteristics of the in-hospital cardiac arrest patients in the pre-pandemic vs. pandemic period in the included trials.

Trials	Country	Study design	Period	Number of patients	Age, years (mean ± SD)	Sex (male) Number/ /Total (%)	Shockable initial rhythm Number/ /Total (%)	ROSC Number/ /Total (%)	Survival to discharge Number/ /Total (%)
Miles et al. 2020	USA	Cohort study	Pre-pandemic	117	66.3 ± 3.5	67 (57.3%)	10/112 (8.9%)	66 (56.4%)	15 (12.8%)
			Pandemic	125	66.8 ± 3.2	82 (65.6%)	4/117 (3.4%)	45 (36.0%)	4 (3.2%)
Roedl et al. 2021	Germany	Retrospective analysis of data prospectively recorded data	Pre-pandemic	84	69.8 ± 3.7	60 (71.4%)	15/84 (17.9%)	65 (77.4%)	NR
			Pandemic	93	67.8 ± 3.5	60 (64.5%)	27/93 (29.0%)	77 (82.8%)	NR
Sultanian et al. 2021	Sweden	Observational registry-based study	Pre-pandemic	532	70.1 ± 18.2	351 (66.0%)	138 (25.9%)	251 (47.2%)	214 (40.2%)
			Pandemic	548	67.8 ± 18.9	327 (60.0%)	116 (21.2%)	257 (46.9%)	214 (39.1%)
Yuriditsky et al. 2020	USA	Single-center retrospective study	Pre-pandemic	55	68.9 ± 5.9	33 (60.0%)	9 (16.4%)	27 (49.1%)	23 (41.8%)
			Pandemic	55	69.8 ± 3.8	48 (87.3%)	6 (10.9%)	21 (38.2%)	16 (29.1%)

NR — not reported; ROSC — return of spontaneous circulation; SD — standard deviation

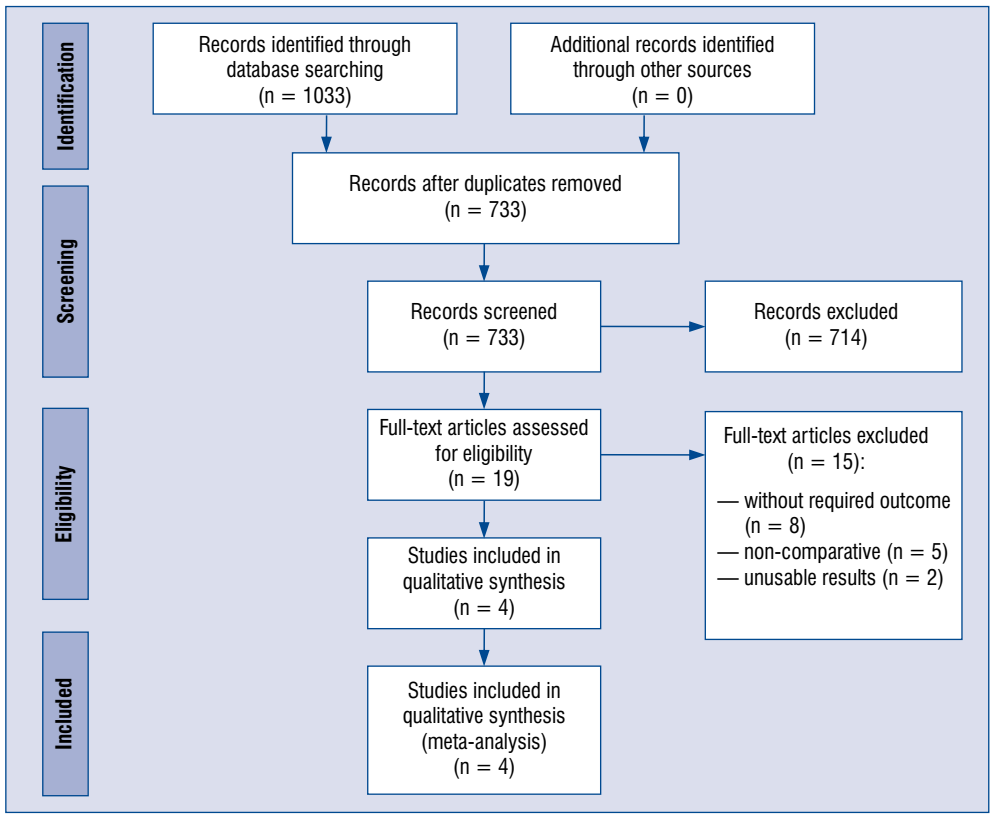

Figure 1. Flow diagram showing stages of database searching and study selection as per Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) guideline.

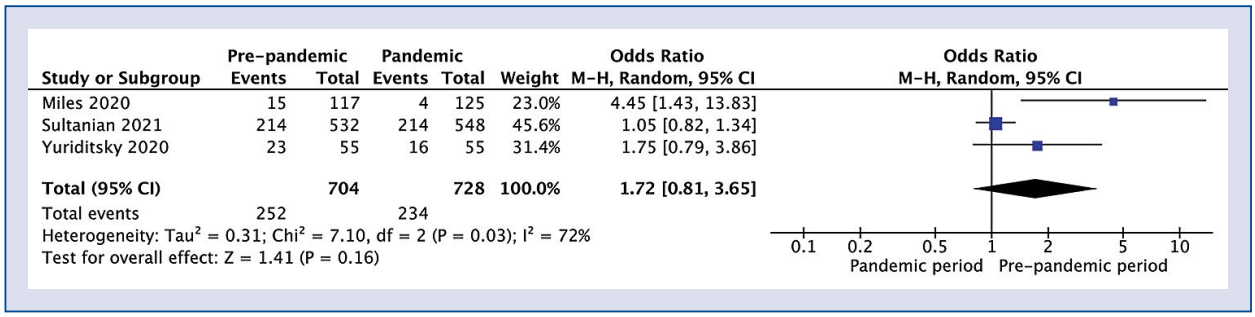

Figure 2. Forest plot of return of survival to hospital discharge between pre-pandemic versus pandemic group. The center of each square represents the weighted odds ratios for individual trials, and the corresponding horizontal line stands for a 95% confidence interval (CI). The diamonds represent pooled results.

Suppl. Table S1). The PRISMA flowchart (Fig. 1) summarizes the outcomes of the search strategy.

Outcomes pre-pandemic vs. pandemic period

A pooled analysis of all outcomes is presented on Figure 2 and **Supplemental Figures S1 and S2.** SHD for the pre-pandemic and pandemic period was reported in 3 studies (n = 1432 patients). It occurred at a numerically higher, but a statistically similar, rate in the pre-pandemic vs. the pandemic period, 35.6% vs. 32.1%, respectively (OR 1.72; 95% CI 0.81–3.65; p = 0.16; I^2 = 72%). ROSC was reported by all 4 studies, with a similar numerically higher but statistically similar relationship, 51.9% vs. 48.7% (OR 1.27; 95% CI 0.78–2.07; p = 0.33; I^2 = 71%), for the pre and during COVID-19 periods, respectively (**Supplementary digital file**). Pooled analysis of cardiac found an arrest recurrence of

24.9% and 17.9% (OR 1.60; 95% CI 0.99–2.57; p = 0.06; I^2 = 32%) in the pre and during COVID-19 cohorts, respectively. Survival with CPC 1 or 2 was reported only by Yuriditsky et al. [15] and was significantly higher in pre-pandemic group compared with pandemic group (27.3 vs. 9.1%; OR 3.75; 95% CI 1.26–11.20; p = 0.02). Overall mortality in pre-pandemic vs. pandemic group was 65.9% and 67.2%, respectively (OR 0.67; 95% CI 0.33–1.34; p = 0.25; I^2 = 76%).

Outcomes in pandemic period

Only 1 study was found, Sultanian et al. [14], that compared IHCA outcomes in pandemic period between COVID-19 and non-COVID-19 patients. In this study SHD between COVID-19 and non-COVID-19 patients was 25.0% vs. 41.8% (OR 0.46; 95% CI 0.26–0.83; p = 0.01). In the case of COVID-19 patients there was a significantly lower ROSC rate compared with non-COVID-19 patients (30.5% vs. 52.6%, respectively; OR 0.40; 95% CI 0.23–0.69; p = 0.001). Ultimately, the overall mortality in the COVID-19 patients was 75.0% and was significantly higher than that in non-COVID-19 patients — 59.3% (OR 2.06; 95% CI 1.15–3.69; p = 0.02). Finally, overall mortality in the present analysis was similar in the pre vs. pandemic groups, 65.9% and 67.2%, respectively (OR 0.67; 95% CI 0.33–1.34; p = 0.25; I^2 = 76%).

Discussion

According to available research, this is the first meta-analysis comparing characteristics and outcomes of IHCA before and during the COVID-19 pandemic. The primary outcome of the study was to measure the survival to hospital discharge or 30 days, whichever came first, although it was expected that mortality rates would be higher during the pandemic, it was found that the survival rates were similar to the pre-pandemic period. There are possible explanations of this phenomenon. During the pre-pandemic time the vast majority of the IHCA happened in the ICU [16], commonly the result of complications from cardiovascular disease, while during the pandemic a shift of IHCA occurring in the standard ward as a result of the pulmonary inflammatory state and fibrosis of the lung tissue [14] was observed [13].

Sustained ROSC was found, defined as stable circulation for at least 20 min [13] was similar in the pre-pandemic period. Interestingly in the cohort by Miles et al. [12] the pre-pandemic group was characterized by much higher ROSC. Although ROSC is generally a positive predictor of survival [17], Sheth et al. [18] presented data which showed that although all patients with COVID-19 who suffered cardiac arrest and achieved ROSC did not achieve SHD.

Consistent with the current primary outcome, a insignificant trend was found (p = 0.06) of lower recurrence of cardiac arrest in the pandemic group. This finding is also likely the result of the different etiology of cardiac arrests in the pre and during pandemic periods. In the pre pandemic period the vast majority of IHCA was caused by the underlying cardiac diseases [19] as opposed to the respiratory background in the COVID-19 era.

In his paper Yuriditsky et al. [15] assessed the functional status using the CPC. This score ranges from 1 (good cerebral performance) to 5 (brain death), with CPC 1 and 2 generally categorized as good neurological outcome and 3 to 5 as poor [20]. It was reported that the pre pandemic group had a statistically significant higher survival with CPC 1 or 2 amounting to 27.3% vs. 9.1% in the COVID-19 cohort. A possible explanation may lie in the location of IHCA resuscitation. In the pre-pandemic period, many resuscitations occurred in an ICU, where early identification and greater resources may result in better outcomes than general ward resuscitations that are found later and may have fewer resources.

When comparing COVID vs. non-COVID, there was lower SHD in COVID patients, 25.0% vs. 41.8%, respectively [14]. This may be because COVID patients were less likely to have a cardiac cause of the arrest, and a respiratory cause was more likely. Such a high discrepancy might be the result of the burden of critical illness with a higher likelihood or requiring ICU admission, invasive mechanical ventilation, vasopresors or renal replacement therapies than the non-COVID-19 cohort [21, 22].

Sultanian et al. [14] also reports statistically significantly lower ROSC rate for COVID-19 positive cohort with only 7.6% of patients presenting with the shockable rhythm. Overall mortality among the COVID-19 patients was 75.0% and was significantly higher than the 59.3% that occurred in non-COVID-19 patients.

Limitations of the study

Although a limitation of the present study was the strict inclusion criteria, which allowed for the inclusion of only 4 papers, it did insure a high quality of results in over 1600 patients. A second limitation is the focus on general epidemiologic

findings, which does not allow for the pinpointing of the specific risk factors that could be used as a guideline for the selection of high-risk patients.

Conclusions

It was found that the IHCA before and during the COVID-19 pandemic had numerically higher but statistically similar outcomes.

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Conflict of interest: None declared

References

1. Rodriguez-Morales AJ, Bonilla-Aldana DK, Balbin-Ramon GJ, et al. History is repeating itself: probable zoonotic spillover as the cause of the 2019 novel coronavirus epidemic. Infez Med. 2020; 28(1): 3–5, indexed in Pubmed: 32009128.
2. 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.
3. Stokes EK, Zambrano LD, Anderson KN, et al. Coronavirus Disease 2019 Case Surveillance - United States, January 22-May 30, 2020. MMWR Morb Mortal Wkly Rep. 2020; 69(24): 759–765, doi: 10.15585/mmwr.mm6924e2, indexed in Pubmed: 32555134.
4. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020; 8(5): 475–481, doi: 10.1016/S2213-2600(20)30079-5, indexed in Pubmed: 32105632.
5. Ayaz A, Arshad A, Malik H, et al. Risk factors for intensive care unit admission and mortality in hospitalized COVID-19 patients. Acute Crit Care. 2020; 35(4): 249–254, doi: 10.4266/acc.2020.00381, indexed in Pubmed: 33172229.
6. Armstrong RA, Kane AD, Kursumovic E, et al. Mortality in patients admitted to intensive care with COVID-19: an updated systematic review and meta-analysis of observational studies. Anaesthesia. 2021; 76(4): 537–548, doi: 10.1111/anae.15425, indexed in Pubmed: 33525063.
7. Shao F, Xu S, Ma X, et al. In-hospital cardiac arrest outcomes among patients with COVID-19 pneumonia in Wuhan, China. Resuscitation. 2020; 151: 18–23, doi: 10.1016/j.resuscitation.2020.04.005, indexed in Pubmed: 32283117.
8. Moher D, Liberati A, Tetzlaff J, et al. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009; 6(7): e1000097, doi: 10.1371/journal.pmed.1000097.
9. Sterne JAc, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016; 355: i4919, doi: 10.1136/bmj.i4919, indexed in Pubmed: 27733354.
10. McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. Res Synth Methods. 2021; 12(1): 55–61, doi: 10.1002/jrsm.1411, indexed in Pubmed: 32336025.
11. 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.
12. Miles JA, Mejia M, Rios S, et al. Characteristics and outcomes of in-hospital cardiac arrest events during the COVID-19 pandemic: a single-center experience from a new york city public hospital. Circ Cardiovasc Qual Outcomes. 2020; 13(11): e007303, doi: 10.1161/CIRCOUTCOMES.120.007303, indexed in Pubmed: 32975134.
13. Roedl K, Söffker G, Fischer D, et al. Effects of COVID-19 on in-hospital cardiac arrest: incidence, causes, and outcome — a retrospective cohort study. Scand J Trauma Resusc Emerg Med. 2021; 29(1): 30, doi: 10.1186/s13049-021-00846-w, indexed in Pubmed: 33557923.
14. Sultanian P, Lundgren P, Strömsöe A, et al. Cardiac arrest in COVID-19: characteristics and outcomes of in- and out-of-hospital cardiac arrest. A report from the swedish registry for cardiopulmonary resuscitation. Eur Heart J. 2021; 42(11): 1094–1106, doi: 10.1093/eurheartj/ehaa1067, indexed in Pubmed: 33543259.
15. Yuriditsky E, Mitchell OJL, Brosnahan SB, et al. Clinical characteristics and outcomes of in-hospital cardiac arrest among patients with and without COVID-19. Resusc Plus. 2020; 4: 100054, doi: 10.1016/j.resplu.2020.100054, indexed in Pubmed: 33403368.
16. Perman SM, Stanton E, Soar J, et al. American Heart Association's Get With the Guidelines® — Resuscitation (formerly the National Registry of Cardiopulmonary Resuscitation) Investigators. Location of In-Hospital Cardiac Arrest in the United States-Variability in Event Rate and Outcomes. J Am Heart Assoc. 2016; 5(10): e003638, doi: 10.1161/JAHA.116.003638, indexed in Pubmed: 27688235.
17. Wampler DA, Collett L, Manifold CA, et al. Cardiac arrest survival is rare without prehospital return of spontaneous circulation. Prehosp Emerg Care. 2012; 16(4): 451–455, doi: 10.3109/10903127.2012.695435, indexed in Pubmed: 22834854.
18. Sheth V, Chishti I, Rothman A, et al. Outcomes of in-hospital cardiac arrest in patients with COVID-19 in New York City. Resuscitation. 2020; 155: 3–5, doi: 10.1016/j.resuscitation.2020.07.011, indexed in Pubmed: 32707146.
19. Moskowitz A, Holmberg MJ, Donnino MW, et al. In-hospital cardiac arrest: are we overlooking a key distinction? Curr Opin Crit Care. 2018; 24(3): 151–157, doi: 10.1097/MCC.0000000000000505, indexed in Pubmed: 29688939.
20. Cummins RO, Chamberlain DA, Abramson NS, et al. Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest: the Utstein Style. A statement for health professionals from a task force of the American Heart Association, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, and the Australian Resuscitation Council. Circulation. 1991; 84(2): 960–975, doi: 10.1161/01.cir.84.2.960, indexed in Pubmed: 1860248.
21. 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.
22. Smereka J, Szarpak L, Gadalla F, et al. Ethical and organizational dilemmas related to the treatment of COVID-19 patients. Disaster Emerg Med J. 2020, doi: 10.5603/demj.a2020.0030.

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Body mass index and long-term outcomes in patients with chronic total occlusions undergoing retrograde endovascular revascularization of the infra-inguinal lower limb arteries

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Abstract

Background: *The aim of the present study is to assess the relationship between body mass index (BMI) and long-term clinical outcomes in retrograde endovascular recanalization (ER) regarding chronic total occlusions (CTOs) of the infra-inguinal lower limb arteries.*

Methods: *The study included patients who underwent retrograde ER of CTOs localized in superficial, popliteal or below-the-knee arteries. During follow-up, major adverse cardiac and cerebrovascular and major adverse lower limb events (MALE) were evaluated. MALE was defined as amputation, target lesion re-intervention, target vessel re-intervention and surgical treatment.*

Results: *The study included 405 patients at the mean age of 67.2 ± 10.4. The authors divided the overall group of patients according to BMI into < 25 (n = 156, 38.5%) and ≥ 25 kg/m^2 (n = 249, 61.5%), and then into < 30 (n = 302, 75.8%) and ≥ 30 kg/m^2 (n = 103, 24.2%). During the average follow-up 1,144.9 ± 664.3 days, the mortality rate was higher in the group of patients with BMI < 25 kg/m^2 (10.5% vs. 5.3%, p = 0.051), and in the group of patients with BMI < 30 kg/m^2 (8.7% vs. 2.9%, p = 0.048). The comparison of Kaplan-Meier curves revealed borderline differences when assessing months to death for the BMI < 25 kg/m^2 (p = 0.057) and BMI < 30 kg/m^2 (p = 0.056) grouping variables.*

Conclusions: *Obese and overweight patients undergoing CTO ER of the lower limb arteries from retrograde access are related to lower death rates during long-term follow-up.* (Cardiol J 2021; 28, 4: 509–518)

Key words: lower limb atherosclerosis, chronic total occlusions, retrograde access, clinical outcomes, body mass index

Introduction

Intermittent claudication is becoming a more frequent symptom due to population aging and progress in the effective treatment of other diseases such as ischemic heart disease or respiratory disorders, which result in reduced exercise tolerance. This, consequently causes a more frequent clinical image of peripheral arterial disease (PAD) symptoms. Endovascular revascularization (ER)

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is the treatment of choice in a majority of patients with symptomatic PAD. In the case of patients diagnosed with chronic total occlusion (CTO) of the lower limb arteries and failure of ER with antegrade access, retrograde access is a treatment option that can be offered prior to referring a patient to a vascular surgeon or possible optimal medical therapy. Several publications estimating long-term results of regular ER of PAD patients have been published [1, 2]. The relationship between body mass index (BMI) and mortality rate in patients treated with percutaneous interventions has been widely investigated in patients with stable coronary artery disease (CAD), acute coronary syndromes and heart failure [3–6]. The relationship between BMI and mortality in patients with PAD, especially those undergoing ER, is scarcely investigated and there are only a few publications available in this area [7–9].

Therefore, the aim of the present study is to evaluate the relationship between BMI and the long-term results of endovascular treatment from retrograde access in patients with PAD.

Methods

Study population

This study was planned as a prospective observational study of consecutive patients who underwent retrograde recanalization of CTO localized in the superficial femoral artery, popliteal artery or below-the-knee arteries. At two experienced and cooperating centers, all consecutive patients were enrolled after at least one unsuccessful antegrade recanalization of CTO who qualified for the retrograde approach. Each patient was also qualified for endovascular treatment after consultation by a vascular surgeon. The main factors disqualifying patients from surgical revascularization were anatomical reasons (lack of vessel circumference in the course of atherosclerosis), morphological (narrow and winding peripheral vessels) or poor clinical condition and high perioperative risk. Antegrade failure was defined as the inability to wire the distal part of the vessel behind the occlusion via the access site, located in the contralateral artery or proximal to the CTO lesion. The inability to wire the distal part of the CTO was both due to a failure to penetrate the lesion or because of a failure to return to the arterial lumen after subintimal recanalization in selected cases with suitable anatomy and morphology of target lesions. According to the local protocol, patients were screened for concomitant diseases, risk factors, and medication prior to the procedure. In all patients before the procedure, the ankle–brachial index was examined and severity of PAD was assessed according to Rutherford and/or Fontaine scale. The decision regarding retrograde recanalization and access site was based on prior angiography. The procedure of retrograde recanalization was performed under local anesthesia and required two access sites: antegrade and retrograde. Both, proximal and distal punctures were done under the guidance of vascular ultrasound and/or fluoroscopy. The choice of the type of antegrade access site was determined by many factors, including anatomical conditioning, type of vascular lesions (dissemination, calcifications, length), technical possibilities (having sufficiently long catheters), type of occlusions, its length and probability of blood flow restoration. For the proximal access site, the contralateral femoral artery was usually used, and 6 Fr vascular sheaths belonged to the most used. The distal access site was usually chosen in the reconnection area of the artery (needle: 12–15 mm, 21 G). In case of instability of distal puncture, 4 Fr vascular sheaths were needed to obtain support during the procedure. In a few cases, the distal access site was also used for the revascularization of more peripheral parts of the artery. The hydrophilic 0.035'' guidewire was used for the antegrade access site. Occlusions were crossed from the retrograde access site with a non-hydrophilic 0.018'' guidewire. After crossing the occlusion with a wire via the retrograde approach, pre-dilatation with a balloon catheter was performed. Stent implantation was based on the decision of the operator. After the procedure, the distal sheet was removed immediately, and the proximal one was maintained for up to 4 h when the femoral artery was punctured, which was conditioned by unfractionated heparin use. Due to dissection, in some cases, the balloon inflations were performed from both ante- and retrograde access (kissing balloon technique) to tear the dissection and facilitate capturing the wire with the diagnostic catheter. The first antegrade puncture site was used to visualize the vessel during the retrograde access procedure and was defined as the angiography first access site. In some patients, due to anatomical, morphological or technical problems, it was not possible to reach the distal part of the artery treated with retrograde access for angiography, and these patients had to undergo puncture of another artery which was defined as the second, third or fourth antegrade angiography access site. In periprocedural treatment, all patients received double antiplatelet therapy: acetylsalicylic acid

75 mg — permanently, and clopidogrel 75 mg for 3 months, a high dose of statin and according to a local protocol, low-molecular-weight heparin for 4 weeks. In the long-term follow-up, which lasted on average 1,144.9 ± 664.3 days, patients were evaluated for major adverse cardiac and cerebrovascular events (MACCE) as well as major adverse limb events (MALE). Data were collected between 2006 and 2016. In this paper, MACCE were predefined as death, stroke/transient ischemic attack, myocardial infarction, percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). MALE was defined as amputation, target lesion re-intervention, target vessel re-intervention and surgical treatment. Due to shortages in the available database, the level of amputation was not highlighted in the presented publication and alike high-, mid- and low-amputations, they were included in the term of overall amputation rate. The protocol complied with the Declaration of Helsinki, and all participants provided written informed consent before enrollment.

Ethical approval and consent to participate

All participants read the purpose statement of the investigation and signed informed consent. This study was approved by the local Research Ethics Committee and was therefore performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

Statistical analysis

Categorical variables are presented as numbers and percentages. Continuous variables are expressed as mean ± standard deviation or median and interquartile range. Normality was assessed using the Shapiro-Wilk test. Equality of variance was assessed using Levene's test. Differences between groups were compared using the Student's or Welch's t-test depending on the equality of variances for normally distributed variables. The Mann-Whitney U test was applied in cases of continuous variables without normal distribution. Categorical variables were compared via the Pearson χ^2 or the Fisher exact test if 20% of cells had a count less than 5. Ordinal variables were compared with the Cochran-Armitage trend test. To analyze survival rate in selected risk groups, Kaplan-Meier curves were drawn. The log-rank statistic was used to test the differences in the outcome between groups. All statistical analyses were performed with JMP®, Version 13.1.0 (SAS Institute INC., Cary, NC, USA).

Results

General characteristics

In total, 405 patients were included in the study. There were 156 (38.5%) patients with BMI < < 25 kg/m^2 and 302 (74.6%) patients with BMI < < 30 kg/m^2. In both groups, patients with lower BMI were older when stratified for BMI < 25 kg/m^2 (68.3 ± 11.1 vs. 66.51 ± 9.8, p = 0.09) and also for BMI < 30 kg/m^2 (68.2 ± 10.7 vs. 64.4 ± 8.9, p = 0.006), compared to patients with a higher BMI. Patients with higher BMI suffered from diabetes more often when stratified for BMI ≥ 25 kg/m^2 (35.9% vs. 59%, p < 0.0001) and for BMI ≥ 30 kg/m^2 (43% vs. 70.9%, p < 0.0001), as well as from CAD when classified for BMI ≥ 25 kg/m^2 (35.3% vs. 45.4%, p = 0.04), and for BMI ≥ 30 kg/m^2 (38.7% vs. 49.5%, p = 0.055). A general characterization of all groups assessed in the current study is presented in Table 1.

Clinical presentation

When stratified for BMI < 25 kg/m^2, the clinical stage of ischemic changes before angioplasty was more advanced in patients with lower BMI, both when using the Rutherford (p = 0.04) and Fontaine classifications (p = 0.01), however, when stratified for BMI < 30 kg/m^2, there were no significant differences in clinical presentation of ischemia before angioplasty between patients with lower and higher BMI (p = 0.6 and p = 0.96). This is presented in Table 2.

Angiography and procedural indices

According to the Trans-Atlantic Inter Society Consensus (TASC II) classification, the authors did not observe any significant differences between patients with lower and higher mean BMI values when stratified for BMI < 25 and < 30 kg/m^2. In general, lesions tended to occur longer in patients with lower BMI in both stratifications, and reached statistical significance for the common femoral artery when stratified for BMI < 25 kg/m^2 (13.4 ± ± 21.8 mm vs. 8 ± 13.8 mm, p = 0.04) and the popliteal artery when stratified for BMI < 30 kg/m^2 (51.2 ± 52.5 mm vs. 34.3 ± 42.9 mm, p = 0.02). Angiographic indices are presented in Table 2.

Clinical endpoints

During the 120-month-long follow-up period, the authors did not observe significant differences in reintervention or amputation rates, the frequency of lower extremity bypass surgery and/

Table 1. General characteristics and clinical presentation.

	Body mass index		P	Body mass index		P
	< 25 kg/m^2	≥ 25 kg/m^2		< 30 kg/m^2	≥ 30 kg/m^2	
General characteristics						
Age [years]	68.3 ± 11.1	66.5 ± 9.8	0.09^W	68.2 ± 10.7	64.4±8.9	0.006^U
Gender, males	91 (58.3%)	162 (65.1%)	0.17^P	192 (63.6%)	61 (59.2%)	0.43^P
COPD	22 (14.1%)	21 (8.4%)	0.07^P	35 (11.6%)	8 (7.8%)	0.27^P
Hypertension	141 (90.4%)	232 (93.2%)	0.31^P	274 (90.7%)	99 (96.1%)	0.08^P
Diabetes	56 (35.9%)	147 (59%)	< 0.0001^P	130 (43%)	73 (70.9%)	< 0.0001^P
Renal failure	23 (14.7%)	44 (17.7%)	0.44^P	46 (15.2%)	21 (20.4%)	0.22^P
CAD	55 (35.3%)	113 (45.4%)	0.04^P	117 (38.7%)	51 (49.5%)	0.055^P
Hyperlipidemia	15 (88.2%)	27 (90%)	1.0^F	30 (88.2%)	12 (92.3%)	1.0^F
Stroke/TIA	13 (8.3%)	12 (4.8%)	0.15^P	22 (7.3%)	3 (2.9%)	0.11^P
Smoking	57 (55.3%)	68 (50%)	0.41^P	92 (50.5%)	33 (57.9%)	0.33^P
Prior PTA	36 (23.1%)	59 (23.7%)	0.88^P	67 (22.2%)	28 (27.2%)	0.3^P
Prior bypass	36 (23.1%)	59 (23.7%)	0.63^P	33 (10.9%)	10 (9.7%)	0.72^P
Clinical presentation before angioplasty						
Rutherford classification:			0.04^{CA}			0.6^{CA}
0	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
1	13 (8.3%)	18 (7.2%)		26 (8.6%)	5 (4.8%)	
2	16 (10.3%)	43 (17.3%)		46 (15.2%)	13 (12.6%)	
3	18 (11.5%)	47 (18.9%)		43 (14.2%)	22 (21.4%)	
4	36 (23.1%)	52 (20.9%)		66 (21.8%)	22 (21.4%)	
5	28 (17.9%)	29 (11.6%)		43 (14.2%)	14 (13.6%)	
6	45 (28.8%)	60 (24.1%)		78 (25.8%)	27 (26.2%)	
Fontaine scale:			0.01^{CA}			0.96^{CA}
2a	16 (10.3%)	21 (8.4%)		32 (10.6%)	5 (4.8%)	
2b	33 (21.1%)	95 (38.1%)		90 (29.8%)	38 (36.9%)	
3	34 (21.8%)	47 (18.9%)		60 (19.9%)	21 (20.4%)	
4	73 (46.8%)	86 (34.5%)		120 (39.7%)	39 (37.9%)	

CA — Cochran–Armitage test for trend; CAD — coronary artery disease; F — Fisher's exact test; P — Pearson's chi-squared test; S — Student's t-test; U — Mann-Whitney U test; PTA — percutaneous transluminal angioplasty; TIA — transient ischemic attack

or stroke as well as transient ischemic attack rates between patients with higher and lower BMI when stratified for < 25 kg/m^2 and < 30 kg/m^2. Nonetheless, death rate at the end of the follow-up period was higher in patients with lower BMI when stratified for BMI < 25 kg/m^2 (10.5% vs. 5.3%, p = 0.051) and for BMI < 30 kg/m^2 (8.7% vs. 2.9%, p = 0.048). This is presented in Table 3. However, the long-rank test considered months to death for grouping variable BMI < 25 kg/m^2 revealed higher death rates in the group of patients with lower BMI, but without statistical significance (p = 0.057). Also, analysis for grouping variable BMI < 30 kg/m^2 demonstrated a significant tendency without statistical significance (p = 0.056). This is presented in Figure 1A and B as well as Table 4. The long-rank test reflecting months to death for grouping variable BMI did not reveal significant differences (p = 0.26) after division into six subgroups (underweight: BMI < 18 kg/m^2, normal-weight: 18 kg/m^2 ≤ BMI < 25 kg/m^2; overweight: 25 kg/m^2 ≤ BMI < 30 kg/m^2; class 1 obesity: 30 kg/m^2 ≤ BMI < 35 kg/m^2; class 2 obesity: 35 kg/m^2 ≤ BMI < 40 kg/m^2; class 3 obesity: BMI ≥ 40 kg/m^2). Nevertheless, during the first 12 months of follow-up, mortality rate was highest in the subgroup of underweight and class 3 obesity patients. This is presented in Table 5 and Figure 2.

Table 2. Procedural indices: angiography, culprit artery and lesion.

	Body mass index		P	Body mass index		P
	< 25 kg/m²	≥ 25 kg/m²		< 30 kg/m²	≥ 30 kg/m²	
TASC II:			0.25[CA]			0.76[CA]
A	23 (16.8%)	41 (19%)		53 (20.1%)	11 (12.4%)	
B	23 (16.8%)	56 (25.9%)		52 (19.7%)	27 (30.3%)	
C	36 (26.3%)	34 (15.7%)		55 (20.8%)	15 (16.8%)	
D	55 (40.1%)	39 (37.9%)		104 (39.4%)	36 (40.4%)	
Treated leg:			0.48[P]			0.3[P]
Left	73 (46.8%)	126 (50.6%)		149 (49.3%)	50 (48.5%)	
Left, right	4 (2.6%)	10 (4%)		8 (2.6%)	6 (5.8%)	
Right	79 (50.6%)	113 (45.4%)		145 (48%)	47 (45.6%)	
Angiography first access site:			0.32[P]			0.18[P]
Brachial	15 (10.6%)	15 (6.8%)		24 (8.9%)	6 (6.4%)	
Femoral	73 (51.4%)	128 (57.7%)		142 (52.4%)	59 (63.4%)	
Radial	54 (38%)	79 (35.6%)		105 (38.7%)	28 (30.1%)	
Angiography number of access sites:			0.58[CA]			0.23[CA]
1	116 (81.7%)	178 (79.5%)		214 (78.7%)	80 (85.1%)	
2	23 (16.2%)	42 (18.7%)		52 (19.1%)	13 (13.8%)	
3	3 (2.1%)	2 (0.9%)		5 (1.8%)	0 (0%)	
4	0 (0%)	2 (0.9%)		1 (0.4%)	1 (1.1%)	
Angiography first access side:			0.8[P]			0.15[P]
Right	100 (70.4%)	155 (69.2%)		191 (70.2%)	64 (68.1%)	
Left	42 (29.6%)	69 (30.8%)		81 (29.8%)	30 (31.9%)	
Iliac artery — SL	35 (24.6%)	42 (18.9%)	0.19[P]	58 (21.2%)	19 (20.9%)	0.94[P]
Deep femoral artery — SL	12 (8.4%)	9 (4.1%)	0.08[P]	19 (7%)	2 (2.2%)	0.09[P]
Common femoral artery:						
Tortuosity: slight	9 (7.9%)	9 (5.5%)	0.43[P]	14 (6.7%)	4 (5.9%)	1.0[F]
Chronic total occlusion	10 (8.7%)	4 (2.4%)	0.02[P]	11 (5.2%)	3 (4.4%)	1.0[F]
Calcification:						
slight	23 (20.2%)	34 (20.9%)	0.11[CA]	46 (22%)	11 (16.2%)	0.2[CA]
severe	11 (9.6%)	6 (3.7%)		14 (6.70%)	3 (4.4%)	
Lesion length [mm]	13.4 ± 21.8	8 ± 13.8	0.04[U]	10.7 ± 18.5	8.6 ± 15.1	0.42[U]
Superficial femoral artery:						
Tortuosity:						
slight	52 (38%)	67 (31.9%)	0.42[CA]	91 (34.9%)	28 (32.6%)	0.65[CA]
severe	3 (2.2%)	6 (2.9%)		7 (2.7%)	2 (2.3%)	
Chronic total occlusion	63 (45%)	103 (47.7%)	0.61[P]	122 (45.9%)	44 (48.9%)	0.61[P]
Calcification:						
extreme	1 (0.73%)	1 (0.5%)	0.65[CA]	2 (0.8%)	0 (0%)	0.46[CA]
severe	30 (21.9%)	53 (25.2%)		64 (24.5%)	19 (22.1%)	
slight	59 (43.1%)	86 (40.9%)		109 (41.8%)	36 (41.9%)	
Lesion length [mm]	107 ± 97	74.8 ± 36.3	0.97[U]	106.9 ± 98.6	108.2 ± 95.9	0.92[U]
Popliteal artery — lesion length	52.4 ± 54.9	43.6 ± 47.7	0.24[U]	51.2 ± 52.5	34.3 ± 42.9	0.02[U]
Tibio-fibular trunk — SL	41 (28.9%)	52 (23.4%)	0.24[P]	74 (27.1%)	19 (20.9%)	0.23[P]
Tibialis anterior artery — SL	70 (49.3%)	105 (47.3%)	0.7[P]	133 (48.7%)	42 (46.1%)	0.67[P]
Peroneal artery — SL	64 (45.1%)	79 (35.6%)	0.07[P]	112 (41%)	31 (34.1%)	0.23[P]
Tibialis posterior artery — SL	86 (60.6%)	106 (47.7%)	0.01[P]	133 (48.7%)	42 (46.1%)	0.67[P]
Contrast volume [mL]	106.5 ± 67.8	119.4 ± 77.4	0.12[U]	110.9 ± 70.7	124.5 ± 82.4	0.19[U]
Hospitalization time [days]	5.44 ± 4.6	5 ± 4.7	0.11[U]	5.4 ± 4.8	4.7 ± 4.3	0.2[U]
Intraprocedural complications	4 (2.8%)	11 (4.9%)	0.32[P]	12 (4.4%)	3 (3.2%)	0.76[F]
Major vascular complications	5 (3.52%)	5 (2.2%)	0.51[F]	9 (3.3%)	1 (1.1%)	0.46[F]
Minor vascular complications	17 (12%)	26 (11.6%)	0.9[P]	33 (12.1%)	10 (10.6%)	0.7[P]

CA — Cochran–Armitage test for trend; F — Fisher's exact test; P — Pearson's chi-squared test; SL — significant lesion; TASC — Trans-Atlantic Inter Society Consensus; U — Mann-Whitney U test

Table 3. Study endpoints.

	Body mass index		P	Body mass index		P
	< 25 kg/m²	≥ 25 kg/m²		< 30 kg/m²	≥ 30 kg/m²	
Re-PTA	47 (30.72%)	72 (29.15%)	0.73[P]	89 (29.97%)	30 (29.13%)	0.87[P]
Days to Re-PTA	130.6 ± 125.4	196.9 ± 339.6	0.47[U]	151.3 ± 202.2	228.2 ± 427.7	0.07[U]
Stroke/TIA	2 (1.3%)	5 (2%)	0.71[F]	5 (1.68%)	2 (1.94%)	1[F]
Days to stroke/TIA	66.5 ± 47.4	130.6 ± 113.9	0.69[U]	150.8 ± 92.1	16 ± 12.7	0.052[U]
Death	16 (10.5%)	13 (5.3%)	0.051[P]	26 (8.7%)	3 (2.9%)	0.048[F]
Days to death	249.4 ± 360.7	537.8 ± 896.9	0.86[U]	310.5 ± 472.5	969.7 ± 1650.9	0.69[U]
Amputation	24 (15.7%)	30 (12.4%)	0.35[P]	38 (12.8%)	16 (16.2%)	0.4[P]
Days to amputation	87.6 ± 103.7	60.9 ± 87.4	0.36[U]	76.1 ± 102.1	64.9 ± 78	0.84[U]
Lower extremity bypass	6 (4.3%)	9 (4.1%)	0.93[P]	10 (3.7%)	5 (5.6%)	0.54[F]
Days to lower extremity bypass	48.5 ± 69.1	95.3 ± 90.8	0.19[U]	128.8 ± 91.2	76.6 ± 83.6	0.15[U]

F — Fisher's exact test; P — Pearson's chi-squared test; PTA — percutaneous transluminal angioplasty; S — Student's t-test; TIA — transient ischemic attacks; U — Mann-Whitney U test

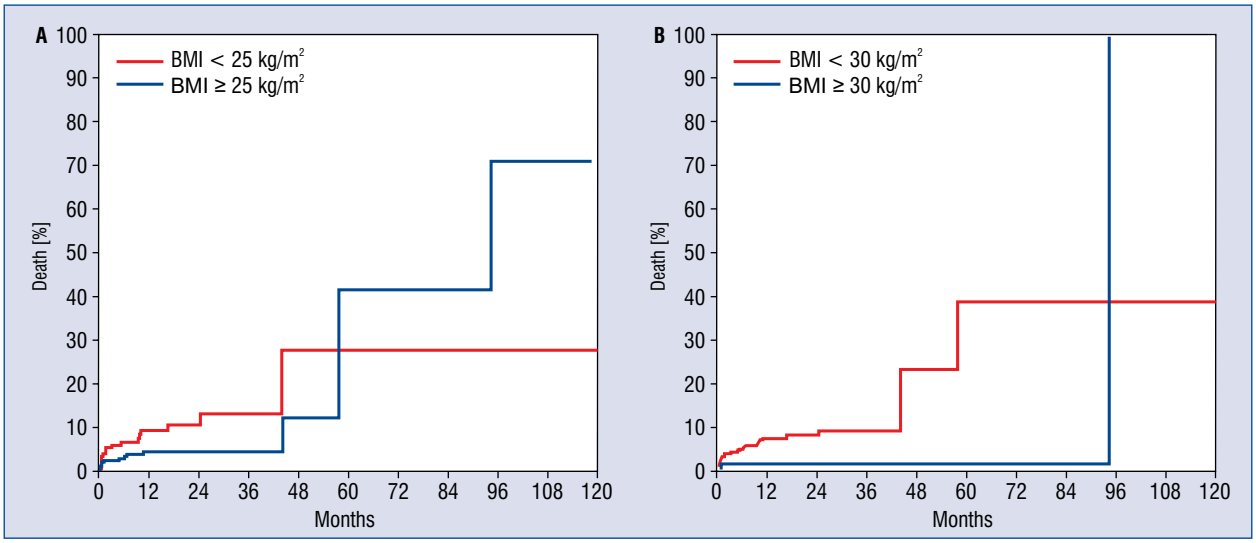

Figure 1. A. Months to death for grouping variable body mass index (BMI) < 25 kg/m². The log-rank test p-value is equal to 0.057; **B.** Months to death for grouping variable BMI < 30 kg/m². The log-rank test p-value is equal to 0.056.

Clinical endpoints and COPD

In the current study, 43 patients diagnosed with chronic obstructive pulmonary disease (COPD; 10.6%), were divided according to BMI, similarly as in the overall group of patients. The authors compared clinical outcomes between patients with BMI < 25 kg/m² (51.2%) and ≥ 25 kg/m² (48.8%) and between patients with BMI < 30 kg/m² (81.4%) and ≥ 30 kg/m² (18.6%). Particular clinical endpoints were higher in patients with lower BMI; however, they did not reach statistical significance when stratified for BMI < 25 kg/m² (reinterventions: 19.05% vs. 9.52%, p = 0.66; deaths: 14.29% vs. 4.76%, p = 0.6 and lower extremity bypass surgery: 21.05% vs. 5%, p = 0.18) and for BMI < < 30 kg/m² (reinterventions: 17.65% vs. 0%, p = 0.57; deaths: 11.76% vs. 0%, p = 0.57; amputations: 14.29% vs. 12.5%, p = 1.0; lower extremity bypass surgery: 15.63% vs. 0%, p = 0.56).

Discussion

The main finding of the current study is that underweight, normal-weight and extremaly obese patients are at increased risk of death prior to endovascular treatment of CTOs of the lower

Table 4. Cumulative risk of study endpoints according to body mass index (BMI) status.

BMI	0 M	12 M	24 M	36 M	48 M	60 M	72 M	84 M	96 M	108 M	120 M
< 25											
At risk	153	92	35	10	5	3	3	3	3	3	2
CNE	0	13	14	15	16	16	16	16	16	16	16
≥ 25											
At risk	247	170	85	23	9	2	2	2	1	1	–
CNE	0	10	10	10	11	12	12	12	13	13	–
< 30											
At risk	297	188	88	25	10	4	4	4	4	4	2
CNE	0	21	22	23	25	26	26	26	26	26	26
≥ 30											
At risk	103	74	32	8	4	1	1	1	–	–	–
CNE	0	2	2	2	2	3	3	3	–	–	–
Total											
At risk	400	262	120	33	14	5	5	5	4	4	2
CNE	0	23	24	25	27	28	28	28	29	29	29

CNE — cumulative number of events, M — months

Table 5. Cumulative risk of death according to body mass index (BMI) in selected intervals.

BMI	0 M	12 M	24 M	36 M	48 M	60 M	72 M	84 M	96 M	108 M	120 M
< 18.5											
At risk	8	2	1	–	–	–	–	–	–	–	–
CNE	0	1	1	–	–	–	–	–	–	–	–
18.5 ≤ BMI < 25											
At risk	145	90	34	10	5	3	3	3	3	3	2
CNE	0	12	13	14	15	15	15	15	15	15	15
25 ≤ BMI < 30											
At risk	144	96	53	15	5	1	1	1	1	1	–
CNE	0	8	8	8	9	10	10	10	10	10	–
30 ≤ BMI < 35											
At risk	77	57	25	8	4	1	1	1	–	–	–
CNE	0	1	1	1	1	2	2	2	–	–	–
35 ≤ BMI < 40											
At risk	15	12	6	–	–	–	–	–	–	–	–
CNE	0	0	0	–	–	–	–	–	–	–	–
BMI ≥ 40											
At risk	11	5	1	–	–	–	–	–	–	–	–
CNE	0	1	1	–	–	–	–	–	–	–	–

CNE — cumulative number of events; M — months

limb infra-inguinal arteries during the long-term follow-up period in comparison to the group of obese patients.

Several studies assessing the impact of BMI calculated before PCI have been published to date [3–5]. It was demonstrated that in the case of underweight, normal-weight and extremely obese patients with a BMI ≥ 35 kg/m^2 present an increased death rate compared to other weights during the long-term follow-up period [3]. This

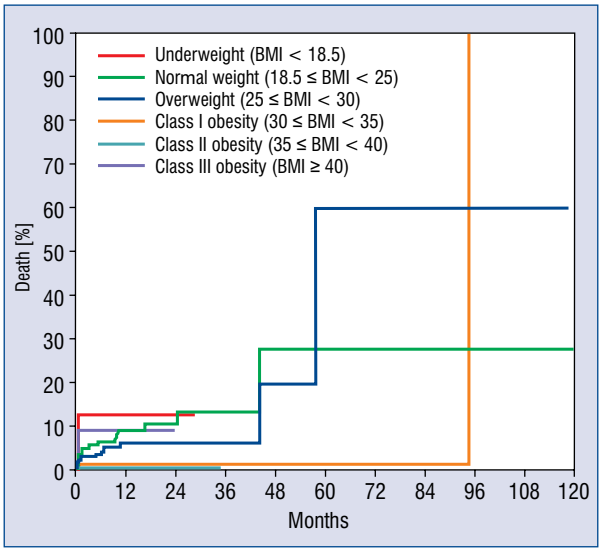

Figure 2. Months to death for grouping variable body mass index (BMI). The log-rank test *p*-value is equal to 0.26.

correlation in patients with CAD treated using PCI has been described as the "obesity paradox". Several explanations and mechanisms have been attributed to this phenomenon. One of them is that obese patients are younger, which correlates to longer survival rate [3]. This relationship was also visible in the current analysis concerning patients with PAD. However, previously published studies combined the lower mean age with smaller rates of co-morbidities and less advanced atherosclerosis [3]. While some patterns of more advanced atherosclerosis like lesion length or the percentage of CTO lesions in patients with lower BMI were observed in the current study, the rate of co-morbidities such as diabetes and CAD was significantly higher in patients from higher BMI groups (≥ 25 kg/m^2 and ≥ 30 kg/m^2). Previously published studies included endocrine status modified by adipose tissue and the size of coronary vessels among the other factors possibly responsible for the protective effect of obesity in patients with CAD treated using PCI [10, 11]. Obesity is widely recognized as a risk factor of atherosclerosis and related complications such as cardiovascular events and mortality. However, there are some data that do not confirm this relationship in patients with CAD [12]. Despite the fact that the World Health Organization endorses the use of BMI as the best measure for screening obesity, some studies demonstrated that it is not sufficient in assessing the amount of adipose tissue but is related to other indices such as waist/hip ratio [13, 14]. Bioelectrical impedance analysis and muscle handgrip strength measurement are among the best devices for estimating muscle mass and adipose tissue [15]. Another factor that may affect mortality in obese patients is better adherence to medical recommendations in the field of pharmacotherapy and prevention in this group of patients [16]. Antiplatelet and antithrombotic therapy related to bleeding complications was also found to have a potential relationship with clinical outcomes after PCI and CAD [17, 18].

The research related to the relationship between long-term survival and BMI in patients with PAD is very limited [7–9]. To our knowledge, this is the first study describing the relationship between BMI and clinical outcomes in patients with PAD treated using angioplasty from retrograde access. The study published by Kumakura et al. [7] including 652 patients with PAD confirmed the presence of the "obesity paradox" phenomenon in this group of patients. The authors indicated glomerular filtration rate, critical limb ischemia (CLI) and diabetes to be among other predictors of mortality in patients with PAD. The study published by Murata et al. [8] including 1,088 patients and comprising 1,306 limbs with critical ischemia treated with endovascular therapy confirmed the previously discovered relationship in patients with CAD treated using PCI. This study demonstrated that underweight patients with CLI are at increased risk of death during the median follow-up of 1.5 years compared to overweight and obese patients. Also, normal weight was associated with poorer survival rate during the follow-up compared to overweight and obese patients [8]. Furthermore, age, heart failure, aortic valve stenosis, renal failure, serum albumin, medication with anticoagulants and non-ambulatory status were found to be negative predictors related to all-cause mortality [8]. Among the possible mechanisms, the authors suggest that malnutrition, related to low triglyceride level in patients with PAD, may be related to increased risk of death [7]. One of the published studies attributed the "obesity paradox" phenomenon in patients with PAD to the presence of concomitant COPD [19]. A similar correlation in patients with COPD between BMI and mortality has been previously demonstrated [20]. The incidence of COPD in the study published by Galal et al. [19] almost reached 47%, while in our study, it was only slightly above 10%. The impact of COPD in the current study was too low to modify the general relationship between BMI and mortality. Moreover, among the subgroup of patients with COPD

in the current study, the relationship between death rate and BMI was not significant during the follow-up period. Considering the discussions on the issue of a number of potential mechanisms contributing to the development of the so-called "obesity paradox" in patients with CAD and PAD treated with percutaneous interventions, the role of sarcopenia has been superficially discussed. It has been demonstrated in several studies that sarcopenia is associated with increased mortality [21, 22]. The so-called U-shaped mortality curve relation to BMI could be owed to sarcopenia in underweight patients, while increased death rates in patients from severe and higher obesity classes may be related to the overwhelming influence of negative factors connected with obesity such as inflammatory processes or oxidative stress and lipid disorders [3].

In the case of patients with reduced body mass, muscle mass plays crucial role, and it has been demonstrated in the group of patients with COPD undergoing rehabilitation that both resistance training as well as endurance training have a positive effect on mortality [23]. For patients with PAD endurance training may be difficult to achieve due to limited walking, but any physical activity leading to increased muscle mass seems to be beneficial and should be recommended for every patient with PAD. In addition, every patient undergoing ER with PAD should be informed about the fact that underweight and lower body weight is associated with increased mortality in the follow-up period. It should be remembered that the risk of revascularization, even in patients with a significantly higher risk of death in the follow-up period due to low body weight at baseline, is lower in patients treated percutaneously than in surgery. Therefore, in the case of limb threat with amputation and the possibility of percutaneous treatment, it does not seem advisable to postpone the procedure in order to increase muscle mass and body weight in terms of improving prognosis.

Limitations of the study

Several limitations can be attributed to the current study. One of them is that the current group of patients was extracted from a group of 834 patients treated from retrograde access and was limited to 405 patients due to lack of BMI data, despite the fact that the BMI deficiencies were random and were not associated with any particular factor. This could have significantly affected the results.

Conclusions

The BMI value at baseline in patients with PAD undergoing ER of CTOs of the infra-inguinal lower limb arteries from retrograde access is associated with mortality during the follow-up period. Underweight and normal-weight persons are at increased risk of death after angioplasty when compared to obese individuals. Therefore, any physical activity leading to increased muscle mass seems to be beneficial and should be recommended to every PAD patient.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of interest: None declared

References

1. Ruzsa Z, Wojtasik-Bakalarz J, Nyerges A, et al. Long-Term follow-up after retrograde recanalization of superficial femoral artery chronic total occlusion. J Invasive Cardiol. 2017; 29(10): 336–339, indexed in Pubmed: 28974660.
2. Evans C, Peter N, Gibson M, et al. Five-year retrograde transpopliteal angioplasty results compared with antegrade angioplasty. Ann R Coll Surg Engl. 2010; 92(4): 347–352, doi: 10.1308/003588410X12664192075099, indexed in Pubmed: 20501022.
3. Angerås O, Albertsson P, Karason K, et al. Evidence for obesity paradox in patients with acute coronary syndromes: a report from the Swedish Coronary Angiography and Angioplasty Registry. Eur Heart J. 2013; 34(5): 345–353, doi: 10.1093/eurheartj/ehs217, indexed in Pubmed: 22947610.
4. Gruberg L, Weissman NJ, Waksman R, et al. The impact of obesity on the short-term and long-term outcomes after percutaneous coronary intervention: the obesity paradox? J Am Coll Cardiol. 2002; 39(4): 578–584, doi: 10.1016/s0735-1097(01)01802-2, indexed in Pubmed: 11849854.
5. Coutinho T, Goel K, Corrêa de Sá D, et al. Combining body mass index with measures of central obesity in the assessment of mortality in subjects with coronary disease: role of „normal weight central obesity". J Am Coll Cardiol. 2013; 61(5): 553–560, doi: 10.1016/j.jacc.2012.10.035, indexed in Pubmed: 23369419.
6. Shah R, Gayat E, Januzzi JL, et al. GREAT (Global Research on Acute Conditions Team) Network. Body mass index and mortality in acutely decompensated heart failure across the world: a global obesity paradox. J Am Coll Cardiol. 2014; 63(8): 778–785, doi: 10.1016/j.jacc.2013.09.072, indexed in Pubmed: 24315906.
7. Kumakura H, Kanai H, Aizaki M, et al. The influence of the obesity paradox and chronic kidney disease on long-term survival in a Japanese cohort with peripheral arterial disease. J Vasc Surg. 2010; 52(1): 110–117, doi: 10.1016/j.jvs.2010.02.008, indexed in Pubmed: 20478682.
8. Murata N, Soga Y, Iida O, et al. Complex relationship of body mass index with mortality in patients with critical limb ischemia

undergoing endovascular treatment. Eur J Vasc Endovasc Surg. 2015; 49(3): 297–305, doi: 10.1016/j.ejvs.2014.10.014, indexed in Pubmed: 25524520.
9. Iida O, Soga Y, Hirano K, et al. Midterm outcomes and risk stratification after endovascular therapy for patients with critical limb ischaemia due to isolated below-the-knee lesions. Eur J Vasc Endovasc Surg. 2012; 43(3): 313–321, doi: 10.1016/j.ejvs.2011.11.025, indexed in Pubmed: 22240338.
10. O'Connor NJ, Morton JR, Birkmeyer JD, et al. Effect of coronary artery diameter in patients undergoing coronary bypass surgery. Northern New England Cardiovascular Disease Study Group. Circulation. 1996; 93(4): 652–655, doi: 10.1161/01.cir.93.4.652, indexed in Pubmed: 8640991.
11. Momin AU, Melikian N, Shah AM, et al. Leptin is an endothelial-independent vasodilator in humans with coronary artery disease: Evidence for tissue specificity of leptin resistance. Eur Heart J. 2006; 27(19): 2294–2299, doi: 10.1093/eurheartj/ehi831, indexed in Pubmed: 16543250.
12. Yusuf S, Hawken S, Ounpuu S, et al. INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004; 364(9438): 937–952, doi: 10.1016/S0140-6736(04)17018-9, indexed in Pubmed: 15364185.
13. World Health Organization. Obesity and Overweight. http://new.who.int/news-room/fact-sheets/detail/obesity-and-overweight (Accessed April 29, 2018).
14. Gelber RP, Gaziano JM, Orav EJ, et al. Measures of obesity and cardiovascular risk among men and women. J Am Coll Cardiol. 2008; 52(8): 605–615, doi: 10.1016/j.jacc.2008.03.066, indexed in Pubmed: 18702962.
15. Januszek R, Siudak Z, Dziewierz A, et al. Chronic obstructive pulmonary disease affects angiographic presentation and outcomes. Authors' reply. Pol Arch Intern Med. 2018; 128(3): 195–196, doi: 10.20452/pamw.4237, indexed in Pubmed: 29600970.
16. Steinberg BA, Cannon CP, Hernandez AF, et al. Medical therapies and invasive treatments for coronary artery disease by body mass: the „obesity paradox" in the Get With The Guidelines database. Am J Cardiol. 2007; 100(9): 1331–1335, doi: 10.1016/j.amjcard.2007.06.019, indexed in Pubmed: 17950785.
17. Delhaye C, Wakabayashi K, Maluenda G, et al. Body mass index and bleeding complications after percutaneous coronary intervention: does bivalirudin make a difference? Am Heart J. 2010; 159(6): 1139–1146, doi: 10.1016/j.ahj.2010.03.011, indexed in Pubmed: 20569731.
18. Mak KH, Bhatt DL, Shao M, et al. The influence of body mass index on mortality and bleeding among patients with or at high-risk of atherothrombotic disease. Eur Heart J. 2009; 30(7): 857–865, doi: 10.1093/eurheartj/ehp037, indexed in Pubmed: 19233855.
19. Galal W, van Gestel YR, Hoeks SE, et al. The obesity paradox in patients with peripheral arterial disease. Chest. 2008; 134(5): 925–930, doi: 10.1378/chest.08-0418, indexed in Pubmed: 18641109.
20. Landbo C, Prescott E, Lange P, et al. Prognostic value of nutritional status in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1999; 160(6): 1856–1861, doi: 10.1164/ajrccm.160.6.9902115, indexed in Pubmed: 10588597.
21. Tang T, Wu L, Yang L, et al. A sarcopenia screening test predicts mortality in hospitalized older adults. Sci Rep. 2018; 8(1): 2923, doi: 10.1038/s41598-018-21237-9, indexed in Pubmed: 29440681.
22. Yang M, Hu X, Wang H, et al. Sarcopenia predicts readmission and mortality in elderly patients in acute care wards: a prospective study. J Cachexia Sarcopenia Muscle. 2017; 8(2): 251–258, doi: 10.1002/jcsm.12163, indexed in Pubmed: 27896949.
23. Iepsen UW, Jørgensen KJ, Ringbaek T, et al. A Systematic Review of Resistance Training Versus Endurance Training in COPD. J Cardiopulm Rehabil Prev. 2015; 35(3): 163–172, doi: 10.1097/HCR.0000000000000105, indexed in Pubmed: 25692720.

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Impact of conscious sedation and general anesthesia on periprocedural outcomes in Watchman left atrial appendage closure

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Abstract

Background: *Transcatheter left atrial appendage closure (LAAC) is performed either in conscious sedation (CS) or general anesthesia (GA), and limited data exist regarding clinical outcomes for the two approaches. The aim of the study was to analyze the effect of CS versus GA on acute outcomes in a large patient cohort undergoing LAAC with a Watchman occluder.*

Methods: *A cohort of 521 consecutive patients underwent LAAC with Watchman occluders at two centers (REGIOMED hospitals, Germany) between 2012 and 2018. One site performed 303 consecutive LAAC procedures in GA, and the other site performed 218 consecutive procedures in CS. The safety endpoint was a composite of major periprocedural complications and postoperative pneumonia. The efficacy endpoint was defined as device success.*

Results: *After a 1:1 propensity score matching, 196 (CS) vs. 115 (GA) patients could be compared. In 5 (2.6%) cases CS was converted to GA. The primary safety endpoint (3.5% [CS] vs. 7.0% [GA], $p = 0.18$) and its components (major periprocedural complications: 2.5% vs. 3.5%, $p = 0.73$; postoperative pneumonia: 2.6% vs. 4.3%, $p = 0.51$) did not differ between the groups. Also, device success was comparable (96.9% vs. 93.9%, $p = 0.24$).*

Conclusions: *In patients undergoing LAAC with the Watchman device, conscious sedation and general anesthesia showed comparable device success rates and safety outcomes. The type of anesthesia for LAAC may therefore be tailored to patient comorbidities, operator experience, and hospital logistics.* (Cardiol J 2021; 28, 4: 519–527)

Key words: atrial fibrillation, left atrial appendage closure, conscious sedation, general anesthesia, Watchman

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Introduction

Left atrial appendage closure (LAAC) is a device-based method for stroke prevention in patients with atrial fibrillation (AF), who have absolute or relative contraindications for oral anticoagulation (OAC) [1, 2]. Substantial evidence exists for the Watchman occluder (Boston Scientific, Marlborough, MA, US), which has been in clinical use since 2005. Compared to warfarin, it provides comparable efficacy in long-term prevention of all-cause stroke. Furthermore, it reduces cardiovascular mortality and major bleeding events, particularly hemorrhagic stroke [3]. Because LAAC is a purely preventive treatment, without any immediate benefit for the patient, it is mandatory to keep periprocedural complications as low as possible. Due to the complex anatomy and topography of the left atrial appendage (LAA), the procedure can be demanding. Procedural success and adverse events depend on several factors, such as patient characteristics and comorbidities, experience of the operating physician and team, technical features of the device, intraprocedural cardiac imaging, and possibly the type of anesthesia. Most centers prefer procedural guidance by transesophageal echocardiography (TEE), which requires either sedation or full anesthesia to improve patient comfort and tolerance of the TEE probe. One option is general anesthesia (GA), which allows control of airways, ventilation, and patient movement. The other is conscious sedation (CS) with the patient spontaneously breathing. Previous studies investigating the type of anesthesia used during other heart disease interventions could not establish superiority of any one method but documented shorter postoperative monitoring or length of hospital stay in CS [4–10]. Data on the impact of CS or GA on periprocedural outcomes in LAAC are lacking. Therefore, the aim of this study was to compare both methods with regard to device success and major periprocedural complications, including postoperative pneumonia, as well as length of postoperative monitoring based on the results of two propensity-matched, real-world registries.

Methods

Study cohort

All consecutive patients, who underwent LAAC with Watchman occluders at two centers (REGIOMED hospitals Coburg and Lichtenfels, Germany), were prospectively enrolled in an observational registry. At the Lichtenfels site, where inclusion started in 2012, all patients were treated exclusively under GA. The Watchman program at the Coburg site started in 2016, and all interventions were performed primarily under conscious sedation (Fig. 1). Indications for LAAC were based on current guidelines and recommendations [1, 2]. Exclusion criteria were active infection, pregnancy, and indications for OAC other than AF. A retrospective post-hoc analysis of demographic characteristics, procedural data, and clinical outcomes was performed for all patients in a standardized manner. Adverse events were adjudicated by a clinical event committee of two independent physicians and, in cases of disagreement, by a third referee. The study complies with the Declaration of Helsinki. It was conducted according to local ethical standards and requirements, and all patients provided written informed consent.

LAAC procedure

The characteristics of the Watchman device and procedural aspects were previously described in detail [11]. Generally, the occluder was implanted via a transseptal puncture and use of a delivery sheath. In both groups, all procedures were performed in a catheterization laboratory and were both guided by TEE and fluoroscopy. However, procedural settings, postoperative monitoring, and antithrombotic medical therapy differed between the two centers: For the GA group, the team comprised 3 to 4 doctors (1 or 2 interventional cardiologists, one TEE guide, one anesthesiologist) and 4 nurses (Fig. 2). All patients were orotracheally intubated and mechanically ventilated. In the majority of cases, the anesthesia was a combination of propofol and an opioid (fentanyl or remifentanil). Extubation was aimed to be performed in the catheterization laboratory immediately after the procedure, whenever possible. The standard protocol provided a postoperative monitoring in the intermediate care (IMC) unit for 24 hours. According to the PROTECT-AF study, postoperative antithrombotic therapy consisted of OAC plus acetylsalicylic acid (ASA) for 45 days followed by dual antiplatelet therapy with ASA and clopidogrel for 6 months [12]. In the CS group, the operating team consisted of 3 cardiologists (2 interventionalists, 1 TEE guide) and 3 nurses, all with expertise in propofol sedation and intensive care unit (ICU) skills (Fig. 2). All patients received local anesthesia with mepivacaine 1% at the puncture site and lidocaine pump spray for introduction of the TEE probe. Patients were spontaneously breathing, and conversion to

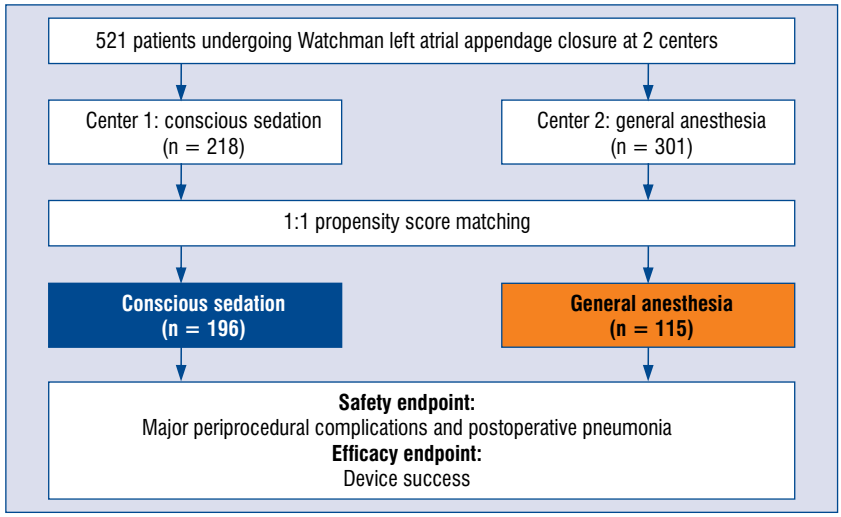

Figure 1. Study flow chart.

GA was only performed in case of respiratory or hemodynamic instability. For sedation, a 1–5 mg bolus of midazolam was administered. In addition, propofol was administered continuously at the lowest dose possible. The standard protocol required 4 hours of postoperative monitoring in the IMC unit. The postprocedural antithrombotic regimen consisted of dual antiplatelet therapy with ASA and clopidogrel for 3 months.

Definitions and endpoints

Demographic, clinical, and procedural characteristics, as well as adverse events and endpoints, were reported according to the current recommendations of the European Heart Rhythm Association and the European Association of Percutaneous Cardiovascular Interventions, the Bleeding Academic Research Consortium (BARC), the Valve Academic Research Consortium criteria, and the Cardiovascular and Stroke Endpoint Definitions for Clinical Trials [13–16]. Device success was defined as correct deployment and implantation of the LAA occluder. Major periprocedural complications included death (< 72 hours after the index procedure), stroke, device embolization, cardiac tamponade or pericardial effusion requiring intervention, major bleeding (> BARC type 3a), need for bailout surgery, need for cardio-pulmonary resuscitation, severe kidney injury, and other relevant complications leading to prolonged hospital stay. The safety endpoint was a composite of the mentioned major periprocedural complications and postoperative pneumonia. The efficacy endpoint was defined as device success.

Statistical analysis

Statistical analyses were performed with the Graph Pad Prism 8 software (GraphPad Inc. La Jolla, California, USA). Categorical variables are presented as actual numbers and percentages and compared using the Fisher's exact test. Continuous variables are summarized as mean ± standard deviation (SD) or as medians with corresponding interquartile range (IQR) and compared using an unpaired t-test. Findings were considered statistically significant at the 0.05 level. We performed a propensity score matching for the likelihood of performing LAAC under conscious sedation or general anesthesia with a ratio of 1:1 with replacement using the R software, the package "MatchIt" and "cobalt" [17–19]. The quality of the matching was assessed in two ways: there was a standardized difference of < 0.10 for each baseline covariable and there was no significant difference in the covariables among the two groups using a univariate logistic regression or unpaired t-test.

Results

Patient characteristics

Between November 2016 and May 2018, 218 patients underwent LAAC with Watchman occluders under CS at the Coburg site, and respectively 303 received Watchman devices under GA at the Lichtenfels site, between February 2012 and April 2017. After a 1:1 propensity score matching, 196 (CS) vs. 115 (GA) patients were compared (Fig. 1). Baseline characteristics are shown in Table 1. The prevalence of female gender (49.0% [CS] vs. 36.5%

Table 1. Baseline characteristics.

	Conscious sedation (n = 196)	General anesthesia (n = 115)	P
Age at time of LAAC [years]	78.0 ± 7.3	77.0 ± 6.8	0.23
Female gender	96 (49.0%)	42 (36.5%)	0.03
Body mass index [kg/m^2]	29.7 ± 6.4	29.5 ± 5.1	0.69
Permanent/persistent AF	105 (53.6%)	77 (67.0%)	0.02
Arterial hypertension	185 (94.4%)	101 (87.8%)	0.04
Diabetes mellitus	67 (34.2%)	40 (34.8%)	0.91
Coronary artery disease	113 (57.7%)	60 (52.2%)	0.35
Prior PCI/CAGB	88 (44.9%)	47 (40.9%)	0.49
LVEF [%]	53.1 ± 11.9	55.1 ± 9.5	0.12
Congestive heart failure	59 (30.1%)	29 (25.2%)	0.36
Glomerular filtration rate [mL/min]	55.3 ± 26.0	56.2 ± 22.8	0.75
Severe lung disease	14 (7.1%)	11 (9.6%)	0.45
Liver disease	12 (6.1%)	17 (14.8%)	0.01
CHA_2DS_2-VASc score	4.8 ± 1.4	4.6 ± 1.7	0.40
HAS-BLED score	3.4 ± 0.8	3.4 ± 0.9	0.63

Categorical variables are expressed as frequencies (n) and percentages (%). Continuous data is reported as mean and standard deviation; AF — atrial fibrillation; CABG — coronary artery bypass grafting; LAAC — left atrial appendage closure; LVEF — left ventricular ejection fraction; PCI — percutaneous coronary intervention

[GA], p = 0.03) and arterial hypertension (94.4% vs. 87.8%, p = 0.04) was higher in the CS group. The rate of permanent/persistent AF (53.6% vs. 67.0%, p = 0.02) and liver disease (6.1% vs. 14.8%, p = 0.01) was higher in the GA group. All other baseline characteristics were comparable, especially age (78.0 ±7.3 [CS] vs. 77.0 ± 6.8 [GA], p = = 0.23), stroke and bleeding risk (CHA_2DS_2-VASC score: 4.8 ± 1.4 vs. 4.6 ± 1.7, p = 0.40; HAS-BLED score: 3.4 ± 0.8 vs. 3.4 ± 0.9, p = 0.63), as well as renal function (glomerular filtration rate [mL/min]: 55.3 ± 26.0 vs. 56.2 ± 22.8, p = 0.75) and severe lung disease (7.1% vs. 9.6%, p = 0.52).

Procedural characteristics

Procedural aspects are depicted in Table 2. All interventions were guided by TEE, apart from 1 case of intracardiac echocardiography in the CS group. In the CS group the rate of implantation attempts (1.2 ± 0.6 [CS] vs. 1.6 ± 0.9 [GA], p ≤ ≤ 0.001) and use of contrast media were lower (median, mL: 50 [IQR 30–60] vs. 90 [IQR 70–113], p ≤ 0.001); furthermore, fluoroscopy (median, min: 7 [IQR 5–10] vs. 10 [IQR 7–19], p ≤ 0.001) and procedure (median, min: 41 [IQR 35–55] vs. 49 [IQR 38–65], p = 0.02) times were shorter. In 5 (2.6%) patients CS was converted to GA: in 1 case due to LAA perforation with cardiogenic shock, in another due to epistaxis with aspiration, and in 3 patients due to respiratory failure. The primary safety endpoint (3.5% [CS] vs. 7.0% [GA], p = 0.18) did not differ significantly between the groups. Also, its components, postoperative pneumonia (2.6% vs. 4.3%, p = 0.51), and major periprocedural complications (2.5% vs. 3.5%, p = 0.73) were comparable (Fig. 3).

In the CS group, 1 case of procedure-related death occurred in an 87-year-old, female patient, who suffered from a major stroke shortly after the intervention. Cerebral computed tomography after 24 hours demonstrated relevant ischemic cerebral infarction, and the patient died 3 days after the index procedure. Device success was comparable between the groups (96.9% vs. 93.9%, p = 0.24). As provided by the standard protocol of each center, postoperative monitoring was significantly shorter in the CS group (median, hours: 4.0 ± 59.9 vs. 24.0 ± 10.8, p = 0.03; Fig. 3). Both groups show large standard deviations due to patients with periprocedural complications, who were treated for several days or weeks in the ICU.

TEE follow-up and 30-day mortality

Due to logistic reasons, the TEE follow-up rate is incomplete in the CS group and differs between the groups (62.2% [CS] vs. 100% [GA], p ≤ 0.0001) (Table 3). Therefore, a numerically lower rate of device-related thrombus was observed in the CS

Table 2. Procedural characteristics.

	Conscious sedation (n = 196)	General anesthesia (n = 115)	P
Conversion from CS to GA	5 (2.6%)		
TEE guidance	194 (99.5%)	115 (100.0%)	0.44
Device success	190 (96.9%)	108 (93.9%)	0.20
Implantation attempts	1.2 ± 0.6	1.6 ± 0.9	< 0.0001
Fluoroscopy time [min]	7 (IQR 5–10)	10 (IQR 7–19)	< 0.0001
Procedure time [min]	41 (IQR 35–55)	49 (IQR 38–65)	0.0002
Total contrast volume [mL]	50 (IQR 30–60)	90 (IQR 70–113)	< 0.0001
Postoperative monitoring [h]	4 (IQR 4-4)	24 (IQR 22–24)	0.03
Length of hospital stay [days]	13 (IQR 6–16)	3 (IQR 3–8)	< 0.0001
Primary safety endpoint	7 (3.5%)	8 (7.0%)	0.18
Postoperative pneumonia	5 (2.6%)	5 (4.3%)	0.39
Major periprocedural complication:	5 (2.5%)	4 (3.5%)	0.64
Death	1 (0.5%)	0 (0.0%)	0.44
Stroke	1 (0.5%)	0 (0.0%)	0.44
Pericardial tamponade	2 (1.0%)	4 (3.5%)	0.13
Major bleeding	3 (1.5%)	4 (3.5%)	0.26
Major access vessel complication	1 (0.5%)	1 (0.9%)	0.70
Need for bailout surgery	0 (0.0%)	0 (0.0%)	1.0
Device embolization	0 (0.0%)	0 (0.0%)	1.0
Severe kidney injury	0 (0.0%)	1 (0.9%)	0.44
Cardiogenic shock	2 (1.0%)	0 (0.0%)	0.28
Need for cardiopulmonary resuscitation	1 (2.5%)	0 (0.0%)	0.28

Categorical variables are expressed as frequencies (n) and percentages (%). Continuous data is reported as mean and standard deviation or as median and interquartile range; CS — conscious sedation; GA — general anesthesia; TEE — transesophageal echocardiography

group (0.8% vs. 5.2%, p = 0.01). The rate of major peri-device leaks (≥ 5 mm) was comparable between the groups (2.8% vs. 1.4%, p = 0.47). Thirty-day mortality was similar for both groups (3.6% vs. 1.4%, p = 0.47) (Fig. 4): In the CS group, 7 patients had died at 30-day follow-up for the following reasons: unexplained death (80 and 88 years old, both male), heart failure (85 and 75 years old, both male), liver failure (70 years old, male), pancreatic cancer (86 years old, male), and stroke (87 years old, female). In the GA group, a 71-year-old male patient died due to unexplained reasons, a 70-year-old male patient due to pneumonia 3 weeks after the index procedure, and an 87-year-old female patient due to spontaneous retroperitoneal hematoma 25 days after the index procedure.

Discussion

Over the last decade, LAAC has become an accepted procedure and is offered in many centers. Commonly, procedural imaging is necessary to guide this often complex intervention. One guiding tool is intracardiac echocardiography, which avoids anesthesia and its associated potential risks. However, most centers use TEE, which is widely available, less expensive, and offers superior imaging quality. In many centers, general anesthesia is used to improve patient comfort and tolerance to the procedure.

Currently, there are limited data regarding the impact of the anesthesiologic strategy in LAAC on procedural, peri-procedural, and later clinical outcomes: A case series in 11 patients investigated LAAC under sedation and noninvasive ventilation [20]. In all patients, clinical outcome was uneventful, with a high degree of satisfaction of the medical team.

The present study is the first that directly compares CS and GA for LAAC with Watchman occluders based on the results of propensity-matched data from two real-world registries.

Our main findings are: (1) CS and GA are equally effective for device success; (2) both meth-

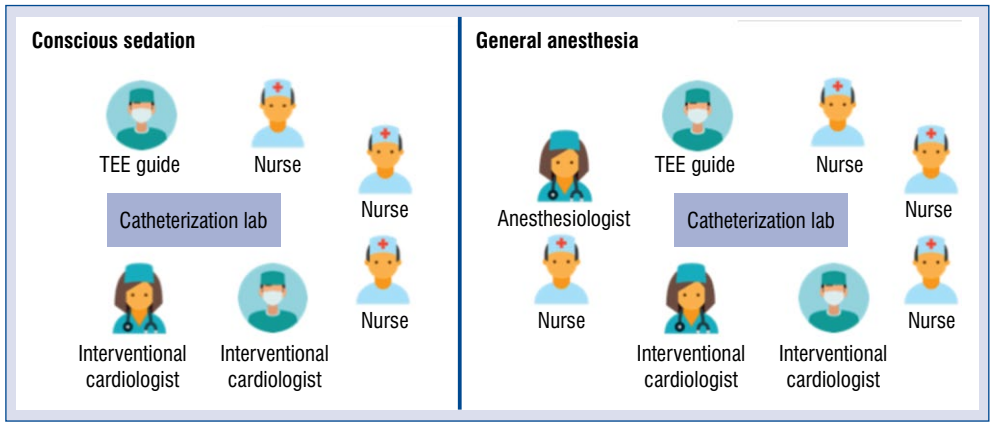

Figure 2. Procedure settings in conscious sedation and general anesthesia; lab — laboratory; TEE — transesophageal echocardiography.

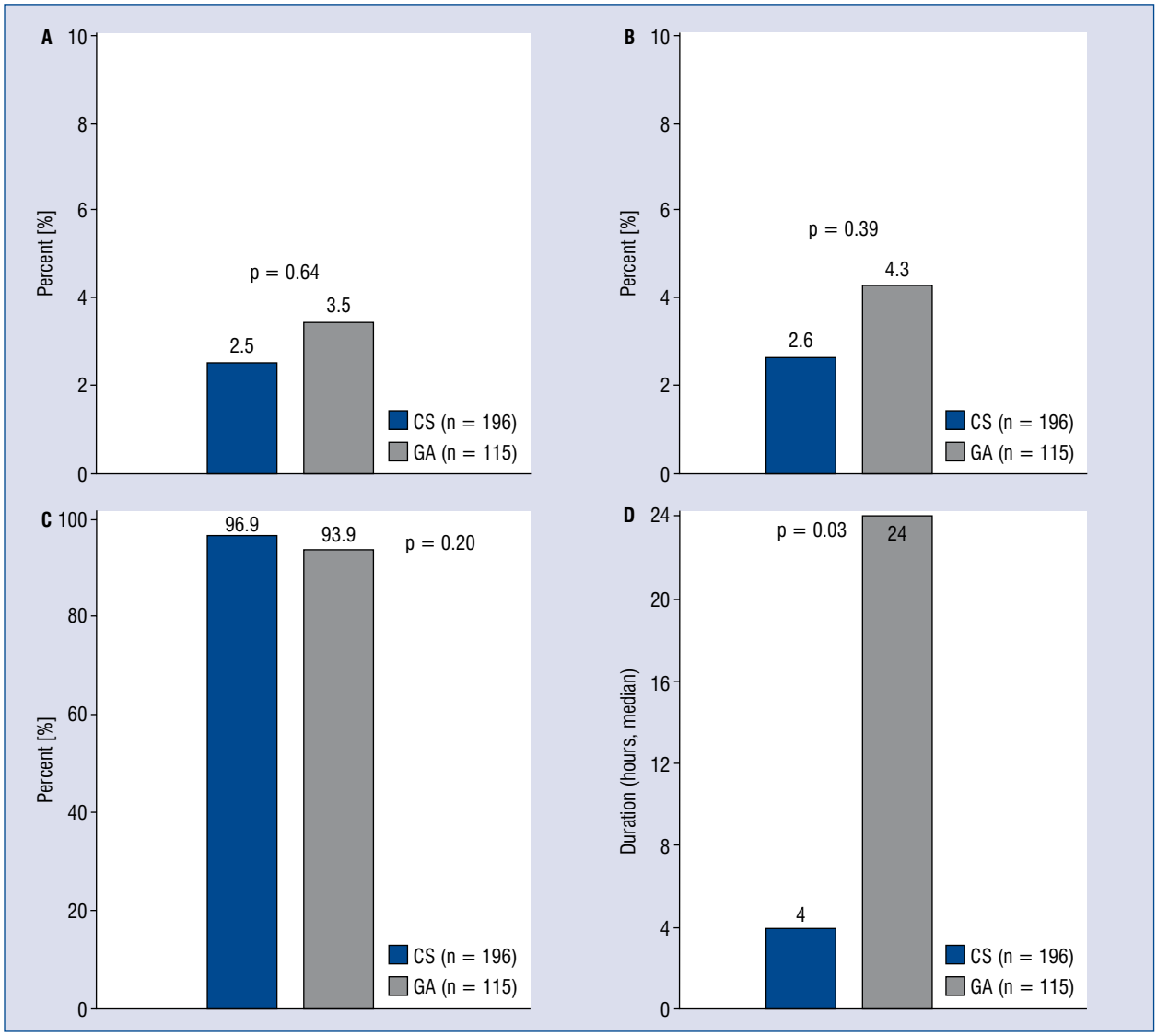

Figure 3. Key variables of periprocedural outcomes; **A.** Major periprocedural complications; **B.** Postoperative pneumonia; **C.** Device success; **D.** Postoperative monitoring; CS — conscious sedation; GA — general anesthesia.

Table 3. Transesophageal echocardiography (TEE) follow-up and 30-day mortality.

	Conscious sedation (n = 196)	General anesthesia (n = 115)	P
TEE performed	122 (62.2%)	115 (100.0%)	< 0.0001
Device-related thrombus	1 (0.8%)	6 (5.2%)	0.01
Peri-device leak (≥ 5 mm)	9 (8.6%)	9 (7.8%)	0.24
30-day mortality	7 (3.6%)	3 (1.4%)	0.47

Categorical variables are expressed as frequencies (n) and percentages (%).

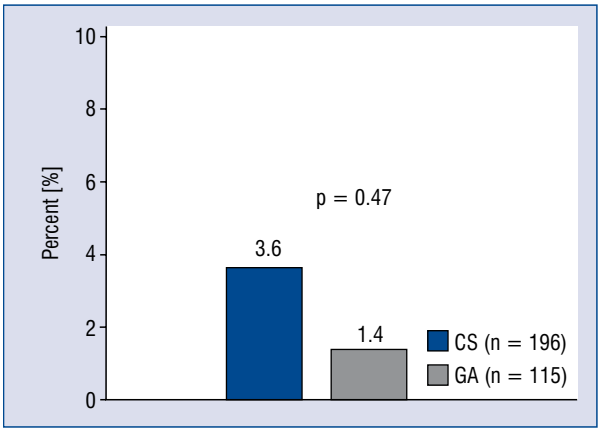

Figure 4. 30-day mortality; CS — conscious sedation; GA — general anesthesia.

ods offer comparable safety with regard to major periprocedural complications and postoperative pneumonia; (3) the type of anesthesia does not affect 30-day mortality; and (4) CS requires shorter postoperative monitoring and less personal and logistic resources.

These observations are in line with other studies that investigated the impact of CS and GA on outcomes in other structural interventions such as percutaneous mitral valve repair or transcatheter aortic valve implantation (TAVI) [4–10]. Those studies report no differences in procedural success or clinical outcomes according to the type of anesthesia. In the present study, device success was comparable to the implant success rate (95.8%) of the worldwide largest National Cardiovascular Data Registry (NCDR) with 38,158 procedures, captured between 2016 and 2018 [21]. The NCDR reports a fairly low rate of major periprocedural complications (1.9%). The rates of adverse events in our cohorts are higher, which may be attributable to the older and more polymorbid patient population of our study with higher CHA_2DS_2-VASc and HAS-BLED scores and the much shorter timeframe of treatment starting from 2012.

Similar to our results, the German Aortic Valve Registry reported shorter procedure and fluoroscopy times for CS [9]. The United States post-Food and Drug Administration approval Watchman registry of 3822 patients reported a median procedure time of 50 min [22]. In comparison, our results with a median of 49 min for the GA and 41 min for the CS group are comparable. Despite speedier interventions in our CS group arm, we observed fewer implantation attempts and lower contrast volume in this group. The most likely reason for this is that in the GA group patient enrollment started 4 years earlier, which affects expertise with the procedure and explains the differences in operation times, contrast use, and implantation attempts between our two groups. The PROTECT-AF trial and the continued access registry showed — as in all interventional procedures — a learning curve of the performing teams with a substantial improvement in procedural speed and success, as well as a significant decrease in procedure-related complications [23]. However, another potential reason for these findings may be the type of anesthesia: General anesthesia avoids excess salivary secretion and consequent coughing and unexpected moving. This enables a more meticulous transseptal puncture, several measurements of the LAA, as well as repetitive re-positioning or replacement of the device if necessary. Therefore, GA is often deemed more appropriate for operators and hospitals at the beginning of their learning curves, whereas CS, which considerably streamlines the procedure, is a valuable option for high-volume centers with experienced operators and teams.

As outlined, in our CS group, 5 (2.6%) patients had to be converted to GA. Respiratory failure with the need for temporary non-invasive ventilation or orotracheal intubation is a common adverse effect of deep conscious sedation, but most of these cases recover rapidly and uneventfully. Indeed, all

3 patients who suffered respiratory depression could be extubated on the same day. Despite choosing CS as the primary anesthesiologic approach, the team has to be prepared for speedy conversion to GA if necessary. In a single logistic regression analysis, we were unable to detect any predictors for respiratory depression in our group, which is due to the low numbers.

Conceptually, CS might be associated with an increased aspiration risk caused by hypersalivation due to the TEE probe. However, studies investigating GA and CS in patients undergoing percutaneous mitral valve repair observed no differences regarding the development of postoperative pneumonia, which is similar to our findings [4, 6]. In those studies, the rate of postoperative pneumonia varied between 3.3% and 6.7%, which is comparable to the rate observed in the present study, in which all patients received peri-interventional prophylactic antibiotics according to the guidelines. Also, for postoperative pneumonia and due to the low event rates, we found no relevant predictors in the logistic regression analysis.

With regard to 30-day mortality, rates were comparable between the groups but higher than observed in the EWOLUTION registry (0.4%) [24]. Nonetheless, after 1 year, the EWOLUTION registry reported a relatively high mortality rate of 9.8%, reflecting the elderly, fragile, and multimorbid LAAC patient population in European countries [25]. Individual patient characteristics such as biological and social status, the burden of comorbidities, quality of life, frailty, and anticipated residual lifespan should be considered when planning LAAC in elderly patients. With regard to postoperative monitoring, the standard protocol of the two centers required 4 hours for CS and 24 hours for GA. Other investigations documented consistently shorter IMC/ICU hours after CS only [4–10]. In addition, Toppen et al. [7] reported a higher quality of life at 30--day follow-up and a decrease in direct costs in patients, who received TAVI under CS. However, shorter postoperative monitoring seems not to affect overall length of hospital stay [4]. In the present study, in the GA group LAAC was performed as an elective procedure, whereas in the CS group patients were mostly hospitalized for other reasons, which is clearly the reason for the longer hospital stay in the latter group.

Limitations of the study

Due to its retrospective, non-randomized, and observational design, as well as the different procedural settings of the GA and CS groups, the present study has several limitations. Due to its relatively small sample size, our study was not powered to detect differences in procedural and clinical outcomes. Despite good comparability of the two groups with regard to baseline characteristic due to propensity score matching, confounders may persist, e.g. differences in the rates of gender, arterial hypertension, permanent AF, and liver disease. Furthermore and importantly, at the Lichtenfels site, patient enrollment started 4 years earlier and included the learning curve of the center, which likely impacted on the longer intervention and fluoroscopy times, as well as more implantation attempts and the use of greater amounts of contrast volume in this group. Regarding TEE follow-up, it was incomplete in the CS group and was not analyzed in a core laboratory, which may have led to an underreporting of device-related thrombus and peri-device leaks in this group.

Conclusions

In patients undergoing LAAC with the Watchman occluder, general anesthesia and conscious sedation provided comparable safety, efficacy, and device success, but CS shortened postoperative monitoring. Therefore, the type of anesthesia for LAAC may be tailored to patient characteristics, operator experience, and hospital logistics.

Conflict of interest: Steffen Gloekler has received a grant from the Swiss Heart Foundation; Johannes Brachmann has received consulting fees from Abbott, St. Jude Medical, Medtronic, Bayer, Liva-nova, Pfizer, Boston Scientific, Boehringer Ingelheim, and Biotronik; Jiangtao Yu has received proctor fees from Boston Scientific. The other authors have no conflicts of interest.

References

1. Kirchhof P, Benussi S, Kotecha D, et al. ESC Scientific Document Group. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016; 37(38): 2893–2962, doi: 10.1093/eurheartj/ehw210, indexed in Pubmed: 27567408.
2. Glikson M, Wolff R, Hindricks G, et al. EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion - an update. EuroIntervention. 2020; 15(13): 1133–1180, doi: 10.4244/EIJY19M08_01, indexed in Pubmed: 31474583.
3. Reddy VY, Doshi SK, Kar S, et al. 5-Year outcomes after left atrial appendage closure: from the PREVAIL and PROTECT AF trials. J Am Coll Cardiol. 2017; 70(24): 2964–2975, doi: 10.1016/j.jacc.2017.10.021, indexed in Pubmed: 29103847.

4. de Waha S, Seeburger J, Ender J, et al. Deep sedation versus general anesthesia in percutaneous edge-to-edge mitral valve reconstruction using the MitraClip system. Clin Res Cardiol. 2016; 105(6): 535–543, doi: 10.1007/s00392-015-0951-z, indexed in Pubmed: 26683202.
5. Horn P, Hellhammer K, Minier M, et al. Deep sedation vs. general anesthesia in 232 patients undergoing percutaneous mitral valve repair using the MitraClip system. Catheter Cardiovasc Interv. 2017; 90(7): 1212–1219, doi: 10.1002/ccd.26884, indexed in Pubmed: 28112459.
6. Patzelt J, Ulrich M, Magunia H, et al. Comparison of deep sedation with general anesthesia in patients undergoing percutaneous mitral valve repair. J Am Heart Assoc. 2017; 6(12), doi: 10.1161/JAHA.117.007485, indexed in Pubmed: 29197832.
7. Toppen W, Johansen D, Sareh S, et al. Improved costs and outcomes with conscious sedation vs general anesthesia in TAVR patients: Time to wake up? PLoS One. 2017; 12(4): e0173777, doi: 10.1371/journal.pone.0173777, indexed in Pubmed: 28379981.
8. Hyman MC, Vemulapalli S, Szeto WY, et al. Conscious Sedation Versus General Anesthesia for Transcatheter Aortic Valve Replacement: Insights from the National Cardiovascular Data Registry Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry. Circulation. 2017; 136(22): 2132–2140, doi: 10.1161/CIRCULATIONAHA.116.026656, indexed in Pubmed: 28864443.
9. Husser O, Fujita B, Hengstenberg C, et al. Conscious Sedation Versus General Anesthesia in Transcatheter Aortic Valve Replacement: The German Aortic Valve Registry. JACC Cardiovasc Interv. 2018; 11(6): 567–578, doi: 10.1016/j.jcin.2017.12.019, indexed in Pubmed: 29566803.
10. Mosleh W, Mather JF, Amer MR, et al. Propensity matched analysis comparing conscious sedation versus general anesthesia in transcatheter aortic valve implantation. Am J Cardiol. 2019; 124(1): 70–77, doi: 10.1016/j.amjcard.2019.03.042, indexed in Pubmed: 31064667.
11. Fountain RB, Holmes DR, Chandrasekaran K, et al. The PROTECT AF (WATCHMAN Left Atrial Appendage System for Embolic PROTECTion in Patients with Atrial Fibrillation) trial. Am Heart J. 2006; 151(5): 956–961, doi: 10.1016/j.ahj.2006.02.005, indexed in Pubmed: 16644311.
12. Holmes D, Reddy V, Turi Z, et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. The Lancet. 2009; 374(9689): 534–542, doi: 10.1016/s0140-6736(09)61343-x.
13. Meier B, Blaauw Y, Khattab AA, et al. EHRA/EAPCI expert consensus statement on catheter-based left atrial appendage occlusion. Europace. 2014; 16(10): 1397–1416, doi: 10.1093/europace/euu174, indexed in Pubmed: 25172844.
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. Kappetein AP, Head SJ, Généreux P, et al. Valve Academic Research Consortium-2. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. EuroIntervention. 2012; 8(7): 782–795, doi: 10.4244/EIJV8I7A121, indexed in Pubmed: 23022744.
16. Hicks KA, Mahaffey KW, Mehran R, et al. 2017 Cardiovascular and stroke endpoint definitions for clinical trials. J Am Coll Cardiol. 2018; 71(9): 1021–1034, doi: 10.1016/j.jacc.2017.12.048, indexed in Pubmed: 29495982.
17. Team RC. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria 2018. https://www r-project org.
18. E. A. S. Daniel E. Ho KI, Gary King. MatchIt: Nonparametric Preprocessing for Parametric Causal Inference. E. A. S. Daniel E. Ho, Kosuke Imai, Gary King. J. Stat. Softw. 2011. http://gking.harvard.edu/matchit.
19. N. G. cobalt: Covariate Balance Tables and Plots. R package version 3.4.1. https://github.com/ngreifer/cobalt. 2018.
20. Zangrillo A, Mazzone P, Oriani A, et al. Noninvasive ventilation during left atrial appendage closure under sedation: Preliminary experience with the Janus Mask. Ann Card Anaesth. 2019; 22(4): 400–406, doi: 10.4103/aca.ACA_145_18, indexed in Pubmed: 31621676.
21. Freeman JV, Varosy P, Price MJ, et al. The NCDR left atrial appendage occlusion registry. J Am Coll Cardiol. 2020; 75(13): 1503–1518, doi: 10.1016/j.jacc.2019.12.040, indexed in Pubmed: 32238316.
22. Reddy VY, Gibson DN, Kar S, et al. Post-Approval U.S. Experience with left atrial appendage closure for stroke prevention in atrial fibrillation. J Am Coll Cardiol. 2017; 69(3): 253–261, doi: 10.1016/j.jacc.2016.10.010, indexed in Pubmed: 27816552.
23. Reddy VY, Holmes D, Doshi SK, et al. Safety of percutaneous left atrial appendage closure: results from the Watchman Left Atrial Appendage System for Embolic Protection in Patients with AF (PROTECT AF) clinical trial and the Continued Access Registry. Circulation. 2011; 123(4): 417–424, doi: 10.1161/CIRCULATIONAHA.110.976449, indexed in Pubmed: 21242484.
24. Boersma LVA, Schmidt B, Betts TR, et al. Implant success and safety of left atrial appendage closure with the WATCHMAN device: peri-procedural outcomes from the EWOLUTION registry. Eur Heart J. 2016; 37(31): 2465–2474, doi: 10.1093/eurheartj/ehv730, indexed in Pubmed: 26822918.
25. Boersma LV, Ince H, Kische S, et al. Efficacy and safety of left atrial appendage closure with WATCHMAN in patients with or without contraindication to oral anticoagulation: 1-year follow-up outcome data of the EWOLUTION trial. Heart Rhythm. 2017; 14(9): 1302–1308, doi: 10.1016/j.hrthm.2017.05.038, indexed in Pubmed: 28577840.

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Comparison of 4-French versus 5-French sheaths for diagnostic coronary angiography via the snuffbox approach

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Abstract

Background: *Although a shorter hemostasis duration would be expected when compared with the conventional radial approach as the diameter of the distal radial artery is smaller than that of the conventional radial artery, the optimal duration of hemostasis in diagnostic coronary angiography (CAG) via the distal radial approach, termed the snuffbox approach, has not been well investigated.*

Methods: *Data from 171 patients were retrospectively collected (55 and 116 patients in the 4-French [Fr] and 5-Fr sheath groups, respectively). The patients had suspected myocardial ischemia and were undergoing diagnostic CAG via the snuffbox approach at a single center between January 2019 and August 2019.*

Results: *The mean age of the study population was 67.6 ± 11.0 years, and 69% were male. The left snuffbox approach was performed in 146 (85.4%) patients. The mean snuffbox puncture time, defined as the time interval between local anesthesia and sheath cannulation, was 145.1 ± 120.8 s. The hemostasis duration was significantly shorter in the 4-Fr sheath group than in the 5-Fr sheath group (70 [62–90] vs. 120 [120–130] min; $p < 0.001$). There were local hematomas, defined as ≤ 5 cm in diameter, at the puncture site in 8 (4.7%) patients. Moreover, there were no conventional and distal radial artery occlusions, assessed by manual pulse, after hemostasis in the study population during hospitalization.*

Conclusions: *Successful hemostasis was obtained within 2 h for diagnostic CAG via the snuffbox approach using the 4-Fr or 5-Fr sheaths.* (Cardiol J 2021; 28, 4: 528–533)

Key words: coronary angiography, coronary catheterization, hemostasis, radial artery

Introduction

The conventional radial artery approach in coronary angiography (CAG) is currently preferred due to several advantages (e.g., reduced vascular complications, patient comfort, and early ambulation) when compared with the femoral approach [1–3]. Because of these advantages, it is recommended as the first and standard approach for CAG and percutaneous coronary intervention (PCI) in the current guidelines [4]. However, radial artery occlusion remains the most common local vascular complication, with a reported incidence of between 0.8% and 30% [5]. Furthermore, significant access-site complications, including pseudoaneurysm and arteriovenous fistulas, which occasionally require surgery or transfusions, cannot be avoided [6].

Recently, the distal radial approach, termed the snuffbox approach, has gained the interest of interventional cardiologists because it may have fewer complications than the conventional radial artery approach. The feasibility of the snuffbox

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approach for coronary catheterization has been demonstrated in several studies, showing potential benefits in terms of less bleeding and few access-site complications [7–14]. With respect to hemostasis in the snuffbox approach, a shorter hemostasis duration would be expected compared with the conventional radial approach as the diameter of the distal radial artery is significantly smaller than that of the conventional radial artery [15, 16]. However, the optimal duration for hemostasis after CAG via the snuffbox approach has not been well investigated. Therefore, the aim of the study was to investigate the hemostasis duration after diagnostic CAG via the snuffbox approach using either a 4-French (Fr) or 5-Fr sheath.

Methods

Data was collected retrospectively from patients with suspected myocardial ischemia, at a single center, who underwent diagnostic CAG via the snuffbox approach between January 2019 and August 2019. A single operator (Y.K.) attempted the snuffbox approach in patients who had a well--palpable pulse in the anatomical snuffbox area. The study protocol was approved by the institutional review board of Chonnam National University Hospital (approval number: CNUH-2019-280), who waived the requirement for informed consent owing to the retrospective observational study design.

Local anesthesia was achieved through a 1-mL lidocaine hydrochloride injection into an anatomical snuffbox with a 26-gauge needle. Thereafter, puncture was performed using a 21-gauge open needle using the anterior wall puncture technique. After a successful puncture, a 0.018-inch hair wire was inserted; this was followed by the insertion of a 4-Fr or 5-Fr radial sheath (Prelude Radial®; Merit Medical, UT, USA). The selection of the sheath size was left at the physician's discretion. After successful sheath cannulation, a cocktail including 2.5 mg of verapamil, 0.2 mg of nitroglycerine, and 3000 units of unfractionated heparin was administered before catheterization in all patients. Hemostasis was obtained using a compressive bandage with gauze (**Suppl. Video 1**). A local hematoma was defined if the hematoma was ≤ 5 cm in diameter according to Early Discharge After Transradial Stenting of Coronary Arteries (EASY) classification I [17].

Statistical analysis

All categorical variables were presented as numbers with percentages and were analyzed using the χ^2 test or Fisher exact test. Continuous variables were expressed as mean with standard deviation or median with interquartile ranges and were compared using the un-paired t-test or Mann-Whitney U test, as appropriate. Statistical analyses were conducted using R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS 22.0 for Windows (SPSS-PC, Chicago, IL, USA).

Results

Between January 2019 and August 2019, there were a total of 474 consecutive patients who had planned to undergo CAG or PCI by single operator. Among them, cases of conventional radial or femoral approach, failed snuffbox punctures, failed CAG, PCI, and CAG using a 6-Fr sheath were excluded. Therefore, a total of 171 patients were selected who underwent successful diagnostic CAG via the snuffbox approach using a 4-Fr (n = 55) or 5-Fr sheath (n = 116) (Fig. 1).

During the study period, the success rate with the snuffbox approach was 97.2% (380/391). Baseline clinical characteristics of the study population, including the 4-Fr and 5-Fr sheath groups, are shown in Table 1. The mean age was 67.6 ± ± 11.0 years and 118 (69.0%) patients were male. There were no differences in body mass index, systolic and diastolic blood pressure, hypertension, diabetes mellitus, chronic kidney disease, and periprocedural anti-thrombotic medication. The 5-Fr sheath group had a higher composition of male than the 4-Fr sheath group. The most common reason for CAG was a suspicious coronary artery disease (95.3%).

The mean and median hemostasis durations were significantly shorter in the 4-Fr sheath group than the 5-Fr sheath group, as shown in Figure 2 (88.4 ± 42.0 and 70 [62–90] min vs. 134.0 ± 35.2 and 120 [120–130] min; $p < 0.001$). With respect to puncture-site complications, there were no conventional and distal radial artery occlusions, assessed by manual pulse, during hospitalization. Local hematomas occurred in 8 (4.7%) cases, including 3 cases in the 4-Fr group and 5 cases in the 5-Fr group. There were no cases of puncture-related local numbness or major bleeding complications requiring surgery or transfusions, as shown in Table 2.

Discussion

In the present study, the median hemostasis durations were about 1 h and 2 h in the 4-Fr and

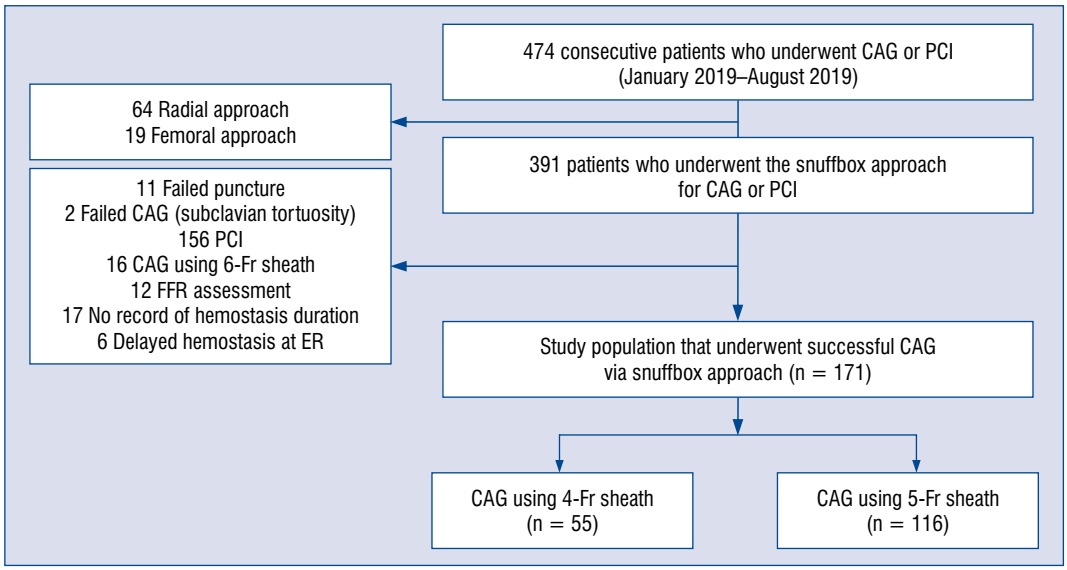

Figure 1. Study flow chart; CAG — coronary angiography; PCI — percutaneous coronary intervention; FFR — fractional flow reserve; ER — emergency room.

Table 1. Baseline clinical characteristics of the study population.

Patients	Total (n = 171)	4 Fr (n = 55)	5 Fr (n = 116)	P
Demographics				
Age [years]	67.6 ± 11.0	68.0 ± 10.3	67.4 ± 11.3	0.752
Male	118 (69.0%)	24 (43.6%)	94 (81.0%)	< 0.001
Body mass index [kg/m^2]	24.9 ± 3.5	24.5 ± 4.1	25.2 ± 3.2	0.345
Vital signs				
SBP [mmHg]	127.8 ± 21.4	129.6 ± 21.2	127.0 ± 21.6	0.462
DBP [mmHg]	76.2 ± 14.2	77.9 ± 12.9	75.4 ± 14.8	0.274
Heart rate [bpm]	76.4 ± 13.5	79.3 ± 13.1	75.0 ± 13.5	0.055
Risk factors				
Hypertension	130 (76.0%)	37 (67.3%)	93 (80.2%)	0.098
Diabetes mellitus	52 (30.4%)	14 (25.5%)	38 (32.8%)	0.428
Dyslipidemia	102 (59.6%)	29 (52.7%)	73 (62.9%)	0.270
Current smoking	27 (15.8%)	6 (10.9%)	21 (18.1%)	0.327
CKD (eGFR < 60 mL/min/1.73 m^2)	42 (24.6%)	12 (21.8%)	30 (25.9%)	0.701
Laboratory findings				
Hemoglobin [g/dL]	13.0 ± 2.0	12.7 ± 1.9	13.1 ± 2.1	0.231
Platelets [10^3/mm^3]	222 ± 67	231± 76	217 ± 63	0.230
PT-INR	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	0.785
Final ACT	244.4 ± 65.2	250.8 ± 67.2	241.4 ± 64.2	0.378
Reasons for CAG				
Investigation for CAD	163 (95.3%)	52 (94.5%)	111 (95.7%)	0.741
Valvular heart disease	8 (4.7%)	3 (5.5%)	5 (4.3%)	0.741
Periprocedural anti-thrombotic medication				
ASA loading	69 (40.4%)	22 (40.0%)	47 (40.4%)	0.949
Clopidogrel loading	90 (52.6%)	34 (61.8%)	56 (48.3%)	0.105
ASA	162 (94.7%)	49 (89.1%)	113 (97.4%)	0.056

→

Table 1 (cont.). Baseline clinical characteristics of the study population.

Patients	Total (n = 171)	4 Fr (n = 55)	5 Fr (n = 116)	P
P2Y12 inhibitor:	159 (93.0%)	49 (89.1%)	110 (94.8%)	0.293
Clopidogrel	153 (89.5%)	48 (87.3%)	105 (90.5%)	
Ticagrelor	6 (3.5%)	1 (1.8%)	5 (4.3%)	
Oral anticoagulation	14 (8.2%)	4 (7.3%)	10 (8.6%)	0.799
UFH or LMWH injection	171 (100%)	55 (100%)	116 (100%)	

Values are presented as mean ± standard deviation or as number (%). ACT — activated clotting time; ASA — acetylsalicylic acid; CAD — coronary artery disease; CAG — coronary angiography; CKD — chronic kidney disease; DBP — diastolic blood pressure; eGFR — estimated glomerular filtration rate; LMWH — low molecular weight heparin; PT-INR — prothrombin time-international normalized ratio; SBP — systolic blood pressure; UFH — unfractionated heparin

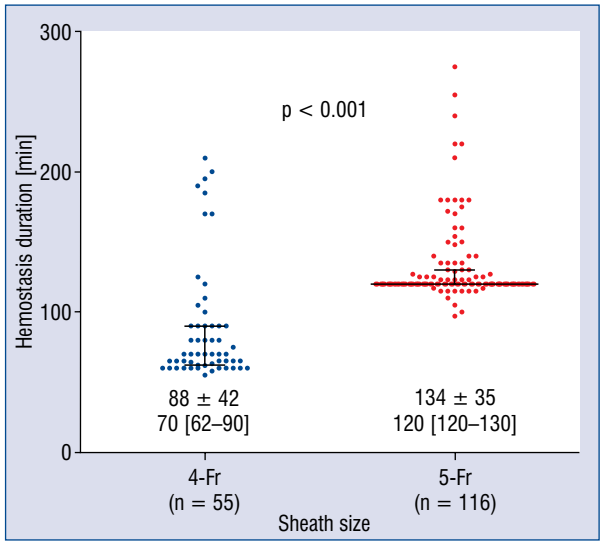

Figure 2. Hemostasis duration during the snuffbox approach according to sheath size.

5-Fr sheath groups, respectively. Moreover, there were no conventional and distal radial artery occlusions in any of the patients during hospitalization. According to available research, this is the first study reporting hemostasis duration during the snuffbox approach according to sheath size.

Although several studies have reported that 3 h could be enough to achieve successful hemostasis with the compressive bandage method or using a radial compression device, they did not suggest an optimal hemostasis duration according to sheath size, in PCI or in CAG [7–9]. Conversely, the current study revealed common hemostasis duration used in patients who underwent diagnostic CAG using a 4-Fr or 5-Fr sheath. Despite the relatively short hemostasis durations (1 h with 4-Fr and 2 h with 5-Fr sheaths), successful hemostasis, without access-site complications, was achieved in most patients; local hematoma (EASY classification I) oc-

Table 2. Snuffbox characteristics and puncture site complications.

Patients	Total (n = 171)	4 Fr (n = 55)	5 Fr (n = 116)	P
Snuffbox approach details				
Puncture time				
Mean [s]	145.1 ± 120.8	161.2 ± 148.3	137.4 ± 105.1	0.288
Median [s]	104 [77.5–163]	105 [84.5–176]	104 [72–152]	0.371
Left snuffbox approach	146 (85.4%)	51 (92.7%)	95 (81.9%)	0.101
Hemostasis duration				
Mean [min]	118.4 ± 40.0	88.4 ± 42.0	134.0 ± 35.2	< 0.001
Median [min]	120 [93.5–125]	70 [62–90]	120 [120–130]	< 0.001
Puncture site complications				
Conventional RA occlusion	0 (0%)	0 (0%)	0 (0%)	
Distal RA occlusion	0 (0%)	0 (0%)	0 (0%)	
Local numbness	0 (0%)	0 (0%)	0 (0%)	
Local hematoma	8 (4.7%)	3 (5.5%)	5 (4.3%)	0.934

Values are presented as mean ± standard deviation or as number (%). RA — radial artery

curred in only 4.7% of the study population. Therefore, diagnostic CAG via the snuffbox approach, using a small size sheath, would be beneficial for patients who require an earlier discharge to return to their daily activities.

There were no conventional radial artery occlusions observed in the present study. Although there is concern that the sheath inserted through the snuffbox approach could damage the conventional radial artery, several studies demonstrated that no conventional radial artery occlusion was observed with successful hemostasis [7–10]. Hemostatic compression after conventional radial approach can lead to blood flow interruption in the conventional radial artery; the absence of blood flow during hemostasis was a potent predictor of conventional radial artery occlusion [18, 19]. Thus, the snuffbox approach could be useful to preserve an access route in patients who may have a repeat coronary catheterization. In addition, the present study suggests that the snuffbox approach may be appropriate in providing an alternative access route in patients with chronic kidney disease who need to preserve their radial artery for the creation of an arteriovenous fistula in the future. However, a further prospective study is needed to confirm the patency of the conventional radial artery after the snuffbox approach using functional and imaging assessment.

Limitations of the study

This study has several limitations. First, this study has the inherent limitations associated with retrospective studies with small sample sizes. Second, the hemostasis duration after the snuffbox approach was evaluated without a control group. Therefore, the presented results should only be regarded as hypothesis generating. Third, although a reduction in the risk of conventional and distal radial artery occlusion is a potential benefit of the snuffbox approach, the occurrence of radial artery occlusion was evaluated only by manual pulse, without vascular ultrasonography. Furthermore, the patency of both radial arteries was not evaluated after discharge. These limitations could lead to an underestimation of access-site complications such as pseudoaneurysm or delayed radial artery occlusion.

Conclusions

Successful hemostasis was obtained within 2 h for diagnostic CAG via the snuffbox approach using the 4-Fr or 5-Fr sheaths. Further, large randomized control trials are needed to confirm the ideal hemostasis duration and the safety of the snuffbox approach in CAG and even PCI.

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Conflict of interest: None declared

References

1. Ferrante G, Rao SV, Jüni P, et al. Radial versus femoral access for coronary interventions across the entire spectrum of patients with coronary artery disease: a meta-analysis of randomized trials. JACC Cardiovasc Interv. 2016; 9(14): 1419–1434, doi: 10.1016/j.jcin.2016.04.014, indexed in Pubmed: 27372195.
2. Jolly SS, Yusuf S, Cairns J, et al. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial. Lancet. 2011; 377(9775): 1409–1420, doi: 10.1016/S0140-6736(11)60404-2, indexed in Pubmed: 21470671.
3. Valgimigli M, Gagnor A, Calabró P, et al. Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: a randomised multicentre trial. Lancet. 2015; 385(9986): 2465–2476, doi: 10.1016/S0140-6736(15)60292-6, indexed in Pubmed: 25791214.
4. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. ESC Scientific Document Group, ESC Scientific Document Group . Considerations for the choice between coronary artery bypass grafting and percutaneous coronary intervention as revascularization strategies in major categories of patients with stable multivessel coronary artery disease: an accompanying article of the task force of the 2018 ESC/EACTS guidelines on myocardial revascularization. Eur Heart J. 2019; 40(2): 204–212, doi: 10.1093/eurheartj/ehy532, indexed in Pubmed: 30165435.
5. Rashid M, Kwok CS, Pancholy S, et al. Radial artery occlusion after transradial interventions: A systematic review and meta-analysis. J Am Heart Assoc. 2016; 5(1), doi: 10.1161/JAHA.115.002686, indexed in Pubmed: 26811162.
6. Dandekar VK, Vidovich MI, Shroff AR. Complications of transradial catheterization. Cardiovasc Revasc Med. 2012; 13(1): 39–50, doi: 10.1016/j.carrev.2011.08.005, indexed in Pubmed: 22115936.
7. Kiemeneij F. Left distal transradial access in the anatomical snuffbox for coronary angiography (ldTRA) and interventions (ldTRI). EuroIntervention. 2017; 13(7): 851–857, doi: 10.4244/EIJ-D-17-00079, indexed in Pubmed: 28506941.
8. Lee JW, Park SW, Son JW, et al. Real-world experience of the left distal transradial approach for coronary angiography and percutaneous coronary intervention: a prospective observational study (LeDRA). EuroIntervention. 2018; 14(9): e995–e99e1003, doi: 10.4244/EIJ-D-18-00635, indexed in Pubmed: 30222122.
9. Ziakas A, Koutouzis M, Didagelos M, et al. Right arm distal transradial (snuffbox) access for coronary catheterization: Initial experience. Hellenic J Cardiol. 2018 [Epub ahead of print], doi: 10.1016/j.hjc.2018.10.008, indexed in Pubmed: 30389385.
10. Soydan E, Akın M. Coronary angiography using the left distal radial approach — An alternative site to conventional radial coronary angiography. Anatol J Cardiol. 2018; 19(4): 243–248, doi: 10.14744/AnatolJCardiol.2018.59932, indexed in Pubmed: 29578203.
11. Kim Y, Ahn Y, Kim MC, et al. Gender differences in the distal radial artery diameter for the snuffbox approach. Cardiol J. 2018;

25(5): 639–641, doi: 10.5603/CJ.2018.0128, indexed in Pubmed: 30394514.
12. Berezhnoi K, Kokov L, Vanyukov A, et al. Complete revascularization via left snuffbox approach in a nonagenarian patient with acute myocardial infarction. Cardiol J. 2018; 25(4): 530–531, doi: 10.5603/CJ.2018.0083, indexed in Pubmed: 30211930.
13. Kim Y, Jeong MH, Kim MC, et al. Successful primary percutaneous coronary intervention in patient with ST-segment elevation myocardial infarction via left snuffbox approach: Patient advantages. Cardiol J. 2019; 26(2): 198–199, doi: 10.5603/CJ.2019.0042, indexed in Pubmed: 31032871.
14. Kim Y, Jeong MH, Kim MC, et al. Successful percutaneous coronary intervention in patients with recanalized thrombus: Saving a radial artery by snuffbox approach. Cardiol J. 2019; 26(3): 292–293, doi: 10.5603/CJ.2019.0057, indexed in Pubmed: 31246265.
15. Kim Y, Ahn Y, Kim I, et al. Feasibility of Coronary Angiography and Percutaneous Coronary Intervention via Left Snuffbox Approach. Korean Circ J. 2018; 48(12): 1120–1130, doi: 10.4070/kcj.2018.0181.
16. Vefali V, Saricam E. The comparison of traditional radial access and novel distal radial access for cardiac catheterization. Cardiovasc Revasc Med. 2019; [Epub ahead of print].
17. Rao SV, Bernat I, Bertrand OF. Remaining challenges and opportunities for improvement in percutaneous transradial coronary procedures. Eur Heart J. 2012; 33(20): 2521–2526, doi: 10.1093/eurheartj/ehs169.
18. Sanmartin M, Gomez M, Rumoroso JR, et al. Interruption of blood flow during compression and radial artery occlusion after transradial catheterization. Catheter Cardiovasc Interv. 2007; 70(2): 185–189, doi: 10.1002/ccd.21058, indexed in Pubmed: 17203470.
19. Pancholy SB, Patel TM. Effect of duration of hemostatic compression on radial artery occlusion after transradial access. Catheter Cardiovasc Interv. 2012; 79(1): 78–81, doi: 10.1002/ccd.22963, indexed in Pubmed: 21584923.

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The effect of *Cistus incanus* herbal tea supplementation on oxidative stress markers and lipid profile in healthy adults

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Abstract

Background: *Oxidative stress and dyslipidemia play a critical role in the development of cardiovascular disease (CVD). Regular intake of polyphenol-rich diets is associated with a reduced risk of CVDs.*

Methods: *The present study was a pilot study with 24 healthy volunteers and was designed to determine if a 12-week administration of Cistus incanus herbal tea, containing phenolic acids and flavonoids, reduces cardiovascular risk factors including oxidative stress and dyslipidemia in healthy adults. Phenolic compounds profile and antibacterial activity of Cistus incanus infusion were also measured.*

Results: *Herbal infusion led to improvement in lipid profile by increase (Δ4%, $p = 0.033$) high-density lipoprotein cholesterol concentration and decrease triglyceride (Δ14%, $p = 0.013$) concentrations. In addition, the Cistus incanus diet was associated with decreased serum concentrations of malondialdehyde (Δ16%, $p < 0.01$) and advanced oxidation protein products (Δ18%, $p < 0.001$).*

Conclusions: *Cistus incanus administration decreases cardiovascular risk factors including oxidative stress and dyslipidemia and this action supports the idea of using Cistus incanus tea on a daily basis as an effective dietary component for prevention of atherosclerotic CVD.* (Cardiol J 2021; 28, 4: 534–542)

Keywords: ***Cistus incanus*, lipid profile, oxidative stress markers**

Introduction

Cistus incanus, a genus belonging to the family of *Cistaceae*, provides a rich source of polyphenols and various Cistus species herbal teas have been used in folk medicine for treatment of diarrhea, fever, and skin disorders. It also has antispasmodic, anti-inflammatory and antimicrobial agents [1]. Currently, numerous producers offer *Cistus incanus* herbal infusion (Cistus tea) or dietary supplements consisting of this plant material, or extracts of it. These products are especially promoted with regard to a high content and diverse profile of polyphenolic substances with strong antioxidant activity [2]. It has been proposed that polyphenols can act as antioxidants by suppression of reactive species formation through enzyme inhibition or the sequestration of trace elements involved

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in the production of free radicals [3]. Reactive oxygen species are involved in pathogenesis of diverse human diseases which play a particular role in cardiovascular diseases [4, 5]. Polyphenols are able to attenuate the oxidation of low-density lipoproteins (LDL), possess vasodilatory and anti-inflammatory activity, and modulate lipid metabolism and apoptotic processes in endothelium [6]. It has been suggested that most of these effects are a consequence of the antioxidant properties of polyphenols; however, other mechanisms based on their interaction with molecular signaling pathways may be involved [2, 7].

Epidemiological studies provide evidence for an inverse relationship between the consumption of polyphenolic substance-rich foods and cardiovascular complications [8]; however, most of the epidemiological studies aimed at investigating cardiovascular benefits of polyphenols have concerned tea, red wine, coca and polyphenol-rich fruits such as grapes. Furthermore, although there are numerous studies evaluating the composition and antioxidant capacities of Cistus infusion, however, clinical studies focused on the influence of *Cistus incanus* on oxidation balance and cardiovascular risk factors are limited [9]. Thus, the purpose of the present study was to investigate the impact of a 3-month supplement of commercially available *Cistus incanus* tea on oxidative stress markers and lipid profile in healthy adults. Additionally, the phenolic compounds profile was determined as well as antibacterial activity of when using *Cistus incanus* aqueous infusions.

Methods

Study subjects

A total of 24 healthy adults were recruited for the study. All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and were approved by the Medical Ethics Committee of Medical University of Gdansk. All participants provided written informed consent.

During the interview, sociodemographic and clinical information was collected. The sociodemographic data included age, and gender. Clinical variables included vascular risk factors: smoking status, alcohol intake, physical activity, lifestyle, and dietary habits. All participants were non-smoking and were sedentary or moderately physically active (at least 2 times a week). All volunteers were instructed not to change their diet or physical activity during the study. The exclusion criteria were: chronic disease, current use of prescribed pharmaceuticals, intense physical activity (up to 3 times a week) and a body mass index (BMI) greater than 25 kg/m^2. The study period was 12 weeks, during which participants would intake a *Cistus incanus* infusion 3 times a day (portion of 2 g of dry tea per day reinfused 3 times in 250 mL of boiling water for 3 min). Dietary compliance was assessed using daily study records completed by the participants.

Analysis of blood samples from subjects

The peripheral fasting blood samples were collected before (baseline) and after 6 and 12 weeks of *Cistus incanus* infusion administration. The serum was separated by centrifugation at 1000×g for 15 min and stored at –80°C pending analysis. Total cholesterol (TC) and triglycerides (TG) were measured by standard enzymatic colorimetric tests (Pointe Scientific Poland). High density lipoproteins (HDLs) were isolated by precipitation of apolipoprotein B (apoB)-containing lipoproteins with dextran sulfate 50000/Mg^{2+} reagent and HDL cholesterol (HDL-C) was determined enzymatically. LDL cholesterol (LDL-C) concentration was calculated using the Friedewald formula. Paraoxonase (PONase) and arylesterase (AREase) activities of paraoxonase-1 (PON-1) were measured based on paraoxon and phenyl acetate hydrolysis, respectively [10, 11]. Malondialdehyde (MDA) concentration was analyzed by fluorescence spectroscopy using a modified thiobarbituric acid-reactive substance [12]. Advanced oxidative protein product (AOPP) determination was performed based on spectrophotometric detection [13].

Plant material

The *Cistus incanus* herb was purchased from a manufacturer in Poland (herbal manufacture ASTRON Józef Tabor). According to the manufacture information, the shrub grows in the Mediterranean Region of Turkey around the city of Antalya, and the shrub's leaves are harvested from May to August.

Determination of total polyphenols and antioxidant activity

The leaves (1.00 g) were brewed with 100 mL of boiling and deionized water for 15 min and the procedure was repeated two times to finally produce the first, second and third infusion. The Folin-Ciocalteu method was used for total phenolic content (TPC) determination [14]. The method described in the European Pharmacopeia monograph for *Betulae* folium was used for total

flavonoid content (TFC) determination [15]. The total phenolic acid content was determined using the spectrophotometric method with Arnov's reagent according to procedures described in the Polish Pharmacopoeia [16]. L-ascorbic acid (AA) was determined by spectrophotometric method [17]. 2,2-diphenyl-1-picrylhydrazyl radical (DPPH) scavenging assay [18] and ferric ion reducing antioxidant power (FRAP) assay [19] were used to determine the reducing antioxidant power of the *Cistus incanus* infusions.

Chromatographic analysis: HPLC conditions

Before HPLC analysis, all the infusions were filtered through a 0.2 μm nylon filter film (Mecherey, Nagel, Germany) and 20 μL of the filtrate was injected into the HPLC system. Chromatographic separation and quantitation of phenolic compounds (gallic, caffeic, chlorogenic, syringic, vanillic, p-coumaric, elagic and ferulic acids, and rutin, isoquercetin, quercetin, myricetin, kaempferol, and luteolin 7-glucoside) were performed on a Hypersil Gold C18 column (250 × 4.6 mm, 5 μm particles, Thermo Scientific, Runcorn, UK) maintained at 35°C, using acetonitrile — 0.2% trifluoroacetic acid solution and water — 0.2% trifluoroacetic acid solution as the mobile phase using a gradient program and monitoring system as previously described [20].

Antibacterial activity

A sample of *Cistus incanus* (2.5 g) was infused three times with 50 mL of boiling, deionised water for 15 min to produce the first, second, and third infusion. The minimal inhibitory concentration (MIC) and minimal bactericidal concentration (MBC) of all the infusions were assessed by the micro-broth dilution method according to the EUCAST (European Committee for Antimicrobial Susceptibility Testing) and CLSI (Clinical and Laboratory Standards Institute) reference procedures. Assays were carried out against selected reference and clinical strains Gram-positive: *Staphylococcus aureus* ATCC 6538, methicillin-resistant *Staphylococcus aureus* 12,673 (clinical isolates), *Staphylococcus epidermidis* ATCC 14,990, methicillin-resistant *Staphylococcus epidermidis* (clinical isolates), *Streptococcus pneumoniae* (clinical isolates), *Bacillus subtilis* ATCC 6633, and Gram-negative bacteria *Escherichia coli* ATCC 8739. Clinical isolates were obtained from St. Albert Specialist Hospital in Gdansk (Independent Public Health Care Facility in Gdansk, Poland).

Statistical analysis

Statistical analysis was performed using the Statistica software package (STATISTICA 12.0 Statsoft Poland). The Shapiro-Wilk test was used to establish data distributions. Continuous variables were expressed as a mean ± standard deviation or median with 25th and 75th percentiles (interquartile range [IQR]). Potential differences among the results were analyzed using a repeated-measures ANOVA with the Tukey multiple comparison test for parametric variables and with the Friedman test for non-parametric data. Statistical significance was set at $p < 0.05$.

Results

The study participants were aged between 23 and 25 years old (21 females and 3 males) with a body mass index (BMI) of 21.3 ± 0.6 kg/m^2. There were no significant differences in BMI during the 12-week period of dietary modification.

Lipid profile and serum oxidative stress parameters

Analysis of the lipid profile revealed a significant increase in HDL-C concentration (47 ± 9 vs. 50 ± 9 mg/dL; $p = 0.033$) and a decrease in TG levels (71 ± 23 vs. 60 ± 24 mg/dL; $p = 0.013$), there were no changes in the concentration of TC and LDL-C over 12 weeks of follow up (Fig. 1). The concentrations of serum oxidative stress markers — MDA and AOPP were measured before and after 6 and 12 weeks of *Cistus incanus* herbal tea supplementation. A reduction of about 16% in MDA concentration (20 ± 5.5 vs. 15 ± 4.9 μmol/L; $p < 0.01$) and 18% in AOPP concentration (66 ± ± 18 vs. 53 ± 17 μmol/L; $p < 0.001$) after the first 6 weeks of *Cistus incanus* intake was observed (Fig. 2). The following 6 weeks of supplementation showed no further significant changes in concentrations of MDA (15 ± 4.9 vs. 15 ± 4.5 μmol/L) and AOPP (53 ± 17 vs. 54 ± 16 μmol/L). There was no significant effect of *Cistus* infusion on PON-1 activities, measured both toward paraoxon and phenyl acetate as substrates (Table 1).

Phenolic content and antioxidant capacity

Total phenolic acids (TPC), flavonoids (TFC), phenolic acids (TPAC) and L-ascorbic acid (AA) contents in multiple aqueous extractions of *Cistus incanus* were determined, the results are presented in Table 2. Analysis of variance and the Duncan multiple range test indicate a significant

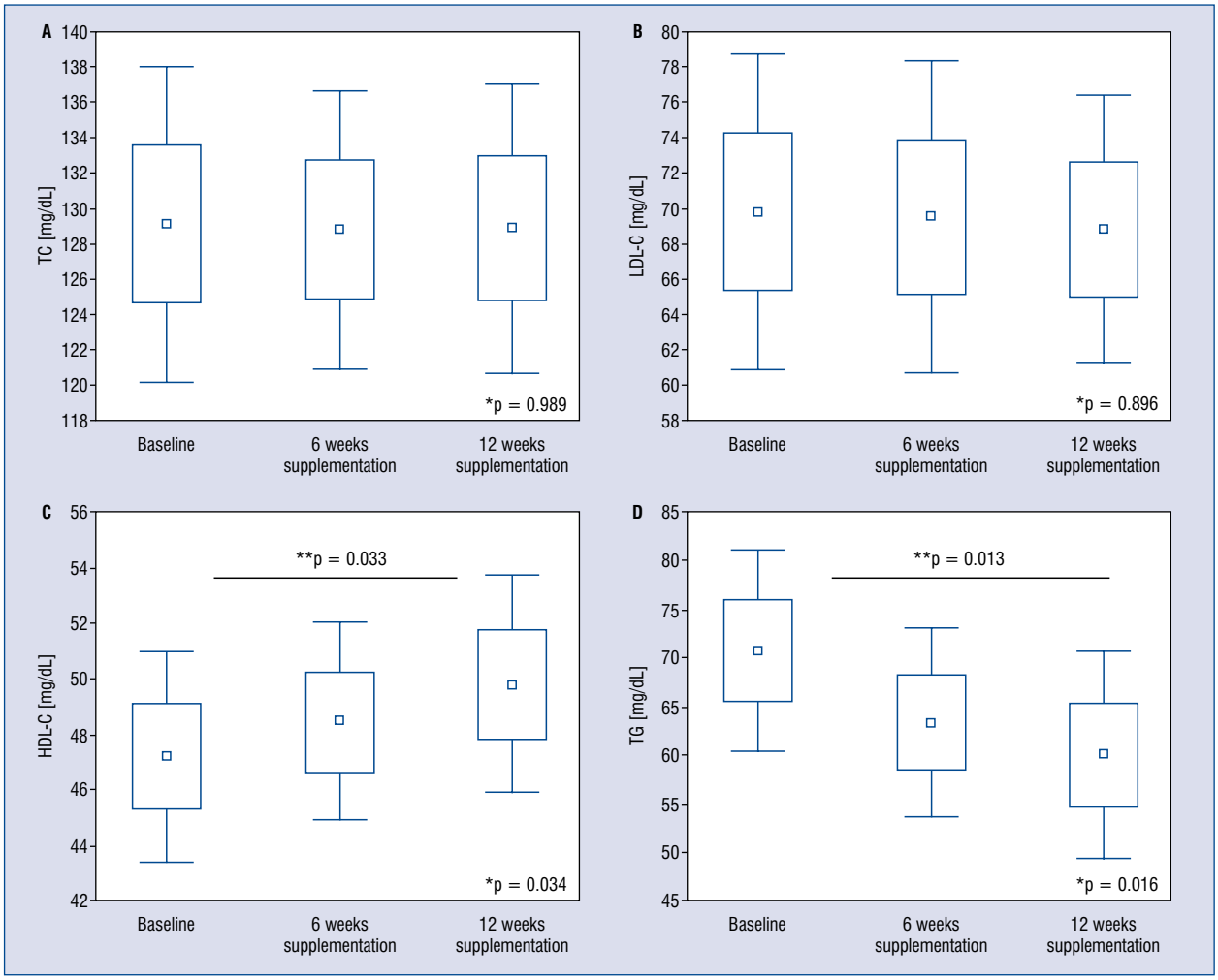

Figure 1. Serum concentrations of total cholesterol (TC) (**A**), low density lipoprotein cholesterol (LDL-C) (**B**), high density lipoprotein cholesterol (HDL-C) (**C**), and triglycerides (TG) (**D**); at baseline, after 6- and 12-weeks supplementation with *Cistus incanus* herbal tea. All values represent means ± standard error. Data were analyzed using a repeated-measures ANOVA (*) with the Tukey post hoc test (**) to determine where differences existed.

influence of multiple extractions ($p < 0.05$) on TPC, TFC, TPAC, and AA. The effects of multiple extractions on the phenolic acids and flavonoids content of Cistus infusions are presented in Tables 3 and 4, respectively. Among phenolic acids the most abundant was gallic acid. Caffeic and vanilic acids were determined only in the first extraction, while chlorogenic, syringic and ferulic acids were not found. In the case of flavonoids, myricetin and isoquercetin were the most abundant, while keampferol was not determined. According to the TPC, TFC, TPAC and AA the content of phenolic acids and flavonoids also gradually decreased and the lowest content was obtained in the third extract of Cistus infusions. The antioxidant capacities of *Cistus incanus* evaluated by DPPH and FRAP assays exhibited a gradual decrease and the lowest activity was obtained in the third extract of Cistus infusions (Table 5).

Antibacterial activity

To investigate the possible antibacterial activity of aqueous *Cistus incanus*, Gram-positive and Gram-negative bacteria strains were used. The values of MIC and MBC are shown in Table 6. For all Gram-positive bacteria, the MIC value was 4 mg/mL and the MBC ranged from 8 to 32 mg/mL, suggesting a bacteriostatic effect. There was no difference in antimicrobial activity of the extracts between successive infusions. No activity was demonstrated against Gram-negative bacteria in the tested concentration range.

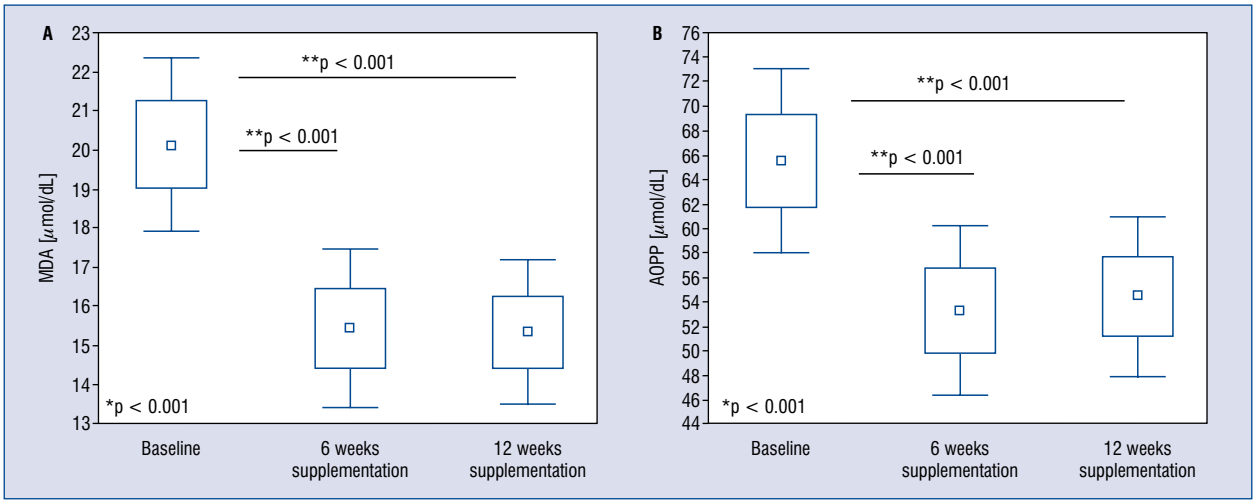

Figure 2. Serum concentrations of malondialdehyde (MDA) (**A**) and advanced oxidative protein products (AOPP) (**B**); at baseline, after 6- and 12-weeks supplementation with *Cistus incanus* herbal tea. All values represent means ± ± standard error. Data were analysed using a repeated-measures ANOVA (*) with the Tukey multiple comparison test (**) to determine where differences existed.

Table 1. Paraoxonase-1 (PON-1) activity before, after 6 and 12 weeks of *Cistus incanus* herbal tea supplementation.

PON-1 activity	Baseline		6 weeks		12 weeks	
	Median	IQR	Median	IQR	Median	IQR
Paraoxonase [U/L]	104	75–187	94	73–193	102	78–195
Arylesterease [kU/L]	211	172–236	211	176–234	206	158–233

*Potential differences among the results were analyzed using the Friedman test; IQR — interquartile range

Table 2. Total phenolic (TPC) and flavonoids (TFC), phenolic acids (TPAC) and L-ascorbic acid (AA) contents in *Cistus incanus* multiple aqueous extractions.

Extraction	TPC [mg GAE/g dw]	TFC [mg QE/g dw]	TPAC [mg CAE/g dw]	AA [mg AA/g dw]
First	98.5 ± 1.3	2.5 ± 0.4	10.9 ± 0.9	0.86 ± 0.05
Second	85.3 ± 1.1	1.8 ± 0.5	9.0 ± 1.1	0.76 ± 0.02
Third	78.5 ± 1.0	1.6 ± 0.9	7.7± 1.8	0.67 ± 0.03

Values are expressed as means ± standard deviation (n = 3); mg GAE/g dw — mg of gallic acid equivalent per gram dry weigh; mg QE/g dw — mg of quercetin equivalent per gram dry weight; mg CAE/g dw — mg of caffeic acid equivalent per gram dry weight; mg AA/g/dw — mg of L-ascorbic acid per gram dry weight

Table 3. The contents of phenolic acids-gallic (GA), caffeic (CA), chlorogenic (CGA), syringic (SA), vanillic (VA), para-coumaric (pCA), elagic (EA), ferulic (FA) in *Cistus incanus* multiple aqueous extractions.

Extraction	GA [μg/g dw]	CA [μg/g dw]	CGA [μg/g dw]	SA [μg/g dw]	VA [μg/g dw]	pCA [μg/g dw]	EA [μg/g dw]	FA [μg/g dw]
First	496.4 ± 3.1	38.5 ± 1.4	ND	ND	26.2 ± 1.2	126.5 ± 2.3	243.6 ± 2.7	ND
Second	340.3 ± 2.4	ND	ND	ND	ND	76.1 ± 2.0	185.3 ± 1.8	ND
Third	260.6 ± 2.1	ND	ND	ND	ND	60.2 ± 1.0	143.4 ± 1.1	ND

Values are expressed as means ± standard deviation (n = 3); ND — not detectable

Limits of detection [μg/mL]: CA — 3.2, CGA — 2.0, SA — 3.8, VA — 7.3, FA — 2.9

Table 4. The content of flavonoids: rutin (RUT), isoquercetin (IsoQ), quercetin (QUE), myricetin (MYR), kaempferol (KAE), 7-luteolin glucoside (L-7gl) in *Cistus incanus* multiple aqueous extractions.

Extraction	RUT [μg/g dw]	IsoQ [μg/g dw]	QUE [μg/g dw]	MYR [μg/g dw]	KAE [μg/g dw]	L-7gl [μg/g dw]
First	548.2 ± 3.3	910.6 ± 3.0	826.5 ± 3.5	1638.4 ± 4.6	ND	432.5 ± 2.7
Second	320.4 ± 3.2	760.3 ± 3.5	780.7 ± 3.1	1054.0 ± 4.0	ND	248.8 ± 3.3
Third	280.0 ± 2.6	222.1 ± 2.4	650.7 ± 2.1	867.2 ± 3.0	ND	178.9 ± 3.5

Values are expressed as means ± standard deviation (n = 3); ND — not detectable
Limit of detection for KAE — 1.7 μg/mL

Table 5. The antioxidant capacities of *Cistus incanus* multiple aqueous extractions evaluated by DPPH and FRAP assays.

Extraction	DPPH [μmol TE/g dw]	FRAP [mmol Fe^{2+}/g dw]
First	82.5 ± 1.8	112.6 ± 2.0
Second	77.0 ± 1.9	100.3 ± 1.4
Third	72.6 ± 1.0	96.6 ± 1.2

Values are expressed as means ± standard deviation in μg/g dw (n = 3); DPPH — 2,2-diphenyl-1-picrylhydrazyl radical; FRAP — ferric reducing/antioxidant power; μmol TE/g dw — μmol Trolox equivalent per gram dry weight; mmol Fe^{2+}/g dw — mmol ion equivalents per gram dry weight

Discussion

The presented results demonstrate that systematic administration of aqueous extract of *Cistus incanus* influences the lipid profile in healthy adults. According to available research, this is the first study to investigate any association between a serum oxidative stress biomarker and a *Cistus incanus* tea-rich diet. The in vivo studies of biological activity of polyphenols seem be especially important because polyphenols are extensively metabolized in the body and their bioavailability may be different. Thus, the relation between the quantity of polyphenols in food and their in vivo activity is not obvious [7, 21].

Excessive uncontrolled lipid and protein oxidation is associated with pathogenesis of various diseases such as atherosclerosis, osteoporosis, cancer, Alzheimer's, and Parkinson's diseases. Among them atherosclerosis is the underlying condition in most cardiovascular diseases being the leading cause of death in Western societies. Oxidation of LDLs is a key mechanism in this chronic systematic disease, leading to the development and progression of the disease. A number of animal studies have demonstrated that consumption of polyphenols limits the incidence of coronary heart disease and an abundance

Table 6. Minimal inhibitory concentration (MIC) and minimal bactericidal concentration (MBC) values of *Cistus incanus* multiple aqueous extracts against reference strain and clinical isolates.

Microorganisms	ATCC No.	MIC [mg/mL]			MBC [mg/mL]		
		First extraction	Second extraction	Third extraction	First extraction	Second extraction	Third extraction
Staphylococcus aureus	6538	4	4	4	8	8	8
Methicillin-resistant *Staphylococcus aureus*	12673	4	4	4	32	32	16
Staphylococcus epidermidis	14990	4	4	4	8	8	8
Methicillin-resistant *Staphylococcus epidermidis*	13199	4	4	4	16	16	16
Streptococcus pneumoniae	Clinical isolate	4	4	4	NA	NA	NA
Bacillus subtilis	6633	4	4	4	8	8	8
Escherichia coli	8739	NA	NA	NA	NA	NA	NA

ATCC — American Type Culture Collection; NA — no antimicrobial activity

of literature has shown that polyphenols effectively protect LDL against oxidation *ex vivo* [4, 5, 22]. In the present study, assessing the effect of herbal supplements on oxidative stress parameters, it was found that the concentration of MDA as a marker of lipid peroxidation, and AOPP as a marker of protein peroxidation, decreased significantly after 6 weeks of use. Data in the literature concerning the impact of phenolic compounds from *Cistus incanus* extract on oxidative balance is poor. However, the increase in antioxidative capacity of plasma following the consumption of other polyphenol-rich food has been widely described. Litvinov et al. [23] showed that even a single dose of tea with or without milk increases plasma antioxidant activity. Increased antioxidative capacity was also observed as a consequence of the systematic intake of wine and beer, as well as fruit and vegetables rich in polyphenols such as strawberries and spinach [2]. It has also been shown that the consumption of polyphenol-rich blackcurrant and apple juice by healthy volunteers significantly reduced the plasma concentrations of MDA [24]. However, data from the impact of red wine consumption on lipid peroxidation is ambiguous [25–27].

Potent inhibition of LDL oxidation is, however, not only suggested by the protective effects of polyphenols against cardiovascular disease. Polyphenols have also been shown to inhibit the invasion and proliferation of smooth muscle cells in the arterial wall, inhibit platelet aggregation, and improve endothelial dysfunction in animal models [28, 29]. Polyphenols may also modify the lipid profile. A significant increase in plasma HDL-C was observed in healthy adults when administered drinks containing coca for 12 weeks [30]. Administration of Bergamot polyphenol extract for 30 days also resulted in increased HDL-C and decreased triglyceride concentrations in hyperlipidemic patients [31]. Data from the study about rich-in-polyphenol teas are, however, contradictory. One meta-analysis found no effects of black tea on TC and serum concentrations of LDL-C and HDL-C [32], while another concluded that consumption of black tea lowered LDL-C, especially in subjects at high cardiovascular risk [33]. In the current study a significant increase in HDL-C concentration was observed and a decrease in TG level during a 3-month supplementation with *Cistus incanus* was also recorded. These results suggest a positive impact on lipid metabolism and confirms a very wide range of potential pro-health attributes of *Cistus incanus*.

Several studies have attempted to elucidate the phenolic composition of *Cistus incanus* [34–37]. Viapiana et al. [20] in their earlier work assessed the phenolic profile and antioxidant capacity of aqueous extract of 15 commercially available samples of *Cistus incanus*, and showed that the place of the origin was the main factor in differentiating the *Cistus incanus* samples. The extracts obtained from Turkish *Cistus incanus* were the richest in total phenolic compounds (TPC), flavonoids (TFC), phenolic acid (TPAC) and ascorbic acid (AA). *Cistus incanus* used in the present study came from Mediterranean part of Turkey around the city of Antalya and — similar to previously analyzed samples from Turkish *Cistus incanus* — myricetin, quercetin, and isoquercetin were the most abundant phenolic compounds, with a content exceeding 800 μg/g dw. Gallic acid and rutin were found at the level ca. 500 μg/g dw, and 7-luteolin glucoside came in ca. 400 μg/g dw.

The antioxidant activities, evaluated with DPPH and FRAP also showed similar results to the previous published range of antioxidative capability of samples from Turkish *Cistus incanus* [20]. Deng et al. [38] determined the antioxidant capacities and total phenolic contents of 56 vegetables, and the levels of TPC, DPPH and FRAP values were lower than results obtained in this study, which seems to confirm *Cistus incanus* tea as a good source of polyphenols in the human diet. However, Konieczynski et al. [39] determined individual phenolic compounds in green and black teas and their total levels were higher than that obtained in the *Cistus incanus* infusions. In earlier studies it was established that aqueous extracts of Cistus exhibit good antimicrobial activity, particularly against bacteria G (+), and to a much lesser extent, affecting the growth of bacteria G (–) [20, 37]. Therefore, in this work it was decided to perform tests mainly in relation to selected G (+) bacteria. The present results confirmed good antimicrobial activity against bacteria G (+). Once again, no activity was demonstrated against G (–) bacteria in the tested concentration range.

According to the commercially included instructions, volunteers participating in the project reinfused the daily portion of *Cistus incanus* 3 times. The study of the multiple extractions effect on the phenolic acids and flavonoids content revealed that *Cistus incanus* tea can be re-infused; however, the first infusion showed higher levels of polyphenols and antioxidant activities, which

gradually decreased in later infusions. There was no difference in antimicrobial activity of the extracts on successive infusions.

Conclusions

This study supports the idea that *Cistus incanus* tea can be a valuable source of polyphenols in the human diet. The supplementations with the commercially available Turkish *Cistus incanus* tea had a positive impact on oxidative stress markers and lipids profile, allowing us to suggest that there are a wide range of pro-health properties of *Cistus incanus*, and beneficial effects on the cardiovascular system may be added.

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References

1. Barrajón-Catalán E, Fernández-Arroyo S, Roldán C, et al. A systematic study of the polyphenolic composition of aqueous extracts deriving from several Cistus genus species: evolutionary relationship. Phytochem Anal. 2011; 22(4): 303–312, doi: 10.1002/pca.1281, indexed in Pubmed: 21259376.
2. Scalbert A, Manach C, Morand C, et al. Dietary polyphenols and the prevention of diseases. Crit Rev Food Sci Nutr. 2005; 45(4): 287–306, doi: 10.1080/1040869059096, indexed in Pubmed: 16047496.
3. Reis JF, Monteiro VV, de Souza Gomes R, et al. Action mechanism and cardiovascular effect of anthocyanins: a systematic review of animal and human studies. J Transl Med. 2016; 14(1): 315, doi: 10.1186/s12967-016-1076-5, indexed in Pubmed: 27846846.
4. Tressera-Rimbau A, Arranz S, Eder M, et al. Dietary Polyphenols in the Prevention of Stroke. Oxid Med Cell Longev. 2017; 2017: 7467962, doi: 10.1155/2017/7467962, indexed in Pubmed: 29204249.
5. Manach C, Mazur A, Scalbert A. Polyphenols and prevention of cardiovascular diseases. Curr Opin Lipidol. 2005; 16(1): 77–84, indexed in Pubmed: 15650567.
6. Oak MH, Auger C, Belcastro E, et al. Potential mechanisms underlying cardiovascular protection by polyphenols: Role of the endothelium. Free Radic Biol Med. 2018; 122: 161–170, doi: 10.1016/j.freeradbiomed.2018.03.018, indexed in Pubmed: 29548794.
7. Pandey KB, Rizvi SI. Plant polyphenols as dietary antioxidants in human health and disease. Oxid Med Cell Longev. 2009; 2(5): 270–278, doi: 10.4161/oxim.2.5.9498, indexed in Pubmed: 20716914.
8. Cutler BR, Petersen C, Anandh Babu PV. Mechanistic insights into the vascular effects of blueberries: Evidence from recent studies. Mol Nutr Food Res. 2017; 61(6), doi: 10.1002/mnfr.201600271, indexed in Pubmed: 27558887.
9. Kalus U, Grigorov A, Kadecki O, et al. Cistus incanus (CYSTUS052) for treating patients with infection of the upper respiratory tract. A prospective, randomised, placebo-controlled clinical study. Antiviral Res. 2009; 84(3): 267–271, doi: 10.1016/j.antiviral.2009.10.001, indexed in Pubmed: 19828122.
10. MacKness B, Mackness MI, Durrington PN, et al. Paraoxonase activity in two healthy populations with differing rates of coronary heart disease. Eur J Clin Invest. 2000; 30(1): 4–10, indexed in Pubmed: 10619995.
11. Nakanishi M, Takanami Y, Maruyama T, et al. The ratio of serum paraoxonase/arylesterase activity using an improved assay for arylesterase activity to discriminate PON1(R192) from PON1(Q192). J Atheroscler Thromb. 2003; 10(6): 337–342, indexed in Pubmed: 15037822.
12. Yokode M, Kita T, Kikawa Y, et al. Stimulated arachidonate metabolism during foam cell transformation of mouse peritoneal macrophages with oxidized low density lipoprotein. J Clin Invest. 1988; 81(3): 720–729, doi: 10.1172/JCI113377, indexed in Pubmed: 3125226.
13. Witko-Sarsat V, Friedlander M, Capeillère-Blandin C, et al. Advanced oxidation protein products as a novel marker of oxidative stress in uremia. Kidney Int. 1996; 49(5): 1304–1313, indexed in Pubmed: 8731095.
14. Singleton V, Orthofer R, Lamuela-Raventós R. [14] Analysis of total phenols and other oxidation substrates and antioxidants by means of folin-ciocalteu reagent. Methods in Enzymology. Academic Press. 1999; 299: 152–178, doi: 10.1016/s0076-6879(99)99017-1.
15. European Pharmacopeia. European Pharmacopoeia. 2002.
16. Polish Pharmacopoeia VI. pp. 150. Warsaw: Polish Pharmacological Society. 2002: 150.
17. Abdelmageed OH, Khashaba PY, Askal HF, et al. Selective spectrophotometric determination of ascorbic acid in drugs and foods. Talanta. 1995; 42(4): 573–579, indexed in Pubmed: 18966266.
18. Tuberoso C, Rosa A, Bifulco E, et al. Chemical composition and antioxidant activities of Myrtus communis L. berries extracts. Food Chemistry. 2010; 123(4): 1242–1251, doi: 10.1016/j.foodchem.2010.05.094.
19. Benzie IF, Strain JJ. The ferric reducing ability of plasma (FRAP) as a measure of "antioxidant power": the FRAP assay. Anal Biochem. 1996; 239(1): 70–76, doi: 10.1006/abio.1996.0292, indexed in Pubmed: 8660627.
20. Viapiana A, Konopacka A, Waleron K, et al. Cistus incanus L. commercial products as a good source of polyphenols in human diet. Industrial Crops and Products. 2017; 107: 297–304, doi: 10.1016/j.indcrop.2017.05.066.
21. Martínez-Huélamo M, Vallverdú-Queralt A, Di Lecce G, et al. Bioavailability of tomato polyphenols is enhanced by process-

ing and fat addition: Evidence from a randomized feeding trial. Mol Nutr Food Res. 2016; 60(7): 1578–1589, doi: 10.1002/mnfr.201500820, indexed in Pubmed: 26887966.
22. Khurana S, Venkataraman K, Hollingsworth A, et al. Polyphenols: benefits to the cardiovascular system in health and in aging. Nutrients. 2013; 5(10): 3779–3827, doi: 10.3390/nu5103779, indexed in Pubmed: 24077237.
23. Litvinov D, Mahini H, Garelnabi M. Antioxidant and anti-inflammatory role of paraoxonase 1: implication in arteriosclerosis diseases. N Am J Med Sci. 2012; 4(11): 523–532, doi: 10.4103/1947-2714.103310, indexed in Pubmed: 23181222.
24. Young JF, Nielsen SE, Haraldsdóttir J, et al. Effect of fruit juice intake on urinary quercetin excretion and biomarkers of antioxidative status. Am J Clin Nutr. 1999; 69(1): 87–94, doi: 10.1093/ajcn/69.1.87, indexed in Pubmed: 9925128.
25. Sharpe PC, McGrath LT, McClean E, et al. Effect of red wine consumption on lipoprotein (a) and other risk factors for atherosclerosis. Qjm. 1995; 88: 101–108.
26. Chopra M, Fitzsimons PE, Strain JJ, et al. Nonalcoholic red wine extract and quercetin inhibit LDL oxidation without affecting plasma antioxidant vitamin and carotenoid concentrations. Clin Chem. 2000; 46: 1162–1170.
27. Puddey IB, Croft KD, Abdu-Amsha Caccetta R, et al. Alcohol, free radicals and antioxidants. Novartis Found Symp. 1998; 216: 51–62; discussion 63, indexed in Pubmed: 9949787.
28. Karim M, McCormick K, Kappagoda CT. Effects of cocoa extracts on endothelium-dependent relaxation. J Nutr. 2000; 130(8S Suppl): 2105S–2108S, doi: 10.1093/jn/130.8.2105S, indexed in Pubmed: 10917930.
29. Wollny T, Aiello L, Di To, et al. Modulation of haemostatic function and prevention of experimental thrombosis by red wine in rats: a role for increased nitric oxide production. Br J Pharmacol. 1999; 127: 747–755.
30. Baba S, Osakabe N, Kato Y, et al. Continuous intake of polyphenolic compounds containing cocoa powder reduces LDL oxidative susceptibility and has beneficial effects on plasma HDL-cholesterol concentrations in humans. Am J Clin Nutr. 2007; 85(3): 709–717, doi: 10.1093/ajcn/85.3.709, indexed in Pubmed: 17344491.
31. Mollace V, Sacco I, Janda E, et al. Hypolipemic and hypoglycaemic activity of bergamot polyphenols: from animal models to human studies. Fitoterapia. 2011; 82(3): 309–316, doi: 10.1016/j.fitote.2010.10.014, indexed in Pubmed: 21056640.
32. Wang D, Chen C, Wang Yu, et al. Effect of black tea consumption on blood cholesterol: a meta-analysis of 15 randomized controlled trials. PLoS One. 2014; 9(9): e107711, doi: 10.1371/journal.pone.0107711, indexed in Pubmed: 25237889.
33. Zhao Y, Asimi S, Wu K, et al. Black tea consumption and serum cholesterol concentration: Systematic review and meta-analysis of randomized controlled trials. Clin Nutr. 2015; 34(4): 612–619, doi: 10.1016/j.clnu.2014.06.003, indexed in Pubmed: 24972454.
34. Petereit F, Kolodziej H, Nahrstedt A. Flavan-3-ols and proanthocyanidins from Cistus incanus. Phytochemistry. 1991; 30(3): 981–985, doi: 10.1016/0031-9422(91)85291-7.
35. Santagati NA, Salerno L, Attaguile G, et al. Simultaneous determination of catechins, rutin, and gallic acid in Cistus species extracts by HPLC with diode array detection. J Chromatogr Sci. 2008; 46(2): 150–156, indexed in Pubmed: 18366875.
36. Riehle P, Vollmer M, Rohn S. Phenolic compounds in Cistus incanus herbal infusions — Antioxidant capacity and thermal stability during the brewing process. Food Res Int. 2013; 53(2): 891–899, doi: 10.1016/j.foodres.2012.09.020.
37. Wittpahl G, Kölling-Speer I, Basche S, et al. The polyphenolic composition of cistus incanus herbal tea and its antibacterial and anti-adherent activity against streptococcus mutans. Planta Med. 2015; 81(18): 1727–1735, doi: 10.1055/s-0035-1557822, indexed in Pubmed: 26291656.
38. Deng GF, Lin Xi, Xu XR, et al. Antioxidant capacities and total phenolic contents of 56 vegetables. J Functional Foods. 2013; 5(1): 260–266, doi: 10.1016/j.jff.2012.10.015.
39. Konieczynski P, Viapiana A, Wesolowski M. Comparison of Infusions from Black and Green Teas (Camellia sinensis L. Kuntze) and Erva-mate (Ilex paraguariensis A. St.-Hil.) Based on the Content of Essential Elements, Secondary Metabolites, and Antioxidant Activity. Food Analytical Methods. 2017; 10(9): 3063–3070, doi: 10.1007/s12161-017-0872-8.

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Kardia Mobile applicability in clinical practice: A comparison of Kardia Mobile and standard 12-lead electrocardiogram records in 100 consecutive patients of a tertiary cardiovascular care center

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Abstract

Background: *Mobile devices are gaining a rising number of users in all countries around the globe. Novel solutions to diagnose patients with out-of-hospital onset of arrhythmic symptoms can be easily used to record such events, but the effectiveness of these devices remain unknown.*

Methods: *In a group of 100 consecutive patients of an academic cardiology care center (mean age 68 ± 14.2 years, males: 66%) a standard 12-lead electrocardiogram (ECG) and a Kardia Mobile (KM) record were registered. Both versions were assessed by three independant groups of physicians.*

Results: *The analysis of comparisons for standard ECG and KM records showed that the latter is of lower quality ($p < 0.001$). It was non-inferior for detection of atrial fibrillation and atrial flutter, showed weaker rhythm detection in pacemaker stimulation ($p = 0.008$), and was superior in sinus rhythm detection ($p = 0.02$), though. The sensitivity of KM to detect pathological Q-wave was low compared to specificity (20.6% vs. 93.7%, respectively, $p < 0.001$). Basic intervals measured by the KM device, namely PQ, RR, and QT were significantly different (shorter) than those observed in the standard ECG method (160 ms vs. 180 ms [$p < 0.001$], 853 ms vs. 880 ms [$p = 0.03$] and 393 ms vs. 400 ms [$p < 0.001$], respectively).*

Conclusions: *Initial and indicative value of atrial fibrillation and atrial flutter detection in KM is comparable to results achieved in standard ECG. KM was superior in detection of sinus rhythm than eye-ball evaluation of 12-lead ECG. Though, the PQ and QT intervals were shorter in KM as compared to 12-lead ECG. Clinical value needs to be verified in large studies, though.* (Cardiol J 2021; 28, 4: 543–548)

Key words: arrhythmia, telemedicine, mobile, electrocardiogram, atrial fibrillation

Introduction

Increasing versatility of mobile devices provides an opportunity to implement them in the diagnosis and follow-up of patients with cardiovascular disorders. Kardia Mobile (KM) (AliveCor Inc., San Francisco, CA, USA) is a portable, mobile, connected electrocardiogram (ECG) device available to iOS and Android platform smartphone owners. It consists of a small device with two conducting plates that wirelessly connect with a smartphone, and an application installed on user smartphones. It enables one-lead ECG recording e.g. in cases of the onset of unsettling symptoms

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(palpitations, chest pain, dyspnea, and others). KM was designed to detect periods of atrial fibrillation (AF), which, if confirmed by the Food and Drug Administration (FDA)-approved algorithm, can then be reported to the physician responsible for the follow-up of a given patient. The accessibility of KM has prompted the present evaluation of its usefulness in comparison with 12-lead ECG recordings in assessing the underlying rhythm and basic ECG parameters (PQ, RR, and QT intervals). The aim herein was to establish protocol, according to evidence-based medicine, on whether it has acceptable sensitivity and specificity, and thus, useful and reliable for medical professionals.

Methods

Recruitment

A total of 100 consecutive patients of mean age 68 ± 14.2, with male subjects constituting 66% of the group of a tertiary cardiovascular care center were included in the study. Baseline characteristics can be found in the Table 1.

The patients were admitted to hospital elective diagnostic and treatment procedures for various cardiac conditions (arrhythmias, conduction disorders, stable coronary disease, hypertension and others). The group consisted of 100 patients consecutively admitted to the documented center between July 1st and July 31st 2015. The inclusion criterium was undergoing regular 12-lead ECG due to standard diagnosis on admission in stable state. All patients who urgently needed medical care were excluded. Upon referral for a 12-lead ECG, each patient was asked to provide informed consent for additional KM ECG recording. All patients agreed to take part in the study. The subjects' clinical state was stable at the time of ECG recording. First a 12-lead ECG was performed and KM ECG was recorded directly after this procedure. Two technicians were responsible for 12-lead ECG measurements and one physician to record KM ECGs.

ECG assessment

Both 12-lead and KM ECG records were analyzed by three independent teams comprised of two cardiologists each. ECG interpretation was carried out according to a previously elaborated online form, consistent with the Polish ECG Description Guidelines [1], which required assessment of the following: ECG quality (good, acceptable, poor), rhythm (sinus rhythm, AF, atrial flutter [AFl] or pacemaker rhythm), presence of pathological Q wave as well as PQ, RR and QT measurements.

Table 1. Patient characteristics.

Baseline demographics	N (%) or mean ± SD
Gender [male]	66 (66.0%)
Age [years]	68.0 ± 14.2
Body mass [kg]	80.7 ±15.9
Height [m]	1.7 ± 0.1
Body mass index	28.0 ± 4.8
Medical history	
Nicotinism (history):	40 (43.5%)
Nicotinism active	9 (9.8%)
Packyears cumulative	33.4 ± 22.5
Diabetes mellitus	20 (20.4%)
Hypertension	67 (68.4%)
Dyslipidemia	45 (46.4%)
Chronic kidney disease:	32 (32.7%)
CKD G2	2 (2.0%)
CKD G3	23 (23.5%)
CKD G4	7 (7.1%)
CKD G5	1 (1.0%)
Thyroid dysfunction:	18 (18.4%)
Hypothyroidism	9 (9.18%)
Hyperthyroidism	9 (9.18%)
COPD:	6 (6.12%)
Parkinson's disease	1 (1.02%)
Cerebrovascular disease	17 (17.35%)
Peripheral artery disease	12 (12.24%)
Cardiovascular history	
Stable angina (angina pectoris)	46 (47.4%)
ACS (admission)	15 (15.31%)
Myocardial infarction (history)	25 (25.5%)
PCI/CABG (history)	27 (27.6%)
Cardiac surgery (other than CABG)	3 (3.1%)
Heart failure:	43 (43.9%)
NYHA II	28 (28.6%)
NYHA III	9 (9.2%)
NYHA IV	6 (6.1%)
LVEF [%]	49 ± 14
Atrial fibrillation:	34 (34.7%)
Paroxysmal	16 (16.33%)
Persistent	4 (4.1%)
Chronic	14 (14.3%)
CIED implanted	34 (34.7%)
Pacemaker:	24 (24.5%)
AAI	2 (2.0%)
VVI	7 (7.1%)
DDD	15 (15.3%)
ICD	5 (5.1%)
CRT	5 (5.1%)
Ablation	6 (6.1%)

ACS — acute coronary syndrome at the time of admission; CABG — coronary artery bypass grafting; CIED — cardiac implantable electronic device; CKD — chronic kidney disease (G2-G5 — CKD stages); COPD — chronic obstructive pulmonary disease; CRT — cardiac resynchronization therapy device; ICD — implantable cardioverter-defibrillator; LVEF — left ventricular ejection fraction measured during the hospitalization; NYHA — New York Heart Association functional classification; PCI — percutaneous coronary intervention

In order to avoid cognitive and measurement bias, all KM ECG records were printed out in 1:1 ratio and assessed in paper-based form. A database comprised of answers provided by the teams. The study protocol and informed consent form was approved by the local bioethics committee.

Statistical analysis

The data were analyzed using adequate statistical tests with the aim of looking for agreement between the two diagnostic methods. In case of disagreement, ECGs were reevaluated by a data committee consisting of three ECG experts, who then provided a final report.

Continuous variables were expressed as mean ± standard deviation, and categorical variables were stored as number of cases or percentage. The Student t-test was used for comparison of continuous variables, while categorical variables were compared using the χ^2 test or the Fisher exact test, as appropriate among the groups. All tests were two-tailed and a p-value of < 0.05 was considered significant. All statistical analyses were performed using MedCalc 17.6 software (MedCalc Software, Ostend, Belgium).

Results

A total of 99 KM ECGs and 100 12-lead ECGs were analyzed. In 1 patient, KM recording was not possible due to an underlying condition (tremors secondary to Parkinson's disease). Comparison of KM ECGs and 12-lead ECGs revealed that the overall quality of the latter was superior (6 vs. 0 — poor, 41 vs. 1 — acceptable, 52 vs. 99 — good, $p < 0.001$). Effectiveness evaluation of KM with regards to rhythm determination was performed by comparing it with 12-lead ECG interpretation. Sensitivity and specificity were tested for the following rhythms:

- sinus rhythm — 98.4% and 74.2% ($p = 0.02$);
- atrial fibrillation — 92.8% and 100% ($p = 0.32$);
- atrial flutter — 100% and 100% (p value not applicable);
- pacemaker rhythm — 53.6% and 100% ($p = 0.008$).

Sensitivity and specificity of KM for pathological Q wave detection was 20.6% and 93.7%, respectively ($p < 0.001$). Mean PQ, RR and QT measurements in KM ECGs and 12-lead ECGs were as follows:

- PQ — 160 ms vs. 180 ms ($p < 0.001$);
- RR — 853 ms vs. 880 ms ($p = 0.03$);
- QT — 393 ms vs. 400 ms ($p < 0.001$).

Discussion

Principal results

With regard to the fact that many life-threatening arrhythmias are non-sustained and occur infrequently, it is justified to search for relatively cheap solutions giving the patient a chance to record an ECG at the onset of unsettling symptoms. Apart from the conventional, clinically-approved methods, recent years have brought a few breakthroughs regarding smartphone-dependent devices enabling such a procedure. Versatility of mobile phones and general access to the Internet has created the possibility to remotely provide the practitioners with information of possible clinical significance, and thus enable them to react in case of an emergency.

Although reliability of such solutions has not yet been thoroughly investigated in randomized clinical trials, some data suggests good compliance and improved patient management. The most obvious application of smartphone-compatible ECG devices that has been brought up is the possibility of screening for patients with paroxysmal AF especially for those who need antithrombotic therapy [2–4].

The present study confirmed that KM, despite its simplicity, provides a record of sufficient quality to diagnose periods of AF. KM has also proven to be reliable while supervising QTc period in patients on dofetilide [5] and in pediatric patients with various arrhythmic disorders [6]. In contrast study revealed that QT measurements in KM ECGs are shorter on average by an average of 7 ms, whereas PQ intervals tend to be shorter by as much as 20 ms (more than a 10% difference compared to the conventional ECG). This phenomenon has not as yet been described in the literature available and may potentially mimic arrhythmia, e.g. pre-excitation syndrome in extreme cases or conceal atrioventricular blocks, but this tendency was not confirmed in this study.

Extremely high sensitivity compared to relatively lower specificity of KM detection of sinus rhythm is a characteristic that potentially was previously heralded by Narasimha et al. [7] who reported that nearly one third of patients declaring alarming symptoms while the ECG was assessed normal by the algorithm. One in four patients in our population ascribed by KM to sinus rhythm category should in fact have been described differently. Based on the construction of the KM device, it is not surprising that it has low sensitivity in detecting pacemaker rhythm, this supports Desteghe et al. [8] findings and recommendations.

According to available research, this is the first study to investigate and compare selected parameters in KM records and conventional 12--lead ECGs. New studies, currently with protocols available [9, 10] will shortly verify the usefulness of the method and the present findings.

New studies being currently conducted can be also groundbreaking in respect to ischemia detection, and thus rapid detection of myocardial infarction in symptomatic patients [11, 12].

Limitations of the study

Despite the prospective design of this study there are some important limitations. Firstly, this is a single center study. Secondly, ECG interpretation is subjective and thus there may have been certain discrepancies. There were only three teams analyzing the records and assessments of ECG quality were subjective according to their expertise which may somehow bias this study. Furthermore, a group of stable subjects were analyzed, which made it impossible to verify KM applicability for cases of acute cardiac events. Finally, the number of patients included in the study is relatively small and a larger group would enable more reliable conclusions.

Comparison with prior work

The onset of certain clinical symptoms such as syncope, palpitations and chest pain may indicate an underlying cardiovascular etiology. Among others, paroxysmal arrhythmias are a potential culprit. Long-term ECG monitoring has proven to be an important measure in diagnosing elusive periods of AF, supraventricular arrhythmias and ventricular arrhythmias [4, 13, 14]. To confirm the relation between the symptoms and arrhythmias, the European Society of Cardiology (ESC) guidelines recommend continuous or intermittent ambulatory ECG monitoring. This procedure also makes it possible to verify if the arrhythmic events are secondary to an ischemic heart disease [13, 15]. An appropriate, long-term ECG screening may warn the clinician of a series of potential adverse clinical events. Sudden cardiac death (SCD), one of the leading direct causes of mortality in the western world, whether secondary to ischemic heart disease or to congenital malfunctioning of the electrical conductance system of the heart, could be in many cases prevented by pharmacotherapy or implantable cardioverter-defibrillator (ICD) implantation [13]. Furthermore, paroxysmal AF is a proven risk factor for stroke, another important cause of mortality and disability in developed societies [16–18]. Up until recently it has been estimated that even 20–40% of ischemic strokes remain idiopathic, but some clinical trials have shown a higher prevalence of paroxysmal AF detectable on a long-term ECG analysis in comparison with a standard 24 h Holter monitoring in this group of patients [19–22]. The KM system was assessed in a study conducted by Halcox et al. [22] in a randomized control trial (REHEARSE-AF study) in a group of patients older than 65 years with an elevated risk of cerebral thromboembolism (CHA_2DS_2-VASc score ≥ 2). The results presented a proactive approach of regular weekly iECG monitoring with the use of KM system may not only be preventive in a medical sense, but also cost-effective in AF detection. This observation opens the discussion over the possibility of a more routine implementation of KM in clinical practice to remotely monitor QT periods.

Rapid diagnosis of AF can prevent cerebral thromboembolic events, and according to recent publication by Rattanawong et al. [23], it can also reduce overall SCD rate. As AF has been reported to provide higher risk of SCD than other associated factors, such as previous myocardial infarction, heart failure or coronary artery disease, preventive measures using quick and easy diagnostic tools such as KM could be undertaken to avoid unnecessary hospitalizations and reduce mortality in this subgroup.

Another important feature of every telemonitoring device that needs to be discussed is its availability. Surveys gathered from subjects enrolled in the SPEAR trial showed a high level of satisfaction and willingness to continue implementing KM ECG testing in the future [4]. Furthermore, all the patients that took part in the present study showed a positive attitude towards KM as well. Such attitudes have also been observed in a recent study by Halcox et al. [22] with patients of advanced age being enthusiastic about such methods.

Patients can be subjected to more personalized care due to the possibility of remote transmission of their ECG records to their physician. In recent years a proactive attitude was positively tested by Klein-Wiele et al. [24], who provided data of successful cooperation between patients, general practitioners and cardiologists. The KM device could be part of a cross-sector telemetric network with rapid response to a patients' worsening state of health by qualified professionals.

Apart from clinical reliability, it also needs to be verified whether smartphone-based ECG controls are not an excessive financial burden for the

health care system. Initial data suggest that there is no long-term difference in cost-efficiency between conventional monitoring and smartphone supervision, while patient self-awareness seems to benefit from remote self-controls [25]. Nevertheless, this is still a matter of debate as the information at hand are scarce.

Kardia Mobile aside, smartphone-based ECG device market constantly expands, offering new solutions for mobile phones with Android operating systems [26], or enabling a context-aware ECG monitoring [27]. Moreover, specifically oriented systems such as Remote Cardio Control (RCC) designed to diagnose signs of myocardial infarction, continue to be created [28]. It can be conceived that in the following years devices encompassing those standards of diagnostic procedures will become a part of routine approach.

It should be also noted that the number of reports considering mobile ECG record is rising. Apart from arrhythmias considered in this study, there is a possibility to record and diagnose other heart rhythm disturbances, including atrioventricular block [29]. This poses even greater area for implementation of these devices into general practitioner practice.

Conclusions

The usefulness of KM is unquestionable in the prevention and rapid detection of AF and AFls in a standard comparable to the conventional method, namely 12-lead ECG. Applying this novel device to routine diagnostics is rather preemptive, as discrepancies in sensitivity of the algorithm may present a possible misinterpretation of the outcome. The clinical need for an easy-to-use mobile ECG is immense, however it is concluded herein, that further studies are needed to confirm diagnostic value.

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Conflict of interest: Lukasz Koltowski and Paweł Balsam are consultants to Medtronic, and Abbott. Lukasz Koltowski is a consultant to Boston Scientific, and Shareholder of SmartMedics Ltd.

References

1. Baranowski R, Bieganowska K, Kozłowski D, et al. Zalecenia dotyczące stosowania rozpoznań elektrokardiograficznych. Kardiol Pol. 2010; 68: 335–390.
2. Olgun Kucuk H, Kucuk U, Yalcin M, et al. Time to use mobile health devices to diagnose paroxysmal atrial fibrillation. Int J Cardiol. 2016; 222: 1061, doi:10.1016/j.ijcard.2015.10.159, indexed in Pubmed: 26522994.
3. Tarakji KG, Wazni OM, Callahan T, et al. Using a novel wireless system for monitoring patients after the atrial fibrillation ablation procedure: the iTransmit study. Heart Rhythm. 2015; 12(3): 554–559, doi: 10.1016/j.hrthm.2014.11.015, indexed in Pubmed: 25460854.
4. Pruszczyk P, Tomaszuk-Kazberuk A, Słowik A, et al. Management of bleeding or urgent interventions in patients treated with direct oral anticoagulants: 2017 recommendations for Poland. Pol Arch Intern Med. 2017; 127(5): 343–351, doi: 10.20452/pamw.3995, indexed in Pubmed:28400546.
5. Chung EH, Guise KD. QTC intervals can be assessed with the AliveCor heart monitor in patients on dofetilide for atrial fibrillation. J Electrocardiol. 2015; 48(1): 8–9, doi: 10.1016/j.jelectrocard.2014.10.005, indexed in Pubmed: 25453194.
6. Nguyen HH, Van Hare GF, Rudokas M, et al. SPEAR Trial: Smartphone Pediatric ElectrocARdiogram Trial. PLoS One. 2015; 10(8): e0136256, doi:10.1371/journal.pone.0136256, indexed in Pubmed: 26295569.
7. Narasimha D, Hanna N, Beck H, et al. Validation of a smartphone-based event recorder for arrhythmia detection. Pacing Clin Electrophysiol. 2018; 41(5): 487–494, doi: 10.1111/pace.13317, indexed in Pubmed: 29493801.
8. Desteghe L, Raymaekers Z, Lutin M, et al. Performance of handheld electrocardiogram devices to detect atrial fibrillation in a cardiology and geriatric ward setting. Europace. 2017; 19(1): 29–39, doi: 10.1093/europace/euw025, indexed in Pubmed: 26893496.
9. Guhl EN, Schlusser CL, Henault LE, et al. Rationale and design of the Atrial Fibrillation health Literacy Information Technology Trial: (AF-LITT). Contemp Clin Trials. 2017; 62: 153–158, doi: 10.1016/j.cct.2017.09.005, indexed in Pubmed: 28923492.
10. Treskes RW, Gielen W, Wermer MJ, et al. Mobile phones in cryptogenic strOke patients Bringing sIngle Lead ECGs for Atrial Fibrillation detection (MOBILE-AF): study protocol for a randomised controlled trial. Trials. 2017; 18(1): 402, doi: 10.1186/s13063-017-2131-0, indexed in Pubmed:28851409.
11. Barbagelata A, Bethea CF, Severance HW, et al. Smartphone ECG for evaluation of ST-segment elevation myocardial infarction (STEMI): Design of the ST LEUIS International Multicenter Study. J Electrocardiol. 2018; 51(2): 260–264, doi: 10.1016/j.jelectrocard.2017.10.011, indexed in Pubmed:29174099.
12. Muhlestein JB, Le V, Albert D, et al. Smartphone ECG for evaluation of STEMI: results of the ST LEUIS Pilot Study.

J Electrocardiol. 2015; 48(2): 249–259, doi: 10.1016/j.jelectrocard.2014.11.005, indexed in Pubmed: 25601407.
13. Priori SG, Blomström-Lundqvist C, Mazzanti A, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J. 2015; 36(41): 2793–2867, doi: 10.1093/eurheartj/ehv316, indexed in Pubmed: 26320108.
14. Solomon MD, Yang J, Sung SH, et al. Incidence and timing of potentially high-risk arrhythmias detected through long term continuous ambulatory electrocardiographic monitoring. BMC Cardiovasc Disord. 2016; 16: 35, doi: 10.1186/s12872-016-0210-x, indexed in Pubmed: 26883019.
15. 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.
16. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke. 1991; 22(8): 983–988, indexed in Pubmed: 1866765.
17. Camm AJ, Lip GYH, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J. 2012; 33(21): 2719–2747, doi: 10.1093/eurheartj/ehs253, indexed in Pubmed: 22922413.
18. 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.
19. Sanna T, Diener HC, Passman RS, et al. CRYSTAL AF Investigators. Cryptogenic stroke and underlying atrial fibrillation. N Engl J Med. 2014; 370(26): 2478–2486, doi: 10.1056/NEJMoa1313600, indexed in Pubmed: 24963567.
20. Gladstone DJ, Dorian P, Spring M, et al. Atrial fibrillation in patients with cryptogenic stroke. N Engl J Med. 2014; 370(26): 2467–2477, doi:10.1056/NEJMoa1311376, indexed in Pubmed: 24963566.
21. Lilli A, Di Cori A. The cold facts of long-term ECG monitoring. Expert Rev Cardiovasc Ther. 2015; 13(2): 125–127, doi: 10.1586/14779072.2015.998201, indexed in Pubmed: 25555394.
22. Halcox JPJ, Wareham K, Cardew A, et al. Assessment of Remote Heart Rhythm Sampling Using the AliveCor Heart Monitor to Screen for Atrial Fibrillation: The REHEARSE-AF Study. Circulation. 2017; 136(19): 1784–1794, doi: 10.1161/CIRCULATIONAHA.117.030583, indexed in Pubmed:28851729.
23. Rattanawong P, Upala S, Riangwiwat T, et al. Atrial fibrillation is associated with sudden cardiac death: a systematic review and meta-analysis. J Interv Card Electrophysiol. 2018; 51(2): 91–104, doi: 10.1007/s10840-017-0308-9, indexed in Pubmed: 29332241.
24. Klein-Wiele O, Faghih M, Dreesen S, et al. A novel cross-sector telemedical approach to detect arrhythmia in primary care patients with palpitations using a patient-activated event recorder. Cardiol J. 2016; 23(4): 422–428, doi: 10.5603/CJ.a2016.0033, indexed in Pubmed: 27320955.
25. Bloss CS, Wineinger NE, Peters M, et al. A prospective randomized trial examining health care utilization in individuals using multiple smartphone-enabled biosensors. PeerJ. 2016; 4: e1554, doi: 10.7717/peerj.1554, indexed in Pubmed: 26788432.
26. Choo KY, Ling HC, Lo YC, et al. Android based self-diagnostic electrocardiogram system for mobile healthcare. Technol Health Care. 2015; 23 Suppl 2: S435–S442, doi: 10.3233/THC-150980, indexed in Pubmed: 26410510.
27. Miao F, Cheng Y, He Yi, et al. A wearable context-aware ECG monitoring system integrated with built-in kinematic sensors of the smartphone. Sensors (Basel). 2015; 15(5): 11465–11484, doi: 10.3390/s150511465, indexed in Pubmed: 25996508.
28. Cinaglia P, Tradigo G, Guzzi PH, et al. Design and Implementation of a Telecardiology System for Mobile Devices. Interdiscip Sci. 2015; 7(3): 266–274, doi: 10.1007/s12539-015-0267-8, indexed in Pubmed: 26223546.
29. Balsam P, Gawalko M, Lodziński P, et al. Atrioventricular block registration with smart phone associated ECG device. Heart Beat J. 2017; 1: 54–55, doi:10.24255/hbj/68109.

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Usefulness of three-dimensional echocardiography for the assessment of ventricular function in children: Comparison with cardiac magnetic resonance, with a focus on patients with arrhythmia

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Abstract

Background: *Focusing on patients with arrhythmia, the aims of this study was to assess ventricular function in children using three-dimensional echocardiography (3D-ECHO) and to compare the results to those obtained with cardiac magnetic resonance (CMR).*

Methods: *The study group consisted of 43 children in whom 3D-ECHO and CMR were performed. Twenty-five patients had a ventricular arrhythmia, 7 left ventricular cardiomyopathies, 9 proved to be healthy. In all children, 3D-ECHO (offline analysis) was used to assess ventricular ejection fraction (EF). The results were compared to CMR using the Bland-Altman analysis and linear regression. The Student paired T-test was used to compare of means between both modalities.*

Results: *The relation between the results derived from both methods is linear (for left ventricle: estimated slope = 1.031, $p < 0.0001$, R-squared = 0.998; for right ventricle: estimated slope = 0.993, $p < 0.0001$, R-squared = 0.998). In spite of minimal mean differences between results for both ventricles and narrow 95% confidence intervals, the paired t-test proved those differences not to be significant ($p > 0.05$) for the right ventricle but statistically significant ($p < 0.05$) for the left ventricle, for which the left ventricular EF calculated in 3D-ECHO was systematically underestimated with a mean difference of –1.8% ± 2.6% ($p < 0.0001$).*

Conclusions: *Three-dimensional echocardiography assessment of both left and right ventricular EF in children showed high significant correlation and agreement with CMR. 3D-ECHO could be a valuable tool in follow-up of children with arrhythmic disorders requiring regular assessment of ventricular function.* (Cardiol J 2021; 28, 4: 549–557)

Key words: three-dimensional echocardiography, cardiac magnetic resonance, ventricular ejection fraction, children, arrhythmia

Introduction

Arrhythmias are considered one of the most significant problems of modern pediatric cardiology. As in the majority of children, no connection to specific structural or functional cardiac abnormality can be found, those cases often are defined as idiopathic. The use of three-dimensional echocardiography (3D-ECHO) for non-invasive assessment of ventricular function is at present widespread and

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universal, especially in adult patients. In pediatric cardiology the method was embraced much later and its exploit is still noncompliant with potential benefits. Being close in accuracy although more feasible and less expensive than cardiac magnetic resonance (CMR) 3D-ECHO may be valuable diagnostic tool especially in groups of children demanding regular assessment of ventricular function.

The aim of the study was to assess ventricular function in children using 3D-ECHO and compare the results to those obtained with CMR, focusing especially on patients with arrhythmia.

Methods

The prospective study included 43 consecutive children hospitalised in the Pediatric Cardiology Department, aged 4 months to 17 years, average 13.7 ± 3.8 years, in whom both 3D-ECHO and CMR were performed due to clinical indications. In all the children electrocardiography (ECG) and 24-hours ECG Holter monitoring were used in diagnostics. In this group, 27 patients suffered from arrhythmia: two supraventricular (one with single extrasystolic beats, one with nodal rhythm), 25 ventricular arrhythmias (in all cases at least one of extrasystolic morphologies was left bundle branch block) classified as mild in 9 patients (single monomorphic beats, less than 20% of arrhythmia in 24-h Holter-ECG monitoring) and severe in 16 children (defined as complex with ventricular tachycardia or over 20% single beats during 24 h). Out of 25 children, in 20 ventricular arrhythmias were classified as idiopathic (no evident source in cardiac morphology or function was detected), three patients fulfilled the criteria of arrhythmogenic right ventricular cardiomyopathy (ARVC), one was diagnosed with Andersen-Tawill syndrome, and in one arrhythmia occurred after surgical repair of ventricular septal defect. Seven patients of the studied cohort were diagnosed with left ventricular cardiomyopathies, 9 patients proved to be healthy either in the course of diagnostics for suspected myocarditis (based on elevated plasma troponin level and/or abnormalities in ECG) or after completed healing process. The characteristics of the studied group are presented in Table 1.

In all patients 3D-ECHO and CMR were performed. In one child ejection fraction (EF) of both ventricles and in one — the right ventricle could not be calculated in CMR due to artefacts connected with excessive arrhythmia. Those patients were not included in the statistical analysis, leaving 42 children for the analysis of left and 41 — right ventricular function. The postprocessing (offline analysis) of echocardiography data was obtained without knowing the results of CMR.

Table 1. Characteristics of the studied group.

Patients' characteristics	Details
Age [years]	13.7 ± 3.8
Sex:	
Boys	26
Girls	17
BSA [m^2]	0.56–2.04; mean 1.61 ± 0.34
Diagnosis:	
Arrhythmia	2
Supraventricular	25
Ventricular	
Severity	
Mild (< 20%/24 h + no VT)	9
Severe (> 20%/24 h and/ or VT)	16
Cause	
Idiopathic	20
ARVC	3
VSD (after operation)	1
ATS	1
LV cardiomyopathy:	7
DCM	3
HCM	2
RCM	1
NCLV	1
Healthy subjects*	9

*Initially suspected or successfully treated myocarditis; ARVC — arrhythmogenic right ventricular cardiomyopathy; ATS — Andersen-Tawill syndrome; BSA — body surface area; DCM — dilated cardiomyopathy; HCM — hypertrophied cardiomyopathy; NCLV — noncompacted left ventricle; RCM — restrictive cardiomyopathy; VSD — ventricular septal defect

3D-ECHO: Image acquisition

All patients underwent standard echocardiography examination (Philips EPIQ system, Netherlands) during which the ECG-gated 3D full-volume data sets were recorded using a matrix X5-1/X7-2 transducer from an apical window in the patients' left lateral decubitus position, possibly while withholding breath. Four consecutive cardiac cycles were registered to obtain optimal resolution. In 2 patients with excessive arrhythmia we recorded only two cardiac cycles and the data proved adequate for further analysis. The left and right ventricles were addressed separately to assure that the data set would contain the whole chamber

with its apical portion and the widest diameter of concordant atrioventricular valve. For the left ventricle standard 4-chamber view was used; for the right ventricle the probe was moved slightly to the left side with its tail tilted posteriorly and counter clockwise to open the apical part and include the full capacity of outflow track in the pyramidal data set. For both ventricles the probe's position and its spatial orientation was controlled by a simultaneous 2-dimensional view of coronal and sagittal planes. At least three full-volume acquisitions for each ventricle were recorded in each patient; the one with the highest quality was assigned for later post processing. In patients with sinus rhythm the recording time approached 3 min, although in patients with arrhythmia it was considerably longer (mean 5 min) because recording of four consecutive sinus beats with no extrasystoly in real time was more challenging.

Postprocessing

Full-volume 3D digital data sets for both left and right ventricle were exported to an external server for offline analysis using dedicated software (TomTec Imaging Systems GMBH, Germany; Image Arena 4.6). For the left ventricle 4D LV-Analysis software was used and for the right ventricle — 4D RV-Function module. For each ventricle analysis, the user identified specific landmarks in end-diastolic and end-systolic views (apex, mitral, and aortic annulus for left ventricle, and additionally ventricular diameter in short axis view along with interventricular septum perimeters for the right ventricle). Based on the landmarks, semi-automatic tracing of endocardium was performed and corrected manually by the software operator. The analysis was performed using high-contrast monitor settings which, from experience, helps to define clearer line to track while manual correction of contour is made. Trabeculae and papillary muscles into ventricular cavity was included. For optimal quality of full-volume data sets the analysis of both ventricles was completed in a mean time of 4 min, and up to 9 min for images of poorer quality requiring more manual tracing. The results of the analysis being systolic function of both ventricles illustrated by EF were automatically calculated from end-diastolic volume (EDV), and end-systolic volume (ESV). A graphic presentation of the results is featured in Figure 1A, B.

Cardiac magnetic resonance

All CMR studies were acquired with a Siemens Magnetom Skyra 3 Tesla scanner (Siemens, Erlangen, Germany). Five patients who were unable to cooperate during the procedure (the youngest or hyperactive children) required general anaesthesia. A routinely used CMR protocol to assess left and right ventricular size and function included initial scout images followed by cine steady-state free precession (SSFP) breath hold sequences in 2-, 3-, and 4-chamber views to set up final imaging planes and a stack of short-axis images from the atrioventricular annulus to the apex. Imaging parameters were as follows: field of view 340 mm, matrix 208, repetition time approximately 39.24 ms, echo time 1.43 ms, flip angle 39 degrees, slice thickness 6–8 mm (depending on the child age), gap 2 mm, in-plane image resolution 1.6 × 1.6 × × 6–8 mm, and temporal resolution 25 phases per cardiac cycle [1, 2]. Images were analysed with the use of a dedicated software. Initially, short-axis SSFP cine images were previewed from the base to the apex in a cinematic mode, then endocardial contours for end-diastole and end-systole of both ventricles were manually traced. Trabeculae and papillary muscles were considered as ventricle cavities. Delineated contours were used for the quantification of ventricular ejection fractions (left ventricular EF [LVEF], and right ventricular EF [RVEF]). The mean time of image acquisition was 40 min (longer in children requiring general anaesthesia — up to 1.5 h). The mean time of image analysis was 20 min.

Statistical analysis

Bland-Altman analysis and linear regression were used to compare results of LVEF and RVEF obtained with 3D-ECHO against CMR acknowledged as the method of reference. A p-value of less than 0.05 was considered statistically significant [3]. For the whole cohort and selected subgroups of patients with arrhythmia the mean differences between 3D-ECHO and CMR results were calculated and the 95% confidence intervals (CIs) determined. Because data were normally distributed (verified by the Shapiro-Wilk test), a paired Student t-test was used to compare means of LVEF and RVEF results obtained from 3D-ECHO and CMR, again using CMR as the method of reference.

All calculations and graphs were made in the R software version 3.3.1. (distributed under the terms of the GNU General Public License).

The study was approved by the Medical University's Ethics Committee. In all patients, written informed consent was obtained from parents and for children older than 16 years of age.

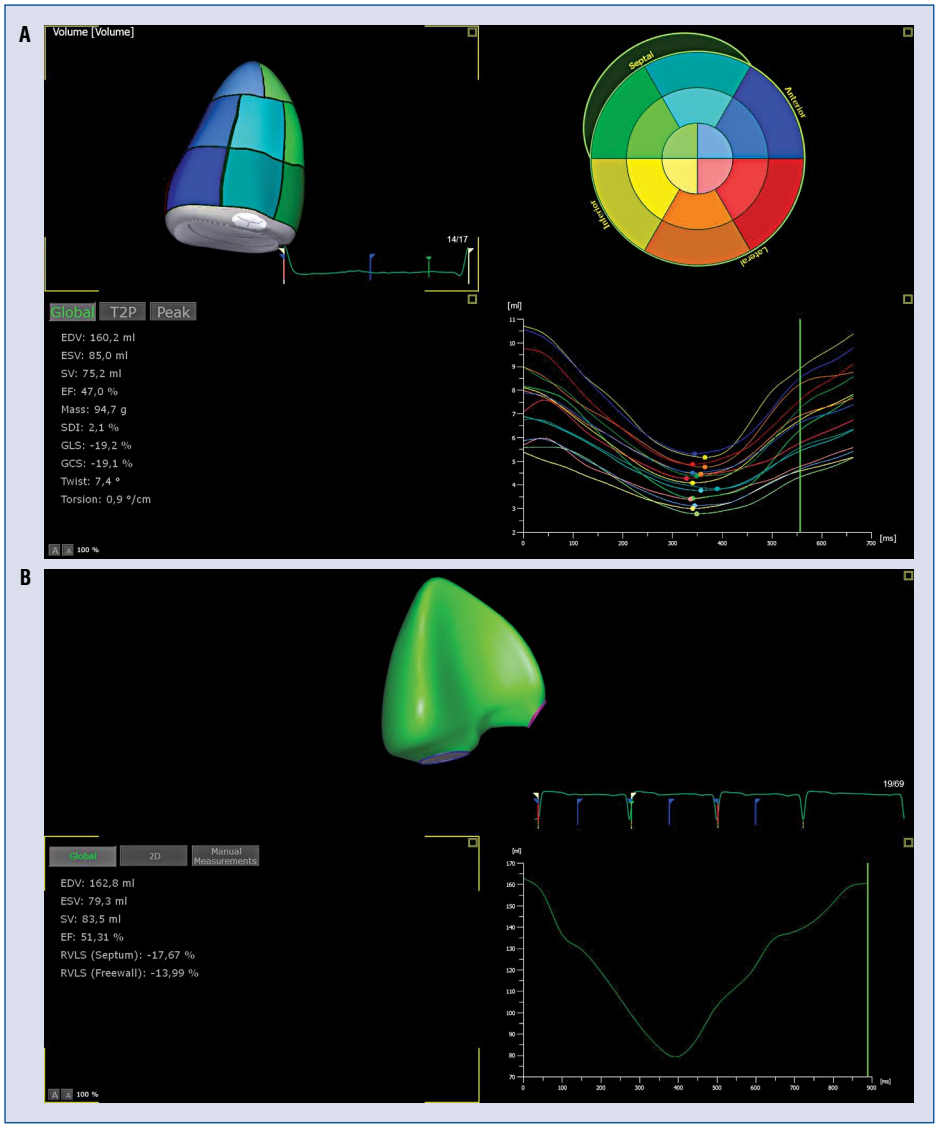

Figure 1. Three-dimensional echocardiography offline analysis; **A.** Left ventricular model with calculated ejection fraction; **B.** Right ventricular analysis results.

Results

Bland-Altman plot proved minor mean differences with narrow limits of agreement between the results obtained with 3D-ECHO and CMR for both LVEF and RVEF, marking very high significant correlation (for LVEF: $r = 0.903$, $p < 0.00001$; for RVEF: $r = 0.966$, $p < 0.00001$) and agreement (Fig. 2A, B). The relation between the results derived from both methods is linear, and it can be approximated by the identity function (Fig. 3A, B).

For LVEF, the estimated slope was 1.031, standard error = 0.007 ($p < 0.00001$), R-squared = = 0.998; the average width of 95% prediction interval was 10.6% ± 5.3%. Comparing LVEF calculated with 3D-ECHO to reference CMR values — in 34% of patients the difference was lower than 1%, in 59% under 2%, in 68% under 3%, and in 78% below 4%. However, the paired Student t-test showed a statistically significant difference between means of LVEF calculated in 3D-ECHO and CMR — both for the whole cohort and in subgroups with arrhythmia ($p < 0.005$). 3D-ECHO results proved to be minimally underestimated comparing to CMR results with mean difference of –1.8 ± 2.6% ($p < 0.0001$) for the whole population, in the subgroup with arrhythmia –2.3 ± 2.5% ($p < 0.0001$), in children with severe ventricular arrhythmia –3.1 ± 2.7% ($p = 0.0006$), and in patients with severe idiopathic ventricular arrhythmia –2.6 ±

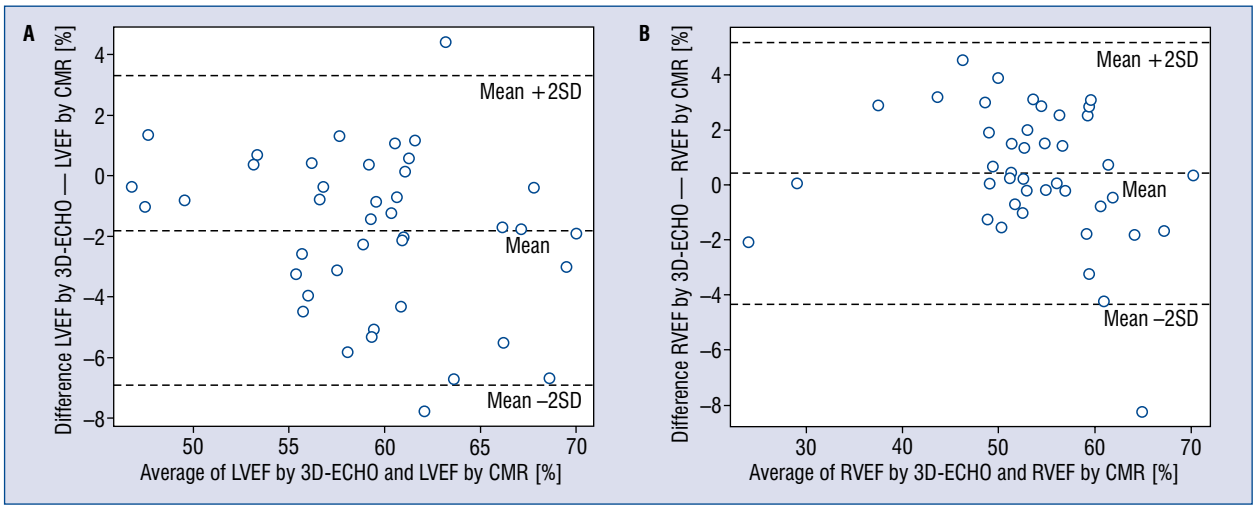

Figure 2. Bland-Altman analysis. Left (**A**) and right (**B**) ventricular ejection fraction (LVEF, RVEF, respectively): mean differences between results of three-dimensional echocardiography (3D-ECHO) and cardiac magnetic resonance (CMR) with limits of agreement.

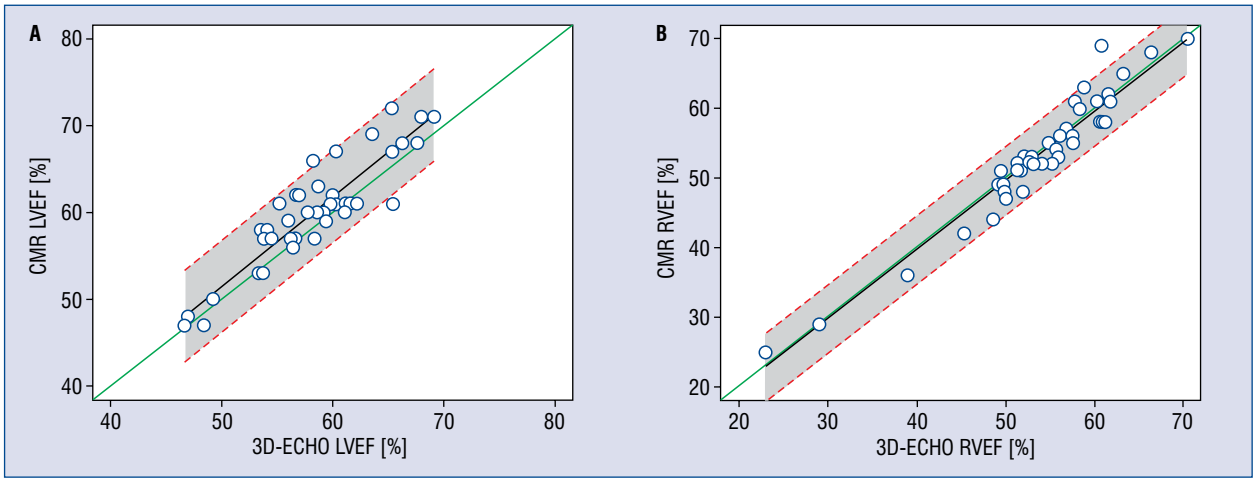

Figure 3. Identity function comparing results of left (**A**) and right (**B**) ventricular ejection fraction (LVEF, RVEF, respectively) between three-dimensional echocardiography (3D-ECHO) and cardiac magnetic resonance (CMR). Regression of Y (CMR) on X (3D-ECHO), with prediction limits. **A.** The average width of prediction interval = 10.6 ± 5.3%; **B.** The average width of prediction interval = 10.0 ± 5.0%.

± 2.8% (p = 0.0088). At the same time the 95% CIs for the whole group studied and arrhythmic subgroups proved to be narrow, marking good consistency of both methods. Also, those underestimations are considered minimal and irrelevant for single patients in clinical practice. The results are presented in Table 2.

For RVEF the estimated slope was 0.993, standard error = 0.007 (p < 0.00001), R-squared = 0.998; average width of 95% prediction interval was 10.0 ± 5.0%. Comparison of RVEF from 3D-ECHO to CMR values in 39% of patients showed the difference below 1%, in 63% under 2%, in 78% under 3%, and in as much as 93% below 4%. Almost perfect agreement was obtained between results of 3D-ECHO and CMR with the paired Student t-test proving the lack of a statistically significant difference between mean values of RVEF calculated in 3D-ECHO and CMR marked by p > 0.05 for the whole cohort and in arrhythmic subgroups. The mean difference between 3D-ECHO and CMR results was 0.4 ± 2.4% for the whole cohort (p = 0.29),

Table 2. Results of left ventricular ejection fraction (LVEF) measurements in three-dimensional echocardiography (3D-ECHO) and cardiac magnetic resonance (CMR) in subgroups of patients: ranges and mean values with standard deviations.

LVEF [%]	3D-ECHO (n = 42)	CMR (n = 42)	95% CI*	P
Study group	Range: 46.6–69.1% Mean: 58.5 ± 5.4%	Range: 47.0–72.0% Mean: 60.3 ± 6.0%	[–2.6, –1.0]	< 0.0001
Arrhythmia (26)	Range: 49.2–69.1% Mean: 59.0 ± 4.7%	Range: 50.0–71.0% Mean: 61.2 ± 5.0%	[–3.3, –1.3]	< 0.0001
Severe ventricular arrhythmia (15)	Range: 49.2–68.0% Mean: 57.9 ± 4.5%	Range: 50.0–71.0% Mean: 60.7 ± 5.2%	[–4.6, –1.6]	0.0006
Severe idiopathic ventricular arrhythmia (12)	Range: 49.2–68.0% Mean: 58.4 ± 4.8%	Range: 50.0–71.0% Mean: 60.7 ± 5.8%	[–4.4, –0.8]	0.0088
ARVC (3)	Range: 53.5–58.7%	Range: 58.0–63.0%	Too small sample for statistical testing	

*Difference = ejection fraction [%] measured by 3D-ECHO – ejection fraction [%] measured by CMR; ARVC — arrhythmogenic right ventricular cardiomyopathy; CI — confidence interval

Table 3. Results of right ventricular ejection fraction (RVEF) measurements in three-dimensional echocardiography (3D-ECHO) and cardiac magnetic resonance (CMR) in subgroups of patients: ranges and mean values with standard deviations.

RVEF [%]	3D-ECHO (n = 41)	CMR (n = 41)	95% CI*	P
Study group	Range: 22.9–70.3% Mean: 54.5 ± 8.8%	Range: 25.0–70.0% Mean: 53.6 ± 9.4%	[–0.3, +1.2]	0.29
Arrhythmia (25)	Range: 22.9–70.3% Mean: 52.8 ± 9.8%	Range: 25.0–70.0% Mean: 52.0 ± 10.1%	[–0.5, +1.2]	0.43
Severe ventricular arrhythmia (14)	Range: 22.9–70.3% Mean: 50.5 ± 11.9%	Range: 25.0–70.0% Mean: 49.1 ±11.9%	[–0.8, +1.7]	0.46
Severe idiopathic ventricular arrhythmia (12)	Range: 48.5–70.3% Mean: 55.2 ± 6.4%	Range: 44.0–70.0% Mean: 53.9 ± 7.1%	[–1.0, +2.0]	0.48
ARVC (3)	Range: 22.9–39.0%	Range: 25.0–36.0%	Too small sample for statistical testing	

*Difference = ejection fraction [%] measured by 3D-ECHO – ejection fraction [%] measured by CMR; ARVC — arrhythmogenic right ventricular cardiomyopathy; CI — confidence interval

0.3 ± 2.2% in the subgroup with arrhythmia (p = = 0.43), 0.5 ± 2.3% in the subgroup with severe ventricular arrhythmia (p = 0.46) and 0.5 ± 2.4% for patients with severe ventricular arrhythmia classified as idiopathic (p = 0.48). The 95% CI for the whole group studied and arrhythmic subgroups proved to be narrow, again marking close agreement with CMR results. The data are presented in Table 3.

Discussion

Arrhythmias are considered one of the most prominent problems in pediatric cardiology [4]. Contrary to the adult population, most cases of arrhythmia in children are classified as idiopathic because no link to cardiac morphology or evident haemodynamic dysfunction can be found [5–8]. In most cases the risk is low and general prognosis is good, patients do not usually require pharmacotherapy, even if extrasystole is common. However, for some arrhythmias the risk of sudden cardiac death is much higher. In diagnostics of ARVC enlarged chamber and deteriorated function of the right ventricle are among the most prominent major criteria, providing in fact half of the definitive diagnosis [9, 10]. The progression of the disease, including deterioration of ventricular function,

may be gradual and diffused in time [11–13]. For that reason, the accurate and regular assessment of ventricular function is crucial in patients with ventricular arrhythmia.

Unfortunately, widely accessible and inexpensive two-dimensional echocardiography (2D-ECHO) offers very biased data because a single-plane view cannot illustrate the complex morphology of the right ventricle [14–17]. CMR is much more accurate in this assessment and is considered the gold standard in calculating ventricular volume and function. Additionally, it offers information about potential myocardial fibrosis or fatty infiltration (helpful in establishing the diagnosis of ARVC, although not included in diagnostic criteria). Unfortunately, its low accessibility and high cost prevent it from being a truly universal tool, especially in patients with severe arrhythmia in whom initially normal right ventricular parameters might yet evolve into cardiomyopathy with time and need to be measured regularly [14]. Furthermore, the use of CMR has significant limitations in a group of infants and small children as well as patients with hyperactivity or anxiety disorders. The procedure is lengthy (at least 40 min) and during that time the patient has to lie still and hold breath on demand; that alone creates a cooperative problem in the pediatric population. For this reason, many patients (5 in the present study cohort) required general anesthesia with all its potential risks. Another group of patients in whom assessment of ventricular volume and function might be challenging is the population with excessive arrhythmia (especially with numerous extrasystolic beats), because the method is ECG-gated and requires 10 consecutive regular (sinus) beats to obtain optimal image resolution. Among the present study group, 2 children with multiple extrasystole, acquisition of optimal images was impossible.

Three-dimensional echocardiography, with its rapid evolution during the last three decades, seems to be an accessible and inexpensive tool for the assessment of cardiac function in clinical practice because it combines the accuracy of magnetic resonance imaging with the already high and constantly expanding accessibility and cost effectiveness of two-dimensional ultrasound systems [18–22]. The image acquisition is faster than CMR and requires fewer consecutive regular heart beats to produce data of adequate quality.

In the current study, focus was concentrated on evaluating the accuracy of 3D-ECHO in accessing ventricular function in children in comparison to CMR as the modality of reference.

In the group of children studied, results of both LVEF and RVEF calculated in 3D-ECHO proved to have a very high correlation and agreement with the data obtained in CMR. This consistency was proven both for the whole cohort and within extracted subgroups — patients with arrhythmic disorders in general, severe ventricular arrhythmias, and among cases of arrhythmia classified as idiopathic.

The mean differences between values of ventricular systolic function (LVEF and RVEF) calculated in 3D-ECHO and CMR were minimal with narrow (< 4%) 95% CI. However, while for the right ventricle the consistency of results between both methods was proven to be almost perfect in the paired Student t-test ($p > 0.05$ interpreted in this case as a lack of significant difference), LVEF proved to be minimally underestimated by 3D-ECHO in the whole population and arrhythmic subgroups with the highest mean difference of $-3.1 \pm \pm 2.7\%$ in the group of patients with severe ventricular arrhythmia. That difference was proven to be statistically significant ($p < 0.05$) by the paired Student t-test although irrelevant in clinical practice. The small 95% CI for mean difference pointed to close agreement with CMR results. This tendency is coherent with data published so far [23].

Published studies have shown good to excellent correlation between LVEF and RVEF measured in 3D-ECHO and CMR with a documented tendency towards minimal (although statistically significant) underestimation of 3D-ECHO results [23, 24]. Most of those studies concerned adults [25–29]. The literature comparing results of 3D-ECHO and CMR in children is much scarcer both in number and resources [27]. It usually addresses specific populations of patients: with congenital or acquired heart disease [30], after heart defect operations (prominently tetralogy of Fallot [31]) or with left ventricular cardiomyopathies [32]. No paper so far has offered data on the comparison between 3D-ECHO and CMR for ventricular function assessment in children with arrhythmia.

Whether impaired LVEF and RVEF are the source or the result of severe arrhythmia, and if ventricular function indeed deteriorates due to arrhythmic disorders, only further studies, especially within the pediatric population diagnosed with arrhythmia in morphologically healthy hearts, will show.

For this reason, systematic, regular, and accurate assessment of ventricular function in children with arrhythmia, even (or maybe especially) idiopathic, is crucial. 3D-ECHO appears to be the

perfect tool for this purpose and a valuable alternative to CMR in this population [26–28, 33–36].

It is suggested herein, that after initial CMR children with arrhythmias and left ventricular cardiomyopathies can be monitored with 3D-ECHO. CMR can be repeated only in cases of deterioration of ventricular function observed in 3D-ECHO.

Limitations of the study

In the present study, attention concentrated on assessing the rank of agreement between 3D-ECHO and CMR results in a pediatric population, focusing prominently on arrhythmic patients in whom imaging was both necessary and technically difficult. Because the population analyzed was small, the problem calls for further study, especially in children with arrhythmia. Comparisons to a control group of healthy children would provide statistical clarity on the subject of potential ventricular dysfunction in patients with arrhythmia preliminarily classified as idiopathic, but it is difficult to gather a group of healthy children in whom CMR was used. One should also keep in mind that children with idiopathic arrhythmia might show a tendency towards deterioration of ventricular function in adulthood; therefore, follow-up assessment can be fruitful.

Conclusions

Three-dimensional echocardiography assessment of both LVEF and RVEF in children shows a high significant correlation and agreement with CMR. 3D-ECHO could be a valuable tool in the follow-up of children with arrhythmic disorders requiring regular assessment of ventricular function.

Conflict of interest: None declared

References

1. Helbing WA, Ouhlous M. Cardiac magnetic resonance imaging in children. Pediatr Radiol. 2015; 45(1): 20–26, doi: 10.1007/s00247-014-3175-x, indexed in Pubmed: 25552387.
2. Barczuk-Falęcka M, Małek ŁA, Roik D, et al. Right ventricular end-systolic area as a simple first-line marker predicting right ventricular enlargement and decreased systolic function in children referred for cardiac magnetic resonance imaging. Clin Radiol. 2018; 73(6): 592.e9–592.e14, doi: 10.1016/j.crad.2018.01.020, indexed in Pubmed: 29519499.
3. Bland JM, Altman DG. Applying the right statistics: analyses of measurement studies. Ultrasound Obstet Gynecol. 2003; 22(1): 85–93, doi: 10.1002/uog.122, indexed in Pubmed: 12858311.
4. Ratcliffe M, Starr N. Patient management exchange: Cardiac arrhythmias in children. J Pediatric Health Care. 2000; 14(3): 0127–0129, doi: 10.1067/mph.2000.106362.
5. Kim SS, Ko SM, Song MG, et al. Assessment of global function of left ventricle with dual-source CT in patients with severe arrhythmia: a comparison with the use of two-dimensional transthoracic echocardiography. Int J Cardiovasc Imaging. 2010; 26(Suppl 2): 213–221, doi: 10.1007/s10554-010-9692-2, indexed in Pubmed: 20798989.
6. Do VB, Tsai WC, Lin YJ, et al. The different substrate characteristics of arrhythmogenic triggers in idiopathic right ventricular outflow tract tachycardia and arrhythmogenic right ventricular dysplasia: new insight from noncontact mapping. PLoS One. 2015; 10(10): e0140167, doi: 10.1371/journal.pone.0140167, indexed in Pubmed: 26488594.
7. Hennig A, Salel M, Sacher F, et al. High-resolution three-dimensional late gadolinium-enhanced cardiac magnetic resonance imaging to identify the underlying substrate of ventricular arrhythmia. Europace. 2018; 20(FI2): f179–f191, doi: 10.1093/europace/eux278, indexed in Pubmed: 29069369.
8. Raymond-Paquin A, Nattel S, Wakili R, et al. Mechanisms and clinical significance of arrhythmia-induced cardiomyopathy. Can J Cardiol. 2018; 34(11): 1449–1460, doi: 10.1016/j.cjca.2018.07.475, indexed in Pubmed: 30404750.
9. Li KaH, Bazoukis G, Liu T, et al. Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) in clinical practice. J Arrhythm. 2018; 34(1): 11–22, doi: 10.1002/joa3.12021, indexed in Pubmed: 29721109.
10. Chungsomprasong P, Hamilton R, Luining W, et al. Left ventricular function in children and adolescents with arrhythmogenic right ventricular cardiomyopathy. Am J Cardiol. 2017; 119(5): 778–784, doi: 10.1016/j.amjcard.2016.11.020, indexed in Pubmed: 28040191.
11. Steinmetz M, Krause U, Lauerer P, et al. Diagnosing ARVC in pediatric patients applying the revised task force criteria: importance of imaging, 12-lead ECG, and genetics. Pediatr Cardiol. 2018 [Epub ahead of print], doi: 10.1007/s00246-018-1875-y, indexed in Pubmed: 29754204.
12. Mast TP, James CA, Calkins H, et al. Evaluation of structural progression in arrhythmogenic right ventricular dysplasia/cardiomyopathy. JAMA Cardiol. 2017; 2(3): 293–302, doi: 10.1001/jamacardio.2016.5034, indexed in Pubmed: 28097316.
13. Mast TP, Taha K, Cramer MJ, et al. The prognostic value of right ventricular deformation imaging in early arrhythmogenic right ventricular cardiomyopathy. JACC Cardiovasc Imaging. 2018 [Epub ahead of print], doi: 10.1016/j.jcmg.2018.01.012, indexed in Pubmed: 29550307.
14. Sarvari SI, Haugaa KH, Anfinsen OG, et al. Right ventricular mechanical dispersion is related to malignant arrhythmias: a study of patients with arrhythmogenic right ventricular cardiomyopathy and subclinical right ventricular dysfunction. Eur Heart J. 2011; 32(9): 1089–1096, doi: 10.1093/eurheartj/ehr069, indexed in Pubmed: 21406439.
15. Pietrzak R, Werner B. Postsystolic shortening is associated with altered right ventricular function in children after tetralogy of Fallot surgical repair. PLoS One. 2017; 12(1): e0169178, doi: 10.1371/journal.pone.0169178, indexed in Pubmed: 28046050.
16. Lipczyńska M, Szymański P, Kumor M, et al. Global longitudinal strain may identify preserved systolic function of the systemic right ventricle. Can J Cardiol. 2015; 31(6): 760–766, doi: 10.1016/j.cjca.2015.02.028, indexed in Pubmed: 25935885.
17. Sano H, Tanaka H, Motoji Y, et al. Right ventricular function and right-heart echocardiographic response to therapy predict long-term outcome in patients with pulmonary hypertension. Can J Cardiol. 2015; 31(4): 529–536, doi: 10.1016/j.cjca.2015.01.027, indexed in Pubmed: 25840102.
18. Rudski L, Lai W, Afilalo J, et al. Guidelines for the Echocardiographic Assessment of the Right Heart in Adults: A Report from

the American Society of Echocardiography. J Am Soc Echocardiogr. 2010; 23(7): 685–713, doi: 10.1016/j.echo.2010.05.010.
19. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015; 28(1): 1–39.e14, doi: 10.1016/j.echo.2014.10.003, indexed in Pubmed: 25559473.
20. Velasco O, Beckett MQ, James AW, et al. Real-Time three-dimensional echocardiography: characterization of cardiac anatomy and function-current clinical applications and literature review update. Biores Open Access. 2017; 6(1): 15–18, doi: 10.1089/biores.2016.0033, indexed in Pubmed: 28303211.
21. Badano LP, Boccalini F, Muraru D, et al. Current clinical applications of transthoracic three-dimensional echocardiography. J Cardiovasc Ultrasound. 2012; 20(1): 1–22, doi: 10.4250/jcu.2012.20.1.1, indexed in Pubmed: 22509433.
22. Surkova E, Muraru D, Aruta P, et al. Current clinical applications of three-dimensional echocardiography: when the technique makes the difference. Curr Cardiol Rep. 2016; 18(11): 109, doi: 10.1007/s11886-016-0787-9, indexed in Pubmed: 27628295.
23. Shimada YJ, Shiota T. A meta-analysis and investigation for the source of bias of left ventricular volumes and function by three-dimensional echocardiography in comparison with magnetic resonance imaging. Am J Cardiol. 2011; 107(1): 126–138, doi: 10.1016/j.amjcard.2010.08.058, indexed in Pubmed: 21146700.
24. Shimada YJ, Shiota M, Siegel RJ, et al. Accuracy of right ventricular volumes and function determined by three-dimensional echocardiography in comparison with magnetic resonance imaging: a meta-analysis study. J Am Soc Echocardiogr. 2010; 23(9): 943–953, doi: 10.1016/j.echo.2010.06.029, indexed in Pubmed: 20797527.
25. Hoffmann R, Barletta G, von Bardeleben S, et al. Analysis of left ventricular volumes and function: a multicenter comparison of cardiac magnetic resonance imaging, cine ventriculography, and unenhanced and contrast-enhanced two-dimensional and three-dimensional echocardiography. J Am Soc Echocardiogr. 2014; 27(3): 292–301, doi: 10.1016/j.echo.2013.12.005, indexed in Pubmed: 24440110.
26. Hamilton-Craig CR, Stedman K, Maxwell R, et al. Accuracy of quantitative echocardiographic measures of right ventricular function as compared to cardiovascular magnetic resonance. Int J Cardiol Heart Vasc. 2016; 12: 38–44, doi: 10.1016/j.ijcha.2016.05.007, indexed in Pubmed: 28616541.
27. Lu X, Nadvoretskiy V, Bu L, et al. Accuracy and reproducibility of real-time three-dimensional echocardiography for assessment of right ventricular volumes and ejection fraction in children. J Am Soc Echocardiogr. 2008; 21(1): 84–89, doi: 10.1016/j.echo.2007.05.009, indexed in Pubmed: 17628408.
28. Park JB, Lee SP, Lee JH, et al. Quantification of right ventricular volume and function using single-beat three-dimensional echocardiography: a validation study with cardiac magnetic resonance. J Am Soc Echocardiogr. 2016; 29(5): 392–401, doi: 10.1016/j.echo.2016.01.010, indexed in Pubmed: 26969137.
29. Jenkins C, Chan J, Bricknell K, et al. Reproducibility of right ventricular volumes and ejection fraction using real-time three-dimensional echocardiography: comparison with cardiac MRI. Chest. 2007; 131(6): 1844–1851, doi: 10.1378/chest.06-2143, indexed in Pubmed: 17400663.
30. Balluz R, Liu L, Zhou X, et al. Real time three-dimensional echocardiography for quantification of ventricular volumes, mass, and function in children with congenital and acquired heart diseases. Echocardiography. 2013; 30(4): 472–482, doi: 10.1111/echo.12132, indexed in Pubmed: 23551607.
31. D'Anna C, Caputi A, Natali B, et al. Improving the role of echocardiography in studying the right ventricle of repaired tetralogy of Fallot patients: comparison with cardiac magnetic resonance. Int J Cardiovasc Imaging. 2018; 34(3): 399–406, doi: 10.1007/s10554-017-1249-1, indexed in Pubmed: 28988308.
32. Windram JD, Dragelescu A, Benson L, et al. Myocardial dimensions in children with hypertrophic cardiomyopathy: a comparison between echocardiography and cardiac magnetic resonance imaging. Can J Cardiol. 2016; 32(12): 1507–1512, doi: 10.1016/j.cjca.2016.06.014, indexed in Pubmed: 27789109.
33. Laser KT, Horst JP, Barth P, et al. Knowledge-based reconstruction of right ventricular volumes using real-time three-dimensional echocardiographic as well as cardiac magnetic resonance images: comparison with a cardiac magnetic resonance standard. J Am Soc Echocardiogr. 2014; 27(10): 1087–1097, doi: 10.1016/j.echo.2014.05.008, indexed in Pubmed: 24969839.
34. Knight DS, Grasso AE, Quail MA, et al. Accuracy and reproducibility of right ventricular quantification in patients with pressure and volume overload using single-beat three-dimensional echocardiography. J Am Soc Echocardiogr. 2015; 28(3): 363–374, doi: 10.1016/j.echo.2014.10.012, indexed in Pubmed: 25499839.
35. Nagata Y, Wu VCC, Kado Y, et al. Prognostic value of right ventricular ejection fraction assessed by transthoracic 3D echocardiography. Circ Cardiovasc Imaging. 2017; 10(2), doi: 10.1161/CIRCIMAGING.116.005384, indexed in Pubmed: 28174197.
36. Kamińska H, Werner B. Three-dimensional echocardiography in the assessment of ventricular function in children: pros, cons, and hopes. Kardiol Pol. 2019; 77(1): 12–17, doi: 10.5603/KP.a2018.0244, indexed in Pubmed: 30575007.

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Optimal timing of contrast-enhanced three-dimensional magnetic resonance left atrial angiography before pulmonary vein ablation

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Abstract

Background: *To achieve high image quality of cardiovascular magnetic resonance (CMR) pulmonary vein (PV) angiography prior catheter ablation in patients with atrial fibrillation, optimal timing of the angiographic sequence during contrast agent passage is important. The present study identified influential cardiovascular parameters for prediction of contrast agent travel time.*

Methods: *One hundred six consecutive patients underwent a CMR examination including three-dimensional (3D) contrast-enhanced PV angiography with real-time bolus tracking prior to catheter ablation. Correct scan timing was characterized by relative signal enhancement measurements in the pulmonary artery, left atrium (LA), and ascending aorta. Furthermore, left- and right-ventricular function, left- and right-atrial dimensions, presence of mitral or tricuspid insufficiencies, and main pulmonary artery diameter were determined.*

Results: *The highest relative signal enhancement in LA demonstrated optimal scan timing. Contrast agent travel time showed wide variability (range: 12–42 s; mean: 18 ± 4 s). On univariate analysis, most cardiovascular parameters correlated with contrast agent travel time while on multivariate analysis left- and right-ventricular function remained the only independent predictors, but overall a poor fit to the data (adjusted R^2, 27.5%) was found.*

Conclusions: *Contrast agent travel time was mainly influenced by left- and right-ventricular function but prediction models poorly fitted the data. Thus, 3D PV angiography prior to PV ablation procedures necessitates real-time assessment, with visual determination of individual contrast agent passage time to ensure consistently high CMR image quality.* (Cardiol J 2021; 28, 4: 558–565)

Key words: cardiovascular magnetic resonance imaging, angiography, pulmonary vein, atrial fibrillation, catheter ablation

Introduction

Atrial fibrillation (AF) is a common type of cardiac arrhythmia with a greater prevalence in the elderly [1] and in patients with cardiac comorbidities. Prior studies revealed the pulmonary veins (PVs) as important triggers for initializing and sustaining AF [2]. Treatment of AF with catheter ablation aimed at the electrical isolation of PVs is nowadays widely employed to prevent recurrent AF [3, 4].

Prior to PV isolation procedures, three-dimensional (3D) imaging of the left atrium (LA) and PV anatomy is recommended for pre-procedural planning and therapy guidance during catheter

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ablation. These high-resolution images allow for accurate assessment of anatomical variants and can be obtained by either multi-detector computed tomography (MDCT) or cardiovascular magnetic resonance (CMR) [4, 5]. However, MDCT exposes the patient to iodinated contrast agents and ionizing radiation [6] and AF is a chronic, progressive disease making repeat examinations during life-time very likely. CMR imaging has the additional benefit of combining PV angiography with functional cardiac imaging or myocardial tissue characterization (e.g. LA fibrosis) during a single-session examination [7]. Consequently, CMR may be considered the preferred imaging approach; the segmented 3D CMR mesh models of the LA and the PVs can be easily co-registered in the electroanatomical mapping systems and subsequently used for catheter guidance during the ablation procedures, thereby significantly reducing overall radiation exposure time [8, 9].

High spatial resolution together with high image quality of contrast-enhanced PV angiography is mandatory for electrophysiological procedures and hence, the optimal scan timing during contrast agent passage plays a pivotal role. Whether the presence of AF during CMR imaging affects the contrast agent travel time has not yet been investigated. Moreover, predicting the optimal scan timing in an individual patient prior to CMR angiography would be highly desirable. Consequently, the present study sought to evaluate various routine cardiovascular parameters with regard to their influence on contrast agent bolus travel time

Table 1. Patient characteristics (n = 106).

Age [years]	62 ± 10
Women	45 (43%)
Sinus rhythm during CMR-study	55 (52%)
Heart rate during CMR-study [1/min]	78 ± 26
Pulmonary disease	6 (6%)
Body mass index [kg/m^2]	29 ± 5
Left ventricular ejection fraction [%]	53 ± 11
Left ventricular end-diastolic volume [mL]	157 ± 54
Cardiac output [L/min]	5.9 ± 1.6
Right ventricular ejection fraction [%]	42 ± 8
Left atrial area [cm^2]	29 ± 8
Right atrial area [cm^2]	24 ± 6
Pulmonary artery diameter [mm]	26 ± 4
Systolic pulmonary artery pressure [mmHg]	27 ± 8
Mitral regurgitation ≥ grade 2	10 (9%)
Tricuspid regurgitation ≥ grade 2	8 (8%)

Data are provided as mean ± standard deviation or number (percent). CMR — cardiovascular magnetic resonance

Methods

Patients

One hundred six consecutive patients (62 ± 10 years, 61 men) with AF or non-isthmus dependent left-atrial flutter underwent CMR imaging prior to clinically indicated catheter ablation. Patients with known contraindications to CMR imaging were not considered. Detailed patient characteristics are provided in Table 1. The study was conducted in accordance with the local institutional review board and the standards of the University of Leipzig ethics committee. Written informed consent was obtained from all patients.

CMR imaging protocol

All CMR examinations were performed using a 1.5T MR scanner system (Philips Ingenia, Best, The Netherlands) equipped with Omega HP gradients (45 mT/m, 200 T/m/s) and a 28-element array coil with full in-coil signal digitalization combined with optical transmission. Conventional cine imaging was performed in all cardiac standard geometries (short axis geometries and long axis geometries, i.e. 4-, 3-, and 2-chamber orientation) using steady-state free precession (SSFP) sequences during end-expiratory breathholds with a prospective electrocardiogram (ECG)-gating acquisition. In addition, a 3D navigator-gated, balanced turbo field echo (bTFE) sequence was acquired in transversal slice orientation with full coverage of the great thoracic vessels. Furthermore, phase-contrast flow measurements were performed for the assessment of the cardiac output. Finally, contrast-enhanced 3D CMR angiography of the LA and PVs was performed during inspiratory breath-holding using a non-ECG triggered spoiled gradient echo sequence (TR/TE/flip angle: 2.2 ms/0.8 ms/30°, isotropic spatial resolution: 1.0 × 1.0 × 1.0 mm^3). During intravenous bolus injection of 0.1 mmol/kg Gad-DTPA (Magnograf®, injection rate 4.0 mL/s) followed by a 25 mL saline flush at the same injection rate, integrated real-time bolus tracking in coronal slice orientation (slice thickness, 150 mm; in-plane spatial resolution, 1.7 × 1.7 mm^2; temporal resolution, 680 ms) allowed for visual determination of the sequence start as performed by a trained CMR operator; the angiographic scan was initiated when the contrast agent bolus arrived in the left atrium.

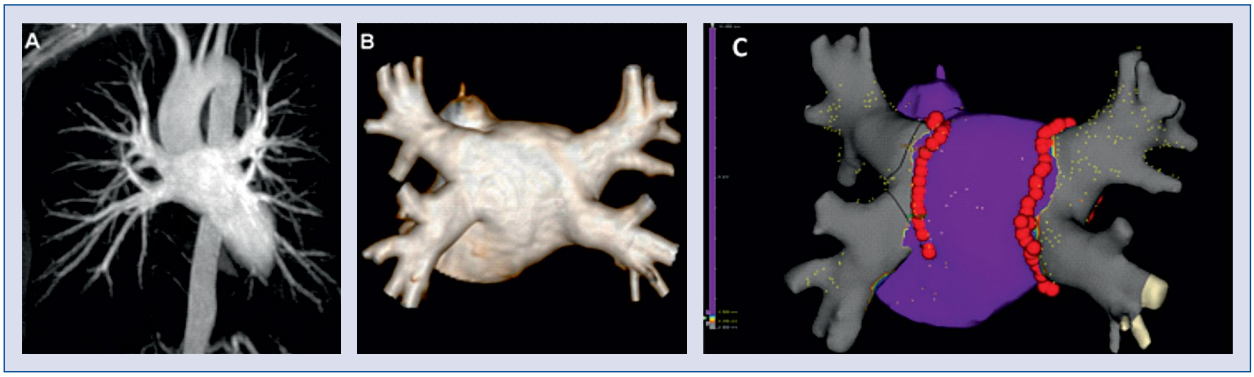

Figure 1. A. Maximum-intensity projection of three-dimensional (3D) contrast-enhanced cardiovascular magnetic resonance (CMR) angiography of the left atrium and pulmonary veins; accurate timing led to the highest relative signal enhancement in left atrium/pulmonary veins; **B.** Segmented volume rendering reconstruction of the left atrium and pulmonary veins; subsequently generated 3D CMR mesh model can be easily integrated into electroanatomical mapping systems for guidance of catheter ablation procedures; **C.** Image fusion of electroanatomical map (EnSite Precision, St. Jude Medical, St. Paul, MN, US) and CMR mesh model of left atrium and pulmonary veins during electrophysiological ablation procedure.

CMR image analysis

Cine imaging was used to determine left-ventricular volumes and function, right-ventricular function and left-/right-atrial size according to standard definitions. Maximal diameter of the main pulmonary artery (PA) was measured on 3D bTFE scan.

In order to objectively determine the correct scan timing of PV angiography, signal intensity measurements were carried out in the PA, the LA, the ascending and descending aorta, and in the adipose tissue of the anterior chest wall; relative signal enhancement was calculated by dividing the maximum signal intensity of the target region by the signal intensity of the reference tissue (= subcutaneous fat).

Echocardiography

In all patients, two-dimensional transthoracic echocardiography was performed within 1 week prior the CMR examination using a commercially available ultrasound system (Vivid 7, General Electric, Milwaukee, WI, USA) equipped with a 3.5 MHz transducer. Recordings were made in parasternal long- and short-axis, as well as apical 4- and 2-chamber views. Valve morphology and function were assessed according to the guidelines of the European Society of Cardiovascular Imaging [10] and the American Society of Echocardiography [11]: the severity of mitral and tricuspid regurgitation was graded on a four-point scale. In addition, systolic pulmonary artery pressure (PAP) was estimated based on tricuspid regurgitation velocity.

Statistical analysis

Continuous variables are stated as mean ± standard deviation if normally distributed. Numbers and ratios were used to describe categorical variables. The Kolmogorov-Smirnov test was used to assess normal distribution. The χ^2 test was used for comparisons between groups in case of categorical variables; the Student t-test was applied for continuous variables. To determine the relationship of contrast agent travel time and cardiovascular parameters, univariate logistic regression analysis was done. Parameters which yielded as statistically significant in univariate logistic regression analyses were assessed by multivariate logistic regression analysis. In addition, univariate and multivariate regression analysis was performed in the subgroups of patients presenting with sinus rhythm or AF during CMR examination and estimation models based on polynomial data fitting were derived. A two-tailed p-value < 0.05 was considered significant.

Results

Patient characteristics

Cardiovascular magnetic resonance examinations were successfully completed in all 106 patients (Fig. 1). Patient demographics are summarized in Table 1.

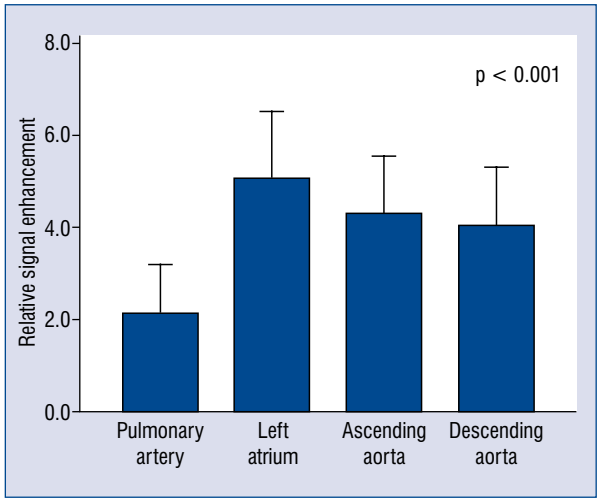

Figure 2. Measurements of relative signal enhancement (mean ± standard deviation) confirmed the highest values in left atrium (5.1 ± 1.5; p < 0.001) in comparison to the pulmonary artery (2.1 ± 1.1), ascending (4.3 ± 1.2) and descending aorta (4.0 ± 1.3), respectively.

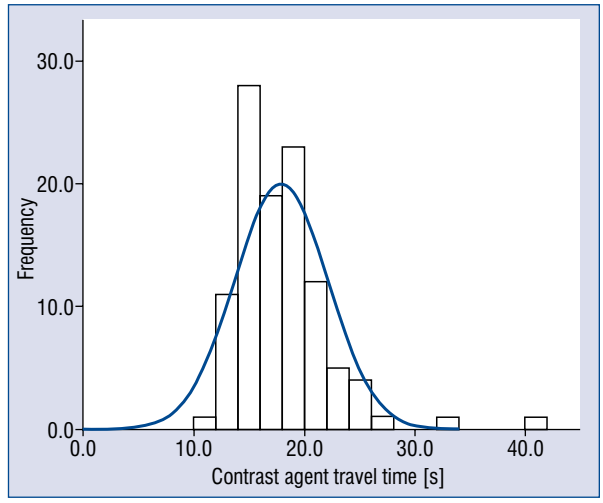

Figure 3. Histogram plot of contrast agent travel time in all patients demonstrated a wide variability (range 12–42 s; mean 18 ± 4 s); the blue line indicates fitted normal distribution.

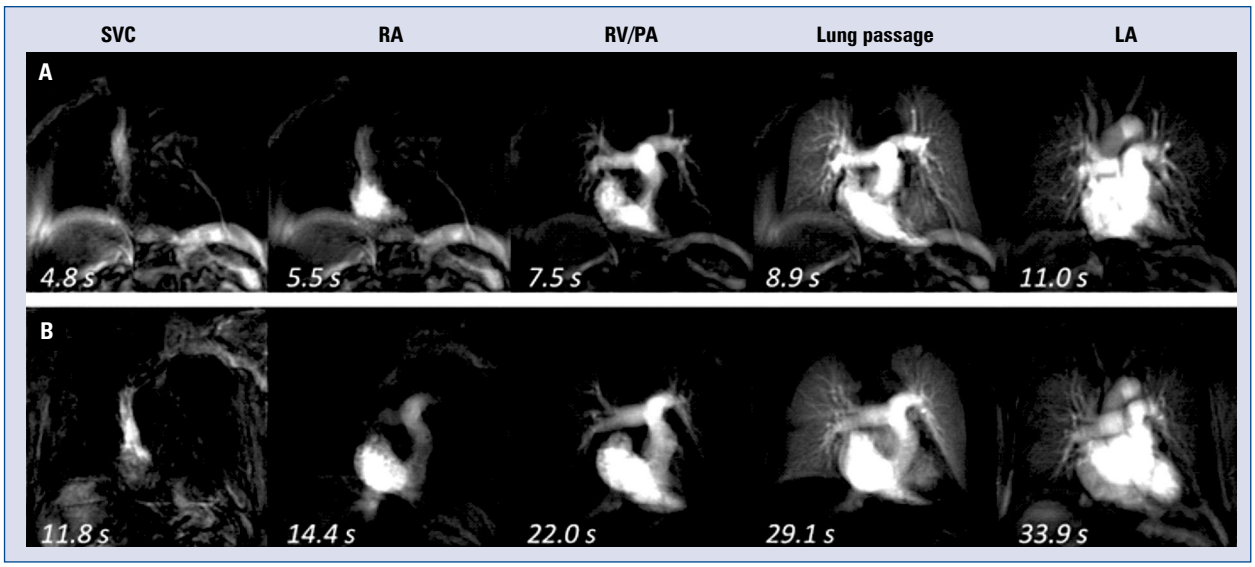

Figure 4. Real-time cardiovascular magnetic resonance (CMR) bolus tracking during contrast agent passage: representative extracted frames of contrast agent bolus passage are shown demonstrating its arrival in superior vena cava (SVC), right atrium (RA), right ventricle (RV)/pulmonary artery (PA), lung and left atrium (LA); subsequently, the three-dimensional angiographic imaging sequence was started; **A.** Sinus rhythm (heart rate 78/min), LV-EF 64%, RV-EF 61%, LA 18 cm^2, RA 17 cm^2, MI grade 1; **B.** Atrial fibrillation (heart rate approx. 100/min), LV-EF 23%, RV-EF 24%, LA 29 cm^2, RA 27 cm^2, MI grade 1; LV — left ventricular; EF — ejection fraction.

Contrast agent travel time

The relative signal enhancement of large thoracic vessels and cardiac cavities served as a quality measure of accurate timing of the 3D angiographic scan with the highest relative signal enhancement observed in the LA (LA 5.1 ± 1.5; PA 2.1 ± 1.1; ascending aorta 4.3 ± 1.2; descending aorta 4.0 ± 1.3; p < 0.001; Fig. 2); in 100% (106/106) and 98% (104/106) of patients relative signal enhancement was found to be higher in the LA when compared to the main PA and the ascending aorta, respectively. The travel time of the contrast agent bolus was normally distributed (Kolmogorov-Smirnov test, p = 0.11) and demonstrated a wide variability (range 12–42 s; mean 18 ± 4 s; median 17 s; Figs. 3, 4).

Table 2. Univariate and multiple linear regression (MLR) analysis (p-values) for the prediction of the real-time tracking time.

	All patients		SR during CMR study		AF during CMR study	
	Univariate	MLR	Univariate	MLR	Univariate	MLR
Age	0.02	0.14	0.07		0.79	
Sex	0.06		0.1		0.22	
SR during CMR-study	0.01	0.95				
Heart rate during CMR-study	0.12		0.63		0.92	
Body mass index	0.36		0.49		0.87	
LVEF	< 0.001	**0.01**	< 0.001	**0.001**	0.03	0.16
LVEDV	0.004	0.17	< 0.001	0.51	0.20	
Cardiac output	0.23		0.21		0.46	
RVEF	< 0.001	**< 0.001**	< 0.001	**0.002**	0.013	0.057
LA	0.001	0.65	0.046	0.34	0.052	
RA	0.001	0.61	0.003	0.30	0.15	
Pulmonary artery diameter	0.02	0.24	0.069		0.28	
Systolic PAP	0.025	0.73	0.035	0.56	0.57	
Mitral regurgitation ≥ grade 2	0.001	0.27	0.008	0.52	0.17	
Tricuspid regurgitation ≥ grade 2	0.01	0.58	0.03	0.85	0.39	

CMR — cardiovascular magnetic resonance; SR — sinus rhythm; AF — atrial fibrillation; LVEF — left ventricular ejection fraction; LVEDV — left ventricular end-diastolic volume; RVEF — right ventricular ejection fraction; LA — left atrial dimension; RA — right atrial dimension; PAP — pulmonary arterial pressure

In order to simulate angiographic scan timing done without real-time display of contrast agent bolus passage, derived mean and median values with an allowed deviation of ± 1 s were employed as "fixed" timing parameters to the current study population: theoretically, such an approach would have yielded successful timing in only 16% and 20% of patients within the predefined ranges of 17–19 s and 16–18 s, respectively.

To determine the influence of various routine cardiovascular parameters on the contrast agent travel time, univariate analysis was performed and revealed a significant correlation of the contrast agent travel time with age, heart rhythm, left and right ventricular ejection fraction (LVEF, RVEF), left ventricular end-diastolic volume, left and right atrial size, PA diameter, presence of mitral or tricuspid regurgitation and systolic PAP, respectively (Table 2). On multivariate analysis, LVEF and RVEF remained the only independent predictors of the contrast agent travel time ($p = 0.002$ and $p < 0.001$, respectively); however, the adjusted R^2 of 27.5% indicated that the regression model poorly fitted the data.

In addition, subgroup analysis in patients presenting with sinus rhythm or AF during the CMR examination was carried out (Table 2) using linear regression analysis: LVEF and RVEF remained the only independent predictors of contrast agent travel time in sinus rhythm patients while in AF patients none of the cardiovascular parameters reached the level of significance (adjusted R^2-values, 54% and 12%, respectively).

In order to derive estimation models for the prediction of contrast agent travel time in patients with sinus rhythm, LVEF and RVEF were employed in polynomial curve fitting procedures. Based on R^2 change, quadratic models were identified to represent a favorable compromise between model complexity and routine applicability (Table 3). Though significant, explaining only an additional 2% or 9% of the variance was considered not to justify rendering the model even more complex and hence, the cubic fit was rejected. Respective estimation models for the calculation of predicted contrast agent travel time are provided in Table 4.

Discussion

The present study evaluated the influence of various cardiovascular parameters on the contrast agent travel time as assessed during contrast-enhanced CMR PV angiography prior to catheter ablation of AF. The main findings were as follows:

Table 3. Polynomial regression analysis to determine the influence of left and right ventricular ejection fraction (LVEF, RVEF) on contrast agent travel time in patients with sinus rhythm (n = 55).

	LVEF			RVEF		
	R^2	Adjusted R^2	R^2 change	R^2	Adjusted R^2	R^2 change
Linear model	0.43	0.42	0.43	0.33	0.32	0.33
Quadratic model	0.56	0.54	0.13	0.55	0.54	0.22
Cubic model	0.58	0.55	0.02	0.64	0.63	0.09

Table 4. Estimation models for calculation of contrast agent travel time (given in seconds) in patients with sinus rhythm.

LVEF-based models	
Linear	Contrast agent travel time [s] = 35 – 0.33 × LVEF
Quadratic	Contrast agent travel time [s] = 58 – 1.4 × LVEF + 0.01 × $LVEF^2$
RVEF-based models	
Linear	Contrast agent travel time [s] = 31 – 0.33 × RVEF
Quadratic	Contrast agent travel time [s] = 61 – 1.8 × RVEF + 0.02 × $RVEF^2$

LVEF — left ventricular ejection fraction (in %); RVEF — right ventricular ejection fraction (in %)

(1) on univariate analysis numerous cardiovascular parameters had an influence on contrast agent travel time, however (2) on multivariate analysis the only independent predictors were identified as LVEF and RVEF; (3) a reliable prediction of the contrast agent travel time was not accurately possible for every individual patient in particular in patients with AF during CMR examination; (4) in the subgroup of patients presenting with sinus rhythm contrast agent travel time may be determined from LVEF and RVEF using the proposed polynomial estimation model; (5) finally, visual determination of contrast agent bolus arrival in the target region (i.e. the LA) using a real-time tracking sequence enabled accurate timing of image data acquisition in all patients.

Three-dimensional angiographic determination of PV and left atrial anatomy can assist in pre-procedural decision making (e.g. cryoablation vs. radiofrequency ablation technique) and is particularly important for anatomical guidance during the ablation procedure [4]. Depending on the operators' preferences, image fusion of pre-procedural CT/ /CMR anatomic 3D reconstructions with electroanatomical maps can contribute in facilitating complex AF ablation procedures [12]. In addition, high-resolution, 3D depiction of the LA and PV morphology resulting from image fusion reportedly increased the safety of the AF ablation procedures [13] and is fundamental in the prevention of rare, but severe procedure-related complications such as PV stenosis [14].

For high-quality, contrast-enhanced 3D CMR angiography accurate timing of bolus arrival in the LA/PV target region is of the essence. Although real-time tracking which permits the direct visualization of the bolus passage has been established for several years, data from a multicenter trial revealed a high proportion of technical failures due to timing errors of up to 25% for CMR angiography of the pulmonary arteries with a proportion of technically inadequate images ranging from 11% to 52% between different centers [15]. Obviously, a reliable prediction of the correct timing to assist the CMR operator would be highly desirable. In the current study population, the distribution of the contrast agent travel time showed a high variability which on theoretical simulation using a fixed timing value (mean or median) would have resulted in 84% or 80% of inaccurately timed angiographic scans, respectively, and thus, leading to inadequate contrast enhancement and impaired image quality in a majority of patients.

Consequently, the current study examined a variety of readily available cardiovascular parameters and tested their influence on the contrast agent travel time with the aim to better predict scan timing. While on univariate analysis several cardiovascular parameters were associated significantly with contrast agent travel time, left and right

ventricular function remained the only independent predictors on multivariate analysis. However, the low adjusted R^2 indicated that the regression model poorly fitted the data. A subgroup analysis of patients presenting with AF during CMR examination demonstrated that prediction of scan timing will almost invariably fail. On the other hand, the subgroup of sinus rhythm patients yielded a considerably higher adjusted R^2 value suggesting that a prediction of the contrast agent travel time may be possible. An estimation model, using a linear fit provided an easily applicable approach in clinical routine by calculating 35 or 31 minus one-third of LVEF or RVEF, respectively. An improved, though more complex estimate could be achieved by applying a quadratic model given in Table 4. However, the adjusted R^2 values indicated that only 54% of the overall variation could be explained by the independent variables LVEF and RVEF. Thus, it must be noted that the possibilities to predict the contrast agent travel time in an individual patient are severely limited.

To overcome these timing challenges, alternative imaging approaches have been introduced. Free-breathing ECG-gated 3D SSFP sequences render the correct timing process needless: in a small patient study [16] a non-contrast enhanced imaging approach proved to be highly accurate with regard to PV diameter measurements when compared to contrast-enhanced CMR angiography. Another study [17] applied an accelerated free-breathing, ECG-triggered contrast-enhanced PV CMR angiographic scan with isotropic spatial resolution using compressed sensing, resulting in even further improvement of vessel sharpness when compared to conventional CMR angiography. However, the fundamental prerequisite for all these ECG-triggered imaging approaches consists in the presence of a regular sinus rhythm. But considering the patient population scheduled for PV angiography prior to electrophysiological ablation procedures, a high proportion of patients will present with AF and, thus, a high heart rate variability. In the present study, nearly half of the patients had AF during the CMR examination (48%) and consequently, a non-ECG triggered imaging approach such as the conventional contrast-enhanced PV angiography is generally preferred.

A widely used alternative to real-time tracking of the contrast agent bolus is the administration of a small test bolus in order to estimate the arrival time in the target region. General disadvantages of test bolus timing include increased examination duration and background contamination by gadolinium (potentially leading to unfavorable pulmonary tissue enhancement and decreased PV conspicuity). More importantly, the arrival times for a small contrast agent dose and the full dose are not necessarily consistent. Finally, taking into account the high heart rate variability of AF patients with concomitant rapid changes of hemodynamics, it is evident that the test bolus strategy can be regarded inherently flawed in this particular patient population.

Finally, another important CMR imaging approach has become available with the advent of time-resolved 3D-CMR angiographic scans (so called "4D-CMR angiography" with time representing the fourth dimension). This scan technique allows the acquisition of full 3D-angiographic datasets of the thorax/large thoracic vessels in a time-resolved manner (i.e. usually every 4 to 6 s) but this is at the expense of spatial resolution. The technique mostly obviates the need for accurate bolus timing since during post-processing a CMR expert selects the single, high signal enhancement 3D-dataset of the LA/the PVs for diagnostic evaluation and volume rendering/ /mesh reconstruction. However, the lower spatial resolution of 4D-angiographic scans (non-isotropic datasets, typically 2.5×2.5 mm^2 in-plane resolution with 5 mm slice thickness) in comparison to bolus-tracking directed 3D-angiographic scans (preserved high isotropic spatial resolution, usually in the range of 1.0×1.0 mm^2 in-plane resolution with 1.0 mm slice thickness) should be taken into account when establishing a routine institutional angiographic protocol: with 4D-CMR angiography small caliper PV anatomical variants (early small caliper branching of PV main ostia or accessory PVs e.g. right middle PVs, isolated roof top veins etc.) may be poorly visible or even missed and, if electrically active, may represent a possible focus for re-occurrence of AF. Hence, at our institution the interventional electrophysiologists generally prefer bolus-tracking directed, high spatial resolution 3D-angiography for anatomical procedural guidance.

Conclusions

For the determination of contrast agent travel time, left and right ventricular function were identified as the only independent predictors but regression models poorly fitted the data, particularly in patients with AF during CMR examination. Thus, 3D, PV angiography prior to PV ablation procedures necessitates real-time assessment

with visual determination of individual contrast agent passage time to ensure consistently high CMR image quality.

Conflict of interest: None declared

References

1. Haim M, Hoshen M, Reges O, et al. Prospective national study of the prevalence, incidence, management and outcome of a large contemporary cohort of patients with incident non-valvular atrial fibrillation. J Am Heart Assoc. 2015; 4(1): e001486, doi: 10.1161/JAHA.114.001486, indexed in Pubmed: 25609415.
2. Haïssaguerre M, Jaïs P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med. 1998; 339(10): 659–666, doi: 10.1056/NEJM199809033391003, indexed in Pubmed: 9725923.
3. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Europace. 2016; 18(11): 1609–1678, doi: 10.1093/europace/euw295.
4. Mansour M, Refaat M, Heist EK, et al. Three-dimensional anatomy of the left atrium by magnetic resonance angiography: implications for catheter ablation for atrial fibrillation. J Cardiovasc Electrophysiol. 2006; 17(7): 719–723, doi: 10.1111/j.1540-8167.2006.00491.x, indexed in Pubmed: 16836666.
5. Löbe S, Hilbert S, Dinov B, et al. High electrical activity at the connection site of previously undetected anomalous pulmonary venous drainage in a patient presenting with atrial fibrillation. Int J Cardiovasc Imaging. 2017; 33(11): 1845–1846, doi: 10.1007/s10554-017-1184-1, indexed in Pubmed: 28589483.
6. Vyas HV, Greenberg SB, Krishnamurthy R. MR imaging and CT evaluation of congenital pulmonary vein abnormalities in neonates and infants. Radiographics. 2012; 32(1): 87–98, doi: 10.1148/rg.321105764, indexed in Pubmed: 22236895.
7. Marrouche NF, Wilber D, Hindricks G, et al. Association of atrial tissue fibrosis identified by delayed enhancement MRI and atrial fibrillation catheter ablation: the DECAAF study. JAMA. 2014; 311(5): 498–506, doi: 10.1001/jama.2014.3, indexed in Pubmed: 24496537.
8. Tops LF, Bax JJ, Zeppenfeld K, et al. Fusion of multislice computed tomography imaging with three-dimensional electroanatomic mapping to guide radiofrequency catheter ablation procedures. Heart Rhythm. 2005; 2(10): 1076–1081, doi: 10.1016/j.hrthm.2005.07.019, indexed in Pubmed: 16188585.
9. Dong J, Dickfeld T, Dalal D, et al. Initial experience in the use of integrated electroanatomic mapping with three-dimensional MR//CT images to guide catheter ablation of atrial fibrillation. J Cardiovasc Electrophysiol. 2006; 17(5): 459–466, doi: 10.1111/j.1540-8167.2006.00425.x, indexed in Pubmed: 16684014.
10. Lancellotti P, Tribouilloy C, Hagendorff A, et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2013; 14(7): 611–644, doi: 10.1093/ehjci/jet105, indexed in Pubmed: 23733442.
11. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr. 2010; 23(7): 685–713; quiz 786, doi: 10.1016/j.echo.2010.05.010, indexed in Pubmed: 20620859.
12. Kistler PM, Rajappan K, Harris S, et al. The impact of image integration on catheter ablation of atrial fibrillation using electroanatomic mapping: a prospective randomized study. Eur Heart J. 2008; 29(24): 3029–3036, doi: 10.1093/eurheartj/ehn453, indexed in Pubmed: 18931059.
13. Kettering K, Greil GF, Fenchel M, et al. Catheter ablation of atrial fibrillation using the Navx-/Ensite-system and a CT-/MRI--guided approach. Clin Res Cardiol. 2009; 98(5): 285–296, doi: 10.1007/s00392-009-0001-9, indexed in Pubmed: 19283334.
14. Hilbert S, Paetsch I, Bollmann A, et al. Pulmonary vein collateral formation as a long-term result of post-interventional pulmonary vein stenosis. Eur Heart J. 2016; 37(31): 2474, doi: 10.1093/eurheartj/ehv753, indexed in Pubmed: 26795444.
15. Stein P, Chenevert TL, Fowler SE. Gadolinium-Enhanced magnetic resonance angiography for pulmonary embolism. Ann Intern Med. 2010; 152(7): 434–443, doi: 10.7326/0003-4819-152-7-201004060-00008.
16. François CJ, Tuite D, Deshpande V, et al. Pulmonary vein imaging with unenhanced three-dimensional balanced steady-state free precession MR angiography: initial clinical evaluation. Radiology. 2009; 250(3): 932–939, doi: 10.1148/radiol.2502072137, indexed in Pubmed: 19164696.
17. Roujol S, Foppa M, Basha TA, et al. Accelerated free breathing ECG triggered contrast enhanced pulmonary vein magnetic resonance angiography using compressed sensing. J Cardiovasc Magn Reson. 2014; 16: 91, doi: 10.1186/s12968-014-0091-z, indexed in Pubmed: 25416082.

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Long-term antibiotic therapy in patients with surgery-indicated not undergoing surgery infective endocarditis

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Abstract

Background: *To date, there is little information regarding management of patients with infective endocarditis (IE) that did not undergo an indicated surgery. Therefore, we aimed to evaluate prognosis of these patients treated with a long-term antibiotic treatment strategy, including oral long term suppressive antibiotic treatment in five referral centres with a multidisciplinary endocarditis team.*

Methods: *This retrospective, multicenter study retrieved individual patient-level data from five referral centres in Spain. Among a total of 1797, 32 consecutive patients with IE were examined (median age 72 years; 78% males) who had not undergone an indicated surgery, but received long-term antibiotic treatment (LTAT) and were followed by a multidisciplinary endocarditis team, between 2011 and 2019. Primary outcomes were infection relapse and mortality during follow-up.*

Results: *Among 32 patients, 21 had IE associated with prostheses. Of the latter, 8 had an ascending aorta prosthetic graft. In 24 patients, a switch to long-term oral suppressive antibiotic treatment (LOSAT) was considered. The median duration of LOSAT was 277 days. Four patients experienced a relapse during follow-up. One patient died within 60 days, and 12 patients died between 60 days and 3 years. However, only 4 deaths were related to IE.*

Conclusions: *The present study results suggest that a LTAT strategy, including LOSAT, might be considered for patients with IE that cannot undergo an indicated surgery. After hospitalization, they should be followed by a multidisciplinary endocarditis team.* (Cardiol J 2021; 28, 4: 566–578)

Key words: suppressive antibiotic treatment, infective endocarditis, surgery

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Introduction

Infective endocarditis (IE) is a severe, complex entity with high morbidity, inhospital mortality (20–30%) [1], and long-term mortality (~45%) [2], despite recent advances in diagnostic and therapeutic strategies [3–5]. The epidemiology of IE has changed [6–8] towards patients with multiple comorbidities, prostheses, devices, congenital heart diseases, or transcatheter procedures [9].

Cardiac surgery and antibiotic treatment are the cornerstones of IE treatment. According to current recommendations [10], more than 70% of patients with IE have an indication for surgery, but less than 50% finally undergo operations, due to surgical risk [11–13]. In-hospital mortality is high (~70%) among patients with surgery indicated not undergoing surgery IE (SINUS-IE). However, information is sparse regarding the clinical characteristics and long-term outcomes for these patients [14].

Clinical guidelines [10] do not specifically mention antibiotic treatment or a recommended treatment duration for patients with SINUS-IE. Oral antibiotics have shown to be effective for shortening intravenous treatment in selected cases of uncomplicated left-sided IE [15]; however, there is a lack information regarding oral long-term antibiotic treatment (LTAT) in the context of SINUS-IE. Moreover, new imaging techniques [16], such as positron emission tomography/computed tomography (PET/CT) might play a role in monitoring responses and establishing an appropriate duration for LTAT [17, 18] in SINUS-IE.

We hypothesized that an approach managed by a multidisciplinary endocarditis team (MDET) that included individualized LTAT, long-term oral suppressive antibiotic treatment (LOSAT) when needed, and close follow-up might improve the long-term prognosis in SINUS-IE. Accordingly, this study aimed to evaluate the clinical characteristics and outcome of patients with SINUS-IE treated with long-term antibiotic regimens in 5 Spanish referral centres.

Methods

Study design and data collection

For this multicenter, retrospective, observational study, patient-level data was collected from local, prospective databases at 5 hospitals in Spain from January 2011 to January 2019. The 5 hospitals were referral centres for IE with cardiac surgery facilities. In addition, MDETs held regular meetings to discuss and evaluate therapeutic strategies for patients with IE.

We included adult patients (age ≥ 18 years) with a definite diagnosis of IE (based on modified Duke criteria/European Society of Cardiology (ESC) criteria, modified in August 2015) and an indication for surgery or device extraction, according to clinical guidelines [10]. None of these patients underwent surgical procedures after an evaluation by the MDET. All these patients survived the index hospitalization with a plan established by the local MDET for long-term intravenous treatment (> 8 weeks) or LOSAT. Patients with fungal IE were excluded. For patients with relapses, only the episode in which the local committee decided to treat with LTAT was included. Patients that had been discharged with a plan for LTAT during follow-up were also included.

Data were obtained on demographics, clinical parameters, diagnostics (imaging, microbiological, and analytical parameters), and follow-up. A simplified, standard case-report form was designed. Data were recorded anonymously and sent to the coordinating institution, where a database was created specifically for this study.

Definitions

Healthcare-associated endocarditis was defined elsewhere [19].

The Charlson comorbidity index [20] (not age adjusted) was used at admission to stratify overall co-morbidity.

Moderate or severe renal disease was defined as an estimated glomerular filtration rate (based on CKD-EPI method) below 60 mL/min/1.73 m^2 at admission.

Surgery was defined as the replacement or repair of the affected heart valve during the index hospitalization.

Indications for surgery were adjudicated prospectively during the index episode by the local MDET, and they included: heart failure, embolic event prevention, and uncontrolled infection [10]. The EuroSCORE [21, 22] (logistic EuroSCORE I and EuroSCORE II) was calculated for all patients. For IEs related to a cardiovascular implantable electronic device (CIED), percutaneous device extraction was considered an indication for surgery.

Follow-up was defined as the period from the day antibiotic treatment for IE was started until death for any reason or the last follow-up. Data was collected at the end of intravenous antibiotic treatment, the beginning of oral antibiotic treatment, when administered, and at the end of an oral antibiotic prescription, after completion.

After discharge for IE, survivors were prospectively followed at regular intervals. Each local MDET established the periodicity of blood cultures, clinical evaluations, and imaging (PET/CT and/or echocardiograms).

Long-term antibiotic treatment (LTAT) was defined as an intravenous or oral antibiotic regimen that exceeded the standard duration (usually < 8 weeks) of the established treatment for an episode of native, device-related, or prosthetic-related IE. When patients were switched to oral treatment, the term **long-term oral suppressive antibiotic treatment (LOSAT)** was used. The MDET determined, a priori, whether the duration of this treatment was time-defined or life-long. However, the treatment durations were re-evaluated at follow-ups. Durations were based on patient status evolution and the response to treatment, according to analytical, clinical, and cardiac imaging parameters. When intravenous treatment was required, an outpatient parenteral antibiotic therapy regimen was preferred.

Relapse was defined as a documented, positive blood culture, caused by the same microorganism that caused the initial IE, and being observed within the first year after completing the standard established antimicrobial treatment.

Mortality was defined as death from any cause during follow-up. The causes of IE-related mortality were: heart failure, stroke, uncontrolled infection, sudden death, and other causes attributable to any IE complication.

Outcomes

Primary outcomes were: infection relapse and mortality at the last follow-up.

Ethics

This study was performed in compliance with the Helsinki Declaration and was approved by the local Ethics Committee of Hospital Universitari Germans Trias i Pujol (Badalona, Barcelona, Spain).

Statistical analysis

Categorical variables are expressed as absolute numbers and percentages. Continuous variables are expressed as the mean and standard deviation (SD) or the median and 25–75 percentile (interquartile range [IQR]), according to the data distribution (normal or non-normal). Survival was evaluated with the Kaplan-Meier method and long-rank test. All analyses were performed with STATA V.13.0 (College Station, Texas, United States).

Results

Baseline characteristics

Between January 2011 and January 2019, 1797 patients with IE were identified in 5 participating centres. Among these, we identified 32 discharged patients with SINUS-IE managed with a LTAT strategy. The median follow-up time from diagnosis was 487 days (IQR: 332–1210 days). The baseline patient characteristics are detailed in Table 1. The mean age was 72.1 ± 17 years and 78% were males. Twenty-one (66%) patients had prosthetic valve endocarditis (PVE). Of these, 20 were left-sided and one was right-sided PVE. Eight patients suffered PVE before 1 year from valvular surgery (early PVE) and the other 13 corresponded to late PVE. Seven patients had CIED-related IE (Table 2). In these cases, the device was either not extracted or incompletely extracted, which were counter-indications for surgery. Four patients had left-sided native valve IE; 17 (53%) had healthcare-associated IE, and 14 (43.7%) had a history of previous IE. Of note, 8 (25%) patients had ascending aorta prosthetic grafts (AAGs; Table 3).

Most patients had comorbidities. The mean Charlson index was 5 points (range: 3–7). The main indication for surgery was uncontrolled infection (75%), and 18 patients had local complications. The main reasons for not undergoing surgery, despite the indication, were: high surgical risk (75%), surgeon refusal, due to an unaffordable technical risk (15.6%), and patient refusal (6.2%).

Analysis of microbiological data, imaging data, treatment, and outcomes

Twenty-four (75%) patients underwent transesophageal echocardiography (TEE) and 20 (63%) patients underwent a PET/CT. Remarkably, in 7 patients (5 with AAGs), the PET/CT established the IE diagnosis after a previous negative or inconclusive TEE.

Blood cultures were positive in 94% of patients. The most prevalent microorganisms were coagulase-negative staphylococci (10/32, 31%) and *Staphylococcus aureus* (7/32, 22%). Blood cultures were negative in 2 patients that had previously received antibiotic treatment. Of these, one had previous cardiac surgery, and the surgery wound culture was positive for *S. epidermidis*; the other had undergone surgery 2 months prior for native aortic valve IE associated with *S. sanguis*; thus, this patient was treated for a relapse/early PVE.

The median duration of parenteral antibiotic treatment was 8 weeks (IQR: 6–12 weeks). In

Table 1. Baseline demographic, clinical, and microbiological characteristics of the study subjects.

Parameters	Overall (n = 32)
Age [years]	72 ± 17
Male sex	25 (78.1)
Healthcare-associated IE	17 (53.1)
Type of infection	
Prosthetic valve IE	21 (65.6)
Early/late PVE	8/13
Intracardiac device-related IE	7 (21.9)
Native IE	4 (12.5)
Clinical history-comorbidities	
Previous cardiac surgery	19 (59.4)
Previous IE	14 (43.8)
Chronic renal failure	14 (43.8)
Hemodyalisis	3 (9.4)
Diabetes mellitus	9 (28.1)
COPD	5 (15.6)
Severe liver disease	4 (12.5)
Cancer	4 (12.5)
HIV	1 (3.1)
Charlson comordity index, median (IQR)	5 (3–7)
Laboratory tests	
Hemoglobin [g/dL]	10.2 ± 2.02
CRP [mg/L], median (IQR)	33 (12–124)
eGFR [mL/min/1.73 m^2]	52.9 ± 24
Echocardiography-PET/CT	
TEE performed	24 (75)
PET/CT performed	20 (62.5)
Control PET/CT performed	12 (37.5)
Local complication	18 (56.3)
Vegetation present	12 (37.5)
Moderate or severe valve regurgitation	8 (25)
Microbiology	
Coagulase-negative staphylococci	10 (31.3)
Staphylococcus aureus	7 (21.9)
Streptococcus spp	4 (12.5)
Enterococcus faecalis	4 (12.5)
Non-HACEK Gram-negative bacili	2 (6.3)
Negative blood cultures	2 (6.3)
Others	3 (9.4)
Complications	
Embolization	8 (25)
Stroke	6 (18.8)
Heart failure	5 (15.6)
Atrioventricular block	3 (9.4)
Shock	1 (3.1)
Indication for surgery	
Hemodynamic	1 (3.1)
Uncontrolled infection	24 (75)
Local complication	18
Embolic	1 (3.1)
Device infection	6 (18.8)
EuroSCORE I (%), median (IQR)	32 (17-46)
EuroSCORE II (%), median (IQR)	9.1 (6.7-14)
Reasons for no surgery	
Unaffordable surgical risk	24 (75)
Patient refusal	2 (6.3)
Intra-surgery clinical complication*	1 (3.1)
Surgeon refusal (technical risk)	5 (15.6)
Outcome	
0 to 60-day mortality	1 (3.1)
Cumulative 3-year mortality	12 (37)
Related to IE	4 (12.5)
Relapses	4 (12.5)

Data are presented as the number (%) and mean ± 1 standard deviation, unless otherwise indicated. *Neurological complication during surgery without valve surgery attempted. COPD — chronic obstructive pulmonary disease; CRP — C-reactive protein; eGFR — estimated glomerular filtration rate; HIV — human immunodeficiency virus; IE — infective endocarditis; IQR — interquartile range; PET/CT — positron emission tomography/computed tomography; PVE — prosthetic valve endocarditis; TEE — transesophageal echocardiography

8 cases, only parenteral LTAT was administered, based on a decision by the local MDET. This treatment lasted 34 weeks (range: 8–34) and was administered in an outpatient or day care setting (Table 4).

Twenty-four (75%) patients were switched to LOSAT after prolonged (12 patients) or adjusted to guidelines (12 patients) parenteral administration. In 23 patients, the MDET initially established LOSAT as a life-long treatment, starting at discharge. The median duration of LOSAT was 277 days (IQR: 73–868).

Nine patients underwent PET/CTs to guide the duration and response to treatment. In these patients, the LOSAT was stopped, based on PET/CT information. None of these patients experienced infection relapse.

Table 2. Description of seven episodes of device infective endocarditis treated with oral long suppressive antibiotic treatment.

Age [years]	Sex	Underlying condition	Etiology	Percutaneous extraction tried	Antibiotic treatment and duration	Final status (follow-up, years)
87	Male	CRF, diabetes	*S. epidermidis*	Yes	CMX 160/800 mg bid Longlife	Relapse (0.2) Alive (3.2)
89	Male	CRF	*S. aureus*	No	CMX 160/800 mg bid Longlife	Death (0.8) Not related
91	Male	CRF	*S. aureus*	No	CMX 160/800 mg bid ↓ LVF 500 mg QD Longlife	Alive (1.6)
88	Female	Diabetes	*S. aureus*	Yes	LVF 500 mg/2 days Longlife	Alive (6.6)
82	Male	CRF, COPD	*S. epidermidis*	No	LVF 250 mg/2 days (+ Rifampicine 300 mg QD 4 months)	Death (3.5) Not related
93	Female	CRF, hepatopathy	*Enterococcus faecalis*	No	Amoxicilin 1 g TD Longlife	Death (0.4) Not related
69	Male	COPD, hepatopathy	*S. epidermidis*	Yes	Amoxicilin 1 g TD Longlife	Alive (0.8)

CMX — cotrimoxazole; COPD — chronic obstructive pulmonary disease; CRF — chronic renal failure; LVF — levofloxacine; bid — bis in die (twice a day); QD — quaque die (once a day); TD — ter in die (three times a day)

Long-term oral suppressive antibiotic treatment comprised a variety of oral antimicrobial classes. In initial treatments, 9 patients received beta-lactams, 9 patients received trimethoprim-sulfamethoxazole (TMP/SMX), 2 patients received clindamycin, and 4 patients received fluoroquinolones (levofloxacin). Others agents were combined with the initial treatment or were used during follow-up, including linezolid (n = 2) and rifampicin (combined with levofloxacin, n = 1). Four (17%) patients experienced adverse drug-related events, including thrombocytopenia (n = 2), associated with linezolid, and digestive intolerance (n = 1) and a skin disorder (n = 1), associated with TMP/SMX. Only 1 of these patients required definitive LOSAT discontinuation. In 2 cases, in vitro resistance was resolved with another antibiotic treatment option. Some antibiotic regimens and doses are described in Tables 2 and 3.

Four patients experienced infection relapses during follow-up. All had positive blood cultures, but no clinical repercussion. The median time to relapse was 144 days (IQR: 72–210). The first relapse was a late PVE associated with *Streptococcus viridans*. An aortic abscess was treated with oral amoxicillin (3 g/day), which was stopped after 1 year, due to clinical stability; subsequently, positive blood cultures were documented. Life-long amoxicillin was re-started, and the patient is currently doing well in follow-up. The second relapse was a CIED-related IE, associated with coagulase-negative *Staphylococcus* and incomplete extraction of the CIED lead. The patient was switched to oral TMP/SMX. After 2 months, positive blood cultures were detected, but without clinical repercussion, and the same antibiotic regimen that was used in the follow-up. The third relapse was a prosthetic valve (Bentall surgery) IE, associated with coagulase-negative *Staphylococcus*. The patient was treated with TMP/SMX LOSAT, but after 5 months, the patient developed in vitro resistance to TMP/SMX. After switching to oral clindamycin, the IE showed a favourable evolution. The fourth relapse was an early PVE, associated with coagulase-negative *Staphylococcus*. The patient was switched to oral linezolid (600 mg bid). After 3 months, during treatment, positive blood cultures were detected, and the treatment was switched to intravenous vancomycin for 4 weeks. Subsequently, the patient was treated with oral TMP/SMX (160/800 mg bid), which was stopped after 1 year, due to stable infection and clinical stability and disease improvement, based on PET/CT.

The estimated overall survival rates were 78% at 1 year and 62% at 3 years (Fig. 1). Only 1 patient died within 60 days, due to an uncontrolled infection during treatment. Twelve patients died between 60 days and 3 years, but only 4 deaths

Table 3. Description of eight cases of prosthetic endocarditis with previous ascending aortic surgery treated with long-term antibiotic treatment including oral long suppressive antibiotic treatment.

Age [years]	Sex	Underlying condition	Type of surgery	Time	Diagnosis	Microbiology	Length of IV ATB [week]	Oral ATB and duration	PET/CT Follow- up	Outcome status (follow-up, years)
57	Male	–	Bentall	Early	TEE–PET/CT+	*Moraxella lacunata*	6	LVF (500 mg bid) 3 months	Yes	Alive (4)
85	Male	–	Dacron Tube AA	Late	TEE–PET/CT+	*S. epidermidis*	9	CMX (160/800 mg bid) Longlife	No	Alive (1)
56	Male	COPD	Bentall	Late	TEE–PET/CT+	*Enterococcus faecalis*	34	No	Yes	Alive (1)
32	Male	–	Bentall DA tube	Early	TEE–PET/CT+	*Enterococcus faecalis*	12	No	Yes	Alive (4)
57	Male	–	Bentall	Early	PET/CT+ TEE+	*S. epidermidis*	13	No	Yes	Alive (1)
44	Male	–	Bentall	Early	TEE+	*S. aureus*	8	LVF (500 mg bid) Longlife	Yes	Alive (5)
63	Male	Diabetes	Bentall	Early	TEE+	*S. epidermidis*	8	CMX (160/800 mg bid) Longlife	No	Recurrence (0.4) Death related (0.7)
71	Male	–	Bentall	Early	TEE–PET/CT+	*Bovis group Streptococcus*	8	Amoxicilin 1 g TD 1 year	Yes	Alive (1)

AA — ascending aorta; ATB — antibiotherapy; CMX — cotrimoxazole; COPD — chronic obstructive pulmonary disease; DA — descending aorta; IV — intravenous; LVF — levofloxacine; PET/CT — positron emission tomography/computed tomography; TD — ter in die (three times a day); TEE — transesophageal echocardiography

Table 4. Description of eight cases of surgery indicated not undergoing surgery infective endocarditis treated with parenteral long term antibiotic treatment.

Age [years]	Sex	Underlying condition	Type of IE	Time	Diagnosis complication	Microbiology	Length of IV ATB [week]	ATB	PET/CT Follow up	Outcome status (follow-up, years)
23	Male	Congenital heart disease	Pulmonar prothesis	Late	PET/CT Pulmonar emboli	*Staphylococcus aureus*	12	Cloxaxilin	Yes	Alive (2.4)
43	Female	NA	Aortic prosthesis	Late	TEE (abscess)	*Cutibacterium acnes*	16	Ceftriaxone (12 weeks) Ertapenem (2 weeks) Daptomicin (2 weeks)	Yes	Alive (2.8)
56	Male	COPD	Bentall	Late	PET/CT+ (abscess)	*Enterococcus faecalis*	34	Ampicilin + ceftriaxone	Yes	Alive (0.9)
32	Male	NA	Bentall DA tube	Early	PET/CT+ (abscess)	*Enterococcus faecalis*	12	Ampicilin + ceftriaxone	Yes	Alive(4)
57	Male	NA	Bentall	Early	PET/CT+ TEE+ (abscess)	*Staphylococcus epidermidis*	13	Daptomicin	Yes	Alive (1)
86	Male	CKD	Aortic prosthesis	Late	TEE (abscess)	*Gemella haemolysans*	10	Ceftriaxone ↓ Penicilin	No	Death (during treatment)
78	Male	Porcelain aorta	Aortic prosthetic	Late	TEE (abcess)	*Viridans* group *Streptococcus*	13	Ceftriaxone	Yes	Alive (1.7)
82	Male	CKD	Aortic prosthesis	Late	TEE (abscess)	*Aerococcus viridans*	9	Linezolid ↓ Ampicilin ↓ Vancomicin ↓ Daptomicin	Yes	Non related death (2)

ATB — antibiotherapy; CKD — chronic kidney disease; COPD — chronic obstructive pulmonary disease; DA — descending aorta; IE — infective endocarditis; IV — intravenous; NA — not applicable; PET/CT — positron emission tomography/computed tomography; TEE — transesophageal echocardiography

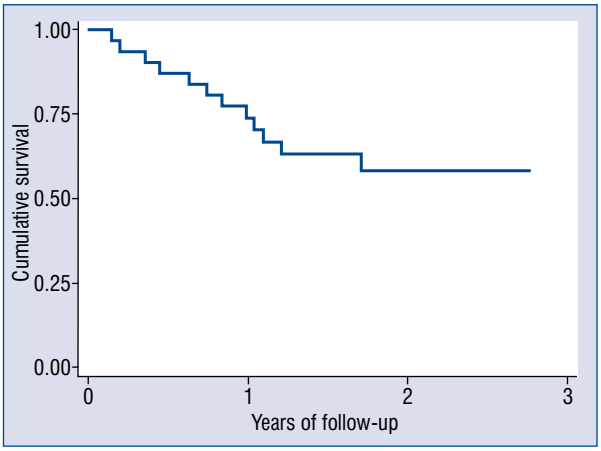

Figure 1. Survival in surgery indicated, but did not undergo surgery for infective endocarditis patients treated with long term antibiotic treatment.

were related to IE (due to uncontrolled infection in 1 patient, stroke in 2 patients, and heart failure in 1 patient). After 3 years of follow-up, 3 more deaths occurred that were unrelated to IE. Of note, in the group with SINUS-IE that had AAGs, only 1 IE-related death occurred after a previous relapse (Table 3), and in the CIED device IE group, 3 deaths occurred that were unrelated to IE (Table 2).

Discussion

According to available research, this study included the largest series (including left sided IE) to date in describing the experiences and outcomes of patients with SINUS-IE treated with LTAT, including those that switched to LOSAT. All previous studies were small, retrospective studies or case reports (Table 5). An overall survival of 62% at 3 years, and only 4 relapses were observed.

Successful IE treatment requires prolonged bactericidal antibiotic treatment and surgery to remove infected material and drain abscesses. Current indications for surgery in IE are well defined in the American Heart Association and ESC guidelines [10, 23]. They include valve dysfunction that leads to heart failure, uncontrolled infection (defined as a paravalvular extension, abscess, or persistent bacteremia), and recurrent/high risk of embolism. More than 50% of patients with IE meet the surgical criteria, according to clinical guidelines [24], but of those, 20–40% do not undergo surgery due to high perioperative risk [11, 14, 25]. In-hospital mortality is high in SINUS-IE, typically due to shock and heart failure; only one third of patients survive past the index hospitalization [14]. In the present study, among the patients with SINUS IE that were treated with LTAT and survived the acute phase of IE, the main indication for surgery was uncontrolled infection (75% of patients), including 18 (56%) patients with local complications (mainly perianular abscesses) detected in imaging.

Guideline recommendations concerning antibiotic treatments and durations are not sufficiently evidence-based for SINUS-IE, due to the lack of randomized controlled trials [9]. The standard treatment for IE is 2–6 weeks of intravenous antibiotic treatment. This treatment is suitable for classical, uncomplicated, prosthetic-, native-, or device-related IE, but clinical guidelines do not mention antibiotic treatment or durations for patients with SINUS-IE. Consequently, patients with SINUS-IE are treated according to local experience, in a heterogeneous manner.

In the present study, 7 patients with local complications received prolonged LTAT. A recent study described treating IE with dalbavancin [26], a long-acting lipoglycopeptide antibiotic with excellent anti-staphylococcal activity and a half-life of 346 h. This treatment might be an attractive option for staphylococcal-associated endocarditis, in patients with SINUS-IE that cannot tolerate oral antibiotic treatment. A recent case study showed a favourable outcome with dalvabancin [27]. In the present study, due to the retrospective design, no patients were treated with dalvabancin.

The role of oral antibiotic therapy in treating IE remains controversial [28]. Oral antibiotics have high bioavailability and have been effective in shortening intravenous treatment and treating selected cases of uncomplicated IE caused by susceptible organisms [15, 28–31]. Recently, an intervention study [32] demonstrated that a rapid switch to oral TMP/SMX reduced the hospital stay and mortality in *S. aureus*-associated IE, including patients with cardiac abscesses or persistent bacteremia. Oral LOSAT for patients with SINUS-IE has only been described in case reports [33], in case series for some specific situations (e.g., fungal IE [34], CIED--related IE [35, 36], aortic grafts [37]), and briefly, in some contemporary series [25] and reviews [9].

Prosthetic graft infection is a fatal complication after thoracic aorta replacement; early mortality was reported to be 25–42% [38]. In the present study, 8 patients with SINUS-IE that developed PVE after a previous surgery involving the aortic root and ascending aorta (Bentall procedure or ascending aorta graft replacement) were treated

Table 5. Review of literature regarding long suppressive antibiotic treatment (LSAT).

Study	N	Sex (male)	Age (mean)	Type of IE	Etiology	LSAT	Follow-up, years (mean)	Relapses	Mortality
Vallejo et al. 2020 (present study)	32	25	72	Prosthetic 21 Native 4 Device related 7	*CNS (10)* *Staphylococcus aureus (7)* *Enterococcus faecalis (4)* *Viridans-group Streptococci (3)* *Str. Gallolyticus ssp. pasterianus (1)* *GNB (2)** *Negative blood cultures (2)* *Others (3)***	*CNS:* — TMP/SMX — Clindamicin — Linezolid — Levofloxacin *S. aureus:* — Levofloxacin — TMP/SMX *Enterococcus:* — Amoxicilin *Streptococci* — Amoxicilin *GNB:* — Cefuroxime — Levofloxacin	3 years	4	12 (4 IE related)
Fernandez Hidalgo et al. 2012 [25]	2 (438)	1	70.9 88.5	Mitral prothesis Aortic prothesis	*S. epidermidis* *Enterococus faecalis*	Unknown Longlife	0.4 years 1.9 years	0	0
Puerta Alcalde et al. 2012 [18]	1	1	78	Bentall	*Streptococcus gallolyticus*	Amoxicilin Longlife	1 year	0	0
Spaziante et al. 2019 [27]	1	1	78	Bioprothesis/ascending aortic graft	*Staphylococcus epidermidis*	Dalvavancin	0.6 years	0	0
Machelart et al. 2019 [44]	7	6	63	Bentall aortic prosthetic	*S. epidermidis (2)* *Streptococcus agalactiae* *Bartonella quintana* *E. faecalis* *Coxiella burnetti*	NA	2.6 years	1	1 (not related)
Lechner et al., 2019 [37]	1	1	58	Aortic prosthetic +aortic graft	*S. aureus*	TMP/SMX	1.5 years	0	0
Ramos et al. 2020 [39]	2 (9)	NA	NA	Aortic graft	NA	Unkown; 12 month/ /18 month	1 year	0	1 (not related)
Baddour et. al. 2001 [36]	51	35	70	Device related	Several	Several	NA	3	3
Tan et al. 2018 [35]	48	35	78	Device related	Several	Several	10 years	6	21 (1 year)
Total patients	145		74					14 (9.6%)	38 (26%)

**Escherichia coli, Moraxella lacunata*; ***Aerococcus viridans, Gemella haemolysans, Cultibacterium acnes;* CNS — coagulase negative Staphylococci; GNB — Gram-negative bacilli; IE — infective endocarditis; NA — not available TMP/SMX — trimetroprim-sulfamethoxazole

with LTAT. Five of these patients were treated orally (two life-long treatments), and only one death occurred during follow-up. The diagnosis and management of PVE after aortic root or ascending aorta graft surgery are difficult and require long--term, combined antibiotic treatment and surgery, when possible [39]. In patients with inconclusive echocardiographic results, a combination of PET/ /CT and cardiac CT is recommended [40, 41] (among our 8 patients, 5 were diagnosed with PET/CT after inconclusive or negative TEEs). Consistent with some previous reports [37, 42–44], the present findings suggested that individualized LTAT might be effective (when there is no valvular dysfunction) in select patients with PVE complicated with AAG infections that are unfit to undergo surgery. Another option could be conservative surgery with valvular replacement and AAG preservation. However, the risk of recurrence is high; thus, chronic antibiotic suppressive treatment has been recommended, in some cases [38].

Positron emission tomography/computed tomography is a functional molecular imaging technique that depicts metabolic activity. Several studies [16, 17, 41] have shown its utility for diagnosing PVE. Recently, ESC IE guidelines [10] have included abnormal activity around a prosthetic valve as a major criterion and embolic phenomena as a minor criterion for diagnosing PVE. In the present study, PET/CT was performed as a diagnostic tool in 62.5% of patients. Additionally, PET/CT has shown promise in monitoring responses to antimicrobial treatment in PVE, as suggested in small observational studies [18]. On the other hand, sometimes, false-negative findings have been attributed to low inflammatory activity at the time of imaging, caused by prolonged antibiotic therapy. In the present study, PET/CT was used to guide the cessation of LOSAT in 9 patients. Those patients had favourable outcomes, after antibiotic treatment was stopped, due to a reduction or termination of metabolic uptake detected with PET/CT. More large-scale studies are warranted to investigate this indication.

In the present study, 7 patients with CIED--related IE were treated with LOSAT. Of these, 3 patients had incomplete percutaneous extractions, and the other 4 had comorbidities that counter-indicated percutaneous extraction, as judged by the MDET. Of these 7 patients, only one experienced a relapse, and no IE-related deaths occurred. LOSAT was also given to select patients with device-related IE that were ineligible for device removal (either surgical or percutaneous) or patients that experienced incomplete removal [45]. Currently, no comparable studies on LOSAT are available. Therefore, the optimal choice, dose, or duration of antibiotic treatment remain undefined; different outcomes have been reported in the few small observational studies that were published [35, 36].

The 5 hospitals included in the present study had a MDET that was comprised of cardiac imaging experts, cardiac surgeons, microbiologists, and infectious disease specialists. Previous studies showed that a team-based approach reduced the 1-year mortality in a mixed cohort of medically and surgically managed patients with IE [46, 47]. Additionally, a recent study [48] showed improved survival in patients that were managed medically. The present study showed that close follow-up and individualized treatment, supported with cardiac imaging, could improve the long-term prognosis in patients with SINUS-IE treated with LTSAT including LOSAT. Based on our experience, we propose an algorithm (Fig. 2) for guiding the management of patients with SINUS-IE and treatment with LOSAT.

Limitations of the study

This study had several limitations. First, antibiotic treatment was heterogeneous, because administration was at the discretion of the physician and the center, according to local protocols. Second, the definition of LOSAT was established ad hoc. Third, patient-level data were retrospective, pooled, and prospectively analyzed. Proposed algorithm is based on our own local experience without previous supporting clinical evidence.

Conclusions

Surgery indicated not undergoing surgery IE remains a dreadful complication, and we lack evidence-driven management guidelines. Herein, it was shown that survivors could achieve a reasonable long-term prognosis with an MDET-based, managed approach, with close follow-up, individualized antibiotic treatment, including LOSAT, and guidance from new imaging techniques. More multicenter prospective studies are needed to validate the proposed algorithm and to establish an appropriate long-term strategy for treating patients with SINUS-IE.

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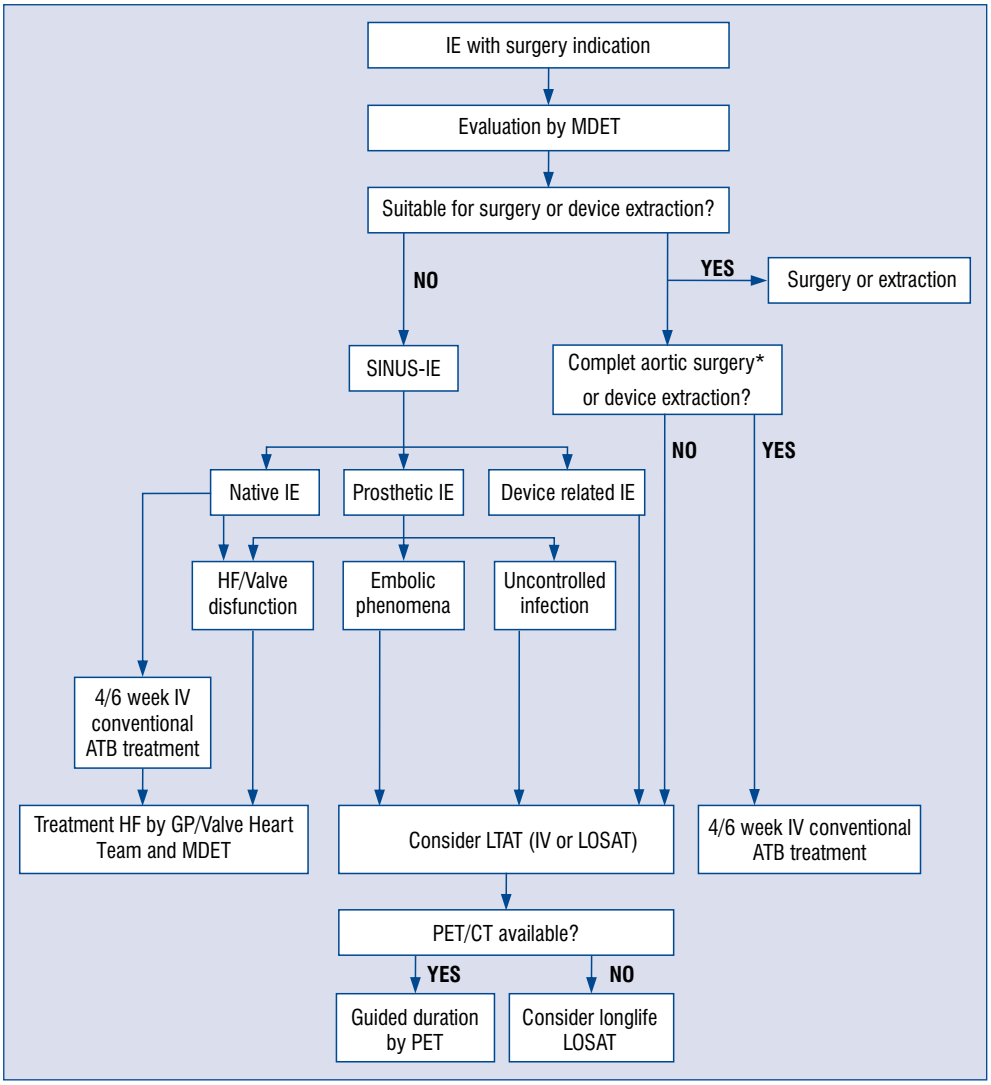

Figure 2. Proposed algorithm for treating surgery indicated, but did not undergo surgery for infective endocarditis (SINUS-IE) with long term antibiotic treatment (LTAT); MDET — multidisciplinary endocarditis team; IE — infective endocarditis; IV — intravenous; HF — heart failure; GP — general practitioner; LOSAT — long-term oral suppressive antibiotic treatment; PET/CT — positron emission tomography/computed tomography; ATB — antibiotherapy; *In cases of ascending aortic graft preservation.

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References

1. Hoen B, Duval X. Infective endocarditis. N Engl J Med. 2013; 368(15): 1425–1433, doi: 10.1056/nejmcp1206782.
2. Østergaard L, Oestergaard LB, Lauridsen TK, et al. Long-term causes of death in patients with infective endocarditis who undergo medical therapy only or surgical treatment: a nationwide population-based study. Eur J Cardiothorac Surg. 2018; 54(5): 860–866, doi: 10.1093/ejcts/ezy156, indexed in Pubmed: 29648662.
3. Thuny F, Grisoli D, Collart F, et al. Management of infective endocarditis: challenges and perspectives. Lancet. 2012; 379(9819): 965–975, doi: 10.1016/S0140-6736(11)60755-1, indexed in Pubmed: 22317840.
4. Cahill TJ, Baddour LM, Habib G, et al. Challenges in Infective Endocarditis. J Am Coll Cardiol. 2017; 69(3): 325–344, doi: 10.1016/j.jacc.2016.10.066, indexed in Pubmed: 28104075.
5. San Román JA, Vilacosta I, López J, et al. Critical questions about left-sided infective endocarditis. J Am Coll Cardiol. 2015; 66(9): 1068–1076, doi: 10.1016/j.jacc.2015.07.016, indexed in Pubmed: 26314535.
6. Olmos C, Vilacosta I, Fernández-Pérez C, et al. The evolving nature of infective endocarditis in spain: a population-based study

(2003 to 2014). J Am Coll Cardiol. 2017; 70(22): 2795–2804, doi: 10.1016/j.jacc.2017.10.005, indexed in Pubmed: 29191329.
7. Delahaye F, Duclos A. Is infective endocarditis changing over time? J Am Coll Cardiol. 2017; 70(22): 2805–2807, doi: 10.1016/j.jacc.2017.10.016, indexed in Pubmed: 29191330.
8. Murdoch DR, Corey GR, Hoen B, et al. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Prospective Cohort Study. Arch Intern Med. 2009; 169(5): 463–473, doi: 10.1001/archinternmed.2008.603, indexed in Pubmed: 19273776.
9. Fernández-Hidalgo N, Almirante B. Current status of infectious endocarditis: New populations at risk, new diagnostic and therapeutic challenges. Enferm Infecc Microbiol Clin. 2018; 36(2): 69–71, doi: 10.1016/j.eimc.2017.11.020, indexed in Pubmed: 29325999.
10. Habib G, Lancellotti P, Antunes M, et al. 2015 ESC Guidelines for the management of infective endocarditis. Eur Heart J. 2015; 36(44): 3075–3128, doi: 10.1093/eurheartj/ehv319.
11. Chu VH, Park LP, Athan E, et al. Association between surgical indications, operative risk, and clinical outcome in infective endocarditis: a prospective study from the International Collaboration on Endocarditis. Circulation. 2015; 131(2): 131–140, doi: 10.1161/CIRCULATIONAHA.114.012461, indexed in Pubmed: 25480814.
12. Iung B, Doco-Lecompte T, Chocron S, et al. AEPEI Study Group. Cardiac surgery during the acute phase of infective endocarditis: discrepancies between European Society of Cardiology guidelines and practices. Eur Heart J. 2016; 37(10): 840–848, doi: 10.1093/eurheartj/ehv650, indexed in Pubmed: 26685134.
13. Habib G, Erba PA, Iung B. et el. Clinical presentation, aetiology and outcome of infective endocarditis. Results of the ESC-EORP EURO-ENDO (European infective endocarditis) registry: a prospective cohort study. Eur Heart J. 2019; 40(39): 3222–3232, doi: 10.1093/eurheartj/ehz620, indexed in Pubmed: 31504413.
14. Vallejo Camazón N, Cediel G, Núñez Aragón R, et al. Short- and long-term mortality in patients with left-sided infective endocarditis not undergoing surgery despite indication. Rev Esp Cardiol (Engl Ed). 2020; 73(9): 734–740, doi: 10.1016/j.rec.2019.09.011, indexed in Pubmed: 31767290.
15. Iversen K, Ihlemann N, Gill SU, et al. Partial oral versus intravenous antibiotic treatment of endocarditis. N Engl J Med. 2019; 380(5): 415–424, doi: 10.1056/NEJMoa1808312, indexed in Pubmed: 30152252.
16. Millar BC, Habib G, Moore JE. New diagnostic approaches in infective endocarditis. Heart. 2016; 102(10): 796–807, doi: 10.1136/heartjnl-2014-307021, indexed in Pubmed: 26908095.
17. Millar BC, de Camargo RA, Alavi A, et al. PET/Computed tomography evaluation of infection of the heart. PET Clin. 2019; 14(2): 251–269, doi: 10.1016/j.cpet.2018.12.006, indexed in Pubmed: 30826023.
18. Puerta-Alcalde P, Cuervo G, Simonetti AF, et al. PET/CT added to Duke criteria facilitates diagnosis and monitoring of long-term suppressive therapy of prosthetic endocarditis. Infect Dis (Lond). 2017; 49(9): 698–701, doi: 10.1080/23744235.2017.1300683, indexed in Pubmed: 28298163.
19. Núñez Aragón R, Pedro-Botet Montoya ML, Mateu Pruñonosa L, et al. Factores asociados y análisis descriptivo de la endocarditis infecciosa adquirida en el entorno hospitalario de un centro terciario de referencia. Enferm Infecc Microbiol Clin. 2013; 31(1): 15–22, doi: 10.1016/j.eimc.2012.03.014.
20. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987; 40(5): 373–383, doi: 10.1016/0021-9681(87)90171-8, indexed in Pubmed: 3558716.
21. Nashef S, Roques F, Michel P, et al. European system for cardiac operative risk evaluation (EuroSCORE). Eur J Cardio-Thoracic Surg. 1999; 16(1): 9–13, doi: 10.1016/s1010-7940(99)00134-7.
22. Nashef SAM, Roques F, Sharples LD, et al. EuroSCORE II. Eur J Cardiothorac Surg. 2012; 41(4): 734–44; discussion 744, doi: 10.1093/ejcts/ezs043, indexed in Pubmed: 22378855.
23. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the american heart association. Circulation. 2015; 132(15): 1435–1486, doi: 10.1161/CIR.0000000000000296, indexed in Pubmed: 26373316.
24. Prendergast BD, Tornos P. Surgery for infective endocarditis: who and when? Circulation. 2010; 121(9): 1141–1152, doi: 10.1161/CIRCULATIONAHA.108.773598, indexed in Pubmed: 20212293.
25. Fernández-Hidalgo N, Almirante B, Tornos P, et al. Immediate and long-term outcome of left-sided infective endocarditis. A 12-year prospective study from a contemporary cohort in a referral hospital. Clin Microbiol Infect. 2012; 18(12): E522–E530, doi: 10.1111/1469-0691.12033, indexed in Pubmed: 23077981.
26. Hidalgo-Tenorio C, Vinuesa D, Plata A, et al. DALBACEN cohort: dalbavancin as consolidation therapy in patients with endocarditis and/or bloodstream infection produced by gram-positive cocci. Ann Clin Microbiol Antimicrob. 2019; 18(1): 30, doi: 10.1186/s12941-019-0329-6, indexed in Pubmed: 31629409.
27. Spaziante M, Franchi C, Taliani G, et al. Serum bactericidal activity levels monitor to guide intravenous dalbavancin chronic suppressive therapy of inoperable staphylococcal prosthetic valve endocarditis: a case report. Open Forum Infect Dis. 2019; 6(11): ofz427, doi: 10.1093/ofid/ofz427, indexed in Pubmed: 31737736.
28. Al-Omari A, Cameron DW, Lee C, et al. Oral antibiotic therapy for the treatment of infective endocarditis: a systematic review. BMC Infect Dis. 2014; 14: 140, doi: 10.1186/1471-2334-14-140, indexed in Pubmed: 24624933.
29. Mzabi A, Kernéis S, Richaud C, et al. Switch to oral antibiotics in the treatment of infective endocarditis is not associated with increased risk of mortality in non-severely ill patients. Clin Microbiol Infect. 2016; 22(7): 607–612, doi: 10.1016/j.cmi.2016.04.003, indexed in Pubmed: 27091094.
30. Heldman AW, Hartert TV, Ray SC, et al. Oral antibiotic treatment of right-sided staphylococcal endocarditis in injection drug users: prospective randomized comparison with parenteral therapy. Am J Med. 1996; 101(1): 68–76, doi: 10.1016/s0002-9343(96)00070-8, indexed in Pubmed: 8686718.
31. Stamboulian D, Bonvehi P, Arevalo C, et al. Antibiotic management of outpatients with endocarditis due to penicillin-susceptible streptococci. Rev Infect Dis. 1991; 13 Suppl 2: S160–S163, doi: 10.1093/clinids/13.supplement_2.s160, indexed in Pubmed: 2017645.
32. Tissot-Dupont H, Gouriet F, Oliver L, et al. High-dose trimethoprim-sulfamethoxazole and clindamycin for Staphylococcus aureus endocarditis. Int J Antimicrob Agents. 2019; 54(2): 143–148, doi: 10.1016/j.ijantimicag.2019.06.006, indexed in Pubmed: 31181351.
33. Cunha BA, Brahmbhatt K, Raza M. Haemophilus parainfluenzae aortic prosthetic valve endocarditis (PVE) successfully treated with oral levofloxacin. Heart Lung. 2015; 44(4): 317–320, doi: 10.1016/j.hrtlng.2015.04.006, indexed in Pubmed: 25998992.
34. Baddour LM. Long-term suppressive therapy for fungal endocarditis. Clin Infect Dis. 1996; 23(6): 1338–1340, doi: 10.1093/clinids/23.6.1338-a, indexed in Pubmed: 8953098.

35. Tan EM, DeSimone DC, Sohail MR, et al. Outcomes in patients with cardiovascular implantable electronic device infection managed with chronic antibiotic suppression. Clin Infect Dis. 2017; 64(11): 1516–1521, doi: 10.1093/cid/cix181, indexed in Pubmed: 28329125.
36. Baddour LM. Long-term suppressive antimicrobial therapy for intravascular device-related infections. Am J Med Sci. 2001; 322(4): 209–212, doi: 10.1097/00000441-200110000-00011, indexed in Pubmed: 11678518.
37. Lechner AM, Pretsch I, Hoppe U, et al. Successful long-term antibiotic suppressive therapy in a case of prosthetic valve endocarditis and a case of extensive aortic and subclavian graft infection. Infection. 2020; 48(1): 133–136, doi: 10.1007/s15010-019-01321-6, indexed in Pubmed: 31123929.
38. Takano T, Terasaki T, Wada Y, et al. Treatment of prosthetic graft infection after thoracic aorta replacement. Ann Thorac Cardiovasc Surg. 2014; 20(4): 304–309, doi: 10.5761/atcs.oa.13-00059, indexed in Pubmed: 23801180.
39. Ramos-Martínez A, Blanco-Alonso S, Calderón-Parra J, et al. Endocarditis in patients with ascending aortic prosthetic graft: a series from a national referral hospital. J Am Coll Cardiol. 2020; 75(18): 2380–2382, doi: 10.1016/j.jacc.2020.03.035, indexed in Pubmed: 32381170.
40. Swart LE, Gomes A, Scholtens AM, et al. Improving the diagnostic performance of f-fluorodeoxyglucose positron-emission tomography/computed tomography in prosthetic heart valve endocarditis. Circulation. 2018; 138(14): 1412–1427, doi: 10.1161/CIRCULATIONAHA.118.035032, indexed in Pubmed: 30018167.
41. Pizzi M, Roque A, Fernández-Hidalgo N, et al. Improving the diagnosis of infective endocarditis in prosthetic valves and intracardiac devices with 18 f-fluordeoxyglucose positron emission tomography/computed tomography angiography. Circulation. 2015; 132(12): 1113–1126, doi: 10.1161/circulationaha.115.015316.
42. Heuzé C, Lepage L, Loubet P, et al. Infective endocarditis after bentall surgery: usefulness of new imaging modalities and outcomes. JACC Cardiovasc Imaging. 2018; 11(10): 1535––1537, doi: 10.1016/j.jcmg.2017.12.007, indexed in Pubmed: 29454780.
43. Saitto G, Russo M, Pugliese M, et al. Infectious aortic root pseudoaneurysm after bentall procedure: to treat or not to treat by redo operation? Aorta (Stamford). 2019; 7(3): 90–92, doi: 10.1055/s-0039-1694013, indexed in Pubmed: 31614379.
44. Machelart I, Greib C, Wirth G, et al. Graft infection after a Bentall procedure: A case series and systematic review of the literature. Diagn Microbiol Infect Dis. 2017; 88(2): 158–162, doi: 10.1016/j.diagmicrobio.2017.03.002, indexed in Pubmed: 28330738.
45. Baddour LM, Cha YM, Wilson WR. Clinical practice. Infections of cardiovascular implantable electronic devices. N Engl J Med. 2012; 367(9): 842–849, doi: 10.1056/NEJMcp1107675, indexed in Pubmed: 22931318.
46. Botelho-Nevers E, Thuny F, Casalta JP, et al. Dramatic reduction in infective endocarditis-related mortality with a management--based approach. Arch Intern Med. 2009; 169(14): 1290–1298, doi: 10.1001/archinternmed.2009.192, indexed in Pubmed: 19636030.
47. Chirillo F, Scotton P, Rocco F, et al. Impact of a multidisciplinary management strategy on the outcome of patients with native valve infective endocarditis. Am J Cardiol. 2013; 112(8): 1171––1176, doi: 10.1016/j.amjcard.2013.05.060, indexed in Pubmed: 23831163.
48. Kaura A, Byrne J, Fife A, et al. Inception of the ‚endocarditis team' is associated with improved survival in patients with infective endocarditis who are managed medically: findings from a before-and-after study. Open Heart. 2017; 4(2): e000699, doi: 10.1136/openhrt-2017-000699, indexed in Pubmed: 29344368.

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The impact of tricuspid annular geometry on outcome after percutaneous edge-to-edge repair for severe tricuspid regurgitation

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Abstract

Background: *Percutaneous tricuspid repair using the edge-to-edge technique is a novel treatment option. More data are needed to better understand which aspects predict a favorable outcome*

Methods: *Twenty high-risk patients (78.6 ± 8.3 years, EuroScore II 9.1 ± 7.7%, STS score 8.8 ± 4.3) with severe symptomatic tricuspid regurgitation (TR) were treated with the MitraClip® system. All patients underwent standardized pre-, peri-, and post-procedural evaluation. Acute success was defined as successful edge-to-edge repair with TR reduction of ≥ 1 grade and survival until hospital discharge.*

Results: *Fifteen (75%) patients showed acute success until discharge and 12 (60%) at 30-day follow-up. In 5 (25%) patients repair failed due to either unsuccessful clip implantation (n = 2), single leaflet device attachment (n = 1), TR reduction < 1 grade (n = 1), or in-hospital death (n = 1). Comparing patients with successful procedure versus those with failed repair revealed similar comorbidities but more severe right heart failure, lower left ventricular ejection fraction, worse renal function, and higher diuretic equivalent doses in the failed repair group. No differences in conventional echocardiographic parameters for TR severity but more dilated tricuspid annulus geometry (tricuspid valve annulus, coaptation depth, tenting area) in the failed repair group were observed. The success rate of non-central/ /non-anteroseptal jet location was only 25%.*

Conclusions: *Tricuspid annulus geometry assessment may be of crucial importance and seems to impact procedural outcomes in patients undergoing edge-to-edge tricuspid valve repair. Further investigations including advanced imaging are needed to better understand and treat this complex valve disease.*
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Key words: tricuspid regurgitation, percutaneous repair, transcatheter treatment, edge-to-edge technique, echocardiography

Introduction

Current guidelines reserve surgical treatment of severe tricuspid regurgitation (TR) almost exclusively to combined left-heart procedures, whereas indications for stand-alone surgery for severe TR are only vaguely described [1–3]. The tricuspid valve (TV) is commonly referred to as "the forgotten valve" because data on single TV surgery are sparse, randomized trials are lacking, and there are no definite criteria guiding indication and timing of TV repair [4–6]. TV disease is mainly of secondary nature due to left-sided heart disease, pulmonary hypertension, atrial fibrillation, or lead-related problems in patients with cardiac implantable electronic devices [7–9]. TV apparatus

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anatomy and pathogenic mechanisms of TR are complex and involve various degrees of right heart remodeling and tricuspid annulus dysfunction. Echocardiographic grading of TR severity has limitations and seems insufficient despite introduction of a 5-stage grading scheme in 2017 with expansion of the 'severe' grade into three subcategories [10]. Recently, a more integrated approach for evaluation of TR disease has been proposed [7, 11].

Patients with severe TR often represent a high-risk surgical population, which relies at least partly on late referral and advanced heart failure (HF) after left-sided heart surgery [12]. The prognosis of functional tricuspid regurgitation (FTR) is poor [13–15]. Benfari et al. [13] recently reported a 5-year survival of 34% and a 10-year survival of only 14% for patients with severe FTR and HF with reduced ejection fraction (HFrEF). Importantly, the excess mortality in TR seems to be independent of pulmonary hypertension and other concomitant clinical parameters, as recent studies suggest [13–17]. Therefore, it can be speculated that TV repair at an earlier disease stage might be favorable before irreversible right ventricular dysfunction and dilatation manifests [16, 18]. Such lessons were learned for the treatment of mitral valve regurgitation the past years. Because FTR is not only a marker for severity of HF disease, but also a major contributor in pathophysiological processes, it represents a potential therapeutic target in patients with HFrEF. Conversely, in-hospital mortality of patients undergoing TV repair or replacement is substantial with reported rates between 8% and 24% [3, 12, 19, 20]. Older age (≥ 60 years) and TV replacement instead of repair can further double the risk for in-hospital death [3].

A novel treatment option for severe TR in patients with high surgical risk is a percutaneous tricuspid valve intervention, where the edge-to-edge-technique using the MitraClip® is most often used. A variety of transcatheter treatment options have been developed which simulate different surgical approaches like suture or ring annuloplasty (e.g. Trialign, TriCinch, and Cardioband or Millipede, respectively), coaptation enhancement (MitraClip, Forma, Pascal), valve replacement (e.g. NaviGate, TriSol, Cavi/BiCavi), or neochordae repair (e.g. Tricentro, TricValve) [21]. Most are still under investigation and are being tested in different phases of research. Recently published data from the TriValve registry showed significant clinical improvement and reduction of 1-year mortality after successful transcatheter tricuspid edge-to-edge repair [22].

However, appropriate patient selection for percutaneous TR repair is of crucial importance. Data on parameters and clinical constellations that translate into procedural success and favorable clinical outcome after transcatheter TV intervention (TTVI) are limited.

The aim of this observational, prospective study was to analyze the clinical, echocardiographic, and procedural characteristics in patients with successful vs. unsuccessful percutaneous tricuspid intervention using the edge-to-edge technique.

Methods

Study design and patient population

All patients undergoing transcatheter TV repair at our institution were prospectively included in our TV registry. Here, we report our first experiences with edge-to-edge repair using the MitraClip® between 12/2017 and 07/2019 after starting this program in high-risk patients. All patients underwent standardized pre-, peri-, and post-procedural evaluation including clinical, echocardiographic and invasive examination. All parameters were prospectively entered into a database. All patients were discussed with the heart team and declined for conventional TV surgery. The safety and feasibility of the procedure, reduction of TR-grade, and clinical outcomes were collected and analyzed at the day of discharge and 30-day follow-up. Successful intervention was defined as successful edge-to-edge repair using one or more MitraClips® with TR reduction of ≥ 1 grade and survival until hospital discharge.

The study was approved by the local ethics committee of the University Hospital of Jena (identification number: 2019-1325-BO) and conducted according to the principles of the Declaration of Helsinki.

Statistical analysis

All parameters were archived in a custom-made database. Statistical calculations were done with SPSS (version 26.0, IBM SPSS statistics). Normal distribution was tested with the Shapiro-Wilks test. Continuous variables are expressed as mean ± standard deviation and analyzed with the unpaired Student t-test. Categorical variables are presented as counts (percentages) and analyzed with χ^2-test or Fisher's exact test for small patient numbers. Statistical significance was assumed for p-values < 0.05 (two-tailed).

Results

Baseline clinical characteristics

A total of 20 high-risk patients (78.6 ± 8.3 years old, EUROScore II 9.1 ± 7.7%, Society of Thoracic Surgeons [STS] score 8.8 ± 4.3) with severe symptomatic TR were treated with the edge-to-edge technique using the MitraClip® system. Baseline clinical characteristics are presented in Table 1. Most patients were in New York Heart Association (NYHA) functional status class III and showed chronic peripheral edema and pleural effusion before TTVI (Table 1). All but 1 patient had concomitant atrial fibrillation, and 18 (90%) patients showed pulmonary hypertension with a mean pulmonary pressure of 31.3 ± 7.5 mmHg. We found concomitant mitral regurgitation of grade ≥ 2 in 11 (55%) patients. Overall, liver function was not reduced, and patients were on moderate dosage of diuretics (24.2 ± 15.6 mg torasemid equivalent dose). Cardiopulmonary exercise test (spiroergometry) could only be performed in 8 (40%) patients due to advanced HF and the frailty of the patient population (exercise capacity 59.1 ± 20.6 W, VO_2 anaerobic threshold 9.1 ± 1.6, VO_2 peak 11.6 ± 2.9). Cardiac index was ≤ 1.8 L/ /min/m^2 in 4 (20%) patients. Concomitant percutaneous repair of the mitral valve, using the edge-to-edge technique as well, was done in 2 (10%) patients before TTVI (Table 1).

Tricuspid regurgitation: Etiology and echocardiographic data

Left ventricular (LV) systolic function was mostly normal or mildly reduced (ejection fraction [EF] 54.3 ± 14.6%) and only 4 (20%) patients had a LVEF below 40% (Table 2). Conversely, 11 (55%) patients had a reduced right ventricle (RV) function with a RV fractional area change < 35% (Table 2). Our patient population showed a mean TR grade of 3.9 ± 0.8 (median 4.0) using the new 5-stage grading scheme, with 13 (65%) patients suffering from massive or torrential TR (Table 2, Fig. 1A, B) [10]. The effective regurgitation orifice area (EROA), TR volume, and TR vena contracta are outlined in Table 2. The etiology of TR was judged as functional in 14 (70%) patients, structural in 5 (25%) patients, and mixed in 1 (5%) patient. Of note, chronic pulmonary disease was only noted in 3 (15%) patients, and concomitant implantable cardioverter-defibrillator or pacemaker leads were detected in 3 (15%) patients (Table 1). The calculated mean TRuE risk score (https://thetruerisk.com [23]) of 7.1 ± 2.3 (median 6.0) in our sample size represents a high risk (75th percentile) for 5-year mortality and therefore a patient population with advanced TR disease.

TTVI: Procedural data, safety, and acute procedural success

Overall, TR clip procedure was safe without any major procedural complications such as emergent surgery, cardiac tamponade, prolonged cardiopulmonary resuscitation, or myocardial infarction. The operator learning curve for TTVI has to be judged as steep. The procedure time of the first two TTVIs was 290 and 314 min, which is rather long. However, the subsequent procedure time shortened and ranged between 54 and 200 min with a mean of 138.2 ± 42.9 min (Table 2).

In total, 15 (75%) patients had a successful intervention. In 5 (25%) patients TTVI failed due to either unsuccessful clip implantation (n = 2), single leaflet device attachment (SLDA) before discharge (n = 1), or TR reduction < 1 grade (n = 1). One patient developed upper gastrointestinal bleeding due to an esophageal Mallory-Weiss tear that needed endoscopic clip application after TTVI. However, there was no transfusion required. There was 1 death due to progressive cardiogenic shock 4 days after the procedure, but the procedure was planned as the last therapeutic option in this terminally ill patient (n = 1, 5% in-hospital mortality).

A mean of 1.8 ± 0.8 clips were implanted per patient: in 14 (70%) patients clips were implanted into the anteroseptal commissure, in 2 (10%) patients solely in the posteroseptal commissure, whereas 3 (15%) patients received clipping of both antero- and posteroseptal commissures (Table 2, Fig. 2). TR grade was significantly reduced from stage 4.0 ± 0.8 at baseline to stage 2.5 ± 1.0 at discharge and 2.8 ± 0.8 at 30-day follow-up in all patients and particularly in patients with successful TTVI (Fig. 1A, B).

We did not see an association between clip location and success rate. However, the main jet location in patients with failed acute success was posteroseptal (n = 3, 60%; Table 2). Of note, in 18 of 20 patients NTR MitraClips were implanted, and following the market launch of the new XTR clips the last 2 patients were successfully treated with XTR MitraClips.

Patients showed similar comorbidities irrespective of procedural success (Table 1). However, patients with a failed TTVI seemed to be sicker because the LVEF was lower, diuretics equivalent doses were higher, renal function was worse, and

Table 1. Clinical characteristics of the patient population (n = 20) at baseline.

	All patients (n = 20)	Acute success (n = 15)	Acute failure (n = 5)	P
Clinical characteristics				
Age [years]	78.6 ± 8.3	80.3 ± 5.2	73.4 ± 13.8	0.11
Male sex	10 (50%)	6 (39.9%)	4 (80%)	0.13
Body mass index [kg/m^2]	27.2 ± 5.7 (27.2)	27.1 ± 6.2 (27)	27.2 ± 4.5 (27.4)	0.97
NYHA class:				**0.015**
II	2 (10%)	**0 (0%)**	**2 (40%)**	
III	14 (70%)	**11 (73.3%)**	**3 (60%)**	
IV	4 (20%)	**4 (26.7%)**	**0 (0%)**	
Ejection fraction > 40%	16 (80%)	13 (86.7%)	3 (60%)	0.22
Edema	18 (90%)	13 (86.7%)	5 (100%)	0.42
Pleural effusion	10 (50%)	7 (46.6%)	3 (60%)	0.61
Ascites	8 (40%)	**4 (26.7%)**	**4 (80%)**	**0.036**
STS score	8.8 ± 4.3 (7.6)	8.4 ± 3.4 (7.9)	9.7 ± 6.9 (6.4)	0.58
EuroScore II	9.1 ± 7.7 (6.6)	9.3 ± 7.3 (7.4)	8.6 ± 9.8 (3.2)	0.87
Concomitant mitral clip	2 (10%)	2(13.3%)	0(0%)	0.42
Comorbidities				
Atrial fibrillation	19 (95%)	15(100%)	4(80%)	0.08
Diabetes	6 (30%)	5(33.3%)	1(20%)	0.59
COPD	3 (15%)	3(19.9%)	0(0%)	0.30
Pacemaker/ICD	3 (15%)	2 (13.3%)	1(20%)	0.74
Previous cardiac surgery	3 (15%)	2(13.3%)	1(20%)	0.74
Pulmonary hypertension	18 (90%)	14(93.3%)	4(80%)	0.42
End stage renal failure requiring dialysis	2 (10%)	1(6.7%)	1(20%)	0.42
Coronary artery disease	5 (25%)	2 (13.3%)	3 (60%)	0.34
Co-medication				
Torasemide equivalent dose [mg]	24.2 ± 15.6 (20)	**20.7 ± 14.6 (20)**	**37.5 ± 12.6 (40)**	**0.052**
Thiazide use	9 (45%)	6 (39.9%)	3 (60%)	0.24
MRA	4 (20%)	4 (26.7%)	0 (0%)	0.27
Oral anticoagulation	15 (75%)	13 (86.7%)	3 (60%)	0.21
Laboratory parameters				
Creatinine [mg/dL]*	1.4 ± 0.4 (1.3)	1.34 ± 0.4 (1.28)	1.53 ± 0.6 (1.5)	0.46
BUN [mg/dL]*	77.8 ± 46.1 (71.9)	73.1 ± 37.1 (71.9)	93.4 ± 73.1 (90.1)	0.46
GFR [mL/min]*	45.2 ± 13.6 (43.1)	44.1 ± 12.0 (43.1)	49.2 ± 20.1 (50.3)	0.53
BNP [pg/mL]	826.7 ± 734.8 (540)	806.9 ± 657.2 (622)	886.2 ± 1023.2 (456)	0.84
Bilirubin [μmol/L]	15.3 ± 5.2 (15)	15.7 ± 5.2 (15)	14.4 ± 5.6 (14)	0.65
ASAT [μmol/L × s]	0.52 ± 0.22 (0.46)	0.54 ± 0.25 (0.48)	0.44 ± 0.13 (0.45)	0.42
ALAT [μmol/L × s]	0.29 ± 0.2 (0.22)	0.31 ± 0.21 (0.28)	0.21 ± 0.12 (0.17)	0.36
Cholinesterasis [μmol/L × s]	98.1 ± 31.2 (99)	102 ± 32.7 (103)	86.2 ± 25.5 (78)	0.35
Hemoglobin [mmol/L]	7.6 ± 0.8 (7.8)	7.5 ± 0.9 (7.6)	7.8 ± 0.4 (7.9)	0.24

Data are shown as mean ± standard deviation (median) or number (percentage). *Patients on dialysis were excluded from analysis of renal function parameters; NYHA — New York Heart Association; STS — Society of Thoracic Surgeons; COPD — chronic obstructive pulmonary disease; ICD — implantable cardioverter-defibrillator; MRA — mineralocorticoid receptor antagonists; BUN — blood urea nitrogen; GFR — glomerular filtration rate; BNP — B-type natriuretic peptide; ASAT — aspartate transaminase; ALAT — alanine aminotransferase

Table 2. Echocardiographic, invasive, and procedural characteristics of the patient population (n = 20).

	All patients (n = 20)	Acute success (n = 15)	Acute failure (n = 5)	P
Echocardiography				
LVEF [%]	54.3 ± 14.6 (60.0)	56.8 ± 13.7 (60)	47.0 ± 16.7 (46)	0.203
RV FAC [%]	35.0 ± 6.3 (33.5)	35.1 ± 6.6 (33)	34.8 ± 6.1 (37.5)	0.95
TV annulus [mm]	45.5 ± 5.6 (45.0)	**43.9 ± 4.6 (44)**	**50.0 ± 6.5 (50)**	**0.032**
Coaptation depth [mm]	7.4 ± 3.2 (7.0)	**6.7 ± 3.1 (6.8)**	**9.8 ± 2.6 (11)**	**0.056**
Tenting area [cm^2]	2.4 ± 1.0 (2.3)	**2.1 ± 0.9 (2.14)**	**3.2 ± 1.0 (3.35)**	**0.025**
TR vena contracta [mm]	11.5 ± 4.3 (10.0)	11.5 ± 4.2 (10)	12.6 ± 4.6 (12)	0.53
EROA [cm^2]	0.73 ± 0.26 (0.76)	0.71 ± 0.28 (0.76)	0.78 ± 0.19 (0.80)	0.59
TR volume [mL/beat]	59.7 ± 19.5 (59)	58.6 ± 20.9 (59)	62.8 ± 15.9 (61)	0.68
TR grade at baseline (5 stages):	4.0 ± 0.8 (4)	3.9 ± 0.8 (4)	4.2 ± 0.8 (4)	0.45
Severe	7 (35%)	6 (40%)	1 (20%)	0.45
Massive	7 (35%)	5 (33.3%)	2 (40%)	
Torrential	6 (30%)	4 (26.7%)	2 (40%)	
Main jet location:				**0.026**
Central	11 (55%)	9 (60%)	2 (40%)	
Anteroseptal	5 (25%)	5 (33.3%)	0 (0%)	
Anteroposterior	0 (0%)	0 (0%)	0 (0%)	
Posteroseptal	4 (20%)	1 (6.7%)	3 (60%)	
Invasive hemodynamics				
Systolic PP [mmHg]	49.2 ± 12.8 (50.5)	50.0 ± 12.3 (53)	46.8 ± 15.8 (45)	0.64
Mean PP [mmHg]	31.3 ± 7.5 (31.0)	31.3 ± 6.8 (32)	31.2 ± 10.2 (30)	0.99
Right atrial pressure [mmHg]	12.9 ± 5.6 (14.0)	12.6 ± 5.7 (12)	13.6 ± 5.6 (15)	0.74
PCWP [mmHg]	20.6 ± 5.6 (20.0)	20.9 ± 5.3 (20)	19.6 ± 7.1 (17)	0.68
CI [L/min/m^2]	2.2 ± 0.5 (2.3)	2.2 ± 0.5 (2.2)	2.2 ± 0.3 (2.4)	0.92
Tricuspid valve intervention				
Procedure duration [min]	170.0 ± 75.8 (150.5)	163.6 ± 65.6 (140)	127.4 ± 60.9 (114)	0.29
Fluoroscopy time [min]	18.8 ± 15.3 (15.4)	19.5 ± 13.3 (16.2)	17.1 ± 11.9 (12.1)	0.73
Total number of clips	1.8 ± 0.8 (2)	1.7 ± 0.6 (2)	1.4 ± 1.1 (1)	0.50
Clip position:				0.23
Anteroseptal	14 (70%)	10 (66.7%)	4 (20%)	
Posteroseptal	2 (10%)	2 (13.3%)	0 (0%)	
Both	3 (15%)	3 (20%)	0 (0%)	
Bleeding requiring transfusion	2 (10%)	1 (6.7%)	1 (20%)	0.20
Acute renal failure	3 (15%)	2 (13.3%)	1 (20%)	0.73
New dialysis	1 (5%)	0 (0%)	1 (20%)	0.08

Data are shown as mean ± standard deviation (median) or number (percentage). LVEF — left ventricular ejection fraction; RV FAC — right ventricle fractional area change; TV — tricuspid valve; TR — tricuspid regurgitation; EROA — effective regurgitation orifice area; PP — pulmonary pressure; PCWP — pulmonary capillary wedge pressure; CI — cardiac index

more often there was evidence of ascites, peripheral edema, and pleural effusion, even though not all parameters reached significance in this relatively small patient group (Table 1). Conversely, patients with failed and successful TTVI had comparable scores on STS and EuroScore II, but most of the aforementioned parameters are not included in these standardized scores, and neither are those validated for single TV procedures. Interestingly, we found no differences regarding invasive hemo-

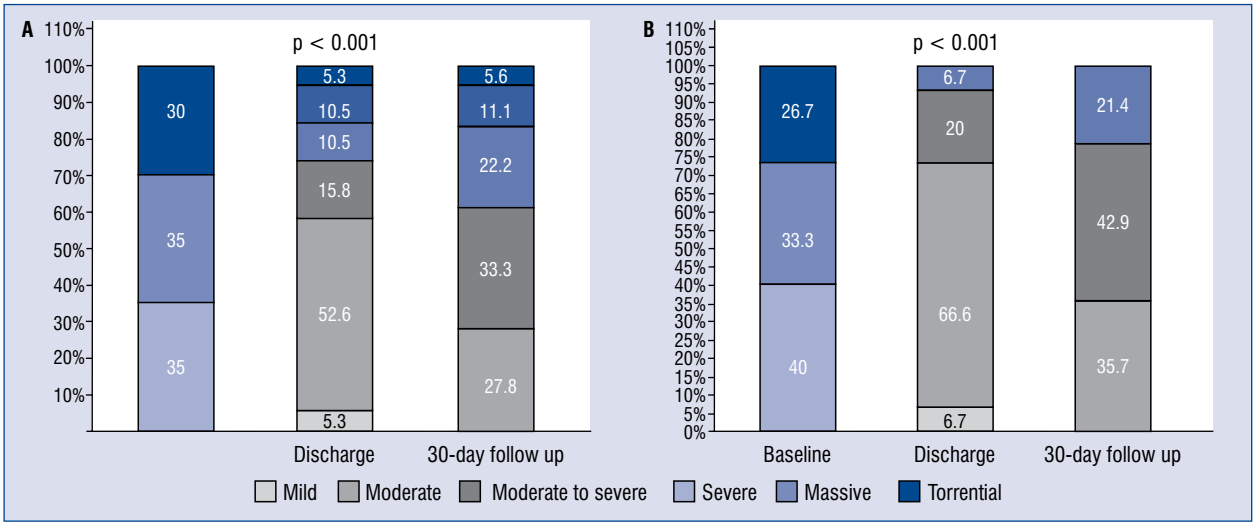

Figure 1. A. Tricuspid regurgitation grade pre- and post-tricuspid valve intervention in the total patient population (n = 20); One patient died before discharge and another patient died within 30 days; **B.** Tricuspid regurgitation grade pre- and post-tricuspid valve intervention in patients with successful transcatheter tricuspid valve intervention at baseline (n = 15); One patient died before discharge and another patient died within 30 days.

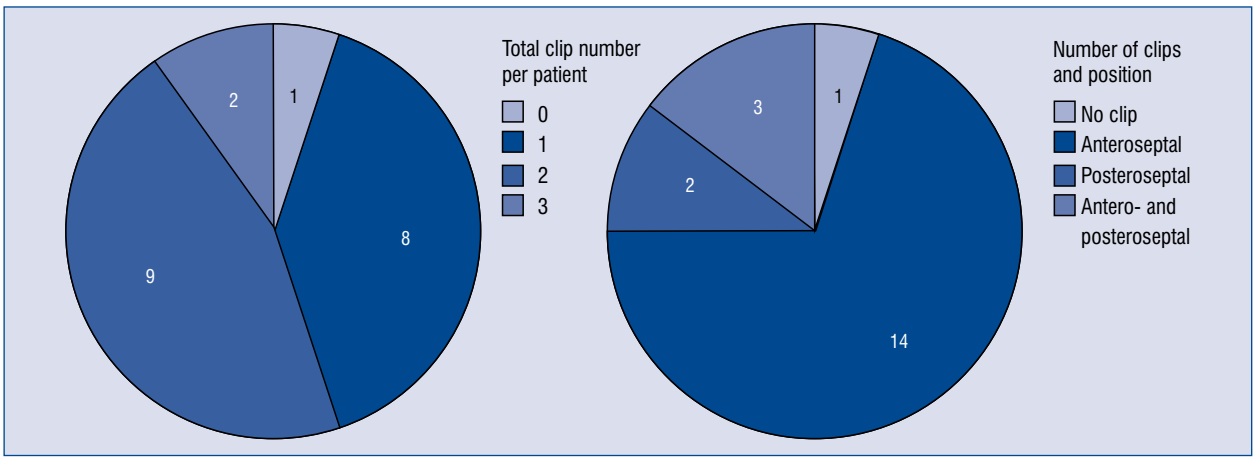

Figure 2. Numbers of clips implanted per patient (left) and leaflet location of implanted clips (right).

dynamics and procedural aspects, as well as RV function (Table 2). There were no differences in conventional echocardiographic parameters for TR severity (vena contracta, EROA, TR grade, TR volume; Table 2). However, echocardiographic parameters describing tricuspid annulus geometry (TV annulus, coaptation depth, tenting area) were significantly larger in patients with failed TTVI (Table 2).

Clinical outcome at 30-day follow-up

The NYHA class improved significantly between baseline and 30-day follow-up, as outlined in Table 3 and Figure 3. At 30-day follow-up, SLDA with worsening of TR was observed in 2 more patients, and 1 patient died due to worsening HF. Thus, the overall 30-day overall success rate was 60% (n = 12) and 30-day mortality was 10% (n = 2). However, the deaths in this cohort were due to progressive and terminal HF despite TTVI rather than due to TTVI. Comparing patients at 30-day follow-up (30-day success, n = 12 vs. 30-day failure, n = 8), we still observed no differences in conventional echocardiographic parameters as mentioned above. In line with the reported acute success data, tricuspid annulus ge-

Table 3. Outcome parameters at discharge and 30-day follow-up in the overall patient population and comparing patients with acute clinical and procedural success versus acute failure.

	All patients (n = 20)	Acute success (n = 15)	Acute failure (n = 5)	P
TR grade at discharge	**2.5 ± 0.96 (2.0)**	**2.1 ± 0.5 (2.0)**	**4.0 ± 0.8 (4.0)**	**< 0.001**
TR grade at 30-day follow-up	**2.8 ± 0.8 (2.5)**	**2.4 ± 0.4 (2.5)**	**4.0 ± 0.8 (4.0)**	**< 0.001**
In-hospital mortality	1 (5%)	0 (0%)	1 (20%)	0.99
30-day mortality	2 (10%)	1 (6.7%)	1 (20%)	0.42
Total hospital stay [days]	12.4 ± 7.5 (8.5)	11.5 ± 6.5 (9)	15.0 ± 10.1 (8)	0.37
ICU stay [days]	3.6 ± 3.9 (2.5)	3.6 ± 4.5 (2)	3.4 ± 1.8 (4)	0.90
SLDA	3 (15%)	2 (13.3%)	1 (20%)	N/A
Time to SLDA [days]	26 ± 19.1 (37)	37.0 ± 0.0 (37)	4	N/A

Data are shown as mean ± standard deviation (median) or number (percentage); TR — tricuspid regurgitation; ICU — intensive care unit; SLDA — single leaflet device attachment

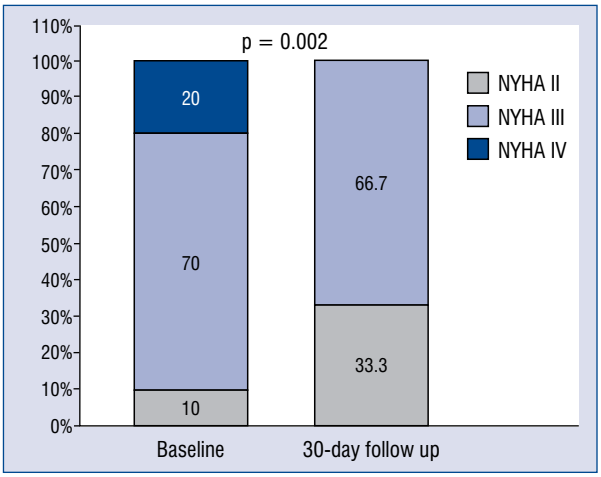

Figure 3. New York Heart Association (NYHA) class at baseline and 30-day follow-up in the total patient population (n = 20); Two patients died within 30 days.

ometry parameters remained larger in the 30-day failure group (tenting area 2.0 ± 0.8 vs. 2.9 ± 1.1 cm^2, p = 0.057; coaptation depth 6.1 ± 2.4 vs. 9.5 ± ± 3.3, p = 0.016; TV annulus 44.6 ± 4.5 vs. 46.8 ± ± 7.1, p = 0.412). Of note, in all patients (n = 3) with a transvalvular implanted lead (cardiac implantable electronic devices [CIED]) TTVI failed at 30-day follow-up (p = 0.02).

Discussion

In this prospective cohort study, we analyzed clinical, procedural, and echocardiographic data on outcomes after TTVI using the edge-to-edge technique. With high initial implantation success (85%) and low in-hospital mortality rate (5%), this procedure is a promising alternative to surgical TV repair or replacement. While our observed 30-day success rate was 60% lower than that reported by other investigators (e.g. 86% in TRILUMINATE and TriValve, 81% by Besler et al. [24]), patient selection seems to play a pivotal role because we included patients with advanced (right-sided) HF [7, 24–26]. The high TRuE risk score of > 6 in our cohort underlines this disease stage and a patient population at high risk [23].

The optimal timing for surgical or transcatheter TV repair remains unclear. RV and tricuspid annular remodeling progress with advanced TR stages and RV failure. Therefore, early TV intervention during TR disease progression using the edge-to-edge technique has been suggested to reverse RV remodeling and failure. Echocardiographic grading of TR severity is complicated and requires extensive operator training due to the complexity of the TV apparatus and its challenging anatomy. Interestingly, we found no differences in "conventional" echocardiographic parameters for TR severity (vena contracta, EROA, TR grade, TR volume) with respect to short-term success. Recently, more sophisticated approaches involving qualitative, quantitative, and semi-quantitative criteria have been proposed. These data require further verification regarding their predictive power [7].

Moreover, identification of the main pathogenic mechanism for TR might have prognostic implications [7]. A decade ago, Min et al. [27] demonstrated that the antero-posterior annulus diameter and tenting volume before tricuspid annuloplasty were independent predictors of residual

TR after surgical correction. Our data underline this observation. We show differences in tricuspid annulus geometry expressed as TV annulus diameter, coaptation depth, and tenting area, which were all significantly larger in the patients with failed percutaneous edge-to-edge repair of TV. However geometric changes of the TV apparatus seem to be an indicator of severity of TR. Therefore, coaptation enhancement strategies like the edge-to-edge technique might be a feasible approach during mid-stage TR disease. Conversely, advanced TR disease is characterized by progressive annular dilatation, RV remodeling, and leaflet tethering, which then result in geometric abnormalities of the TV apparatus. In light of this, combined approaches with additional annuloplasty or TV replacement strategies might be the preferable treatment option for later stages of TR. On the other hand, there might be "a point of no return" during TR disease progression, reflecting the underlying left and/or right HF. As we know from the published trials COAPT and MITRA-FR for percutaneous treatment of functional mitral regurgitation, valve regurgitation needs also to be graded and judged with respect to atrial and ventricular dimensions and function [28, 29].

In our patient cohort, TTVI failed in most patients with the main jet located non-centrally and non-anteroseptally (success rate 25%, 1 out of 4). However, jet location can be verified as a predictor for procedural outcome of the edge-to-edge repair and is in agreement with previously published data [22, 24]. Only 3 of our patients (15%) had a CIED, compared to 26% in the TriValve registry. However, all 3 CIED patients failed TTVI at 30-day follow-up, which is contrary to the reported success rate of 78.6% in the TriValve cohort [30]. This difference in outcome might be related to our sample size or possibly due to patient selection. The main jet location in the TriValve registry was in the favorable central/ /anteroseptal location in CIED patients, which is contrary to our CIED patients [30].

Comparing our patient data with those of a previously published large cohort study on FTR, there are distinct differences regarding the patient population [13]. Contrary to Benfari et al. [13], our cohort is of mixed nature regarding LV function including both HFrEF and HF with preserved ejection fraction patients. Moreover, we found atrial fibrillation in all of our patients compared to only 48% of the severe FTR patients in the Benfari cohort. Atrial fibrillation is seen as a major contributor to FTR and is strongly related to severe FTR because it can lead to right atrium and thus annulus dilation even in the absence of pulmonary hypertension [31, 32]. However, because FTR is related to a variety of cardiac dysfunction, detailed classification of associated TR pathology, especially for the group of functional TR, and studies on therapeutic options with respect to the origin of TR disease are needed. On the other hand, studies on surgical TR repair could show that survival is not affected by the cause of TR but rather by HF stage and comorbidities [18].

Some studies reported excess mortality for FTR as a result of underlying pulmonary hypertension and/or right/left HF [33–35]. This concept has been challenged in the past years, because several studies could show that FTR is an independent predictor for survival [13, 16, 17]. This calls not only for a specific treatment of TR but also for an effort on early identification of FTR patients; in particular, if other cardiac pathologies such as atrial fibrillation are present with the resulting need for close clinical monitoring.

Limitations of the study

This is an observational, prospective cohort study reporting a single-center experience with a small sample size and multiple comparisons. Thus, patient bias and significances appearing by chance cannot be excluded completely. The findings of our study have to be judged as hypothesis-generating and should be verified by further studies. However, the overall available patient population for isolated TV procedures is limited. In other studies, such as the recently published Triluminate registry, an average of only 4 patients per study site was included during a comparable time period [25].

Conclusions

Our data suggest the significance of tricuspid annulus geometry, which seems to impact short--term outcomes after percutaneous edge-to-edge repair of TR. Further investigations and possibly more sophisticated interventional approaches involving the tricuspid annulus are needed to better understand and treat this complex valve disease.

Conflict of interest: None declared

References

1. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017; 38(36): 2739–2791, doi: 10.1093/eurheartj/ehx391, indexed in Pubmed: 28886619.

2. Chikwe J, Itagaki S, Anyanwu A, et al. Impact of concomitant tricuspid annuloplasty on tricuspid regurgitation, right ventricular function, and pulmonary artery hypertension after repair of mitral valve prolapse. J Am Coll Cardiol. 2015; 65(18): 1931–1938, doi: 10.1016/j.jacc.2015.01.059, indexed in Pubmed: 25936265.
3. Zack CJ, Fender EA, Chandrashekar P, et al. National trends and outcomes in isolated tricuspid valve surgery. J Am Coll Cardiol. 2017; 70(24): 2953–2960, doi: 10.1016/j.jacc.2017.10.039, indexed in Pubmed: 29241483.
4. Navia JL, Brozzi NA, Klein AL, et al. Moderate tricuspid regurgitation with left-sided degenerative heart valve disease: to repair or not to repair? Ann Thorac Surg. 2012; 93(1): 59–67; discussion 68, doi: 10.1016/j.athoracsur.2011.08.037, indexed in Pubmed: 22093694.
5. Benedetto U, Melina G, Angeloni E, et al. Prophylactic tricuspid annuloplasty in patients with dilated tricuspid annulus undergoing mitral valve surgery. J Thorac Cardiovasc Surg. 2012; 143(3): 632–638, doi: 10.1016/j.jtcvs.2011.12.006, indexed in Pubmed: 22244561.
6. Kim JB, Yoo DG, Kim GS, et al. Mild-to-moderate functional tricuspid regurgitation in patients undergoing valve replacement for rheumatic mitral disease: the influence of tricuspid valve repair on clinical and echocardiographic outcomes. Heart. 2012; 98(1): 24–30, doi: 10.1136/heartjnl-2011-300403, indexed in Pubmed: 21930721.
7. Taramasso M, Benfari G, van der Bijl P, et al. Transcatheter versus medical treatment of patients with symptomatic severe tricuspid regurgitation. J Am Coll Cardiol. 2019; 74(24): 2998–3008, doi: 10.1016/j.jacc.2019.09.028, indexed in Pubmed: 31568868.
8. Addetia K, Muraru D, Veronesi F, et al. 3-Dimensional echocardiographic analysis of the tricuspid annulus provides new insights into tricuspid valve geometry and dynamics. JACC Cardiovasc Imaging. 2019; 12(3): 401–412, doi: 10.1016/j.jcmg.2017.08.022, indexed in Pubmed: 29153573.
9. Chang JD, Manning WJ, Ebrille E, et al. Tricuspid valve dysfunction following pacemaker or cardioverter-defibrillator implantation. J Am Coll Cardiol. 2017; 69(18): 2331–2341, doi: 10.1016/j.jacc.2017.02.055, indexed in Pubmed: 28473139.
10. Hahn RT, Zamorano JL. The need for a new tricuspid regurgitation grading scheme. Eur Heart J Cardiovasc Imaging. 2017; 18(12): 1342–1343, doi: 10.1093/ehjci/jex139, indexed in Pubmed: 28977455.
11. Badano LP, Hahn R, Rodríguez-Zanella H, et al. Morphological assessment of the tricuspid apparatus and grading regurgitation severity in patients with functional tricuspid regurgitation: thinking outside the box. JACC Cardiovasc Imaging. 2019; 12(4): 652–664, doi: 10.1016/j.jcmg.2018.09.029, indexed in Pubmed: 30947907.
12. Kilic A, Saha-Chaudhuri P, Rankin JS, et al. Trends and outcomes of tricuspid valve surgery in North America: an analysis of more than 50,000 patients from the Society of Thoracic Surgeons database. Ann Thorac Surg. 2013; 96(5): 1546–52; discussion 1552, doi: 10.1016/j.athoracsur.2013.06.031, indexed in Pubmed: 24070702.
13. Benfari G, Antoine C, Miller WL, et al. Excess mortality associated with functional tricuspid regurgitation complicating heart failure with reduced ejection fraction. Circulation. 2019; 140(3): 196–206, doi: 10.1161/CIRCULATIONAHA.118.038946, indexed in Pubmed: 31117814.
14. Topilsky Y, Maltais S, Medina Inojosa J, et al. Burden of tricuspid regurgitation in Patients diagnosed in the community setting. JACC Cardiovasc Imaging. 2019; 12(3): 433–442, doi: 10.1016/j.jcmg.2018.06.014, indexed in Pubmed: 30121261.
15. Topilsky Y, Nkomo VT, Vatury O, et al. Clinical outcome of isolated tricuspid regurgitation. JACC Cardiovasc Imaging. 2014; 7(12): 1185–1194, doi: 10.1016/j.jcmg.2014.07.018, indexed in Pubmed: 25440592.
16. Nath J, Foster E, Heidenreich PA. Impact of tricuspid regurgitation on long-term survival. J Am Coll Cardiol. 2004; 43(3): 405–409, doi: 10.1016/j.jacc.2003.09.036, indexed in Pubmed: 15013122.
17. Agricola E, Marini C, Stella S, et al. Effects of functional tricuspid regurgitation on renal function and long-term prognosis in patients with heart failure. J Cardiovasc Med (Hagerstown). 2017; 18(2): 60–68, doi: 10.2459/JCM.0000000000000312, indexed in Pubmed: 26258726.
18. Kim JB, Jung SH, Choo SJ, et al. Surgical outcomes of severe tricuspid regurgitation: predictors of adverse clinical outcomes. Heart. 2013; 99(3): 181–187, doi: 10.1136/heartjnl-2012-302856, indexed in Pubmed: 23038792.
19. Ratnatunga C, Edwards MB, Dore C, et al. Tricuspid valve replacement: UK heart valve registry mid-term results comparing mechanical and biological prostheses. Ann Thoracic Sur. 1998; 66(6): 1940–1947, doi: 10.1016/s0003-4975(98)01183-7.
20. Moraca RJ, Moon MR, Lawton JS, et al. Outcomes of tricuspid valve repair and replacement: a propensity analysis. Ann Thorac Surg. 2009; 87(1): 83–88, doi: 10.1016/j.athoracsur.2008.10.003, indexed in Pubmed: 19101275.
21. Chang CC, Veen KM, Hahn RT, et al. Uncertainties and challenges in surgical and transcatheter tricuspid valve therapy: a state-of-the-art expert review. Eur Heart J. 2020; 41(20): 1932–1940, doi: 10.1093/eurheartj/ehz614, indexed in Pubmed: 31511897.
22. Mehr M, Taramasso M, Besler C, et al. 1-Year outcomes after edge-to-edge valve repair for symptomatic tricuspid regurgitation: results from the trivalve registry. JACC Cardiovasc Interv. 2019; 12(15): 1451–1461, doi: 10.1016/j.jcin.2019.04.019, indexed in Pubmed: 31395215.
23. Alushi B, Beckhoff F, Leistner DM, et al. 5938 Mortality risk stratification in patients with severe tricuspid regurgitation: Insights from the Tricuspid Regurgitation REgistry (TRuE). Eur Heart J. 2019; 40(Suppl 1), doi: 10.1093/eurheartj/ehz746.0088.
24. Besler C, Orban M, Rommel KP, et al. Predictors of procedural and clinical outcomes in patients with symptomatic tricuspid regurgitation undergoing transcatheter edge-to-edge repair. JACC Cardiovasc Interv. 2018; 11(12): 1119–1128, doi: 10.1016/j.jcin.2018.05.002, indexed in Pubmed: 29929631.
25. Nickenig G, Weber M, Schueler R, et al. 6-Month outcomes of tricuspid valve reconstruction for patients with severe tricuspid regurgitation. J Am Coll Cardiol. 2019; 73(15): 1905–1915, doi: 10.1016/j.jacc.2019.01.062, indexed in Pubmed: 30999993.
26. Braun D, Nabauer M, Orban M, et al. One-year results of transcatheter treatment of severe tricuspid regurgitation using the edge-to-edge repair technique. EuroIntervention. 2018; 14(4): e413–e415, doi: 10.4244/EIJ-D-18-00186, indexed in Pubmed: 29741485.
27. Min SY, Song JM, Kim JH, et al. Geometric changes after tricuspid annuloplasty and predictors of residual tricuspid regurgitation: a real-time three-dimensional echocardiography study. Eur Heart J. 2010; 31(23): 2871–2880, doi: 10.1093/eurheartj/ehq227, indexed in Pubmed: 20601392.
28. Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter mitral-valve repair in patients with heart failure. N Engl J Med.

2018; 379(24): 2307–2318, doi: 10.1056/NEJMoa1806640, indexed in Pubmed: 30280640.
29. Obadia JF, Messika-Zeitoun D, Leurent G, et al. Percutaneous repair or medical treatment for secondary mitral regurgitation. N Engl J Med. 2018; 379(24): 2297–2306, doi: 10.1056/NEJMoa1805374, indexed in Pubmed: 30145927.
30. Taramasso M, Gavazzoni M, Pozzoli A, et al. Outcomes of TTVI in patients with pacemaker or defibrillator leads: data from the trivalve registry. JACC Cardiovasc Interv. 2020; 13(5): 554–564, doi: 10.1016/j.jcin.2019.10.058, indexed in Pubmed: 31954676.
31. Topilsky Y, Khanna A, Le Tourneau T, et al. Clinical context and mechanism of functional tricuspid regurgitation in patients with and without pulmonary hypertension. Circ Cardiovasc Imaging. 2012; 5(3): 314–323, doi: 10.1161/CIRCIMAGING.111.967919, indexed in Pubmed: 22447806.
32. Zhou X, Otsuji Y, Yoshifuku S, et al. Impact of atrial fibrillation on tricuspid and mitral annular dilatation and valvular regurgitation. Circ J. 2002; 66(10): 913–916, doi: 10.1253/circj.66.913, indexed in Pubmed: 12381084.
33. Mutlak D, Lessick J, Khalil S, et al. Tricuspid regurgitation in acute heart failure: is there any incremental risk? Eur Heart J Cardiovasc Imaging. 2018; 19(9): 993–1001, doi: 10.1093/ehjci/jex343, indexed in Pubmed: 29346535.
34. Neuhold S, Huelsmann M, Pernicka E, et al. Impact of tricuspid regurgitation on survival in patients with chronic heart failure: unexpected findings of a long-term observational study. Eur Heart J. 2013; 34(11): 844–852, doi: 10.1093/eurheartj/ehs465, indexed in Pubmed: 23335604.
35. Koelling TM, Aaronson KD, Cody RJ, et al. Prognostic significance of mitral regurgitation and tricuspid regurgitation in patients with left ventricular systolic dysfunction. Am Heart J. 2002; 144(3): 524–529, doi: 10.1067/mhj.2002.123575, indexed in Pubmed: 12228791.

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In-hospital outcomes of mechanical complications in acute myocardial infarction: Analysis from a nationwide Spanish database

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Abstract

Background: *Mechanical complications represent an important cause of mortality in myocardial infarction (MI) patients. This is a nationwide study performed to evaluate possible changes in epidemiology or prognosis of these complications with current available strategies.*

Methods: *Information was obtained from the minimum basis data set of the Spanish National Health System, including all hospitalizations for acute myocardial infarction (AMI) from 2010 to 2015. Risk-standardized in-hospital mortality ratio was calculated using multilevel risk adjustment models.*

Results: *A total of 241,760 AMI episodes were analyzed, MI mechanical complications were observed in 842 patients: cardiac tamponade in 587, ventricular septal rupture in 126, and mitral regurgitation due to papillary muscle or chordae tendineae rupture in 155 (there was more than one complication in 21 patients). In-hospital mortality was 59.5%. On multivariate adjustment, variables with significant impact on in-hospital mortality were: age (OR 1.06; 95% CI 1.04–1.07; $p < 0.001$), ST-segment elevation AMI (OR 2.91; 95% CI 1.88–4.5; $p < 0.001$), cardiogenic shock (OR 2.35; 95% CI 1.66–3.32; $p < 0.001$), cardio-respiratory failure (OR 3.48; 95% CI 2.37–5.09; $p < 0.001$), and chronic obstructive pulmonary disease (OR 1.85; 95% CI 1.07–3.20; $p < 0.001$). No significant trends in risk-adjusted in-hospital mortality were detected (IRR 0.997; $p = 0.109$). Cardiac intensive care unit availability and more experience with mechanical complications management were associated with lower adjusted mortality rates (56.7 ± 5.8 vs. 60.1 ± 4.5; and 57 ± 6.1 vs. 59.9 ± 5.6, respectively; $p < 0.001$).*

Conclusions: *Mechanical complications occur in 3.5 per thousand AMI, with no significant trends to better survival over the past few years. Advanced age, cardiogenic shock and cardio-respiratory failure are the most important risk factors for in-hospital mortality. Higher experience and specialized cardiac intensive care units are associated with better outcomes.* (Cardiol J 2021; 28, 4: 589–597)

Key words: myocardial infarction, mechanical complications, ventricular septal rupture, papillary muscle rupture, cardiac tamponade

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Introduction

Myocardial infarction-related mechanical complications (MI-MC) are uncommon but are frequently associated with severe morbidity and mortality. Presentation can vary from sudden cardiac death, typically related to pulseless electrical activity due to tamponade in free wall rupture, to asymptomatic tachycardia, with a new low-sternal murmur in some patients.

Data from different studies suggest that reperfusion therapy reduces the incidence of MI-MC when successful and performed in a timely manner [1, 2], but MI-MC still carry a very poor prognosis, despite important advancements in mechanical circulatory support [3–7]. The dismal outcomes of conservative therapy [8], leave surgical correction as a practically inevitable option with results depending on the clinical scenario, experience and appropriate timing [8–11]. Percutaneous closure of septal defects is a possible alternative to surgery, but are usually reserved for patients considered too ill to be operated on and with experience limited to a small number of centers and operators [12].

The past few years have witnessed a considerable growth of new imaging modalities and adjunctive therapies for the pre and postoperative support of MI-MC [3, 5, 6, 13–15]. However, most studies are limited to single-center experiences and by relatively small sample sizes. In addition, hospital characteristics may have an impact in the outcomes of patients with MI [16]. Accordingly, we performed a large nationwide retrospective study to analyze contemporary epidemiology of MI-MC, specifically examining recent trends in prevalence and to provide new insight into the impact of currently available supportive and corrective treatments on in-hospital mortality.

Methods

Data source, population and design

The present study is a retrospective longitudinal study using information provided by the minimum basis data set (MBDS) of the Spanish National Health System (SNHS). The MBDS is an administrative, anonymized database, with no information available linking variables to individual patients. Thus, no specific institutional review board authorization or patient informed consent documents were necessary [17]. All episodes with a principal discharge diagnosis of acute myocardial infarction (AMI) from January 2010 to December 2015 were included. The diagnosis of AMI was identified by international classification of diseases-9th Revision Clinical modification (ICD--9-CM) codes 410.*1 (410.71 for non-ST elevation AMI-NSTEMI-), MI-MC were identified by ICD--9-CM secondary codes 423.3 (cardiac tamponade), 429.71 (ventricular septal defect, acquired), 429.6 (rupture of papillary muscle), and 429.5 (rupture of chordae tendineae). Cardiac tamponade associated with cardiac surgery (codes 996.03, 996.70-79) or coronary interventions (998.2) were excluded.

Patients discharged alive at home within 1 day after admission, or with missing important demographics or principal diagnoses were excluded. To avoid duplications, transfers to other centers were only excluded if we were unable to identify the destination hospital. Secondary diagnoses were included in groups of risk factors as described by Pope et al. [18], updated each year by the Agency for Health Research and Quality. The quality of this MBDS for the study of acute coronary syndromes has been previously validated [19].

Hospital characteristics

Hospitals were qualified as having cardiac intensive care units (cICU) if they had: 1) a comprehensive critically-ill patient management capability, including those requiring invasive mechanical ventilation, and 2) administrative adscription of the cICU to the cardiology department.

Statistical analysis

Continuous variables were expressed as a mean (standard deviation) and categorical variables were expressed as numbers and rates. The Student t-test was used to compare two categories and ANOVA corrected by the Bonferroni test to compare three or more. Categorical variables were compared by the χ^2 test or Fisher's exact test.

Since the probability of a patient dying is, indeed, a combination of their individual risk factors (case mix) and the quality of care provided (performance), the risk-standardized in-hospital mortality ratio (RSMR) was defined as the ratio between predicted and expected mortality, multiplied by the crude rate of mortality. RSMR was calculated using multilevel logistic regression models developed by the Medicare and Medicaid Service for risk adjustment, adapted to the structure of the MBDS database. Hospitals were modelled as random intercept considering both inter-hospital variability and clinical and demographic variables [20–22]. For the adjustment model, we considered only comorbidities with an odds ratio (OR) > 1.0. The type of AMI (non-ST-segment elevation myocardial

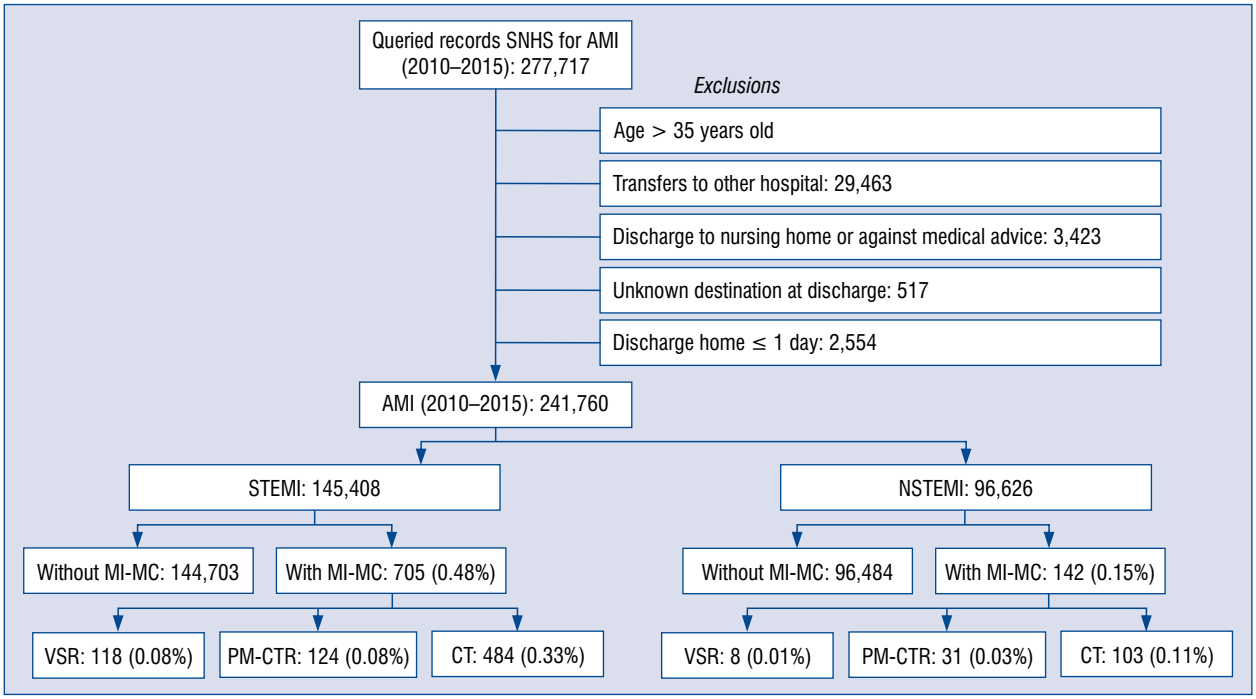

Figure 1. Flow chart of study population; SNHS — Spanish National Health System; AMI — acute myocardial infarction; STEMI — ST-segment elevation myocardial infarction; NSTEMI — non-ST-segment elevation myocardial infarction; MI-MC — myocardial infarction related mechanical complication; VSR — ventricular septal repture; PM-CTR — papillary muscle or chordae tendinae rupture; CT — cardiac tamponade.

infarction [NSTEMI] vs. ST-segment elevation myocardial infarction [STEMI]) was included in the adjustment models. All factors included in the final models and their coefficients were calculated from the present data. Levels of significance for selecting and eliminating risk factors were $p < 0.05$ and $p \geq 0.10$, respectively.

Calibration of models was assessed by calculating risk terciles of the in-hospital mortality observed and expected obtained by the logistic multilevel model. In order to evaluate the goodness of fit, a significant decrease in the statistical likelihood ratio test compared to the null model was tested. Discrimination was assessed by calculating the receiver operating characteristics curves and their corresponding area under the curve (AUROC).

Temporal trends for in-hospital mortality during the observed period were modelled using the Poisson regression analysis with year as the only independent variable. Incidence rate ratios (IRR) and their 95% confidence intervals (95% CI) were calculated. All statistical tests were two-sided. and the level of significance for p-values was set at 0.05. Statistical analysis was performed using STATA 13 and SPSS 21.0.

To discriminate between high and low volume centres a K means clustering algorithm was used, excluding hospitals with < 1 cases of MC admissions in the study period. The mathematical model was developed with two-thirds of the dataset and validated with the remaining one third.

Results

Prevalence of MI-MC

A total 277,717 episodes of MI were identified in the MBDS during the study period (2010–2015). Figure 1 depicts the study flow-chart. A total of 13% of AMI episodes were excluded, the majority of which (10.6%) for being discharged to other unidentified hospitals (**Suppl. Table 1**). From the 241,760 AMI selected for analysis, MI-MC were present in 842 patients (3.5 per thousand), and 25 patients had more than one MI-MC, resulting in a total number of mechanical complications of 863. Cardiac tamponade unrelated to cardiac procedures was present in 67.4% of MI-MC cases (n = 863). A ventricular septal defect was detected in 14.6% and mitral regurgitation in 17.9% (rupture of papillary muscle in 9.6% and rupture of chordae tendineae in 8.3%). MI-MC incidence rate was higher in STEMI than NSTEMI (4.8 vs. 1.5 per thousand; p = 0.002).

There was a statistically significant trend to an increase of MI-MC throughout 2010–2015 (3.1 per

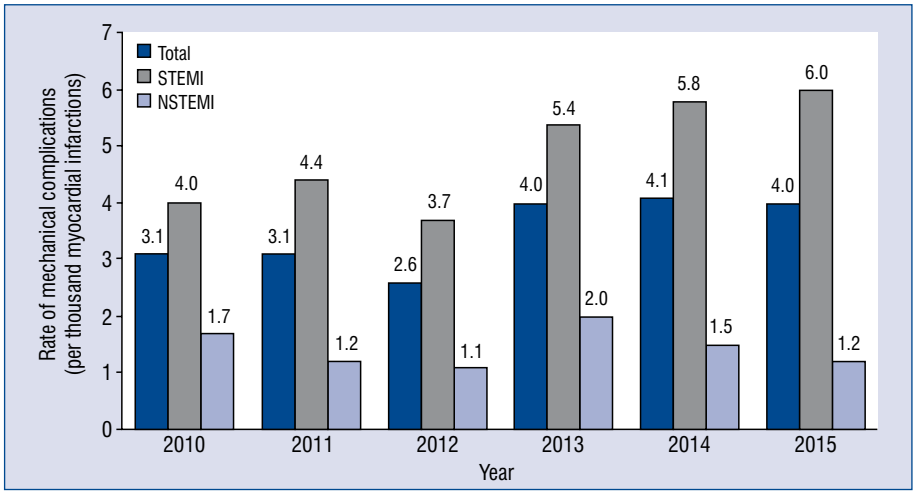

Figure 2. Trends in rates of mechanical complications in ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI).

thousand AMI vs. 4.0 per thousand AMI; IRR 1.10; 95% CI 1.07–1.13; $p < 0.001$) with higher rates between 2013–2015 related with a higher incidence of MC in STEMI (Fig. 2). The trend towards MI-MC increase was due to cardiac tamponade (IRR 1.1, 95% CI 1.04–1.14; $p < 0.001$), without significant changes in the other groups.

Differences between AMI patients with or without MI-MC are displayed in Table 1. MI-MC patients were older (72.4 ± 11 vs. 68.6 ± 14; $p < 0.001$), with a higher prevalence of female sex (36.7% vs. 30.3%; $p < 0.001$), and higher rates of cardiac failure, cardiogenic shock or cardio-respiratory failure and renal failure.

Risk factors associated with any MI-MC were older age, female sex, presentation with STEMI instead of NSTEMI, presence of valvular heart disease or chronic pulmonary disease and cardiogenic shock (**Suppl. Table 2**). The clinical characteristics associated with cardiac tamponade were: older age, presentation with STEMI instead of NSTEMI and cardiogenic shock (**Suppl. Table 3**). Risk factors for ventricular septal rupture (VSR) were: female sex (OR 1.86; 95% CI 1.29–2.67; $p < 0.001$), prior MI (OR 1.63; 95% CI 1.12–2.36; $p = 0.01$), history of congestive heart failure (OR 2.23; 95% CI 1.53–3.26; $p < 0.001$), and presentation with STEMI (OR 6.29; 95%CI 3.03–13.07; $p < 0.001$) and cardiogenic shock (HR 9.44; 95% CI 6.34–14.05; $p < 0.001$; **Suppl. Table 4**). Patients with papillary muscle or chordae tendinae rupture more frequently had a valvular heart disease, presentation with STEMI and cardiogenic shock (**Suppl. Table 5**).

Management of MI-MC

A percutaneous coronary intervention (PCI) was performed in 55.7% of the patients with AMI-MC, a significantly lower rate compared with AMI without MI-MC (59.7%; $p = 0.009$). However, coronary artery bypass graft surgery (CABG) procedures were more frequent in MI-MC (11.3 vs. 1.8; $p < 0.001$). Along the study period, there was a higher trend to use of PCI (IRR 1.12; 95% CI 1.08–1.17; $p < 0.001$) and CABG (IRR 1.16; 95% CI 1.06–1.28; $p = 0.002$), but no significant changes in trends for mitral valve replacement or other major cardiac surgery (IRR 0.99; $p = 0.13$ and IRR 0.99; $p = 0.05$; respectively; **Suppl. Fig. 1**).

In-hospital outcomes

In-hospital crude mortality rate in MI-MC patients was 59.5%, while mortality in patients without MI-MC was 9.6% ($p < 0.001$). The in-hospital mortality was 59.1% for cardiac tamponade (344 episodes), 66.7% for VSR (84 episodes), and 58.1% for papillary muscle/chordae rupture (90 episodes: 63.9% for papillary muscle rupture and 51.4% for rupture of chordae tendineae). The mortality was 81% when there were two MI-MC in the same AMI episode (17 episodes). There were no significant changes on in-hospital crude mortality rates during the 2010–2015 period (IRR 0.99; $p = 0.7$).

Table 2 shows the differences in risk factors between each MI-MC. Congestive heart failure, cardio-respiratory failure and shock, and renal failure were more frequent in VSR and mitral regurgitation-related complications, compared to the cardiac tamponade scenario. NSTEMI was rela-

Table 1. Differences between acute myocardial infarction (MI) patients with and without mechanical complications (MC).

Variables	MI without MC (n = 240,918)	MI with MC (n = 842)	P
Age [years]	68.6 ± 14.0	72.4 ± 11.1	< 0.001
Female sex	30.3%	36.7%	< 0.001
Cardiovascular risk factors:			
Smoking (ICD-9-CM code: V15.82)	40.1%	16.9%	< 0.001
Hypertension (CC 95)	49.2%	43.6%	< 0.001
Dyslipidemia (CC 25)	15.0%	9.5%	< 0.001
Diabetes mellitus (CC 17-19. 123)	32.4%	23.0%	< 0.001
Cardiovascular disease:			
Peripheral artery disease*	7.2%	8.7%	0.135
Prior myocardial infarction (ICD-9-CM code: 410.01 y 410.11)	44.8%	29.5%	< 0.001
History of PCI (ICD-9-CM code: V45.82 y 996.72)	12.0%	7.6%	< 0.001
Congestive heart failure (CC 85)	22.6%	34.4%	< 0.001
Valvular heart disease (CC 106-108)	7.1%	8.2%	0.251
Comorbidity:			
Renal failure (CC 135-140)	15.8%	27.0%	< 0.001
Chronic obstructive pulmonary disease (CC 111)	7.5%	9.7%	0.015
Metastatic cancer, acute leukemia and other severe cancers (CC 8-9)	1.2%	0.6%	0.118
Acute MI presentation:			
STEMI (410.x1 except 410.71)	60.1%	83.7%	< 0.001
Cardiogenic shock (ICD-9-CM code: 785.51)	4.5%	35.2%	< 0.001
Cardio-respiratory failure and shock* (CC 84 except 785.51)	9.1%	29.0%	< 0.001
Pneumonia (CC 114-116)	2.3%	4.6%	< 0.001
Percutaneous coronary intervention	57.9%	55.7%	0.009
Coronary artery bypass graft surgery	1.8%	11.3%	< 0.001

PCI — percutaneous coronary intervention; STEMI — ST-segment elevation myocardial infarction; CC — condition categories (Pope et al. [18])
*Peripheral artery disease (ICD-9-CM codes: 040.0. 440.0. 440.1. 440.20. 440.21. 440.22. 440.23. 440.24. 440.29. 440.30. 440.31. 440.32. 440.4. 441.00. 441.01. 441.01. 441.02. 441.03. 441.1. 441.2. 441.3. 441.4. 441.5. 441.6. 441.7. 441.9. 442.0. 442.1. 442.2. 442.3. 442.81. 442.82. 442.83. 442.84. 442.89. 442.9. 443.1. 443.21. 443.22. 443.23. 443.24. 443.29. 443.81. 443.82. 443.89. 443.9. 444.01. 444.09. 444.1. 444.21. 444.21. 444.22. 444.81. 444.89. 444.9. 445.01. 445.02. 445.81. 445.89. 447.1. 447.2. 447.3. 447.5. 447.6. 447.70. 447.71. 447.72. 447.73. 447.8. 447.9. 448.0. 557.0. 557.1. 557.9. 593.81. 785.4)

tively more frequent in the subgroup with rupture of papillary muscle or chordae tendineae.

In the multilevel risk adjustment model, several variables were independently associated with in-hospital mortality for AMI, including age, diabetes mellitus, cerebrovascular disease and STEMI presentation (**Suppl. Table 6**). Presentation of any MI-MC was also a strong predictor of in-hospital mortality (OR 9.16; 95% CI 7.65–10.99; p < 0.001). Applying the AMI model to the population with MI--MC only four variables had a significant effect: age (OR 1.06; 95% CI 1.04–1.07; p < 0.001), STEMI instead of NSTEMI (OR 2.90; 95% CI 1.87–4.50; p < 0.001), cardiogenic shock (OR 2.34; 95% CI 1.66–3.31; p < 0.001), and cardio-respiratory failure (OR 3.48; 95% CI 2.4–5.01; p < 0.001) (Table 3). This model showed a fair discriminative ability (AUROC 0.78; 95% CI 0.75–0.80) and good calibration (p < 0.001). PCI and cardiac surgery were independent risk-protective procedures for in-hospital mortality in MI-MC (OR 0.37; 95% CI 0.27–0.50; p < 0.001 and OR 0.43; 95% CI 0.30–0.62; p < 0.001, respectively).

In-hospital mortality risk-adjustment models for each MI-MC showed significant differences in risk factors and their weight (Table 4). However, in all of them, cardiogenic shock and/or cardio-respiratory failure were strong predictors of in-hospital mortality. Age was an independent risk factor only in VSR.

Risk-standardized in-hospital mortality ratio for MI-MC patients estimated with this model was

Table 2. Differences among types of mechanical complications, baseline characteristics and comorbidities.

Variables	Cardiac tamponade	Ventricular septal rupture	Papillary muscle/chordae tendinae rupture	Two MC
N	582	126	155	21
Age [years]	71.78 ± 10.9	73.8 ± 10.0	73.0 ± 12.3	75.5 ± 12.9*
Female sex	35.2%	46.0%	34.19%	33.3%
Cardiovascular risk factors:				
Smoking (ICD-9-CM code: V15.82)	10.1%	4.8%	10.3%	4.8%
Hypertension (CC 95)	44.5%	43.7%	38.1%*	28.6%
Dyslipidemia (CC 25)	30.2%	27.0%	27.7%*	23.8%
Diabetes mellitus (CC 17-19. 123)	24.4%	24.6%	16.8%*	23.8%
Cardiovascular disease:				
Peripheral artery disease	9.1%	9.5%	5.8%	4.8%
Prior myocardial infarction (ICD-9-CM code: 410.01 y 410.11)	34.5%	49.2%*	14.2%*	33.35
History of PCI (ICD-9-CM code: V45.82 y 996.72)	7.6%	7.9%	6.5%*	0.0%
Congestive heart failure (CC 85)	26.3%*	47.6%*	54.8%*	38.1%
Comorbidity:				
Renal failure (CC 135-140)	22.2%*	41.3%	32.3%*	19.1%
Chronic obstructive pulmonary disease (CC 111)	10.5%	10.3%	5.8%	4.8%
Metastatic cancer, acute leukemia and other severe cancers (CC 8-9)	0.7%	0.0%	0.7%	0.0%
Dementia or other specified brain disorders (CC 51-53)	2.6%	4.8%	4.5%	4.8%
Trauma, other injuries (CC 166-168. 170-174)	16.5%*	15.1%	6.5%	4.8%
Acute myocardial infarction presentation				
NSTEMI (410.71)	17.7%	6.4%*	20.0%*	0.0%*
Cardiogenic shock (ICD-9-CM code: 785.51)	30.2%*	47.6%*	45.2%*	47.6%
Cardio-respiratory failure (CC 84 except 785.51)	28.7%	24.65	35.5%*	42.9%
Pneumonia (CC 114-116)	5.0%	2.4%	4.5%	0.0%

*$p < 0.01$; MC — mechanical complications; PCI — percutaneous coronary intervention; NSTEMI — non ST-segment elevation myocardial infarction; CC — condition categories (Pope et al. [18])

58.5% for the whole period 2010–2015, without significant changes along the studied period (IRR 0.997; 95% CI 0.993–1; $p = 0.10$), while RSMR trend for MI without MC showed a steady decrease (IRR 0.97; 95% CI 0.96–0.98; $p < 0.001$; **Suppl. Fig. 2**).

Hospital characteristics and impact of availability of cICU

The availability of cICU was associated with a lower RSMR (56.5 ± 5.7 hospitals with cICU vs. 60.2 ± 5.7 without cICU; $p < 0.001$; OR 0.60; 95% CI 0.42–0.87; $p = 0.007$). An association was also found between higher experience in MI-MC management (11 or more MC during the study period) and lower RSMR (57 ± 6.1 vs. 59.9 ± 5.6; $p < 0.001$).

Discussion

The present study represents one of the largest series of patients with MI-MC. The main findings are: 1) the rates of MI-MC are 3.5 per thousand MI, similar to other contemporary series and with a small increase in the past few years [23, 24]; 2) the most frequent MI-MC is cardiac tamponade (2.4 per thousand), most likely related to free wall rupture, as PCI or CABG-related tamponade were excluded from this analysis, followed by mitral valve complications and VSR; 3) despite application of current adjunctive and corrective therapies, in-hospital mortality rates are still very high, varying from 59.1% and 58.1% in cardiac tamponade and papillary muscle/chordae tendineae rupture, respectively, to 63.9% in VSR; 4) age, heart failure

Table 3. Multivariate analysis for in-hospital mortality of patients with acute myocardial infarction with mechanical complications.

Risk factor	Odds ratio	95% CI	P
Age (18–44 years):			
45–54	1.57	0.19–3.81	0.829
55–64	1.04	0.17–3.05	0.657
65–74	1.77	0.25–4.25	0.964
75–84	3.68	0.59–9.92	0.219
85–94	8.19	1.24–24.54	0.025
≥ 95	19.94	0.00–0.00	0.981
STEMI (410.*1 except 410.71)	2.91	1.94–4.49	< 0.001
Cardiogenic shock (ICD-9-CM code: 785.51)	2.35	1.83–3.62	< 0.001
Cardio-respiratory failure (%) (CC 84 except 785.51)	3.48	2.10–4.37	< 0.001
Chronic obstructive pulmonary disease (CC 111)	1.85	1.07–3.19	0.027
Percutaneous coronary intervention*	0.37	0.27–0.50	< 0.001
Other major surgery*	0.43	0.30–0.62	< 0.001

*Effect of the interventions on the risk-adjustment basal model; CI — confidence interval; NSTEMI — non-ST-segment elevation myocardial infarction; CC — condition categories (Pope et al. [18])

Table 4. Variables independently associated with in-hospital, all-cause mortality adjusted by risk in a multilevel logistic regression model for different mechanical complications.

Risk factor	CT		VSR		PM/CT rupture	
	OR	95% CI	OR	95% CI	OR	95% CI
STEMI (410.*1, except 410.71)	2.43	1.52–4.00				
Cardiogenic shock (ICD-9-CM code: 785.51)			9.97	3.35–29.69	4.68	1.89–11.62
Cardio-respiratory failure and shock (CC 84 except 785.51)	3.09	2.01–4.73			3.35	1.38–8.11
Acute myocardial infarction (CC 86)	2.18	1.18–4.05				

CT — cardiac tamponade; VSR — ventricular septal rupture; PM/CT — papillary muscle or chordae tendineae rupture; OR — odds ratio; CI — confidence interval; STEMI — ST-elevation myocardial infarction; CC — condition category (Pope et al. [18])

and cardiogenic shock are strong predictors of in-hospital mortality; 5) hospitals with specialized cardiac critical care units, managed by Cardiology Departments, present better results.

The current results differ from a large database in the United States, in which MI-MC occurred in 0.27% of all STEMI patients, and 0.06% in NSTEMI, with a lower presence of free-wall rupture, (0.01%, compared to 0.21% for ventricular septal defects and 0.05% for papillary muscle rupture) [24]. Importantly, the study by Elbadawi et al. [24] used the ICD-9 code 553.9 for "free-wall rupture". This code matches with "hernia of unspecified site without mention of obstruction or gangrene" and is not used in the Spanish MBDS for the description of post-MI free-wall rupture. Despite the important limitation of including tamponade as a clinical correlate of free-wall rupture, the present estimations are more in accordance with our clinical experience and other reports [1]. However, the two databases provide similar results regarding a relatively stable prevalence of MI-MC over the past few years and the steady high mortality rates.

Therapeutic options for MI-MC apparently do not impact survival, despite advances in peripheral mechanical circulatory support and various corrective techniques [1, 11, 15, 24]. Surgical techniques for the repair of the infarcted tissue of ventricular septal defects have been stable over the past decades and the relatively low prevalence has limited surgeons' experience to a small number of cases per year, even in high-volume centres. Percutaneous closure of ventricular septal defects appears feasible, but greatly challenged by the anatomical complexity of the defects and carries a high risk of recurrences due to the friable borders of the infarcted septum [12].

Unfortunately, the possible contribution of mechanical support manoeuvres, especially veno-arterial extracorporeal membrane oxygenation (VA-ECMO) or percutaneous VSR repair could not be addressed in this study due to difficulties with non-uniform codification within the MDBS. Advanced age, cardio-respiratory failure and cardiogenic shock were the main independent predictors of total mortality in this study.

Current guidelines recommend centralizing the care of patients with cardiogenic shock in highly specialized centres [25], since this approach has been consistently associated with better outcomes in this clinical setting [26]. In this study, the availability of an cICU and higher experience in the management of these patients were both associated with higher survival rates, probably reflecting the effect of specialized training and expertise in the diagnosis and management of MI with complications.

Limitations of the study

This study has a number of limitations that have to be considered. First, this is a retrospective analysis. The use of administrative records to estimate outcomes has been widely applied to research on health service outcomes [27, 28]. Second, 10.6% of episodes were not included in the study population for being discharged to other acute general hospitals. This elimination process was necessary to avoid duplications and because in-hospital outcomes for these patients were not available. Third, as mentioned, the diagnosis of free wall rupture is not clearly specified in ICD-9 codes and therefore cardiac tamponade was used as probably infarct-related, after excluding those clearly caused by invasive procedures. We believe this variable served as a correlate of free-wall rupture, but it is not a substitute for autopsy or surgically-proven rupture, because another cause could be epistenocardic or inflammatory pericarditis. However, the mortality rates observed in this study (59.1%) are not typical of post-infarction pericarditis. In addition, a certain degree of misdiagnosis could not be excluded, as some patients may present with sudden death or electromechanical dissociation without imaging or autopsy confirmation of cardiac tamponade. With respect to the adjustment models, there are confounding factors that are impossible to identify, but may have a significant impact. The presence of cardio-respiratory failure and shock is under-estimated in MBDS. The secondary diagnoses employed as risk-adjustment variables may correspond to conditions that are present on admission or to complications that may occasionally reflect inadequate treatment. Nevertheless, the models used in this study compare favourably against models published elsewhere regarding predictive capacity [29]. Finally, limited information on detailed clinical characteristics such as time between beginning of symptoms and primary PCI and between culprit vessel revascularization and diagnosis of MI-MC precluded more detailed analysis of predictors of different complications and outcomes.

Future perspectives

Much work needs to be done in reducing mortality in this complex scenario. There is an urgent need to explore the role of different circulatory support modalities, especially in VSR, and the impact of emerging interventional techniques, ideally in a prospective, randomized design.

Conclusions

Myocardial infarction-mechanical complications occur in 3.5 per thousand MIs and are more typically related to STEMI, with a slight increase in prevalence over the past years. Cardiac tamponade is the most frequent presentation, accounting for 69% of all MI-MC. These conditions still carry a very high mortality risk, that has not been changing over the past few years. Advanced age and cardiogenic shock are the most important risk factors for in-hospital mortality. Availability of highly specialised and experienced CICU favourably impact in-hospital outcomes in this complex scenario.

Data availability

The data underlying this article were provided by the Ministry of Health by permission. Data will be shared on request to the corresponding author with the permission of the Ministry of Health.

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References

1. Puerto E, Viana-Tejedor A, Martínez-Sellés M, et al. Temporal trends in mechanical complications of acute myocardial infarction in the elderly. J Am Coll Cardiol. 2018; 72(9): 959–966, doi: 10.1016/j.jacc.2018.06.031, indexed in Pubmed: 30139440.
2. Figueras J, Alcalde O, Barrabés JA, et al. Changes in hospital mortality rates in 425 patients with acute ST-elevation myocardial infarction and cardiac rupture over a 30-year period. Circulation. 2008; 118(25): 2783–2789, doi: 10.1161/CIRCULATIONAHA.108.776690, indexed in Pubmed: 19064683.
3. Chen L, Chen K, Ni H, et al. Veno-Arterial ECMO in the setting of post-infarct ventricular septal defect: a bridge to surgical repair. Heart Lung Circ. 2018; 27(6): 771–772, doi: 10.1016/j.hlc.2017.06.731, indexed in Pubmed: 29706181.
4. Obadia B, Théron A, Gariboldi V, et al. Extracorporeal membrane oxygenation as a bridge to surgery for ischemic papillary muscle rupture. J Thorac Cardiovasc Surg. 2014; 147(6): e82–e84, doi: 10.1016/j.jtcvs.2014.03.003, indexed in Pubmed: 24680391.
5. Giuliani L, Archilletti F, Rossi S, et al. Impella CP and Veno-Arterial Extracorporeal Membrane Oxygenator as a sequential add-on combination circulatory support in ST-segment elevation myocardial infarction complicated by cardiogenic shock. Cardiovasc Revasc Med. 2019; 20(11S): 60–62, doi: 10.1016/j.carrev.2019.08.002, indexed in Pubmed: 31488363.
6. Wernly B, Seelmaier C, Leistner D, et al. Mechanical circulatory support with Impella versus intra-aortic balloon pump or medical treatment in cardiogenic shock-a critical appraisal of current data. Clin Res Cardiol. 2019; 108(11): 1249–1257, doi: 10.1007/s00392-019-01458-2, indexed in Pubmed: 30900010.
7. Schäfer A, Werner N, Westenfeld R, et al. Clinical scenarios for use of transvalvular microaxial pumps in acute heart failure and cardiogenic shock - A European experienced users working group opinion. Int J Cardiol. 2019; 291: 96–104, doi: 10.1016/j.ijcard.2019.05.044, indexed in Pubmed: 31155332.
8. Lemery R, Smith HC, Giuliani ER, et al. Prognosis in rupture of the ventricular septum after acute myocardial infarction and role of early surgical intervention. Am J Cardiol. 1992; 70(2): 147–151, doi: 10.1016/0002-9149(92)91266-7, indexed in Pubmed: 1626498.
9. Arnaoutakis GJ, Zhao Y, George TJ, et al. Surgical repair of ventricular septal defect after myocardial infarction: outcomes from the Society of Thoracic Surgeons National Database. Ann Thorac Surg. 2012; 94(2): 436–43; discussion 443, doi: 10.1016/j.athoracsur.2012.04.020, indexed in Pubmed: 22626761.
10. Li H, Zhang S, Yu M, et al. Profile and outcomes of surgical treatment for ventricular septal rupture in patients with shock. Ann Thorac Surg. 2019; 108(4): 1127–1132, doi: 10.1016/j.athoracsur.2019.03.101, indexed in Pubmed: 31075249.
11. Goldsweig AM, Wang Y, Forrest JK, et al. Ventricular septal rupture complicating acute myocardial infarction: Incidence, treatment, and outcomes among medicare beneficiaries 1999––2014. Catheter Cardiovasc Interv. 2018; 92(6): 1104–1115, doi: 10.1002/ccd.27576, indexed in Pubmed: 29513365.
12. Sabiniewicz R, Huczek Z, Zbroński K, et al. Percutaneous closure of post-infarction ventricular septal defects-an over decade-long experience. J Interv Cardiol. 2017; 30(1): 63–71, doi: 10.1111/joic.12367, indexed in Pubmed: 28078714.
13. Davidsen C, Packer EJS, Løland KH, et al. Impella use in acute myocardial infarction complicated by cardiogenic shock and cardiac arrest: Analysis of 10 years registry data. Resuscitation. 2019; 140: 178–184, doi: 10.1016/j.resuscitation.2019.04.022, indexed in Pubmed: 31009694.
14. Ostadal P, Rokyta R, Kruger A, et al. Extra corporeal membrane oxygenation in the therapy of cardiogenic shock (ECMO-CS): rationale and design of the multicenter randomized trial. Eur J Heart Fail. 2017; 19 Suppl 2: 124–127, doi: 10.1002/ejhf.857, indexed in Pubmed: 28470919.
15. Hernández Jd. Mechanical Complications in Elderly Patients With Myocardial Infarction. J Am Coll Cardiol. 2018; 72(9): 967–969, doi: 10.1016/j.jacc.2018.06.032.
16. Bertomeu V, Cequier Á, Bernal JL, et al. In-hospital mortality due to acute myocardial infarction. relevance of type of hospital and care provided. RECALCAR study. Rev Esp Cardiol (Engl Ed). 2013; 66(12): 935–942, doi: 10.1016/j.rec.2013.06.006, indexed in Pubmed: 24774106.
17. Registro de altas de hospitalización: CMBD del Sistema Nacional de Salud. Glosario de términos y definiciones. Portal estadístico SNS [actualizado Sep 2016]. p. 5-6.
18. Pope GC, Ellis RP, Ash AS, et al. Diagnostic cost group hierarchical condition category models for Medicare risk adjustment. Health Economics Research Inc, Waltham, MA 2000.
19. Bernal JL, Barrabés JA, Íñiguez A, et al. Clinical and administrative data on the research of acute coronary syndrome in spain. Minimum basic data set validity. Rev Esp Cardiol (Engl Ed). 2019; 72(1): 56–62, doi: 10.1016/j.rec.2018.01.026, indexed in Pubmed: 29747944.
20. Shahian DM, Normand SL, Torchiana DF, et al. Cardiac surgery report cards: comprehensive review and statistical critique. Ann Thorac Surg. 2001; 72(6): 2155–2168, doi: 10.1016/s0003-4975(01)03222-2, indexed in Pubmed: 11789828.
21. Normand S-LT, Glickman ME, Gatsonis CA. Statistical methods for profiling providers of medical care: issues and applications. J Am Statistical Association. 1997; 92: 803–814.
22. Goldstein H, Spiegelhalter D. League tables and their limitations: statistical issues in comparisons of institutional performance. J Royal Statistical Society. Series A (Statistics in Society). 1996; 159(3): 385, doi: 10.2307/2983325.
23. French JK, Hellkamp AS, Armstrong PW, et al. Mechanical complications after percutaneous coronary intervention in ST-elevation myocardial infarction (from APEX-AMI). Am J Cardiol. 2010; 105(1): 59–63, doi: 10.1016/j.amjcard.2009.08.653, indexed in Pubmed: 20102891.
24. Elbadawi A, Elgendy IY, Mahmoud K, et al. Temporal trends and outcomes of mechanical complications in patients with acute myocardial infarction. JACC Cardiovasc Interv. 2019; 12(18): 1825–1836, doi: 10.1016/j.jcin.2019.04.039, indexed in Pubmed: 31537282.
25. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016; 37(27): 2129–2200, doi: 10.1093/eurheartj/ehw128, indexed in Pubmed: 27206819.
26. Shaefi S, O'Gara B, Kociol RD, et al. Effect of cardiogenic shock hospital volume on mortality in patients with cardiogenic shock. J Am Heart Assoc. 2015; 4(1): e001462, doi: 10.1161/JAHA.114.001462, indexed in Pubmed: 25559014.
27. van Walraven C, Jennings A, Taljaard M, et al. Incidence of potentially avoidable urgent readmissions and their relation to all-cause urgent readmissions. CMAJ. 2011; 183(14): E1067–E1072, doi: 10.1503/cmaj.110400, indexed in Pubmed: 21859870.
28. Krumholz HM, Wang Y, Mattera JA, et al. An administrative claims model suitable for profiling hospital performance based on 30-day mortality rates among patients with an acute myocardial infarction. Circulation. 2006; 113(13): 1683–1692, doi: 10.1161/CIRCULATIONAHA.105.611186, indexed in Pubmed: 16549637.
29. Sendra Gu, Sarría-Santamera A. Iñigo Martínez J. Desarrollo de un modelo de ajuste por el riesgo para el infarto agudo de miocardio en España: comparación con el modelo de charlson y el modelo ICES. Aplicaciones para medir resultados asistenciales. Revista española de salud pública. 2006; 80: 665–677.

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Homocysteine and long-term recurrent infarction following an acute coronary syndrome

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Abstract

Background: *There are no well-established predictors of recurrent ischemic coronary events after an acute coronary syndrome (ACS). Higher levels of homocysteine have been reported to be associated with an increased atherosclerotic burden. The primary endpoint was to assess the relationship between homocysteine at discharge and very long-term recurrent myocardial infarction (MI).*

Methods: *1306 consecutive patients with ACS were evaluated (862 with non-ST-segment elevation ACS [NSTEACS] and 444 with ST-segment elevation myocardial infarction [STEMI]) discharged from October 2000 to June 2003 in a single teaching-center. The relationship between homocysteine at discharge and recurrent MI was evaluated through bivariate negative binomial regression accounting for mortality as a competitive event.*

Results: *The mean age was 66.8 ± 12.4 years, 69.1% were men, and 32.2% showed prior diabetes mellitus. Most of the patients were admitted for an NSTEACS (66.0%). The median (interquartile range) GRACE risk score, Charlson comorbidity index, and homocysteine were 144 (122–175) points, 1 (1–2) points, and 11.9 (9.3–15.6) μmol/L, respectively. In-hospital revascularization was performed in 26.3% of patients. At a median follow-up of 9.7 (4.5–15.1) years, 709 (54.3%) deaths were registered and 779 recurrent MI in 478 (36.6%) patients. The rates of recurrent MI were higher in patients in the upper homocysteine quartiles ($p < 0.001$). After a multivariate adjustment, homocysteine along its continuum remained almost linearly associated with a higher risk of recurrent MI ($p = 0.001$) and all-cause mortality ($p < 0.001$).*

Conclusions: *In patients with ACS, higher homocysteine levels identified those at a higher risk of recurrent MI at very long-term follow-up.* (Cardiol J 2021; 28, 4: 598–606)

Key words: homocysteine, acute coronary syndrome, recurrent myocardial infarction, coronary artery disease, risk factors

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Introduction

Ischemic heart disease (IHD) remains the leading cause of death worldwide, despite advances in prevention, diagnosis, and treatment [1]. Identifying those at a higher risk of new cardiovascular ischemic events is essential for tailoring monitoring and therapeutics. Unfortunately, there are not well established biomarkers for predicting the risk of long-term recurrent myocardial infarction (MI) after an episode of acute coronary syndrome (ACS).

Mild elevations of homocysteine, a toxic sulfhydryl-containing amino acid formed during the demethylation of methionine, have been associated with an increased incidence of cardiovascular, cerebrovascular, or peripheral vascular diseases [2–5]. Although the exact biological pro-atherogenic effect of homocysteine remains to be determined, multiple mechanisms have been proposed. Among them, endothelial dysfunction, direct effects on platelets, smooth muscle proliferation, oxidative modification of low-density lipoproteins, endothelial-leukocyte interactions, and inhibition of fibrinolysis have been described in vitro and in vivo studies [6–9]. However, some studies failed to confirm the relationship between higher homocysteine and adverse clinical events [10, 11]. Most of these studies were performed in a healthy population, with a median follow-up of up to 5 years, and evaluated time to a first event [3, 8, 9]. According to available research, there is no data in the literature endorsing the role of homocysteine for predicting long-term recurrent MI in patients with established IHD.

In this work, the aim was to evaluate whether homocysteine was associated with total long-term recurrent MI in a historical cohort of patients with ACS.

Methods

Population and protocol

A total of 1606 consecutive patients were hospitalized in a single-teaching center with a diagnosis of ACS from October 2000 to August 2003. None of these patients were transferred from other hospitals due to unsatisfactory clinical progress. Patients who died (n = 119) during the index admission were excluded from this analysis. Additionally, 181 patients without homocysteine assessment were excluded. Finally, 1306 patients comprised the final population for this analysis (862 with non-ST-segment elevation ACS [NSTEACS] and 444 with ST-segment elevation MI [STEMI]) (see flow chart in **Suppl. Fig. 1**). The baseline characteristics between those with and without homocysteine assessment are shown in **Supplementary Table 1**. ACS definition and treatment were based on current guidelines operating at the time of patient inclusion [12–14]. The Charlson comorbidity index [15] and the Global Registry of Acute Coronary Events (GRACE) score [16] were determined in all patients.

For STEMI patients, fibrinolysis was the main reperfusion strategy at the time of enrolment. It was indicated in those presenting with ST-segment elevation (greater than 0.1 mV in two or more contiguous leads) or new left bundle branch block and clinical history suggesting acute MI, and time to therapy of 12 hours or less. Rescue percutaneous coronary intervention was considered when the pharmacological reperfusion strategy failed [13, 14]. In patients with NSTEACS, an initial non-invasive strategy was applied. Cardiac catheterization during the index hospitalization was indicated in patients with persistent or recurrent episodes of symptomatic ischemia with or without associated electrocardiogram changes, and in those presenting shock, severe pulmonary congestion, or continuing hypotension [13, 14]. The treatment strategy followed was established by current national and international guides operating at the time of the study [13, 14].

Written informed consent was obtained from each patient included in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The study protocol has been priorly approved by the Institution's ethics committee on research on humans.

Blood samples

Plasma total homocysteine at discharge, which includes the sum of protein-bound and free homocysteine, was measured by immunoassay of polarization of fluorescence (Axsym system, Abbott). The coefficients of variation within and between days for the analysis were ≤ 5%.

Outcome definition and follow-up

Recurrent spontaneous MI was selected as the primary endpoint, whereas all-cause mortality was considered as a secondary endpoint. Patient clinical status and endpoint ascertainment were routinely evaluated by trained cardiologists during ambulatory clinic visits or through a review of the hospital or outpatient national electronic medical records. Only spontaneous MI was selected as an endpoint. Spontaneous MI was defined as an eleva-

tion of myocardial markers (troponin I or creatine kinase-MB mass) associated with chest pain or compatible symptoms or ST-segment deviation [12]. Personnel in charge of events adjudication were blinded to the clinical data and exposures.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range [IQR]) when appropriate. Differences among homocysteine quartiles were tested with the ANOVA or Kruskal-Wallis rank test, respectively. Discrete variables were presented as percentages and compared with the χ^2 test.

Time to death and first MI (adjusting for death as a competing event) across quartiles of homocysteine were plotted with the Kaplan-Meier and cumulative incidence function plots. Differences among the quartiles were tested with the log-rank test and Gray's test, respectively. The primary endpoint (recurrent MI) was evaluated by determining the incidence rate ratio (IRR), which is a risk estimate used for this type of method. To that end, a negative binomial regression was used to assess the association between homocysteine and the number of total recurrent MI during the entire follow-up. Because an increase of MI is most likely associated with an increased risk of subsequent death, it has been suggested that any analysis of recurrent admissions should also account for death as a competitive and terminal event. Thus, coefficients from this method were estimated by accounting for the positive correlation among the recurrent outcome and death as a terminal event, by linking the two simultaneous equations (rehospitalization count and death) with shared frailty [17]. Thus, within the same model, we obtain estimates of risk for both endpoints. Covariate selection was performed based on previous medical knowledge. The multivariable fractional polynomial method was used to determine the appropriate functional form of continuous covariates [18]. The covariates included in the final predictive model for both endpoints were: gender, type of ACS (NSTEACS vs. STEMI), GRACE risk score, Charlson comorbidity index, and revascularization during the index hospitalization.

A two-sided p-value of < 0.05 was set as the threshold for statistical significance. All analyses were performed with Stata 15.1 (Stata Statistical Software, Release 15 [2017]; StataCorp LP, College Station, TX, USA).

Results

The mean age of the patients was 66.8 ± 12.4 years. Most of the patients were admitted for an NSTEACS (66.0%) and showed troponin elevation (69.5%). The proportion of males was 69.1%, 32.2% showed prior diabetes mellitus, 19.4% exhibited Killip class > I and 26.3% were revascularized during the index hospitalization. The median (IQR) GRACE risk score, Charlson comorbidity index, and homocysteine were 144 (122–175) points, 1 (1–2) points, and 11.9 (9.3–15.6) μmol/L, respectively.

Baseline characteristics among homocysteine quartiles

Baseline characteristics among homocysteine quartiles are presented in Table 1. Patients in the upper quartiles of homocysteine were older, more frequently males, and more often showed a history of hypertension, IHD, and Killip class > I during the index hospitalization. Also, they exhibited a higher GRACE score and the Charlson index.

Homocysteine and risk of long-term recurrent MI

At a median follow-up of 9.7 (4.5–15.1) years, 709 (54.3%) deaths were registered and 779 recurrent MI in 478 (36.6%) patients (Fig. 1). The number of recurrent MIs per patient were 1, 2, 3 and > 3 in 299 (22.9%), 112 (8.6%), 37 (2.8%), and 32 (2.3%) patients, respectively. Patients in the upper quartile of homocysteine showed the highest cumulative incidence rates of a first MI during the entire follow-up (Fig. 2). Similarly, the rates of total MI were also higher in patients in the upper quartile (per 100-person-year): 4.1, 3.6, 3.8, and 7.3 for Q1, Q2, Q3, and Q4, respectively $p < 0.001$). After a multivariate adjustment, including established prognosticators and accounting for death as a terminal event, homocysteine along its continuum remained almost linearly associated with a higher risk of recurrent MI ($p = 0.001$), as is presented in Figure 3. When analyzed as quartiles, compared to those in the lower quartile, only patients in the upper quartile showed a significantly increased risk of recurrent MI (IRR = 1.42, 95% confidence interval [CI] 1.11–1.81, $p = 0.005$).

Subgroup analyses revealed a non-differential effect across most representative subgroups such as age (≤ 65 vs. > 65 years), gender, history of diabetes, prior IHD, type of ACS (NSTEACS vs. STEMI), and Charlson comorbidity index (above vs. below median), as depicted in **Supplementary**

Table 1. Baseline characteristics among homocysteine quartiles.

Variables	Q1 (0.67–9.27 μmol/L) (n = 326)	Q2 (9.28–11.92 μmol/L) (n = 327)	Q3 (11.93–15.55 μmol/L) (n = 327)	Q4 (15.60–92.3 μmol/L) (n = 326)	P-value for trend
Demographics and medical history					
Age [years]	62.1 ± 12.7	65.5 ± 11.0	66.8 ± 12.2	73.0 ± 11.0	< 0.001
Sex (male)	203 (62.3%)	230 (70.3%)	242 (74.0%)	228 (69.9%)	0.020
Hypertension	176 (54.0%)	206 (63.0%)	197 (60.2%)	225 (69.0%)	< 0.001
Diabetes	116 (35.6%)	106 (32.4%)	101 (30.9%)	97 (29.7%)	0.100
Dyslipidemia	152 (46.6%)	139 (42.5%)	143 (43.7%)	122 (37.4%)	0.031
Smoker	121 (37.1%)	104 (31.8%)	111 (33.9%)	72 (20.1%)	< 0.001
Prior smoker	70 (21.5%)	85 (26.0%)	99 (30.3%)	101 (31.0%)	0.003
Family history of IHD	45 (13.8%)	30 (9.2%)	24 (7.3%)	21 (6.4%)	0.001
Prior IHD	105 (32.2%)	112 (34.2%)	124 (37.9%)	157 (48.2%)	< 0.001
Prior MI	56 (17.2%)	69 (21.1%)	69 (21.1%)	91 (27.9%)	0.002
Previous PCI	21 (6.4%)	18 (5.5%)	19 (5.8%)	14 (4.3%)	0.677
Previous CABG	11 (3.4%)	18 (5.5%)	10 (3.1%)	18 (5.5%)	0.431
Charlson comorbidity index [points][a]	1 (1–2)	1 (1–2)	1 (1–2)	1.5 (1–2)	< 0.001
ACS type:					0.210
STEMI	114 (35.0%)	116 (35.5%)	116 (35.5%)	98 (30.1%)	
NSTEACS	212 (65.0%)	211 (64.5%)	211 (64.5%)	228 (69.9%)	
Killip class > I	52 (15.9%)	46 (14.1%)	56 (17.1%)	99 (30.4%)	< 0.001
GRACE score [points]	136 (110–165)	139 (118–170)	144 (124–173)	164 (136–196)	< 0.001
Vital signs on admission					
Heart rate [bpm]	85 ± 19	83 ± 19	84 ± 17	87 ± 22	0.073
SBP [mmHg]	145 ± 26	144 ± 24	147 ± 24	145 ± 26	0.542
Electrocardiogram and echocardiography					
ST segment deviation	175 (53.7%)	167 (51.1%)	173 (52.9%)	150 (46.0%)	0.088
LVEF [%][b]	60 ± 13	59 ± 12	58 ± 13	56 ± 14	0.002
Laboratory					
Creatinine [mg/dL]	0.97 ± 0.49	1.05 ± 0.40	1.16 ± 0.85	1.62 ± 1.23	< 0.001
Total cholesterol [mg/dL][c]	194 ± 49	194 ± 38	192 ± 44	192 ± 41	0.626
Troponin I elevation (> 1 ng/mL)[d]	215 (67.6%)	216 (67.5%)	220 (69.2%)	236 (75.5%)	0.092
Revascularization during admission					
Coronary angiography	184 (56.4%)	162 (49.5%)	168 (51.4%)	121 (37.1%)	< 0.001
Revascularization	105 (32.2%)	91 (27.8%)	87 (26.6%)	60 (18.4%)	< 0.001

Continuous variables are expressed as mean (standard deviation) unless otherwise specified. [a]Values are expressed as median (interquartile range); [b]Data available in 976 (74.7%) patients; [c]Data available in 1298 (99.4%) patients; [d]Data available in 1277 (97.8%) patients; ACS — acute coronary syndrome; CABG — coronary artery by-pass graft; GRACE — Global Registry of Acute Coronary Events; IHD — ischemic heart disease; LVEF — left ventricle ejection fraction; MI — myocardial infarction; NSTEACS — non-ST-segment elevation acute coronary syndrome; PCI — percutaneous coronary intervention; SBP — systolic blood pressure; STEMI — ST-segment elevation acute myocardial infarction

Figures 2, 3a and 3b. A significant differential association was found for the GRACE risk score (above vs. below median: p-value for interaction: 0.003). This interaction revealed the magnitude of the association between homocysteine and the risk of recurrent MI was greater in those with GRACE risk scores below the median (**Suppl. Fig. 3c**).

A sensitivity analysis, forcing treatments at discharge (antiplatelets [dual treatment with acetylsalicylic acid plus clopidogrel], renin–angiotensin–aldosterone inhibitors, beta-blockers, and statins) and hemoglobin (as a potential confounder) as covariates into the multivariate analysis, showed that homocysteine remained positively associated

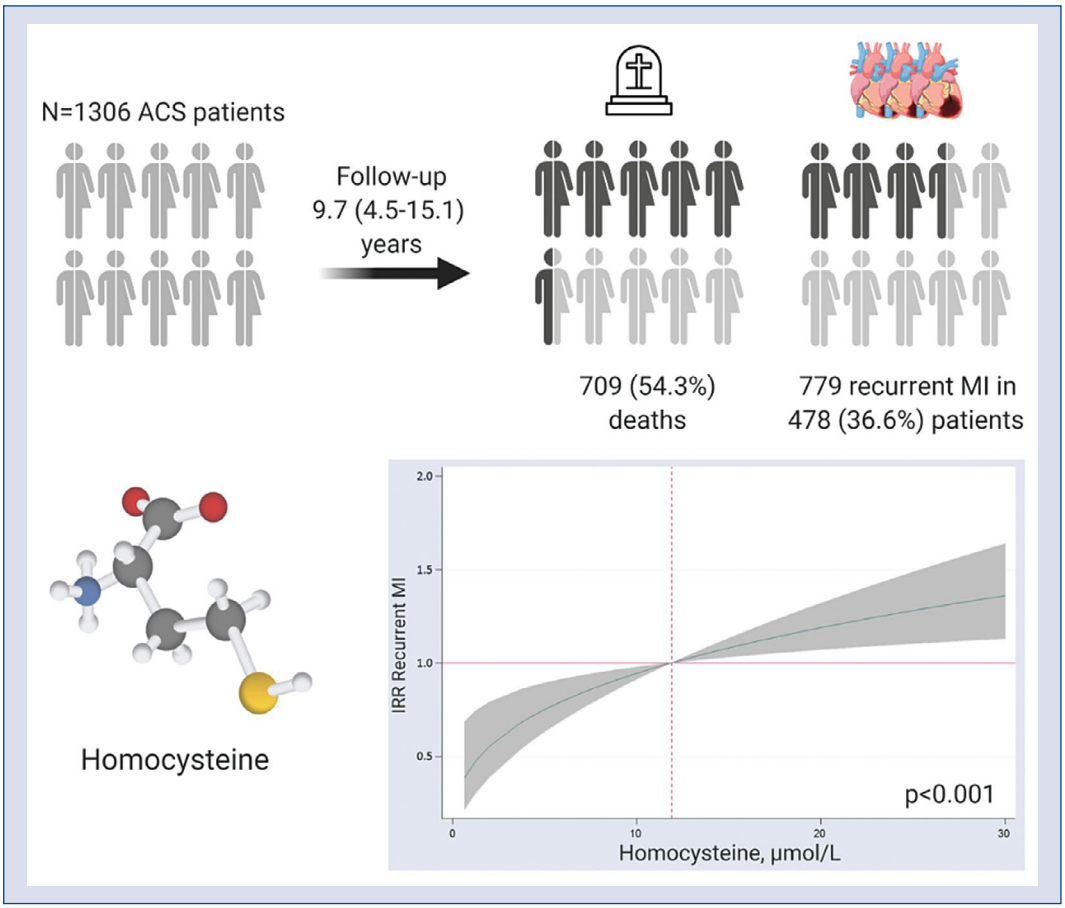

Figure 1. Graphical abstract.

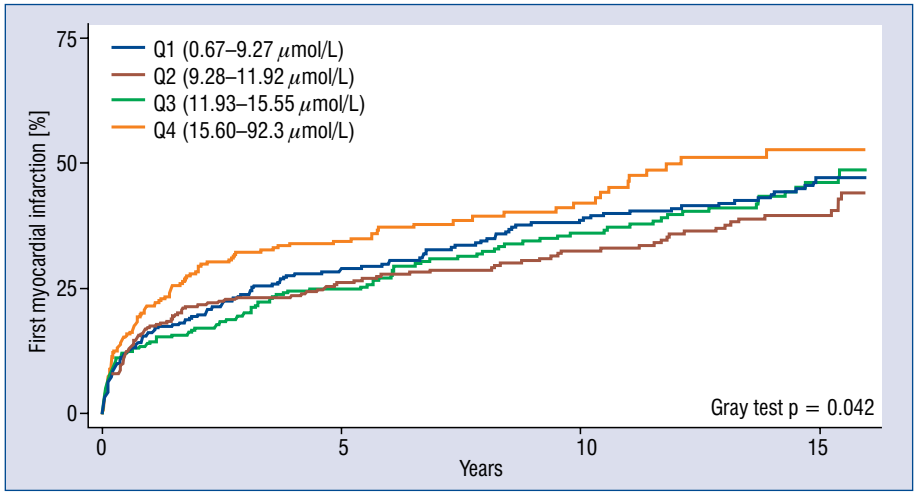

Figure 2. Time to a first myocardial infarction among homocysteine quartiles.

with the risk of MI (p = 0.002). Indeed, under this multivariate scenario, patients in the upper vs. lowest quartile displayed a significant excess of risk (IRR = 1.41, 95% CI 1.10–1.80, p = 0.006).

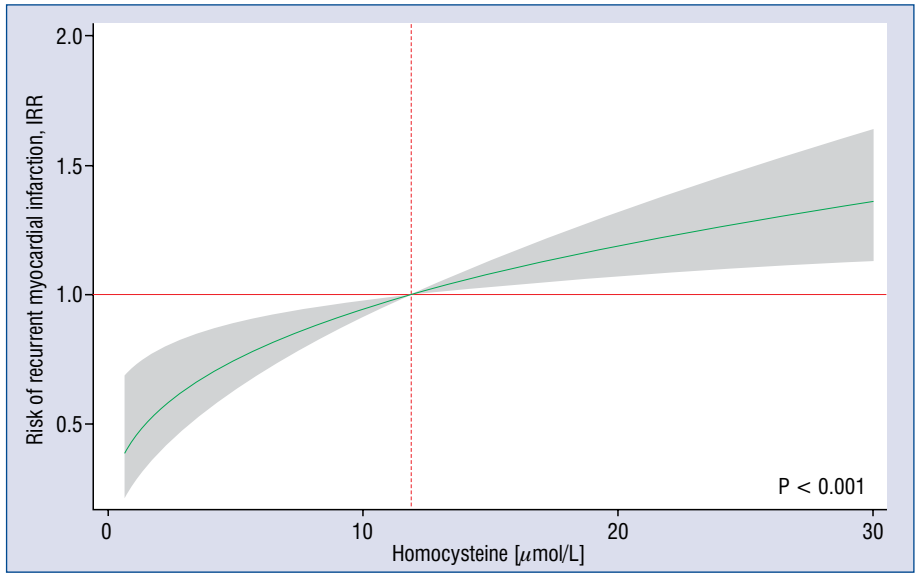

Figure 3. Homocysteine and baseline hazard of recurrent reinfarction; IRR — incidence rate ratio.

Homocysteine and risk of long-term mortality

During the follow-up, the incidence of death (per 100-person-year) significantly increased across homocysteine quartiles (3.7, 4.9, 5.7, and 10.7 for Q1, Q2, Q3, and Q4, respectively; $p < 0.001$). The Kaplan-Meier curves revealed a stepwise and sustained separation of the curves through the entire follow-up, especially for patients belonging to the upper quartile (Fig. 4A). Multivariate analysis confirmed that higher homocysteine during index admission was associated with a higher risk of death ($p < 0.001$). This adjusted association also revealed an almost linear gradient of risk (Fig. 4B). When compared to patients in the lower quartile, adjusted-risk estimates showed a significative and stepwise increase of risk for Q2 (1.25, 95% CI 0.95–1.63, $p = 0.107$), Q3 (1.41, 95% CI 1.08–1.84, $p = 0.012$), and Q4 (2.00, 95% CI 1.53–2.61, $p < 0.001$).

Discussion

This work evaluated the relationship between homocysteine and recurrent MI and mortality at very long-term follow-up in a historical cohort of consecutive non-selected patients with an ACS. The main finding herein, is that those patients with higher homocysteine values, assessed during hospitalization for an ACS, showed a higher risk of recurrent MI and mortality. Both associations were independent of traditional and relevant prognosticators and potential confounders. These findings support the role of homocysteine in the pathogenesis of new acute coronary events in patients with coronary artery disease (CAD).

Homocysteine and atherosclerosis

Homocysteine, a sulfur-containing amino acid, is an intermediate product formed as a result of the catabolism of methionine. It is known that severe hyperhomocysteinemia (>100 μmol/L) in patients with homozygous homocystinuria is associated with premature atherosclerosis [19]. Although this is a very rare pathology, minor elevated levels (15–30 μmol/L) have been described in up to 7% of the population [20].

The suggested mechanisms involved in homocysteine-induced atherosclerosis include: a) endothelial injury, which appears to be mediated by oxidative stress [21]; b) smooth muscle proliferation [22]; c) oxidative modification of low-density lipoproteins [6, 23, 24]; d) endothelial-leukocyte interactions [25]; e) reduced fibrinolytic activity [9, 26], and f) direct effects on platelets [27]. However, the specific weight of each of these mechanisms remains elusive, especially because many observations have been obtained from in vitro studies with homocysteine concentrations much higher than found in humans [8].

Homocysteine and prognosis in CAD

Several epidemiological studies have described a high prevalence of elevated plasma levels of homocysteine in patients with CAD, stroke,

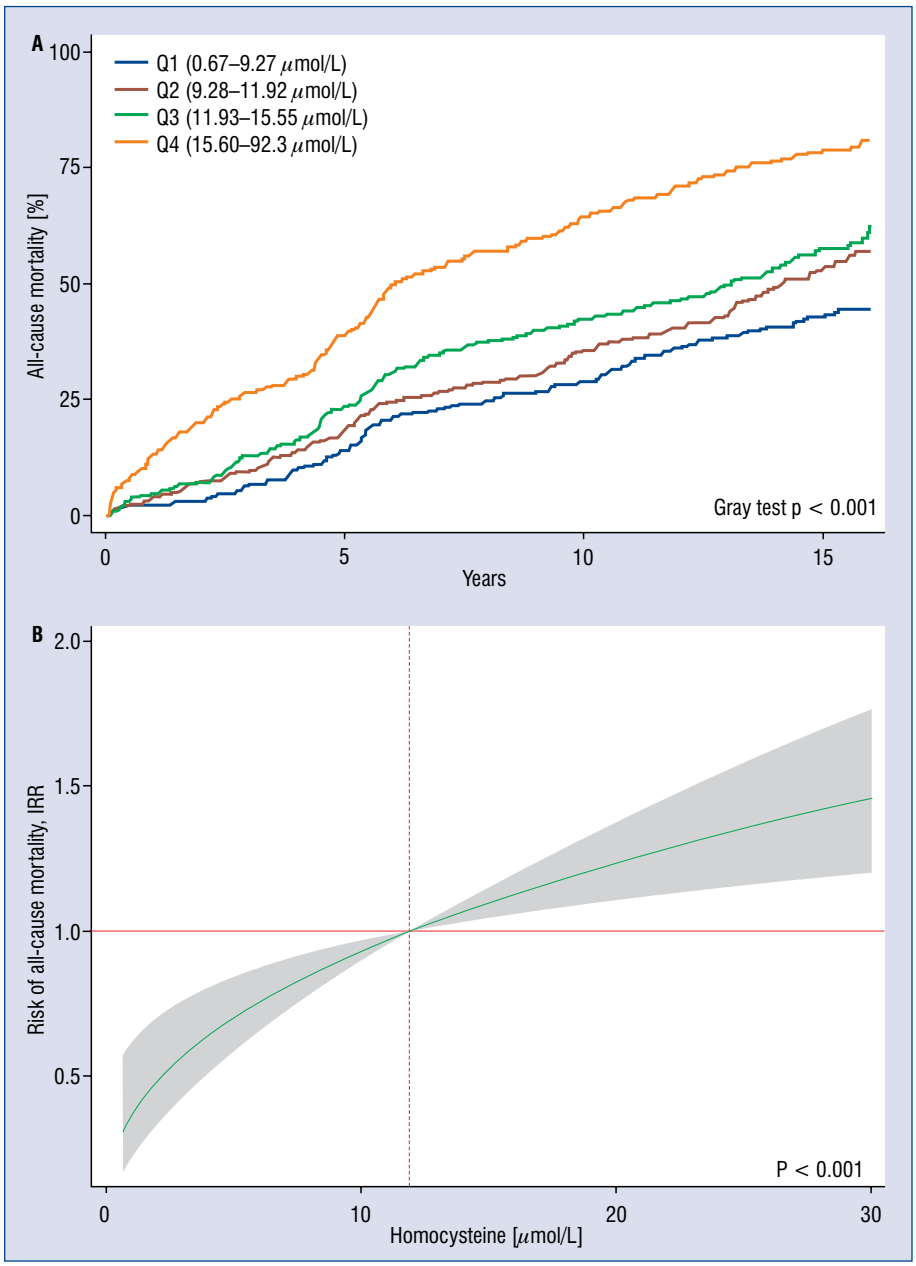

Figure 4. Homocysteine and all-cause mortality; **A.** Time to all-cause mortality among homocysteine quartiles; **B.** Baseline hazard of all-cause mortality; IRR — incidence rate ratio.

peripheral artery disease, and venous thrombosis [2–5]. Prospective studies correlated serum homocysteine levels to long-term outcomes in patients with STEMI [28], NSTACS [3], and without previous CAD [29]. In a meta-analysis, Boushey et al. [30] estimated that a 5-mmol/L homocysteine increment elevates CAD risk by as much as cholesterol increases of 0.5 mmol/L. However, other authors failed to confirm this association [10, 11]. For example, Ubbink et al. [11] showed no significant increase in CAD in those with higher homocysteine values in 2290 men in the Caerphilly cohort during a 5-year follow-up. Also, some randomized clinical trials, performed in subject with and without CAD, have failed to demonstrate any benefit in terms of reducing major cardiovascular events by lowering the homocysteine levels with diet supplementation with folic acid and B vitamins [31–33].

More recently, a higher risk of short-term mortality and nonfatal ischemic events has been reported in patients with NSTEACS [34] and STEMI [35]. In these studies, the risk of new recurrent coro-

nary ischemic events at long-term follow-up was not addressed. Thus, this is the first study showing that higher levels of homocysteine are related to a higher risk of new coronary ischemic events.

Clinical implications

Reinfarction risk prediction in patients with established CAD is still an unmet need. The utility of homocysteine measurement after an index MI is not well-established. According to the present findings, higher levels of homocysteine may identify a subset of patients at a higher risk of new coronary ischemic events. These patients may probably benefit from a closer follow-up and more aggressive treatment. Further studies are necessary to confirm the present findings in cohorts with more contemporary treatments, elucidate the mechanisms behind these findings, and re-evaluate the long-term effects of therapies for reducing homocysteine in patients with prior ACS.

Strengths and limitations

The main strength of the present study is the very-long follow-up, which allowed recording a large number of repeated new ischemic coronary events. Some important limitations need to be addressed: a) this is an observational single-center study, which may influence the applicability of these results to other populations; b) the generalization of our findings to the current era is limited by the fact that revascularization strategies and medical treatment have substantially changed. In addition, given the low proportion of patients that received coronary artery bypass during the index admission, the potential differential effect of type of revascularization along the continuum of homocysteine could not be evaluated; c) we did not assess the revascularization procedures nor medical treatment changes during the post-discharge follow-up, which may operate as important confounders; d) finally, in this study the longitudinal trajectory of homocysteine was not measured, precluding to infer how its trajectory may be associated with the risk of recurrent MI. Nevertheless, it has been reported that the occurrence of an MI does not change homocysteine plasma levels [36].

Conclusions

In patients with ACS, higher homocysteine levels identified those at a higher risk of recurrent MI very long-term follow-up. The present study results provide new evidence about the utility of homocysteine as a potential risk predictor of new coronary ischemic events. Further contemporary studies are warranted to re-evaluate the applicability of the present findings to more contemporary cohorts and the role of homocysteine as a therapeutic target in this scenario.

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Conflict of interest: None declared

References

1. Benjamin EJ, Muntner P, Alonso A, et al. American Heart Association Council on E, Prevention Statistics C, Stroke Statistics S. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. Circulation. 2019; 139: e56–e528.
2. Selhub J. The many facets of hyperhomocysteinemia: studies from the Framingham cohorts. J Nutr. 2006; 136(6 Suppl): 1726S–1730S, doi: 10.1093/jn/136.6.1726S, indexed in Pubmed: 16702347.
3. Fácila L, Nuñez JE, G VB, et al. Early determination of homocysteine levels in acute coronary syndromes, is it an independent prognostic factor? Int J Cardiol. 2005; 100(2): 275–279, doi: 10.1016/j.ijcard.2004.09.001, indexed in Pubmed: 15823635.
4. Bostom AG, Rosenberg IH, Silbershatz H, et al. Nonfasting plasma total homocysteine levels and stroke incidence in elderly persons: the Framingham Study. Ann Intern Med. 1999; 131(5): 352–355, doi: 10.7326/0003-4819-131-5-199909070-00006, indexed in Pubmed: 10475888.
5. Anderson JL, Muhlestein JB, Horne BD, et al. Plasma homocysteine predicts mortality independently of traditional risk factors and C-reactive protein in patients with angiographically defined coronary artery disease. Circulation. 2000; 102(11): 1227–1232, doi: 10.1161/01.cir.102.11.1227, indexed in Pubmed: 10982535.
6. Holvoet P, Collen D. Oxidized lipoproteins in atherosclerosis and thrombosis. FASEB J. 1994; 8(15): 1279–1284, doi: 10.1096/fasebj.8.15.8001740, indexed in Pubmed: 8001740.
7. McCully KS. Macromolecular basis for homocystein-induced changes in proteoglycan structure in growth and arteriosclerosis. Am J Pathol. 1972; 66(1): 83–96, indexed in Pubmed: 5009253.
8. Thambyrajah J, Townend JN. Homocysteine and atherothrombosis--mechanisms for injury. Eur Heart J. 2000; 21(12): 967–974, doi: 10.1053/euhj.1999.1914, indexed in Pubmed: 10901508.
9. Tofler GH, D'Agostino RB, Jacques PF, et al. Association between increased homocysteine levels and impaired fibrinolytic potential: potential mechanism for cardiovascular risk. Thromb Haemost. 2002; 88(5): 799–804, indexed in Pubmed: 12428097.

10. Folsom AR, Nieto FJ, McGovern PG, et al. Prospective study of coronary heart disease incidence in relation to fasting total homocysteine, related genetic polymorphisms, and B vitamins: the Atherosclerosis Risk in Communities (ARIC) study. Circulation. 1998; 98(3): 204–210, doi: 10.1161/01.cir.98.3.204, indexed in Pubmed: 9697819.
11. Ubbink JB, Fehily AM, Pickering J, et al. Homocysteine and ischaemic heart disease in the Caerphilly cohort. Atherosclerosis. 1998; 140(2): 349–356, doi: 10.1016/s0021-9150(98)00139-7, indexed in Pubmed: 9862278.
12. Myocardial infarction redefined: a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. Eur Heart J. 2000; 21(18): 1502–1513, doi: 10.1053/euhj.2000.2305, indexed in Pubmed: 10973764.
13. Ryan TJ, Antman EM, Brooks NH, et al. 1999 update: ACC/AHA guidelines for the management of patients with acute myocardial infarction. A report of the American College of Cardiology/ /American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). J Am Coll Cardiol. 1999; 34: 890–911.
14. Ryan T, Anderson J, Antman E, et al. ACC/AHA guidelines for the management of patients with acute myocardial infarction. J Am Coll Cardiol. 1996; 28(5): 1328–1419, doi: 10.1016/s0735-1097(96)00392-0.
15. Tang EW, Wong CK, Herbison P. Global Registry of Acute Coronary Events (GRACE) hospital discharge risk score accurately predicts long-term mortality post acute coronary syndrome. Am Heart J. 2007; 153(1): 29–35, doi: 10.1016/j.ahj.2006.10.004, indexed in Pubmed: 17174633.
16. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987; 40(5): 373–383, doi: 10.1016/0021-9681(87)90171-8, indexed in Pubmed: 3558716.
17. Xu X, Hardin J. Regression models for bivariate count outcomes. Stata J. 2018; 16(2): 301–315, doi: 10.1177/1536867x1601600203.
18. Royston P, Sauerbrei W. Multivariable Model-Building: A Pragmatic Approach to Regression Analysis Based on Fractional Polynomials for Modelling Continuous Variables. Wiley, Chichester, UK 2008.
19. McCully KS. Vascular pathology of homocysteinemia: implications for the pathogenesis of arteriosclerosis. Am J Pathol. 1969; 56(1): 111–128, indexed in Pubmed: 5792556.
20. Ueland PM, Refsum H. Plasma homocysteine, a risk factor for vascular disease: plasma levels in health, disease, and drug therapy. J Lab Clin Med. 1989; 114(5): 473–501, indexed in Pubmed: 2681479.
21. Berman RS, Martin W. Arterial endothelial barrier dysfunction: actions of homocysteine and the hypoxanthine-xanthine oxidase free radical generating system. Br J Pharmacol. 1993; 108(4): 920–926, doi: 10.1111/j.1476-5381.1993.tb13487.x, indexed in Pubmed: 8485631.
22. Heinecke JW, Rosen H, Suzuki LA, et al. The role of sulfur-containing amino acids in superoxide production and modification of low density lipoprotein by arterial smooth muscle cells. J Biol Chem. 1987; 262(21): 10098–10103, indexed in Pubmed: 3038867.
23. Naruszewicz M, Mirkiewicz E, Kłosiewicz-Latoszek L. Modification of low density lipoproteins from hypertriglyceridemic patients by macrophages in vitro and the effect of bezafibrate treatment. Atherosclerosis. 1989; 79(2-3): 261–265, doi: 10.1016/0021-9150(89)90133-0, indexed in Pubmed: 2597235.
24. Parthasarathy S. Oxidation of low-density lipoprotein by thiol compounds leads to its recognition by the acetyl LDL receptor. Biochim Biophys Acta. 1987; 917(2): 337–340, doi: 10.1016/0005-2760(87)90139-1, indexed in Pubmed: 3801507.
25. Dudman NP, Temple SE, Guo XW, et al. Homocysteine enhances neutrophil-endothelial interactions in both cultured human cells and rats In vivo. Circ Res. 1999; 84(4): 409–416, doi: 10.1161/01.res.84.4.409, indexed in Pubmed: 10066675.
26. Speidl WS, Nikfardjam M, Niessner A, et al. Mild hyperhomocysteinemia is associated with a decreased fibrinolytic activity in patients after ST-elevation myocardial infarction. Thromb Res. 2007; 119(3): 331–336, doi: 10.1016/j.thromres.2006.02.011, indexed in Pubmed: 16616324.
27. McDonald L, Bray C, Field C, et al. Homocystinuria, thrombosis, and the blood-platelets. Lancet. 1964; 1(7336): 745–746, doi: 10.1016/s0140-6736(64)92852-1, indexed in Pubmed: 14107984.
28. Fan Y, Wang J, Zhang S, et al. Homocysteine enhances the predictive value of the GRACE risk score in patients with ST-elevation myocardial infarction. Anatol J Cardiol. 2017; 18(3): 182–193, doi: 10.14744/AnatolJCardiol.2017.7798, indexed in Pubmed: 28782750.
29. Acevedo M, Pearce GL, Jacobsen DW, et al. Serum homocysteine levels and mortality in outpatients with or without coronary artery disease: an observational study. Am J Med. 2003; 114(8): 685–688, doi: 10.1016/s0002-9343(03)00123-2, indexed in Pubmed: 12798457.
30. Boushey CJ, Beresford SA, Omenn GS, et al. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease. Probable benefits of increasing folic acid intakes. JAMA. 1995; 274(13): 1049–1057, doi: 10.1001/jama.1995.03530130055028, indexed in Pubmed: 7563456.
31. Study of the Effectiveness of Additional Reductions in C, Homocysteine Collaborative G, Armitage JM, Bowman L, Clarke RJ, Effects of homocysteine-lowering with folic acid plus vitamin B12 vs placebo on mortality and major morbidity in myocardial infarction survivors: a randomized trial. JAMA. 2010; 303: 2486–2494, doi: 10.1001/jama.2010.840, indexed in Pubmed: 20571015.
32. Albert CM, Cook NR, Gaziano JM, et al. Effect of folic acid and B vitamins on risk of cardiovascular events and total mortality among women at high risk for cardiovascular disease: a randomized trial. JAMA. 2008; 299(17): 2027–2036, doi: 10.1001/jama.299.17.2027, indexed in Pubmed: 18460663.
33. Toole JF, Malinow MR, Chambless LE, et al. Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death: the Vitamin Intervention for Stroke Prevention (VISP) randomized controlled trial. JAMA. 2004; 291(5): 565–575, doi: 10.1001/jama.291.5.565, indexed in Pubmed: 14762035.
34. Hultdin J, Thøgersen AM, Jansson JH, et al. Elevated plasma homocysteine: cause or consequence of myocardial infarction? J Intern Med. 2004; 256(6): 491–498, doi: 10.1111/j.1365-2796.2004.01415.x, indexed in Pubmed: 15554950.
35. Nevado JB, Imasa MS. Homocysteine predicts adverse clinical outcomes in unstable angina and non-ST elevation myocardial infarction: implications from the folate intervention in non-ST elevation myocardial infarction and unstable angina study. Coron Artery Dis. 2008; 19(3): 153–161, doi: 10.1097/MCA.0b013e3282f52910, indexed in Pubmed: 18418231.
36. Ma Yi, Li Li, Geng XB, et al. Correlation between hyperhomocysteinemia and outcomes of patients with acute myocardial infarction. Am J Ther. 2016; 23(6): e1464–e1468, doi: 10.1097/MJT.0000000000000130, indexed in Pubmed: 25405897.

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A new approach to ticagrelor-based de-escalation of antiplatelet therapy after acute coronary syndrome. A rationale for a randomized, double-blind, placebo-controlled, investigator-initiated, multicenter clinical study

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Abstract

The risk of ischemic events gradually decreases after acute coronary syndrome (ACS), reaching a stable level after 1 month, while the risk of bleeding remains steady during the whole period of dual antiplatelet treatment (DAPT). Several de-escalation strategies of antiplatelet treatment aiming to enhance safety of DAPT without depriving it of its efficacy have been evaluated so far.

We hypothesized that reduction of the ticagrelor maintenance dose 1 month after ACS and its continuation until 12 months after ACS may improve adherence to antiplatelet treatment due to better tolerability compared with the standard dose of ticagrelor. Moreover, improved safety of treatment and preserved anti-ischemic benefit may also be expected with additional acetylsalicylic acid (ASA) withdrawal. To evaluate these hypotheses, we designed the Evaluating Safety and Efficacy of Two Ticagrelor-based De-escalation Antiplatelet Strategies in Acute Coronary Syndrome — a randomized clinical trial (ELECTRA-SIRIO 2), to assess the influence of ticagrelor dose reduction with or without continuation of ASA versus DAPT with standard dose ticagrelor in reducing clinically relevant bleeding and maintaining anti-ischemic efficacy in ACS patients.

The study was designed as a phase III, randomized, multicenter, double-blind, investigator-initiated clinical study with a 12-month follow-up (ClinicalTrials.gov Identifier: NCT04718025; EudraCT number: 2020-005130-15). (Cardiol J 2021; 28, 4: 607–614)

Key words: acute coronary syndrome, ticagrelor, antiplatelet therapy, de-escalation, ELECTRA-SIRIO 2

Introduction

Elevated rates of ischemic events clustering during the first month after acute coronary syndrome (ACS) is reflective of elevated platelet reactivity during this period. The risk of major adverse cardiovascular events (MACE), including cardiovascular death, myocardial infarction (MI), and stroke, gradually decreases, reaching a stable level after 1 month, while the risk of bleeding is

mainly related to the type and dosage of antiplatelet drugs and remains steady during the whole period of dual antiplatelet treatment (DAPT). Therefore, in the earliest phase after ACS, the ischemic component should be especially targeted with potent antiplatelet strategies, whereas after the clinical stabilization occurs, de-escalation of the antiplatelet therapy may be justified [1–8]. Treatment with ticagrelor or prasugrel is recommended over clopidogrel due to better efficacy, albeit with more bleeding complications. These higher bleeding rates have provoked trials investigating de-escalation from ticagrelor or prasugrel to clopidogrel in the hope of reducing bleeding without increasing rates of thrombotic events [4, 5]. Several strategies aiming to enhance the safety of antiplatelet treatment without depriving it of its efficacy have been evaluated so far.

Replacing a potent P2Y12 receptor inhibitor (prasugrel or ticagrelor) with a weaker one (clopidogrel) was the first de-escalation strategy tested. In the TOPIC study downgrading of DAPT (from prasugrel or ticagrelor to clopidogrel) 1 month after ACS was associated with a net clinical benefit mainly driven by a significant reduction in bleeding complications, while the risk of recurrent ischemic events remained unchanged [9]. The limitations of this study, including small study sample size (645 patients), non-homogenous treatment at baseline and in the control arm (prasugrel or ticagrelor), and moderate adherence to the treatment, warrant cautious interpretation of these results. On the other hand, the SCOPE registry (n = 1363) reported switching from clopidogrel to novel P2Y12 receptor inhibitors to be safe, while a downgrade was an independent predictor of net adverse cerebrovascular events in patients with ACS [10]. The safety and efficacy of early de-escalation of antiplatelet treatment from prasugrel to clopidogrel were tested in the TROPICAL-ACS study (n = 2610) [11]. High platelet reactivity is associated with an increased risk of recurrent ischemic events, while the use of clopidogrel is burdened with high inter-individual variability of the antiplatelet effect and the possibility of drug interactions [12]. Hence, platelet function testing was applied for guidance of de-escalation of antiplatelet treatment in this study. In the de-escalation group as much as 39% of patients required a switch-back to prasugrel due to insufficient platelet inhibition with clopidogrel defined as high platelet reactivity [11]. The primary endpoint, defined as net clinical benefit (cardiovascular death, MI, stroke, or bleeding grade 2 or higher according to Bleeding Academic Research Consortium [BARC] criteria) 1 year after randomization, occurred in 7% of patients in the guided de-escalation group and in 9% of patients in the control group ($p_{non\text{-}inferiority} = 0.0004$; hazard ratio [HR] 0.81; 95% confidence interval [CI] 0.62–1.06, $p_{superiority} = 0.12$). The prevalence of ischemic events (cardiovascular death, MI, and stroke) was 3% in both study arms, while the prevalence of BARC grade 2 or higher was 5% and 6%, respectively. Despite of the lack of significant differences in the whole study population, subgroup analyses revealed a net clinical benefit from guided de-escalation in ST-segment elevation MI patients, subjects ≤ 70 years of age, and those without diabetes. Summing up, this investigator-initiated, randomized, open-label, assessor-blinded, multicenter trial showed that platelet function testing-guided de-escalation from prasugrel to clopidogrel was non-inferior to standard treatment with prasugrel at 1 year after percutaneous coronary intervention (PCI) in terms of net clinical benefit in patients with ACS [11].

Kheiri et al. [13] conducted a meta-analysis (3 randomized clinical trials with 3391 patients) aimed at evaluating the clinical outcomes of antiplatelet de-escalation based on switching from prasugrel or ticagrelor to clopidogrel compared with continuation of DAPT with more potent P2Y12 receptor inhibitor in patients treated with PCI. The net clinical outcome (composite of bleeding or thrombotic events) was significantly reduced in the group switched to clopidogrel; however, no differences between the groups in a separate analysis for MACE, as well as for bleedings, were found [13].

Pharmacodynamic data show that reduction of ticagrelor bioavailability by one-third significantly decreases the antiplatelet effect of ticagrelor in patients with acute MI, but not in subjects without ACS [14–16]. More pronounced ticagrelor-induced platelet inhibition seen in a stable setting compared with MI reflects the excessive platelet activation occurring during the initial phase of ACS. Subsequently, the enhanced platelet reactivity and aggregation decrease over time when ACS patients become stable [17–22]. This observation was confirmed in a sub-study of the PEGASUS-TIMI 54 trial showing similar platelet inhibition with reduced (60 mg b.i.d) and standard (90 mg b.i.d) maintenance doses in stable patients more than 1 year after MI, despite one-third lower ticagrelor plasma concentrations in the lower dose arm [23–25]. Recently, we demonstrated in a randomized, pharmacodynamic trial that a reduced ticagrelor maintenance dose of 60 mg b.i.d. provides a comparable antiplatelet effect to the standard

90 mg b.i.d. dose in patients already 1 month post MI, when the disease proceeds to its stable phase. Importantly, no differences in the prevalence of on-ticagrelor high platelet reactivity between patients receiving the reduced and standard maintenance doses was observed in this trial [26, 27].

The number of studies reporting clinical outcomes in coronary artery disease patients receiving reduced maintenance dose of ticagrelor is limited; however, available results indicate that in a stable setting this strategy offers improved safety with preserved efficacy in the prevention of thrombotic events [7]. The PEGASUS-TIMI 54 study showed comparable clinical efficacy of two ticagrelor doses (90 mg b.i.d. and 60 mg b.i.d.) administered with acetylsalicylic acid (ASA); however, better tolerability of treatment with the lower dose was observed in stable patients 1 year after MI [23].

Another strategy to optimize antiplatelet treatment, by adjusting its potency to time-changing required platelet inhibition, has been validated in the TWILIGHT study [28]. The primary endpoint was the first occurrence of BARC type 2, 3, or 5 bleeding between randomization and 1 year in a time-to-event analysis. The key secondary endpoint was the first occurrence of death from any cause, nonfatal MI, or nonfatal stroke in a time-to--event analysis. The results of this randomized trial showed that in 7119 high-risk patients who had undergone PCI and were treated with ticagrelor 90 mg b.i.d. and ASA for 3 months, subsequent monotherapy with ticagrelor resulted in substantially fewer bleeding events than in the ticagrelor plus ASA arm (4.0% vs. 7.1%, respectively; HR 0.56; 95% CI 0.45–0.68; $p < 0.001$), without any ischemic harm over a period of 1 year; the key secondary endpoint occurred in 3.9% of patients in both study arms [28]. Even in high-risk patients after complex PCI, the DAPT downgrade to ticagrelor monotherapy was associated with lower incidence of bleeding without increased risk of ischemic events compared with continuation of DAPT [29, 30].

Khan et al. [31] performed a Bayesian network meta-analysis comparing early de-escalation of DAPT (1–3 months) to monotherapy with either P2Y12 inhibitor or ASA versus 12 months de-escalation of DAPT after PCI with drug-eluting stent. Among the 7 trials included (35,821 patients), 52.6% of patients presented with ACS. No significant differences in terms of ischemic endpoints among different DAPT strategies were found; however, early de-escalation of DAPT to monotherapy with a P2Y12 inhibitor instead of ASA might be a safer approach compared with 12 months of DAPT in patients treated with PCI [31].

Taking into account these data, we hypothesized that reduction of ticagrelor maintenance dose to 60 mg b.i.d. 1 month after ACS and its continuation until 12 months may improve adherence to antiplatelet treatment due to better tolerability compared with DAPT including standard dose ticagrelor. Moreover, based on the TWILIGHT study results [29], improved safety of treatment and preserved anti-ischemic benefit with additional ASA withdrawal may also be expected. To evaluate these hypotheses, we designed the Evaluating Safety and Efficacy of Two Ticagrelor-based De-escalation Antiplatelet Strategies in Acute Coronary Syndrome — a randomized clinical trial (ELECTRA-SIRIO 2), to assess the influence of ticagrelor dose reduction with or without continuation of ASA versus DAPT with standard-dose ticagrelor in reducing clinically relevant bleeding and maintaining anti-ischemic efficacy in ACS patients.

Current standard of treatment according to the guidelines

In ACS patients DAPT with a P2Y12 receptor inhibitor on top of ASA is recommended for 12 months to reduce platelet reactivity and adverse thrombotic events (class of recommendation I) [1, 2, 4]. However, in specific clinical scenarios the DAPT duration can be shortened (< 12 months), extended (> 12 months), or modified (switching DAPT, DAPT de-escalation), and these decisions depend on individual clinical judgement being driven by the patient's ischemic and bleeding risk, the occurrence of adverse events, comorbidities, co-medications, and availability of drugs [2]. Early discontinuation of P2Y12 receptor inhibitor therapy 3 months after non-ST-elevation ACS should be considered in those who are at high bleeding risk (High Bleeding Risk according to Academic Bleeding Consortium — ABC-HBR criteria or ≥ 25 score in PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual AntiPlatelet Therapy — PRECISE-DAPT score) (class of recommendation IIa) [4]. Termination of treatment with ASA 3–6 months after ACS in patients treated with PCI with stent implantation should be considered, depending on the balance between bleeding and ischemic risk (class of recommendation IIa). Moreover, patients at very high bleeding risk, i.e. those who experienced bleeding episode within a month preceding the index ACS or those scheduled for surgical intervention in the

early future, may benefit from 1-month DAPT comprising ASA and clopidogrel, with the intention to continue monotherapy with clopidogrel afterwards (class of recommendation IIa) [4].

De-escalation of treatment with P2Y12 receptor inhibitor (e.g. switch from prasugrel or ticagrelor to clopidogrel) may be considered in patients after ACS deemed unsuitable for potent platelet inhibition. De-escalation may be unguided, based solely on clinical judgment or guided by platelet function testing or CYP2C19 genotyping, depending on the patient's risk profile and availability of respective assays (class of recommendation IIb) [4].

Dual antiplatelet treatment with ASA and P2Y12 receptor inhibitor (ticagrelor may be preferred over clopidogrel and prasugrel) or with a low dose of rivaroxaban is recommended in subjects without atrial fibrillation at high/moderate ischemic risk and low bleeding risk beyond 12 months post ACS (class of recommendation IIa/IIb) [4, 5].

Adherence to DAPT after ACS

Despite the numerous advantages of a potent antiplatelet treatment, this therapy is also burdened with non-negligible side effects, greatly related to bleeding. These adverse effects quite often require medical attention or lead to discontinuation of treatment. Of note, the rate of premature discontinuation of antiplatelet treatment in the landmark PLATO study was 23% of patients receiving ticagrelor and 22% treated with clopidogrel, which shows the magnitude of the problem [17]. Premature discontinuation of antiplatelet therapy, especially in invasively treated ACS patients, may lead to detrimental cardiovascular and thrombotic events, such as recurrent ACS or stent thrombosis [12, 17–21, 32, 33].

Premature discontinuation of treatment with ticagrelor in the PEGASUS-TIMI 54 was mostly driven by non-serious adverse events that occurred primarily early after randomization, and it was more common in patients receiving standard compared with reduced ticagrelor maintenance dose [23–25]. Thus, better adherence to treatment would be expected with low-dose ticagrelor in real-life practice.

The ELECTRA-SIRIO 2 study

The ELECTRA-SIRIO 2 study was designed as a phase III, randomized, multicenter, double-blind, placebo-controlled, investigator-initiated clinical study with a 12-month follow-up (ClinicalTrials.gov Identifier: NCT04718025; EudraCT number: 2020-005130-15). The study is aimed to test two ticagrelor-based de-escalation strategies versus standard treatment.

During the first month after ACS subjects from all three arms will receive a standard DAPT with ticagrelor 90 mg b.i.d and 100 mg ASA once daily. Patients assigned to the control group will continue this standard treatment for a total of 12 months, while in both experimental arms after 1 month the maintenance dose of ticagrelor will be reduced to 60 mg b.i.d. Then, 3 months after ACS, treatment with ASA will be terminated in one of the experimental arms. The primary safety composite endpoint of this study is the first occurrence of type 2, 3, or 5 bleeding according to the BARC criteria, occurring during the first 12 months after ACS. The primary efficacy endpoint is the composite of time to death from any cause, first nonfatal MI, or first nonfatal stroke.

Special care will be applied with regard to adherence to the study treatment (tablet counting at follow-up visits and evaluation with use of the Adherence in Chronic Diseases Scale). The adherence to treatment is of vast importance because early termination of ticagrelor leaves the ACS patients in the monotherapy arm unprotected against ischemic consequences, such as recurrent ACS [34–40].

To increase adherence to treatment all patients will undergo continuous multilevel educational and motivational interventions according to the Multilevel Educational and Motivational Intervention in Patients After Myocardial Infarction (MEDMOTION) project, including assessment with the Readiness for Hospital Discharge after Myocardial Infarction Scale at the end of hospitalization, and with the Functioning in Chronic Illness Scale during follow-ups [41–48].

Summary

To date, de-escalation of antiplatelet therapy in ACS patients based on lowering the dose of ticagrelor with or without discontinuation of ASA has not been tested in a large randomized clinical trial.

Taking into account existing evidence, one would expect equal clinical efficacy of reduced and standard maintenance doses of ticagrelor already after 1 month post ACS based on their documented antiplatelet effects. The two antiplatelet de-escalation strategies proposed in the ELECTRA-SIRIO 2 study are expected to essentially decrease the incidence of clinically significant bleeding events

during the first year after ACS, without negative impact on the antithrombotic efficacy. In contrast to the platelet function testing-guided de-escalation strategy applied in the TROPICAL-ACS study [11], the strategy proposed in the ELECTRA-SIRIO 2 study does not require a platelet reactivity assessment, making this step-down approach more feasible for wide application in clinical practice.

Moreover, the quality of life in post-ACS patients on the tested regimen may increase due to lower incidence of dyspnea, an adverse effect typical for ticagrelor. This assumption is based on observations from the PEGASUS-TIMI 54 trial, where dyspnea occurred less frequently in patients who received the lower dose of ticagrelor compared with those treated with the standard dose (16% vs. 19%) [23–25]. Thus, a lower number of patients are expected to permanently and prematurely discontinue ticagrelor.

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References

1. Valgimigli M, Bueno H, Byrne RA, et al. ESC Scientific Document Group, ESC Committee for Practice Guidelines (CPG), ESC National Cardiac Societies. 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.
2. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019; 40(2): 87–165, doi: 10.1093/eurheartj/ehy394, indexed in Pubmed: 30165437.
3. Adamski P, Adamska U, Ostrowska M, et al. New directions for pharmacotherapy in the treatment of acute coronary syndrome. Expert Opin Pharmacother. 2016; 17(17): 2291–2306, doi: 10.1080/14656566.2016.1241234, indexed in Pubmed: 27677394.
4. Collet JP, Thiele H, Barbato E, et al. ESC Scientific Document Group. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2021; 42(14): 1289–1367, doi: 10.1093/eurheartj/ehaa575, indexed in Pubmed: 32860058.
5. Kubica J, Adamski P, Niezgoda P, et al. Prolonged antithrombotic therapy in patients after acute coronary syndrome: A critical appraisal of current European Society of Cardiology guidelines. Cardiol J. 2020; 27(6): 661–676, doi: 10.5603/CJ.a2020.0132, indexed in Pubmed: 33073857.
6. Adamski P, Adamska U, Ostrowska M, et al. Evaluating current and emerging antithrombotic therapy currently available for the treatment of acute coronary syndrome in geriatric populations. Expert Opin Pharmacother. 2018; 19(13): 1415–1425, doi: 10.1080/14656566.2018.1510487, indexed in Pubmed: 30132731.
7. Claassens DMf, Sibbing D. De-escalation of antiplatelet treatment in patients with myocardial infarction who underwent percutaneous coronary intervention: a review of the current literature. J Clin Med. 2020; 9(9), doi: 10.3390/jcm9092983, indexed in Pubmed: 32942754.

8. Kubica J, Adamski P, Paciorek P, et al. Treatment of patients with acute coronary syndrome: Recommendations for medical emergency teams: Focus on antiplatelet therapies. Updated experts' standpoint. Cardiol J. 2018; 25(3): 291–300, doi: 10.5603/CJ.a2018.0042, indexed in Pubmed: 29671864.
9. Cuisset T, Deharo P, Quilici J, et al. Benefit of switching dual antiplatelet therapy after acute coronary syndrome: the TOPIC (timing of platelet inhibition after acute coronary syndrome) randomized study. Eur Heart J. 2017; 38(41): 3070–3078, doi: 10.1093/eurheartj/ehx175, indexed in Pubmed: 28510646.
10. De Luca L, D'Ascenzo F, Musumeci G, et al. Incidence and outcome of switching of oral platelet P2Y12 receptor inhibitors in patients with acute coronary syndromes undergoing percutaneous coronary intervention: the SCOPE registry. EuroIntervention. 2017; 13(4): 459–466, doi: 10.4244/EIJ-D-17-00092, indexed in Pubmed: 28374678.
11. Sibbing D, Aradi D, Jacobshagen C, et al. Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial. Lancet. 2017; 390(10104): 1747–1757, doi: 10.1016/s0140-6736(17)32155-4.
12. Navarese EP, Khan SU, Kołodziejczak M, et al. Comparative efficacy and safety of oral P2Y inhibitors in acute coronary syndrome: network meta-analysis of 52 816 patients from 12 randomized trials. Circulation. 2020; 142(2): 150–160, doi: 10.1161/CIRCULATIONAHA.120.046786, indexed in Pubmed: 32468837.
13. Kheiri B, Osman M, Abdalla A, et al. De-Escalation of antiplatelet therapy in patients with acute coronary syndrome undergoing percutaneous coronary intervention: a meta-analysis of randomized clinical trials. J Cardiovasc Pharmacol Ther. 2019; 24(2): 153–159, doi: 10.1177/1074248418809098, indexed in Pubmed: 30419754.
14. Kubica J, Adamski P, Ostrowska M, et al. Morphine delays and attenuates ticagrelor exposure and action in patients with myocardial infarction: the randomized, double-blind, placebo-controlled IMPRESSION trial. Eur Heart J. 2016; 37(3): 245–252, doi: 10.1093/eurheartj/ehv547, indexed in Pubmed: 26491112.
15. Hobl EL, Reiter B, Schoergenhofer C, et al. Morphine decreases ticagrelor concentrations but not its antiplatelet effects: a randomized trial in healthy volunteers. Eur J Clin Invest. 2016; 46(1): 7–14, doi: 10.1111/eci.12550, indexed in Pubmed: 26449338.
16. Kubica J, Kubica A, Jilma B, et al. Impact of morphine on antiplatelet effects of oral P2Y12 receptor inhibitors. Int J Cardiol. 2016; 215: 201–208, doi: 10.1016/j.ijcard.2016.04.077, indexed in Pubmed: 27128531.
17. Adamski P, Ostrowska M, Navarese EP, et al. Pharmacodynamic and clinical efficacy of reduced ticagrelor maintenance doses in patients with coronary artery disease. Curr Med Res Opin. 2021; 37(2): 195–206, doi: 10.1080/03007995.2020.1854207, indexed in Pubmed: 33211543.
18. Adamski P, Buszko K, Sikora J, et al. Determinants of high platelet reactivity in patients with acute coronary syndromes treated with ticagrelor. Sci Rep. 2019; 9(1): 3924, doi: 10.1038/s41598-019-40628-0, indexed in Pubmed: 30850677.
19. Ostrowska M, Kubica J, Adamski P, et al. Stratified approaches to antiplatelet therapies based on platelet reactivity testing. Front Cardiovasc Med. 2019; 6: 176, doi: 10.3389/fcvm.2019.00176, indexed in Pubmed: 31850373.
20. Adamski P, Sikora J, Laskowska E, et al. Comparison of bioavailability and antiplatelet action of ticagrelor in patients with ST-elevation myocardial infarction and non-ST-elevation myocardial infarction: A prospective, observational, single-centre study. PLoS One. 2017; 12(10): e0186013, doi: 10.1371/journal.pone.0186013, indexed in Pubmed: 29023473.
21. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009; 361(11): 1045–1057, doi: 10.1056/NEJMoa0904327, indexed in Pubmed: 19717846.
22. Wiviott S, Braunwald E, McCabe C, et al. TRITON-TIMI 38 Investigators. Prasugrel versus copidogrel in patients with acute coronary syndromes. N Engl J Med. 2007; 357(20): 2001–2015, doi: 10.1056/nejmoa0706482, indexed in Pubmed: 17982182.
23. Bonaca MP, Bhatt DL, Cohen M, et al. PEGASUS-TIMI 54 Steering Committee and Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med. 2015; 372(19): 1791–1800, doi: 10.1056/NEJMoa1500857, indexed in Pubmed: 25773268.
24. Storey RF, Angiolillo DJ, Bonaca MP, et al. Platelet inhibition with ticagrelor 60 mg versus 90 mg twice daily in the PEGASUS-TIMI 54 trial. J Am Coll Cardiol. 2016; 67(10): 1145–1154, doi: 10.1016/j.jacc.2015.12.062, indexed in Pubmed: 26965534.
25. Bonaca MP, Bhatt DL, Oude Ophuis T, et al. Long-term tolerability of ticagrelor for the secondary prevention of major adverse cardiovascular events: a secondary analysis of the PEGASUS-TIMI 54 trial. JAMA Cardiol. 2016; 1(4): 425–432, doi: 10.1001/jamacardio.2016.1017, indexed in Pubmed: 27438319.
26. Kubica J, Adamski P, Buszko K, et al. Rationale and Design of the Effectiveness of LowEr maintenanCe dose of TicagRelor early After myocardial infarction (ELECTRA) pilot study. Eur Heart J Cardiovasc Pharmacother. 2018; 4(3): 152–157, doi: 10.1093/ehjcvp/pvx032, indexed in Pubmed: 29040445.
27. Kubica J, Adamski P, Buszko K, et al. Platelet inhibition with standard vs. lower maintenance dose of ticagrelor early after myocardial infarction (ELECTRA): a randomized, open-label, active-controlled pharmacodynamic and pharmacokinetic study. Eur Heart J Cardiovasc Pharmacother. 2019; 5(3): 139–148, doi: 10.1093/ehjcvp/pvz004, indexed in Pubmed: 30689800.
28. Mehran R, Baber U, Sharma S, et al. Ticagrelor with or without Aspirin in High-Risk Patients after PCI. N Engl J Med. 2019; 381(21): 2032–2042, doi: 10.1056/nejmoa1908419, indexed in Pubmed: 31556978.
29. Dangas G, Baber U, Sharma S, et al. Ticagrelor with or without aspirin after complex PCI: the TWILIGHT-COMPLEX analysis. J Am Coll Cardiol. 2020; 75(19): 2414–2424, doi: 10.1016/j.jacc.2020.03.011, indexed in Pubmed: 32240761.
30. Gelbenegger G, Schoergenhofer C, Jilma B, et al. Efficacy and safety of ticagrelor monotherapy in patients undergoing percutaneous coronary intervention: a meta-analysis. Clin Pharmacol Ther. 2021 [Epub ahead of print], doi: 10.1002/cpt.2226, indexed in Pubmed: 33668076.
31. Khan SU, Khan MZ, Khan MS, et al. De-escalation of antiplatelets after percutaneous coronary intervention: a bayesian network meta-analysis of various de-escalation strategies. Eur Heart J Cardiovasc Pharmacother. 2020 [Epub ahead of print], doi: 10.1093/ehjcvp/pvaa025, indexed in Pubmed: 32271872.
32. Pietrzykowski Ł, Kasprzak M, Michalski P, et al. Therapy discontinuation after myocardial infarction. J Clin Med. 2020; 9(12): 4109, doi: 10.3390/jcm9124109, indexed in Pubmed: 33352811.
33. Kołodziejczak M, Navarese E, Kubica J. Rationale and design of PREvalence of DyspneA in patients treated with TicagrelOR (PREDATOR) program. Med Res J. 2018, doi: 10.5603/mrj.a2018.0037.

34. Kubica A, Obońska K, Fabiszak T, et al. Adherence to antiplatelet treatment with P2Y12 receptor inhibitors. Is there anything we can do to improve it? A systematic review of randomized trials. Curr Med Res Opin. 2016; 32(8): 1441–1451, doi: 10.1080/03007995.2016.1182901, indexed in Pubmed: 27112628.
35. Kubica A, Kasprzak M, Obońska K, et al. Discrepancies in assessment of adherence to antiplatelet treatment after myocardial infarction. Pharmacology. 2015; 95(1-2): 50–58, doi: 10.1159/000371392, indexed in Pubmed: 25592409.
36. Kubica A. Self-reported questionnaires for a comprehensive assessment of patients after acute coronary syndrome. Med Res J. 2019; 4(2): 106–109, doi: 10.5603/mrj.a2019.0021.
37. Kosobucka A, Michalski P, Pietrzykowski Ł, et al. The impact of readiness to discharge from hospital on adherence to treatment in patients after myocardial infarction. Cardiol J. 2020 [Epub ahead of print], doi: 10.5603/CJ.a2020.0005, indexed in Pubmed: 32037501.
38. Kubica A, Kosobucka A, Fabiszak T, et al. Assessment of adherence to medication in patients after myocardial infarction treated with percutaneous coronary intervention. Is there a place for newself-reported questionnaires? Curr Med Res Opin. 2019; 35(2): 341–349, doi: 10.1080/03007995.2018.1510385, indexed in Pubmed: 30091642.
39. Kosobucka A, Michalski P, Pietrzykowski Ł, et al. Adherence to treatment assessed with the Adherence in Chronic Diseases Scale in patients after myocardial infarction. Patient Prefer Adherence. 2018; 12: 333–340, doi: 10.2147/PPA.S150435, indexed in Pubmed: 29551891.
40. Pietrzykowski Ł, Michalski P, Kosobucka A, et al. Medication adherence and its determinants in patients after myocardial infarction. Sci Rep. 2020; 10(1): 12028, doi: 10.1038/s41598-020-68915-1, indexed in Pubmed: 32694522.
41. Kosobucka A, Pietrzykowski Ł, Michalski P, et al. Impact of readiness for discharge from the hospital on the implementation of the therapeutic plan. Med Res J. 2020; 5(4): 256–264, doi: 10.5603/mrj.a2020.0047.
42. Michalski P, Kasprzak M, Siedlaczek M, et al. The impact of knowledge and effectiveness of educational intervention on readiness for hospital discharge and adherence to therapeutic recommendations in patients with acute coronary syndrome. Med Res J. 2020, doi: 10.5603/mrj.a2020.0023.
43. Kubica A, Kosobucka A, Michalski P, et al. Self-reported questionnaires for assessment adherence to treatment in patients with cardiovascular diseases. Med Res J. 2018; 2(4): 115–122, doi: 10.5603/mrj.2017.0015.
44. Kubica A, Gruchała M, Jaguszewski M, et al. Adherence to treatment — a pivotal issue in long-term treatment of patients with cardiovascular diseases. An expert standpoint. Med Res J. 2018; 2(4): 123–127, doi: 10.5603/mrj.2017.0016.
45. Buszko K, Pietrzykowski Ł, Michalski P, et al. Validation of the Functioning in Chronic Illness Scale (FCIS). Med Res J. 2018; 3(2): 63–69, doi: 10.5603/mrj.2018.0011.
46. Pietrzykowski Ł, Michalski P, Kosobucka A, et al. Knowledge about health and disease in obese patients after myocardial infarction. An observational study. Med Res J. 2018; 2(4): 135–140, doi: 10.5603/mrj.2017.0018.
47. Buszko K, Kosobucka A, Michalski P, et al. The readiness for hospital discharge of patients after acute myocardial infarction: a new self-reported questionnaire. Med Res J. 2017; 2(1): 20–28, doi: 10.5603/mrj.2017.0004.
48. Kubica A, Adamski P, Bączkowska A, et al. The rationale for Multilevel Educational and Motivational Intervention in Patients after Myocardial Infarction (MEDMOTION) project is to support multicentre randomized clinical trial Evaluating Safety and Efficacy of Two Ticagrelor-based De-escalation Antiplatelet Strategies in Acute Coronary Syndrome (ELECTRA-SIRIO 2). Med Res J. 2020; 5(4): 244–249, doi: 10.5603/mrj.a2020.0043.

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Provisional drug-coated balloon treatment guided by physiology on de novo coronary lesion

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Abstract

Although drug-eluting stents (DES) have become the mainstay of percutaneous coronary intervention, late and very late stent thrombosis remains a concern. Drug-coated balloons (DCB) have the advantage of preserving the anti-restenotic benefits of DES while minimizing potential long-term safety concerns. Currently the two methods to ensure successful DCB treatment of a stenotic lesion are angiography or physiology-guided DCB application. This review will evaluate these two methods based on previous evidence and make suggestions on how to perform DCB treatment more efficiently and safely. (Cardiol J 2021; 28, 4: 615–622)

Key words: drug-coated balloon, coronary artery disease, physiology, fractional flow reserve, diameter stenosis, de novo lesion

Introduction

The successful restoration of coronary flow is the goal of percutaneous coronary intervention (PCI) for obstructive coronary artery disease. Due to the limitations of accurately measuring blood flow in clinical practice, anatomical assessment using diameter stenosis (DS) or minimal lumen diameter by coronary angiography has been used to guide the procedure. However, coronary angiography alone is inherently limited by its inability to provide information pertaining to the functional significance of stenoses. Fractional flow reserve (FFR) was developed as a technique to enable physiological assessment of coronary lesions. FFR expresses the maximum achievable blood flow to the myocardium supplied by a stenotic artery as a fraction of normal maximum flow. As such, it provides an objective measure of the hemodynamic significance of an epicardial stenosis and FFR-guided PCI is associated with a better prognosis than angiography-guided PCI [1].

Drug-coated balloons (DCB) provide local drug delivery after successful balloon angioplasty

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(BA) to inhibit restenosis, however concerns over acute vessel closure, have hampered their use for de novo lesions. During the BA era, Bech et al. [2] demonstrated that patients with a residual DS of ≤ 35% and an FFR value after BA of ≥ 0.90 had excellent clinical outcomes to 2-years. Further, in a previous study, it was demonstrated that DCB treatment after successful BA with a resultant FFR value ≥ 0.75 was safe and effective, without the additional risk of acute vessel closure [3].

One of the advantages using a DCB over drug-eluting stent (DES) is the short duration of dual antiplatelet therapy (DAPT) especially in patients with high risk of bleeding, and in those with contraindications to long term DAPT, since they require only 1 month of DAPT. Although the latest data from the Onyx ONE and EVOVE Short DAPT studies demonstrated that 1 to 3 months of DAPT is noninferior to the standard 12-month DAPT in terms of the risk of stent thrombosis [4, 5], neoatherosclerosis with DES is inevitable over time, and this is known to progress faster than de novo lesions, resulting in stent failure manifesting as restenosis and thrombosis [6]. Nevertheless, unlike the BA era, there are now two available options — DCB and DES — for the local delivery of antiproliferative drugs allowing patients to receive different treatment options. There have been many efforts to examine the pros and cons of DCB compared to DES, and an indication standard for DCB treatment is expected in the near future. This review discusses a safe and effective method for the use of DCBs in the treatment of obstructive coronary artery disease.

Optimal lesion preparation for DCB application

The use of DCBs has been proven to be very effective for in-stent restenosis (ISR) and is recommended by European, German, and Asia-Pacific consensus groups [7–9]. Although DCB treatment is a reasonable option for ISR, recurrent target lesion failure (TLF) still occurs in some patients after treatment. Optimal lesion preparation for ISR plays an important role in reducing adverse clinical outcomes after DCB treatment. The RIBS IV study investigated the treatment of patients with DES-ISR, and showed that re-stenting with a DES reduced the 1-year composite outcome of cardiac death, myocardial infarction (MI), and target vessel revascularization (TVR) compared with using a DCB (10% vs. 18%; hazard ratio [HR]: 0.58; 95% confidence interval [CI]: 0.35–0.98; p = 0.04). However, this benefit was driven in part due to sub-optimal lesion preparation and inadequate flow after balloon angioplasty in the DCB arm [10]. Another recent study showed that modifiable independent predictors of recurrent TLF were residual DS after lesion preparation, DCB-to-stent ratio, and DCB inflation time [11]. In their study, TLF occurred in 20.3% and the best cutoff values were 20%, 0.91, and 60 s for residual DS, DCB-to-stent ratio, and DCB inflation time, respectively. TLF rates were significantly higher in groups with residual DS ≥ 20% (34.7% vs. 12.5%; HR: 2.15; 95% CI: 1.86–2.48; p < 0.001), DCB-to-stent ratio ≤ 0.91 (46.4% vs. 21.9%; HR: 2.02; 95% CI: 1.75–2.34; p < 0.001), and inflation time ≤ 60 s (26.2% vs. 14.0%; HR: 1.82; 95% CI: 1.36–2.45; p < 0.001). When classifying ISR lesions by combination of three procedure-related factors, TLF occurred in 8.3% in the fully optimized procedure group and 66.7% in the non-optimized group (p < 0.001), demonstrating clearly that fully optimized DCB treatment with ideal lesion preparation, sufficient dilatation, and prolonged inflation could reduce TLF. Appropriate lesion preparation can create an environment that allows homogeneous drug delivery to the lesion efficiently and thus, has a significant impact on the efficacy and safety of DCB treatment.

There is no evidence of criteria for optimal lesion preparation for de novo coronary artery lesions. In ISR as well as in de novo lesions, conventional lesion preparation is performed using a non- or semi-compliant balloon. In complex lesions, however, the use of high-pressure non-compliant balloons or scoring/cutting balloons should be considered to provide better lesion preparation. The shortcomings of conventional balloon angioplasty include balloon slippage and edge dissections, post procedure, and these problems could be reduced with the use of a scoring balloon, which may also allow enhanced local drug uptake.

In an early intravascular ultrasound evaluation study comparing cutting balloons with conventional balloons for the treatment of ISR, the luminal area acute gain was larger in the cutting balloon group due to more effective tissue extrusion, while late loss was smaller [12]. Cutting or scoring the neointimal plaque lessens the elastic and fibrotic continuity of the internal fibrous layer and makes the tissue more amenable to being pushed outward through the stent struts. In the ISAR-DESIRE 4 study, neointimal modification with scoring balloon before DCB was compared with standard DCB therapy in patients with ISR [13]. Pre-dilatation with a scoring balloon resulted in a significantly lower

rate of in-segment percentage DS (35.0 ± 16.8% vs. 40.4 ± 21.4%, p = 0.047) and binary angiographic restenosis rate (18.5% vs. 32.0%, p = 0.026) at 6–8 month follow-up. The results demonstrated that the use of a scoring balloon improves the complete expansion of a re-stenosed stent, neointimal modification, and homogeneous drug delivery and hence, increases the anti-restenotic efficacy of DCB treatment.

ST-segment elevation myocardial infarction (STEMI) is the most representative disease of atherothrombotic lesions. In STEMI patients, stent implantation reduces target lesion revascularization (TLR), however, it tends to increase the long-term risk of stent-related events such as stent thrombosis and ISR [14–16]. In the majority of STEMI patients, rapid restoration of coronary flow is the main purpose of treatment, and this can be achieved by a combined approach of pharmacologic and interventional treatments without stenting. Thrombus aspiration is an adjunctive non-pharmacological strategy during primary PCI designed to improve epicardial and myocardial reperfusion. However, recent studies failed to show the clinical benefit of aspiration thrombectomy in STEMI patients due to insufficient removal of thrombus at the culprit lesion [17–19].

Stenting has been shown to reduce the need for TVR in acute MI, however, this was not associated with a significant reduction in mortality or reinfarction compared with BA [20]. To avoid the long-term risk of stent-related events in STEMI patients, a DCB strategy in primary PCI could be a safe and feasible alternative strategy to DES treatment if coronary flow is restored and no significant residual stenosis persists after balloon dilatation or thrombo-suction. Before using a DCB, successful thrombus aspiration is important and has beneficial effects considering that adequate lesion preparation helps facilitate homogeneous drug delivery. In the REVELATION study, a DCB strategy was noninferior to DES in STEMI patients in terms of FFR assessed at 9 months (0.92 ± 0.05 vs. 0.91 ± ± 0.06, p = 0.27), and during follow-up, only 2 patients received a non-urgent TLR (1 in each group) [21]. One option in STEMI patients where coronary flow is restored and no significant residual stenosis is observed after balloon pre-dilatation, is medical treatment with an anticoagulant and antiplatelet agent without any further immediate intervention, followed by a repeat coronary angiogram after 1–2 weeks to decide whether to use a DCB or DES. The high risk of restenosis and stent thrombosis in patients with a chronic total occlusion (CTO) is still a major problem. In the PEPCAD-CTO study, the use of DCB plus BMS was associated with similar clinical results and a non-significantly higher in-stent late loss compared with DES [22]. The DCB only approach studies for CTO cases are scarce but recent registry data has suggested it was a feasible and well-tolerated treatment method if the pre-dilatation result is good [23]. In their feasibility and safety study, the incidence of angiographic restenosis was 11.8% at mean 8-month follow-up, which were similar or lower than prior CTO studies using either DES or BMS. Furthermore, late lumen gain was found in 67.6% of patients and was caused by an increase in vessel size rather than plaque regression.

When a DES is used after successful recanalization of a CTO, the stent may be undersized because the lesion was occluded, and the vessel did not grow soon after reperfusion. CTO lesions have negative remodeled distal vessels because they have not had any flow for a long time. After BA, antegrade flow increases and vessels become larger, however this may take from several weeks to months. Therefore, immediately after balloon angioplasty of a CTO, it is easy to under-estimate the true vessel size, increasing the risk of stent under-sizing and subsequent risks of restenosis, late stent mal-apposition and stent thrombosis. Moreover, the metallic cage can inhibit positive remodeling leaving a small luminal size after vessel recovery. However, after treatment with a DCB, it is possible that vessels will return to their original size over time, which is one of the greatest advantages of DCB treatment in CTO lesions. Furthermore, in cases of DCB only treatment, the presence of heavy calcification could support the vessel as a DES does, and could give the vessel a chance to grow and heal. However, larger, randomized controlled trials are necessary to further evaluate the DCB-only approach for CTO lesions.

Provisional strategy guided by physiology

According to the German Consensus Group, lesion characteristics determined by angiography after BA can identify acceptable lesion preparation by assessing for the absence of a flow-limiting dissection and a non-significant residual DS ≤ 30% [8]. Angiographically significant parameters after BA are residual DS > 30% or dissection type C or more. Recently it was demonstrated that DCB treatment could be performed safely and effectively after successful BA (Thrombolysis In Myocardial Infarction [TIMI] flow grade 3 after BA) with an FFR value ≥ 0.75, without any increased risk of

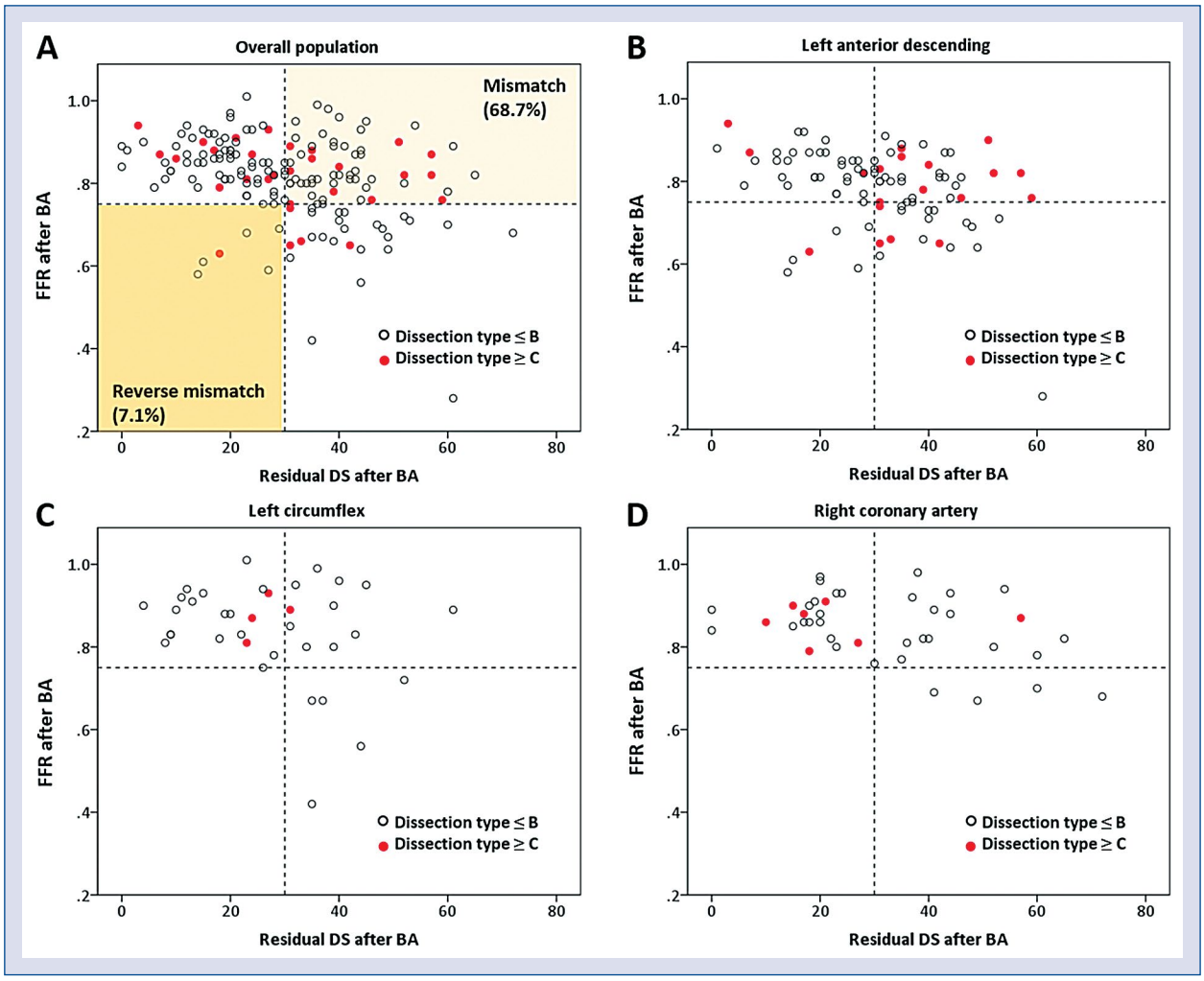

Figure 1. Correlation between fractional flow reserve (FFR) after balloon angioplasty (BA) and residual diameter stenosis (DS); **A.** Overall population; **B.** Left anterior descending artery; **C.** Left circumflex artery; **D.** Right coronary artery. Reused with permission from: [1].

acute vessel closure and a lower rate of restenosis. Of note, a high frequency of non-concordance was found between angiographic and functional characteristics when using an FFR after BA cutoff of 0.75 to define functionally significant lesions [1]. The results showed a mismatch of 68.7% (residual DS > 30% and FFR after BA ≥ 0.75) with a reverse mismatch (residual DS ≤ 30% and FFR after BA < 0.75) in 7.1% (Fig. 1A). If these mismatch lesions were treated solely using angiography, as recommended by the German consensus group, all of them should be treated with stent implantation, since the residual DS was above 30%, even though the post-balloon FFR was > 0.75. Previous mid- and long-term follow-up studies in patients with an FFR after BA ≥ 0.75 showed comparable clinical outcomes between DCB and stent treatments [1, 3, 24]. Therefore, FFR-guided DCB treatment could safely reduce the number of unnecessary stent implantations in this mismatch population. In the reverse mismatch population, the guidelines suggest using a DCB over a stent, since the residual DS was ≤ 30%. If the guidelines are followed, only severe dissections (type C dissection) should be treated with a stent, whilst the rest of them could receive DCB treatment (6.0% of DS ≤ 30%) [1]. It is well known that in patients with functionally significant stenoses, FFR-guided PCI decreases the need of urgent revascularization compared with medical therapy alone [25]. Thus, these reverse mismatch lesions pose a higher clinical risk of future events and it is appropriate for them to be treated with stent implantation.

In the left anterior descending artery (LAD) the majority of lesions with severe dissection had an FFR after BA of ≥ 0.75 which was independent

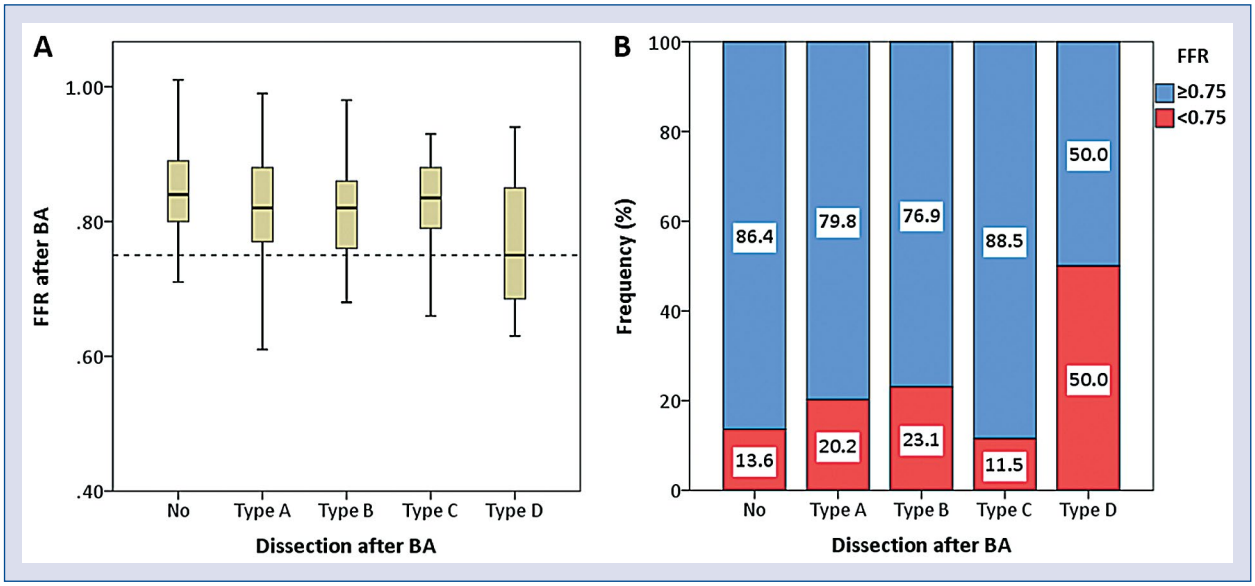

Figure 2. Fractional flow reserve (FFR) after balloon angioplasty (BA) according to dissection type; **A.** Distribution of FFR; **B.** Proportion of high and low FFR groups. Modified with permission from: [1].

of the severity of the dissection (Fig. 1B). Of note, all severe dissections in non-LAD lesions had an FFR after BA ≥ 0.75 (Fig. 1C, D). The dissection type after BA does not correlate with residual FFR as seen in Figure 2. Thus, FFR after BA measurements in LAD lesions could be recommended not just to reduce the number of stents in mismatch lesions, but also to prevent future adverse clinical events in reverse mismatch lesions, while lesions in the circumflex and right coronary artery could be safely treated with angiography alone. FFR-guided DCB treatment has several advantages compared to angiography-guided DCB application. A recent recommendation from an Asia-Pacific consensus group reported both angiographic and functional criteria for large de novo coronary lesions [9].

The provisional strategy guided by physiology for de novo lesions are summarized in Figure 3. The first step for successful DCB treatment is to achieve optimal lesion preparation by pre-dilation balloon (non-compliant or scoring/cutting balloons) or a non-balloon device like atherectomy or rotablator. A balloon to artery ratio of 0.8 to 1.0 and an inflation pressure higher than nominal should be used. Thrombus aspiration for patients with STEMI should be performed in appropriate situations. The acceptable angiographic and functional criteria after BA to perform DCB treatment are TIMI grade 3 flow and FFR ≥ 0.75. In this FFR-guided DCB strategy, if the FFR after BA is ≥ 0.75, DCB treatment can be performed

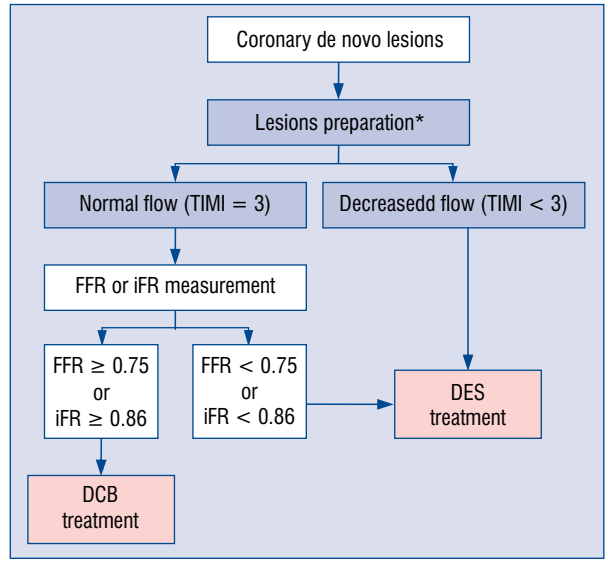

Figure 3. Provisional drug-coated balloon (DCB) strategy guided by fractional flow reserve (FFR). The acceptable angiographic and functional criteria after balloon angioplasty to perform DCB treatment are Thrombolysis In Myocardial Infarction (TIMI) 3 grade flow and FFR ≥ 0.75; iFR — instantaneous wave-free ratio; DES — drug-eluting stent. *Lesion preparation by optimal sized balloon (balloon-to-vessel ratio 0.8–1.0) or non-balloon catheters.

safely [3, 24]. The provisional DCB treatment guided by physiology aims to provide safer DCB treatment based on physiology according to all

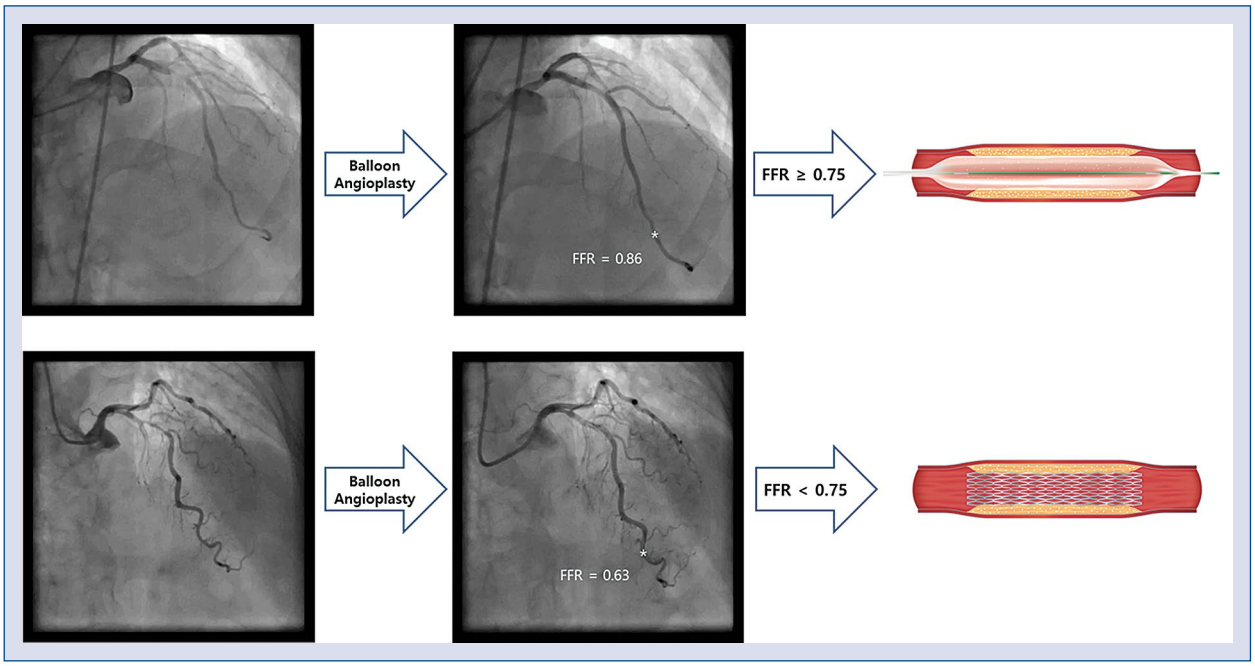

Figure 4. Representative cases for provisional drug-coated balloon strategy guided by fractional flow reserve (FFR).

anatomical changes like dissection presence or severity, and residual stenosis occurring after BA. In a previous study comparing angiography to FFR--guided DCB treatment for 167 lesions, there was a mismatch in 68.7% (57 of 83) of the population and a reverse mismatch in 7.1% (6 of 84) [1]. If an angiography-guided strategy was used, 57.5% (96 of 167) would need treatment with a DES, whilst using an FFR-guided strategy only 19.2% (32 of 167) need a DES; this 66.7% reduction in stent usage occurred without increasing safety concerns. Lesions in the reverse mismatch population pose a higher clinical risk of future events however whilst the angio-guided approach recommends treating with a DCB since the residual DS is < 30%, the FFR-guided approach recommends treating with a DES since the residual FFR is < 0.75 and hence, it could prevent possible future events.

Recently, it was demonstrated that instantaneous wave-free ratio (iFR), an alternative measure that does not require the administration of adenosine, measured right after BA is safe and effective for de novo coronary lesions [26]. The cutoff value of iFR right after BA used to define functionally nonsignificant residual stenotic lesions was 0.86 that iFR-guided paclitaxel-coated balloon treatment is safe and effective for de novo major epicardial coronary lesions with good anatomical patency at 9-month follow-up and showed good long-term clinical outcomes in patients with iFR ≥ 0.86 after BA. As alternative methods to FFR or iFR, functional coronary imaging, quantitative flow ratio, have recently emerged, allowing wire--free functional assessment of stenosis severity based on a computational fluid dynamics model or mathematical assumptions of coronary flow. Although previous studies have demonstrated excellent correlations and diagnostic agreements with FFR [27, 28], an evaluation of the diagnostic performance and agreement of QFR using FFR or iFR as reference standards in the situation of BA is needed (Figs. 3, 4).

Medical treatment

Easy to heal and the lower risk of target lesion thrombosis in lesions treated with a DCB makes prolonged DAPT therapy unnecessary. The European Society of Cardiology guideline recommends 6 months of DAPT treatment, however, shorter durations of 1–3 months after DCB have not been associated with any increased risk of long-term adverse outcomes compared with BMS or DES [7]. Looking at the previous data, when 1st generation DES was used, stent thrombosis occurred 0.6% per year [29], and 2nd generation stent occurred 0.3% of stent thrombosis per year [30]. In the BASKET--SMALL 2 study for small de novo lesions

(n = 758 patients), DCB was non-inferior to DES for major adverse cardiovascular events (cardiac death, non-fatal MI, and target vessel revascularization) for up to 12 months (7.5% vs. 7.3%; HR 0.97 [95% CI 0.58–1.64], p = 0.918) [31]. The thrombosis rate (probable or definite) in DCB treated lesions was numerically lower than DES (0.8% vs. 1.1%; HR 0.73 [0.16–3.26]) despite DAPT being continued for only 1 month in the DCB arm and 6–12 months in the DES arm. Major bleeding in DCB arm was also numerically lower than the DES arm (1.1% vs. 2.4%; HR 0.45 [0.14–1.46]).

High-intensity statin therapy may provide incremental clinical benefits after DCB application. It is well known that statin treatment causes plaque regression and improves clinical outcomes when used for either primary or secondary prevention. BA creates iatrogenic plaque dissection and causes plaque redistribution, and DCB provides local drug delivery to prevent restenosis. After DCB treatment, cholesterol-lowering drugs may cause greater plaque regression compared to statin only treatment without PCI. Regarding the effects of statin therapy, a previous study demonstrated that a clear reduction of lipid core was only observed in thin-cap fibroatheromas, suggesting that changes in plaque composition following statin therapy might occur earlier and to a greater degree in vulnerable plaque compared to stable plaque [32]. Another study showed that DCB treatment with high dose statins caused persistent patency with plaque redistribution without chronic elastic recoil and restored coronary blood flow resulting in increased lumen areas at follow-up [33]. These results suggest that there will be regression of plaque after DCB treatment through high dose statin therapy. Therefore, high intensity statin therapy can reinforce the efficacy of DCB treatment.

Conclusions

For successful DCB treatment, optimal lesion preparation using optimally sized scoring balloons is essential. Ideal lesion preparation should be assessed by measuring flow status using physiological indexes such as FFR rather than by estimating stenotic severity from angiography alone. Although not all coronary lesions require FFR measurement, if the lesion subtends a large amount of myocardium such as lesions in the proximal LAD, they should be assessed with FFR. The physiology-guided provisional strategy suggests that DCB treatment should only be performed if adequate coronary flow is obtained after optimal balloon angioplasty, with newer generation DES used in cases of inadequate flow. For successful DCB treatment, there is a need for better technology that can make plaque modifications safe and effective. In addition, the importance of medical treatment to maximize the effect of DCB (anti-thrombotics and cholesterol-lowering drugs) cannot be overemphasized.

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References

1. Chung JH, Lee KE, Her AY, et al. Comparison of fractional flow reserve and angiographic characteristics after balloon angioplasty in de novo coronary lesions. Int J Cardiovasc Imaging. 2019; 35(11): 1945–1954, doi: 10.1007/s10554-019-01649-y, indexed in Pubmed: 31214851.
2. Bech GJ, Pijls NH, De Bruyne B, et al. Usefulness of fractional flow reserve to predict clinical outcome after balloon angioplasty. Circulation. 1999; 99(7): 883–888, doi: 10.1161/01.cir.99.7.883, indexed in Pubmed: 10027810.
3. Her AY, Shin ES, Lee JM, et al. Paclitaxel-coated balloon treatment for functionally nonsignificant residual coronary lesions after balloon angioplasty. Int J Cardiovasc Imaging. 2018; 34(9): 1339–1347, doi: 10.1007/s10554-018-1351-z, indexed in Pubmed: 29696453.
4. Kedhi E, Latib A, Abizaid A, et al. Rationale and design of the Onyx ONE global randomized trial: A randomized controlled trial of high-bleeding risk patients after stent placement with 1 month of dual antiplatelet therapy. Am Heart J. 2019; 214: 134–141, doi: 10.1016/j.ahj.2019.04.017, indexed in Pubmed: 31203158.
5. Mauri L, Kirtane AJ, Windecker S, et al. Rationale and design of the EVOLVE Short DAPT Study to assess 3-month dual antiplatelet therapy in subjects at high risk for bleeding undergoing percutaneous coronary intervention. Am Heart J. 2018; 205: 110–117, doi: 10.1016/j.ahj.2018.08.004, indexed in Pubmed: 30218844.
6. Yahagi K, Kolodgie FD, Otsuka F, et al. Pathophysiology of native coronary, vein graft, and in-stent atherosclerosis. Nat Rev Cardiol. 2016; 13(2): 79–98, doi: 10.1038/nrcardio.2015.164, indexed in Pubmed: 26503410.
7. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019; 40(2): 87–165, doi: 10.1093/eurheartj/ehy394, indexed in Pubmed: 30165437.
8. Kleber FX, Rittger H, Bonaventura K, et al. Drug-coated balloons for treatment of coronary artery disease: updated recommendations from a consensus group. Clin Res Cardiol. 2013; 102(11): 785–797, doi: 10.1007/s00392-013-0609-7, indexed in Pubmed: 23982467.
9. Her AY, Shin ES, Bang LH, et al. Drug-coated balloon treatment in coronary artery disease: Recommendations from an Asia-Pacific Consensus Group. Cardiol J. 2021; 28(1): 136–149, doi: 10.5603/CJ.a2019.0093, indexed in Pubmed: 31565793.

10. Alfonso F, Pérez-Vizcayno MJ, Cárdenas A, et al. A Prospective Randomized Trial of Drug-Eluting Balloons Versus Everolimus-Eluting Stents in Patients With In-Stent Restenosis of Drug-Eluting Stents: The RIBS IV Randomized Clinical Trial. J Am Coll Cardiol. 2015; 66(1): 23–33, doi: 10.1016/j.jacc.2015.04.063, indexed in Pubmed: 26139054.
11. Rhee TM, Lee JM, Shin ES, et al. Impact of optimized procedure-related factors in drug-eluting balloon angioplasty for treatment of in-stent restenosis. JACC Cardiovasc Interv. 2018; 11(10): 969–978, doi: 10.1016/j.jcin.2018.02.002, indexed in Pubmed: 29798774.
12. Muramatsu T, Tsukahara R, Ho M, et al. Efficacy of cutting balloon angioplasty for in-stent restenosis: an intravascular ultrasound evaluation. J Invasive Cardiol. 2001; 13(6): 439–444, indexed in Pubmed: 11385165.
13. Kufner S, Joner M, Schneider S, et al. ISAR-DESIRE 4 Investigators. Neointimal Modification With Scoring Balloon and Efficacy of Drug-Coated Balloon Therapy in Patients With Restenosis in Drug-Eluting Coronary Stents: A Randomized Controlled Trial. JACC Cardiovasc Interv. 2017; 10(13): 1332–1340, doi: 10.1016/j.jcin.2017.04.024, indexed in Pubmed: 28683939.
14. Gonzalo N, Barlis P, Serruys PW, et al. Incomplete stent apposition and delayed tissue coverage are more frequent in drug-eluting stents implanted during primary percutaneous coronary intervention for ST-segment elevation myocardial infarction than in drug-eluting stents implanted for stable/unstable angina: insights from optical coherence tomography. JACC Cardiovasc Interv. 2009; 2(5): 445–452, doi: 10.1016/j.jcin.2009.01.012, indexed in Pubmed: 19463469.
15. Nakazawa G, Finn AV, Joner M, et al. Delayed arterial healing and increased late stent thrombosis at culprit sites after drug-eluting stent placement for acute myocardial infarction patients: an autopsy study. Circulation. 2008; 118(11): 1138–1145, doi: 10.1161/CIRCULATIONAHA.107.762047, indexed in Pubmed: 18725485.
16. Stone SG, Serrao GW, Mehran R, et al. Incidence, predictors, and implications of reinfarction after primary percutaneous coronary intervention in ST-segment-elevation myocardial infarction: the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction Trial. Circ Cardiovasc Interv. 2014; 7(4): 543–551, doi: 10.1161/CIRCINTERVENTIONS.114.001360, indexed in Pubmed: 24939928.
17. Fröbert O, Lagerqvist Bo, Olivecrona GK, et al. TASTE Trial. Thrombus aspiration during ST-segment elevation myocardial infarction. N Engl J Med. 2013; 369(17): 1587–1597, doi: 10.1056/NEJMoa1308789, indexed in Pubmed: 23991656.
18. Higuma T, Soeda T, Yamada M, et al. Does residual thrombus after aspiration thrombectomy affect the outcome of primary PCI in patients with ST-segment elevation myocardial infarction? An optical coherence tomography study. JACC Cardiovasc Interv. 2016; 9(19): 2002–2011, doi: 10.1016/j.jcin.2016.06.050, indexed in Pubmed: 27712735.
19. Jolly SS, Cairns JA, Yusuf S, et al. TOTAL Investigators. Randomized trial of primary PCI with or without routine manual thrombectomy. N Engl J Med. 2015; 372(15): 1389–1398, doi: 10.1056/NEJMoa1415098, indexed in Pubmed: 25853743.
20. De Luca G, Suryapranata H, Stone GW, et al. Coronary stenting versus balloon angioplasty for acute myocardial infarction: a meta-regression analysis of randomized trials. Int J Cardiol. 2008; 126(1): 37–44, doi: 10.1016/j.ijcard.2007.03.112, indexed in Pubmed: 17544528.
21. Vos NS, Fagel ND, Amoroso G, et al. Paclitaxel-Coated balloon angioplasty versus drug-eluting stent in acute myocardial infarction: the REVELATION randomized trial. JACC Cardiovasc Interv. 2019; 12(17): 1691–1699, doi: 10.1016/j.jcin.2019.04.016, indexed in Pubmed: 31126887.
22. Wöhrle J, Werner GS. Paclitaxel-coated balloon with bare-metal stenting in patients with chronic total occlusions in native coronary arteries. Catheter Cardiovasc Interv. 2013; 81(5): 793–799, doi: 10.1002/ccd.24409, indexed in Pubmed: 22511572.
23. Köln PJ, Scheller B, Liew HB, et al. Treatment of chronic total occlusions in native coronary arteries by drug-coated balloons without stenting - A feasibility and safety study. Int J Cardiol. 2016; 225: 262–267, doi: 10.1016/j.ijcard.2016.09.105, indexed in Pubmed: 27741486.
24. Shin ES, Ann SH, Balbir Singh G, et al. Fractional flow reserve-guided paclitaxel-coated balloon treatment for de novo coronary lesions. Catheter Cardiovasc Interv. 2016; 88(2): 193–200, doi: 10.1002/ccd.26257, indexed in Pubmed: 26423017.
25. De Bruyne B, Pijls NHJ, Kalesan B, et al. FAME 2 Trial Investigators. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med. 2012; 367(11): 991–1001, doi: 10.1056/NEJMoa1205361, indexed in Pubmed: 22924638.
26. Chung JH, Shin ES, Her AY, et al. Instantaneous wave-free ratio-guided paclitaxel-coated balloon treatment for de novo coronary lesions. Int J Cardiovasc Imaging. 2020; 36(2): 179–185, doi: 10.1007/s10554-019-01707-5, indexed in Pubmed: 31598811.
27. Collet C, Onuma Y, Sonck J, et al. Diagnostic performance of angiography-derived fractional flow reserve: a systematic review and Bayesian meta-analysis. Eur Heart J. 2018; 39(35): 3314–3321, doi: 10.1093/eurheartj/ehy445, indexed in Pubmed: 30137305.
28. Xu Bo, Tu S, Qiao S, et al. Diagnostic accuracy of angiography-based quantitative flow ratio measurements for online assessment of coronary stenosis. J Am Coll Cardiol. 2017; 70(25): 3077–3087, doi: 10.1016/j.jacc.2017.10.035, indexed in Pubmed: 29101020.
29. Daemen J, Wenaweser P, Tsuchida K, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. Lancet. 2007; 369(9562): 667–678, doi: 10.1016/S0140-6736(07)60314-6, indexed in Pubmed: 17321312.
30. von Birgelen C, van der Heijden LC, Basalus MWZ, et al. Five-Year outcome after implantation of zotarolimus- and everolimus-eluting stents in randomized trial participants and nonenrolled eligible patients: a secondary analysis of a randomized clinical trial. JAMA Cardiol. 2017; 2(3): 268–276, doi: 10.1001/jamacardio.2016.5190, indexed in Pubmed: 28114618.
31. Jeger RV, Farah A, Ohlow MA, et al. BASKET-SMALL 2 Investigators. Drug-coated balloons for small coronary artery disease (BASKET-SMALL 2): an open-label randomised non-inferiority trial. Lancet. 2018; 392(10150): 849–856, doi: 10.1016/S0140-6736(18)31719-7, indexed in Pubmed: 30170854.
32. Hwang DS, Shin ES, Kim SJ, et al. Early differential changes in coronary plaque composition according to plaque stability following statin initiation in acute coronary syndrome: classification and analysis by intravascular ultrasound-virtual histology. Yonsei Med J. 2013; 54(2): 336–344, doi: 10.3349/ymj.2013.54.2.336, indexed in Pubmed: 23364965.
33. Ann SH, Balbir Singh G, Lim KH, et al. Anatomical and Physiological Changes after Paclitaxel-Coated Balloon for Atherosclerotic De Novo Coronary Lesions: Serial IVUS-VH and FFR Study. PLoS One. 2016; 11(1): e0147057, doi: 10.1371/journal.pone.0147057, indexed in Pubmed: 26824602.

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RESEARCH LETTER

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Three-dimensional reconstruction of conventional catheter angiography-identified coronary artery aneurysms and ectasias

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Coronary artery aneurysms and ectasias (CAAE) occur in the course of atherosclerotic or connective tissue/inflammatory disease [1]. Focal dilations ≥ 1.5 times greater than the adjacent segments' reference diameter (RD) are typically described as an 'aneurysms' (example in Fig. 1A, B), whereas the term 'ectasia' is usually used for diffuse and long-segmental dilations [2].

Coronary artery aneurysms and ectasias are mostly incidental findings of conventional coronary artery angiography (CAG, 1.2–4.9%) [1]. Some CAAEs occur in relation to coronary stenosis [1]. CAEAs disturb coronary flow and may enhance thrombus formation, serving as a culprit for acute myocardial infarction and sudden cardiac death [1, 3]. Furthermore, CAAE progressive enlargement may result in its rupture and cardiac tamponade [1]. A significant diagnostic and clinical problem of CAAE [1] starts with the present lack of a standardized definition; an issue largely related to limitations of CAAE characterization using CAG planar images [2]. Indeed, conventional (catheter) CAG characterization of CAAEs may be prone to significant errors [2, 4].

In a series of consecutive CAGs in our database [5], we evaluated the feasibility of routine three-dimensional (3D) CAAE characterizations using a commercially available 3D image angiographic reconstruction system (CAAS Workstation 7.4, Pie Medical Imaging, The Netherlands). The system is semi-automated; it involves identification of the region of interest and delineation of CAAE and reference segments [4]. To enable 3D reconstruction (3DR), the software requires calibration and planar image characteristics including rotation and angulation details [6]. Specifically, a 'green-zone' for 3DR feasibility needs to be established, with the two planes having a difference of at least 30 degrees as a fundamental requirement [6].

Beyond routine CAAE characteristics such as the feeding vessel RD, CAAE mean diameter, maximal diameter and length, several new parameters were evaluated such as the length of CAAE segment, with dilation exceeding the RD > 1.0-fold, > 1.5-fold, and > 2.0-fold. Measurements were performed with the agreement of two angiographic Corelab analysts.

Out of 20 consecutive CAAE angiograms in the sample, 15 (75%) were suitable for 3DR as per the software-demanded parameters. The reasons for 3DR unsuitability were as follows: lack of the software 'green-zone' for any of the available

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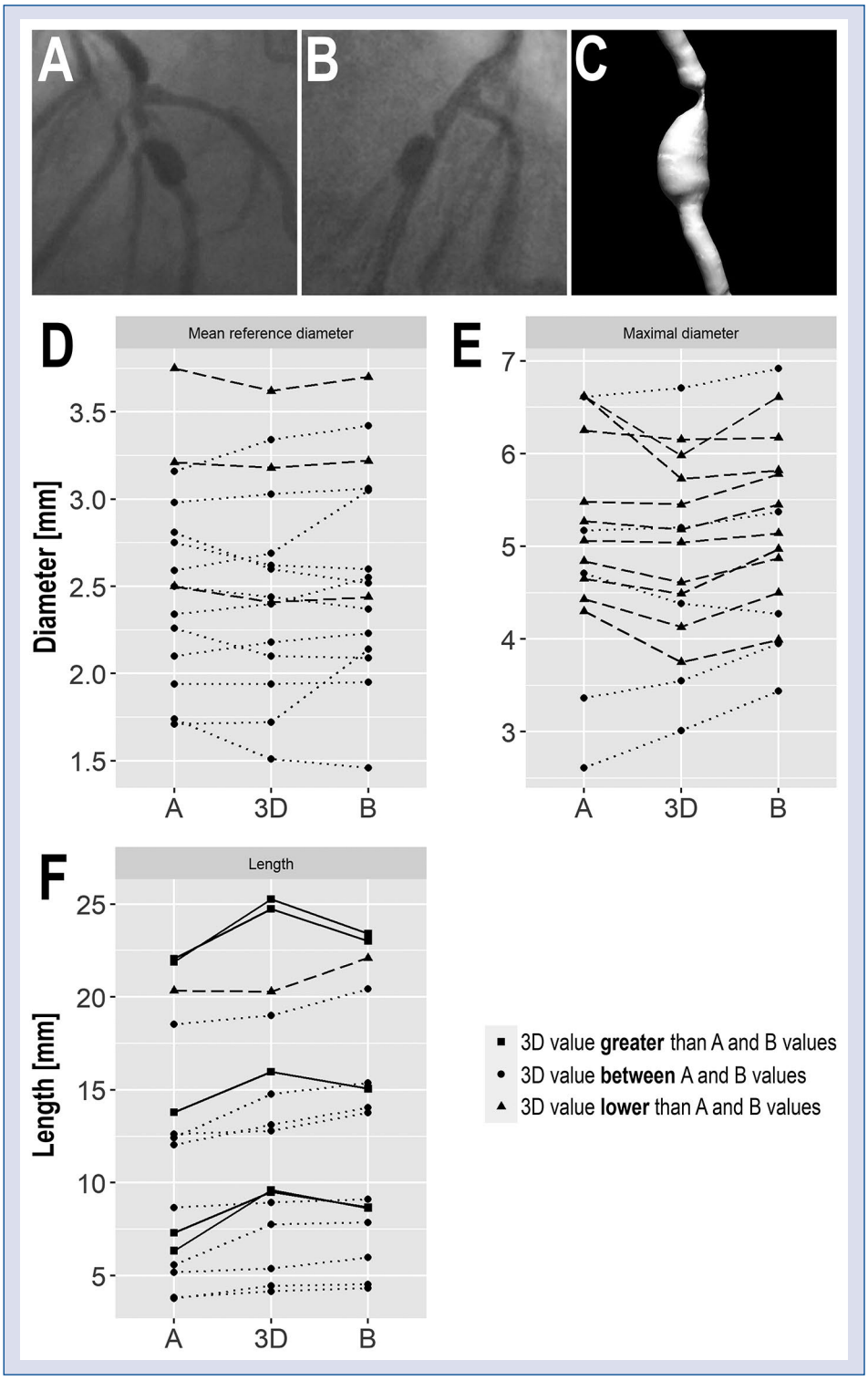

Figure 1. Typical example of coronary artery aneurysms and ectasias (CAAE) raw planar images and three-dimensional (3D) reconstruction (3DR), and the individual data charts for all studied CAAEs; **A–C.** Typical example of an CAAE two-dimensional (2D) planar images (**A**, **B**) and its 3DR (**C**); **D**–**E.** Relations between the 2D and 3D numeric values for CAAE (**D**) reference diameter, (**E**) maximal diameter and (**F**) length.

two-dimensional (2D) projections (3 out of 5 cases), poor recording quality in one of the two required projections (1 case) and CAEA overlap with a large branch of another artery in one of the two projections in the 'green' zone (1 case). Table 1 shows, for each major coronary segment, suggested projec-

Table 1. Guideline on two-dimensional angiography projections spatial distribution to enable three--dimensional reconstruction (as per each major coronary segment). According to [6] (modified). Note that per-patient optimal angulations may vary, and an adjustment of the projection(s) may be needed.

Coronary artery	Projection 1	Projection 2
Left main and bifurcation	RAO 20, caudal 40	RAO 0, caudal 10
Left circumflex artery	LAO 10, caudal 25	RAO 25, caudal 25
LAD and diagonal(s)	RAO 0, cranial 40	RAO 30, cranial 15
RCA proximal, RCA mid	LAO 40, caudal 0	RAO 0, caudal 0
RCA distal	LAO 40, caudal 0	LAO 30, caudal 30

LAD — left anterior descending artery; LAO — left anterior obilque; RAO — right anterior obilque; RCA — right coronary artery

tions to enable 3DR; these should be considered in prospective data acquisition.

Significant stenoses (> 50% of lumen diameter) were present at the proximal end in 6 and distal end in 4 CAAEs, with both in 1 CAAE. One-third CAAEs had a maximal diameter > 2 times greater than RD. 3DR average values (range) [mm] were as follows: RD 2.52 (1.51–3.62), mean diameter 3.90 (2.45–5.45), maximal diameter 4.89 (3.01–6.71), length 13.05 (4.15–25.27), length of segment dilated > 1 RD 12.10 (3.52–24.01), > 1.5 RD 7.94 (2.31–22.11), and > 2 RD 3.89 (3.25–6.49). The CAAE volume, as obtained via 3D reconstruction, was 144.86 (33–402) mm^3. The following differences between the 2D and 3D parameters [mm] were identified: RD 0.05 (0.02–0.09; 2.30%; p = 0.0072), mean diameter 0.12 (0.01–0.22; 2.84%; p = 0.0312), maximal diameter 0.22 (0.12–0.32; 4.19%; p = 0.0004), length –0.69 (–1.30 – –0.08; –5.50%; p = 0.0284), length of fragment dilated > 1 RD –0.77 (–1.32 – –0.22; –7.61%; p = 0.0095), > 1.5 RD –0.22 (–0.82 – –0.38; p = 0.4404) and > 2 RD 0.08 (–0.29–0.14; 11.84%; p = 0.4566). Individual relations between the 2D and 3DR numeric values for CAAE RD, maximal diameter and length are shown in Figure 1.

Principal findings from this work, evaluating performance of an angiographic 3DR software in relation to its application for CAAE characteristics, are the following: (1) CAAE 3DR appears feasible for a majority of CAAEs identified on routine CAG; (2) numeric parameters of 3D-reconstructed CAAEs are not a "simple" mean of those in 2D projections; and (3) not infrequently (> 40%, see Fig. 1D–F) the numeric values of 3D assessment fall outside the 2D planar values (Fig. 1D–F), suggesting potential new information from 3DR. In addition, 3DR enabled evaluation of the CAAE volume; a parameter not available on 2D projections that may have a prognostic value [1, 2]. Despite the fact that the 2D and 3D parameters appeared significantly correlated, some 3D measurements fell below conventional CAG measurements whereas others fell above (Fig. 1). Thus, on 3DR, CAEAs may tend to appear longer and narrower than on plain 2D projections; an observation that requires further elucidation.

While these findings require confirmation in a larger CAAE series in relation to computed tomography angiography (CTA), their consistency in the present sample of unselected routine angiograms with CAAE suggests that CAAE 3DR based on standard CAG images might provide new information relevant to monitoring the course of the disease and patient risk. Indeed, autopsy data show that CAAEs often have a complex 3D structure whose prior knowledge would have, in a proportion of cases, affected management [2]. Optimizing the methodology of CAAEs qualitative and quantitative evaluation based on routine image acquisition may play a role in both triggering the intervention and selecting the type of intervention (percutaneous vs. surgical) [2]. Stent revascularisation of lesions involving CAAE poses particular difficulties in relation to stent sizing (diameter, length) and the risk (and consequences) of stent malapposition [7]. On the other hand, aneurysm formation may occur as a late complication of (drug-eluting in particular) stent use [8].

Computed tomography angiography is today the #1 tool to obtain CAAE 3D characteristics [4]. CTA, however, it is not performed prior to CAG identification of CAAE but, rather, as a subsequent step in arbitrarily selected cases [9]. Importantly, CTA resolution is > 2-fold lower than that of CAG (≈ 0.5 vs. ≈ 0.2 mm) [6, 7], and CTA is prone to gating-related (increased heart rate, arrhythmias) and calcifications-related artifacts [4]. Further-

more, CTA following CAG requires another contrast medium dose and X-ray exposure [10]. For these reasons it would be of interest to employ 3D reconstructions as a potential replacement of CTA verification or as a guidance to selective CTA use. This is one of the major issues of interest today [9, 10]; thus CAAE 3D reconstruction against CTA in a larger series of patients is required to fully validate this method.

In conclusion, present findings indicate that CAAE 3DR using routinely-acquired planar CAG images may be feasible for a majority of CAAE identified on CAG. In a significant proportion of CAAEs, the numeric values of (both the conventional and novel) CAAE parameters may fall beyond the 2D projection values. Thus, 3DR may provide information quantitatively (and perhaps prognostically) different from the one based on analysis of standard 2D images.

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References

1. Devabhaktuni S, Mercedes A, Diep J, et al. Coronary artery ectasia — a review of current literature. Curr Cardiol Rev. 2016; 12(4): 318–323, doi: 10.2174/1573403x12666160504100159, indexed in Pubmed: 27142049.
2. Kawsara A, Núñez Gil IJ, Alqahtani F, et al. Management of Coronary Artery Aneurysms. JACC Cardiovasc Interv. 2018; 11(13): 1211–1223, doi: 10.1016/j.jcin.2018.02.041, indexed in Pubmed: 29976357.
3. Musiałek P, Tekieli Ł, Pieniazek P, et al. How should I treat a very large thrombus burden in the infarct-related artery in a young patient with an unexplained lower GI tract bleeding? EuroIntervention. 2011; 7(6): 754–5; discussion 756, doi: 10.4244/EIJV7I6A119, indexed in Pubmed: 21986333.
4. Díaz-Zamudio M, Bacilio-Pérez U, Herrera-Zarza MC, et al. Coronary artery aneurysms and ectasia: role of coronary CT angiography. Radiographics. 2009; 29(7): 1939–1954, doi: 10.1148/rg.297095048, indexed in Pubmed: 19926755.
5. Chmiel J, Książek MK, Stryszak W, et al. Temporal changes in the pattern of invasive angiography use and its outcome in suspected coronary artery disease: implications for patient management and healthcare resources utilization. Adv Interv Cardiol. 2018; 14(3): 247–257, doi: 10.5114/aic.2018.78327, indexed in Pubmed: 30302100.
6. CAAS Workstation 7.4 User Manual, Pie Medical Imaging, Maastricht, The Netherlands 2011.
7. Dingli P, Gonzalo N, Escaned J, et al. Intravascular ultrasound-guided management of diffuse stenosis. Radcliffe Cardiology. 2018: 1–18, doi: 10.15420/rc.2018.m005.
8. Hong SJ, Kim H, Ahn CM, et al. Coronary artery aneurysm after second-generation drug-eluting stent implantation. Yonsei Med J. 2019; 60(9): 824–831, doi: 10.3349/ymj.2019.60.9.824, indexed in Pubmed: 31433580.
9. Iwańczyk S, Araszkiewicz A, Borger M, et al. Endocan expression correlated with total volume of coronary artery dilation in patients with coronary artery ectasia. Adv Interv Cardiol. 2020; 16(3): 294–299, doi: 10.5114/aic.2020.99264, indexed in Pubmed: 33597994.
10. Adamson PD, Newby DE. Non-invasive imaging of the coronary arteries. Eur Heart J. 2019; 40(29): 2444–2454, doi: 10.1093/eurheartj/ehy670, indexed in Pubmed: 30388261.

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The use of the Gunning Fog Index to evaluate the readability of Polish and English drug leaflets in the context of Health Literacy challenges in Medical Linguistics: An exploratory study

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To achieve more satisfactory outcomes, healthcare providers need to communicate with the patients effectively, mainly in terms of language used between both parties [1]. Numerous studies have revealed that medical jargon may be highly incomprehensible for patients, and the less-educated and marginalized groups are particularly sensitive to this kind of communication [2]. The language used in patient materials includes difficult terms which cannot be easily understood without a formal education and this may be the reason why drug leaflets — the primary source of drug-related information for most patients — are considered unfriendly for their users [3]. Low readability of drug leaflets is associated with poorer patient adherence to recommended therapy; thus, it can have a significant impact on achieved outcomes, and the rate of therapeutic success, particularly in chronic diseases [4]. Different techniques aimed at evaluating the readability of written texts have been widely used in medicine and pharmacy for more than two decades. Among other tools, the Gunning Fox Index (FOG index) is one of the most frequently applied in modern linguistics [5]. What should be emphasized here, in our opinion, readability is also important from an ethical point of view. Participants in clinical trials should provide informed consent before being introduced to a study or control group. Informed consent, however, is also the matter of language which is used between trialists and patients; the use of difficult language may limit a patient's ability to provide informed consent.

The presented study aimed at comparing Polish and English (United Kingdom) drug leaflets (patient-oriented documents) in terms of readability. Readability was investigated using the above-mentioned FOG index. The selection of leaflets was based on convenient sampling. In each case, a different part of the leaflets was selected. Moreover, in terms of language variation, the analogous part of drug leaflets was used to achieve greater opportunities to compare the results. English texts were analysed using http://gunning-fog-index.com/; Polish by using http://www.jasnopis.pl. *Jasnopis* provides additional comments which were attached to the analysis (qualitative analysis). Results were presented in additional comments corresponding to United States of America grade level, and explanation obtained from the *Jasnopis* website. Three drug leaflets were selected: drugs containing i) metoprolol tartrate — in this case, warnings and precautions were analysed; ii) carvedilol — indications were analysed so as to evaluate readability, and iii) a fixed-dose combination (FDC) contains three active pharmaceutical ingredients (a combination of perindopril, indapamide, and amlodipine was selected) — 'how to take the drug' section was analysed.

Table 1 summarizes the findings revealed by our analysis. First of all, the overall value of the FOG index should be considered as relatively too

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Table 1. Results of analysis.

	Extract	Result and interpretation
1a	Do not take Metoprolol Tartrate tablets if you. Are allergic to metoprolol, other beta-blockers or any other ingredients of this medicine (listed in section 6). Suffer with heart conduction or rhythm problems. Have severe or uncontrolled heart failure. Are in shock caused by heart problems. Suffer with blocked blood vessels, including blood circulation problems (which may cause your fingers and toes to tingle or turn pale or blue). Have a slow heart rate or have suffered a heart attack which has been complicated by a significantly slow heart rate. Suffer from a tight, painful feeling in the chest in periods of rest (Prinzmetal's angina). Have or have had breathing difficulties or asthma including COPD (chronic obstructive pulmonary disease). Causing cough, wheezing or breathlessness, phlegm or an increase in chest infections). Suffer with untreated phaeochromocytoma (high blood pressure due to a tumour near the kidney). Suffer from increased acidity of the blood (metabolic acidosis). Have low blood pressure. Suffer with diabetes associated with frequent episodes of low blood sugar (hypoglycaemia). Have liver or kidney disease or failure. Are given other medicines for blood pressure by injection especially verapamil, diltiazem or disopyramide.	The FOG index is: 12.16 (12) The number of words in extract: 187. The number of 3+ syllable words: 35. High school senior. Fairly simple language, understandable for high school students.
1b	Kiedy nie stosować leku Betaloc ZOK. Jeśli pacjent ma uczulenie na metoprololu winian lub którykolwiek z pozostałych składników tego leku (wymienionych w punkcie 6). Jeśli pacjent ma uczulenie na inne leki blokujące receptory β-adrenergiczne, np. atenolol, propranolol. Jeśli u pacjenta występuje. **Wstrząs kardiogenny.** Zespół chorego węzła zatokowego (chyba że wszczepiony jest rozrusznik serca). **Blok przedsionkowo-komorowy II lub III stopnia.** **Niewyrównana niewydolność serca** (duszność, obrzęk okolicy kostek). Bradykardia (zwolnienie rytmu serca poniżej 45 skurczów na minutę). Bardzo niskie ciśnienie tętnicze, które może powodować omdlenie. **Ciężkie zaburzenia krążenia w tętnicach obwodowych.** **Kwasica metaboliczna.** Nieleczony guz chromochłonny nadnerczy. **Podejrzenie świeżego zawału mięśnia sercowego, jeśli czynność serca jest wolniejsza niż 45 skurczów na minutę, odstęp PQ jest dłuższy niż 0,24 s lub ciśnienie skurczowe jest mniejsze niż 100 mmHg.** Jeśli pacjentowi podawane są (krótko- lub długotrwale) leki o działaniu inotropowym dodatnim, **pobudzające receptory β-adrenergiczne**.	The FOG index is: 11.94 (12) The number of words in extract: 131. The number of 4+ syllable words: 17. High school senior. Fairly simple language, understandable for high school students. Additional comments from *Jasnopis:* — the text should be considered as difficult for average Polish user, — significantly more difficult parts of the text were highlighted in bold font (typeface).
2a	Talk to your doctor or pharmacist before using Metoprolol Tartrate 50 mg tablets if you. Have a history of allergic reactions, for example to insect stings, foods or other substances. Have diabetes mellitus (low blood sugar levels may be hidden by this medicine). Have controlled heart failure. Have a slow heart rate or blood vessel disorder. Suffer from treated phaeochromocytoma (high blood pressure due to tumors near the kidney). Have or have suffered from psoriasis (severe skin rashes). Have liver cirrhosis. Are elderly. Have myasthenia gravis. If you suffer from dry eyes.	The FOG index is: 9.33 (9) The number of words in extract: 92. The number of 3+ syllable words: 13. High school freshman. Simple language understandable for junior high school pupils.

→

Table 1 (cont.). Results of analysis.

	Extract	Result and interpretation
2b	Przed rozpoczęciem stosowania leku Betaloc ZOK należy omówić to z lekarzem. Należy poinformować lekarza, jeśli u pacjenta występuje. Astma oskrzelowa, świszczący oddech lub inne, podobne zaburzenia oddychania albo reakcje alergiczne, np. na jad owadów, pokarm lub inne substancje. Jeśli u pacjenta kiedykolwiek wystąpił napad astmatyczny lub świszczący oddech — nie należy stosować tego leku bez konsultacji z lekarzem. **Ból w klatce piersiowej, spowodowany dławicą Prinzmetala.** **Zaburzenia krążenia lub niewydolność serca.** Choroba wątroby. Blok serca I° (zaburzenia przewodzenia w sercu). Chromanie przestankowe (męczenie się i słabnięcie jednej lub obu nóg podczas chodzenia). Cukrzyca (lekarz może zalecić zmianę dawek leków przeciwcukrzycowych). Nadczynność tarczycy — lek Betaloc ZOK może maskować objawy. **Guz chromochłonny nadnerczy.** Łuszczyca.	The FOG index is: 9.68 (10) The number of words in extract: 87. The number of 4+ syllable words: 4. High school sophomore. Simple language understandable for high school pupils. Additional comments from *Jasnopis*: — the text should be considered as difficult for average Polish user, — significantly more difficult parts of the text were highlighted in bold font (typeface).
3a	Carvedilol belongs to a group of medicines called beta-blockers that work by relaxing and widening the blood vessels. This makes it easier for your heart to pump blood around the body and reduces blood pressure and strain on your heart. Carvedilol is used: For the treatment of high blood pressure (hypertension). For the treatment of chest pain that occurs when the arteries that supply your heart with blood carrying oxygen are narrowed which results in less oxygen reaching your heart muscles (angina). For the treatment of weakening of the heart muscle (heart failure), in combination with other medicines.	The FOG index is: 11.43 (11) The number of words in extract: 98. The number of 3+ syllable words: 12. High school junior. Simple language understandable for high school pupils.
3b	Lek Dilatrend w postaci tabletek o mocy 6,25 mg, 12,5 mg lub 25 mg zawiera substancję czynną. **Karwedylol, którego działanie polega na rozszerzaniu naczyń krwionośnych poprzez blokowanie receptorów adrenergicznych typu alfa1 oraz hamowaniu aktywności układu renina–angiotensyna–aldosteron poprzez blokadę receptorów beta.** Lek Dilatrend wskazany jest w leczeniu. Przewlekłej niewydolności serca (stabilnej postaci przewlekłej niewydolności serca o łagodnym, **umiarkowanym i ciężkim nasileniu), jako uzupełnienie zazwyczaj stosowanego leczenia podstawowego.** **Nadciśnienia tętniczego.** Stabilnej choroby wieńcowej. Pacjentów po przebytym zawale mięśnia serca ze stwierdzonymi zaburzeniami czynności lewej komory (frakcja wyrzutowa lewej komory (LVEF) ≤ 40%).	The FOG index is: 13.43 (13) The number of words in extract: 81. The number of 4+ syllable words: 8. College freshman. A language quite difficult, understandable for undergraduate students. Additional comments from *Jasnopis:* — very complicated and professional text, understanding of which may require specialist knowledge, — significantly more difficult parts of the text were highlighted in bold font (typeface).
4a	Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure. Swallow the tablet with a glass of water preferably in the morning and before a meal. Your doctor will decide on the correct dose for you. This will normally be one tablet once a day. If you take more Coverdine than you should. Taking too many tablets may cause you blood pressure to become low or even dangerously low sometimes associated with nausea, vomiting, cramps, dizziness, sleepiness, mental confusion, oliguria (passing less urine than is normal), anuria (no production or passing of urine). You may feel lightheaded, faint, or weak. If blood pressure drop is severe enough shock can occur. Your skin could feel cool and clammy and you could lose consciousness. Seek immediate medical attention if you take too many Coverdine tablets. If you forget to take Coverdine.	The FOG index is: 11.97 (12) The number of words in extract: 243. The number of 3+ syllable words: 38. High school senior.

→

Table 1 (cont.). Results of analysis.

	Extract	Result and interpretation
	It is important to take your medicine every day as regular treatment is more effective. However, if you forget to take a dose of Coverdine, take the next dose at the usual time. Do not take a double dose to make up for a forgotten dose. If you stop taking Coverdine. As the treatment for high blood pressure is usually life-long, you should discuss with your doctor before stopping this medicinal product. If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.	
4b	Ten lek należy zawsze stosować zgodnie z zaleceniami lekarza lub farmaceuty. W razie wątpliwości należy zwrócić się do lekarza lub farmaceuty. Tabletkę należy połknąć, popijając szklanką wody, najlepiej rano, przed posiłkiem. Lekarz określi odpowiednią dawkę dla pacjenta. Zazwyczaj zalecana dawka to jedna tabletka raz na dobę. Zastosowanie większej niż zalecana dawki leku Triplixam. Zażycie zbyt wielu tabletek może spowodować, że ciśnienie tętnicze obniży się, nawet w niebezpiecznym stopniu, czemu czasami mogą towarzyszyć nudności, wymioty, kurcze, zawroty głowy, senność, dezorientacja, skąpomocz (wydalanie mniejszej ilości moczu niż zwykle), bezmocz (brak wytwarzania lub wydalania moczu). Pacjent może odczuwać „pustkę" w głowie, może wystąpić uczucie omdlewania lub słabnięcia. Jeśli obniżenie ciśnienia tętniczego jest znaczne, może wystąpić wstrząs, w przypadku którego skóra staje się chłodna i wilgotna, a pacjent może stracić przytomność. W razie zażycia zbyt wielu tabletek leku Triplixam należy niezwłocznie skontaktować się z lekarzem lub zgłosić się do oddziału pomocy doraźnej najbliższego szpitala. Pominięcie przyjęcia leku Triplixam. Ważne jest, aby przyjmować lek codziennie, ponieważ regularne stosowanie zapewnia skuteczniejsze działanie. Jeśli jednak pominie się dawkę leku Triplixam, następną dawkę należy przyjąć o zwykłej porze. Nie należy stosować dawki podwójnej w celu uzupełnienia pominiętej dawki. Przerwanie stosowania leku Triplixam. Leczenie wysokiego ciśnienia tętniczego jest zwykle długotrwałe, dlatego przed przerwaniem przyjmowania tego leku należy skontaktować się z lekarzem. W razie jakichkolwiek dalszych wątpliwości związanych ze stosowaniem tego leku należy zwrócić się do lekarza, farmaceuty lub pielęgniarki.	The FOG index is: 13.01 (13) The number of words in extract: 230. The number of 4+ syllable words: 6. College freshman. A language quite difficult, understandable for undergraduate students.

Sources of extracts: 1a — English version – metoprolol — precautions; 1b — Polish version — metoprolol — precautions; 2a — English version — metoprolol — warnings; 2b — Polish version — metoprolol — warnings; 3a — English version — carvedilol — indication(s); 3b — Polish version — carvedilol — indication(s); 4a — English version — fixed-dose combination — how to take the drug/use of drug; 4b — Polish version — fixed-dose combination — how to take the drug/use of drug

high and varies from the language understood by junior high school pupils (metoprolol, English leaflet) to language which is comprehended by undergraduate students (FDC, Polish leaflet). Taking into consideration that a relatively significant part of society may not achieve these levels of education, the language used in drug leaflets, at least those under evaluation, seem to be too difficult. Moreover, the present findings significantly exceed the readability guidelines authorized by the National Institutes of Health and the American Medical Association, which strongly recommend that these kinds of documents should not be written at greater than a sixth-grade reading level (lower intermediate level) [6]. Since overall capacity for understanding medical information deteriorates with aging, and the use of drugs is more frequent among the elderly, current findings revealed that the situation seems to be even worse than it would have, resulting from a simple analysis of the association between the complexity of language and level of education. Moreover, the number of complex words, though defined differently in Polish and English, varies from 4 to 38; still, this number might be considered too high, and the language requires substantial simplification. Although the aim of this paper is not qualitative, some qualitative aspects should be mentioned, at least briefly.

Polish drug leaflets contain some highly specialized vocabulary, which is understood only by people with a medical background. Among other examples, it is worth citing the following expressions: '*blok przedsionkowo-komorowy II lub III stopnia, wstrząs kardiogenny, niewyrównana niewydolność serca*' (as it was used in the analyzed material). Hopefully, in the last example, the drug leaflet contains symptoms of unstable heart failure, which may be helpful for patients to correctly recognize their condition. '*Guz chromochłonny nadnerczy*' is a term recognized in both language versions; however, in the English one, an easier descriptive form was added: 'high blood pressure due to a tumor near the kidney'. This explanation does not denote an explanation of the disease, rather is focused on the most important and life-threatening symptoms of the tumor, particularly important from the perspective of drug-disease interaction. This approach is also identified in the case of a more common disease (psoriasis); symptoms of this condition were described in the English version. Finally, the Polish sentences are significantly longer than English, which can be seen in this example: '*podejrzenie świeżego zawału mięśnia sercowego, jeśli czynność serca jest wolniejsza niż 45 skurczów na minutę, odstęp PQ jest dłuższy niż 0,24 s lub ciśnienie skurczowe jest mniejsze niż 100 mmHg*' (as it was used in the analyzed material). This sentence contains highly precise values, which are difficult for patients to interpret.

Numerous studies have revealed that patient-oriented documents contain difficult language which may be an important problem for patients. Huang et al. [7] revealed that ophthalmologic online patient education materials are written in the style highly above that recommended by experts; in terms of the FOG index, authors estimated it in the range from 12.4 to 18.4, which is even higher than noticed in this study. A level higher than recommended was also observed in a similar study aimed at evaluating the readability of online patient information for vestibular schwannoma [5]. Also, materials for pregnant women are provided above recommendations, and only 0.5% of materials analyzed by Storr et al. [8] were written below grade six. Even documents provided by the medical association need substantial improvement in terms of readability as it was depicted by Betschart et al. [9], who highlighted some improvements in quality of documents prepared by European Association of Urology; however, much more effort should be paid in order to achieve acceptable transparency.

Although the value of the FOG index of both analyzed language variation is comparable, the qualitative analysis revealed that the Polish language version seems to be more difficult for patients, due to the significant number of highly-specialized vocabulary, length of sentences, and lack of easy explanations of some medical terms. Nevertheless, a more advanced analysis should be performed to provide further more valid evidence, e.g. different kinds of research tools may add new relevant findings. It is worth remembering that the present study is exploratory.

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References

1. Aronson L. Medical linguistics. J Gen Intern Med. 2007; 22(12): 1781, doi: 10.1007/s11606-007-0314-1, indexed in Pubmed: 17924173.
2. Bittner A, Jonietz A, Bittner J, et al. Translating medical documents into plain language enhances communication skills in medical students--A pilot study. Patient Educ Couns. 2015; 98(9): 1137–1141, doi: 10.1016/j.pec.2015.05.024, indexed in Pubmed: 26095344.
3. Pires C, Vigário M, Cavaco A. Readability of medicinal package leaflets: a systematic review. Rev Saude Publica. 2015; 49: 4, doi: 10.1590/s0034-8910.2015049005559, indexed in Pubmed: 25741660.
4. Swieczkowski D, Mogielnicki M, Cwalina N, et al. Medication adherence in patients after percutaneous coronary intervention due to acute myocardial infarction: From research to clinical implications. Cardiol J. 2016; 23(5): 483–490, doi: 10.5603/CJ.a2016.0048, indexed in Pubmed: 27439366.
5. Spiers H, Amin N, Lakhani R, et al. Assessing readability and reliability of online patient information regarding vestibular schwannoma. Otol Neurotol. 2017; 38(10): e470–e475, doi: 10.1097/MAO.0000000000001565, indexed in Pubmed: 28885483.
6. Weiss BD. Health literacy and patient safety: help patients understand. Manual for clinicians. 2nd ed. American Medical Association, American Medical Foundation, Chicago (IL) 2007.
7. Huang G, Fang CH, Agarwal N, et al. Assessment of online patient education materials from major ophthalmologic associations. JAMA Ophthalmol. 2015; 133(4): 449–454, doi: 10.1001/jamaophthalmol.2014.6104, indexed in Pubmed: 25654639.
8. Storr T, Maher J, Swanepoel E. Online nutrition information for pregnant women: a content analysis. Matern Child Nutr. 2017; 13(2), doi: 10.1111/mcn.12315, indexed in Pubmed: 27353248.
9. Betschart P, Zumstein V, Bentivoglio M, et al. Readability assessment of online patient education materials provided by the European Association of Urology. Int Urol Nephrol. 2017; 49(12): 2111–2117, doi: 10.1007/s11255-017-1695-7, indexed in Pubmed: 28905177.

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Late lumen enlargement and plaque regression after drug-coated balloon treatment for an isolated ostial lesion of a diagonal branch

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A 55-year-old man was admitted with worsening effort angina for over 1 week. Hypertension was the only coronary risk factor in this patient, and resting electrocardiography and echocardiography findings, as well as cardiac enzyme levels were normal. Coronary angiography revealed ostial stenosis of the first diagonal branch (90% diameter narrowing) (Fig. 1A, **Suppl. Video 1**). The patient declined complex stent implantation but agreed to receive drug-coated balloon (DCB) treatment. Informed consent was obtained, and the patient underwent careful evaluation.

The ostium of the diagonal branch was dilated several times using a 3.0 × 13 mm scoring balloon at a pressure of 10 atm, followed by placement of a DCB (3.0 × 20 mm), which was inflated to a pressure of 8 atm for 60 s. Final angiography revealed no significant dissection or residual ostial stenosis of the diagonal branch and the main vessel of the left anterior descending artery (Fig. 1B, **Suppl. Video 1**). Intravascular ultrasound revealed increased luminal area with plaque dissection at the ostium of the diagonal branch (Fig. 1B4, arrow), and the patient's angina was resolved. Nine-month follow-up angiography (Fig. 1C, **Suppl. Video 1**) and intravascular ultrasound findings confirmed excellent results with plaque reduction (Fig. 1C1–C5) and a healed dissected ostial plaque (Fig. 1C4).

Percutaneous coronary intervention for isolated ostial lesions is challenging. It was observed that DCB treatment resulted in a significant reduction in the plaque burden with ostial lumen enlargement without any left anterior descending artery compromise. These findings suggest that DCB treatment may potentially be indicated for ostial lesions, particularly in patients who refuse to undergo stenting.

Conflict of interest: None declared

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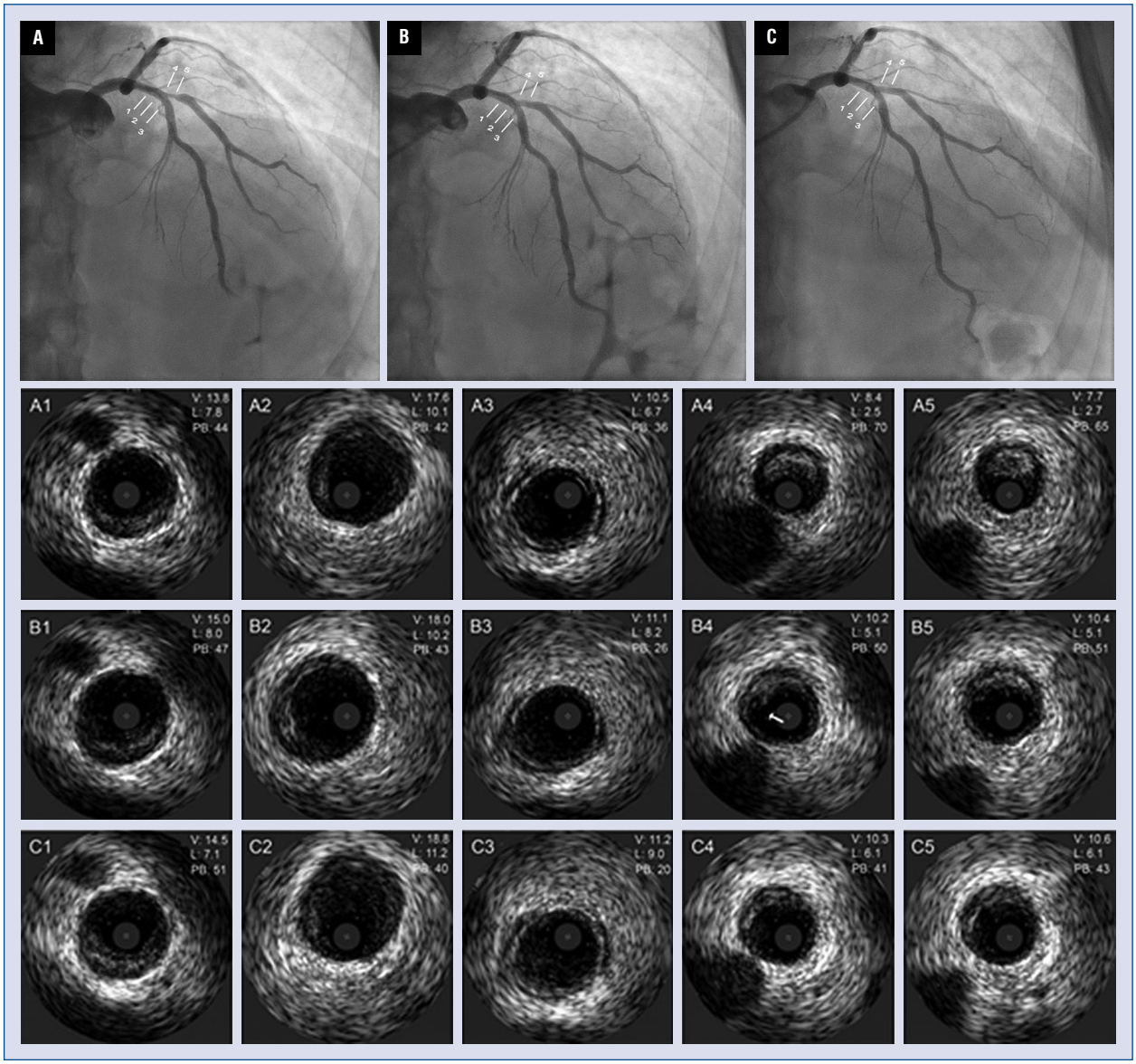

Figure 1. Pre-procedure images (**A**), post-drug-coated balloon treatment images (**B**), follow-up angiographic images (**C**), and those coupled with serial corresponding intravascular ultrasound images. Nine-month follow-up intravascular ultrasound showing significantly increased luminal area with a decreased plaque area at the ostium of the diagonal branch without a significant change in the main vessel of the left anterior descending artery; V — vessel area (mm^2); L — lumen area (mm^2); PB — plaque burden (%).

VIA MEDICA

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Intravascular lithotripsy of an underexpanded stent following unsuccessful rotational atherectomy in a patient with severely calcified coronary artery

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A 66-year-old man with hypertension was admitted to hospital with non-ST-segment elevation myocardial infarction. Emergency coronary angiography demonstrated critical stenosis in the medial and distal segment of the right coronary artery (RCA) (Fig. 1A). During the same procedure rotational atherectomy was unsuccessfully attempted, because the RotaWire guide wire (Boston Scientific, Marlborough, USA) did not reach the distal part of the RCA. One month later another RCA rotational atherectomy was attempted using the RotaLink System (Boston Scientific, Marlborough, USA). Rotablation with 1.5 burr was performed followed by predilatation with two noncompliant (NC) balloons (2.5 × 20 mm) and (3.0 × 20 mm) (Fig. 1B). Afterwards, two drug-eluting stents (Onyx, USA) (3.0 × 30 mm) distally and (3.5 × 38 mm) proximally were implanted. Despite postdilatation with NC balloons (3.5 × 12 mm, 14 atm and 4.0 × × 12 mm, 24 atm) it was not possible to expand the proximal stent optimally (Fig. 1C).

In the next step, we decided to attempt adjunctive intravascular lithotripsy for stent optimalization in the proximal RCA. Shockwave balloon was delivered in the underexpanded stent and 8 rounds of 10 pulses were applied (with balloon inflation at 2–4–6 atm) (Fig. 1D). Postdilatation with a NC high-pressure balloon 4.0 × 12 mm (infl. 18–20 atm) was used to optimize the final result (Fig. 1E). The angiography confirmed significant expansion of the implanted stent with residual 20% diameter stenosis (Fig. 1F).

Rotational atherectomy was performed to reduce the volume of calcium in the vessel and to prepare it for the stent implantation. However, massive calcification of the RCA was a major obstacle for the optimal stent expansion despite NC balloons for the postdilatation applied. The intravascular lithotripsy procedure is an alternative for the management of stent underexpansion due to calcific coronary artery disease.

Conflict of interest: None declared

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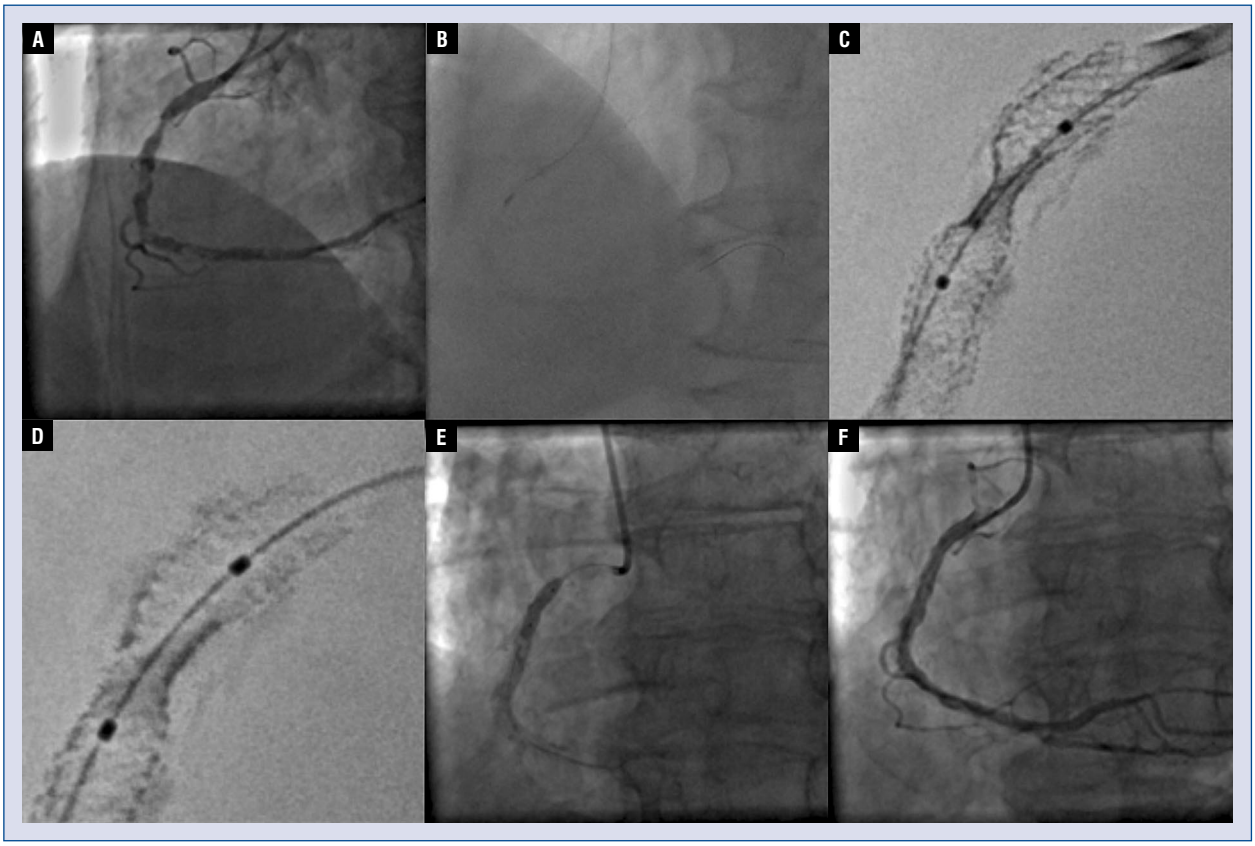

Figure 1. A. Severely calcified artery disease at the medial and distal part of the right coronary artery (RCA); **B.** Rotational atherectomy with 1.5 burr; **C.** Underexpanded proximal stent in the RCA — CLEAR stent view; **D.** Angiography after intravascular lithotripsy on CLEAR stent visualization; **E.** Postdilatation with 4.0 noncompliant high-pressure balloon; **F.** Final angiographic result.

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The focal takotsubo syndrome presenting with the snail-like left ventricle

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Focal takotsubo syndrome (TTS) is a rare, atypical type of TTS reported in 2004 as anterior akinesis of the left ventricle (LV) with no coronary changes. Based on the International Takotsubo Registry, it occurs in about 1.5% of cases. To date, this uncommon form has not been called anything other than "focal". Typical left ventricular apical ballooning resembled a *takotsubo* (jap. *tako* — octopus, *tsubo* — pot), hence the then-novel disease was named after it. In our observation, the LV in focal TTS can resemble a snail in imaging studies.

A 70-year-old female was referred to the hospital due to severe angina. It started 2 days before admission caused by severe emotional distress. The electrocardiogram showed ST-segment elevation in leads II, III, and aVF, with a QTc interval of 454 ms, a heart rate of 74 bpm and increased high sensitivity troponin I levels (3.4 ng/mL), while the maximum B-type natriuretic peptide concentration did not exceed 120 pg/mL. Vital signs remained stable. The patient was subsequently qualified for urgent cardiac catheterization, which revealed no obstructive coronary artery disease and akinesis of the mid-anterior heart segment on ventriculography. The LV shape during systole resembled a snail (Fig. 1A, B, **Suppl. Video 1**). Echocardiography confirmed the presence of LV anterior wall akinesis (Fig. 1C, D), which was visualized objectively with longitudinal strain (Fig. 1E). However, the echo abnormalities were transient — a feature typical for TTS. The patient remained asymptomatic and was discharged home on the 6th day of hospitalization. Contractile disfunction was not observed after a 5-week follow-up.

In such cases, even if the initial imaging is not typical for TTS (snail-like image) and clinical suspicion is high, TTS should not be excluded.

Conflict of interest: None declared

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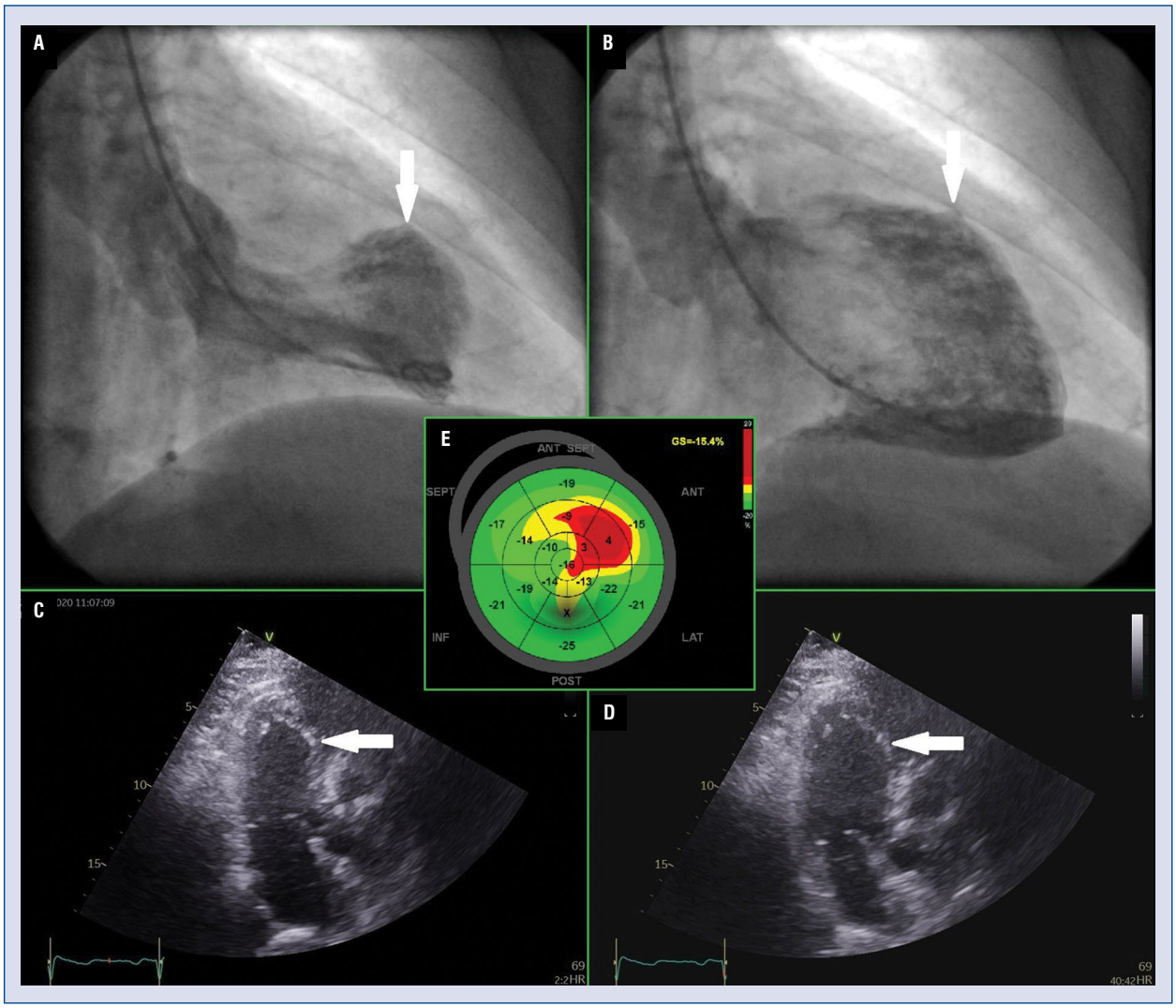

Figure 1. Ventriculography showing the snail-like shape of left ventricle (LV) and focal akinesis of its anterior wall in systole (**A**) and LV in diastole (**B**). The same regional wall motion abnormalities were observed in echocardiography during systole (**C**) and in diastole (**D**). White arrows mark the akinetic segment. Display of regional longitudinal strain (Bull's Eye Plot) showed abnormal LV longitudinal strain, systolic lengthening of mid anterolateral segment (**E**).

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Acute coronary syndrome featuring dynamic J waves

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A 59-year-old male patient with a history of percutaneous coronary intervention (PCI) to the left anterior descending (LAD) artery presented because of angina at rest. Admission electrocardiography (ECG) (Fig. 1A) revealed at least 0.05 mV ST-segment depression at the J point in leads II, aVF, aVL, I, and V3–V6, at least 0.1 mV ST-segment elevation (STE) at the J point in leads aVR and V1 with STE in lead aVR > V1 and notch-type J waves in leads aVL and I. Coronary angiography performed due to refractory angina showed high-grade lesions in the LAD and left circumflex (LCx) arteries. Electrocardiography (Fig. 1B) after PCI to a proximal LCx artery culprit lesion (Fig. 1C) revealed resolution of ST-segment changes, reduction of J waves amplitude in lead aVL and disappearance of J waves in lead I. His serum troponin I peaked at 3.5 ng/mL (normal < 0.5 ng/mL). He was discharged following staged PCI of the LAD artery lesions (Fig. 1C).

Ischemia-induced J waves have been widely reported in vasospastic angina and less frequently in acute myocardial infarction; in both these clinical entities, they have been shown to confer an increased risk of ventricular fibrillation. They are registered in ECG leads facing the ischemic territory and followed by STE in persistent ischemia. Accordingly, ischemia-induced J waves would be useful in localizing the infarct-related artery. The dynamic J waves presented herein were clearly ischemia-induced as no other conditions reported to induce J waves such as hypothermia, hypercalcemia or Brugada syndrome were documented. This case highlights that dynamic J waves registered in leads aVL and I in patients with acute coronary syndrome suggest the presence of a culprit lesion in the LCx artery.

Conflict of interest: None declared

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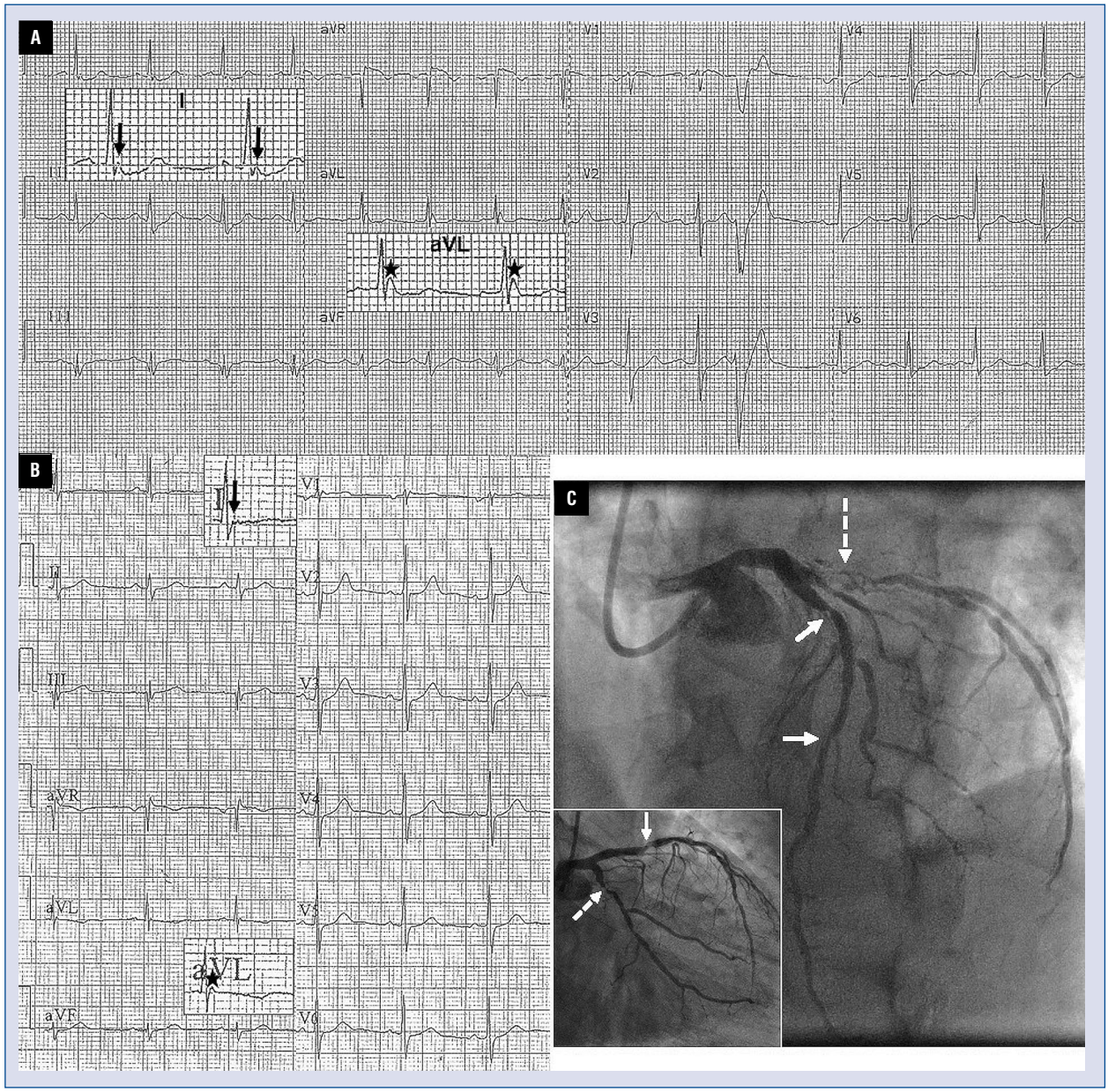

Figure 1. Electrocardiogram (ECG) on admission (**A**) and after percutaneous coronary intervention (PCI) to the culprit artery (**B**) and coronary angiographic images at baseline (**C**). ECG on admission: note the notch-type J waves in lead I (embedded panel: arrows) and in lead aVL (embedded panel; asterisks) where they were particularly prominent (> 0.1 mV). ECG after PCI to a left circumflex (LCx) artery culprit lesion depicted J waves of reduced amplitude (< 0.1 mV) in lead aVL (embedded panel; asterisk) and absent J waves in lead I (embedded panel; arrow). Note, that leads V2 and V3 have been reversed. Baseline coronary angiography depicted a high-grade, hazy stenosis with irregular borders (dotted arrows) in the proximal LCx artery (culprit lesion) and bystander high-grade lesions in the left anterior descending artery (solid arrows).

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Coronary steal syndrome: A greedy neighbour!

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A 71-year-old male, known for quadruple coronary artery bypass grafting in 2002 (left internal mammary artery [LIMA] to the left anterior descending [LAD] coronary artery and first diagonal branch and two saphenous vein grafts, to the first marginal and the intermediate arteries), was admitted for unstable angina in 2019. A cardiac positron emission tomography-computed tomography (PET-CT) showed moderate-to-severe ischemia in the distal LAD territory and a coronary flow reserve below 1.0, related to coronary steal (Fig. 1A, B). Coronary angiogram revealed a subtotal ostium stenosis of the saphenous veins' grafts to the intermediate artery — treated by percutaneous coronary intervention with drug eluting stent implantation (Resolute Onyx 4.0 mm × 18 mm, Medtronic MN, USA) — and an unligated LIMA side branch (Fig. 1C).

Subsequently, using left transradial access, transcatheter occlusion of the LIMA side branch was performed with one vascular plug (MVP® 18 mm-MicroVascular plug, Reverse Medical, Medtronic) (Fig. 1D–F) and two hydrocoils (AZUR® Hydrocoil Pushable-18, Terumo, Tokyo, Japan) deployed through a 21G Terumo-Progreat® microcatheter. The two hydrocoils were added since there was persistent flow post MicroVascular plug deployment, probably in relation with the double antiplatelet therapy and the 5000 UI of heparin injected after radial puncture.

At 3 month follow-up, the patient was free of angina and the cardiac PET-CT showed complete coronary flow reserve normalization and significant improvement of the LAD ischemia (Fig. 1G, H). The coronary angiogram at 6 months, showed a very good result with a complete occlusion of the LIMA side branch (Fig. 1I).

Coronary steal due to an unligated LIMA side branch is a potential cause of reversible ischemia in coronary artery bypass grafting patients. A transcatheter approach using vascular plugs and coil embolization, provides good results.

Conflict of interest: None declared

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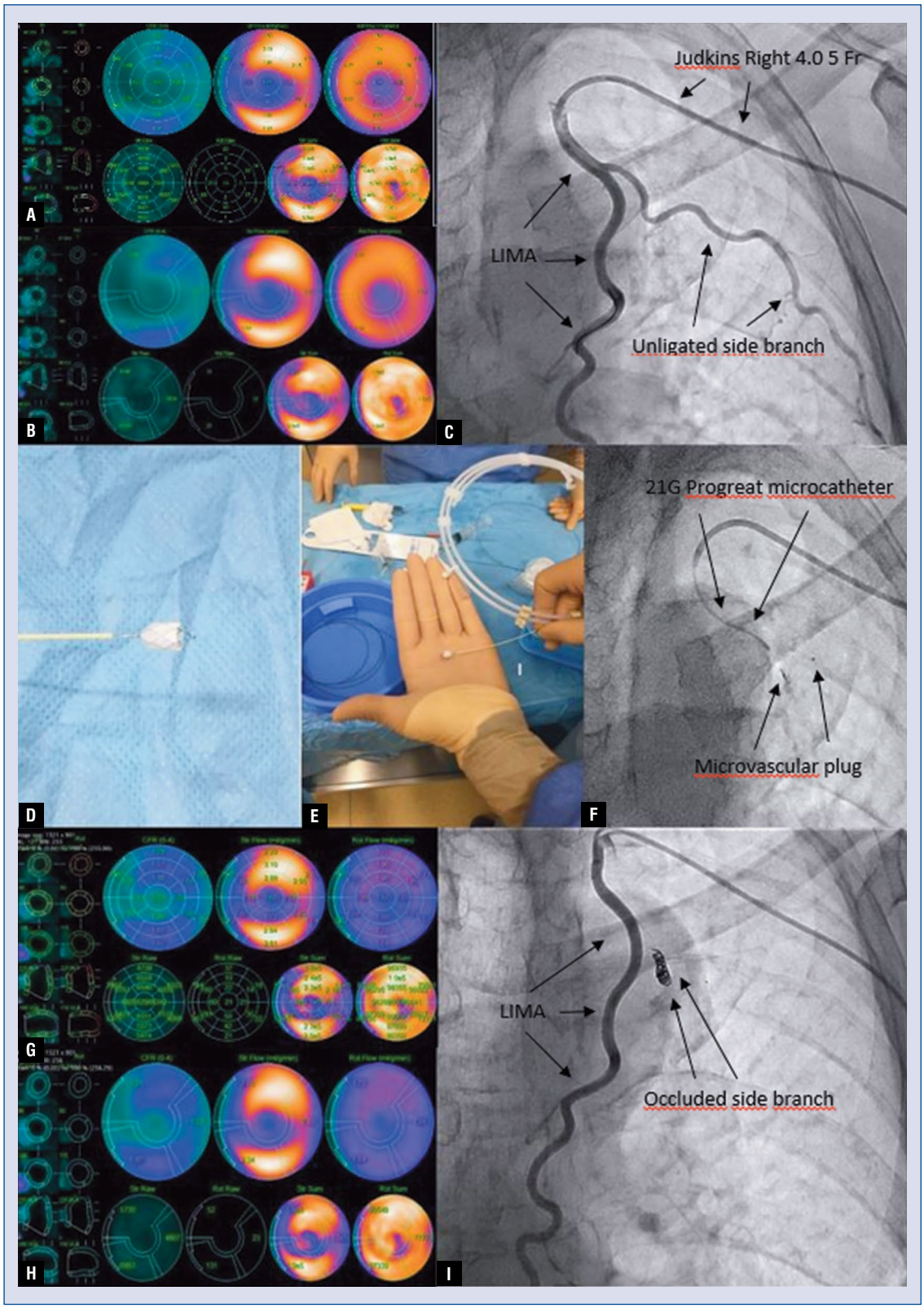

Figure 1. A. Positron emission tomography-computed tomography (PET-CT) before side branch occlusion showing ischemia in 18% of the left ventricle in the distal left anterior descending coronary artery territory; **B.** Signs of coronary steal with coronary flow reserve below 1.0; **C.** Coronary angiography showing the unligated side branch; **D, E.** Reverse Medical MVP® 18 mm-MicroVascular plug; **F.** MicroVascular plug deployment; **G, H.** PET-CT post side branch occlusion showing no residual ischemia and complete coronary flow reserve normalization; **I.** Final coronary angiography showing the occluded side branch; LIMA — left internal mammary artery.

VIA MEDICA

LETTER TO THE EDITOR

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Coronary physiology and percutaneous intervention managed with gadolinium road mapping and intravascular ultrasound in hyperthyroidism

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Introduction

The incidence of iodine-induced thyrotoxicosis after the administration of iodinated contrast agent remains low in various patient cohorts (0.2% to 1.9% [1, 2]). In patients with coexisting subclinical hyperthyroidism and ischemic heart disease, however, contrast administration may provoke or worsen its clinical condition requiring additional endocrinology treatment and clinical follow-up after the initial coronary angiography (CAG) or percutaneous coronary intervention (PCI) [3]. Alternative contrast agents — such as gadolinium — replacing iodinated contrast media during coronary angiography have been introduced previously in small cohorts and case reports to avoid nephrotoxicity [4, 5], contrast allergy [6], or iodinated-contrast-induced thrombocytopenia [7]. The present study, describes a case using a low amount of gadolinium for coronary anatomy reconstruction assisting the coronary physiology and imaging guided PCI in an elderly patient with acute coronary syndrome (ACS) who was simultaneously diagnosed with hyperthyroidism.

Case report

An 85-year-old-man, with a history of coronary artery disease (CAD), was referred to the documented center with severe ongoing chest pain and progressive dyspnea. The patient had a prior PCI of the right coronary artery and distal left circumflex artery (LCX) performed 1 year prior to the current admission to hospital. Additionally, the patient had severe peripheral artery disease and had undergone multiple prior percutaneous transluminal angioplasty of the limbs. Relevant coronary risk factors included hypertension, hypercholesterinemia and positive family history of CAD. The patient was hemodynamically stable, and on physical examination no relevant abnormalities were detected. Initial laboratory testing revealed an elevated level of high sensitive troponin T and a normal level of creatine kinase (CK), and creatine kinase myocardial band (CK-MB). An electrocardiogram showed no relevant ST segment changes, and transthoracic echocardiography showed normal biventricular function (left ventricular ejection fraction of 55%) without significant valve disease. The estimated glomerular filtration rate was 74 mL/min/1.73 m^2. Additionally, thyroid stimulating hormone was suppressed, 0.11 μlU/L (normal range [NR] 0.27–4.2 μlU/L), whereas T_3 (4.2 pmol/L [NR 3.1–6.8 pmol/L]) and T_4 was normal (16.7 pmol/L [NR 12–22 pmol/L]). Due to the possibly underlying subclinical hyperthyroidism, an endocrinological consultation took place which revealed the first diagnosis of an ongoing thyroid autonomy.

A decision was made to proceed with invasive CAG within 72 hours due to intermediate risk, using low-dose gadolinium for anatomy road mapping.

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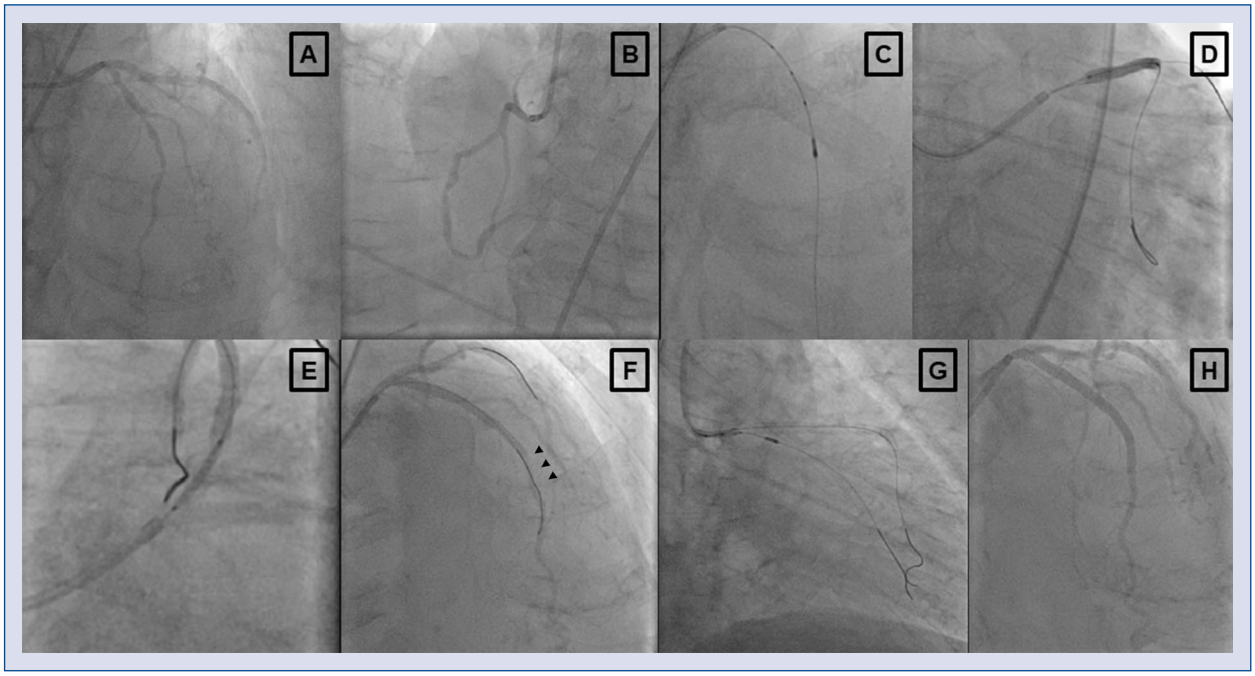

Figure 1. Percutaneous coronary intervention road mapping with intra-arterial gadolinium injection assisting fractional flow reserve coronary physiology assessment and intravascular ultrasound (IVUS) guided stent implantation; **A, B.** Left and right coronary injections with gadolinium; **C.** IVUS in the left anterior descending artery (LAD); **D, E.** Predilation of the proximal LAD and stenting; **F.** Distal edge dissection (arrowhead); **G.** IVUS in the left circumflex artery; **H.** Final result.

According to a previously reported risk of cardiac arrhythmia and potential hemodynamic instability [8], 5 mg of metoprolol intravenously (relative beta-1 selectivity) was administered, defibrillator paddles were applied, hemodynamics were continuously measured and 1–2 cc first time injections before angiography of the left and right coronaries were administered (Fig. 1A, B). Coronary physiology assessment of fractional flow reserve (FFR) (Comet pressure wire, Boston Scientific, Natick, Massachusetts, USA) was performed. At maximum hyperemia, FFR of the left anterior descending artery (LAD) was positive (0.77), whereas LCX remained functionally insignificant (0.89). Thereafter proceeding with PCI, exchanging for regular workhorse wire (Sion Blue [Asahii Intecc. Nagoya, Japan]) and evaluating the plaque burden, vessel diameter and lesion length (Fig. 1C) with intravascular ultrasound (IVUS [Eagle Eye, Philips Volcano, Amsterdam, Netherlands]). Two drug eluting stents were implanted (2.5 × 12 mm, 2.75 × 38 mm) in the middle and proximal LAD segments. After post-dilation optimal stent expansion was confirmed with control IVUS (Fig. 2). Total procedure and fluoroscopy times were 55 and 10 minutes, respectively. 35 mL of gadolinium was used overall. The patient was discharged on dual antiplatelet therapy on the 4th day post-PCI. Endocrinology control was scheduled to evaluate the thyroid autonomy 2 weeks post-PCI, and thiamazole was added to his therapy at discharge.

Discussion

This report illustrates the concept of using gadolinium to map the coronary anatomy in patients with absolute contraindication of using conventional iodinated contrast agents, that can assist coronary physiology and IVUS for percutaneous management of CAD without any iodinated contrast use.

The incidence of iodine-induced thyrotoxicosis after administration of iodinated contrast agent remains low, which mostly results in subclinical hyperthyroidism in euthyroid patients regardless [1, 2]. Nevertheless, coexisting subclinical hyperthyroidism and ischemic heart disease combined with iodinate contrast load after CAG has a significant impact on worsening its clinical conditions that may require further treatment, clinical follow-up or even re-hospitalization after 1 year of CAG/PCI [3]. Bonelli et al. [3] analyzed an 810

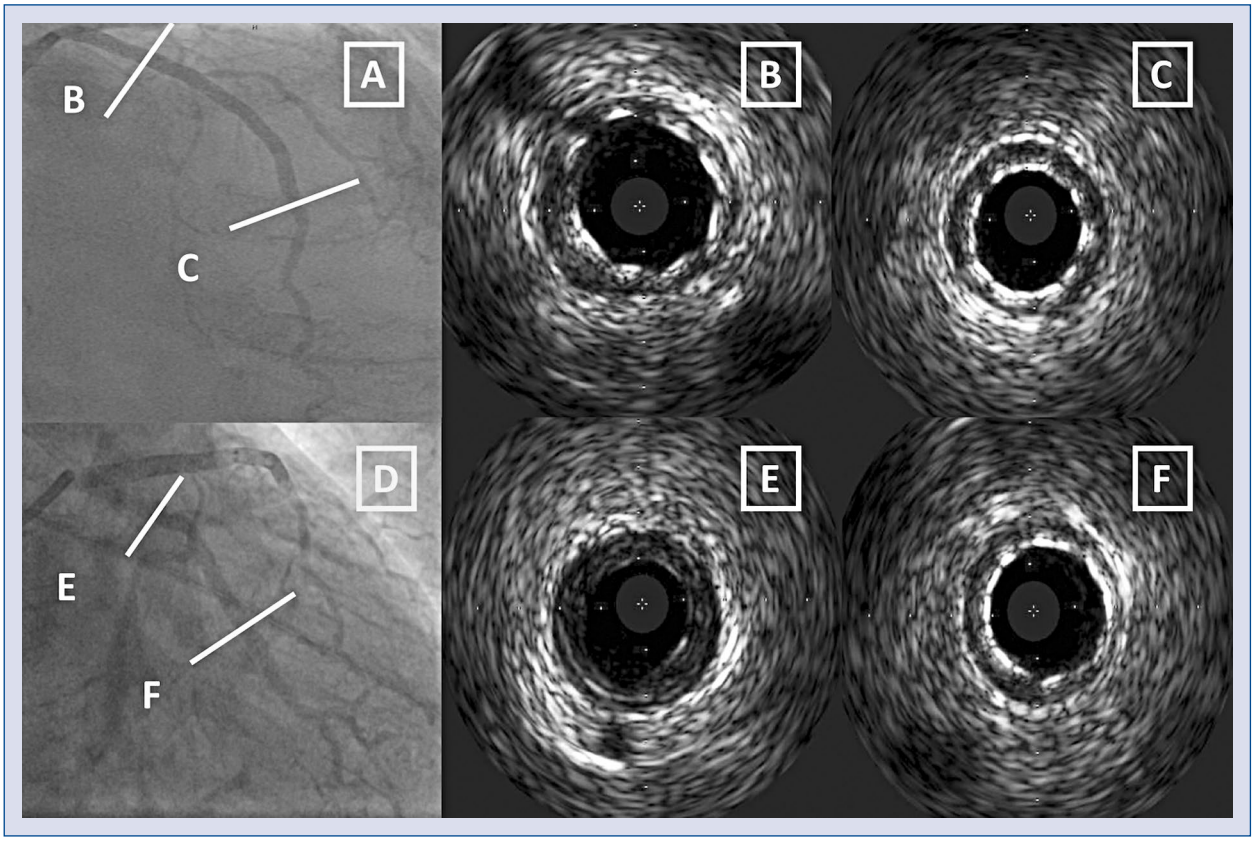

Figure 2. Images of intravascular ultrasound (IVUS) pullbacks performed in the left anterior descending artery (LAD), and the left circumflex artery (LCX); **A–C.** Pullback IVUS images of the LAD; **D–F.** Pullback IVUS images of the LCX.

patient cohort without known thyroid diseases who had undergone elective CAG. At baseline, 7.2% of the patients had hyperthyroidism, that increased to 10% after CAG. Independent predictors of hyperthyroidism development were baseline free T_4 levels, thyroid nodules, age > 60, male gender, and positive family history of thyroid diseases. Despite endocrinology follow up and therapy optimization, 4.2% at 3 months, and 2.5% at one year still had hyperthyroidism [3]. Additionally, in elderly patients, the risk of thyrotoxicosis after CAG with underlying thyroid disease is increased [9], and can be potentially life threatening, that may lead to cardiac tachyarrhythmias, heart failure, pulmonary arterial hypertension, pulmonary embolism, and cardiomyopathy.

Current guidelines propose early decision making on timing of angiography and possible intervention, especially in high-risk patient subgroups (elevated cardiac biomarkers at baseline, coexisting diabetes mellitus, Global Registry of Acute Coronary Events Risk Score [GRACE score > 140], age of 75 ≤ years) with the ultimate goals of reducing length of hospital stay, refractory ischemia and mortality. In the present report, the patient's GRACE score was 137, thus current ESC/EACTS guidelines indicates invasive treatment in < 72 hours (Class I, Level A) [10]. The use of coronary physiology (such as FFR or instant wave-free ratio) has been established as a feasible and effective option for culprit lesion identification in ACS patients with multivessel disease, nevertheless its prognostic value remains limited [10]. Moreover, identification of the culprit lesion remains challenging in a non-negligible number of cases with non-ST elevation ACS, that may require additional tools — such as intravascular imaging — which may further assist clinical decision making. Coronary physiology combined with intravascular imaging (IVUS in the current report) provides a meticulous assessment of plaque instability and flow limitation, that has also confirmed the need for intervention in the aforementioned clinical scenario where conventional iodinated contrast use was not amenable.

Zero contrast and ultra-low contrast use [11] during PCIs treatment of complex CAD (such as chronic total occlusions) has been previously reported. The latter studies, however, reported

contrast administration (zero contrast PCI was defined < 15 mL use of contrast medium), or recent diagnostic angiography was available before PCI that served as a road map for these technically challenging cases.

The use of gadolinium, as an alternative option for replacing iodinated contrast media for coronary angiography has been previously introduced [8], however its use has been limited due to (a) lower image quality, (b) potential adverse events of ventricular tachycardia/fibrillation or hemodynamic instability, and (c) its relatively high cost. The combination of IVUS and gadolinium has been reported to overcome an adverse reaction of iodinated contrast induced thrombocytopenia [7].

Applying gadolinium only for coronary road mapping (limiting its use only for the initial and final angiography) in combination with coronary physiology and IVUS is a potential option to guide complex coronary interventions with the benefit of fully avoiding using low osmolality iodinated contrast agents and hindering nephrotoxicity, adverse allergic reactions or thyrotoxicosis post-PCI. Before gadolinium injection, precautionary steps are mandatory to avoid adverse cardiac events. Herein, protocol included the following steps: (a) administration of intravenous beta-blocker, (b) applying defibrillator paddles, (c) monitoring arterial pressure, (d) avoiding pressure dampening of guiding catheters (use of guiding catheters with side holes however, could further reduce image quality), (e) and adding slow and low amounts of test injections.

Conclusions

This report demonstrates the feasibility of a concept combining gadolinium, IVUS, and coronary physiology to treat patients with CAD and severe coexisting comorbidities that can be aggravated by iodinated contrast media.

Conflict of interest: Kambis Mashayekhi, MD: honoraria/consulting fees from Ashai Intecc, Boston, Medtronic, Teleflex, Cardinal Health, Abboth, Biotronik, Terumo, AstraZeneca, Daiichi Sankyo; Remaining authors: nothing to disclose.

References

1. Marraccini P, Bianchi M, Bottoni A, et al. Prevalence of thyroid dysfunction and effect of contrast medium on thyroid metabolism in cardiac patients undergoing coronary angiography. Acta Radiol. 2013; 54(1): 42–47, doi: 10.1258/ar.2012.120326, indexed in Pubmed: 23125395.
2. Hintze G, Blombach O, Fink H, et al. Risk of iodine-induced thyrotoxicosis after coronary angiography: an investigation in 788 unselected subjects. Eur J Endocrinol. 1999; 140(3): 264–267, doi: 10.1530/eje.0.1400264, indexed in Pubmed: 10216523.
3. Bonelli N, Rossetto R, Castagno D, et al. Hyperthyroidism in patients with ischaemic heart disease after iodine load induced by coronary angiography: Long-term follow-up and influence of baseline thyroid functional status. Clin Endocrinol (Oxf). 2018; 88(2): 272–278, doi: 10.1111/cen.13494, indexed in Pubmed: 29023926.
4. Rieger J, Sitter T, Toepfer M, et al. Gadolinium as an alternative contrast agent for diagnostic and interventional angiographic procedures in patients with impaired renal function. Nephrol Dial Transplant. 2002; 17(5): 824–828, doi: 10.1093/ndt/17.5.824, indexed in Pubmed: 11981070.
5. Sayin T, Turhan S, Akyürek O, et al. Gadolinium:nonionic contrast media (1:1) coronary angiography in patients with impaired renal function. Angiology. 2007; 58(5): 561–564, doi: 10.1177/0003319707303640, indexed in Pubmed: 17906283.
6. Juneman E, Saleh L, Thai H, et al. The use of gadolinium in patients with contrast allergy or renal failure requiring coronary angiography, coronary intervention, or vascular procedure. Catheter Cardiovasc Interv. 2011; 78(5): 747–754, doi: 10.1002/ccd.22907, indexed in Pubmed: 21780275.
7. Cubero-Gómez J, Márquez FG, la-Llera LDd, et al. Severe thrombocytopenia induced by iodinated contrast after coronary angiography: The use of gadolinium contrast and intravascular ultrasound as an alternative to guide percutaneous coronary intervention. Rev Port Cardiol. 2017; 36(1): 61.e1–61.e4, doi: 10.1016/j.repce.2016.12.009.
8. Kälsch H, Kälsch T, Eggebrecht H, et al. Gadolinium-based coronary angiography in patients with contraindication for iodinated x-ray contrast medium: a word of caution. J Interv Cardiol. 2008; 21(2): 167–174, doi: 10.1111/j.1540-8183.2007.00340.x, indexed in Pubmed: 18312304.
9. Ledingham D, Carey P, Junejo S. The dangers of iodine-based contrasts in an elderly patient with thyroid disease. BMJ Case Rep. 2015; 2015, doi: 10.1136/bcr-2014-207657, indexed in Pubmed: 25804944.
10. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019; 40(2): 87–165, doi: 10.1093/eurheartj/ehy394, indexed in Pubmed: 30165437.
11. Ali ZA, Karimi Galougahi K, Nazif T, et al. Imaging- and physiology-guided percutaneous coronary intervention without contrast administration in advanced renal failure: a feasibility, safety, and outcome study. Eur Heart J. 2016; 37(40): 3090–3095, doi: 10.1093/eurheartj/ehw078, indexed in Pubmed: 26957421.