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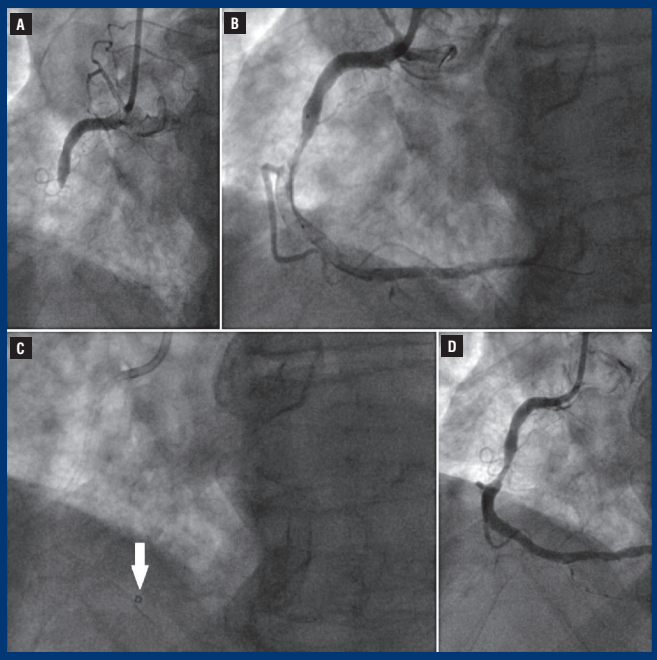

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Impaired coronary flow reserve in patients with poor type 2 diabetes control: Preliminary results from prospective microvascular dysfunction registry

Lukasz Niewiara[1, 2], Pawel Kleczynski[1, 3], Bartlomiej Guzik[1, 3], Piotr Szolc[1, 3], Jakub Baran[1, 3], Jakub Podolec[1, 3], Marta Diachyshyn[1], Krzysztof Zmudka[1, 3], Jacek Legutko[1, 3]

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Abstract

Background: *Type 2 diabetes (DM) is a common comorbidity associated with cardiovascular disease, especially when poor glucose control is present. Extracardiac microcirculatory complications prevalence is well documented, however coronary microcirculatory dysfunction (CMD) seem to be underreported in this group.*

Methods: *The present study analyzed coronary physiology measurements (coronary flow reserve [CFR], index of microcirculatory resistance [IMR], resistance reserve ratio [RRR]) in 47 diabetic patients (21 subjects with poor glycemia control defined as fasting glucose levels > 7.2 mmol/L and 26 with normal fasting glucose), and compared to 54 non-diabetic controls, who had undergone coronary angiography due to symptoms of chronic coronary syndrome. The median age of patients was 65.5 [59.0; 73.0] years old, 74% male, similar in terms of cardiovascular risk factors and prior myocardial infarction. Insulin was used by 19% of diabetic patients with poor glucose control and by 15% of those with DM and low fasting glucose.*

Results: *Prevalence of CMD was 38% in poor glycemia control patients, 27% in DM-patients with proper glucose control and 31% of non-diabetics. Median CFR values were the lowest in poor DM control patients compared to both, normal fasting glucose (1.75 [1.37; 2.32] vs. 2.30 [1.75; 2.85], $p = 0.026$) and to non-diabetics (1.75 [1.37; 2.32] vs. 2.15 [1.50; 2.95], $p = 0.045$). Levels of IMR, RRR and microvascular resistance reserve did not differ significantly between compared groups ($p > 0.05$ for all comparisons).*

Conclusions: *Poor glycemia control in type 2 DM might be associated with a higher prevalence of CMD driven by decreased coronary flow reserve, however, further research in larger groups of patients should be performed to confirm this observation.* (Cardiol J 2024; 31, 2: 185–192)

Keywords: coronary artery disease, coronary microcirculatory dysfunction, diabetes mellitus, coronary flow reserve, index of microcirculatory resistance

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Introduction

Type 2 diabetes mellitus (DM) is a common comorbidity in the general population with a prevalence increasing worldwide, frequently diagnosed in patients with cardiovascular disease [1]. It leads to a wide range of vascular and non-vascular complications especially when associated with poor glucose control [1, 2]. Despite the improvement in medical treatment, diabetic patients still have an increased risk for microvascular and macrovascular complications compared to non-diabetic subjects [3]. Moreover, it has been recognized that coronary microvascular dysfunction (CMD) is an early condition in DM that may precede macrovascular disease leading to an accelerated development of obstructive coronary artery disease (CAD) [4]. Coronary flow reserve (CFR) is an index of microvascular function in patients without significant epicardial coronary artery stenosis and has been used to disclose impaired microcirculation by the means of bolus thermodilution [5]. The index of microcirculatory resistance (IMR) has been proposed as a simple, specific and reproducible invasive method of assessing coronary microcirculation, also relying on thermodilution [6]. IMR provides a measurement of the minimum achievable microcirculatory resistance in a target coronary artery territory, enabling a quantitative assessment of the microvascular integrity. Nevertheless, the presence and related pathological mechanisms underlying CMD in diabetic patients with poor DM control are still under-reported, following the limited ability to reliably assess coronary microcirculation. Therefore, the aim herein, was to assess the impact of higher fasting glucose levels on prevalence of CMD in patients with type 2 DM.

Methods

In this prospective cohort study, patients with symptoms of chronic coronary syndromes aged > 18 years with at least one borderline (i.e. > 40% and < 90% diameter stenosis) coronary lesion were included. Patients with significant CAD, acute coronary syndromes, decompensated heart failure, severe valvular disease, hypertrophic cardiomyopathy, chronic inflammatory disease, rheumatic disease, and an active neoplasm were excluded. The study protocol conformed with the ethical guidelines of the 1975 Declaration of Helsinki with later amendments. All patients gave informed consent. The study was approved by the institutional ethical board (application number 122.6120.262.2015, 19 Nov 2015).

Glucose metabolism assessment/optimal glycemiacontrol in diabetes

A fasting glucose level of 7.2 mmol/L was used to differentiate between patients with optimal diabetes control (Group B) and poor glycemiacontrol (Group C), as this value is needed to achieve HbA1c glucose levels < 7.0% [7]. HbA1c levels itself were measured by the High Performance Liquid Chromatography (HPLC) method, however, the methodology was changed during study recruitment and therefore it was not used to differentiate between good and poor glycemiacontrol. Non-diabetic patients were qualified as the control (Group A).

Invasive coronary angiography and physiological measurements

Invasive coronary angiography was recorded with standard perpendicular projections, using a 6 French diagnostic catheter. Quantitative coronary angiography (QCA) was performed by an independent core lab analyst blinded to the results of coronary physiology, with the use of the edge detection system (CAAS 5.7 QCA system, Pie Medical).

Resting full-cycle ratio (RFR)

The RFR was calculated as the lowest filtered Pd/Pa (a mean distal coronary pressure [Pd] to aortic pressure [Pa]) value from four consecutive cardiac cycles, using Coroflow software ver. 3.0 (Abbott, US). A value of 0.89 was set as a cut-off for significant epicardial stenosis [8].

Fractional flow reserve (FFR)

Fractional flow reserve was calculated as a mean distal coronary pressure (Pd) to aortic pressure (Pa) ratio during stable hyperemia achieved with a continuous intravenous infusion of 140 μg/ /kg/min of adenosine, using a Pressure Wire X sensor (Abbott, US) and Coroflow software ver. 3.0 (Abbott, US) [9, 10].

Coronary flow reserve (CFR)

Thermodilution-based CFR was assessed using Pressure Wire X (Abbott, US) with the achievement of full hyperemia with continuous intravenous infusion of 140 μg/kg/min of adenosine [11]. An abnormal value of CFR < 2.0 was assumed and was attributed to coronary microcirculatory dysfunction when no significant epicardial stenosis was present [12].

Index of microcirculatory resistance (IMR)

Hyperemic mean time of saline transit and distal coronary pressures during full hyperemia were used for the IMR calculation [6]. FFR values obtained during hyperemia were used to calculate corrected IMR, according to Yongs' formula [13]. The cut-off value for abnormal IMR was ≥ 25.

Resistive reserve ratio (RRR)

A resistive reserve ratio was calculated using IMR, baseline mean transit time and distal coronary pressure to assess vasodilatory microcirculation capacity [14].

Microvascular resistance reserve (MRR)

Coronary flow reserve, baseline aortic pressures and hyperemic coronary distal pressures were used to calculate MRR (Equation 1), as proposed by De Bruyne et al. [15, 16].

$$MRR = CFR \times \frac{P_{aortic\ at\ rest}}{P_{distal\ at\ hyperemia}} \quad \text{(Equation 1)}$$

Coronary microcirculatory dysfunction

Patient was diagnosed with CMD when abnormal values of IMR (≥ 25) or CFR < 2.0 (in case of no significant stenosis) were recorded in any of tested vessels [12].

Statistical analysis

Normality of values distribution was assessed with the Shapiro-Wilk test. Continuous values were presented as a mean with standard deviation for normal distribution and otherwise as a median with interquartile range. Comparisons between multiple groups were performed using ANOVA F-test and the Kruskal-Wallis test, respectively. Categorical variables were presented as proportions of groups and compared using χ^2 test. A criterion of $\alpha \leq 0.05$ for two-sided test was considered significant. Calculations were performed using R language version 4.0 (R Foundation for Statistical Computing, Vienna, Austria), with Tidyverse package ecosystem for computation and ggplot2 package for visualization.

Results

Patient level analysis

Group characteristics. In this prospective observational study 101 patients, 54 non-diabetic (Group A), 26 with well controlled diabetes (Group B) and 21 with poor controlled diabetes (Group C) were included. Median age of patients was 65 years and was similar in all groups. About 25% of analyzed patients were female. All groups were similar in terms of body mass index (BMI), history of arterial hypertension, dyslipidemia, or prior myocardial infarction (MI). Left ventricular ejection fraction (LVEF) was similar in all groups, however poor controlled DM patients had higher left ventricular mass index compared to non-diabetics (128 vs. 96 g/m^2, p = 0.004 for post hoc analysis). All patients were diagnosed with chronic coronary syndromes, without any significant differences in terms of angina according to Canadian Cardiovascular Society (CCS) class on admission. All groups were also similar in terms of antiplatelet therapy, statin use, beta-blockers or antihypertensive drugs. Detailed patient characteristics are presented in Table 1.

Diabetes treatment and glycemia control. Over 60% of all diabetic patients used metformin without significant differences between groups B and C. Patients with poor controlled DM were treated with insulin more often than well controlled diabetic patients (20% vs. 15%, p = 0.02 for χ^2 test). Neither of these groups of patients used SGLT2 inhibitors nor GLP-1 inhibitors. Patients with poor controlled DM had significantly higher levels of fasting glucose compared to non-diabetics and well controlled DM (median 9.9 [8.1; 11.0] mmol/L vs. 5.4 [5.1; 6.0] mmol/L, p < 0.001 and 9.9 mmol/L vs. 5.8 [5.3; 6.7] mmol/L, p < 0.001 in *post hoc* analysis, respectively). Similarly, HbA1c levels were significantly higher in patients with poor controlled DM as compared to both, well controlled DM and non-diabetics (7.7 [6.6; 7.9]% vs. 6.1 [5.6; 6.7]%, p = 0.004 and 7.7 [6.6;7.9]% vs. 5.7 [5.3; 5.9]% mmol/L, p < 0.001, respectively). In all cases diabetes was diagnosed prior to the index hospitalization. A detailed comparison of groups is presented in Table 1.

CMD diagnosis. Microcirculatory dysfunction prevalence was the highest in group C (38% of patients with poor glycemic control), however the difference between groups was not statistically significant. Details are presented in Figure 1.

Per vessel analysis

Alongside with patient level analysis, per vessel analysis was performed. Detailed results are presented in Table 2.

Coronary angiography. A total of 157 coronary arteries were analyzed, predominantly (over 57%) left anterior descending (LAD). Median diameter stenosis was 45% with interquartile range (IQR) from 40% to 50%. RFR values were similar in all compared groups, with median of 0.89 (p = 0.877).

Table 1. Baseline patient characteristics, pharmacotherapy, and laboratory results.

	Total (n = 101)	Group A (Non-diabetic; n = 54)	Group B (Well controlled DM; n = 26)	Group C (Poor controlled DM; n = 21)	P value
Demography and medical history					
Age [years]	65.5 [59.0;73.0]	64.5 [59.0;69.8]	68.0 [63.0;74.0]	66.0 [59.0;73.0]	0.274
Female sex	26 (25.7%)	14 (25.9%)	9 (34.6%)	3 (14.3%)	0.285
BMI [kg/m^2]	28.1 [26.0;31.8]	27.9 [25.0;31.2]	29.1 [27.7;30.9]	29.6 [26.0;35.3]	0.091
Dyslipidemia or statin use	92 (91.1%)	47 (87.0%)	24 (92.3%)	21 (100%)	0.257
Arterial hypertension	97 (96.0%)	52 (94.5%)	25 (96.2%)	20 (100%)	0.811
Prior AMI	25 (27.8%)	11 (23.9%)	10 (41.7%)	4 (20.0%)	0.197
Smoking status:					0.192
Never	52 (55.9%)	26 (53.1%)	17 (70.8%)	9 (45.0%)	
Current or former	41 (44.1%)	23 (46.9%)	7 (29.2%)	11 (55.0%)	
Angina according to CCS scale:					0.656
0	21 (20.8%)	9 (16.7%)	6 (23.1%)	6 (28.6%)	
1	30 (29.7%)	17 (31.5%)	8 (30.8%)	5 (23.8%)	
2	36 (35.6%)	20 (37.0%)	7 (26.9%)	9 (42.9%)	
3	14 (13.9%)	8 (14.8%)	5 (19.2%)	1 (4.76%)	
Dyspnea according to NYHA class:					0.891
0	56 (55.4%)	32 (59.3%)	13 (50.0%)	11 (52.4%)	
1	12 (11.9%)	6 (11.1%)	4 (15.4%)	2 (9.52%)	
2	30 (29.7%)	14 (25.9%)	9 (34.6%)	7 (33.3%)	
3	3 (2.97%)	2 (3.70%)	0 (0.00%)	1 (4.76%)	
Laboratory results					
Hemoglobin [g/dL]	13.8 [12.9;15.0]	14.0 [13.4;14.9]	13.4 [12.1;14.3]	14.0 [12.7;15.6]	0.096
LDL [mmol/L]	2.22 [1.79;2.86]	2.24 [1.92;2.80]	2.05 [1.64;2.26]	2.51 [2.14;3.45]	0.069
TG [mmol/L]	1.29 [0.93;1.82]	1.29 [0.90;1.81]	1.20 [0.94;1.64]	1.52 [1.03;1.92]	0.451
eGFR CKD	78.0 [65.0;90.0]	80.0 [72.0;90.5]	73.5 [60.5;83.2]	86.0 [57.0;93.0]	0.110
Fasting glucose [mmol/L]	5.80 [5.30;7.20]	5.40 [5.10;6.00]	5.80 [5.32;6.68]	9.90$^{\#}$ [8.10;11.0]	**< 0.001**
HbA1c [%]	5.80 [5.50;6.50]	5.70 [5.30;5.90]	6.05$^{\#\#}$ [5.57;6.67]	7.70$^{\#}$ [6.55;7.90]	**< 0.001**
CMD final diagnosis					0.381
CMD	32 (31.7%)	17 (31.5%)	7 (26.9%)	8 (38.1%)	
Non-CMD	19 (18.8%)	7 (13.0%)	8 (30.8%)	4 (19.0%)	
Revascularization	50 (49.5%)	30 (55.6%)	11 (42.3%)	9 (42.9%)	
Echocardiography					
LVEF [%]	55.0 [50.0;60.0]	58.5 [50.0;60.0]	56.0 [50.5;60.0]	50.0 [40.0;60.0]	0.054
LVMI [g/m^2]	106 [88.9;128]	95.7 [86.8;115]	108 [83.0;130]	128 [108;139]$^{\#}$	**0.006**
Coronary artery disease:					0.190
Single vessel	51 (51.0%)	26 (48.1%)	18 (69.2%)	7 (35.0%)	
Dual vessel	38 (38.0%)	21 (38.9%)	7 (26.9%)	10 (50.0%)	
Triple vessel	11 (11.0%)	7 (13.0%)	1 (3.85%)	3 (15.0%)	
Gensini score	9.50 [6.00;14.0]	10.0 [7.00;15.6]	7.25 [5.00;11.0]	9.50 [5.00;11.5]	0.255
SBP [mmHg]	136 [122;151]	131 [120;151]	136 [120;150]	146 [134;156]	0.339
Pharmacotherapy					
Metformin	29 (28.7%)	NA	16 (61.5%)$^{\#\#}$	13 (65.0%)$^{\#}$	< 0.001
Insulin	8 (7.92%)	NA	4 (15.4%)	4 (20.0%)	0.002
ASA	91 (90.1%)	49 (90.7%)	21 (80.8%)	21 (100%)	0.095
ACEI/ARB	91 (91.0%)	49 (90.7%)	25 (96.2%)	17 (85.0%)	0.462
Statin use	99 (98.0%)	53 (98.1%)	26 (100%)	20 (95.2%)	0.439
Beta-blockers	86 (85.1%)	44 (81.5%)	23 (88.5%)	19 (90.5%)	0.604
Non-dihydropyridines CCA	9 (9.00%)	3 (5.56%)	2 (8.00%)	4 (19.0%)	0.205
Dihydropyridines CCA	33 (32.7%)	17 (31.5%)	10 (38.5%)	6 (28.6%)	0.744

Data are shown as number (%) or mean [interquartile range]; ACEI/ARB — angiotensin converting enzyme inhibitor/angiotensin receptor blocker; AMI — acute myocardial infarction; BMI — body mass index; CCA — calcium channel antagonist; CMD — coronary microcirculatory dysfunction; eGFR-CKD — estimated glomerular filtration rate using CKD-EPI formula; LDL — low density lipoprotein; LVEF — left ventricle ejection fraction; LVMI — left ventricle mass index; NA — not applicable; NYHA — New York Heart Association; SBP — systolic blood pressure; TG — triglycerides; $^{\#}p < 0.05$ Group C vs. A; $^{\#\#}p < 0.05$ Group B vs. A

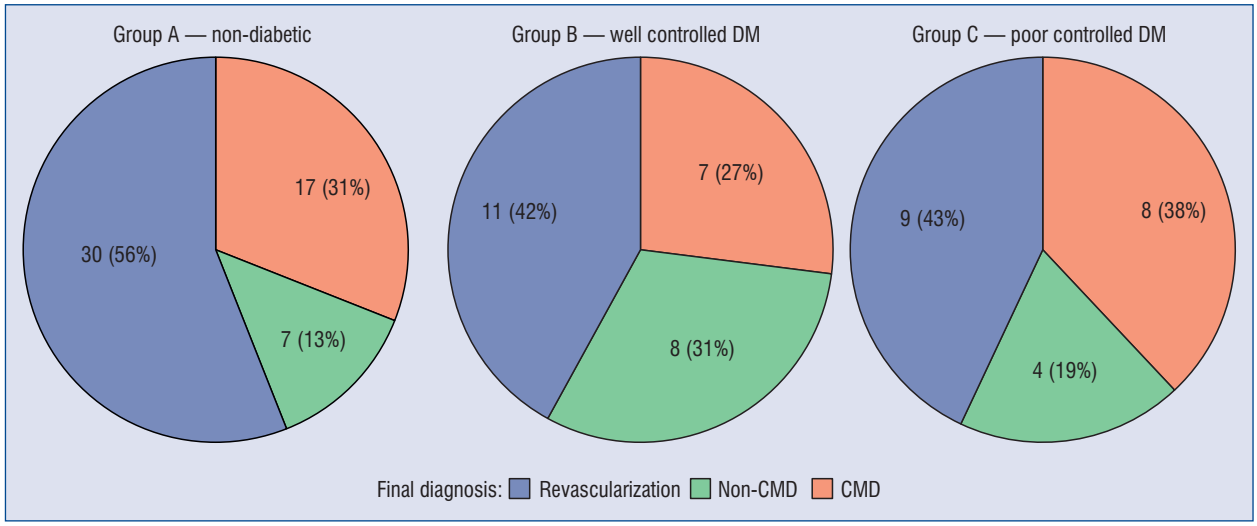

Figure 1. Coronary microcirculatory dysfunction prevalence according to diabetes mellitus (DM) status. Patients without diabetes (Group A), well controlled DM (Group B) and poor controlled DM (Group C); CMD — coronary microvascular dysfunction; p = 0.37.

Table 2. Per vessel analysis of coronary angiography and coronary physiology measurements.

	Total (n = 157)	Group A (Non-diabetic; n = 90)	Group B (Well controlled DM; n = 31)	Group C (Poor controlled DM; n = 36)	P value
Vessel diagnosed					0.270
LAD	88 (57.1%)	48 (54.5%)	20 (64.5%)	20 (57.1%)	
LCx	39 (25.3%)	20 (22.7%)	7 (22.6%)	12 (34.3%)	
RCA	27 (17.5%)	20 (22.7%)	4 (12.9%)	3 (8.57%)	
QCA					
Diameter stenosis	45.0 [40.0;50.0]	45.0 [40.0;50.0]	46.0 [39.0;48.0]	45.5 [40.5;48.5]	0.917
Reference diameter	2.67 [2.38;2.97]	2.67 [2.48;2.97]	2.78 [2.54;3.04]	2.51 [2.29;2.93]	0.314
Physiologic measurements					
RFR	0.89 [0.84;0.94]	0.90 [0.85;0.94]	0.89 [0.83;0.93]	0.89 [0.84;0.94]	0.877
FFR	0.84 [0.78;0.91]	0.83 [0.76;0.90]	0.84 [0.78;0.90]	0.84 [0.80;0.91]	0.640
FFR ≤ 0.80	51 (32.5%)	31 (35.5%)	11 (29.0%)	9 (25.7%)	0.636
CFR	2.10 [1.50;2.70]	2.15 [1.50;2.95]	2.30 [1.75;2.85]	1.75 [1.37;2.32] $^{\#,\#\#}$	0.020
RRR	2.70 [1.80;3.70]	2.60 [1.90;3.90]	3.00 [2.10;3.85]	2.65 [1.60;3.30]	0.100
MRR	2.85 [1.98;3.89]	2.71 [1.97;3.97]	3.19 [2.11;4.16]	3.05 [1.74;3.31]	0.573
IMR	19.8 [13.1;28.5]	21.1 [12.8;30.1]	21.9 [15.3;27.9]	15.2 [12.7;21.9]	0.095

Data are shown as number (%) or mean [interquartile range]; CFR — coronary flow reserve; FFR — fractional flow reserve; IMR — index of myocardial resistance; LAD — left anterior descending artery; LCx — left circumflex branch; QCA — quantitative coronary angiography; RCA — right coronary artery; RFR — resting full cycle ratio; RRR — relative resistive ratio; $^{\#}$p < 0.05 Group C vs. B; $^{\#\#}$p < 0.05 Group C vs. A

Median FFR value was 0.84 and did not differ between groups. In 51 cases (32% of vessels), lesions were hemodynamically significant (i.e., FFR ≤ 0.80), and were qualified for revascularization.

CFR, IMR, RRR and MRR measurements results. CFR values were significantly lower in patients with poor controlled DM as compared to both, non-diabetic and well controlled DM group

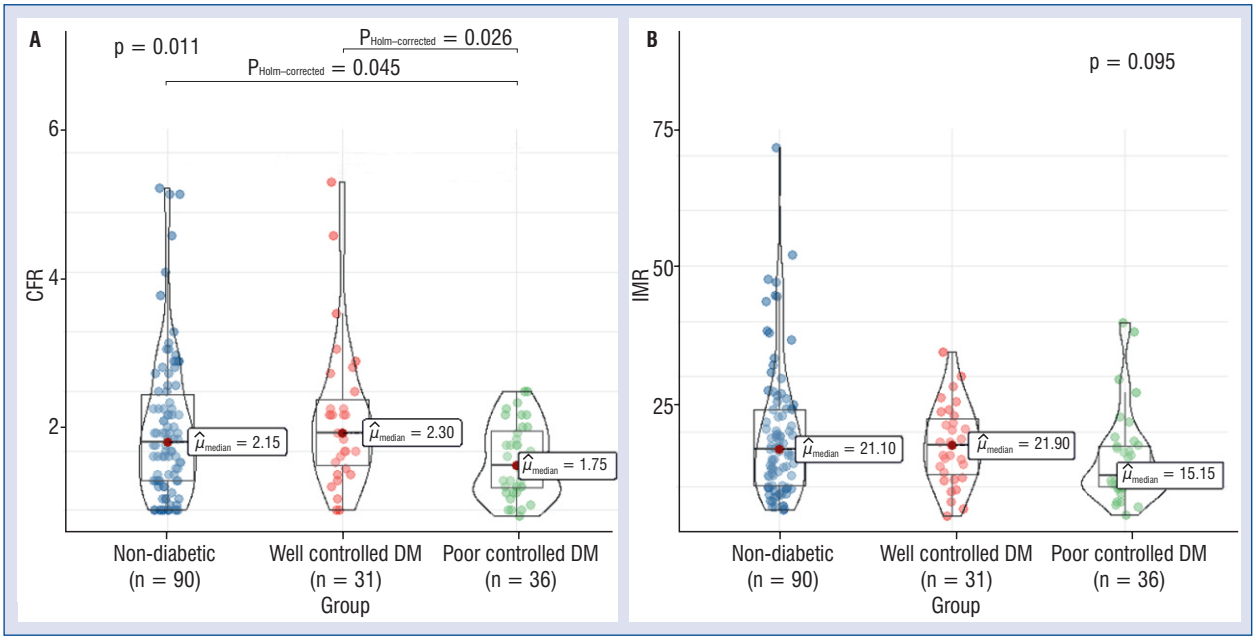

Figure 2. Microcirculatory indices comparison; **A.** Coronary flow reserve (CFR) values according to diabetes status; **B.** Index of Microcirculatory Resistance (IMR) levels according to diabetes status; DM — diabetes mellitus.

(1.75 vs. 2.3, p = 0.026, 1.75 vs. 2.15, p = 0.026, respectively, overall p = 0.02). RRR was the highest in patients with well controlled DM, however the difference was not statistically significant. Similarly, no significant difference in IMR and MRR values between analyzed groups were observed. Detailed results are presented in Table 2 and Figure 2.

Discussion

The present study aimed to compare CMD prevalence in type 2 DM patients with well controlled diabetes and subjects with poor DM control. The main findings of this study are following: (1) in patients with poor controlled diabetes there are lower CFR values as compared to both with non-diabetic patients and patients with good fasting glucose levels; (2) level of coronary microcirculatory dysfunction may be associated with fasting glucose levels.

Microcirculatory dysfunction usually precedes structural myocardial changes; thus, the evolving ability to an early assessment of CMD holds great potential for risk stratification and patient therapy. In the current study, CMD prevalence measured by thermodilution derived indices was highest in the poor glucose control group and was present in 38% of patients. No similar data was found using CMD definition from current European Society of Cardiology (ESC) guidelines on chronic coronary syndromes and based on thermodilution assessment [12]. Noninvasive studies, as reported by Osborne et al. [17] suggest even higher prevalence of CMD to be present in over 59% diabetic patients diagnosed with positron emission tomography (PET) myocardial perfusion imaging. Similarly, Murthy et al. [3] observed impaired CFR in over 51% of diabetic patients in PET imaging.

In diabetic patients several risk factors of CMD were reported, including presence of arterial hypertension, dyslipidemia or higher BMI levels [5]. In the present analysis there were no significant differences between groups in terms of arterial hypertension nor presence of dyslipidemia, moreover almost all patients in our cohort were treated for these reasons. On the other hand, numerically higher median value of BMI was observed in group with poor glycemic control, without achieving a statistically significant level.

CFR values in diabetes

Increased prevalence of CMD in DM patients might be driven by decreased CFR values, increased IMR or both. In the present cohort CFR values were significantly lower in poor glucose control group and IMR levels were similar between all three groups. In recently published study by Gallinoro et al. [16], patients without significant coronary stenosis and DM type 2 had lower CFR values, mean 2.38, compared to non-diabetic

patients, however this analysis consisted of only 21 DM patients and authors did not elaborate on dependence of CFR on glucose levels [16]. Similar observation were made by Leung et al. [18], who reported CFR value of 2.76 in anterior coronary circulation and 4.35 in posterior coronary circulation in 32 diabetic patients, both significantly lower than measured in non-diabetic patients. The current analysis included a higher number; 47 patients with DM type 2, and results suggested that lower CFR values might be associated with poor glycemia control.

In exploratory analysis, CFR values were used as a surrogate to calculate novel index proposed recently by De Bruyne et al. [15], and found no significant difference between MRR values in analyzed groups, even though MRR was numerically higher in both diabetic groups when compared to the non-diabetic control.

CFR values according to glucose levels

Large epidemiological studies have shown a link between glucose levels and diabetic microvascular complications [19–21]. Moreover, intensive diabetes therapy leading to lower HbA1c levels has been proven to influence course of cardiovascular complications in DM patients [22]. Mechanism in which CFR is impaired by poor glycemia control remains unclear. Glucose level variability amplitude has been recently reported to correlate with CFR values, regardless of DM presence [23]. Furthermore, impaired coronary flow velocity ratio was associated with significantly higher fasting glucose concentration in diabetic women. Noteworthy, the difference was not observed in men [24]. In the present analysis, CFR values were significantly lower in poor controlled diabetes compared to both non-diabetics and patients with diabetes and fasting glucose < 7.2 mmol/L. This result is consistent with published data, however further research in larger populations is needed to confirm the above mentioned observation.

Limitations of the study

The present study results should be interpreted considering some limitations. This study is a preliminary report of results obtained from a relatively small group of patients, which might influence the significance level of comparisons, on the other hand a group of 47 diabetic patients seems to be one of the biggest cohorts who have been diagnosed with thermodilution based on invasive indices to date. Unfortunately, data on diabetes duration was not available in patient medical records.

Secondly, the glycemia control in patients was assessed by fasting glucose serum concentration, not by the HbA1c levels, as at the time of study recruitment HPLC methodology was still evolving, with no single standard. On the other hand, 7.2 mmol/L cut off value is a good predictor of obtaining HbA1c levels < 7.0%, which is the current goal of treatment according to ESC guidelines [1].

Thirdly, coronary microcirculatory dysfunction was diagnosed using indirect thermodilution based methodology, however IMR and CFR measurements are among methods proposed by contemporary chronic coronary syndromes ESC guidelines [25]. Taking into consideration above, results of presented study are rather hypothesis generating, and requires further research.

Conclusions

It was found that in patients with poor controlled diabetes there are lower CFR values as compared both with non-diabetic patients and patients with good fasting glucose levels. Moreover, level of coronary microcirculatory dysfunction may be associated with fasting glucose levels.

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Conflict of interest: None declared

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Repeat cryoablation as a redo procedure for atrial fibrillation ablation: Is it a good choice?

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Abstract

Background: *Ablation of atrial fibrillation (AF), both cryoballoon ablation (CBA) and radiofrequency catheter ablation (RFCA), have demonstrated to be safe and effective. About 1 in 3 patients may face a redo due to recurrence and the best technique is unknown. The aim of this study is to assess the efficacy of CBA as a repeat procedure in patients with prior CBA or RFCA.*

Methods: *A nation-wide CBA registry (RECABA) was analyzed and patients were compared who had previously undergone CBA (Prior-CB) or RFCA (Prior-RF). The primary endpoint was AF recurrence at 12 months after a 3-month blanking period. A survival analysis was performed, univariate and multivariate Cox models were also built.*

Results: *Seventy-four patients were included. Thirty-three (44.6%) were in the Prior-CB group and 41 (55.4%) in the Prior-RF. There were more reconnected pulmonary veins in the Prior-RF than in Prior-CB group (40.4% vs.16.5%, p = 0.0001). The 12-month Kaplan–Meier estimate of freedom from AF recurrence after the blanking period was 61.0% (95% confidence interval [CI] 41.4–75.8%) in the Prior-CB, and 89.2% (95% CI 73.6–95.9%) in the Prior-RF group (p = 0.002). Multivariate Cox regression pointed Prior-CB as the sole independent predictor of AF recurrence, with an adjusted hazard ratio of 2.67 (95% CI 1.05–6.79).*

Conclusions: *Repeat CBA shows higher rates of AF recurrences compared to CBA after a previous RFCA despite presenting less reconnected veins at the procedure. These data suggest that patients with AF recurrence after CBA may benefit from other ablation techniques after a recurrence.*

RECABA is registered at clinicaltrials.gov with the Unique Identifier NCT02785991. (Cardiol J 2024; 31, 2: 193–204)

Keywords: cryoablation, atrial fibrillation, catheter ablation, radiofrequency catheter ablation

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Introduction

Pulmonary vein (PV) isolation is a well-established, safe, and effective treatment for symptomatic atrial fibrillation (AF) [1, 2]. Radiofrequency catheter ablation (RFCA) and cryoballoon (CB) ablation (CBA) have shown similar results in randomized trials [3, 4]. Nevertheless, between 15% and 43% of patients may require a repeat AF ablation procedure due to symptomatic recurrence [5–7]. It is, however, not established which is the most suitable ablation technique for patients undergoing a repeat AF ablation and the possible influence of the technique used in the index procedure. The use of CBA for repeat ablation has been studied in small works with conflicting results [8–12]. The aim of this study is to evaluate the efficacy of CBA as a redo procedure for patients with prior AF ablation, by either CBA or RFCA.

Methods

Study design

The Spanish Registry of Cryoballoon Ablation (RECABA) [13] (NCT02785991) was an observational, prospective, nation-wide, multicenter study of cryoballoon AF ablation in Spanish centers. Patients were enrolled between September 2016 and January 2019. Inclusion criteria were: 1) person older than 18 years, 2) eligible for CBA according to local practice, 3) life expectancy longer than 1 year, and 4) signed informed consent.

Presented herein, is a post-hoc retrospective analysis of patients who were included for a repeat AF ablation and the previous procedure could be either CBA or RFCA. AF classification as paroxysmal (PAF) or persistent (PerAF) followed the current European Society of Cardiology guidelines at the inclusion period [14]. Data were gathered during a baseline visit at the procedure and at an established 12-month follow-up visit. For this analysis, the selected patients were those who completed a 12-month follow-up. Ethics Committee approval was obtained following local regulations, and the study was conducted in compliance with the Declaration of Helsinki and Spanish laws and regulations (Royal Decree 1090/2015, Royal Decree 1616/2009, Order SAS/3470/2009 of 16 December). The study was approved by the IRB, Comité Ético de Investigación Clínica de Euskadi (CEIC-E) on May 9, 2016. All patients signed informed consent upon inclusion.

Objective and endpoints

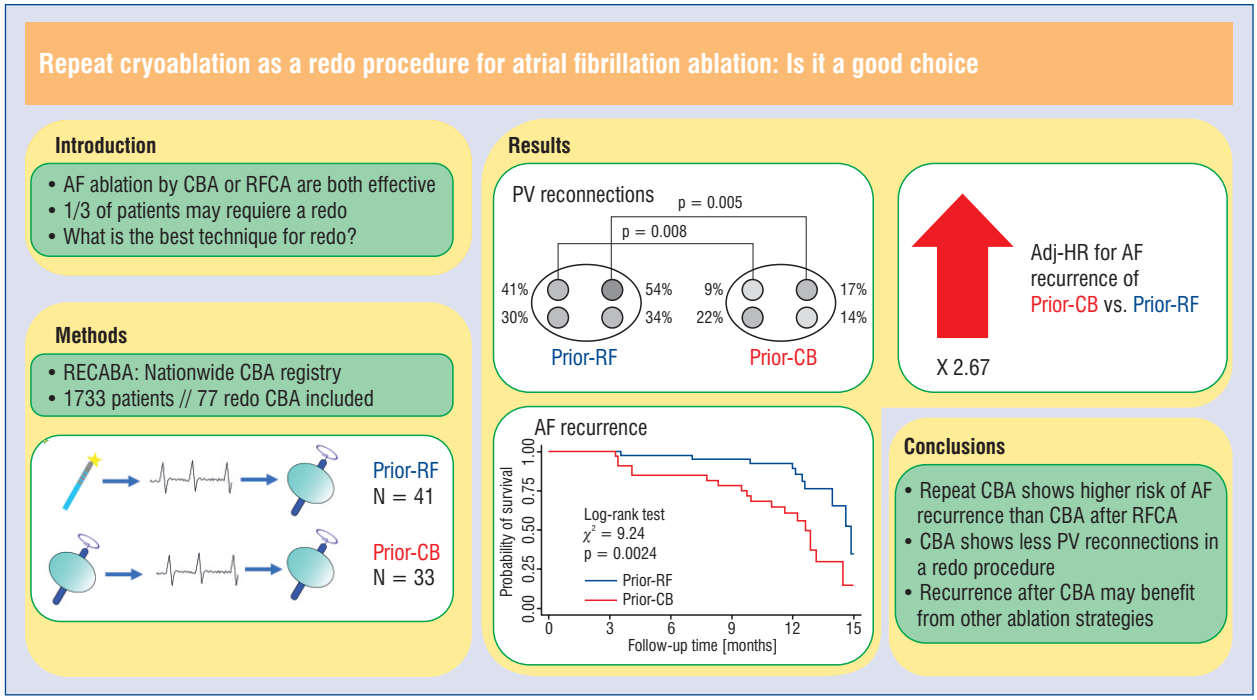
The main purpose of RECABA was to assess the standard clinical practice of CBA in Spanish centers. Considering the aim of this analysis, two groups were defined within the population, including: 1) Prior-CB: Patients referred for CBA who had undergone a previous CBA, and 2) Prior-RF: Patients referred for CBA who had undergone previous RFCA. The primary endpoint of the study was freedom from AF at 12 months after a 3-month blanking period. Secondary endpoints were clinical characteristics of the patients, dose and biophysical variables of CBA applications, vein reconnection pattern, and efficacy and safety of the procedure in the defined groups.

Cryoballoon ablation

The description of CBA has been widely reported elsewhere [15–17]. In the RECABA study, each center followed their local standards practices. In general, the procedure took place under sedation or general anesthesia. Left atrial access was performed using a dedicated needle followed by a heparin bolus. Anticoagulation status was monitored using activated clotting time with a target of 300–350 s. A 23- or 28-mm second-generation cryoballoon catheter (ArticFront ADV; Medtronic, Inc.) was deployed in the left atrium through a dedicated delivery sheath (Flexcath of Flexcath ADV; Medtronic, Inc.). Operators used a dedicated inner-lumen diagnostic catheter (Achieve of Achieve ADV; Medtronic, Inc.) to monitor local vein electrograms status during freeze applications. The initial presence of electrograms in PVs were considered reconnections. Number and length of CB applications were at the discretion of local operator, including applications on PVs isolated in previous procedures or the use of bonus freeze-applications. The use of adenosine challenge and the length of the post isolation waiting period were at the discretion of the operator. The procedure endpoint was the persistent isolation of all PVs.

Post-ablation management and follow-up

Patient's anticoagulation and antiarrhythmic drug regime followed local protocols and were at the treating cardiologist discretion. Follow-up visits were in accordance with local practice, with a pre-stablished 12-month follow-up visit. Arrhythmia detection could be based on Holter monitoring, event recording systems, implantable devices, and/



Central illustration. Graphical abstract showing group definition, pulmonary veins reconnection pattern, Kaplan-Meier survival curves and main findings; Adj-HR — adjusted hazard ratio; AF — atrial fibrillation; CBA — cryoballoon ablation; PV — pulmonary veins; RECABA — *Registro Español de Crioablación de con Balón* — Spanish registry of cryoballoon ablation; RFCA — radiofrequency catheter ablation; Prior-RF — patients subjected to cryoballoon ablation after a failed previous radiofrequency atrial fibrillation ablation; Prior-CB — patients subjected to cryoballoon ablation after a failed previous cryoballoon atrial fibrillation ablation.

/or in-clinic electrocardiogram (ECG) recording. AF recurrence was defined as an AF event lasting longer than 30 s registered by the abovementioned methods.

Statistical analysis

Quantitative variables are summarized with means and standard deviations or median and interquartile range when appropriate. Differences between groups were assessed using the t-test, or the Kruskal-Wallis test when a parametric test could not be performed. Categorical variables are summarized with percentages and differences assessed by the Pearson χ^2 test. The Kaplan-Meier method was used to build event-curves of survival from the primary endpoint and to calculate the 12-month freedom from AF estimates for each group. Log-rank test assessed the difference between groups. Univariate and multivariate Cox proportional-hazards regression models were built to evaluate possible predictors of AF-recurrence. Predictors were included in the multivariate model when a significance level of p-value below 0.10 was achieved. Statistical significance was assumed for two-sided p-values below 0.05. Data were analyzed using STATA v.15 software (StataCorp LLC).

Results

Population baseline characteristic

In total, 1733 patients from 27 Spanish centers were included in RECABA between September 2016 and January 2019. Seventy-seven (4.3%) patients underwent CBA as a redo procedure due to recurrence after an index procedure and 74 completed a 12-month follow-up visit and were included in this analysis. Thirty-three (44.6%) subjects had undergone a previous CBA (Prior-CB group) and 41 (55.4%) a previous RFCA (Prior-RF group) (Central illustration). Twenty-seven (36.5%) patients were female and mean age was 58.8 ± 10.2 years. Additionally, 60 (81.1%) subjects had PAF and 14 (18.9%) had PerAF.

Table 1 summarizes patients baseline characteristics. Thirty-one patients from the Prior-CB group (93.9%) underwent a sole index procedure, while 30 from the Prior-RF (73.2%) underwent more than one preceding AF ablation procedures ($\chi^2 = 5.4$, $p = 0.02$).

Table 1. Patients baseline characteristics and between groups differences. Categorical data are summarized in number and percentage.

	All patients (n = 74)		Prior-CB (n = 33; 44.59%)		Prior-RF (n = 41; 55.41%)		P-value
Age [years]	58.8	10.2	57.2	12.1	60.0	8.3	0.251
Female sex	27	36.5%	15	45.45%	12	29.30%	0.151
Weight [kg]	81.22	15.3	84.5	15.9	78.6	14.4	0.1
Height [cm]	171.9	11.3	171.0	11.6	172.6	11.1	0.6
BMI [kg/m^2]	27.5	4.4	28.9	4.6	26.4	3.8	**0.01**
Obesity: BMI > 30 kg/m^2	20	27.3%	13	39.4%	7	17.1%	**0.03**
Persistent AF	14	18.92%	6	18.18%	8	19.51%	0.885
Time since AF onset							0.51
< 1 year	10.2	10.2	1	3.03%	0	0.00%	
1–5 years	36.5%	36.5%	12	36.36%	14	34.15%	
> 5 years	15.3	15.3	20	60.61%	27	65.85%	
Number of previous procedures	1	1–1	1	1–1	1	1–2	**0.024**
Heart disease	5	6.76%	0	0.00%	5	12.20%	**0.038**
Ischemic heart disease	2	2.70%	0	0.00%	2	4.88%	0.198
Tachymyocardiopathy	2	2.70%	0	0.00%	2	4.88%	0.198
Hypertrophic cardiomyopathy	1	1.35%	0	0.00%	1	2.44%	0.366
Heart failure	4	5.41%	1	3.03%	3	7.32%	0.418
Risk factors							
Hypertension	32	43.24%	14	42.42%	18	43.90%	0.898
Diabetes mellitus	5	6.76%	1	3.03%	4	9.76%	0.252
Dyslipidemia	25	33.78%	12	36.36%	13	31.71%	0.674
Current smoking	8	10.81%	2	6.45%	6	15.38%	0.243
Peripheral vascular disease	3	4.05%	0	0.00%	3	7.32%	0.113
Stroke/TIA	1	1.35%	1	3.03%	0	0.00%	0.262
OSA	7	9.46%	7	21.21%	0	0.00%	**0.002**
$CHADS_2$ Score	1	(0–1)	0	0–1	1	0–1	0.634
CHA_2DS_2-VASC Score	1	(0–2)	1	0–2	1	1–2	0.666
Pacemaker carrier	2	2.70%	1	3.03%	1	2.27%	0.876
Physical activity							0.987
None	45	63.38%	21	63.64%	24	63.16%	
Mild (less 150 min/week)	14	19.72%	6	18.18%	8	21.05%	
Moderate (150–300 min/week)	10	14.08%	5	15.15%	5	13.16%	
Intense (> 300 min/week)	2	2.82%	1	3.03%	1	2.63%	
Antiarrhythmic drugs							
Current use of AAD	62	84.93%	30	90.91%	32	80.00%	0.195
Flecainide	41	66.13%	21	70.00%	20	62.50%	0.533
Propafenone	5	8.06%	2	6.67%	3	9.38%	0.696
Amiodarone	11	17.74%	4	13.33%	7	21.88%	0.379
Dronedarone	3	4.84%	1	3.33%	2	6.25%	0.593
Sotalol	3	4.84%	2	6.67%	1	3.12%	0.516
Beta-blockers	50	67.57%	22	66.67%	28	68.29%	0.882
CCB	5	7.14%	3	9.68%	2	5.13%	0.463

→

Table 1 (cont.). Patients baseline characteristics and between groups differences. Categorical data are summarized in number and percentage.

	All patients (n = 74)		Prior-CB (n = 33; 44.59%)		Prior-RF (n = 41; 55.41%)		P-value
Cardiac imaging							
LVEF:							0.688
> 50	60	95.24%	24	96%	36	94.74%	
35–50	2	3.17%	1	4%	1	2.63%	
< 35%	1	1.59%	0	0.00%	1	2.63%	
LVH	9	14.29%	2	8.00%	7	18.42%	0.247
LA enlargement	33	53.23%	17	70.83%	16	42.11%	**0.027**
Left PV							0.885
2 veins	60	81.08%	27	81.82%	33	80.49%	
Common trunk	14	18.92%	6	18.18%	8	19.51%	
Right PV							0.99
2 veins	62	84.93%	28	84.85%	34	85.00%	
Common trunk	2	2.74%	1	3.03%	1	2.50%	
> 2 veins	9	12.33%	4	12.12%	5	12.50%	

Quantitative data are summarized either with mean and standard deviation or median and interquartile range when appropriate. P-values in bold when reaching statistical significance ($p < 0.05$); AAD — antiarrhythmic drug; AF — atrial fibrillation; BMI — body mass index; CB — cryoballoon; CCB — calcium channel blocker; LA — left atrium; LVEF — left ventricular ejection fraction; LVH — left ventricular hypertrophy; OSA — obstructive sleep apnea; PV — pulmonary vein; RF — radiofrequency; TIA — transient ischemic attack

The median CHA_2DS_2-VASc score was 1 (interquartile range [IQR] 0–2) with no differences between groups (Kruskal-Wallis test $p = 0.67$). Overall, 84.9% of patients were on anti-arrhythmic drugs (AADs) at the time of the procedure, 1.6% had left ventricular ejection fraction below 35%, and 53.2% of subjects had a dilated left atrium (LA) defined as either LA diameter larger than 40 mm or LA area larger than 20 cm^2.

Cryoballoon ablation

Table 2 summarizes procedural data. From 74 procedures, 60 (82.2%) were performed using a single 28-mm CB, without differences between groups ($\chi^2 = 2.04$, $p = 0.361$).

Routine bonus freeze-application was more common in the Prior-CB group, with 51.6% of patients vs. 13.9% of the Prior-RF group ($p = 0.003$). Adenosine challenge was not used in any patient. The average procedure duration was 115.1 ± 44.5 min, with no differences between groups. In total, 49 (66.2%) patients were on AAD at discharge, being flecainide the most common AAD prescribed with 59.6% of patients, followed by amiodarone in 19.1% of them, without existing differences between groups. Patients were discharged on anticoagulation, with 66.2% of them on a direct oral anticoagulant drug, also without differences between groups.

Pulmonary vein reconnections after a previous procedure

Sixty-three out of 156 (40.4%) veins were reconnected in the Prior-RF group as compared with 17 out of 103 (16.5%) in the Prior-CB group (χ^2 test $p = 0.0001$). The mean number of reconnected PVs per patient was 0.5 ± 0.7 in the Prior-CB group vs. 1.5 ± 1.4 in the Prior-RF group. T-test = 3.8, $p = 0.0003$. The most frequently reconnected PV in the Prior-RF group was the left superior pulmonary vein (LSPV) with 54.1%, whereas in the Prior-CB group it was the right inferior PV with 22.2%, without statistically significant differences within groups. The 66.7% of the Prior-RF group and 40% of Prior-CB left common trunks were reconnected, without statistically significant differences between groups (χ^2 test $p = 1$). Both superior PVs were more commonly reconnected in the Prior-RF group than in the Prior-CB group, with 41% vs. 9% in right superior pulmonary vein (RSPV) (χ^2 test $p = 0.008$) and 54.1% vs 17% in LSPV (χ^2 test $p = 0.005$). Table 3 and Figure 1 show the pattern of vein reconnection within Prior-RF and Prior-CB groups.

Table 2. Procedure-related data and between group differences.

	All patients (n = 74)		Prior-CB (n = 33; 44.59%)		Prior-RF (n = 41; 55.41%)		P-value
Balloon size:							0.361
28 mm	60	82.2%	27	81.8%	33	82.5%	
23 mm	11	15.1%	6	18.2%	5	12.5%	
28 mm + 23 mm	2	2.7%	0	0.0%	2	5.0%	
Sedation method:							**0.001**
General anesthesia	5.0	6.8%	2	6.1%	3	7.3%	
Light sedation	47.0	63.5%	14	42.4%	33	80.5%	
Deep sedation	22.0	29.7%	17	51.5%	5	12.2%	
Assisted transeptal puncture	5.0	6.8%	3.0	9.1%	7.0	17.1%	0.318
Base rhythm:							0.984
Sinus rhythm	59.0	80.8%	26	78.8%	33	82.5%	
Atrial fibrillation	10.0	13.7%	5	15.2%	5	12.5%	
Typical flutter	2.0	2.7%	1	3.0%	1	2.5%	
Atypical flutter	2.0	2.7%	1	3.0%	1	2.5%	
Number of CB applications (median IQR)	6	5–7	6	5–7	6	4–8	0.63
Total cryoablation dose [min]	17.11	5.97	16.96	5.66	17.85	6.57	0.31
Number of reconnected veins (mean SD)	1.08	1.25	0.52	0.71	1.54	1.40	**0.0003**
Number of reconnected veins (median IQR)	1	0–2	0	0–1	1	1–3	**0.0002**
All veins already isolated	30	40.5%	20	60.6%	10	24.4%	**0.002**
Average TTI [s]	42.90	33.84	39.17	33.42	44.19	34.55	0.7074
Average temperature at isolation [°C]	–28.58	9.79	–28.27	8.62	–28.70	10.35	0.913
Average nadir temperature [°C]	–43.84	5.56	–44.00	6.04	–43.72	5.20	0.837
Average CBD per application [s]	177.95	29.53	175.09	30.10	180.26	29.23	0.4577
Average thawing time [s]	33.89	10.66	30.63	8.49	36.28	11.55	0.0581
Average time to –30°C [s]	38.26	8.14	38.14	6.92	38.35	9.08	0.9285
Total left atrial time [min]	71.94	29.02	64.08	23.37	78.45	31.93	0.073
Post-isolation waiting period (n)	12	16.9%	4	12.1%	8	21.1%	0.317
Post-isolation waiting period [min]	18.4	8.15	16.3	5.54	19.5	6.91	0.541
Total procedure duration [min]	115.09	44.46	112.15	47.75	117.46	42.08	0.613
Total fluoroscopy time [min]	31.29	15.38	29.42	13.70	32.83	16.66	0.351
Electrical cardioversion during procedure	19	26.0%	9	28.1%	10	24.4%	0.718
CTI ablation	3	4.1%	1	3.1%	2	4.9%	0.708
AAD on discharge	47	64.4%	22	66.7%	25	62.5%	0.711
Flecainide	28	59.6%	13	59.1%	15	60.0%	
Amiodarone	9	19.1%	4	18.2%	5	20.0%	
Dronedarone	3	6.4%	1	4.6%	2	8.0%	
Propafenone	4	8.5%	2	9.1%	2	8.0%	
Sotalol	3	6.4%	2	9.1%	1	4.0%	
Other	3	0.3%	0	0.0%	0	0.0%	
Discharge anticoagulation with DOAC (vs. AVK)	49	66.2%	24	71.7%	25	61.0%	0.288
Bonus application strategy:							**0.003**
Routine bonus application	21	31.3%	16	51.6%	5	13.9%	
Depending on vein	14	20.9%	6	19.4%	8	22.2%	

Categorical data are summarized in number and percentage. Quantitative data are summarized either with mean and standard deviation or median and interquartile range when appropriate (number of reconnected pulmonary veins, while presenting a not normal distribution, is summarized in both ways to facilitate comparison with other published works). P-values in bold when reaching statistical significance ($p < 0.05$); AAD — anti-arrhythmic drug; AVK — anti-vitamin-K anticoagulant drug; CB — cryoballoon; CBD — cryoablation dose; CTI — cavo-tricuspid isthmus; DOAC — direct oral anticoagulant; IQR — interquartile range; RF — radiofrequency; SD — standard deviation; TTI — time to isolation. Time from the beginning of a freeze application until vein isolation is achieved.

Table 3. Pulmonary vein reconnection pattern in patients undergoing a repeat procedure.

	Prior RF (n = 41)		Prior CB (n = 33)		P-value
Total number of reconnected veins	63/156 (40.4%)		17/103 (16.5%)		0.0001
Number of reconnected veins per patient:					0.008
0	10	24.4%	20	60.6%	
1	16	39.0%	9	7.3%	
2	4	9.8%	4	2.1%	
3	6	14.6%	0	0.0%	
4	4	9.8%	0	0.0%	
5	1	2.4%	0	0.0%	
Left, n (%):					
LSPV	20	54.1%	4	17.4%	0.005
LIPV	12	34.3%	3	13.6%	0.0848
Left common trunk	2	66.7%	2	40.0%	1
Right, n (%):					
RSVP	16	41.0%	2	9.1%	0.0086
RIVP	11	29.7%	6	22.2%	0.5019

The table shows the proportion of reconnected veins and differences between groups performing a χ^2 test; CB — cryoballoon; LIPV — left inferior pulmonary vein; LSPV — left superior pulmonary vein; RF — radiofrequency; RIPV — right inferior pulmonary vein; RSVP — right superior pulmonary vein

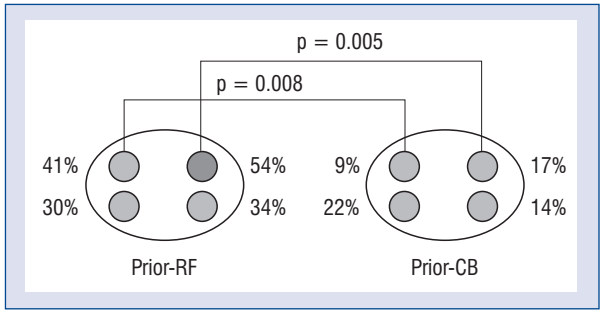


Figure 1. Distribution of pulmonary vein reconnection in patients who had undergone a previous radiofrequency ablation (Prior-RF) or cryoballoon ablation (Prior-CB). Pearson's χ^2 test performed to show differences in the proportion of reconnection for each vein between groups.

Procedural and peri-procedural adverse events

Only 1 patient in the Prior-RF group had a procedural adverse event which presented as temporary phrenic nerve palsy and none of the Prior-CB patients had any procedural adverse events. More detailed information on adverse events in the RECABA study is described elsewhere [13].

Follow-up and AF recurrences

Patients included in this analysis were followed for a mean of 12.6 ± 1.8 months. AF detection was performed with an ECG at clinic visit in 35.1% of patients, 62.1% received a Holter monitor and 2.7% a loop recorder. There were no differences between groups (χ^2 test p = 0.28). Kaplan-Meier survival estimates of 12-month freedom from AF recurrence were 61.0% (95% confidence interval [CI]: 41.4–75.8%) for the Prior-CB group and 89.2% (95% CI: 73.6–95.9%) for the Prior-RF group. Log-rank test for equality of survival function χ^2 = 9.24, p = 0.002. Figure 2 depicts the Kaplan-Meier curves.

Table 4 shows univariate Cox regression models of possible predictors of AF recurrence. Figure 3 depicts the multivariate model that points to prior CBA as the sole independent predictor of AF recurrence, adjusted by obesity, obstructive sleep apnea, CHA_2DS_2-VASc score equal or greater than 2 points and finding all PVs already isolated. Prior-CB patients had more than double the likelihood of AF recurrence, with and adjusted hazard ratio of 2.67 (95% CI: 1.05–6.79). There were 6 hospitalizations in 5 patients due to AF-related events not linked to the procedure.

Discussion

The study results demonstrated that repeat CBA shows higher rates of AF recurrences compared to after a previous RFCA. Multivariate Cox regression pointed Prior-CB as the only

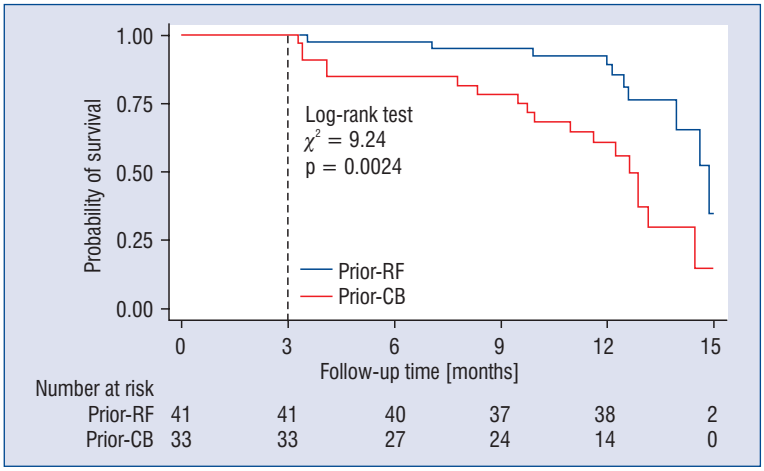


Figure 2. Kaplan-Meier survival curves for atrial fibrillation recurrence after a 3-month blanking period. Log-rank test is performed to compare the predefined groups, showing significant differences between them; Prior-RF — patients subjected to cryoballoon ablation after a failed previous radiofrequency atrial fibrillation ablation; Prior-CB — patients subjected to cryoballoon ablation after a failed previous cryoballoon atrial fibrillation ablation.

Table 4. Univariate Cox regression models of possible predictors of atrial fibrillation (AF) recurrence.

Predictors of AF recurrence	Hazard ratio	95% CI	P-value
Prior-CB vs. Prior-RF	3.15	1.44–6.88	**0.004**
Number of previous procedures	0.91	0.40–2.03	0.812
All PVs already isolated	2.05	0.97–4.31	**0.060**
Age (≥ 65 years)	0.90	0.38–2.13	0.818
Obesity (BMI ≥ 30 kg/m^2)	2.73	1.22–6.14	**0.015**
Female sex	1.71	0.77–3.81	0.191
Obstructive sleep apnea	4.88	1.73–13.74	**0.003**
Hypertension	1.84	0.83–3.93	0.118
Persistent AF	0.93	0.38–2.3	0.875
CHA_2DS_2-VASc ≥ 2	2.03	0.92–4.46	0.078
No physical exercise	1.71	0.75–3.91	0.204
Structural heart disease	0.72	0.10–5.41	0.753
LA enlargement	1.10	0.49–2.48	0.813
Heart failure	1.04	0.14–7.86	0.968
LVEF < 50%	1.07	0.14–7.86	0.968
Bonus strategy	1.68	0.73–3.85	0.220

P-values in bold when reaching the prespecified threshold to be included in the multivariate model (p < 0.10); AF — atrial fibrillation; BMI — body mass index; CB — cryoballoon; CHA_2DS_2-VASc — Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, Stroke or transient ischemic attack, Vascular disease, Age 65–74 years, Sex category; CI — confidence interval; LA — left atrium; LVEF — left ventricular ejection fraction; PVs — pulmonary veins; RF — radiofrequency

independent predictor of AF recurrence in the present series. These data suggest that patients with AF recurrence after CBA may benefit from another ablation technique after a recurrence. In summary, RFCA may be more suitable for repeat procedures for the ability of performing non-PV related ablations.

Pulmonary vein reconnection after a previous procedure

In the present study, a larger number of reconnected PVs are described in patients after a previous RFCA procedure (40.4%, 1.5 ± 1.4 per patient) than after a previous CBA (16.5%,

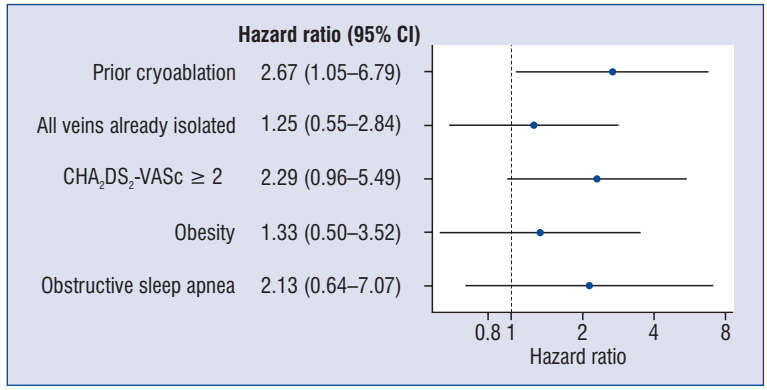


Figure 3. Multivariate Cox regression model of atrial fibrillation recurrence. Being subjected to cryoballoon ablation after a failed previous cryoballoon atrial fibrillation ablation vs. a previous radiofrequency catheter ablation was the only independent predictor of atrial fibrillation recurrence; CI — confidence interval; CHA_2DS_2-VASc — Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, Stroke or transient ischemic attack, Vascular disease, Age 65–74 years, Sex category.

0.5 ± 0.7 per patient) and an overall low number of reconnected PVs in the latter group.

Ciconte et al. [18] described a 20.4% of reconnected PVs after an index CBA (1.2 PV per patient) vs. 36.1% after contact-force RFCA (1.8 PV per patient), with a similar pattern as in the current study. In their series, LSPV were less frequently reconnected after CBA than after RFCA (8% vs. 38%). Pointing in this direction is also noted in Kuck et al. [19] analyzing the repeat procedures after the FIRE and ICE trial. They report an average of 2.1 reconnected PV per patient after RFCA vs. 1.4 after CBA. Moreover, there were less reconnected LSPV in the CBA group (28% vs. 60%) and a trend in RSPV (29% vs. 52%).

However, other published works did not find differences. Zeljkovic et al. [20] presented a series of patients with an index CBA or RFCA that underwent a repeat procedure using RFCA. The average reconnected PVs per patient were 2.1 for CBA and 2.2 for RFCA. In addition, Cheung et al. [21] analyze the repeat procedures from the CIRCA-DOSE trial, where patients were randomized to contact-force RFCA, 2-min CBA, or 4-min CBA. There were no differences in the reconnection pattern in those patients submitted to a repeat procedure, with a median and IQR of 2 (1–2), 2 (1–3), and 1 (1–4) of reconnected PVs per patient, respectively. Glowniak et al. [8] presented a similar series of patients with an index CBA or RFCA that underwent CBA as a repeat procedure. In their series, there was a larger proportion of reconnected PVs with 66.9% after an index RFCA and 51.5% after CBA.

In general, the present results are driven by a high burden of isolated veins after an index CBA, while reconnection pattern after RFCA is more like the abovementioned studies. These can be explained by the difficulties in keeping the catheter stable while ablating the LSPV ridge and LA roof at RSPV antrum. On the other hand, the CBA technique has improved in recent years, with standardized dosing protocols and lessons learnt from repeat procedures that may have led to more durable PV isolations in current procedures [16, 17, 22–28].

Cryoballoon ablation after an index procedure

Despite the abovementioned differences in PV reconnections between the Prior-CB and Prior-RF groups, no differences could be found in the number of CB freeze-applications, nadir temperature, thawing time, or fluoroscopy time. This means that it was common to perform CB applications on previously isolated veins, maybe aiming to perform wider, more antral lesions.

In the present series, up to 60.6% of Prior-CB patients had no reconnected PVs in the redo procedure, compared to 24.4% in the Prior-RF group. Being CBA, a technique designed to perform only PV isolation, it is intuitive to think that another round of freeze applications on already-isolated PVs will not be of much effect.

There were also slightly more patients in the Prior-CB group that used a 23-mm CB. This could be in the setting of changing the balloon size from the previous procedure as has been proposed, aiming to change the effect of CBA on an already ablated atrium [12].

Atrial fibrillation recurrence

According to available research, this is the largest series of patients that used CBA as a redo technique, with 33 patients. Data regarding a second CBA as a repeat ablation procedure are scarce. Schade et al. [11] published a series in 2013 of 47 patients that underwent a second CBA after AF recurrence. They used the first-generation CB (Artic Front, Medtronic) for both procedures and the rates of subjects with 1, 2, 3, or 4 reconnected PVs were 19.1%, 47.6%, 30.9%, and 2.4%, respectively. The pattern of reconduction was evenly distributed, which was between 63% of LSPV and 43% of right inferior pulmonary vein (RIPV). Sixty percent of patients remained AF-free after 12 months. Westra et al. [12] tried a different approach. They performed repeat ablations in 40 patients with recurrent AF after an index CBA, a repeat CBA using a different sized CB (i.e., changing from 23-mm to 28-mm in the second procedure and vice versa). The first procedures were performed with either the first- or second-generation CB and the repeat CBA only with the second-generation CB. Vein reconnection rates were 36% after first--generation CB (1.4 PVs per patient) and 18% for second-generation one (0.7 PVs per patient). The 1-year AF recurrence-free survival rate was 70%, with no differences regarding the index procedure balloon generation. The use of a 23-mm CB failed to be a predictor of recurrence in the current series, which could be driven by a small number of patients. However, the use of different sized CB remains an interesting concept.

The clinical outcomes of Glowniak's study differ from the present results. In his series, both groups (CBA after and index CBA or RFCA) reach a 70.3% AF-free survival rate at 15 months. This divergence may be driven by the differences in PV reconnections. Their patients present more reconnected veins in the repeat CBA group (51.5% vs. 16.5% in the current series) which may be the reason for the AF recurrence and therefore solved with a new CBA. However, the current Prior-CB group has lower reconnection rates and relapse could be driven by non-PV triggers, which would not benefit from another PV isolation-only procedure [29]. Nevertheless, regression analysis showed that a Prior-CB was the strongest predictor of recurrence, overcoming the rate of already isolated veins (Fig. 3). This could mean that this effect is not only driven by the rate of reconnected PVs, but by the previous CBA procedure itself and thus selecting a population with worse arrhythmic prognosis.

On the other hand, the Prior-RF group had better outcome with a survival estimate of almost 90% at 12 months, which is consistent to other published works. De Regibus et al. [30] used a second-generation CB in 47 patients with recurrent AF after RFCA. Fifty-three percent of patients presented with one reconnected PV, 23.4% with 2, 17% with 3, and 6.4% with all-four PVs reconnected. After a follow-up of 15 months, 83% remained AF-free after a 3-month blanking period. Verlato et al. [9] share a work, where they alternate the ablation technique for the repeat procedure (i.e., index CBA followed by RFCA and vice versa). They included 349 patients in the RF-then-CB group and 125 in the CB-then-RF group. Ablation of non-PV triggers, left atrial flutter or cavo-tricuspid isthmus in the redo RFCA procedure was at the operators' discretion. They showed a reconnection rate of 3.7 PVs per patient in the RF-then-CB group and 1.4 PVs the CB-then-RF, and an outcome of freedom from AF at 12 months after a 3-month blanking period of 76.6% vs. 89.1%, respectively. Forty--seven percent of patients in the CB-then-RF group underwent additional non-PV ablation. The RF--then-CB population is represented in the current study and presents a similar outcome, while the CB-then-RF shows the best results. These findings are consistent with those herein, and points in the direction that RFCA may be more suitable for repeat procedures for the ability of performing non-PV ablations.

Limitations of the study

This is a non-predefined analysis of a prospective cohort study, with a limited number of patients compared to the whole population included. However, it is the largest cohort of patients with CBA as a redo procedure with 74 patients. The main limitation of the present study is the lack of procedural data from previous ablations, like the size or generation of the CB used, the CB application protocol or if RFCA consisted of more than PVI. Another limitation would be the method for AF detection, as only 2.7% of patients would receive an insertable loop recorder.

Nevertheless, this does not invalidate the present work since results are consistent with previously published data and the groups were mostly homogeneous. Moreover, RECABA was a multicentric study focused on describing everyday practice, and having present results despite heterogenous protocols weighed more on validating them.

Conclusions

Pulmonary vein reconnections are more frequently found in patients submitted to repeat AF ablation after an index RFCA than after an index CBA. Patients submitted to a repeat CBA have more AF recurrences than those that undergo CBA as a redo after an index RFCA. These data suggest that patients with AF recurrence after CBA may benefit from other ablation techniques after a recurrence.

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Impact of calcification on Murray law-based quantitative flow ratio for physiological assessment of intermediate coronary stenoses

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Abstract

Background: *To investigate the influence of coronary calcification on the diagnostic performance of Murray law-based quantitative flow ratio (μQFR) in identifying hemodynamically significant coronary lesions referenced to fractional flow reserve (FFR).*

Methods: *A total of 571 intermediate lesions from 534 consecutive patients (66.1 ± 10.0 years, 67.2% males) who underwent coronary angiography and simultaneous FFR measurement were included. Calcific deposits were graded by angiography as none or mild (spots), moderate (involving ≤ 50% of the reference vessel diameter), and severe (> 50%). Performance of μQFR to detect functional ischemia (FFR ≤ 0.80) was evaluated, including diagnostic parameters and areas under the receiver-operating curves (AUCs).*

Results: *The discrimination of ischemia by μQFR was comparable between none/mild and moderate/severe calcification (AUC: 0.91, 95% confidence interval: 0.88–0.93 vs. AUC: 0.87, 95% confidence interval: 0.78–0.94; p = 0.442). No statistically significant difference was observed for μQFR between the two categories in sensitivity (0.70 vs. 0.69, p = 0.861) and specificity (0.94 vs. 0.90, p = 0.192). Moreover, μQFR showed significantly higher AUCs than quantitative coronary angiographic diameter stenosis in both vessels with none/mild (0.91 vs. 0.78, p < 0.001) and moderate/severe calcification (0.87 vs. 0.69, p < 0.001). By multivariable analysis, there was no association between calcification and μQFR-FFR discordance (adjusted odds ratio: 1.529, 95% confidence interval: 0.788–2.968, p = 0.210) after adjustment for other confounding factors.*

Conclusions: *Murray law-based quantitative flow ratio demonstrated robust and superior diagnostic performance for lesion-specific ischemia compared with angiography alone regardless of coronary calcification.* (Cardiol J 2024; 31, 2: 205–214)

Keywords: calcification, fractional flow reserve, coronary artery disease, diagnosis, quantitative flow ratio

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Introduction

Although fractional flow reserve (FFR) has been shown as an effective tool in guiding revascularization to improve clinical outcomes and life quality in patients with stable coronary artery disease, it was underutilized in clinical practice mainly due to prolonged procedure time, increased medical expenses, and vasodilation-induced discomfort [1–3]. To overcome these limitations, several methods were developed based on computational fluid dynamics to simulate coronary artery flow without the requirement of any pressure wire or hyperemic agent [4]. Of these, angiography-derived quantitative flow ratio (QFR) was demonstrated to have good diagnostic performance for detecting lesion-specific ischemia, superior to conventional diameter stenosis, in recent multicenter trials using invasive FFR as the reference standard [5–7]. However, this technique requires two optimal angiographic images from at least 25 degrees apart, which is not always available in routine cardiac catheterization. Moreover, its accuracy might be influenced by individual variations in a semi-automatic drawing of vessel contour and frame counting.

Recently, an updated algorithm called Murry law-based QFR (μQFR) has been proposed for functional evaluation of coronary stenosis severity [8]. This artificial intelligence (AI)-assisted approach could realize one-stop automatic hemodynamic assessment from a single angiographic view, which greatly simplifies the calculation process and reduces the amount of manual handling. A recent post hoc analysis of 306 patients in the FAVOR (Functional Diagnostic Accuracy of Quantitative Flow Ratio in Online Assessment of Coronary Stenosis) II China study has demonstrated its excellent correlation and agreement with FFR [8]. Despite the good performance of μQFR in the overall population, the effect of coronary calcification on imaging-derived non-hyperemic physiological assessment was not fully addressed. In this study, it was sought to evaluate the diagnostic accuracy of μQFR in vessels with different degrees of calcification and to compare μQFR versus angiography alone in identifying the physiological significance of calcified and non-calcified coronary arteries with invasive FFR as the reference standard.

Methods

Study population

Electronic medical records between December 2012 and April 2021 were initially screened from consecutive patients with coronary artery disease and at least one intermediate lesion by visual estimation (30–70% diameter stenosis) who underwent coronary angiography and simultaneous FFR measurements at the documented institution. Exclusion criteria were as follows: left-main disease, acute myocardial infarction within 72 hours, presence of myocardial bridge, in-stent restenosis in the interrogated vessel, insufficient image quality for QFR computation, and severe overlap of vessels by angiography. This study was approved by the institutional ethics committee of Zhongda Hospital and the requirement of informed consent was waived due to the retrospective manner.

Coronary angiography and FFR measurement

All patients received coronary angiography via the radial artery using a 5-French or 6-French system. Angiographic datasets were acquired at 15 frames/s using a monoplane radiographic system (AXIOM Artis, Siemens, Erlangen, Germany). The severity of calcification was determined based on angiography as described by Karacsonyi et al. [9]: none or mild (spotty calcification), moderate (involving ≤ 50% of the reference vessel diameter), and severe calcification (involving > 50% of the reference vessel diameter). After the assessment was completed by an experienced analyst (Dr. Xiaoguo Zhang), 20% of the images were randomly selected from each type of calcification and re-evaluated by another interventionalist (Dr. Renhua Sun). A strong inter-observer agreement was confirmed by a weighted kappa coefficient of 0.897 (95% confidence interval [CI]: 0.775–1.019, $p < 0.001$).

A 0.014-inch pressure guidewire (Certus, St. Jude Medical, St. Paul, Minnesota, USA) was equalized to the aortic pressure before being positioned distal to the lesion. Maximum hyperemia was induced by intravenous infusion of adenosine-5'--triphosphate (ATP) at 140 μg/kg/min for at least 2 minutes. During the steady phase of maximum hyperemia, the FFR value was calculated as the ratio of mean distal coronary pressure (Pd) to simultaneous mean aortic pressure (Pa). The threshold was defined as FFR ≤ 0.80 to indicate functional ischemia [1]. The details of the procedure have been described in our previous reports [10, 11].

μQFR computation and quantitative analysis

Offline computation of μQFR was performed using commercial software (AngioPlus Core, Shanghai Pulse Medical Technology Inc., Shanghai,

China) by a certified analyst (Dr. Xiaoguo Zhang) who was blinded to patient characteristics and FFR information. The details of μQFR analysis and its good repeatability have been described previously [8]. From an optimal angiographic view with minimal vessel overlap, contrast flow velocity was calculated and a keyframe with sharp lumen contour at the stenotic segment was selected for subsequent analysis. The delineation of the lumen contour and reconstruction of the reference diameter function was then performed by AI algorithms according to the Murray fractal law. Proximal and distal reference vessel diameters were corrected manually when needed. Ultimately, μQFR values were obtained for both major epicardial arteries and their side branches. Parameters of quantitative coronary angiography (QCA) were also available from the software simultaneously, including diameter stenosis (QCA-DS), lesion length, and minimal lumen diameter.

Statistical analysis

The normality of quantitative data was examined using histograms and Q-Q plots. Continuous variables were expressed as mean ± standard deviation or median with interquartile range and were compared using the Student t-test or Mann-Whitney U test as appropriate. Categorical variables were expressed as counts (percentages) and were compared using the chi-square test. The association and agreement between μQFR and invasive FFR were analyzed by the Spearman's correlation coefficients and the Bland-Altman plots, respectively. The correlation coefficients were compared using a z-test on Fisher z transformation [12]. Diagnostic variables of μQFR and QCA-DS to detect functionally significant lesions were assessed on a per-vessel level across different calcification subgroups. The "N-1" chi-square test was used for comparing these variables of μQFR between the two calcification subgroups [13]. Receiver-operating characteristics curves were used for μQFR and angiographic parameters to measure their discriminatory powers for identifying lesion-specific ischemia with invasive FFR as the reference standard. The area under the curves (AUCs) was compared according to the method by DeLong et al. [14]. Multivariate logistic regression was used to exclude the influence of confounding factors on the relationship between calcification and μQFR-FFR discordance. All statistical analyses were performed with SPSS version 25.0 (IBM Corp., Armonk, New York, USA), Stata/SE 15.0 (StataCorp, College Station, TX, USA), GraphPad Prism version 8.2.1 for macOS (GraphPad Software, San Diego, California, USA), and MedCalc® Statistical Software version 20.022 (MedCalc Software bvba, Ostend, Belgium). A two-tailed p-value < 0.05 was considered statistically significant.

Results

Patient and lesion characteristics

The flow diagram of patient selection is shown in Figure 1. Of the 677 patients initially screened, 534 patients (mean age 66.1 ± 10.0 years, 67.2% males) with 571 de novo lesions were eventually available for this analysis. Forty-six (8.6%) patients had a previous history of myocardial infarction and 461 (86.3%) patients presented stable angina. The average QCA-DS was 38.0 ± 8.3% and there were 387 (67.8%) lesions located in the left descending artery. The mean FFR was 0.85 ± 0.08, with 150 (26.3%) vessels being physiologically significant (FFR ≤ 0.80).

There were 496 (86.9%) lesions with no or mild calcification, 46 (8.1%) lesions with moderate calcification, and 29 (5.1%) lesions with severe calcification. Compared with those with no or mild calcification, patients with moderate or severe calcification were older and had a lower body mass index with less prevalence of single-vessel disease (Table 1). Moderately or severely calcified lesions were more likely to be located in the left anterior descending artery with a higher degree of QCA-DS, longer length, lower FFR, and μQFR (Table 2). The distribution of angiographic diameter stenosis and physiological indexes is shown in Figure 2.

Correlation and agreement between μQFR and FFR

There was a good correlation between μQFR and FFR for both none/mildly (Spearman's *rho* = 0.768; $p < 0.001$) and moderately/severely (Spearman's *rho* = 0.760; $p < 0.001$) calcified coronary arteries (Fig. 3A, B), with no significant difference between the two correlation coefficients (z-statistic = 0.152, $p = 0.879$). A Bland-Altman analysis also showed a good agreement between μQFR and FFR for both none/mildly (mean difference = 0.009 ± 0.053) and moderately/severely (mean difference = 0.005 ± ± 0.056) calcified coronary arteries (Fig. 3C, D).

μQFR and angiography for detecting functionally significant lesions in different calcification groups

As shown in Figure 4, high discriminatory power was demonstrated by receiver-operating

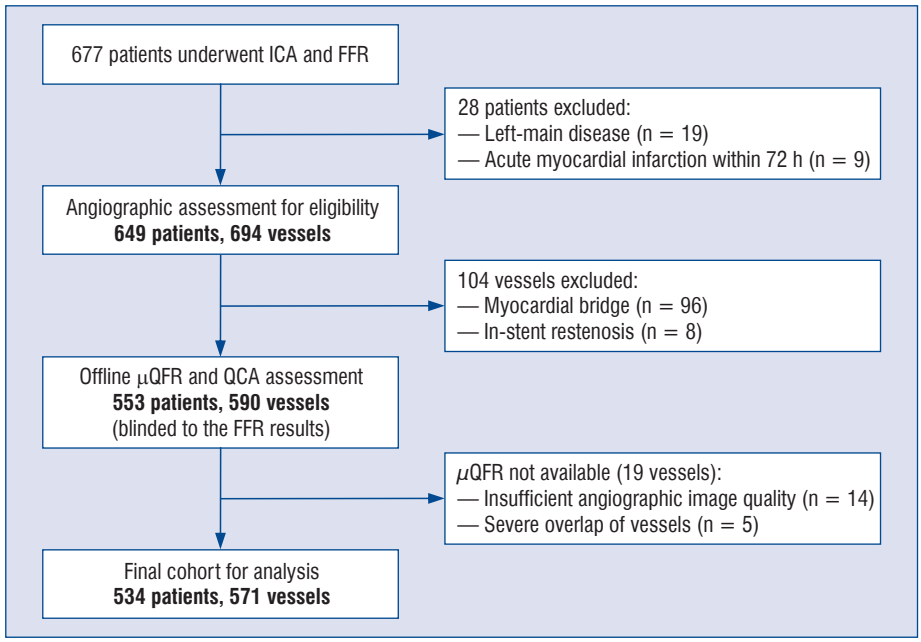


Figure 1. Flow diagram of patient selection; μQFR — Murray law-based quantitative flow ratio; FFR — fractional flow reserve; ICA — invasive coronary angiography; QCA — quantitative coronary angiography.

Table 1. Baseline characteristics of included patients stratified by quantity of calcium.

Variables	Quantity of calcium		P
	None or mild (n = 461)	Moderate or severe (n = 73)	
Age [years]	65.7 ± 10.1	68.9 ± 8.8	0.012
Male	307 (66.6)	52 (71.2)	0.433
BMI [kg/m^2]	25.2 ± 3.4	23.8 ± 3.3	0.002
Systolic pressure [mmHg]	137.2 ± 19.1	134.8 ± 18.6	0.323
Diastolic pressure [mmHg]	79.1 ± 11.8	77.9 ± 11.1	0.391
Hypertension	345 (74.8)	57 (78.1)	0.550
Diabetes mellitus	131 (28.4)	19 (26.0)	0.673
Dyslipidemia	218 (47.3)	35 (47.9)	0.917
Current smoker	150 (32.5)	26 (35.6)	0.603
Prior MI	39 (8.5)	7 (9.6)	0.749
Prior PCI	110 (23.9)	23 (31.5)	0.160
Multivessel disease	253 (54.9)	59 (80.8)	< 0.001
Clinical symptoms:			1.000
Stable angina	397 (86.1)	64 (87.7)	
Unstable angina	55 (11.9)	8 (11.0)	
NSTEMI	9 (2.0)	1 (1.4)	

Values are given as mean ± standard deviation or number (%); BMI — body mass index; MI — myocardial infarction; NSTEMI — non-ST-segment elevation myocardial infarction; PCI — percutaneous coronary intervention

characteristics curve analysis in both none/mildly and moderately/severely calcified arteries with no statistically significant difference (AUC: 0.91, 95% CI: 0.88–0.93 vs. AUC: 0.87, 95% CI: 0.78–0.94, p = 0.421). Per-vessel diagnostic parameters of μQFR among different calcification subgroups are shown in Table 3. No significant difference was found for μQFR in both sensitivity (0.70 vs.

Table 2. Lesion characteristics stratified by quantity of calcium.

Variables	Quantity of calcium		P
	None or mild (n = 496)	Moderate or severe (n = 75)	
Interrogated vessels:			0.226
LAD	331 (66.7)	56 (74.7)	
LCX	84 (16.9)	7 (9.3)	
RCA	81 (16.3)	12 (16.0)	
Lesion location:			0.054
Proximal	243 (49.0)	46 (61.3)	
Middle	220 (44.4)	28 (37.3)	
Distal	33 (6.7)	1 (1.7)	
QCA parameters:			
QCA-DS [%]	37.8 ± 8.4	39.8 ± 7.3	0.043
MLD [mm]	1.81 (1.54, 2.17)	1.77 (1.52, 2.10)	0.419
Lesion length [mm]	19.3 (11.7, 30.2)	24.9 (16.7, 34.4)	0.002
Tandem lesions	56 (11.3)	12 (16.0)	0.241
FFR	0.87 (0.81, 0.91)	0.81 (0.77, 0.86)	< 0.001
FFR ≤ 0.80	114 (23.0)	36 (48.0)	< 0.001
μQFR	0.89 (0.82, 0.93)	0.83 (0.76, 0.89)	< 0.001
μQFR ≤ 0.80	104 (21.0)	29 (38.7)	0.001

Values are given as mean ± standard deviation or median (25th–75th percentiles) or number (%); μQFR — Murray law-based quantitative flow ratio; FFR — fractional flow reserve; LAD — left anterior descending artery; LCX — left circumflex; MLD — minimum lumen diameter; QCA — quantitative coronary angiography; QCA-DS — quantitative coronary angiographic diameter stenosis; RCA — right coronary artery

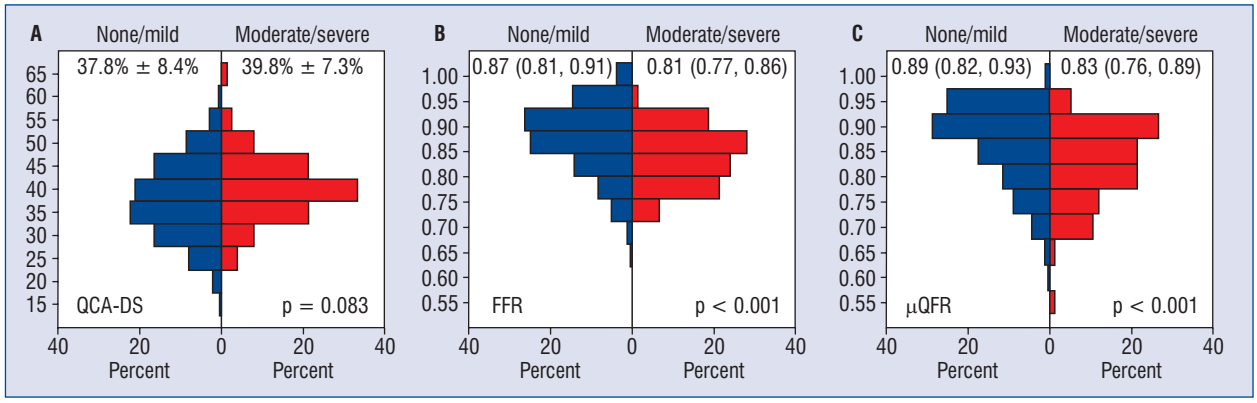


Figure 2. Distribution of angiographic diameter stenosis and physiological indices. There was no significant difference in the distribution of quantitative coronary angiographic diameter stenosis (QCA-DS) (**A**) according to calcification whereas significant difference existed in the distribution of fractional flow reserve (FFR) (**B**) and Murray law-based quantitative flow ratio (μQFR) (**C**) between the two calcification groups. Values are given as mean ± standard deviation or median (25th–75th percentiles).

0.69, p = 0.861) and specificity (0.94 vs. 0.90, p = 0.192) between the two groups whereas there was a relatively higher proportion of overall μQFR-FFR discordance among vessels with moderate or severe calcification (20.5% vs. 12.0%, p = 0.045). On a per-vessel level, μQFR exhibited superior discrimination to QCA-DS and lesion length for detecting functionally significant lesions, regardless of the degree of calcification (Fig. 4).

To exclude the influence of confounding factors on the relationship between diagnostic accuracy and calcification, a multivariable analysis was performed by entering both calcification and baseline variables that might be associated with μQFR-FFR

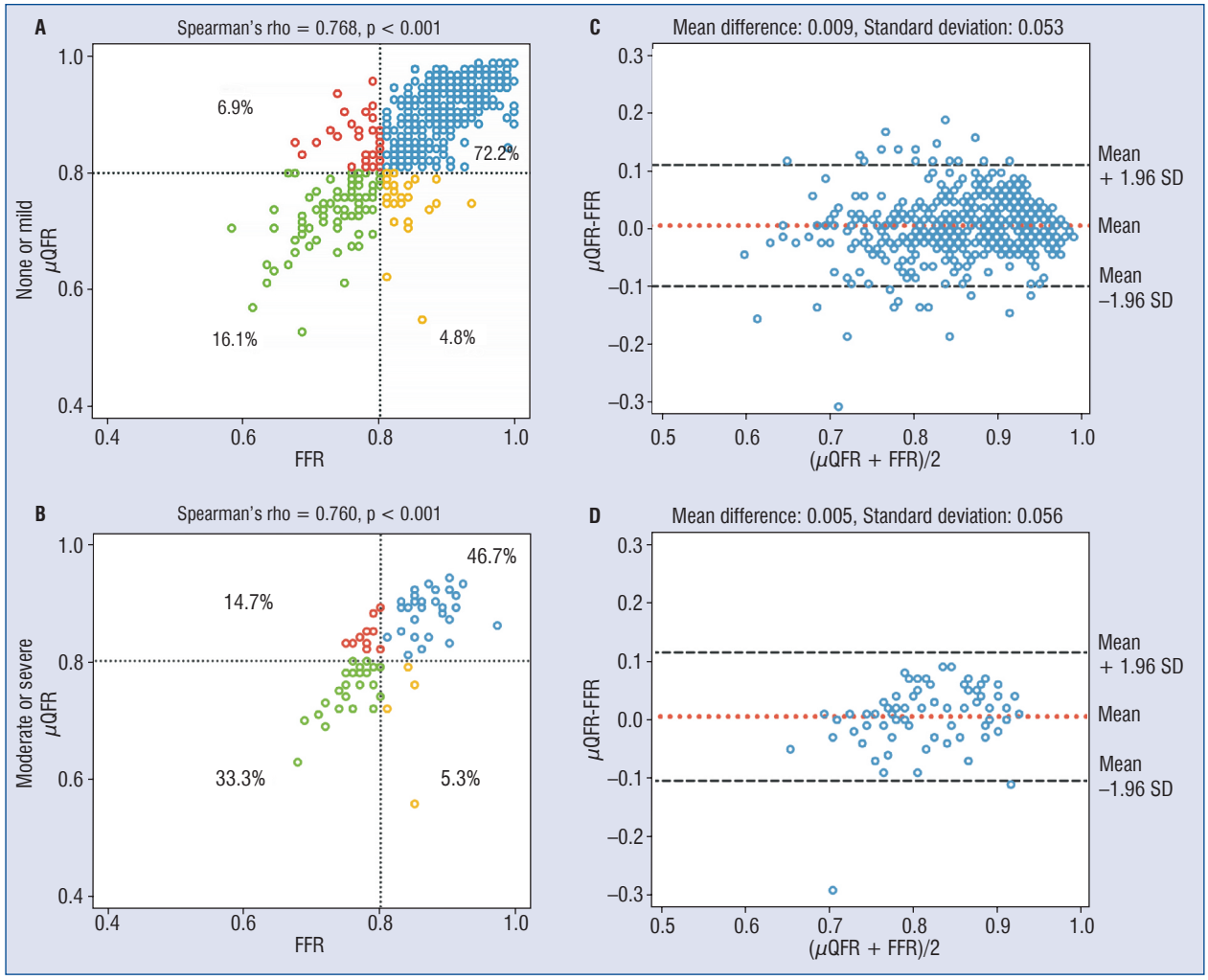


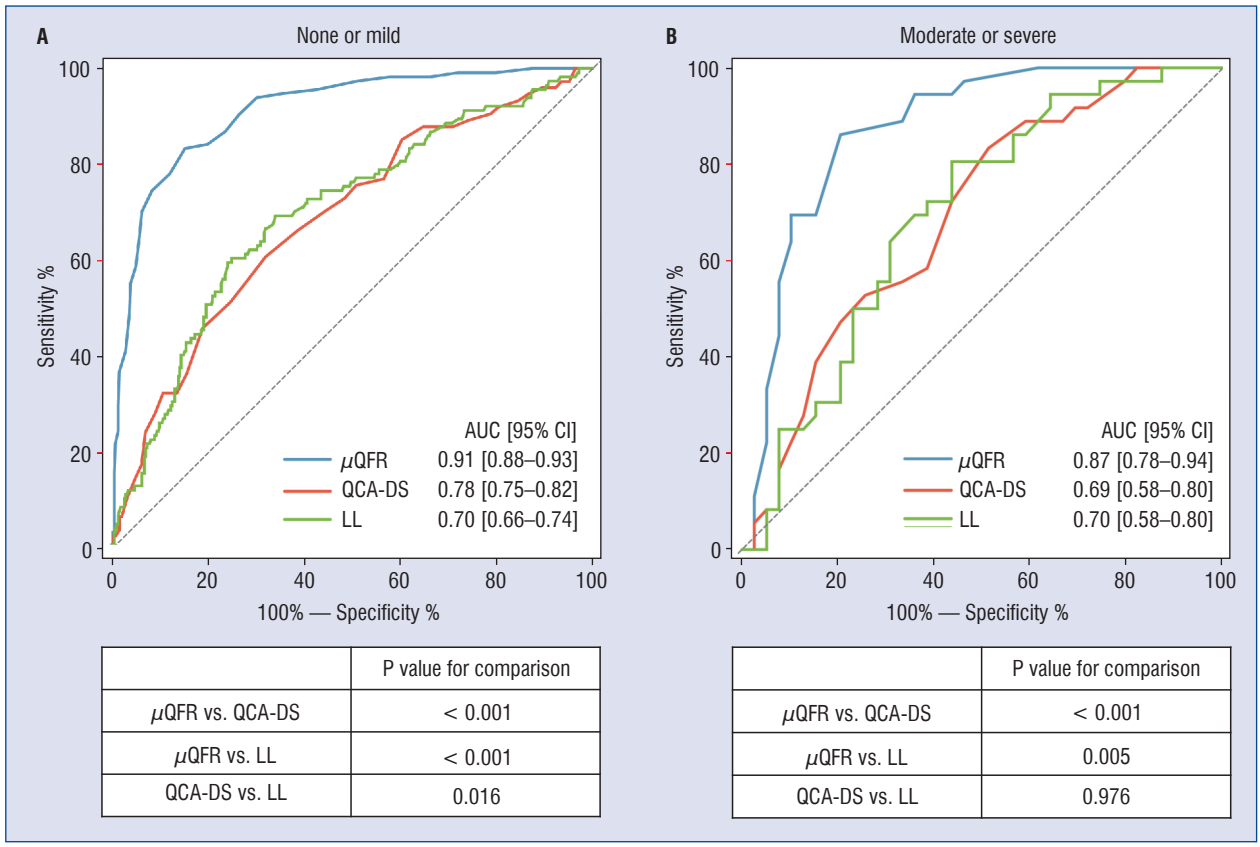
Figure 3. The correlation and agreement between Murray-law based quantitative flow ratio (μQFR) and invasive fractional flow reserve (FFR); **A**, **B**. μQFR showed a significant correlation with FFR regardless of calcification severity. μQFR-FFR discordance occurred in 11.7% and 20.0% of vessels with none/mild and moderate/severe calcification, respectively; **C**, **D**. Bland-Altman plots showed that there was a good agreement between μQFR and FFR in both two calcification categories.

discordance into the model (**Suppl. Table S1**). The results showed that dyslipidemia, QCA-DS, and lesion length were independently associated with overall μQFR-FFR discordance whereas the presence of moderate or severe calcification (adjusted odds ratio [OR]: 1.529, 95% CI: 0.788–2.968, p = 0.210) was not responsible for the misclassification of μQFR (Table 4). A representative case of μQFR and angiography with FFR is shown in Figure 5.

Discussion

In this study, the diagnostic performance of μQFR in coronary arteries with different degrees of calcification was investigated, using invasive FFR as the reference standard. Results showed that μQFR, the latest generation of AI-assisted hydrodynamic algorithm for angiographic images, had a good accuracy to identify functional ischemia in angiographically intermediate coronary lesions and this robust performance was not significantly influenced by the quantity of calcium. Furthermore, μQFR provided an incremental value over conventional angiography alone for the physiological assessment of coronary lesions in both calcified and non-calcified coronary arteries.

Coronary calcification is a challenge for imaging-derived FFR simulation because it may potentially compromise the recognition of vascu-



	P value for comparison
μQFR vs. QCA-DS	< 0.001
μQFR vs. LL	< 0.001
QCA-DS vs. LL	0.016

	P value for comparison
μQFR vs. QCA-DS	< 0.001
μQFR vs. LL	0.005
QCA-DS vs. LL	0.976

Figure 4. The per-vessel receiver characteristic operating curves of Murray-law based quantitative flow ratio (μQFR) and quantitative coronary angiographic-derived parameters for identifying functional ischemia. In both vessels with none/mild (**A**) and moderate/severe (**B**) calcification, μQFR showed a higher discrimination for functional ischemia than quantitative coronary angiographic diameter stenosis (QCA-DS) and lesion length (LL); AUC — area under the receiver-operating curve; CI — confidence interval.

Table 3. Per-vessel diagnostic performance of μQFR stratified by quantity of calcium.

	Quantity of calcium	
	None or mild	**Moderate or severe**
Overall population	N = 496	N = 75
Accuracy	0.88 (0.85–0.91)	0.80 (0.69–0.88)
Sensitivity	0.70 (0.61–0.78)	0.69 (0.52–0.84)
Specificity	0.94 (0.91–0.96)	0.90 (0.76–0.97)
PPV	0.77 (0.69–0.83)	0.86 (0.71–0.94)
NPV	0.91 (0.89–0.93)	0.76 (0.66–0.84)

Values are given as n with corresponding 95% confidence intervals. Positive test results are defined as μQFR ≤ 0.80 with invasive fractional flow reserve ≤ 0.80 as the reference standard; μQFR — Murray law-based quantitative flow ratio; QCA-DS — quantitative coronary angiographic diameter stenosis; NPV — negative predictive value; PPV — positive predictive value

lar lumen and the drawing of arterial shape [15]. However, the specific impact of calcium deposits on the accuracy of AI-assisted μQFR is not well understood. According to available research, this is the first study to examine the performance of μQFR in coronary arteries with and without calcification. Herein, results suggested that μQFR provided high and incremental diagnostic value than angiography alone for the detection of functional ischemia regardless of calcium burden, which

Table 4. Adjustment of confounding factors in the relationship between calcification and overall μQFR-FFR discordance.

	Adjusted OR (95% CI)	P
Male	0.829 (0.416–1.653)	0.594
Dyslipidemia	1.819 (1.062–3.115)	0.029
Current smoking	1.386 (0.781–2.461)	0.265
Prior PCI	1.690 (0.962–2.971)	0.068
Multivessel disease	1.161 (0.632–2.136)	0.630
QCA-DS, 10%	1.719 (1.221–2.419)	0.002
Lesion length, 10 mm	1.338 (1.100–1.626)	0.003
Moderate/severe calcification	1.529 (0.788–2.968)	0.210

The multivariate logistic regression model was performed using the enter method to include all covariates; μQFR — Murray law-based quantitative flow ratio; CI — confidence interval; FFR — fractional flow reserve; MLD — minimum lumen diameter; OR — odds ratio; PCI — percutaneous coronary intervention; QCA-DS — quantitative coronary angiographic diameter stenosis

is similar to previous findings on FFR derived from coronary computed tomography angiography (CT-FFR) [16–18]. A recent post hoc analysis of the FAST-FFR (FFR_{angio} Accuracy versus Standard FFR) study also confirmed that calcification did not affect the sensitivity or specificity of FFR derived from coronary angiography [19]. This phenomenon might be explained by the complexity of the hemodynamic numerical simulation. The computation of μQFR is not only based on combined geometrical data but also includes contrast flow velocity [20], which means that calcification is only involved a small part of this process.

Theoretically, arterial intimal calcification could protrude into the coronary lumen, resulting in vascular stenosis and subsequently reduced blood flow [21]. However, calcification might have little effect on intracoronary pressure. Coronary artery calcification was not associated with the pressure gradient before and after the administration

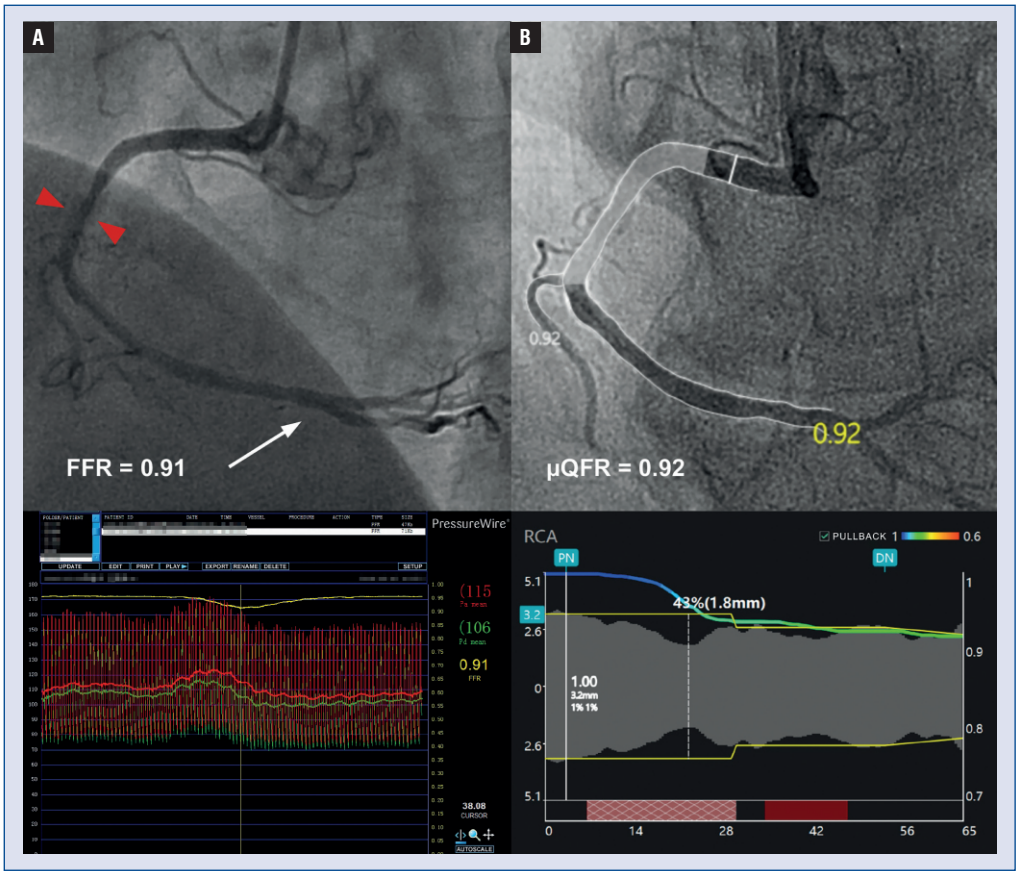


Figure 5. Representative images of Murray-law based quantitative flow ratio (μQFR) analysis in a severe calcified coronary lesion without functional ischemia; **A.** Coronary angiography shows an intermediate lesion at the proximal segment of the right coronary artery with severe calcification (red arrowhead), with a wire-based fractional flow reserve (FFR) of 0.91; **B.** Artificial-intelligence-assisted quantitative coronary angiography and color-coded μQFR computation (μQFR = 0.92).

of adenosine [22]. Lesion length (82%), QCA-DS (64%), and minimum lumen diameter (55%) were reported as the most frequently used variables in the 11 clinical prediction models for FFR whereas calcification was only used in one of them (9%) [23]. Velangi et al. [24] also found that only lesion length and low-attenuation plaque were significant independent predictors of ischemia detected by FFR although spotty calcification was predictive of abnormal FFR on univariate analysis. Interestingly, the association between calcification and overall μQFR-FFR discordance was abolished when lesion length was included in the multivariable model, suggesting that atherosclerotic burden may have a greater influence on blood flow than calcification. To some extent, calcification may be more a reflection of plaque vulnerability than physiological severity [25]. However, its role in plaque homeostasis still awaits further investigation given its complex relationship with lipids and obesity [26, 27].

Unlike previous studies on CT-FFR [16–18], a slight decline was observed in diagnostic accuracy of μQFR among vessels with moderate or severe calcification, that is the overall probability that a patient is correctly classified, which reflected the same aspect as μQFR-FFR discordance. Considering that this value is highly dependent on disease prevalence [28], the relationship was further evaluated between calcification and μQFR-FFR discordance to eliminate the influence of confounding factors. By multivariable analysis, the presence of moderate or severe calcification was not associated with μQFR--FFR discordance after adjustment for age, multivessel disease, lesion location, and lesion length. Furthermore, only a small proportion of vessels was not eligible for μQFR computation due to suboptimal image quality (none due to severe calcification). These findings further support the present hypothesis that AI-assisted μQFR may overcome the influence of calcification on fluoroscopic images with superior performance to angiography alone, thereby probably improving the clinical decision-making and outcomes for patients with coronary artery disease. However, it was noted that a conventional threshold (μQFR ≤ 0.80 or QCA-DS ≥ 50%) may impair their diagnostic performance for detection of functional ischemia in such a population with less calcification and atherosclerotic burden. Therefore, the cutoff of μQFR needs to be further refined according to the severity of calcification and stenosis.

Limitations of the study

There are several limitations that should be addressed. Firstly, a retrospective, single-center design may increase the susceptibility to bias despite a relatively large population. To avoid the influence of subjective factors, angiographic images were blinded when reviewed. Secondly, coronary calcification was determined based on angiography rather than intravascular ultrasound which is more sensitive to evaluating the burden and morphology of calcium. Finally, there was a relatively low prevalence of severe vascular calcification in the present study, although this represented the real--world situation. Large, multicenter, prospective studies are still warranted to validate the current findings in a broad spectrum of participants.

Conclusions

In conclusion, AI-assisted μQFR demonstrated high discrimination of hemodynamically significant coronary lesions regardless of calcium burden. In the setting of coronary calcification, μQFR can still provide incremental value over angiography alone for the physiological assessment of coronary lesions. Further randomized studies are necessary to determine the optimum threshold for μQFR--guided strategy and its impact on clinical outcomes in patients with severe coronary calcification.

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Treatment of high- and intermediate-high-risk pulmonary embolism by the Pulmonary Embolism Response Team: Focus on catheter-directed therapies

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Abstract

Background: *Multidisciplinary Pulmonary Embolism Response Teams (PERTs) were established to individualize the treatment of high-risk (HR) and intermediate-high-risk (IHR) pulmonary embolism (PE) patients, which pose a challenge in clinical practice.*

Methods: *We retrospectively collected the data of all HR and IHR acute PE patients consulted by PERT CELZAT between September 2017 and October 2022. The patient population was divided into four different treatment methods: anticoagulation alone (AC), systemic thrombolysis (ST), surgical embolectomy (SE), and catheter-directed therapies (CDTx). Baseline clinical characteristics, risk stratification, PE severity parameters, and treatment outcomes were compared between the four groups.*

Results: *Of the 110 patients with HR and IHR PE, 67 (61%) patients were treated with AC only, 11 (10%) with ST, 15 (14%) underwent SE, and 17 (15%) were treated with CTDx. The most common treatment option in the HR group was reperfusion therapy, used in 20/24 (83%) cases, including ST in 7 (29%) patients, SE in 5 (21%) patients, and CTDx in 8 (33%) patients. In contrast, IHR patients were treated with AC alone in 63/86 (73%) cases. The in-hospital mortality rate was 9/24 (37.5%) in the HR group and 4/86 (4.7%) in the IHR group.*

Conclusions: *The number of advanced procedures aimed at reperfusion was substantially higher in the HR group than in the IHR PE group. Despite the common use of advanced reperfusion techniques in the HR group, patient mortality remained high. There is a need further to optimize the treatment of patients with HR PE to improve outcomes.* (Cardiol J 2024; 31, 2: 215–225)

Keywords: catheter-directed therapies, high-risk pulmonary embolism, intermediate-high-risk pulmonary embolism, pulmonary embolism, Pulmonary Embolism Response Team

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Introduction

Pulmonary embolism (PE) remains the third most frequent acute cardiovascular disease, with an estimated prevalence of 100–200 cases per 100,000 people in the United States [1–3]. Obstruction of pulmonary arteries causes variable clinical manifestations, ranging from mild symptoms to cardiac arrest and death. The presence of hemodynamic instability along with the Pulmonary Embolism Severity Index (PESI) or simplified PESI (sPESI) score, troponin elevation, and evidence of right ventricle (RV) dysfunction allows us to stratify patients into high (HR), intermediate-high (IHR), intermediate-low, and low risk of early (30-day) mortality [3].

Between 1993 and 2012, in-hospital mortality due to PE declined from 7.1% to 3.2%, despite a higher number of PE-related hospitalizations during the preceding two decades [4]. Similarly, mortality in high-risk PE has decreased significantly, but the availability of advanced treatment methods remains suboptimal [5]. As well as diagnostics improvements, PE therapeutic options have expanded, especially for HR and IHR patients. Currently, in addition to standard anticoagulant therapy, treatment methods include systemic thrombolysis (ST), surgical embolectomy (SE), catheter-directed thrombectomy (CDT), catheter--directed thrombolysis (CDL), and extracorporeal membrane oxygenation (ECMO) [6]. Whereas most low-risk and intermediate-low-risk PE patients can be effectively treated with anticoagulants alone, patients with HR and IHR PE remain a therapeutic challenge, requiring more advanced treatment in addition to anticoagulation [7, 8]. This, in turn, results in an increased risk of treatment-related adverse events such as bleeding, and it requires individual risk-to-benefit consideration [9, 10].

Consequently, Pulmonary Embolism Response Teams (PERTs) were established for multidisciplinary collaboration between various specialists to facilitate the choice of optimal therapy for patients with PE [11]. PERT activity focuses particularly on HR and IHR PE; the guidelines do not cover specific issues related to patients in these subgroups, and thus the individualized approach is crucial [3, 12]. The first studies evaluating the effectiveness of PERT interventions showed improved survival rates and reduced bleeding events during the acute phase of PE treatment [13, 14]. However, a meta-analysis of 9 controlled studies showed no difference in the survival rate between the pre-PERT and PERT eras, despite the increased use of advanced treatment options [15]. These discrepancies could be explained by the fact that individual PERTs differ significantly with respect to the characteristics of the patients they consult, applied treatment strategies, and achieved results, because qualification for the specific intervention depends on local experience and available treatment modalities [15, 16]. Considering the gap in evidence in the European Society of Cardiology (ESC) guidelines regarding HR and IHR PE patients and the differences in expertise between local PERTs, a detailed assessment of PERT activities and outcomes is crucial.

To understand the factors associated with treatment outcomes and to optimize future treatment decisions, we analyzed the characteristics and treatment modalities of HR and IHR PE patients within our local PERT, the Center for the Management of Pulmonary Embolism (CELZAT), which was established in Warsaw in 2017 [17]. Considering recent technological developments in the field of catheter-directed therapies (CDTx), we provided a detailed analysis of the CDTx techniques applied within our PERT.

Methods

We retrospectively collected the data of all HR and IHR acute PE patients consulted by PERT CELZAT between September 2017 and October 2022. The diagnosis of PE was confirmed in all patients by computed tomography pulmonary angiogram (CTPA). IHR PE was defined as RV dysfunction detected by transthoracic echocardiography or CTPA and elevated troponin-T levels. HR PE was defined as hemodynamic instability or the need for cardiopulmonary resuscitation, according to the current ESC Guidelines on Acute Pulmonary Embolism [3, 17].

The HR and IHR patient population was divided into four different therapeutic subgroups: AC alone, ST, SE, and CDTx. AC alone was defined as the administration of unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), vitamin K antagonists, or direct oral anticoagulants without additional PE-specific therapies. ST referred to the intravenous administration of recombinant tissue plasminogen activator (rtPA). SE was defined as the surgical removal of the pulmonary thrombi following the incision of pulmonary arteries under extracorporeal circulation, with aorta clamping and administration of cardioplegia [18]. CDTx included CDT, CDL, or a combination of both. For CDL, a Fountain 5 F infusion catheter (Merit Medical Systems, Inc., South Jordan, UT, USA) was used, consisting of a 10-cm infusion segment inserted in

the pulmonary arteries to deliver the thrombolytic drug through gradient side holes on the catheter. For CDT, 3 thrombectomy systems were applied: Indigo CAT8 XTORQ (Penumbra Inc., Alameda, CA, USA), Indigo CAT12 XTORQ (Penumbra Inc., Alameda, CA, USA), and Cleaner XT™ (Argon Medical Devices, Plano, TX, USA). Indigo CAT8 is an aspiration thrombectomy-based system that implements automatic suction through an 8 F catheter and uses a retractable separator that moves back and forth, facilitating thrombus fragmentation [19]. Indigo CAT12 has an improved algorithm that controls automatic valves, reducing blood loss and optimizing clot removal [20]. Cleaner XT™ is a 6 F rotational thrombectomy system, utilizing a sinuous-shaped radio-opaque wire that rotates at approximately 4000 rounds per minute, facilitating gentle mechanical declotting [21]. Details of the CDTx methods applied by our PERT have previously been described [22].

Baseline clinical characteristics, risk stratification, and PE severity parameters were compared between the four treatment groups. Information about clinical and treatment data was obtained from medical records. Obesity was defined as a body mass index of 30.0 kg/m^2 or higher. As a comorbidity on admission, stroke was defined as both hemorrhagic and ischemic. A recent hospitalization, surgery, or trauma was defined as an episode that occurred within 1 month before the onset of PE. In-hospital outcomes included frequency of (i) mortality, (ii) stroke, (iii) recurrent PE/deep vein thrombosis, and (iv) bleeding complications as defined by the International Society on Thrombosis and Hemostasis (ISTH).

Statistical analysis

Statistical analysis was conducted using IBM SPSS Statistics, version 27.0 (IBM, Sheffield, UK). Categorical variables were presented as numbers and percentages. Continuous variables are presented as mean and standard deviation or median with interquartile range. The chi-square test for categorized variables and one-way ANOVA or the Kruskal–Wallis test for continuous variables were used to determine differences between groups, depending on the distribution. A p-value below 0.05 was considered significant.

Results

Patient risk groups

Figure 1 shows the flow chart of subsequent patients consulted by PERT CELZAT and included in the analysis. Among 244 patients consulted by PERT since its establishment in September 2017, 134 (55%) patients have been diagnosed with low- and intermediate-low-risk PE and 110 (45%) patients with HR or IHR PE. Of the 110 patients included in the analysis, 24 (22%) patients met the criteria of HR PE and 86 (78%) patients presented with IHR PE. The therapeutic strategies in the HR and IHR groups, including the number of patients undergoing each treatment, are listed in Figure 1. Overall, 67 (61%) patients were treated with AC only, 11 (10%) were treated with ST, 15 (14%) patients underwent SE, and in 17 (15%) cases CTDx was performed.

Proportion of treatment methods according to the patient risk group

The proportion of treatment methods in PE risk subgroups is shown in Figure 1. Therapeutic modalities applied following CELZAT activation in the HR and IHR groups are presented in Figure 2. In the HR group, 20 out of 24 (83%) patients received reperfusion therapy, including ST in 7 (29%) patients, SE in 5 (21%) patients, and CTDx in 8 (33%) patients. The reperfusion method was abandoned in 4 (17%) patients due to a critical clinical condition caused by comorbidities. In the IHR group, 63 out of 86 (73%) patients were treated with AC alone and 23 (27%) patients received reperfusion therapy, including ST in 4 (5%) patients, SE in 10 (12%) patients, and CTDx in 9 (11%) patients. The indications for ST in IHR patients included clinical deterioration during AC with UFH or LMWH. The indication for SE was the presence of a thrombus in transit or acute PE on top of the chronic thromboembolism, corresponding to chronic thromboembolic pulmonary hypertension. If chronic thromboembolic pulmonary hypertension was confirmed, a pulmonary endarterectomy was performed in addition to SE.

Patient clinical characteristics

Table 1 presents a comparison of baseline characteristics of patients with HR and IHR PE, divided into four groups according to the primary treatment method: AC alone (67 patients, 61%), ST (11 patients, 10%), SE (15 patients, 14%), and CDTx (17 patients, 15%). There were no significant differences between the treatment groups regarding sex, symptoms presented on admission and most of the comorbidities, and other venous thromboembolism risk factors, depending on the treatment strategy.

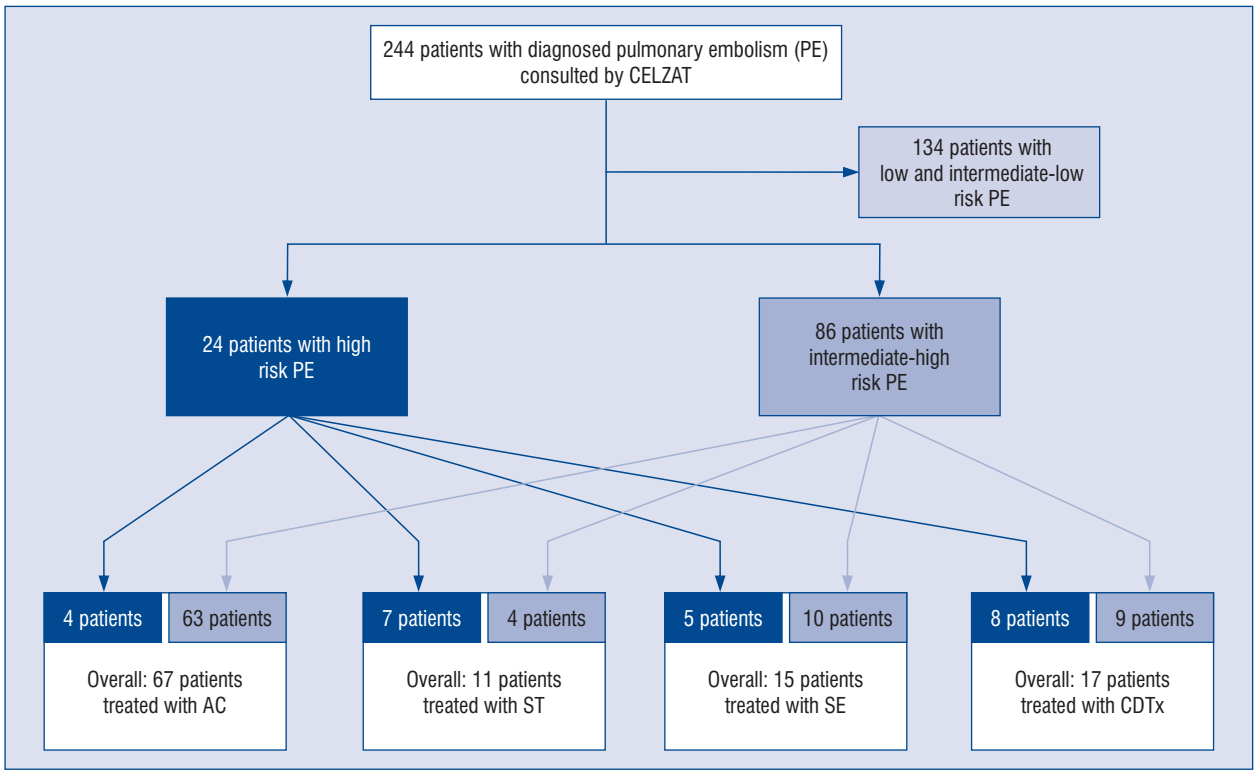

Figure 1. Flow chart of patients treated by Pulmonary Embolism Response Teams Center for the Management of Pulmonary Embolism (CELZAT); AC — anticoagulation alone; CDTx — catheter-directed therapies; PE — pulmonary embolism; SE — surgical embolectomy; ST — systemic thrombolysis.

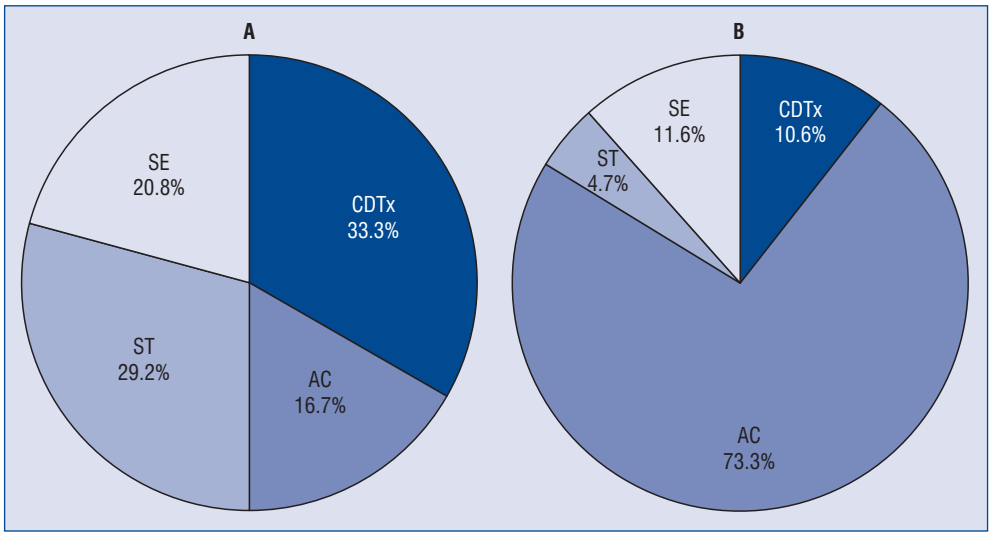

Figure 2. Therapeutic modalities applied following Pulmonary Embolism Response Team activation in high-risk (**A**) and intermediate-high-risk (**B**) pulmonary embolism subgroups, respectively; AC — anticoagulation alone; CDTx — catheter-directed therapies; SE — surgical embolectomy; ST — systemic thrombolysis.

Outcomes

The in-hospital outcome events according to mortality risk group and treatment method are shown in Table 2. The rate of in-hospital mortality was 11.8% (13/110), including 37.5% in the HR group (9/24) and 4.7% in the IHR group (4/86).

There were 4 (3.6%) minor bleeding events and 5 (4.5%) major bleeding events that required

Table 1. Baseline characteristics of patients treated with anticoagulation alone, systemic thrombolysis, surgical embolectomy, and catheter-directed therapies.

	Overall	Anticoagulation alone	Systemic thrombolysis	Surgical embolectomy	Catheter-directed therapies	P
Total (n)	110	67	11	15	17	
High risk (%)	24	4 (16.7)	7 (29.2)	5 (20.8)	8 (33.3)	
Intermediate-high risk (%)	86	63 (73.2)	4 (4.7)	10 (11.6)	9 (10.5)	
Baseline characteristics						
Age [years]	60.4 ± 16.3	63.5 ± 14.5	60.5 ± 16.5	50.2 ± 16.9	59.2 ± 13.5	**0.03**
Sex, male	59 (53.6%)	40 (59.7%)	4 (36.4%)	6 (40.0%)	9 (52.9%)	0.33
Symptoms on admission						
Dyspnea	89 (80.9%)	50 (74.6%)	8 (72.7%)	14 (93.3%)	17 (100%)	0.05
Chest pain	40 (36.4%)	25 (37.3%)	7 (63.6%)	3 (20.0%)	5 (29.4%)	0.13
Syncope	27 (24.5%)	17 (25.4%)	3 (27.3%)	2 (13.3%)	5 (29.4%)	0.73
Cough	13 (11.8%)	10 (14.9%)	2 (18.2%)	1 (6.7%)	0 (0%)	0.30
Pneumonia	11 (10.0%)	6 (9.0%)	1 (9.1%)	4 (26.7%)	0 (0%)	0.09
DVT	69 (62.7%)	43 (64.2%)	7 (63.6%)	12 (80.0%)	7 (41.2%)	0.15
Comorbidities						
Malignancy	28 (25.5%)	14 (20.9%)	1 (9.1%)	2 (13.3%)	5 (29.4%)	0.53
Coronary artery disease	14 (12.7%)	8 (11.9%)	0 (0%)	2 (13.3%)	2 (11.8%)	0.68
Chronic heart failure	9 (8.2%)	6 (9.0%)	1 (9.1%)	2 (13.3%)	0 (0.0%)	0.56
Atrial fibrillation	6 (5.5%)	5 (7.5%)	0 (0%)	0 (0%)	1 (5.9%)	0.56
Arterial hypertension	57 (51.8%)	35 (52.2%)	4 (36.4%)	7 (46.7%)	11 (64.7%)	0.5
COPD	5 (4.5%)	4 (6.0%)	0 (0%)	0 (0%)	1 (5.9%)	0.66
Diabetes mellitus	24 (21.8%)	12 (17.9%)	3 (27.3%)	4 (26.7%)	5 (29.4%)	0.67
Obesity	34 (30.9%)	17 (25.4%)	5 (45.5%)	6 (40.0%)	6 (35.3%)	0.43
Chronic kidney disease	9 (8.2%)	4 (6.0%)	1 (9.1%)	1 (6.7%)	3 (17.6%)	0.47
Stroke	10 (9.1%)	3 (4.5%)	0 (0%)	3 (20.0%)	4 (23.5%)	**0.02**
Depression	5 (4.5%)	3 (4.5%)	1 (9.1%)	1 (6.7%)	0 (0.0%)	0.69
Known thrombophilia	4 (3.6%)	2 (3.0%)	1 (9.1%)	0 (0%)	1 (5.9%)	0.61
Other VTE risk factors						
Smoking	25 (22.7%)	19 (28.4%)	1 (9.1%)	2 (13.3%)	3 (17.6%)	0.34
Indwelling catheter	4 (3.6%)	2 (3.0%)	0 (0%)	0 (0%)	2 (11.8%)	0.23
Hormonal therapy	7 (6.4%)	2 (3.0%)	1 (9.1%)	3 (20.0%)	1 (5.9%)	0.11
Recent hospitalization	28 (25.5%)	20 (29.9%)	1 (9.1%)	2 (13.3%)	5 (29.4%)	0.32
Recent surgery	11 (10.0%)	7 (10.4%)	1 (9.1%)	0 (0%)	3 (17.6%)	0.42
Recent trauma	8 (7.3%)	6 (9.0%)	0 (0%)	0 (0%)	2 (11.8%)	0.42
Prior PE	5 (4.5%)	2 (3.0%)	0 (0%)	1 (6.7%)	2 (11.8%)	0.38
Prior DVT	19 (17.3%)	14 (20.9%)	2 (18.2%)	2 (13.3%)	1 (5.9%)	0.51
PESI class						
I–II	37 (33.6%)	26 (38.8%)	3 (27.3%)	6 (40.0%)	2 (11.8%)	
III	30 (27.3%)	23 (34.3%)	3 (27.3%)	2 (13.3%)	2 (11.8%)	**0.005**
IV	18 (16.4%)	7 (10.4%)	0 (0%)	5 (33.3%)	6 (35.3%)	
V	25 (22.7%)	11 (16.4%)	5 (45.5%)	2 (13.3%)	7 (41.2%)	
Score	99 (75–123)	92 (72–107)	87 (66–109)	104 (75–119)	123 (112–174)	**0.006**
sPESI						
Score	1.55 ± 1.18	1.25 ± 1.06	2.00 ± 1.34	1.60 ± 1.18	2.41 ± 1.06	**0.001**
Clinical severity						
Intubation	13 (11.8%)	4 (6.0%)	3 (27.3%)	1 (6.7%)	5 (29.4%)	**0.02**
ICU admission	93 (84.5%)	51 (76.1%)	10 (90.9%)	15 (100%)	17 (100%)	**0.02**
Intracardiac thrombi	8 (7.3%)	2 (3.0%)	0 (0%)	6 (40.0%)	0 (0%)	**< 0.001**

Data are shown as number (percentage) or mean ± standard deviation or median (interquartile range). COPD — chronic obstructive pulmonary disease; DVT — deep vein thrombosis; ICU — intensive care unit; PE — pulmonary embolism; PESI — Pulmonary Embolism Severity Index; sPESI — simplified Pulmonary Embolism Severity Index; VTE — venous thromboembolism

Table 2. In-hospital mortality and outcome events according to risk categories and treatment methods.

	Overall	Anticoagulation alone	Systemic thrombolysis	Surgical embolectomy	Catheter-directed therapies
In-hospital mortality	**13 (11.8%)**	**6 (9.0%)**	**2 (18.2%)**	**0 (0%)**	**5 (29.4%)**
High risk	9 (37.5%)	4 (100%)	1 (14.3%)	0 (0%)	4 (50%)
Intermediate-high risk	4 (4.7%)	2 (3.2%)	1 (25.0%)	0 (0%)	1 (11.1%)
Major bleeding	**5 (4.5%)**	**2 (3.0%)**	**1 (9.1%)**	**1 (6.7%)**	**1 (5.9%)**
High risk	3 (12.0%)	1 (25.0%)	1 (14.3%)	1 (20.0%)	0 (0%)
Intermediate-high risk	2 (2.3%)	1 (1.6%)	0 (0%)	0 (0%)	1 (11.1%)
Minor bleeding	**4 (3.6%)**	**1 (1.6%)**	**3 (27.3%)**	**0 (0%)**	**0 (0%)**
High risk	2 (8.2%)	0 (0%)	2 (28.6%)	0 (0%)	0 (0%)
Intermediate-high risk	2 (2.3%)	1 (1.6%)	1 (25.0%)	0 (0%)	0 (0%)

blood transfusion and/or modification of AC therapy. There were 2 (1.8%) strokes in HR patients treated with thrombolysis. There was one fatal recurrence of PE in the IHR patient treated with systemic full-dose thrombolysis.

Catheter-directed therapies

Information about the indication for CTDx, the exact choice of treatment method, the sPESI and PESI score, the dose of rtPA, and treatment outcome are shown in Table 3. In the CDTx group, 8 (47%) patients met the criteria of HR PE, and 9 (53%) patients were evaluated as IHR PE. N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) concentrations decreased following transcatheter intervention in 90% of patients whose measurements were performed before and after the procedure. The concentrations of NT-proBNP on admission and at discharge are shown in Table 4.

In the CDL group, all patients received rtPA, with dosing varying between individuals. Three patients received 1 mg/h rtPA infusions for 10–24 h. In 1 case, a bolus of 20 mg rtPA was administered via infusion catheter at the initiation of treatment, followed by a continuous infusion of 1 mg/h for 20 h (the total dose was 40 mg of rtPA).

Complications in the CDL group occurred only in 1 patient and were related to a massive thigh hematoma, which was treated conservatively with a subsequent reduction of the anticoagulant dose. For this reason, an inferior vena cava filter was implanted on the 4th day after the CDL procedure. No other procedure-related thrombotic or bleeding events occurred in the CDTx group.

In 4 cases, an inferior vena cava filter was implanted, and the main indication was the inability to administer full-dose anticoagulant treatment.

Of the 4 in-hospital deaths in the HR group, 2 occurred in patients in whom the procedure was performed during or after cardiopulmonary resuscitation. One in-hospital death in the IHR group was observed in a patient who developed acute abdomen the day after the procedure. An autopsy was not conducted, so the exact cause of death remains unknown.

Discussion

In this manuscript, we present our experience regarding the treatment of patients with HR and IHR PE by local PERT. The main findings of our analysis are that (i) PERT consultations were more frequent in IHR PE patients, compared to HR PE (35.8% vs. 10%); (ii) the majority of patients with HR received at least one form of reperfusion therapy (ST, SE, or CDTx), while most IHR PE patients were treated with AC alone; (iii) the mortality rate in HR PE patients remains high; and (iv) CDTx was performed at a similar rate in HR and IHR patients (47% vs. 53%) and led to significant clinical improvement with a low adverse event rate.

A few studies have already demonstrated improved survival in the PERT era compared to the pre-PERT era [13, 23]. However, some studies revealed that despite a significant increase in the use of advanced treatments, the improvement in mortality rates is of borderline significance [14, 24]. This might be associated with a lack of standardized algorithms to select patients for advanced PE therapies and variable operator experience due to the imperfect effectiveness of CDTx, especially in patients with HR PE or comorbidities like malignancy. For example, our recent analysis of cancer-associated thrombosis demonstrated that oncological patients have similar in-hospital

Table 3. Clinical information about patients undergoing catheter-directed therapies.

No.	Sex, age [years]	PE risk	Indication for CDTx	sPESI score	PESI score	Treatment	Cumulative rtPA dose	Outcome at discharge
1	M, 72	High	History of ischemic stroke in the last 6 months	3	232	CDT	N/A	In-hospital death
2	F, 76	Intermediate-high	No improvement after 24-h anticoagulation treatment	2	116	CDT	N/A	In-hospital death
3	F, 54	Intermediate-high	History of ischemic stroke in the last 6 months	2	114	CDT + IVCf	N/A	III NYHA FC
4	F, 56	High	History of ischemic stroke in the last 6 months	2	126	CDT	N/A	III NYHA FC
5	M, 63	Intermediate-high	High risk of cancer-related bleeding	2	123	CDT	N/A	I NYHA FC
6	M, 49	Intermediate-high	No improvement after 24-h anticoagulation treatment	1	79	CDL + IVCf	40 mg	I NYHA FC
7	F, 47	Intermediate-high	No improvement after 24-h anticoagulation treatment	2	87	CDL	24 mg	I NYHA FC
8	M, 45	Intermediate-high	No improvement after 24-h anticoagulation treatment	2	95	CDL	10 mg	I NYHA FC
9	F, 65	High	Recent major orthopedic surgery	3	195	CDT + CDL + IVCf	20 mg	II NYHA FC
10	F, 51	High	Severe general condition due to metastatic cancer	4	131	CDT + CDL	20 mg	In-hospital death
11	M, 44	High	Intervention during CPR	2	124	CDT + ST	140 mg	In-hospital death
12	F, 53	Intermediate-high	History of hemorrhagic stroke	3	123	CDT + SE	N/A	III NYHA FC
13	M, 65	High	Infection after ICD implantation, respiratory failure	5	175	CDT	N/A	II NYHA FC
14	M, 36	High	Intervention after cardiac arrest and CPR	3	196	CDT + ST	2 × 50 mg	In-hospital death
15	M, 74	High	Recent pelvic fracture, treated surgically	3	174	CDT	N/A	II NYHA FC
16	M, 62	Intermediate-high	Recurrence of PE during anticoagulation therapy	1	112	CDT + IVCf	N/A	II NYHA FC
17	F, 84	Intermediate-high	No improvement after 24-h anticoagulation treatment	1	84	CDL	10 mg	II NYHA FC

CDT — catheter-directed thrombectomy; CDL — catheter-directed thrombolysis; CPR — cardiopulmonary resuscitation; F — female; ICD — implantable cardioverter-defibrillator; IVCf — inferior vena cava filter; M — male; N/A — not applicable; NYHA FC — New York Heart Association Functional Classification; PE — pulmonary embolism; PESI — Pulmonary Embolism Severity Index; sPESI — simplified PESI; SE — surgical embolectomy; ST — systemic thrombolysis; rtPA — recombinant tissue plasminogen activator

Table 4. N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) measurements before and after catheter directed therapies.

Case no.	Risk group	Treatment	NT-proBNP [pg/mL]		
			At admission	At discharge	Difference
1	High	CDT	24120	Death	N/A
2	Intermediate-high	CDT	12523	Death	N/A
3	Intermediate-high	CDT + IVCf	476	1515	+1039
4	High	CDT	N/D	1229	N/A
5	Intermediate-high	CDT	1974	483	–1491
6	Intermediate-high	CDL + IVCf	4029	499	–3530
7	Intermediate-high	CDL	3072	66	–3006
8	Intermediate-high	CDL	1463	126	–1337
9	High	CDT + CDL + IVCf	682	191	–491
10	High	CDT + CDL	19857	Death	N/A
11	High	CDT + ST	N/D	Death	N/A
12	Intermediate-high	CDT + SE	3767	1577	–2190
13	High	CDT	5220	4937	–283
14	High	CDT + ST	991	Death	N/A
15	High	CDT	2130	N/D	N/A
16	Intermediate-high	CDT + IVCf	891	350	–541
17	Intermediate-high	CDL	14956	404	–14552

CDT — catheter-directed thrombectomy; CDL — catheter-directed thrombolysis; IVCf — inferior vena cava filter; N/A — not applicable; N/D — no data; SE — surgical embolectomy; ST — systemic thrombolysis

survival rates to non-oncological patients but worse long-term outcomes because of their underlying neoplastic disease [25]. Hence, our analysis is crucial to understand the factors associated with treatment outcomes and optimize future treatment decisions of PERT.

Considering the unsatisfactory outcomes, especially in HR PE patients, multiple technologies are being developed to improve CDL and CDT. However, the clinical efficacy of CDTx has been demonstrated only in single-arm trials with surrogate endpoints, warranting caution when interpreting the results. In a previously published meta-analysis of 11 studies including 65,589 patients, 30-day mortality was 2-fold lower in the CDTx group than in the ST group (7.3 vs. 13.6%; odds ratio [OR]: 0.51, 95% confidence interval [CI]: 0.38–0.69, $p < 0.001$). The rates of adverse events such as myocardial injury, cardiac arrest, stroke, and major bleeding complications were lower in the CDTx group compared to the ST group ($p < 0.001$ for all) [26]. In the present publication, patients treated with CDTx accounted for 7% of all PERT consultations (17/240), with 8 out of 17 (47%) patients in the HR group. Among patients treated with CDTx, the overall mortality was 29% (5/17), with substantially lower mortality in IHR patients compared to those with HR PE (11% vs. 50%, respectively). A meta-analysis of 1168 patients showed that 30-day mortality in IHR PE patients treated with CDL was 0% (95% CI: 0–0.5%). In turn, a much higher 30-day mortality rate (8.0%, 95% CI: 3.2–14.0%) was observed in HR PE patients treated with CDL, confirming the survival rate discrepancies between these two groups observed in our analysis [27]. The high mortality rate in HR PE patients in our study might be because patients qualified for CDTx were often so-called "no-other--option" patients and at much higher mortality risk, as assessed by the PESI score, compared to patients qualified for ST. Such a high mortality rate indicates that HR patients with contraindications for ST are an especially vulnerable subgroup who require immediate evaluation and therapy optimization to maximize their chances of survival.

Regarding CDL efficacy, all patients in our study were treated successfully and discharged from the hospital with New York Heart Association class improvement. Importantly, they all had IHR PE, and in 90% of them a decrease in NT-proBNP levels was noted after the intervention. Concerning the safety of the CDTx procedures, only 1 patient

developed a complication after CDL — a thigh hematoma treated conservatively, considered a major adverse event with a hemoglobin drop from 11.7 to 7.9 g/dL. In other studies, minor bleeding events, including hematomas, occurred in 9% to 27% of cases [28, 29]. In a meta-analysis, the major bleeding rate of CDL for HR and IHR PE patients was 4.6%, most of which required transfusion [30]. In turn, no adverse events occurred in 13 patients treated with CDT, similarly to our study. As for the Indigo aspiration system, the EXTRACT-PE Trial showed that only 1.7% of patients experienced major complications [31]. As well as clinical trials, a MAUDE database report presented real-world data regarding the device's safety [32]. Out of 2118 reports gathered during the study period, only 67 (3.2%) were related to the Indigo aspiration system, and the most common failures were lightning unit malfunction and rotating hemostasis valve malfunction. Three (4.5%) patients died during the observation. Considering the types of thrombectomy and the amount of equipment offered by different companies, a comparison of different CDT devices is needed to find the best efficacy by using many modalities synergistically and tailoring the device to the needs of each patient.

Recently, a clinical consensus statement regarding CDTx has been published by the ESC Working Group on Pulmonary Circulation and Right Ventricular Function, which is a practical guide for CDTx and is complementary to the current guidelines [33]. Also, the Polish PERT Initiative has published an expert opinion on the use of CDTx in high-risk PE patients [34]. The introduction of PERTs, along with the publication of the ESC consensus statement, is an ideal moment to implement new devices, develop standardized protocols for CDL and CDT, and establish directions for future research [35–37].

Limitations of the study

A major limitation of our study is the small number of patients receiving interventional treatment within the PERT. In addition, this is a single PERT experience. Furthermore, data regarding baseline characteristics, procedural data, and outcomes were extracted from medical records. In some cases, data were missing due to an emergency clinical situation (e.g., a procedure performed during cardiopulmonary resuscitation) or in-hospital mortality.

Conclusions

PERT-CELZAT consultations resulted in primary reperfusion therapy in 83% of HR PE patients with an observed high mortality rate (37.5%), and in 26.7% of IHR PE patients with 4.7% mortality. CDTx was used in 15.5% of cases (17/110), and the results are still suboptimal, especially in the HR PE group, likely due to the initially severe condition of patients who qualified for CDTx. The therapy of patients with PE requires an individual approach due to the specificity of the disease, as well as concomitant risk factors or complications, which make the decision regarding the choice of treatment difficult and require interdisciplinary discussion, preferably within an expert group such as a PERT. Because there are no clear data from randomized controlled trials regarding the possible advantage of any transcatheter treatment, a PERT should have experience with various therapeutic methods, adjusting the choice of therapy to the patient's unique clinical situation. Due to the constant development of CDTx technologies, the PERT armamentarium will undoubtedly expand, which may translate into better treatment results. There is an urgent need to (i) establish more detailed selection criteria that might improve clinical outcomes in HR and IHR PE patients, especially those who qualified for CDTx, and (ii) compare currently available treatment methods to improve outcomes further.

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Complete revascularization based on angiography derived fractional flow reserve versus incomplete revascularization in patients with ST-segment elevation myocardial infarction

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Abstract

Background: *Nearly half of ST-segment elevation myocardial infarction (STEMI) patients present with significant multivessel coronary artery disease, they are at high risk of subsequent adverse events. Whether complete revascularization guided by coronary angiography-derived fractional flow reserve (caFFR) further reduces such events risk is not fully investigated.*

Methods: *In this study, 367 consecutive STEMI patients who underwent successful primary percutaneous coronary intervention (PCI) were enrolled. caFFR of all three coronary vessels were measured, including 367 culprit vessels and 703 non-culprit vessels. Complete revascularization was defined as post-PCI caFFR > 0.8 of all three coronary vessels. The primary endpoint was major adverse cardiovascular events (MACE; a composite of cardiovascular death, non-fatal recurrent myocardial infarction, ischemia-driven revascularization and non-fatal stroke/transient ischemic attacks) during follow-up.*

Results: *At a median follow-up of 3.8 years, MACE had occurred in 39 patients of the 220 (17.7%) in the complete revascularization group as compared with 49 patients of the 131 (37.4%) in the incomplete revascularization group (hazard ratio 1.9; 95% confidence interval 1.2–3.0; p = 0.005). The incomplete revascularization in culprit vessels evaluated by caFFR showed the highest risk for MACE occurrence.*

Conclusions: *In STEMI patients with multivessel coronary artery disease, incomplete revascularization based on caFFR might contribute to identifying patients at high-risk.* (Cardiol J 2024; 31, 2: 226–234)

Keywords: ST-segment elevation myocardial infarction, primary percutaneous coronary intervention, complete revascularization, coronary angiography-derived fractional flow reserve, major adverse cardiovascular events

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Introduction

Despite primary percutaneous coronary intervention (PPCI) as the preferred reperfusion strategy in ST-segment elevation myocardial infarction (STEMI) patients, STEMI remains one of the leading causes of death around the world [1]. They are at a high risk of subsequent adverse events related to both the stented segment and non-culprit lesions beyond the stented segment [2]. It is reported that up to 40–50% STEMI patients present with significant multivessel coronary artery disease (MVD) [3]. Based on strong evidence, complete revascularization in STEMI patients with multivessel disease is recommended by current guidelines. However, optimal methods to evaluate the severity of non-culprit lesions and timing of revascularization have not been adequately investigated [4]. On the one hand, non-culprit lesions are often discovered incidentally during PPCI, and they may be severely stenotic but are not necessarily unstable. Routine revascularization in stable coronary artery plaques may not improve long-term prognosis [5]. In addition, even opening non-culprit artery at a staged procedure in the subacute STEMI phase, repeated invasive procedures and the associated risks are potential obstacles. On the other hand, DANAMI--3-PRIMULTI [6] and Compare-Acute trial [7] showed that fractional flow reserve (FFR)-guided complete revascularization of non-infarct-related lesions in the acute phase of PPCI improved clinical outcomes compared with treatment of the infarct--related artery (IRA) only.

Although FFR measurement has been the gold standard in assessing functional severity of the epicardial coronary stenosis, it is far from widely used in STEMI patients. In terms of additional non-culprit vessel wire manipulation and the administration of adenosine, it is inconvenient to carry out FFR measurement during PPCI. The coronary angiography-derived FFR (caFFR), without using invasive pressure-wire measurement and hyperemic stimulus, overcomes these constraints and shows high diagnostic accuracy by using wire--derived FFR as the reference standard [8].

In this study, the aim was to use a noninvasive method of caFFR to explore the incremental value of complete revascularization over only culprit-vessel revascularization among STEMI patients in long-term prognosis.

Methods

The data are available to other researchers on reasonable request from the corresponding author.

Study design

This was a retrospective cohort study conducted at the Peking University First Hospital. STEMI patients who underwent PPCI between January 1, 2015 and December 31, 2020 were consecutively enrolled. The STEMI diagnosis was based on the fourth universal definition of myocardial infarction (MI) [9]. The PPCI was the preferred reperfusion strategy in patients within 12 h of symptom onset or > 12 h with evidence of ongoing ischemia and was performed expeditiously by an experienced team. Patients were excluded if they had been scheduled for coronary artery bypass grafting (CABG) after angiography; had an angiographic image that could not measure caFFR of culprit vessels; lack of adequate angiograms of non-culprit vessels. The STEMI culprit vessels were determined by identifying intraluminal thrombus embolization on angiography, ischemic electrocardiography changes, and/or wall motion abnormalities on echocardiography. All patients received evidence-based medical management adherence to guidelines. Clinical data were extracted from electronic medical records by trained physicians using a standardized data collection form. This study was approved by the institutional review board of the Peking University First Hospital and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline [10].

caFFR measurement

Detailed measurements of caFFR have been previously described [8]. In brief, the caFFR was calculated by validated software (FlashAngio, Rainmed, China). To calculate caFFR, at least two angiographic projections separated by ≥ 30° without vessel overlap are required. Flow velocity (V') and mean aortic pressure (Pa') were used by a proprietary computational pressure-flow dynamics method to solve the Navier-Stokes equation, computing a pressure drop (ΔP) along the generated mesh of the coronary artery as FFR = = (Pa'-ΔP)/Pa' [8]. All three main coronary arteries were measured caFFR if possible. The caFFR was computed in the equation above by researchers in an independent institution blinded to the patients' clinical data. In this study, all three main coronary arteries were defined of caFFR indexes > 0.8 as complete functional complete revascularization, otherwise, any artery of caFFR ≤ 0.8 was deemed as an incomplete revascularization. If patients with MVD underwent staged PCI in non-IRA, the caFFR value that performed in the staged PCI was used. The "tips and tricks" of caFFR measurements is provided in the **Supplementary material**.

Clinical outcomes

The primary end point of the study was the major adverse cardiovascular events (MACE; a composite of cardiovascular death, nonfatal recurrent MI, ischemia-driven revascularization and nonfatal stroke/transient ischemic attacks [TIA]) during follow-up. The secondary end points were all-cause death and individual parts of the primary end point. The definitions for cardiovascular outcomes are according to the uniform standard [11]. Cardiovascular death included any death resulting from cardiovascular causes. Nonfatal recurrent MI was defined based on evidence of myocardial necrosis combined with supporting myocardial ischemia presentation. The ischemia-driven revascularization was defined as a revascularization procedure with clinical ischemia evidence, including recurrent angina or positive test. Non-fatal stroke/TIA is defined as episodes of neurological dysfunction caused by cerebrovascular injury with or without acute infarction. The safety endpoint was in-hospital bleeding events classified according to the Bleeding Academic Research Consortium (BARC) types 2, 3, and 5 [12]. The follow-up clinical outcomes were obtained from telephone interviews and electronic medical record systems by January 2022. The standardized telephone interviews were conducted by trained physicians, who were blinded to the results of the caFFR measurements. If patients reported that they had been hospitalized, their hospital records were consulted and recorded. Clinical and safety end points were verified by other blinded adjudication physicians.

Statistical analysis

Continuous variables were presented as mean ± standard deviation and compared using the Student *t* test when normally distributed or as median (interquartile range) and compared with the Wilcoxon rank sum test when with skewed distribution. For categorical variables, data were reported as numbers and percentages and compared using the χ^2 test or Fisher exact test as appropriate. Cumulative incidences of the MACE outcome and each component of MACE (cardiovascular death, nonfatal recurrent MI, ischemia-driven revascularization and nonfatal stroke/TIA) through follow-up were estimated using cause-specific hazards models by treating non-cardiac death as competing events, differences were evaluated using the Gray test. Parameters showing clinical significance and significant statistical associations ($p < 0.01$) with MACE in univariable analysis were included into the multivariable model. The adjusted model included age, sex, diabetes, hypertension, creatine kinase-MB peak value, symptom onset to reperfusion time, estimated glomerular filtration rate, low-density lipoprotein cholesterol. A two-sided alpha level of 0.05 was considered as statistically significant. All statistical analyses were conducted using Stata software, version 16.0 (StataCorp).

Results

Patients and baseline characteristics

Overall, there were 512 STEMI patients in Peking University First Hospital who received PPCI from January 2015 to December 2020. Patients requiring CABG after coronary angiography (5 patients) were excluded, caFFR could not be measured (59 patients), lacking adequate angiographic imaging of non-culprit vessels (81 patients). Finally, 367 patients with STEMI underwent PPCI were included in the study (Fig. 1). Table 1 summarizes the baseline characteristics of the STEMI patients enrolled in the study. Among them, 359 (97.8%) patients' culprit lesions were treated with stent implantation, and 8 (2.2%) patients only received thrombus aspiration. There were 71 (19.3%) patients who underwent staged revascularization of non-IRA lesions in the acute setting of STEMI. The average number of stents were 1.3 ± 0.7. The left anterior descending was the most frequently interrogated vessel (49.6%).

Assessment of caFFR

In total, 367 STEMI patients with 367 culprit vessels and 703 non-culprit vessels finally included in the study. There were 133 (36.2%) patients presented with MVD. Based on the post-PCI caFFR, 232 (63.2%) patients were distinguished with functional complete revascularization (all three main coronary vessels post-PCI caFFR > 0.8) and 135 (36.8%) with incomplete revascularization (any coronary vessels post-PCI caFFR ≤ 0.8). Most culprit vessels (94.0%) reached functional revascularization (post-PCI caFFR > 0.8), and 68.4% patients post-PCI caFFR more than 0.9 after PPCI. In non-culprit vessels, the proportions were 88.2% and 73.7%, respectively. Baseline characteristics did not differ significantly among the groups (Table 1). Moreover, there were 22 (6.0%) patients post-PCI caFFR of culprit vessels below 0.8. The median post-PCI caFFR value of culprit vessels was 0.93 (0.90–0.95).

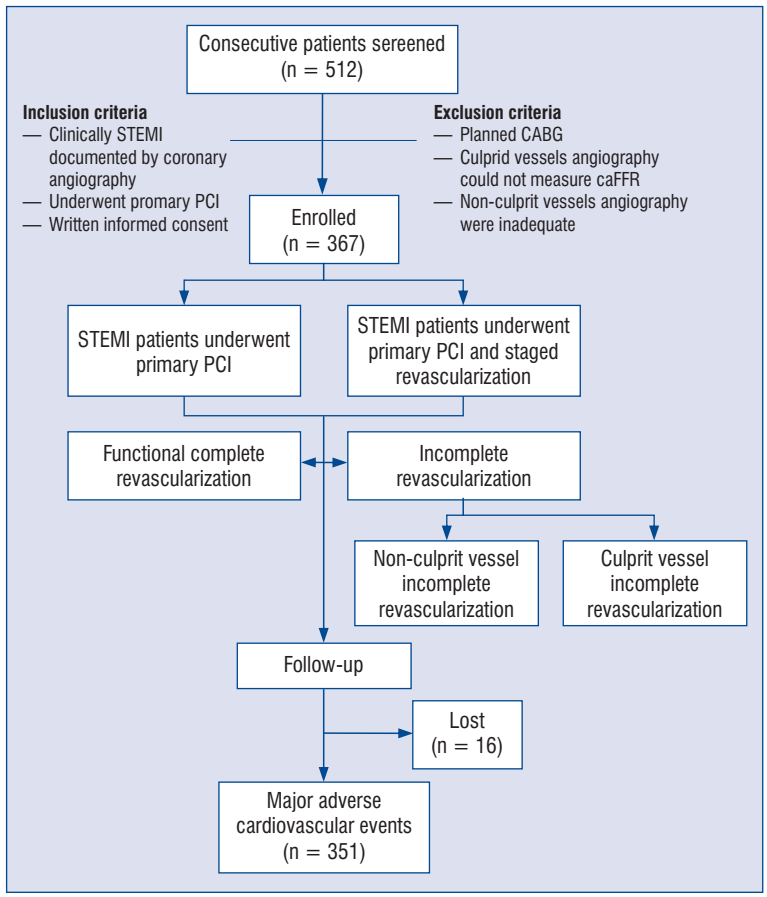

Figure 1. Flowchart for the study; CABG — coronary artery bypass grafting; caFFR — coronary angiography-derived fractional flow reserve; PCI — percutaneous coronary intervention; STEMI — ST-segment elevation myocardial infarction.

Long-term clinical outcome

The median follow-up duration was 3.8 (2.3–5.5) years. No difference in outcomes for safety endpoints between functional complete revascularization and incomplete revascularization group were recorded (**Suppl. Table 2**). The BARC ≤ 2 bleeding events had occurred in 2 (0.86%) and 0 patients, respectively (p = 0.534), and there were no BARC 3 or 5 bleeding events in both groups. During follow-up, 16 (4.4%) patients were lost, and 88 (25.1%) patients experienced MACEs (Table 2). The cumulative incidence of patient-oriented MACEs was significantly higher in the incomplete revascularization group when compared with the functional complete revascularization group (37.4% vs. 17.7%, respectively), mainly driven by an apparent difference in the occurrence of nonfatal recurrent MI (Fig. 2). Patients presented with incomplete revascularization suffered from a two-fold increase in the risk of MACEs (hazard ratio [HR] 1.9; 95% confidence interval [CI] 1.2–3.0; p = 0.005), after adjusted for age, sex, diabetes, hypertension, creatine kinase-MB peak value, symptom onset to reperfusion time, estimated glomerular filtration rate, and low-density lipoprotein cholesterol (Fig. 3A). Notably, patients with culprit vessel incomplete revascularization showed the worst prognosis (**Suppl. Table 1**, Fig. 3B).

In addition, among patients who underwent staged revascularization in the acute setting of STEMI, caFFR of non-IRAs was also measured and grouped complete revascularization based on post-staged PCI caFFR. There were 5 patients who underwent PCI of non-culprit lesions as a single-stage procedure, and 51 patients underwent PCI of non-culprit lesions as a staged procedure. The results remained unchanged after reanalysis. The complete revascularization predicted better outcomes compared to incomplete revascularization (11.9% vs. 29.9%, HR 2.14; 95% CI 1.26–3.65; p = 0.005) after adjusted for age, sex, diabetes, hypertension, creatine kinase-MB peak value, symptom onset to reperfusion time, estimated glomerular filtration rate and low-density lipoprotein cholesterol (Table 3).

Table 1. Patients' baseline characteristics.

Clinical characteristics	Overall (n = 367)	Functional complete revascularization (n = 232)	Incomplete revascularization (n = 135)	P
Male sex	300 (81.7%)	197 (84.9%)	103 (76.3%)	0.039
Age [year]	63.0 ± 12.8	61.9 ± 13.0	64.4 ± 13.4	0.088
Body mass index [kg/m^2]	25.2 ± 3.5	25.5 ± 3.4	24.6 ± 3.7	0.019
Diabetes mellitus	105 (28.6%)	53 (22.8%)	52 (38.5%)	0.001
Hypertension	224 (61.0%)	136 (58.6%)	88 (65.2%)	0.214
Dyslipidemia	117 (31.9%)	77 (33.2%)	40 (29.6%)	0.480
Previous or current smoker	245 (66.8%)	165 (71.1%)	80 (59.3%)	0.020
Previous MI	20 (5.4%)	14 (6.0%)	6 (4.4%)	0.518
Previous PCI	31 (8.4%)	24 (10.3%)	7 (5.2%)	0.087
Previous CABG	0	0	0	/
Peripheral artery disease	15 (4.1%)	9 (3.9%)	6 (4.4%)	0.792
History of CHF	1 (0.3%)	0	1 (0.7%)	0.368
Chronic kidney disease	10 (2.7%)	2 (0.9%)	8 (5.9%)	0.006
Previous stroke/TIA	40 (10.9%)	23 (9.9%)	17 (12.6%)	0.427
Systolic BP [mmHg]	119.7 ± 20.8	122.8 ± 19.3	114.3 ± 22.2	<0.001
Diastolic BP [mmHg]	71.2 ± 13.7	73.9 ± 13.1	66.7 ± 13.7	<0.001
Heart rate [bpm]	78.7 ± 16.3	78.1 ± 14.2	79.9 ± 19.5	0.334
Killip class:				0.154
I	297 (80.9%)	192 (83.1%)	104 (77.0%)	
II-IV	40 (19.1%)	39 (16.9%)	31 (23.0%)	
Laboratory tests				
Leukocyte [10^9/L]	10.2 ± 3.5	10.2 ± 3.7	10.3 ± 3.0	0.748
Hemoglobin [g/L]	141.3 ± 18.3	143.4 ± 16.6	137.7 ± 20.5	0.007
Platelet [10^9/L]	207.0 (173.8–253.0)	220.7 ± 133.3	225.2 ± 72.9	0.717
eGFR [mL/min/1.73 m^2]	74.6 ± 21.2	76.1 ± 19.4	72.1 ± 23.7	0.135
Blood glucose [mmol/L]	7.6 (6.2–9.7)	7.3 (6.0–9.5)	8.2 (6.6–10.6)	0.010
Triglyceride [mmol/L]	1.4 (1.0–2.1)	1.3 (1.0–2.2)	1.4 (0.9–2.1)	0.978
Total cholesterol [mmol/L]	4.5 ± 1.2	4.4 ± 1.1	4.5 ± 1.3	0.312
LDL cholesterol [mmol/L]	2.7 ± 0.8	2.7 ± 0.8	2.8 ± 0.8	0.264
HDL cholesterol [mmol/L]	1.0 ± 0.2	1.0 ± 0.2	1.0 ± 0.3	0.905
CK-MB peak value [ng/mL]	237.0 (110.6–397.7)	240.0 (109.9–404.1)	235.5 (109.4–385.5)	0.176
Procedural characteristics				
Infarct-related vessel:				< 0.001
Left anterior descending	182 (49.6%)	134 (57.8%)	48 (35.6%)	
Left circumflex artery	42 (11.4%)	27 (11.6%)	15 (11.1%)	
Right coronary artery	143 (39.0%)	71 (30.6%)	72 (53.3%)	
Radial artery access	328 (89.4%)	216 (93.1%)	112 (83.0%)	0.002
Thrombus aspiration	154 (42.0%)	103 (44.4%)	51 (37.8%)	0.215
Symptom onset to reperfusion time [h]	4.5 (3.0–7.6)	4.4 (2.9–7.6)	4.6 (3.1–8.0)	0.308
Stent implantation numbers	1.3 ± 0.7	1.3 ± 0.6	1.4 ± 0.7	0.205
Intra-aortic balloon pump	17 (4.6%)	4 (1.7%)	13 (9.6%)	0.001
Medication at hospital discharge				
ASA	360 (99.4%)	229 (99.6%)	131 (99.2%)	1.000
Ticagrelor	110 (30.0%)	73 (31.7%)	37 (28.0%)	0.460
Clopidogrel	253 (68.9%)	158 (68.1%)	95 (72.0%)	0.513
Statins	360 (99.4%)	228 (99.1%)	132 (100.0%)	0.535
Beta-blocker	313 (86.5%)	201 (87.4%)	112 (84.9%)	0.325
ACEI/ARB	296 (81.8%)	198 (86.1%)	98 (74.2%)	0.005

Data are presented as median (interquartile range), number (%), or mean ± standard deviation; ACEI/ARB — angiotensin converting enzyme inhibitors/angiotensin receptor blocker; ASA — acetylsalicylic acid; BP — blood pressure; CABG — coronary artery bypass grafting; CHF — chronic heart failure; CK-MB — creatine kinase-MB; eGFR — estimated glomerular filtration rate; HDL — high density lipoprotein; LDL — low density lipoprotein; MI — myocardial infarction; PCI — primary percutaneous coronary intervention; TIA — transient ischemic attacks

Table 2. Major adverse cardiovascular events during follow-up in functional complete revascularization vs. incomplete revascularization.

Follow-up	All patients				Adjusted model 1		Adjusted model 2	
	Functional complete revascularization (n = 220)	Incomplete revascularization (n = 131)	Unadjusted HR (95% CI)	P	Adjusted HR (95% CI)	P	Adjusted HR (95% CI)	P
Cardiovascular death	10 (4.5)	11 (8.4)	1.86 (0.79–4.39)	0.159	0.97 (0.31–3.08)	0.963	1.13 (0.38–3.36)	0.825
Nonfatal recurrent MI	2 (0.9)	11 (8.4)	9.02 (2.00–40.65)	0.004	10.58 (2.00–55.86)	0.005	4.59 (1.33–15.90)	0.016
Ischemia-driven revascularization	23 (10.5)	20 (15.3)	1.47 (0.81–2.69)	0.207	1.59 (0.83–3.03)	0.159	1.33 (0.54–3.32)	0.538
Stroke/TIA	5 (2.3)	7 (5.3)	2.27 (0.73–7.08)	0.156	1.97 (0.63–6.21)	0.246	1.90 (0.58–6.20)	0.288
MACE	39 (17.7)	49 (37.4)	2.26 (1.49–3.45)	< 0.001	1.91 (1.21–3.01)	0.005	1.86 (1.08–3.21)	0.025
All-cause death	18 (8.2)	22 (16.8)	2.12 (1.13–3.95)	0.019	1.55 (0.78–3.05)	0.208	1.91 (0.95–3.86)	0.070

Adjusted model 1 was adjusted for age, sex, diabetes, hypertension, creatine kinase-MB peak value, symptom onset to reperfusion time, estimated glomerular filtration rate, low-density lipoprotein cholesterol; The adjusted model 2 included age, sex, diabetes, hypertension, symptom onset to reperfusion time, estimated glomerular filtration rate, low-density lipoprotein cholesterol and intra-aortic balloon pump used; CI — confidence interval; HR — hazard ratio; MACE — major adverse cardiovascular events; MI — myocardial infarction; TIA — transient ischemic attacks

Figure 2. Major adverse cardiovascular events during follow-up; MI — myocardial infarction; TIA — transient ischemic attacks; the blue column represents functional complete revascularization group; the gray column represents incomplete revascularization group.

Figure 3. Cumulative incidence curves of the primary end point.

Table 3. Reanalysis of major adverse cardiovascular events during follow-up in functional complete revascularization vs. incomplete revascularization.

Outcomes	Functional complete revascularization (n = 260)	Incomplete revascularization (n = 107)	Crude HR (95% CI)	P	Adjusted HR (95% CI)	P
Cardiovascular death	10 (4.5)	11 (8.4)	2.83 (1.20–6.67)	0.017	1.36 (0.47–3.88)	0.569
Nonfatal recurrent MI	2 (0.9)	11 (8.4)	6.05 (1.86–19.65)	0.003	6.02 (1.72–21.05)	0.005
Ischemia-driven revascularization	23 (10.5)	20 (15.3)	1.54 (0.64–3.66)	0.334	1.42 (0.57–3.52)	0.455
Nonfatal stroke/TIA	5 (2.3)	7 (5.3)	2.62 (0.84–8.11)	0.096	2.14 (0.67–6.88)	0.201
MACEs	31 (11.9)	32 (29.9)	2.85 (1.74–4.67)	< 0.001	2.14 (1.26–3.65)	0.005
All-cause death	18 (8.2)	22 (16.8)	3.17 (1.70–5.91)	< 0.001	1.99 (1.01–3.94)	0.047

Adjusted for age, sex, diabetes, hypertension, creatine kinase-MB peak value, symptom onset to reperfusion time, estimated glomerular filtration rate, low-density lipoprotein cholesterol; CI — confidence interval; HR — hazard ratio; MACE — major adverse cardiovascular events; MI — myocardial infarction; TIA — transient ischemic attacks

Discussion

In this retrospective study, it was proved that functional incomplete revascularization guided by caFFR might contribute to identifying high-risk STEMI patients. The incomplete revascularization may have an adverse effect on long-term prognosis, especially in culprit vessels. After PPCI, there remain a few culprit vessels suffering from suboptimal function revascularization, and these patients are at the highest risk for MACEs, which was driven mainly by increased occurrence of recurrent MI. Although PPCI is the preferred reperfusion strategy for STEMI patients, the reality is that STEMI patients continue to be at a high risk of future adverse events related to both the culprit lesions and residual non-culprit lesions. These patients often have multivessel disease that cause the future acute events. However, the universal recognized revascularization strategy for non--culprit lesions has not been established. Several randomized clinical trials have shown that complete revascularization is beneficial compared to only culprit lesions revascularization [6, 7, 13–15]. In the COMPLETE trial [15], having randomized over 4000 STEMI patients with multivessel disease, proved that complete-revascularization strategy can lead to a significant reduction in the risk of cardiovascular death or new MI at a median follow-up of 3 years. The complete revascularization resulted in a 26% lower risk of a composite of death from cardiovascular causes or new MI, and nearly half the risk with a culprit-lesion-only PCI strategy in the composite of death from cardiovascular death, new MI and ischemia-driven revascularization. Regardless of when the non-culprit-lesion PCI was taken, the benefit of complete revascularization consistently existed.

In clinical practice, determining which lesions cause ischemia and warrant revascularization based on visual estimation from coronary angiography cannot accurately predict a lesions' functional severity. As a well-established technique in assessing the functional severity of coronary lesions, FFR is the preferred management strategy in patients with MVD [16]. The index of FFR ≤ 0.80 defines hemodynamically significant stenosis that requires revascularization with an accuracy of more than 90% [16]. In the FAME study, FFR-guided PCI strategy significantly reduced the rate of the primary endpoint (composite of death, MI, and repeat revascularization) at 1 year than angiography-guided PCI, as well as contrast agent and stents implantation [17]. Furthermore, the DANAMI-3-PRIMULTI

trial [6] and Compare-Acute trial [18], large randomized trials, showed that complete revascularization guided by FFR in STEMI patients with multivessel disease significantly reduced the risk of future MACE, even in the acute setting of PPCI. Recently, FRAME-AMI trial (NCT02715518) also proved that FFR-guided complete revascularization is superior to angiography-guided strategy in acute MI patients from East Asia. However, FFR has not been frequently used in patients with an acute coronary syndrome, mainly owing to concerns with additional procedural time and cost. Of note, FFR measurements required hyperemic conditions have a risk of morbidity from arrhythmia.

The caFFR, without using invasive pressure-wire measurement and hyperemic stimulus, overcomes these constraints and shows high diagnostic accuracy by using wire-derived FFR as the reference standard [8]. It has been confirmed that caFFR measurement is in good correlation and agreement with wire-based FFR both before and after PCI [8, 19–21]. Several studies proved that STEMI with multivessel disease patients can benefit from quantitative flow ratio-guided complete revascularization in the stages of acute MI [22–24]. However, few studies reported caFFR-guided strategy in STEMI patients. Although a prevalence of microvascular dysfunction in both culprit and non-culprit vessels questioning the accuracy of caFFR measurement in the STEMI acute setting, the index of caFFR might be overestimated. Thus, the cut-value of caFFR ≤ 0.8 is still useful and crucial for guiding additional revascularization.

In the present study, additional evidence is provided that complete revascularization is important for prognosis. Not only for providing information for non-culprit vessels revascularization strategy, but also for culprit vessels optimization treatment. Nearly 6% patients' culprit vessels in the current study did not reach functional complete revascularization after PPCI, and these patients have shown the worst prognosis in the long-term. Therefore, identifying these high residual risk patients by caFFR at index of PPCI and to further optimize outcome by additional procedures and intensive secondary prevention are clinically significant.

Limitations of the study

The present study has usual limitations inherent in retrospective studies. Some patients had to be excluded because of insufficient angiography to measure caFFR. Although confounding factors were adjusted for in the models as much as possible, potential unmeasured confounding factors may still exist. Moreover, STEMI patients may present with microvascular dysfunction in non-culprit vessels, a reduced caFFR accuracy due to microvascular dysfunction cannot be excluded.

Conclusions

In STEMI patients with MVD, caFFR-based incomplete revascularization may contribute to identifying patients at high-risk and take further comprehensive multiple interventions to improve prognosis as early as possible.

Conflict of interest: None declared

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Coronary laser with simultaneous contrast injection for the treatment of stent underexpansion

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Abstract

Background: *Stent underexpansion is a challenge in interventional cardiology. Some off-label treatments, such as rotational atherectomy, intravascular lithotripsy and coronary lasing, have been used to overcome the problem. The purpose of this study is to evaluate the safety and efficacy of coronary laser atherectomy with simultaneous contrast injection and subsequent balloon dilation to optimize stent expansion.*

Methods: *Coronary laser atherectomy with simultaneous contrast injection was used. After lasing, non-compliant balloon dilation at high pressure was performed to overcome the underexpanded point. The average increase in the minimum stent area (MSA) was measured by intravascular ultrasound (IVUS), and any complication related to the technique was evaluated. Additionally, major adverse cardiovascular events (MACE), consisting of death from any cause, new myocardial infarction (MI) and target lesion revascularization, were scrutinized in a long-term follow-up.*

Results: *Sixteen underexpanded stents were treated with laser between August 2017 and November 2022. In all cases but one, IVUS was used to evaluate the MSA before and after lasing. The MSA showed an average increase of 2.34 ± 1.57 mm^2 (95% confidence interval [CI]: 1.47–3.21; $p < 0.001$) after laser application and balloon inflation. No complication related to the technique was detected. During a follow-up period of a median (interquartile range) of 457 (50–973) days, the combined MACE assessed by Kaplan-Meier estimator showed an event-free rate of 0.82 (95% CI: 0.59–1).*

Conclusions: *Coronary laser with simultaneous contrast injection is a safe method to optimize a stent underexpansion, with an acceptable event-free rate in long-term follow-up.* (Cardiol J 2024; 31, 2: 235–242)

Keywords: percutaneous coronary intervention, excimer laser coronary angioplasty

Introduction

Percutaneous coronary intervention (PCI) with eventual stent implantation is the standard therapy for significant atherosclerosis lesions in most cases. Plaque preparation before stenting, especially in calcified lesions, is crucial to obtaining optimal results after stent deployment. Interventional cardiologists are increasingly dealing with more complex lesions, which demand, in some circumstances, careful debulking using specific techniques before stent implantation.

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Figure 1. Koninklijke Philips N.V. (San Diego, CA, USA) CVX-300 excimer laser coronary atherectomy system with its monorail catheter.

Stent underexpansion is associated with a higher risk of stent thrombosis and restenosis [1, 2]; therefore, ensuring adequate lesion debulking is crucial for optimal stent deployment. Some balloon undilatable lesions are easily identified under fluoroscopy by visualizing a waist in the balloon; however, at other times, a precise diagnosis requires intravascular imaging [3]. Indeed, optimal stent expansion using intravascular ultrasound (IVUS) has been associated with lower target vessel revascularization compared with angiographic guidance alone [4]. The ideal scenario is to avoid stent underexpansion, but if the stent remains constrained following implantation despite appropriate inflation pressure, typical conventional treatment is limited to high-pressure non-compliant (NC) balloon inflation. However, a few off-label therapies have been described in interventional cardiology to solve this unexpected problem, such as rotational atherectomy and intravascular lithotripsy (IVL) [5, 6]. IVL is safe to perform in freshly implanted stents and it does not significantly damage the polymer [7], with reported low effectiveness in lumen diameter gain in case of IVL therapy directly after stenting and in ostial location [8]. Excimer laser coronary atherectomy (ELCA™ Coronary Laser Atherectomy Catheter; Koninklijke Philips N.V. San Diego, CA, USA) can potentially debulk and ablate the tissue around the underexpanded stent and subsequently assist in balloon dilation within the stent as evidenced in several studies [9, 10].

The purpose of this study is to report a single-center experience in the efficacy and safety of ELCA with simultaneous contrast injection in a series of patients with underexpanded stents.

Methods

This is a retrospective, single-center study of consecutive patients with underexpanded stents in whom ELCA with concurrent contrast injection was used to assist posterior balloon inflation and to optimize the minimum stent area (MSA) assessed by IVUS. Stent underexpansion was defined as a focal angiographic stenosis of ≥ 30% after stent deployment. Calcification was assessed with fluoroscopy examination and checked by IVUS as a calcified ring surrounding the stent underexpanded point. MSA was assessed by IVUS before laser application except in one case in which the IVUS probe was unable to cross the lesion. After laser delivery and subsequent balloon inflation, MSA was measured once again by IVUS. An ELCA 0.9 mm or 1.4 mm X-80 Vitesse RX Catheter (Koninklijke Philips N.V.; Fig. 1) was used with simultaneous contrast injection during laser delivery. After 2–3 rounds of ELCA within the underexpansion area, a NC balloon inflation fit for stent size was performed until a considerable improvement in the waist or stent underexpanded point was appreciated. Laser energy was applied using an on-off method consisting of laser energy activation for 10 s with a 5 s pause after each lasing period. The laser catheter was slowly advanced over a 0.014 inch coronary guidewire at a speed of 1 mm/s, through the underexpanded point and not beyond the stent, according to the recommendations of the device manufacturer [11, 12]. Final

residual stenosis after laser delivery and balloon inflation was assessed by visual inspection.

The main purpose of the present study was to evaluate the efficacy of ELCA with simultaneous contrast injection for stent underexpansion in terms of MSA improvement. Additionally, the procedural safety was evaluated with the assessment of the following variables: coronary dissection, vessel perforation, slow-flow or no-reflow phenomenon and peri-procedural myocardial infarction (MI). Moreover, clinical follow-up in all patients was performed in order to assess any major adverse cardiac events (MACE), consisting of the combination of all cause-mortality, new MI or target lesion revascularization (TLR). To evaluate the procedural efficacy, MSA was measured before and after ELCA, plus balloon dilation and the mean increase in this parameter was assessed in the entire series. Additionally, an increase of at least 1 mm^2 in MSA after coronary lasing plus balloon inflation was evaluated individually in all cases. Patient follow-up was caried out through a clinical history review and phone call if needed. All patients signed an informed consent before undergoing the procedure.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation and compared with a paired Student t-test. Categorical variables were represented as proportion and percentage and compared using a chi-square or Fisher exact test as appropriate. The paired t-test was used to find the gain in MSA measured by IVUS after lasing and balloon dilation. The MACEs were assessed as time-to--event data using the Kaplan-Meier statistic. Data analyses were performed using SPSS Statistics v.23 (IBM Corp., Armonk, NY, USA). A p-value < 0.05 was considered statistically significant.

Results

Between August 2017 and November 2022, 16 cases of underexpanded stents were treated in our cath lab using ELCA with simultaneous contrast injection technique. The mean age of patients was 71 ± 11 years, 2 (12.5%) were women and 13 (81.3%) were diabetics. In terms of diagnosis, 8 (50%) presented with stable angina and 7 (43.8%) with non-ST-segment elevation MI; 1 (6.2%) had recently suffered a ST-segment elevation MI. A 0.9-mm laser catheter was used in 13 (81.3%) cases and a 1.4-mm one in 3 (18.7%). The laser energy and frequency mean values were 57.8 ± 11.1 mJ/mm^2 and 42.2 ± 18.5 Hz, respectively, with laser application duration a median of 100 (80–115) s. In 13 (81.3%) cases, the treated artery was the right coronary artery and in 3 (18.7%), the left anterior descending coronary artery. The average vessel reference diameter was 3 mm and the mean stent diameter and length where laser energy was applied were 3.33 mm and 35.5 mm, respectively. In 10 (62.5%) out of 16 cases, the ELCA technique with simultaneous contrast administration was used as soon as stent underexpansion was detected, and in 6 (37.5%), the procedure was performed in a second step, an average of 18.8 ± 11 days after the first procedure. In 9 (56.3%) cases, the ELCA technique was used after a NC balloon failed to overcome the underexpanded point, and in the remaining 7 (43.7%) cases, a coronary laser was used without prior balloon dilation (Table 1). The MSA assessed by IVUS showed an average increase of 2.34 ± 1.57 mm^2 (confidence interval [CI]:

Table 1. Basal and procedural details

Parameters	N = 16
Age	71 ± 11
Female	2 (12.5%)
Hypertension	14 (87.5%)
Diabetes	13 (81.3%)
Vessel:	
LAD	3 (18.7%)
RCA	13 (81.3%)
Diagnosis:	
Stable angina	8 (50%)
NSTEMI	7 (43.8%)
STEMI	1 (6.2%)
Size of excimer laser:	
0.9 mm	13 (81.3%)
1.4 mm	3 (18.7%)
Intravascular ultrasound	15 (93.8%)
Balloon (pre-laser):	
Yes	9 (56.3%)
No	7 (43.7%)
Lasing:	
Acute phase	10 (62.5%)
Staggered procedure	6 (37.5%)
Fluency [mJ/mm^2]	57.8 ± 11.1
Frequency [Hz]	42.2 ± 18.5

LAD — left anterior descending coronary artery; NSTEMI — non--ST-segment elevation myocardial infarction; RCA — right coronary artery; STEMI — ST-segment elevation myocardial infarction

Table 2. Quantitative intravascular ultrasound features

	Pre ELCA (n = 15)	Post ELCA (n = 15)	P
MSA	5.79 ± 2.24	8.13 ± 2.4	< 0.001
↑MSA ≥ 1 mm^2		11 (73.3%)	

ELCA — excimer laser coronary atherectomy; MSA — minimum stent area

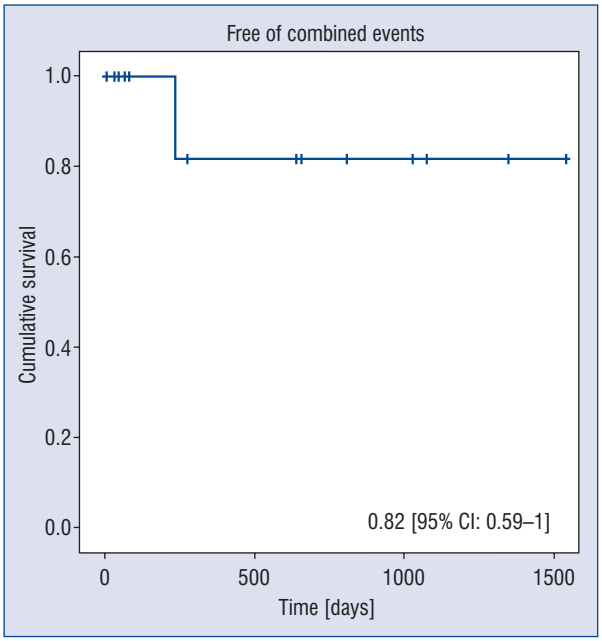

Figure 2. Kaplan-Meier estimator illustrating the event-free rate of the combined major adverse cardiovascular events including death from any cause, new myocardial infarction and target lesion revascularization during a median (interquartile range) follow-up of 457 (50–973) days; CI — confidence interval.

1.47–3.21; p < 0.001) after laser application and NC balloon inflation (Table 2). The average final residual stenosis was 15%. No complications related to the procedure, such as coronary perforation, dissection, slow flow, the no reflow phenomenon or peri-procedural MI, were experienced in the present series. Upon a median (interquartile range) follow-up of 457 (50–973) days, the combined MACE, consisting of all-cause mortality, new MI or TLR assessed by the Kaplan-Meier estimator, showed an event-free rate of 0.82 (95% CI: 0.59–1; Fig. 2) mainly at the expense of 2 (12.5%) deaths due to non-cardiovascular cause. Any new MI or TLR was detected during the follow-up period.

Discussion

The main finding of this single-centre study was that ELCA with simultaneous contrast injection is safe and efficacious as an adjuvant therapy for the treatment of stent underexpansion with an acceptable patient prognosis during the follow-up period.

Excimer laser coronary angioplasty transmits ultraviolet light energy with the ability to ablate inorganic material via a photochemical, photothermal and photomechanical mechanism [9, 13]. Moreover, the interaction of laser energy with the contrast medium can generate microbubbles with pressure pulses > 100 atm [14]. As a result, ELCA can weaken or ablate the underlying tissue surrounding the underexpanded stent, facilitating posterior balloon dilation within the stent.

Stent underexpansion is a challenge for interventionists, and all efforts must be made to avoid such unexpected complications. Calcific coronary lesions require adequate debulking necessitating in some cases the use of high pressure NC balloon dilation instead of conventional NC [15]. MSA > 80% of the average (proximal and distal) reference lumen area has been considered as a target for stent optimization and is associated with low adverse event rate and consequently the latter cut-off is recommended by experts to be adopted in clinical practice [16]. There are some non-conventional treatments to overcome stent underexpansion if post-dilation with a NC balloon fails. The rotational atherectomy technique, academically termed stent ablation, has been used to resolve this complication. However, this strategy runs the potential risk of burr entrapment within the stent, which requires specific techniques aimed to retrieve the device trapping [17, 18]. Cui et al. [5] described an elegant method for the use of stent ablation with a rotablator guided by IVUS and based on the burr size selection principle of 'downsize first and upsize last'. The latter technique consists of using a first burr 0.1–0.2 mm smaller and a second burr 0.1––0.2 mm larger than the minimum lumen diameter. The authors did not experience any burr entrapment, although in 81.8% of procedures, a new stent was implanted.

Intravascular lithotripsy delivers a pulsatile sonic pressure wave via a balloon positioned within the coronary artery with the ability to fracture intimal and medial calcification and energy passing atraumatically through the surrounding noncalcified tissue [19]. IVL has been used as an off-label technique to treat underexpanded stents with

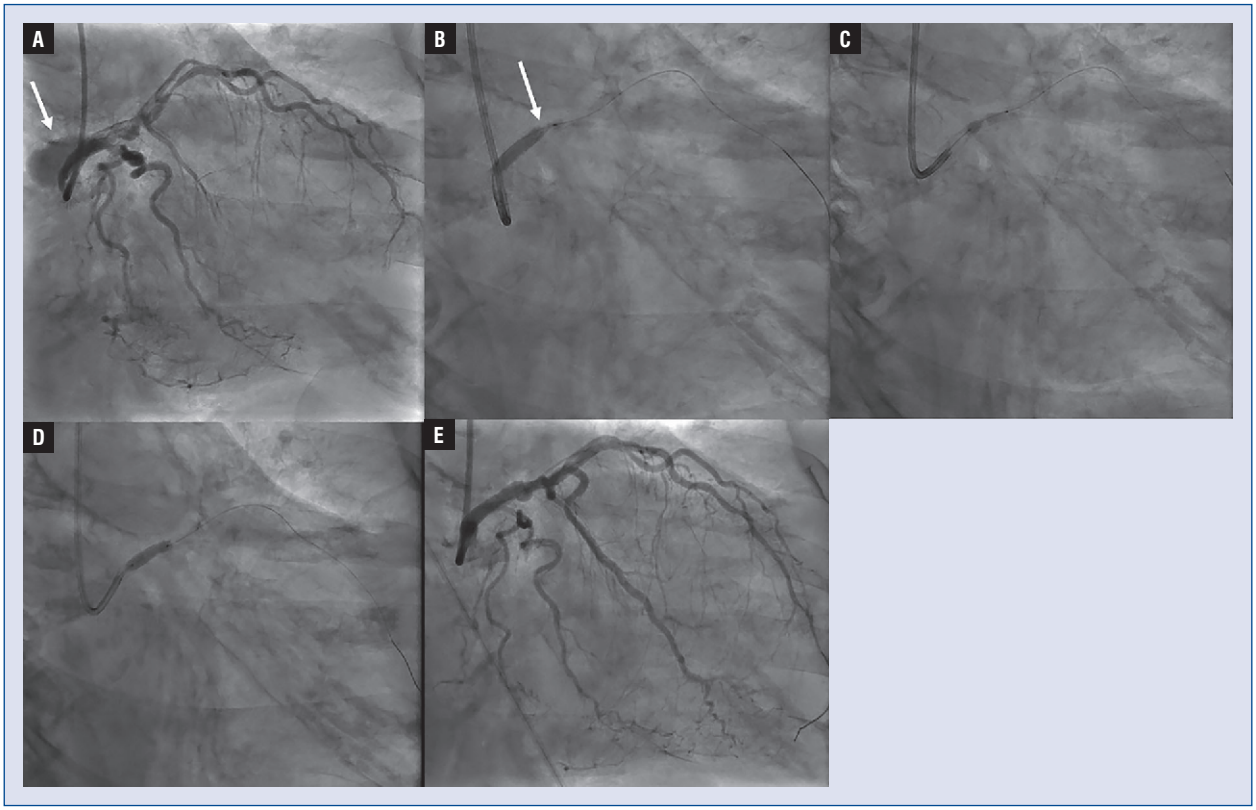

Figure 3. An 87-year-old woman admitted to the documented center due to non-ST-segment elevation myocardial infarction underwent a coronary angiogram. A severe calcified stenosis of the left anterior descending coronary artery (LAD) proximal segment was appreciated during the coronary angiogram, although the injection provoked left main (LM) dissection, which spread antegradely as well as retrogradely to the sinus of Valsalva and ascending aorta (**A**). Any additional injection was avoided, and in order to seal the dissection, the operator decided to implant a direct 3.5 × 16 mm drug eluting stent (DES) in LM-LAD after verifying the correct positioning of the guidewire into the true lumen by intravascular ultrasound (IVUS). However, an important underexpansion in the distal part of the stent was detected (**B**). Dilation with a non-compliant 3.5 × 12 mm balloon could not overcome the underexpanded point (**C**), and an intravascular lithotripsy (IVL) balloon was unable to cross the lesion. The IVUS probe did not cross the tight point either. Excimer laser coronary atherectomy 0.9 mm with a fluency and frequency of 45 mJ/mm^2 and 25 Hz, respectively, and simultaneous contrast injection was used. Afterward, the same non-compliant balloon overcame the stent underexpansion (**D**). The proximal and mid segment of the LAD was significantly diseased, so the procedure was completed by applying a cutting balloon and IVL and implanting a second DES, overlapped with the previous one. A successful angiographic result was achieved with a complete sealing of the dissection at the level of the sinus of Valsalva (**E**), and the patient had an uneventful hospital stay.

promising results [6], although in some severe underexpanded cases, the placement of balloon lithotripsy can be challenging [3], such as in a case illustrated in the present series (Fig. 3). Besides, its effect can be partly attenuated by metal rings of freshly implanted stent [8].

Wańha et al. [20] used IVL aimed to optimize stent underexpansion in 62 patients and achieved a relative stent expansion > 80% as a primary efficacy endpoint in 72.6% of the cases.

One of the basic rules of ELCA usage in the coronary artery is the need to wash out the blood and contrast media with saline serum before laser delivery. The combination of pulsed-wave application of an ultraviolet wave in an on-off method with saline flushing during energy delivery prevents side effects such as dissection or perforation due to coronary wall heating [14, 21]. In fact, both blood and iodinated contrast media contain non-aqueous cellular macromolecules, such as proteins, which can absorb the majority of the excimer laser, creating cavitating microbubbles at the site of energy delivery, which increase the risk of coronary wall injury [22]. By contrast, saline flushing during laser

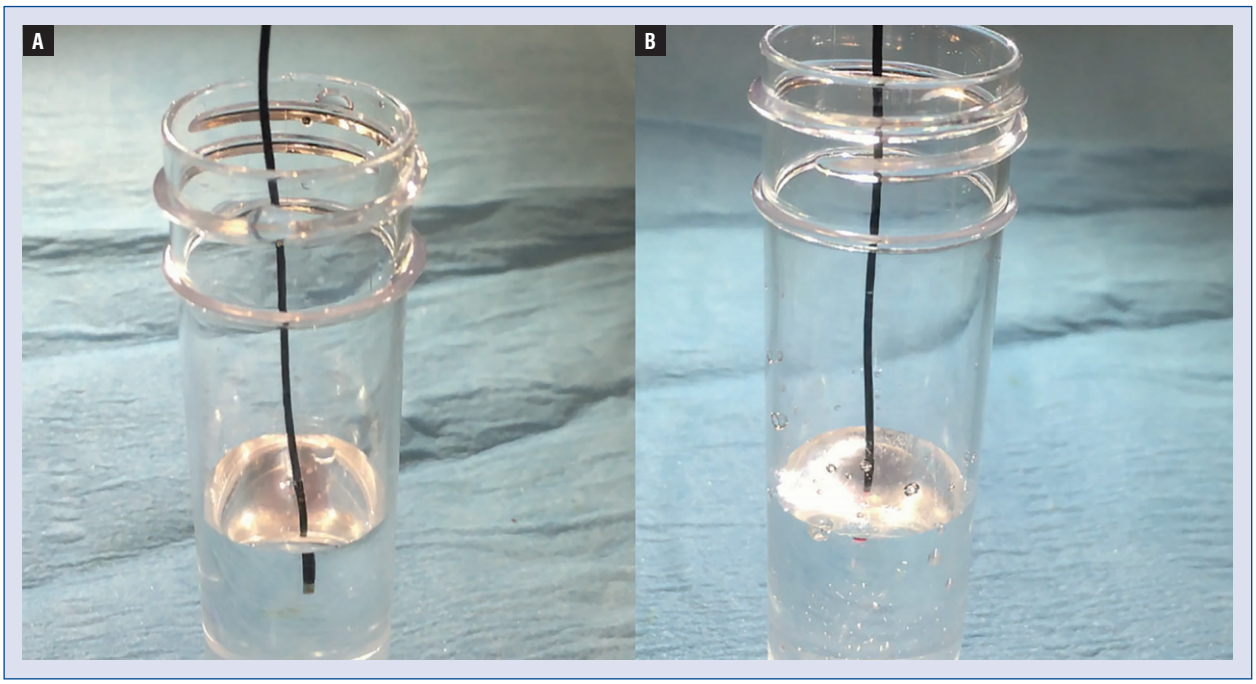

Figure 4. On bench study of laser interaction with saline and contrast milieu. While the saline milieu avoids microbubble formation (**A**), laser interaction with contrast creates a large number of microbubbles (**B**).

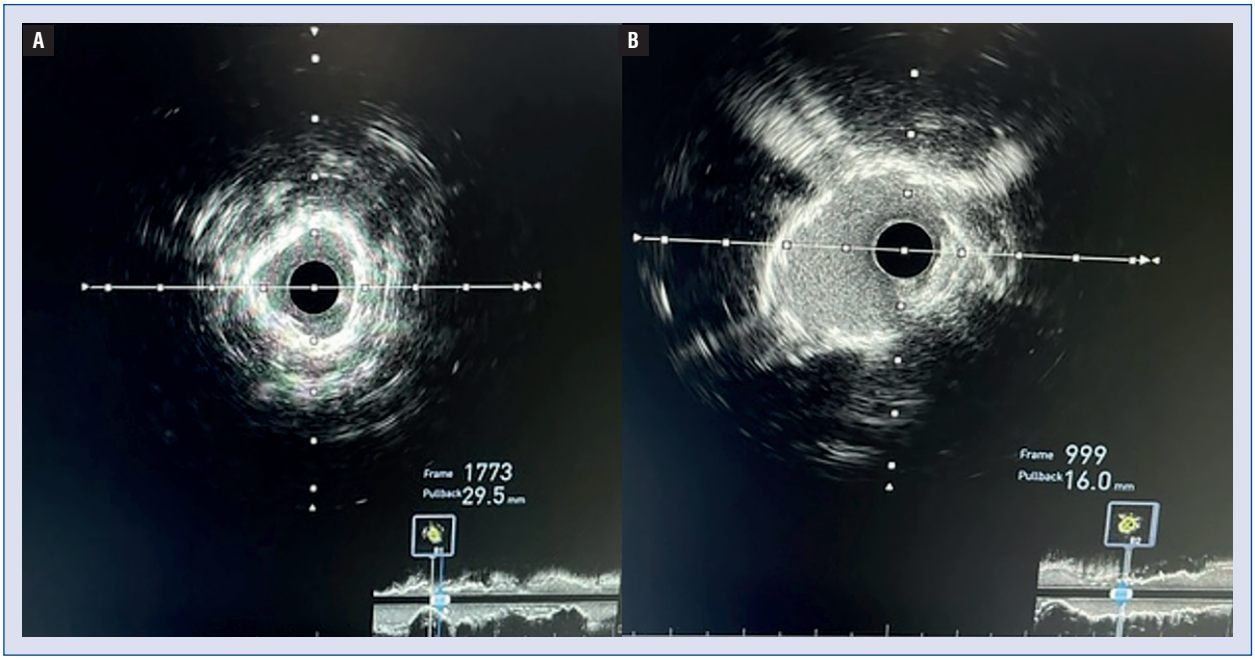

Figure 5. Stent underexpansion circled by a calcified ring (**A**). After laser ablation with simultaneous contrast injection and balloon dilatation the minimum stent area improved significantly (**B**).

delivery avoids the formation of microbubbles in the milieu (Fig. 4).

Concomitant contrast administration during laser delivery and the subsequent creation of microbubbles can weaken and disrupt the fibrotic or calcified tissue beneath the stent strut surrounding the underexpanded stent (Fig. 5) [23]. Indeed, the cardiovascular laser society recommends the

use of contrast injection at the highest fluence and repetition rate (80 mJ/mm^2 and 80 Hz), called "explosion technique" in complex lesions such as stent underexpasion, stent restenosis and calcific lesions resistant to balloon dilation for experienced operators [24].

Nan et al. [25] reported the results of 26 patients who underwent ELCA-contrast assisted angioplasty for an underexpanded stent using high energy and a frequency level of 80 mJ/mm^2 and 80 Hz, respectively. The authors achieved ≤ 20% residual stenosis in 58% of cases and a complication rate of 15%, including one acute coronary perforation. Unlike the latter study, a high laser energy level was not used in the current cases and additional intravascular imaging was employed.

Latib et al. [10] used ELCA with concurrent contrast injection in 28 patients with underexpanded stent unsolved despite high-pressure balloon inflation. The authors achieved a successful result in 27 (96.4%) cases, defined as an increase of at least 1 mm^2 in the MSA on IVUS or an increase of at least 20% in the minimal stent diameter by quantitative coronary analysis, following redilation with the same NC balloon. In this series, IVUS could be performed before and after ELCA in 17 out of 28 cases. In the current series, IVUS examination was performed in all but one case in which the IVUS probe could not cross the underexpanded point. Although the mean increase in MSA in our experience was statistically significant in the entire series, using the criteria of an increase of at least 1 mm^2, a procedural success rate of 73.3% was achieved.

One of the main advantages of laser ablation is that the ELCA catheter can be advanced over any 0.014-inch guidewire, in addition to the fact that laser energy delivery does not ablate the stent struts. This is the main difference between laser ablation and the rotational atherectomy technique, which necessarily involves a partial ablation of stent struts and presumably requires implantation of a new stent. In fact, in the present series no new stents were implanted in any underexpanded points.

In order to minimize the risk of the procedure with ELCA ablation in this scenario, precautions must be taken to avoid laser delivery beyond the stent segment, because vessel perforation with this off-label technique is not unlikely, considering that the pressure pulses can exceed 100 atm when simultaneous contrast injection is used, as mentioned earlier.

Limitations of the study

The main limitation of this study is the lack of a control branch using only a NC balloon instead of ELCA plus balloon post-dilatation. The absence of a control group makes it difficult to establish the real efficacy of ELCA as an adjuvant technique for the treatment of stent underexpansion. The definitive facilitating role of laser ablation in stent underexpansion scenarios is limited in the present cohort due to the limited number of cases treated with this adjuvant therapy. Besides, this study has some limitations inherent to any other retrospective studies

Conclusions

Based on our experience, coronary laser with concurrent contrast injection as a coadjuvant therapy aiming to treat stent underexpansion is a safe and effective method and is associated with an acceptable event-free rate in long-term follow-up.

Conflict of interest: None declared

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Statins and the risk of pancreatic cancer: A systematic review and meta-analysis of 2,797,186 patients

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Abstract

Background: *Statin use in many studies is related to the improvement of a patients' condition including reducing the risk of various malignancies. Herein, is a systematic review and meta-analysis to examine the evidence on the association between statin therapy and the risk of the occurrence of pancreatic cancer, mainly in terms of decreased risk of developing pancreatic cancer among patients using statin therapy in the long-term perspective.*

Methods: *PubMed, Web of Science, Scopus and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from database inception to December 1st, 2021. Random effect models were used to estimate summary odds ratios (OR) and the corresponding 95% confidence intervals (CI).*

Results: *A total of 26 studies comprising 2,797,186 patients were included. Polled analysis showed that pancreatic cancer occurrence in statin vs. no-statin group varied and amounted to 0.4% vs. 0.6% (OR = 0.83; 95% CI: 0.72–0.96; I^2 = 84%; p = 0.01).*

Conclusions: *In summary, the present analysis shows that overall statins use is significantly associated with a reduction in risk of pancreatic cancer. However, these results were not confirmed for the randomized controlled trial subgroup. Further prospective studies are needed to confirm the current results.* (Cardiol J 2024; 31, 2: 243–250)

Keywords: pancreatic cancer, pancreatic malignancy, statin, risk, systematic review, meta-analysis

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Introduction

Due to the fact that pancreatic cancer is usually diagnosed in advanced stages, i.e., the presence of distant metastases is identified in more than 50% of patients at the time of diagnosis, this malignant neoplasm remains one with the worst prognosis [1]. Even considering the introduction of modern chemotherapeutic regimens (FOLFIRINOX, nab-paclitaxel with gemcitabine) and the development of pancreatic surgery — the 5-year survival rate remains low, especially compared to other solid tumors [2, 3]. Screening tests are only recommended in patients at very high risk of developing pancreatic cancer, for example, in certain genetic syndromes. Moreover, there is also no clear consensus on the type of screening (computed tomography, magnetic resonance imaging, endoscopic ultrasound) as well as the frequency of recommended testing [4]. The search for ways to reduce the risk of developing pancreatic cancer has led to providing rather general health-related recommendations, including a balanced diet, maintaining a healthy body weight, physical activity, or quitting smoking [5].

In addition, the search for relationships between pharmacotherapy (particularly long-term) and the risk of pancreatic cancer, particularly in the context of a reduced risk of developing this malignancy is highly warranted. Scientists have long highlighted the relationship between the use of acetylsalicylic acid (ASA) and a reduction in the risk of solid tumors, including pancreatic cancer — although the relationship is not as clear as it is in the case of, for example, colorectal cancer [6]. ASA has a pleiotropic effect, and the key to observing its impact on reducing the risk of pancreatic cancer is the length of its use [7]. Studies are also examining a connection between nonsteroidal anti-inflammatory drug (NSAIDs) use and the risk of pancreatic cancer [8]. Due to the fact that NSAIDs constitute a heterogeneous group of drugs and patients use anti-inflammatory drugs both chronically and sporadically — depending on the need and pain level — it is challenging to find any well-established relationship [9, 10].

On the other hand, due to the population potential and the fact that statins are used in long-term therapy, it is not surprising that scientists are interested in looking for evidence on the impact of their use on cancer risk [11]. Basic science research seems to indicate that there is a pancreatic carcinogenesis mechanism that can be influenced by statins [12]. From a clinical point of view, thanks to statins, one can obtain better control over the risk factors of pancreatic cancer, including the metabolic profile and obesity. Moreover, in patients diagnosed with pancreatic cancer, especially metastatic, statins appear to improve overall survival [13]. It may be related to the chemosensitizing properties of statins. Bearing in mind the evidence from basic science, preclinical studies in animal models as well as clinical observations, it is reasonable to conduct epidemiological observations aimed at demonstrating the relationship between long-term statin use and the risk of pancreatic cancer [14]. Conflicting results of observational studies, high heterogeneity of populations covered by epidemiological observations, and finally, different methodologies applied in studies make it difficult to analyze the available data objectively.

The above-mentioned factors, have mainly contradictory results in epidemiological observations and have led to the necessity of conducting a systematic review of the literature and a meta-analysis — which findings may be valuable in designing other prospective scientific studies. Thus, the present study conducted a systematic review and meta-analysis to examine the evidence on the association between statin therapy and the risk of occurrence of pancreatic cancer, mainly in terms of decreased risk of developing pancreatic cancer among patients using statin therapy in the long-term perspective.

Methods

The current study was designed as a systematic review and meta-analysis. It was performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement [15]. The study protocol has been deposited in the PROSPERO database prior to the start of the study. No protocol changes were made during the study. Due to the nature of the study (meta-analysis), the bioethical commission approval was not required.

Literature search

A computerized literature search of PubMed, Web of Science, Scopus and Cochrane Central Register of Controlled Trials (CENTRAL) was performed from each databases' inception to December 1st, 2021. To increase the probability of identifying all relevant articles, a specific research equation was formulated for each database, using the following keywords: "pancreatic malignancy" OR "pancreatic cancer" OR "pancreatic neoplasm"

AND "statin" OR "autorvastatin" OR "fluvastatin" OR "cerivastatin" OR "lovastatin" OR "resuvastatin" OR "pravastatin" OR "simvastatin". Additionally, the reference list of the eligible trial and relevant review articles were crosschecked to identify additional pertinent studies.

Inclusion and exclusion criteria

Studies that were included in this meta-analysis had to fulfill the following PICOS criteria: 1) Participants, patients were 18 years old or older; 2) Intervention, treatment with statin; 3) Comparison, treatment without statin; 4) Outcomes, pancreatic cancer occurrence; 5) Study design: retrospective and prospective trials published in English. Studies were excluded if they were reviews, animal studies, case reports, letters, conference or poster abstracts, or articles not containing original data.

Data extraction

Two reviewers (K.S. and L.S.) independently extracted the following information from each included article. From studies that met the inclusion eligibility criteria, the following data were extracted into predefined Microsoft Excel spreadsheet (Microsoft Corp., Redmond, WA, USA): a) Study characteristic (i.e.: first author, year of publication, country, study design); b) Participant characteristics (i.e.: number of participants, age, sex); c) Main study outcomes (i.e.: incidence of pancreatic cancer in each study group). Potential disagreements were resolved by discussion with third reviewer (K.J.F.).

Risk of bias

Two reviewers (K.S. and L.S.) independently assessed the risk of bias using the Cochrane "Risk of Bias" tool. The RoB-2 tool was used to assess the risk of bias among randomized controlled trials (RCT) [16], and ROBINS-I tool for non-randomized trials [17], respectively. Any disagreements between the two reviewers in the evaluation process were resolved by discussion with third reviewer (M.J.J.). The risk of bias assessments was visualized using the Robvis application [18].

Statistical analysis

The meta-analysis was conducted using the Review Manager, version 5.4EN (RevMan; The Cochrane Collaboration, Oxford, UK). A p value less than 0.05 was accepted as statistically significant. For each study, event numbers in relation to the pancreatic cancer occurrence were collected. The pooled results are presented as odds ratios (OR) and 95% confidence intervals (CI). Random-effects models were used as they considered both sampling variance within the different trials and the variation in the underlying effect across studies. The quality of the heterogeneity was assessed by means of the Cochran's Q and I^2 statistics. Heterogeneity was determined with the I^2 statistic, in which the results range from 0% to 100%. Heterogeneity was interpreted as not observed when $I^2 = 0\%$, low when $I^2 = 25\%$, medium when $I^2 = 50\%$, and high when $I^2 = 75\%$ [19].

Results

Search results and characteristics of studies

As illustrated in Figure 1, 712 studies were identified in the literature search, and 47 were selected for full-text review. A total of 26 studies [20–45] met the inclusion criteria and were included in the analysis, comprising 2,797,186 patients. A manual search did not identify any new eligible studies. Baseline data and other details are shown in **Supplementary Table S1**. Two studies were randomized controlled trials [26, 40] and other trials were non-RCTs [20–25, 27–39, 41–45]. The results of the assessment of risk of bias among the 4 included studies are provided in **Supplementary Figures S1–S4**.

Meta-analysis

Twenty-six studies reported impact of statin use on pancreatic cancer occurrence. Polled analysis of those trials showed that pancreatic cancer occurrence in statin vs. no-statin group varied and amounted to 0.4% vs. 0.6% (OR = 0.83; 95% CI: 0.72–0.96; $I^2 = 84\%$; p = 0.01; Fig. 2). Sub-analysis showed that pancreatic cancer occurrence in statin vs. no-statin group in RCT was at the same level 0.3% (OR = 0.99; 95% CI: 0.44–2.23; $I^2 = 0\%$; p = 0.99), but in the non-RCT pancreatic cancer occurrence was 0.4% in the statin group, and 0.6% in the non-statin group (OR = 0.83; 95% CI: 0.72–0.96; $I^2 = 86\%$; p = 0.01).

When matched data were included in pooled analysis occurrence on pancreatic cancer 0.4% in the statin group compared to 0.5% for the non-statin group (OR = 0.85; 95% CI: 0.71–0.95; $I^2 = 85\%$; p = 0.01).

The analysis of the effect of the duration of taking statins showed no statistically significant differences with the incidence of cancer in the group of patients who took statins < 48 months and ≥ 48 months, respectively (5.7% vs. 5.1%; OR = 1.20; 95% CI: 0.98–1.45; $I^2 = 64\%$; p = 0.07; Fig. 3).

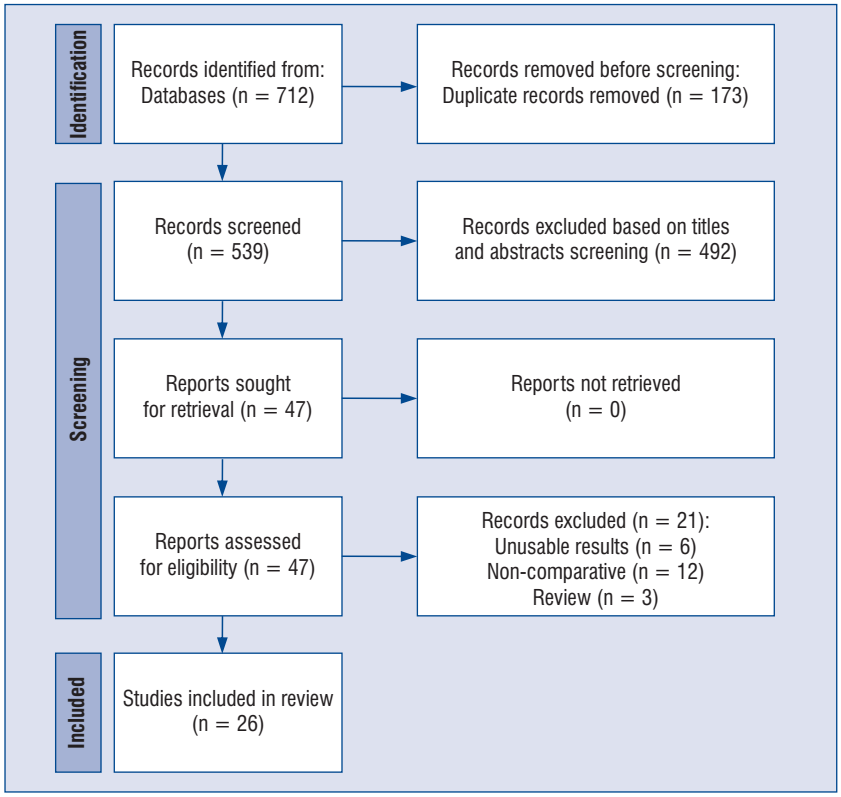

Figure 1. Flow diagram showing stages of database searching and study selection as per Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) guideline.

Discussion

This meta-analysis indicates the protective role of statins in the prevention of pancreatic cancer. Although due to the high heterogeneity of the studies included in the meta-analysis and the observational nature of the studies — especially in the case of case-control studies (retrospective analysis), strong recommendations regarding the use of statins in the prevention of pancreatic cancer are impossible to provide. Similar conclusions as in the present meta-analysis can be found in the meta-analysis published in 2019, which included 26 studies [46]. Archibugi et al. [47] also showed that long-term use of statins (especially atorvastatin) might be associated with a significant reduction in the risk of developing pancreatic cancer (OR 0.70; 95% CI: 0.60–0.82; $p < 0.001$). Previous observations, however, indicated that the protective effect of statins on the development of pancreatic cancer is more questionable, especially at doses routinely used in the treatment of lipid disorders. The use of higher doses has not been routinely recommended due to the patients' worries of side effects [48]. However, it is changing nowadays with the new guidelines and new treatment goals. Finally, our meta-analysis should be understood to be taking into consideration the difference between the pancreatic cancer occurrence between two subcategories: i) RCTs and; ii) Observational studies. Results obtained from observational studies are at a higher risk of bias compared to data obtained from RCTs. A sub-analysis was conducted to minimize bias in our meta-analysis. In addition, the previous meta-analyzes were created over 2 years ago, therefore, considering the significant development of medical sciences, it seems necessary to conduct a new analysis [45, 47]. Moreover, the high heterogeneity of the studies included in the analysis and the slight difference in effect additionally strengthen the need for another meta-analysis. In the correspondence accompanying this paper, it was suggested that it would be important to conduct research aimed at investigating the association between statins and other drugs used simultaneously on the prognosis in pancreatic cancer. One should also pay attention to the dose-response relationship — a research hypothesis could be made that higher doses of statins should show a greater protective effect [49, 46].

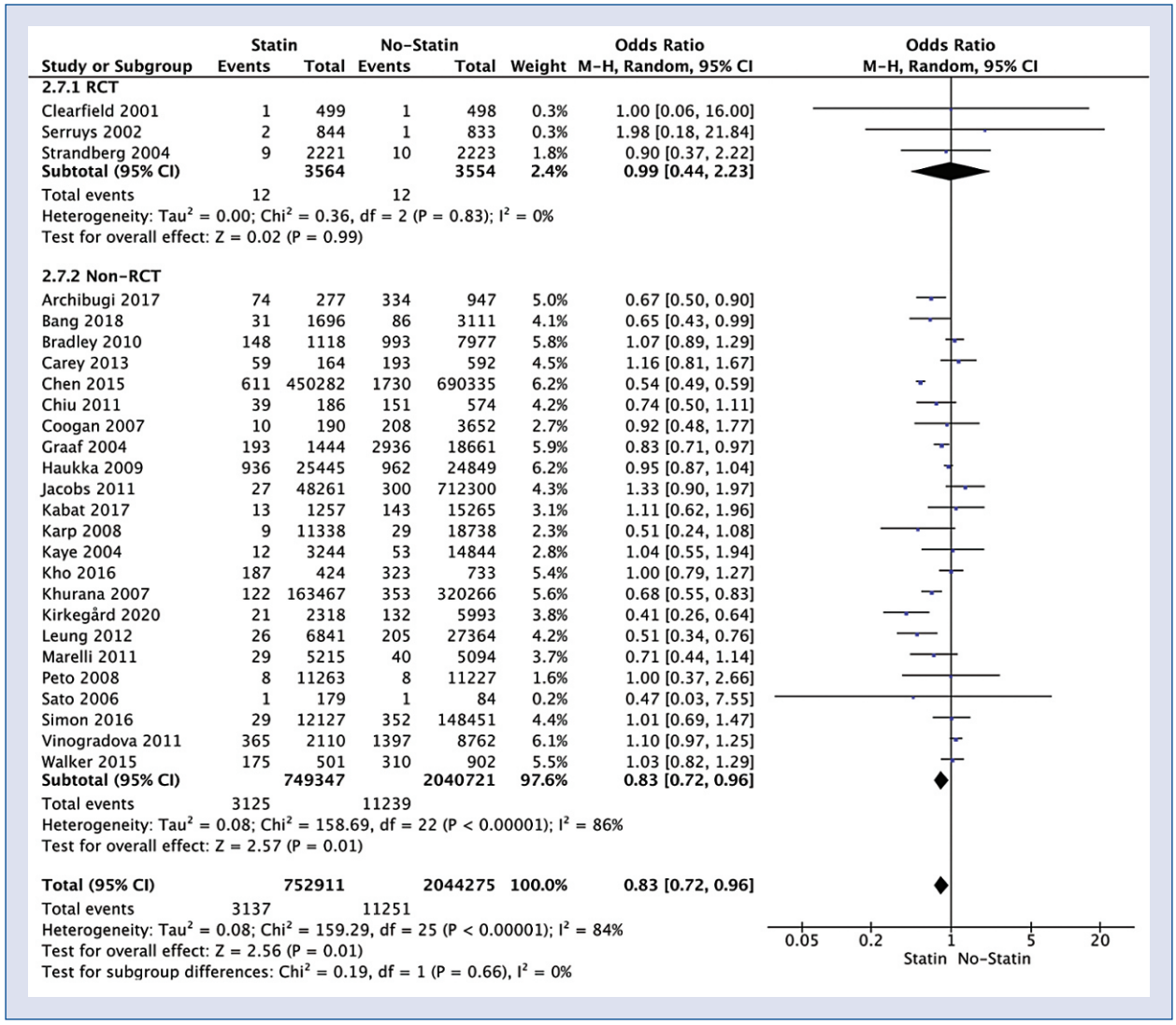

Figure 2. Forest plot of pancreatic cancer occurrence rate among statin vs. non-statin groups. The center of each square represents the weighted risk ratios for individual trials, and the corresponding horizontal line stands for a 95% confidence interval (CI). The diamonds represent pooled results.

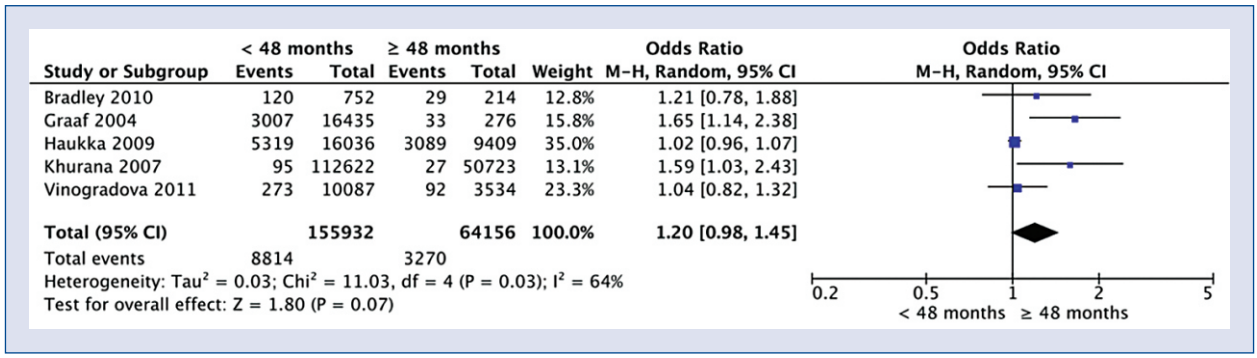

Figure 3. Forest plot of pancreatic cancer occurrence rate among patients who are taking statin less than 48 months and more than 48 months, respectively. The center of each square represents the weighted risk ratios for individual trials, and the corresponding horizontal line stands for a 95% confidence interval (CI). The diamonds represent pooled results.

It is worth highlighting here that the systematic reviews and meta-analyses conducted to date have focused mainly on determining the impact of long-term therapy on the prognosis of patients with diagnosed pancreatic cancer. One such meta-analysis showed a significantly better prognosis in patients diagnosed with pancreatic cancer (meta-hazard ratio [HR] = 0.75; 95% CI: 0.59–0.90; $p < 0.001$) compared to patients not receiving such treatment [50]. As in our meta-analysis, a significant limitation is the diversity of the population included in the review. A better prognosis of pancreatic cancer patients using statins has also been shown in another meta-analysis [51]. Similar observations were identified in another meta-analysis that included 14 studies. An interesting finding is a positive effect on outcomes in patients with the resectable disease, not seen in locally advanced or metastatic disease. This observation should encourage further research focused on reducing the risk of recurrence in patients undergoing treatment with the assumption of a radical cure [52]. The previously published systematic review of 2008 should be considered obsolete given new scientific evidence that has emerged since then [53]. In turn, the review that included studies describing the survival effects of both metformin and statins in patients diagnosed with pancreatic cancer was based on only 8 statin studies — although the article was published in 2018 [54]. These relationships, however, seem to be less potent than in the case of, for example, the influence of statins on progression of liver cirrhosis [55]. Newer data published recently from Norwegian registry pointed out, that statin users had lower mortality from pancreatic cancer (HR = 0.86, 95% CI: 0.76–0.97), and this association was more pronounced in users of hydrophilic (e.g., rosuvastatin) rather than lipophilic (e.g., atorvastatin) statins [56]. In a Japanese registry of 100,537 statin users vs. 326,033 non-statin users, after adjustments using inverse probability of treatment weighting, the statin exposure group was associated with a decreased incidence of pancreatic cancer (HR = 0.84; 95% CI: 0.72–0.99) [57]. It is striking, that this 14–16% relative reduction is almost identical in those 2 papers like in the present meta-analysis.

Further research should focus on the selection of populations in which statin use will be associated with a more significant reduction in the risk of developing pancreatic cancer compared to the general population. The starting point may be, in particular, the predictors that increase the risk of pancreatic cancer, especially the modifiable ones, e.g., a prospective observational study conducted among patients with nicotinism, the main modifiable risk factor for pancreatic cancer, next to obesity. Conducting a prospective clinical trial aimed at verifying the hypothesis that long-term statin use reduces the risk of developing pancreatic cancer would undoubtedly dispel doubts about the role of statins in the prevention of pancreatic cancer. Due to the long observation period necessary to demonstrate such a relationship, conducting a prospective clinical trial is highly difficult. It may turn out to be more convenient, as mentioned above, to design a clinical trial among a specified cohort of patients with a significantly increased risk of pancreatic cancer, e.g., in the family variant of this disease or specific genetic diseases.

Conclusions

The present analysis shows that overall statins use is significantly associated with a reduction in risk of pancreatic cancer. However, these results were not confirmed for the RCT sub-group. Further prospective studies are needed to confirm current results.

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Conflict of interest: None declared

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High-density lipoprotein cholesterol to apolipoprotein A-1 ratio is an important indicator predicting in-hospital death in patients with acute coronary syndrome

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Abstract

Background: *Dyslipidemia plays a pivotal role in the pathogenesis of acute coronary syndrome (ACS). This study aims to investigate the value of two indices associated with lipid metabolism, low-density lipoprotein cholesterol to apolipoprotein B ratio (LBR) and high-density lipoprotein cholesterol to apolipoprotein A-1 ratio (HAR), to predict in-hospital death in patients with ACS.*

Methods: *This single-center, retrospective, observational study included 3,366 consecutive ACS patients in Zhongda Hospital, Southeast University from July 2013 to January 2018. The clinical and laboratory data were extracted, and the in-hospital death and hospitalization days were also recorded.*

Results: *All patients were equally divided into four groups according to quartiles of HAR: Q1 (HAR < 1.0283), Q2 ($1.0283 \leq$ HAR < 1.0860), Q3 ($1.0860 \leq$ HAR < 1.1798), and Q4 (HAR ≥ 1.1798). Overall, HAR was positively associated with the counts of neutrophils and monocytes, whereas negatively correlated to lymphocyte counts. HAR was negatively correlated to left ventricular ejection fraction (LVEF). Compared to other three groups, in-hospital mortality (vs. Q1, Q2, and Q3, $p < 0.001$) and hospitalization length (vs. Q1, Q2, and Q3, $p < 0.001$) were significantly higher in the Q4 group. When grouped by LBR, however, there was no significant difference in LVEF, in-hospital mortality, and hospitalization length among groups. After adjusting potential impact from age, systolic blood pressure, creatine, lactate dehydrogenase, albumin, glucose, and uric acid, multivariate analysis indicated that HAR was an independent factor predicting in-hospital death among ACS patients.*

Conclusions: *HAR had good predictive value for patients' in-hospital death after the occurrence of acute coronary events, but LBR was not related to in-hospital adverse events.* (Cardiol J 2024; 31, 2: 251–260)

Keywords: low-density lipoprotein cholesterol to apolipoprotein B ratio, high-density lipoprotein cholesterol to apolipoprotein A-I ratio, acute coronary syndrome, in-hospital death

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Introduction

Acute coronary syndrome (ACS), mainly caused by atherosclerotic plaque rupture, erosion or calcified nodule, is characterized as acute myocardial ischemia, cardiomyocyte necrosis, and subsequent inflammation [1, 2]. Dyslipidemia is known as an important risk factor for the occurrence of ACS, and lipid management plays a pivotal role in the secondary prevention after the occurrence of ACS to improve patient prognosis. There are more studies are focused on blood lipids of ACS patients [3].

The components of blood lipids consist of triglycerides, cholesterol, phospholipids, free fatty acids and cholesterol esters. Among plasma lipoproteins, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) are widely studied in cardiovascular diseases. The main function of LDL is to transport endogenous cholesterol from the liver to other organs [4], and the function of HDL is to reverse the process of cholesterol being transported from outside to inside the liver. The protein part of plasma lipoprotein is called apolipoprotein (Apo), and up until now, more than 20 apolipoproteins have been isolated from human plasma [4]. HDL contains 70% ApoA-I, 20% ApoA-II, and lecithin-cholesterol transferase (LCAT) [5]. ApoA-I mainly recognizes HDL receptors and activates LCAT. LDL owns a receptor that specifically recognizes ApoB-100. After the LDL in plasma binds to the LDL receptor through ApoB-100, it is endocytosed by the cells to exert its effect [4].

There is an apolipoprotein B (ApoB) molecule in each LDL particle. Therefore, the level of ApoB represents the number of LDL particles in the plasma. The LDL particle size can be estimated indirectly through LDL-C/ApoB ratio (LBR) [6]. The optimal cut-off value of LBR is 1.2, which corresponds to the LDL diameter of 25.5 nm and also distinguishes small dense LDL (sdLDL) from large buoyant LDL [6, 7]. The Québec Cardiovascular Study has shown that patients with sdLDL (LDL diameters ≤ 25.5 nm) have a significant increase in the incidence of coronary heart disease (CHD) [8]. Plasma concentration of sdLDL is significantly associated with risk of atherosclerotic cardiovascular disease (ASCVD) [9].

Plasma level of HDL cholesterol (HDL-C) is inversely related to the risk of CHD [10], and a higher concentration of ApoA-I is also associated with reduced cardiovascular disease (CVD) risk [11]. HDL containing major protein ApoA-I is beneficial for vascular protection, and the beneficial cardiovascular effects of HDL and ApoA-I infusion therapy have been previously reported [12–14].

However, in the inflammatory response, the role of HDL as an anti-inflammatory may transform into that of pro-inflammatory particles [15]. HDL can be modified by inflammatory proteins such as acute-phase proteins and complement factors, further leading to impaired antioxidant capacity, which is associated with increased oxLDL levels [16]. Such HDL with function impairment is commonly called "dysfunctional HDL". The increased HDL-C/apoA-I ratio (HAR) may reflect the impaired ability of cholesterol-rich HDL particles to absorb excess cholesterol from peripheral tissues and progressive atherosclerotic plaques [17].

This study aims to study the roles of LBR and HAR in predicting the in-hospital death of ACS patients.

Methods

Study design and population

This single-center, retrospective, observational study was approved by the Ethics Committee of Zhongda Hospital affiliated to Southeast University (2020ZDSYLL164-P01). The requirement of informed consents was waived due to the retrospective nature. In total, 3,366 patients were included from Zhongda Hospital, Southeast University from July 2013 to January 2018, including 761 unstable angina, 1,325 ST-segment elevation myocardial infarction (STEMI) and 1,280 non-STEMI patients (Fig. 1). Inclusion criteria included: (1) age > 18 years old; (2) Diagnosed as ACS according to the guideline for diagnosis and treatment of ACS [18]. Exclusion criteria included: (1) Lactating and pregnant women; (2) Suffering from serious diseases with a life expectancy < 6 months, such as advanced malignant tumors; (3) Acute and chronic inflammatory diseases, such as chronic obstructive pulmonary disease, hepatitis, rheumatic and rheumatoid diseases.

Data collection

The demographic data, medical history, laboratory and imaging examination results at admission were all extracted from the electronic medical record system (Yidu Cloud, China). Collected variables included age, sex, smoking history, high blood pressure, diabetes history, Killip classification, systolic blood pressure (SBP), alamine aminotransferase (ALT), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), blood urea nitrogen (BUN), uric acid (UA), troponin I, albumin (ALB), direct

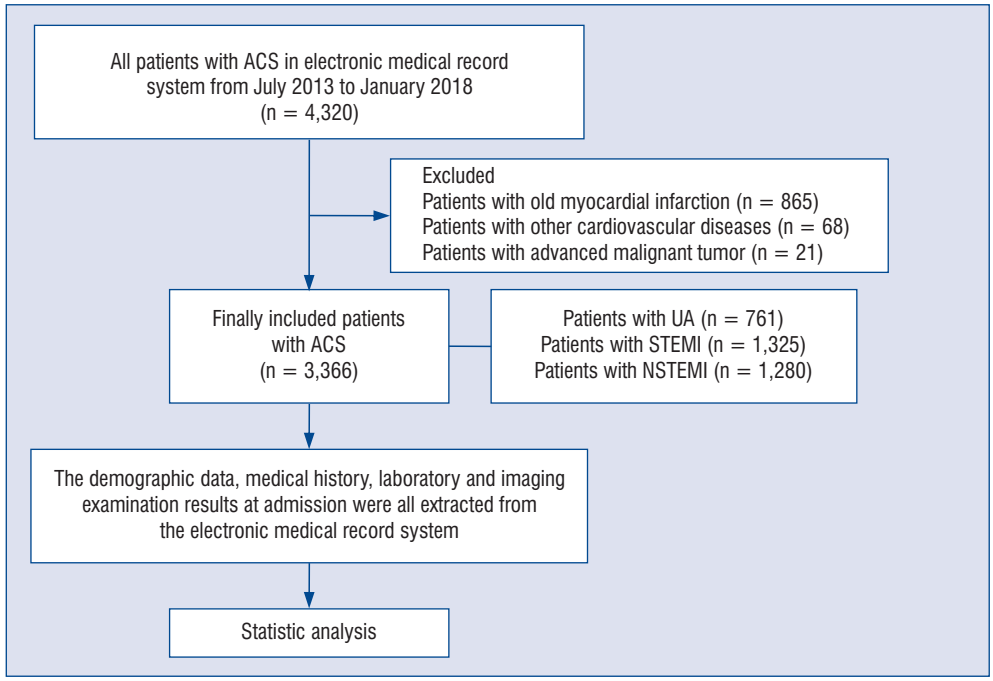

Figure 1. The flow chart of enrolled patients. The total number of patients with acute coronary syndrome (ACS) in electronic medical record system from July 2013 to January 2018 was 4,320. Among them, 865 patients were diagnosed as old myocardial infarction, and 68 patients were diagnosed as other cardiovascular diseases such as coronary heart disease and myocarditis. There were also 21 patients with advanced malignant tumor who were excluded. Finally, 3,366 patients with ACS were included in this study; UA — unstable angina; STEMI — ST-segment elevation myocardial infarction; NSTEMI — non-ST-segment elevation myocardial infarction.

bilirubin (DBil), creatine, glucose (GLU), neutrophils, lymphocytes, monocytes, white blood cells (WBC), platelet (PLT), hemoglobin (Hb), D-dimer, glycosylated hemoglobin (HbA1C), and left ventricular ejection fraction (LVEF). Lipid profile was also recorded, including total cholesterol (TC), triglyceride (TG), HDL-C, LDL cholesterol (LDL-C), ApoA1, ApoB1, and Lpa. In-hospital death and hospitalization days were recorded.

Statistical analysis

Data was analyzed by SPSS 23.0 and GraphPad Prism 8. The Shapiro-Wilk test was used for judging normality. Continuous numerical variables conforming to the normal distribution were expressed as mean ± standard deviation (SD), and one-way ANOVA analysis was used for comparison among multiple groups. Data following the non-normal distribution was described as median (interquartile range), and the Mann-Whitney U test was used for comparison between multiple groups. The χ^2 test was used for comparison of binary variables. The Pearson analysis was used for correlation analysis between HAR and other variables. Univariate and multivariate logistic regression analyses were used for adjusting potential confounding factors to determine indepdent factors of in-hospital death.

Results

Basic characteristics of patients

This study enrolled 3,366 patients with a diagnosis of ACS, which were subsequently divided into four groups according to quartiles of HAR, Q1 (Quartile 1, < 1.0283), Q2 (Quartile 2, 1.0283–1.0860), Q3 (Quartile 3, 1.0860–1.1798), Q4 (Quartile 4, ≥ 1.1798). As age increased, the HAR also increased ($p < 0.001$). Age in Q4 group was significantly higher than the Q1 group (73.17 ± 13.21 vs. 69.85 ± 12.85). Neutrophil and WBC counts were also markedly increased, whereas lymphocyte count was decreased in Q4 group, compared with Q1 group ($p < 0.001$ for all). The level of D-dimer and BUN in Q4 group were also higher than in Q1 group ($p < 0.001$), while levels of ALB and Hb were significantly decreased ($p < 0.001$). There was no significance in GLU ($p = 0.132$), HbA1C ($p = 0.120$) and diabetes history ($p = 0.316$) among these groups (Table 1).

Table 1. Basic characteristics of patients.

Characteristics	Quartile 1 (n = 841)	Quartile 2 (n = 842)	Quartile 3 (n = 842)	Quartile 4 (n = 841)	P
Age [years]	69.85 ± 12.85	71.05 ± 12.75	72.10 ± 13.06	73.17 ± 13.21	< 0.001***
Sex, male	581 (69.08%)	643 (76.37%)	580 (68.88%)	550 (65.40%)	< 0.001***
Smoking	349 (41.50%)	359 (42.64%)	350 (41.67%)	303 (36.03%)	0.025*
SBP [mmHg]	134.22 ± 21.11	133.45 ± 21.00	131.41 ± 22.31	131.09 ± 22.79	0.060
Laboratory examination:					
WBC [10^9/L]	8.29 ± 3.34	8.42 ± 3.77	8.73 ± 3.79	9.67 ± 4.98	< 0.001***
Neutrophils [10^9/L]	6.14 ± 3.27	6.32 ± 3.67	6.66 ± 3.67	7.66 ± 4.61	< 0.001***
Lymphocytes [10^9/L]	1.54 ± 0.66	1.51 ± 0.68	1.46 ± 0.62	1.33 ± 0.66	< 0.001***
ALT [U/L]	27.00 (17.00, 43.50)	26.00 (17.00, 41.00)	26.00 (16.00, 42.00)	27.00 (16.00, 48.00)	0.343
AST [U/L]	31.00 (21.00, 86.00)	30.00 (20.00, 70.00)	35.00 (20.00, 92.00)	42.00 (22.00, 115.00)	< 0.001***
LDH [U/L]	233.00 (183.73, 380.00)	215.00 (169.89, 350.25)	243.00 (175.00, 432.36)	292.00 (190.50, 563.56)	< 0.001***
Troponin I [ng/mL]	0.86 (0.15, 5.06)	0.79 (0.12, 4.77)	1.29 (0.21, 7.78)	1.81 (0.27, 9.49)	< 0.001***
LDL-C [mmol/L]	2.62 ± 0.83	2.63 ± 0.88	2.77 ± 0.86	2.67 ± 0.95	0.003**
HDL-C [mmol/L]	1.02 ± 0.25	1.07 ± 0.18	1.16 ± 0.23	1.13 ± 0.32	< 0.001***
BUN [mmol/L]	6.58 ± 3.95	6.81 ± 4.51	7.01 ± 4.59	8.86 ± 7.72	< 0.001***
Uric acid [μmol/L]	345.32 ± 110.22	350.08 ± 114.22	347.65 ± 112.93	363.99 ± 144.26	0.007**
TC [mmol/L]	4.19 ± 1.07	4.30 ± 1.10	4.53 ± 1.19	4.42 ± 1.29	< 0.001***
Triglyceride [mmol/L]	1.76 ± 1.14	1.78 ± 1.29	1.67 ± 1.38	1.65 ± 1.56	0.111
Albumin [g/L]	38.06 ± 4.62	37.60 ± 4.79	37.80 ± 4.89	36.21 ± 5.34	< 0.001***
Direct bilirubin [μmol/L]	3.30 (2.35, 4.70)	3.30 (2.40, 4.53)	3.30 (2.20, 4.50)	3.10 (2.00, 4.60)	0.177
Creatinine [μmol/L]	78.00 (66.00, 97.00)	83.00 (69.00, 103.00)	84.00 (69.00, 107.00)	90.00 (71.00, 126.00)	< 0.001***
Lipoprotein a [mg/L]	319.93 ± 300.74	320.39 ± 267.35	335.08 ± 241.660	351.75 ± 288.33	0.057
Glucose [mmol/L]	8.36 ± 4.29	8.01 ± 3.98	8.11 ± 3.98	8.42 ± 4.50	0.132
ApoB [g/L]	0.78 ± 0.23	0.78 ± 0.22	0.81 ± 0.21	0.79 ± 0.23	0.005**
ApoA-I [g/L]	1.10 ± 0.29	1.01 ± 0.17	1.03 ± 0.21	0.87 ± 0.27	< 0.001***
Platelet [10^9/L]	199.23 ± 63.15	196.69 ± 63.43	197.73 ± 62.91	198.58 ± 68.90	0.865
Hemoglobin [g/L]	132.51 ± 19.99	133.11 ± 20.67	131.21 ± 21.12	124.48 ± 23.92	< 0.001***
HbA1C [%]	7.06 ± 1.17	6.97 ± 0.99	7.00 ± 0.98	7.08 ± 1.04	0.120
D-dimer [μg/L]	132.14 (61.50, 301.25)	164.00 (98.84, 330.12)	196.00 (107.00, 424.19)	257.67 (123.80, 620.50)	< 0.001***
LVEF	0.60 ± 0.11	0.60 ± 0.11	0.58 ± 0.12	0.57 ± 0.12	< 0.001***
Cardiac arrest	38 (4.52%)	45 (5.34%)	66 (7.84%)	71 (8.44%)	0.002**
Hospitalization days	7.00 (5.00, 10.00)	7.00 (5.00, 11.00)	7.00 (5.00, 11.00)	8.00 (5.00, 13.00)	< 0.001***
Death	32 (3.80%)	39 (4.63%)	63 (7.48%)	65 (7.73%)	< 0.001***
Killip (≥ II)	124 (14.74%)	126 (14.96%)	175 (20.78%)	217 (25.80%)	< 0.001***
Previous history:					
Diabetes	292 (34.72%)	267 (31.71%)	263 (31.24%)	288 (34.24%)	0.316
Hypertension	584 (69.44%)	600 (71.26%)	580 (68.88%)	578 (68.73%)	0.657
Number of affected coronary vessels:					0.061
Single vessel	140 (16.65%)	131 (15.56%)	150 (17.81%)	102 (12.13%)	
Double vessels	201 (23.90%)	199 (23.63%)	194 (23.04%)	200 (23.78%)	
Triple vessels	500 (59.45%)	512 (60.81%)	498 (59.15%)	539 (64.09%)	
ACS types:					< 0.001***
Unstable angina	218 (25.92%)	222 (26.37%)	183 (21.73%)	138 (16.41%)	
STEMI	317 (37.69%)	307 (36.46%)	334 (39.67%)	367 (43.64%)	
NSTEMI	306 (36.39%)	313 (37.17%)	325 (38.60%)	336 (39.95%)	
PCI treatment	714 (84.90%)	711 (84.44%)	772 (91.69%)	785 (93.34%)	< 0.001***
Medication on admission:					
Antidiabetic drugs	207 (24.61%)	180 (21.45%)	181 (21.65%)	172 (20.45%)	0.194
Antihypertensive drugs	606 (72.06%)	619 (73.78%)	594 (71.05%)	588 (69.92%)	0.344
Antiplatelet drugs	819 (97.38%)	818 (97.50%)	806 (96.41%)	816 (97.03%)	0.549
Beta-blocker drugs	663 (78.83%)	678 (80.81%)	661 (79.07%)	685 (81.45%)	0.454
Statins	809 (96.20%)	804 (95.83%)	778 (93.06%)	784 (93.22%)	0.003**
Nitrates	641 (76.22%)	650 (77.47%)	626 (74.88%)	637 (75.74%)	0.655

Continuous data, conforming to normal distribution and homogeneity of variance, was described as mean ± standard deviation (M ± SD); otherwise, it was described by quartiles [median (25%, 75%)]. Categorical data was presented as frequency (percentage);
*p < 0.05; **p < 0.01; ***p < 0.001; SBP — systolic blood pressure; WBC — white blood cells; ALT — alanine aminotransferase; AST — aspartate aminotransferase; LDH — lactate dehydrogenase; LDL-C — low-density lipoprotein cholesterol; HDL-C — high-density lipoprotein cholesterol; BUN — blood urea nitrogen; TC — total cholesterol; HbA1C — glycosylated hemoglobin; LVEF — left ventricular ejected fraction; ACS — acute coronary syndrome; STEMI — ST-segment elevation myocardial infarction; NSTEMI — non ST-segment elevation myocardial infarction; PCI — percutaneous coronary intervention

Table 2. Correlation among high density lipoprotein cholesterol/ApoA-I, low density lipoprotein cholesterol/ApoB and common variables.

Variables	Pearson analysis of HDL-C/ApoA-I		Pearson analysis of LDL-C/ApoB	
	r	p	r	p
Age [years]	0.073	< 0.001***	–0.085	< 0.001***
SBP [mmHg]	–0.055	0.001**	0.039	0.023*
ALT [U/L]	0.046	0.006**	–0.026	0.126
LDH [U/L]	0.069	< 0.001***	0.001	0.968
BUN [mmol/L]	0.161	< 0.001***	–0.080	< 0.001***
Uric acid [μmol/L]	0.063	< 0.001***	0.008	0.638
Albumin [g/L]	–0.169	< 0.001***	0.134	< 0.001***
Creatinine [μmol/L]	0.122	< 0.001***	–0.055	0.001**
Glucose [mmol/L]	0.008	0.655	–0.011	0.511
WBC [10^9/L]	0.119	< 0.001***	–0.012	0.492
Neutrophil [10^9/L]	0.138	< 0.001***	–0.024	0.172
Lymphocyte [10^9/L]	–0.130	< 0.001***	0.075	< 0.001***
Hemoglobin [g/L]	–0.140	< 0.001***	0.109	< 0.001***
D-dimer [μg/L]	0.140	< 0.001***	–0.060	0.005**
HbA1C [%]	0.024	0.163	0.014	0.421
hsCRP [mg/L]	0.297	< 0.001***	–0.103	< 0.001***
LVEF	–0.121	< 0.001***	–0.017	0.321

*p < 0.05; **p < 0.01; ***p < 0.001; SBP — systolic blood pressure; ALT — alanine aminotransferase; LDH — lactate dehydrogenase; BUN — blood urea nitrogen; WBC — white blood cells; HbA1C — glycosylated hemoglobin; hsCRP — high sensitivity C reactive protein; LVEF — left ventricular ejection fraction

The population was also divided into four groups according to quartiles of LBR (**Suppl. Table S1**), Q1: < 3.1094, Q2: 3.1094–3.3317, Q3: 3.3317–3.5620, Q4: ≥ 3.5620. In contrast, age was gradually lower in the higher LBR group. There was no significance in WBC count in different LBR groups, although lymphocyte count was increased in the higher LBR group. Despite no significance in GLU levels among the four groups (p = 0.549), the proportion of patients with diabetes history declined gradually as the LBR increased (p = 0.017).

Pearson correlation analysis of HAR

HAR was positively correlated to age (r = 0.073, p < 0.001), ALT (r = 0.046, p = 0.006), BUN (r = 0.161, p < 0.001), UA (r = 0.063, p < 0.001), creatinine (Cr) (r = 0.122, p < 0.001), D-dimer (r = 0.140, p < 0.001). HAR was negatively related to SBP (r = –0.055, p = 0.001), ALB (r = –0.169, p < 0.001), Hb (r = –0.140, p < 0.001) (Table 2, Fig. 2). Regarding inflammatory markers, HAR was positively associated with high sensitivity C-reactive protein (hsCRP) (r = 0.297, p < 0.001), neutrophils (r = 0.138, p < 0.001), and WBC (r = 0.119, p < 0.001), while it was negatively correlated to lymphocyte counts (r = –0.130, p < 0.001) (Table 2, Fig. 2). HAR was not associated with diabetes related indicators, such as HbA1C (r = 0.024, p = 0.163) and GLU (r = –0.008, p = 0.655) (Table 2). By contrast, LBR was negatively related to age (r = –0.085, p < 0.001), BUN (r = –0.080, p < 0.001), ALB (r = 0.134, p < 0.001), Cr (r = –0.055, p = 0.001), hsCRP (r = –0.103, p < 0.001) and D-dimer (r = –0.060, p = 0.005), and positively associated with SBP (r = 0.039, p = 0.023) and lymphocyte count (r = 0.075, p < 0.001) (Table 2).

High HAR was associated with adverse cardiac function and longer hospitalization periods

Left ventricular ejection fraction was gradually decreased as HAR increased, reaching the lowest ejection fraction in Q4 group (p < 0.001) (Table 1). Meanwhile, Pearson analysis showed that HAR was negatively related to LVEF (r = –0.121, p < 0.001) (Table 2). Therefore, higher HAR may indicate the deterioration of cardiac function. Compared to other three groups, hospitalization days (p < 0.001) were also higher in Q4 group, which demonstrated that

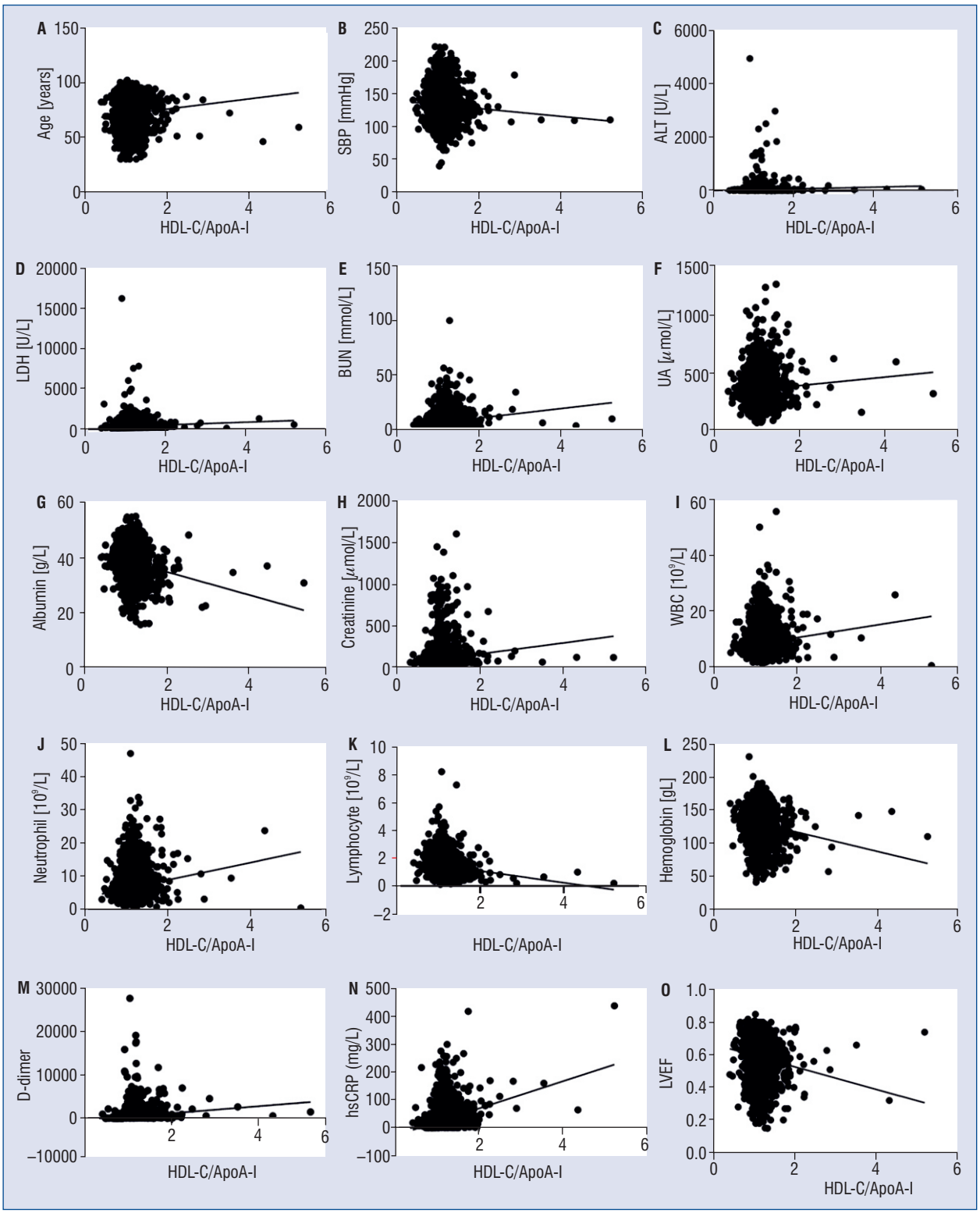

Figure 2. Pearson correlation analysis of HDL-C/ApoA-I ratio (HAR). HAR was positively correlated to age (r = 0.073, p < 0.001; **A**), alamine aminotransferase (ALT; r = 0.046, p = 0.006; **C**), lactate dehydrogenase (LDH; r = 0.069, p < 0.001; **D**), blood urea nitrogen (BUN; r = 0.161, p < 0.001; **E**), uric acid (UA; r = 0.063, p < 0.001; **F**), creatinine (r = 0.122, p < 0.001; **H**), white blood cells (WBC, r = 0.119, p < 0.001; **I**), neutrophil (r = 0.138, p < 0.001; **J**), high sensitivity C reactive protein (hsCRP; r = 0.297, p < 0.001; **N**), D-dimer (r = 0.140, p < 0.001; **M**). HAR was negatively related to systolic blood pressure (SBP; r = –0.055, p = 0.001; **B**), albumin (r = –0.169, p < 0.001; **G**), lymphocyte (r = –0.130, p < 0.001; **K**), hemoglobin (r = –0.140, p < 0.001; **L**) and left ventricular ejection fraction (r = –0.121, p < 0.001; **O**); *p < 0.05; **p < 0.01; ***p < 0.001.

Table 3. Multiple linear regression of high density lipoprotein cholesterol (HDL-C)/ApoA-I predicting in-hospital days in acute coronary syndrome patients.

Parameters	Univariate linear regression			Multiple linear regression		
	HR	95% CI	P	HR	95% CI	P
Age [years]	0.118	0.097–0.139	< 0.001***	0.074	0.052–0.096	< 0.001***
Uric acid [μmol/L]	0.003	0.001–0.006	0.006**	–	–	–
Albumin [g/L]	–0.342	–0.397 to –0.288	< 0.001***	–0.176	–0.236 to –0.115	< 0.001***
Creatinine [μmol/L]	0.011	0.009–0.014	< 0.001***	0.007	0.004–0.009	< 0.001***
LVEF	–12.252	–14.610 to –9.894	< 0.001***	–8.164	–10.540 to –5.788	< 0.001***
HDL-C/ApoA-I	4.287	2.933–5.640	< 0.001***	2.221	0.888–3.553	0.001**

**p < 0.01; ***p < 0.001; HR — hazard ratio; CI — confidence interval; LVEF — left ventricular ejected fraction

high HAR was associated with longer hospitalization periods. The in-hospital mortality (p < 0.001) and hospitalization days (p < 0.001) were both increased in Q4 group, compared to the other three groups (Table 1). Univariate and variate linear regression were used for determing the role of HAR in predicting in-hospital days. Significant variables in univariate regression were enrolled into multilinear regression by "Stepwise" methods. Finally, HAR was an independent predictor of hospitalizaition time after ACS (hazard ratio [HR]: 2.221, 95% confidence interval [CI]: 0.888–3.553, p = 0.001), which meant the in-hospital days prolonged 2 days when HAR increased by 1 unit (Table 3). When grouped by LBR, there was no significance in LVEF (p = 0.221), in-hospital mortality (p = 0.05) and hospitalization days (p = 0.226) (**Suppl. Table S1**).

HAR, rather than LBR, was an independent factor predicting in-hospital death in ACS patients

Next, predictors of in-hospital death in ACS patients were analyzed. Univariate logistic regression showed that sex (female), age, SBP (90–140 mmHg), SBP (≥ 140 mmHg), Cr (> 81 μmol/L), ALT, LDH, AST, ALB (≥ 40 g/L), GLU, UA, PT, LVEF, cardiac arrest, Killip (≥ II), percutaneous coronary intervention treatment, antidiabetic drugs, antihypertensive drugs, antiplatelet drugs, beta-blocker drugs, statins, nitrates and HAR were all important variables predicting in-hospital death (Table 4). Significant variables in univariate analysis were enrolled and analyzed in variate logistic regression by "Forward Likelyhood Ratio". Variate analysis showed that HAR was an important factor predicting in-hospital death after adjusting for age (HR: 1.068, 95% CI: 1.050–1.087, p < 0.001), SBP (90–140 mmHg) (HR: 0.243, 95% CI: 0.121–0.488, p < 0.001), SBP (≥ 140 mmHg) (HR: 0.134, 95% CI: 0.063–0.286, p < 0.001), Cr (> 81 μmol/L) (HR: 3.525, 95% CI: 2.266–5.483, p < 0.001), LDH (HR: 1.000, 95% CI: 1.000–1.000, p = 0.007), ALB (≥ 40 g/L) (HR: 0.580, 95% CI: 0.356–0.945, p = 0.029), GLU (HR: 1.055, 95% CI: 1.026–1.084, p < 0.001), LVEF (HR: 0.041, 95% CI: 0.011–0.158, p < 0.001) and antiplatelet drugs (HR: 0.468, 95% CI: 0.234–0.935, p = 0.031) (Table 4). These results indicated that HAR was an independent predictor of in-hospital death after ACS. Univariate regression analysis showed that LBR can predict in-hospital death (HR: 0.629, 95% CI: 0.434–0.912, p = 0.014), however, variate regression analysis showed no significance in LBR for predicting in-hospital death (**Suppl. Table S2**).

Discussion

In this study, it was found that HAR was positively related to inflammatory cells counts and negatively correlated to LVEF. Moreover, the proportion of acute myocardial infarction, the hospitalization days and the in-hospital mortality in the high HAR group were significantly increased. LBR, as an indicator of LDL particle size, had no significant correlation with WBC and neutrophil counts. LBR had no significance with LVEF, hospitalization days and in-hospital mortality. HAR was an important predictor of in-hospital death after ACS, rather than LBR, which may result from the impaired ability of HDL particles to absorb excess cholesterol indicated by the increased level of HAR.

The ARIC study found that HDL-C was negatively associated with the incidence of CHD in a 10 year follow-up of 12,339 residents from 4 communities [19]. However, dal-OUTCOMES study

Table 4. Logistic regression of high density lipoptotein cholesterol (HDL-C)/ApoA-I predicting in-hospital death in acute coronary syndrome patients.

Parameters	Univariate logistic regression			Variate logistic regression		
	HR	95% CI	P	HR	95% CI	P
Sex (female)	1.762	1.317–2.359	< 0.001***	1.848	1.327–2.575	< 0.001***
Age [years]	1.086	1.070–1.102	< 0.001***	1.068	1.050–1.087	< 0.001***
SBP (< 90 mmHg)						
SBP 90–140 mmHg	0.122	0.068–0.219	< 0.001***	0.243	0.121–0.488	< 0.001***
SBP ≥ 140 mmHg	0.078	0.041–0.149	< 0.001***	0.134	0.063–0.286	< 0.001***
Albumin (< 40 g/L)						
Albumin ≥ 40 g/L	0.236	0.149–0.373	< 0.001***	0.580	0.356–0.945	0.029*
Creatinine (≤ 81 μmol/L)						
Creatinine > 81 μmol/L	6.122	4.056–9.240	< 0.001***	3.525	2.266–5.483	< 0.001***
ALT [U/L]	1.001	1.000–1.002	0.001**	–	–	–
AST [U/L]	1.000	1.000–1.001	0.083	–	–	–
LDH [U/L]	1.000	1.000–1.001	< 0.001***	1.000	1.000–1.000	0.007**
Glucose [mmol/L]	1.077	1.051–1.104	< 0.001***	1.055	1.026–1.084	< 0.001***
Uric acid [μmol/L]	1.003	1.002–1.004	< 0.001***	–	–	–
Prothrombin time [s]	1.023	1.010–1.037	0.001**	–	–	–
HDL-C/ApoA-I	2.600	1.565–4.320	< 0.001***	1.831	1.010–3.321	0.046*
LVEF	0.005	0.002–0.014	< 0.001***	0.041	0.011–0.158	< 0.001***
Killip (≥ II)	2.645	1.955–3.579	< 0.001***	–	–	–
Cardiac arrest	0.000	0.000–0.000	0.974	–	–	–
PCI treatment	1.351	0.898–2.034	0.149	–	–	–
Antidiabetic drugs	1.106	0.786–1.556	0.564	–	–	–
Antihypertensive drugs	0.541	0.402–0.727	< 0.001***	–	–	–
Antiplatelet drugs	0.424	0.228–0.790	0.007**	0.468	0.234–0.935	0.031*
Statins	0.665	0.384–1.152	0.146	–	–	–
Nitrates	0.804	0.582–1.113	0.189	–	–	–
Beta-blocker drugs	0.610	0.441–0.844	0.003**	–	–	–

*p < 0.05; **p < 0.01; ***p < 0.001; HR — hazard ratio; CI — confidence interval; SBP — systolic blood pressure; ALT — alanine aminotransferase; LDH —lactate dehydrogenase; AST — aspartate aminotransferase; LVEF — left ventricular ejected fraction; PCI — percutaneous coronary intervention

showed that dalcetrapib, a cholesteryl ester transfer protein (CETP) inhibitor, can increase the HDL-C level, but failed to reduce the risk of adverse outcomes in patients with a recent ACS [20]. It has been reported that HDL-C was an indicator of HDL quantity, and the quality was more important than the quantity due to the loss of anti-atherosclerosis function [20]. ApoA-I is an important protein component of HDL with anti-atherosclerosis function. Changes in the quantity and type of proteins and lipids bound by HDL particles and oxidative modification of the components can lead to the loss of this function, becoming "dysfunctional HDL" [21]. HAR may reflect the change in the cholesterol content of each HDL particle [22].

Mainly explored herein, was the predictive ability of HAR in predicting the prognosis of ACS patients. In the present study, it was found that HAR was positively correlated with inflammatory cell counts, hsCRP and LDH, emerging as a potential marker of inflammation. LDH is closely associated with myocardial injury diseases and liver injury, and hsCRP is a common marker of inflammatory diseases. The LBR was not significantly correlated with inflammatory cell counts. HAR was also related to the in-hospital mortality and hospitalization days. After adjusting for age, sex, SBP, Cr, LDH, ALB, GLU, LVEF, and antiplatelet drugs, HAR was shown to be an important factor in predicting in-hospital mortality.

The PRIME study showed that in France and Northern Ireland, HDL-C was not associated with CHD incidence and only ApoA-I could predict the incidence of CHD after adjusting for lipid and non-lipid parameters [11]. A Mendelian randomization study showed HDL characteristics (such as size and cholesterol content) were associated with CHD, instead of HDL-C and ApoA-I levels [23]. These previous studies supported that HAR is not a valuable biomarker for CHD. However, in the current study, it was demonstrated that HAR was associated with the risk of in-hospital death in the ACS population. In a retrospective study of 2,566 patients receiving assessment of atherosclerotic plaque with intravascular ultrasound, plaque progression measured by percent atheroma volume and total atheroma volume was attenuated in patients with higher HAR [24]. In the IDEAL study, higher HDL-C was consistent with a higher risk of CHD when adjusting for age, gender, smoking, ApoB and ApoA-I [25]. An occupational cohort study involved 263,340 people showed that increasing HAR ratio quartiles was positively associated with mortality of CVD ($p = 0.016$), and the adjusted HR of CVD in the highest HAR ratio quartile to the lowest was 2.37 (95% CI: 0.89–6.37), which demonstrated that increasing HAR was an important risk factor for CVD [22].

Since HAR and LBR were both similarly important ratios in CVDs, further study compared the role of LBR in ACS patients. It has been reported that LBR was negatively associated with CHD [26]. In a case-cohort study, LBR ≤ 1.2 can predict CHD in patients with type 2 diabetes after adjusting confounders [27]. CHD and diabetes mellitus status were both independent factors predicting the minimum LBR, and LBR may play an important role in risk stratification in diabetic patients with CHD [28]. In a prospective cohort study with 9.9 ± 4.6 years follow-up of 1,687 patients with established atherosclerosis, Cox regression showed that LBR can predict major adverse cardiac events after adjusting some variables such as age, gender, smoking history, body mass index, etc. [29]. However, the relationship between LBR and ACS has rarely been reported. The present study showed LBR was not related to hospitalization days of ACS patients. Incidence of in-hospital death gradually decreased with the increase of LBR quartiles, although without any statistical significance. Different from HAR, LBR was not an independent predictor of in-hospital death.

Limitations of the study

There are some limitations of the current study. First, this study did not actually measure the particle size of LDL and the proportion of dysfunctional HDL. Instead, representative related markers (HAR and LBR) were used to evaluate the relationship between the quality and type of lipids in the blood and the prognosis of ACS. Second, as a retrospective study, confounding factors have an influence on the results, but variate logistic regression was used to eliminate the influence of confounding factors as much as possible.

Conclusions

In conclusion, it was found that HAR had an important predictive value in the in-hospital death after ACS, while the LBR, which represents the size of the LDL particle size, was not related to the adverse prognosis. These results show that more attention needs to be paid to HDL-C and ApoA-I in coronary artery disease, not only LDL-C and ApoB.

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Conflict of interest: None declared

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Prevalence and prognosis of anxiety, insomnia, and type D personality in patients with myocardial infarction: A Spanish cohort

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Abstract

Background: *It has been suggested that patients with myocardial infarction and non-obstructive coronary arteries (MINOCA) have more psycho-emotional disorders than patients with obstructive coronary artery disease (MICAD). The aim of this study is to compare the prevalence of anxiety, insomnia, and type D personality between MINOCA and MICAD and their impact on prognosis.*

Methods: *Patients with myocardial infarction undergoing coronary angiography were prospectively enrolled. Psychological questionnaires were completed by each patient during admission.*

Results: *Among a total of 533 patients, 56 had MINOCA and 477 had MICAD. There were no differences in the prevalence of anxiety and insomnia between both groups: trait anxiety median value (M) MINOCA = 18 (11–34) vs. MICAD M = 19 (12–27), p = 0.8; state anxiety MINOCA M = 19 (11–29) vs. MICAD M = 19 (12.2–26), p = 0.6; and insomnia MINOCA M = 7 (3–11) vs. MICAD M = 7 (3–12), p = 0.95. More MINOCA patients had type D personality (45.0% vs. 28.5%, p = 0.03). At 3-year follow-up, there were no differences in mortality between MINOCA and MICAD (hazard ratio [HR] 0.78, 95% confidence interval [CI] 0.28–2.17) in major adverse cerebral or cardiovascular events (MACCE) (HR 0.71, 95% CI 0.38–1.31). Scores of trait anxiety and negative affectivity were significantly associated with MACCE (HR 1.65, 95% CI [1.05–2.57]; HR 1.75, 95% CI [1.11–2.77], respectively). High insomnia levels were associated with greater mortality (HR 2.72, 95% CI [1.12–6.61]).*

Conclusions: *Anxiety and insomnia levels were similar between patients with MINOCA and those with MICAD, whilst the prevalence of type D personality was higher in the MINOCA than in the MICAD group. Higher scores in trait anxiety, insomnia, and negative affectivity were related to a worse prognosis at 3-year follow-up.* (Cardiol J 2024; 31, 2: 261–270)

Keywords: anxiety, infarction, insomnia, myocardial infarction and non-obstructive coronary arteries (MINOCA), type D personality

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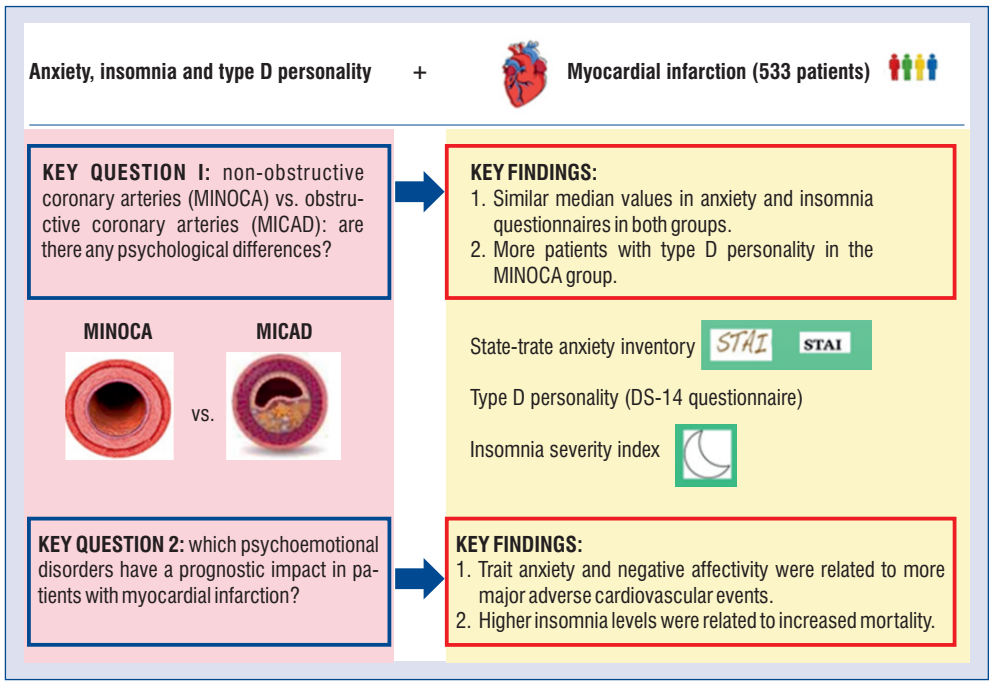

Central illustration. Anxiety, insomnia, and type D personality must be studied both in patients with myocardial infarction with non-obstructive coronary arteries (MINOCA) and in patients with myocardial infarction with coronary artery disease (MICAD), in order to identify those who might benefit from psychological attention.

Introduction

Myocardial infarction (MI) is related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries, leading to decreased myocardial blood flow. The patient may have underlying obstructive coronary artery disease (MICAD), but sometimes non-obstructive or no coronary artery disease is found at angiography (MINOCA). This type of MI can represent as much as 5–11% of the total MI according to different series [1–3].

Although some studies suggest a relationship between mental health and cardiovascular disease [4, 5], the initial approach of patients with MI does not usually include the evaluation of psychological disorders.

There are studies that correlate insomnia and type D personality with heart failure [6, 7], and there is a well-established relationship between depression and coronary heart disease [8, 9]. However, there is controversial evidence regarding MI and its relationship with anxiety, insomnia, and type D personality [10–13].

It has been suggested that patients with MINOCA have more emotional stress than patients with MICAD. These data are difficult to interpret because of the heterogeneity of MINOCA definitions, which have continuously changed in the past few years [14, 15]. Also, there is no evidence regarding which psychological questionnaires may have prognostic value in patients with MINOCA. To the best of our knowledge, this is the first study that compares psycho-emotional disorders in MICAD and MINOCA patients with standardized questionnaires.

The objectives were as follows: 1) to compare levels of anxiety, insomnia, and type D personality through validated questionnaires between patients with MINOCA and MICAD and 2) to determine if any of these psycho-emotional disorders were related to significant differences in prognosis. The main prognostic variable was the combination of major adverse cerebral and cardiovascular events (MACCE), which included stroke, MI, cardiovascular readmission, or death from any cause (Central illustration).

Methods

All consecutive patients admitted to Getafe University Hospital (Madrid, Spain), who underwent coronary angiography for MI between July 2017 and December 2021 were prospectively enrolled.

Inclusion criteria were as follows: being 18 years of age or older, fulfilling the MI criteria according to the 4th Universal Definition of Infarction [16], and undergoing a coronary angiography during admission. The exclusion criterion was the inability to sign informed consent.

The diagnosis of MINOCA was made according to the following criteria: 1) MI according to the 4th Universal Definition of Infarction [16]; 2) non-obstructive coronary arteries on angiography (no coronary artery stenosis ≥ 50%); and 3) no specific alternate diagnosis for the clinical presentation. The latest European and American guideline definitions were used [17, 18], therefore excluding patients with myocarditis and takotsubo.

The study protocol complied with the Declaration of Helsinki, and it was approved by the local institutional review committee.

Procedure

The questionnaires referring to anxiety, insomnia, and type D personality were completed by each patient (self-administrated test) during hospitalization. The three questionnaires are presented below:

— **State-Trait Anxiety Inventory (STAI)** adapted and validated in Spanish [19]. STAI is a self-report assessment device that includes separate measures of state of anxiety (STAI-S) and trait anxiety (STAI-T). The STAI-S measurement assesses how the individual feels "right now". Subjects were asked to rate the intensity of their anxious feelings on a 4-point scale regarding their experience of feelings as follows: not at all, somewhat, moderately so, or very much so. The STAI-T explains how the individuals generally feel by rating themselves on a 4-point scale as follows: almost never, sometimes, often, or almost always. Each type of anxiety has its own scale of 20 different questions. Scores range from 0 to 60, with higher scores correlating with greater anxiety;

— **The Type D Scale-14 (DS-14)** adapted and validated in Spanish [20]. Type D personality is characterized by two personality traits: negative affectivity (NA) and social inhibition (SI). NA is the tendency to experience negative emotions and feelings of dysphoria, anxiety, irritability, and apprehension, including vulnerability to anxiety and depression. SI is the tendency to inhibit the expression of emotions, paired with interpersonal stress and the failure to adapt. Participants respond to each item on a 5-point Likert scale (0 = false, 1 = rather false, 2 = neutral, 3 = rather true, 4 = true). The NA and SI scales can be scored (0–28 points) to assess these personality traits independently. A score of 10 or more on both scales is used to classify the patient as having a type D personality (type D = NA ≥ 10 + IS ≥ 10);

— **Insomnia Severity Index (ISI)** adapted and validated in Spanish [21, 22]. It is a 7-item questionnaire assessing the nature, severity, and impact of insomnia. The usual recall period is the "last month" and the dimensions evaluated are as follows: severity of sleep onset, sleep maintenance, early morning awakening problems, sleep dissatisfaction, interference of sleep difficulties with daytime functioning, noticeability of sleep problems by others, and distress caused by the sleep difficulties. A 5-point Likert scale is used to rate each item (0 = no problem; 4 = very severe problem), yielding a total score ranging from 0 to 28 points. The total score is interpreted as follows: absence of insomnia (0–7 points); subthreshold insomnia (8–14 points); moderate insomnia (15–21 points); and severe insomnia (22–28 points).

Statistical analysis

Qualitative variables were represented as a percentages (%). Differences between groups were calculated with the χ^2 test. The scores obtained in the questionnaires were presented as medians (p25–p75), and the differences between groups were calculated with the Mann-Whitney U test. Normal continuous variables were presented as mean ± standard deviation, and the differences between groups were established with Student's test. Events at follow-up were analyzed and represented with Cox regression and Kaplan-Meier method using the log-rank test for comparison between both groups. Median time at follow-up was 942 days (511–1375).

Results

There was a total of 546 patients with MI undergoing coronary angiography, and 533 signed the informed consent. Of them, 56 presented with MINOCA (10.5%) and 477 presented with MICAD (89.5%). The different questionnaires were completed as follows: STAI 60.8% (324 patients, 43 MINOCA and 281 MICAD), ISI 61.3% (327 patients, 43 MINOCA and 284 MICAD), and DS-14 59.5% (317 patients, 40 MINOCA and 277 MICAD).

Table 1. Baseline characteristics: personal background.

	MINOCA (n = 56)	MICAD (n = 477)	P
Women	31 (55.4%)	111 (23.4%)	< 0.01
Age [years]	66.8 ± 13.7	66.5 ± 13.7	0.88
Smokers	13 (26%)	169 (41.2%)	0.03
Diabetes mellitus	13 (23.2%)	150 (31.5%)	0.20
Dyslipidemia	31 (56.4%)	255 (53.7%)	0.70
Hypertension	41 (73.2%)	276 (58%)	0.03
Myocardial infarction	6 (10.7%)	79 (16.7%)	0.21
Heart failure	3 (5.4%)	23 (4.8%)	0.72
Stroke	4 (7.1%)	30 (6.3%)	0.71
Peripheral vascular disease	3 (5.4%)	39 (8.2%)	0.60
Chronic kidney disease	4 (7.1%)	52 (10.9%)	0.38
Chronic lung disease	6 (10.7%)	52 (10.9%)	0.96
PCI	2 (3.6%)	55 (11.6%)	0.06
AF/atrial flutter	9 (16.1%)	35 (7.4%)	0.03
Cancer	6 (10.7%)	51 (10.7%)	1
Allergies	10 (17.9%)	44 (9.2%)	0.04
Psychiatric disease	8 (14.3%)	50 (10.5%)	0.40
Previous treatment:			
Acetylsalicylic acid	12 (21.4%)	122 (25.6%)	0.52
Other antiplatelet therapy	3 (5.4%)	30 (6.3%)	1
Beta-blockers	11 (19.6%)	106 (22.3%)	0.61
ACE inhibitors	21 (37.5%)	134 (28.2%)	0.15
ARB	10 (17.9%)	79 (16.6%)	0.82
Statins	26 (46.4%)	197 (41.6%)	0.48
Nitrates	3 (5.4%)	36 (7.6%)	0.78

Values expressed as number (%) or mean value ± standard deviation; ACE — angiotensin-converting enzyme; AF — atrial fibrillation; ARB — angiotensin receptor blocker; MICAD — myocardial infarction with coronary artery disease; MINOCA — myocardial infarction with non-obstructive coronary arteries; PCI — percutaneous coronary intervention

Table 2. Characteristics at admission and during hospitalization.

	MINOCA (n = 56)	MICAD (n = 477)	P
Angina	37 (66.1%)	386 (80.9%)	< 0.01
Heart rate [bpm]	78.8 ± 16.8	79.4 ± 19.1	0.80
SBP [mmHg]	151.1 ± 28.1	140.8 ± 30.0	0.01
Troponin T hs [ng/L]	748.9 ± 1893.1	2419.8 ± 5960.5	< 0.01
Creatinine kinase [U/L]	320.2 ± 366.6	908.3 ± 1185.3	< 0.01
Hemoglobin [g/dL]	13.9 ± 1.7	14.2 ± 1.9	0.18
Cholesterol [mg/dL]	170.2 ± 41.9	164.1 ± 45.1	0.35
Creatinine [mg/dL]	1.3 ± 1.9	1.2 ± 1.5	0.72
Electrocardiogram:			
AF/atrial flutter	10 (17.9%)	28 (5.9%)	< 0.01
ST segment elevation or depression	13 (23.2%)	292 (62.3%)	< 0.01
Killip I	54 (98.1%)	424 (89.8%)	0.04
Pulmonary edema, reinfarction, hemorrhage	1 (1.8%)	33 (6.9%)	0.21
Primary angioplasty	6 (10.7%)	230 (48.2%)	< 0.01
Ejection fraction < 40%	3 (5.4%)	75 (15.8%)	0.04

All values express number (%) or mean value ± standard deviation; AF — atrial fibrillation; MICAD — myocardial infarction with coronary artery disease; MINOCA — myocardial infarction with non-obstructive coronary arteries; SBP — systolic blood pressure; Troponin T hs: Elecsys test (Roche), cut-off value 14 ng/L

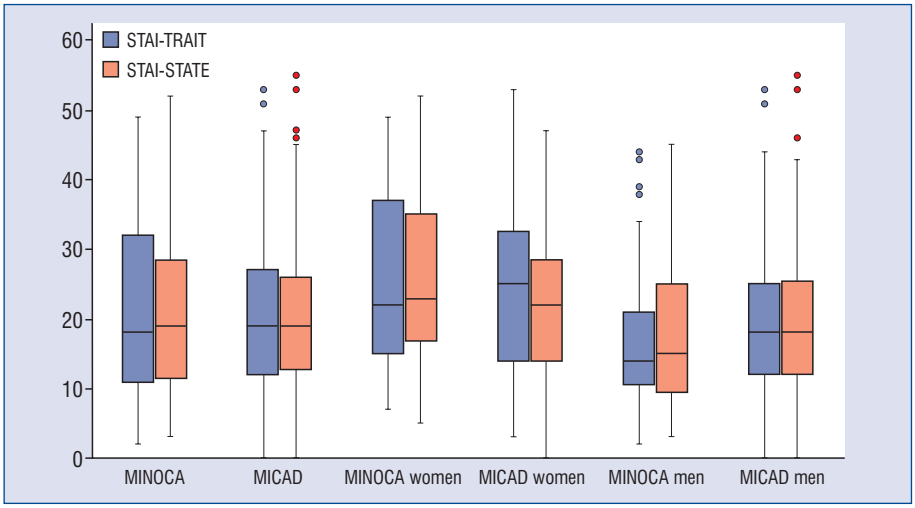

Figure 1. State-trait anxiety inventory (STAI) median score in all groups. Box plot. The boxes on the left (blue) represent the median score value for the trait anxiety component of the STAI questionnaire. The boxes on the right (red) represent the median score value for the state anxiety component of the STAI questionnaire. The boxes cover the interquartile interval, where 50% of the data are found. No significant differences were found between patients with myocardial infarction with non-obstructive coronary arteries (MINOCA) and patients with myocardial infarction with coronary artery disease (MICAD). Also, there were no differences when analyzing both groups by sex.

Characteristics at baseline and during admission are presented in Tables 1 and 2.

There were more women in the MINOCA group (55.4% vs. 23.4%, $p < 0.01$), but the age was similar in both groups: MINOCA 66.8 ± 13.7 and MICAD 66.5 ± 13.6, $p = 0.9$. Regarding traditional cardiovascular risk factors, there were more smokers in the MICAD group (41.2% vs. 26%, $p = 0.03$) and MINOCA patients had more hypertension (73.2% vs. 58%, $p = 0.03$). There were no differences in diabetes (31.5% vs. 23.2%, $p = 0.2$) or dyslipidemia (53.7% vs. 56.4%, $p = 0.7$).

The principal mechanisms underlying MINOCA were unknown (48.2%), followed by type II MI (19.6%) and vasospasm (10.7%). Disruption of plaque comprised 8.9% of the cases. The least common mechanisms were coronary dissection (8.1%) and emboli (4.5%). Although not all patients were able to complete the questionnaires, there were no differences in baseline characteristics between those who completed the questionnaires and those who did not. However, there were significant differences in their clinical course, so that patients with a poorer prognosis could not complete as many questionnaires as the rest of patients: worse Killip classification (95.7% vs. 15.5%, $p < 0.01$); higher levels of biomarkers (troponin T [ng/L] 1832.9 ± ± 3931.0 vs. 2989.1 ± 7938.1, $p = 0.04$; creatinine kinase [U/L] 721.4 ± 968.8 vs. 1079.3 ± 1378.7, $p < 0.01$); ejection fraction below 40% (9.9% vs. 22.8%, $p < 0.01$); more in-hospital complications (3.9% vs. 10.6%, $p < 0.01$); and more ST segment alterations (52.1% vs. 68%, $p < 0.01$).

Anxiety

The median (M) score value in STAI was similar in both groups: MINOCA STAI-T M = 18 (11–34) vs. MICAD M = 19 (12–27), $p = 0.8$; MINOCA STAI-S M = 19 (11–29) vs. MICAD M = 19 (12.2-26), $p = 0.6$ (Fig. 1).

Because women had higher punctuation levels than men, data were analyzed separately without finding statistical differences between sexes: STAI-T in women with MINOCA M = 22 (13–27) vs. women with MICAD M = 25 (13–32); $p = 0.9$. STAI-S in women with MINOCA M = 23 (16–37) vs. women with MICAD M = 21 (13.5–28.5), $p = 0.2$. In a similar way, there were no differences between men: STAI-T in men with MINOCA M = 14 (10–21) vs. men with MICAD M = 18 (12–25), $p = 0.48$; STAI-S in men with MINOCA M = 15 (9–25) vs. men with MICAD M = 18 (12–26), $p = 0.35$.

Insomnia

There were no differences in insomnia levels between both groups: MINOCA M = 7 (3–11) vs. MICAD M = 7 (3–12), $p = 0.95$ (Fig. 2).

Analyzing it by sex, the scores remained similar: women with MINOCA M = 9 (3.5–11.5)

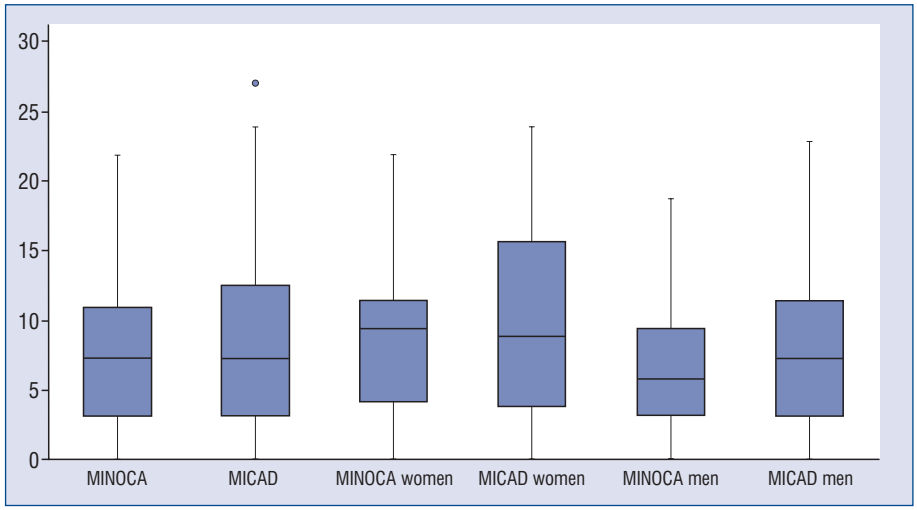

Figure 2. Insomnia severity index (ISI) median score in all groups. Box plot. The boxes (blue) represent the median value obtained in the ISI score in each subgroup. The boxes cover the interquartile interval, where 50% of the data are found. No significant differences were found between patients with myocardial infarction with non-obstructive coronary arteries (MINOCA) and patients with myocardial infarction with coronary artery disease (MICAD). Also, there were no differences when analyzing both groups by sex.

vs. women with MICAD M = 8 (3.2–15), p = 0.6; men with MINOCA M = 5 (3–9.7) vs. men with MICAD M = 7 (3–11), p = 0.77.

Type D personality

The proportion of patients with type D personality was higher in the MINOCA than in the MICAD group (45.0% vs. 28.5%, p = 0.03). 55% of women with MINOCA had type D personality vs. 31.3% of women with MICAD (p = 0.05). In the group of men with MINOCA, 35% had type D personality vs. 27.7% in the group of men with MICAD (p = 0.48) (Fig. 3).

There were no significant differences when the two personality traits that comprise the scale were analyzed: NA in MINOCA M = 13 (8–19.8) vs. MICAD M = 11 (6–17), p = 0.2; SI in MINOCA M = 8 (4–14.8) vs. MICAD M = 8 (4–13), p = 0.36.

Prognosis

From the total group of patients with MI (n = 533), 12 died during hospitalization (2.1%). Follow-up was lost in 7 (1.3%) patients, and 514 were followed, of whom 55 had MINOCA and 459 MICAD. There were no significant differences in the follow-up between the groups. The median follow-up was 942 days (MINOCA 938 and MICAD 950, p = 0.78), and cases were censored at 1095 days (3 years).

There were no differences in mortality between MINOCA and MICAD at 3 years follow-up (hazard ratio [HR] 0.78, 95% confidence interval [CI] 0.28–2.17, p = 0.63), or in MACCE (HR 0.71, 95% CI 0.38–1.31, p = 0.27) (Figs. 4, 5). The incidence of MI, stroke, and cardiovascular readmission was also similar between both groups (HR 2.04, 95% CI 0.69–6.07, p = 0.20; HR 1.19, 95% CI 0.15–9.65, p = 0.87; and HR 0.68, 95% CI 0.35–1.36, p = 0.28, respectively).

In the total group of patients with MI, we analyzed if the score in STAI-T had any relationship with MACCE at follow-up. For that, we considered two groups according to their median score values (24 points in women and 17 in men). A total of 321 patients were analyzed, 160 of whom were above the median value. This group had more MACCE (HR 1.65, 95% CI 1.05–2.57, p = 0.03), but there were no differences in mortality (HR 1.61, 95% CI 0.67–3.89, p = 0.28).

In the STAI-S questionnaire, the median score was 18 points for men and 22 for women. There was no relationship between a higher score and survival (HR 1.22, 95% CI 0.52–2.88, p = 0.64) or MACCE (HR 0.86, 95% CI 0.55–1.33, p = 0.50).

The median score in the ISI questionnaire allowed us to differentiate two groups of patients: those without insomnia (n = 165) and those with some grade of insomnia (mild, moderate, or severe insomnia; n = 159). Patients with some grade of insomnia had higher mortality (HR 2.72, 95% CI 1.12–6.61, p = 0.02), but there

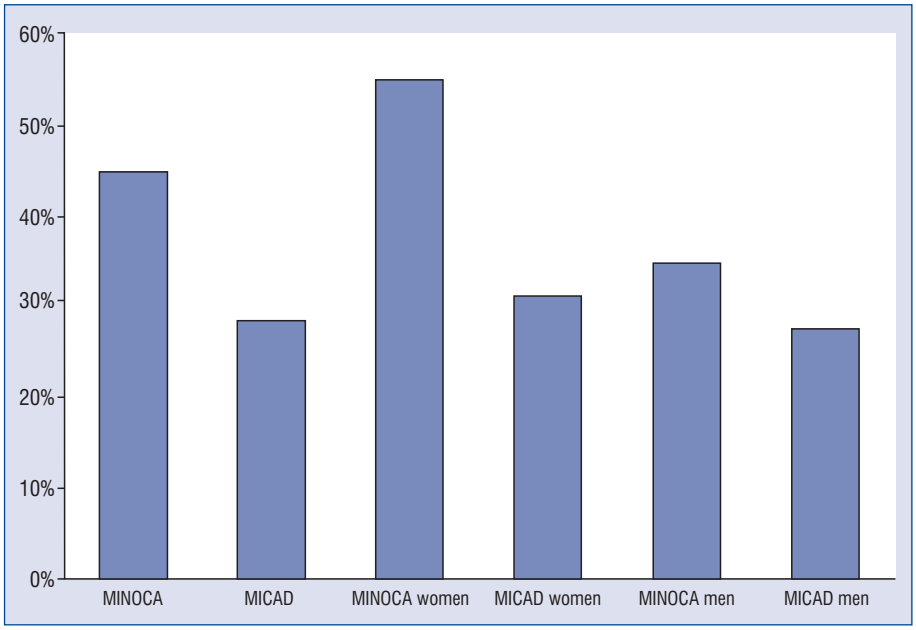

Figure 3. Patients with type D personality. Each column (blue) represents the percentage of patients with type D personality in each group. There were more patients with type D personality in the myocardial infarction with non-obstructive coronary arteries (MINOCA) group (45%) compared to the myocardial infarction with coronary artery disease (MICAD) group (28.5%), p = 0.03. Also, there were more women with MINOCA and type D personality (55%) than women with MICAD and type D personality (31.3%), p = 0.05. There were no statistically significant differences between men in both groups.

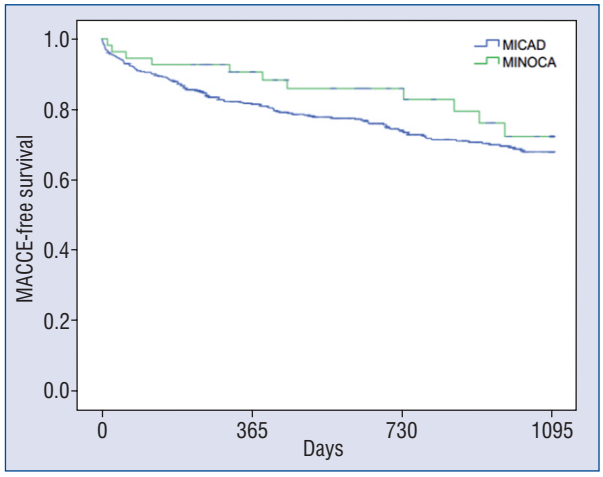

Figure 4. Major adverse cerebral and cardiovascular event (MACCE)-free survival in patients with myocardial infarction with non-obstructive coronary arteries (MINOCA) vs. myocardial infarction with coronary artery disease (MICAD). The graphic represents the Kaplan-Meier curves of MACCE during 3 years of follow-up. There were no differences between patients with MINOCA and patients with MICAD (hazard ratio 0.71, 95% confidence interval 0.38–1.31, p = 0.27).

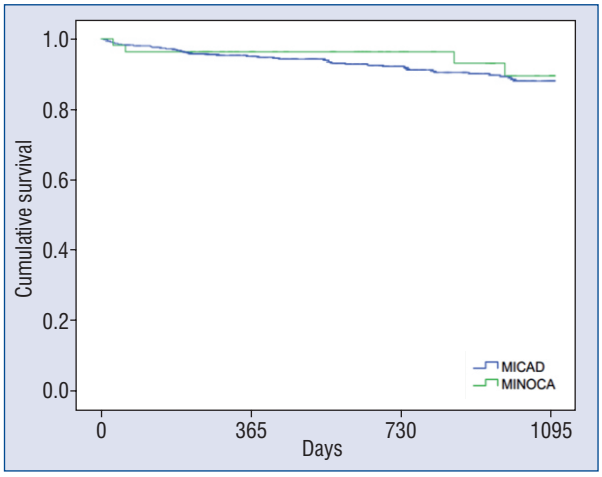

Figure 5. Cumulative survival in patients with myocardial infarction with non-obstructive coronary arteries (MINOCA) vs. myocardial infarction with coronary artery disease (MICAD). The graphic represents the Kaplan-Meier curves of cumulative survival in patients with MINOCA and in patients with MICAD. No differences were found (hazard ratio 0.78, 95% confidence interval 0.28–2.17, p = 0.63).

were no differences in MACCE (HR 1.03, 95% CI 0.67–1.58, p = 0.89).

There were no differences in mortality between patients with type D personality (n = 96) vs. those without type D personality (n = 218) (HR 0.88, 95% CI 0.34–2.25, p = 0.79), nor in MACCE (HR 0.89, 95% CI 0.54–1.45, p = 0.64). Patients with more than 10 points in the NA scale (n = 172) had more MACCE than those with less than 10 points (n = 142) (HR 1.75, 95% CI 1.11–2.77, p = 0.02), but there were no differences in mortality (HR 1.01, 95% CI 0.43–2.33, p = 0.98).

Discussion

There is controversy in the literature about the relationship between anxiety and MI, and there are very few data about psycho-emotional disorders in MINOCA. The fact that takotsubo was initially included in the MINOCA group may explain the results of some studies in which higher levels of anxiety were found. The relationship between emotional or physical stress and myocardial injury in takotsubo syndrome has been widely studied [23, 24].

Pais et al. [15] initially described some statistically significant differences in the variable "stress" between MINOCA and MICAD patients. However, those data were registered as a single dichotomous variable (yes/no), and no standardized questionnaires were used. Now that the latest consensus documents establish that patients with takotsubo do not belong to the MINOCA group, there is no evidence that MINOCA patients have more emotional disorders. Only Domínguez-Rodríguez et al. [25] studied anxiety in MINOCA patients in Spain excluding takotsubo. Even in that context, the only significant result was that women with MINOCA had more phobic anxiety than men, without finding any differences in global anxiety by sex.

The SA-45 questionnaire was used in that study, which collected information about anxiety and other psycho-behavioral aspects, but with no references to state or trait anxiety, in contrast to the STAI questionnaire. Also, the patients with MINOCA were not compared to patients with MICAD.

In our study, it is interesting that state anxiety does not correlate with a worse prognosis. This means that the anxiety levels during an acute event do not define more MACCE at follow-up. It is the anxiety trait component that gives information about the patient's baseline anxiety, and it seems to be more important in the development of MACCE. It is the first time that the distinction between both types of anxiety shows prognostic value in patients with MI, regardless of the presence or absence of coronary obstruction.

Regarding type D personality, although the first Denollet studies [26, 27] suggested that it was related to an increase in cardiovascular disease and a worse prognosis [28, 29], there are subsequent studies that do not prove its association with ischemic heart disease. Findings across studies are inconsistent; several studies have failed to find any associations between type D personality and cardiovascular outcomes and provided ambiguous evidence regarding whether type D personality can predict cardiovascular heart disease. The most significant study is the one performed by Meyer's group [30], in which patients with coronary disease and a coronary angiography completed the DS-14 questionnaire. They were classified as "type D" and "not type D", and there were no prognostic differences at 5-year follow-up between the groups. Even when analyzing NA and SI, they observed that a higher score in each of them did not correlate with a worse prognosis. In fact, there was a tendency of SI to be a "protective factor" in MACCE. This is similar to our study, in which there was no relationship between type D personality and worse prognosis.

However, more MACCE was observed with a score over 10 points in the NA item. This is similar to the study of Han et al. [31], in which patients with MI had more MACCE with higher levels of NA.

Regarding insomnia, there are no gathered data on MINOCA patients in Spain. A meta-analysis of Sofi et al. [32] reflects the fact that there is a relationship between patients with insomnia and a higher incidence of cardiovascular disease, and Aastebøl Frøjd et al. [33] correlated insomnia with more MACCE in patients with coronary heart disease.

The study of Zhu [34] showed an association between sleep disorders in MINOCA patients and greater mortality and MACE. However, each study used a different questionnaire to diagnose insomnia.

Hence, this study demonstrates the need to use more structured and standardized questionnaires in every hospital to have more realistic prognostic data. It can be helpful to formalize the registration of psycho-emotional disorders during admission. In that way, the most useful data could be used in cardiac rehabilitation programs to improve secondary prevention.

It may be more effective to present an individualized strategy depending on each patient's profile. A multicenter study will be necessary because the patients with cardiovascular risk factors and who also associate high levels of trait anxiety, insomnia, or negative affectivity will probably benefit from a specific plan with a mental health professional.

Limitations of the study

The main limitation in this study is the small number of patients with MINOCA. This can be explained by the strict inclusion criteria according to the latest guidelines. This was an insufficient sample size for some subgroup analyses and more patients will be needed for concrete results.

Another inherent limitation was the selection bias regarding in-hospital evolution between patients who completed the questionnaires and those who did not. In a significant way, those who could not complete the questionnaires had a more severe MI: ST segment alterations, worse Killip class, worse ejection fraction, more in-hospital complications, and higher myocardial damage markers. There were two reasons that could explain this fact: first, the patients who were more critically ill may not have been physically able to complete the questionnaires. Second, our hospital does not have a 24-hour service for primary angioplasty, and some patients had to be transferred to another hospital for intervention. Although in most cases they came back to our center, sometimes this could not be done due to in-hospital complications, so some of them did not have the opportunity to complete our questionnaires. The inherent selection bias to self-administered questionnaires during hospital admission for an MI was minimized in two ways: 1) If the patient was weak or had vision problems (such as in elderly people), they could receive help from a family member to write the answers down. Under no circumstances could hospital staff help or influence any patient when completing the questionnaires; 2) The inherent nature of the questionnaires used in this study (trait vs. state anxiety and specific instructions at the top of the questionnaires) allow differentiation between the patient's psychological state during admission and during their everyday life.

Conclusions

After performing an exhaustive analysis with standardized questionnaires, we did not find any differences in the prevalence of anxiety and insomnia between patients with MINOCA and those with MICAD. There were more patients with type D personality in the MINOCA than in the MICAD group. In patients with MI, a higher score in the trait anxiety, insomnia, and negative affectivity questionnaires was related to a worse prognosis at 3-year follow-up.

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Conflict of interest: None declared

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Effect of delayed hospitalization on 3-year clinical outcomes according to renal function in patients with non-ST-segment elevation myocardial infarction

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Abstract

Background: *We evaluated the effect of delayed hospitalization (symptom-to-door time [STD] ≥ 24 h) on 3-year clinical outcomes according to renal function in patients with non-ST-segment elevation myocardial infarction (NSTEMI) undergoing new-generation drug-eluting stent (DES) implantation.*

Methods: *A total of 4513 patients with NSTEMI were classified into chronic kidney disease (CKD) (estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m^2, n = 1118) and non-CKD (eGFR ≥ 60 mL/min/1.73 m^2, n = 3395) groups. They were further sub-classified into groups with (STD ≥ 24 h) and without (STD < 24 h) delayed hospitalization. The primary outcome was the occurrence of major adverse cardiac and cerebrovascular events (MACCE), defined as all-cause death, recurrent myocardial infarction, any repeat coronary revascularization, and stroke. The secondary outcome was stent thrombosis.*

Results: *After multivariable-adjusted and propensity score analyses, the primary and secondary clinical outcomes were similar in patients with or without delayed hospitalization in both CKD and non-CKD groups. However, in both the STD < 24 h and STD ≥ 24 h groups, MACCE (p < 0.001 and p < 0.006, respectively) and mortality rates were significantly higher in the CKD group than in the non-CKD group. However, stent thrombosis rates were similar between the CKD and non-CKD groups and between the STD < 24 h and STD ≥ 24 h groups.*

Conclusions: *Chronic kidney disease appears to be a much more important determinant of MACCE and mortality rates than STD in patients with NSTEMI.* (Cardiol J 2024; 31, 2: 271–284)

Keywords: chronic kidney disease, drug-eluting stent, non-ST-segment elevation myocardial infarction, pre-hospital delay

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Introduction

The Harmonizing Outcomes with RevasculariZatiON and Stents in Acute Myocardial Infarction (HORIZON-AMI) trial [1] showed that early infarct-related artery (IRA) patency is an independent predictor of lower 1-year mortality in patients with ST-segment-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI) (2.5% vs. 3.9%, p = 0.04). Current guidelines [2–4] recommend that the early invasive strategy (coronary angiography [CAG] and PCI within 24 h of admission) is preferred over the delayed invasive strategy in patients with non-STEMI (NSTEMI) and those with at least one high-risk criterion. However, the early invasive strategy did not always result in decreased mortality compared with the delayed invasive strategy in high-risk patients with NSTEMI [5–7]. Thus, the optimal timing of PCI in NSTEMI is yet to be fully evaluated, and more data are needed. In patients with STEMI, recent [8] and previous research [9] show that long-term mortality is strongly related to total ischemic time rather than door-to-balloon time (DTB). In contrast, in patients with NSTEMI, very few studies have investigated the long-term clinical outcomes in patients with delayed hospitalization (symptom-to-door time [STD] ≥ 24 h) [10]. The prevalence of chronic kidney disease (CKD) in patients with NSTEMI is from 25–30% [11, 12] to as much as 42.9% [12] compared with 30.5% in patients with STEMI. In patients with acute myocardial infarction (MI) and estimated glomerular filtration rate (eGFR) below 81.0 mL/min/1.73 m^2, each drop in eGFR by 10 mL/min/1.73 m^2 was associated with a hazard ratio for death and nonfatal cardiovascular outcomes of 1.10 (95% confidence interval [CI] 1.08–1.12) [11] Although CKD leads to high mortality and morbidity in patients with NSTEMI [13], patients with CKD have rarely been included in NSTEMI randomized clinical trials [14]. Therefore, data on the long-term effects of delayed hospitalization on long-term clinical outcomes according to renal function in patients with NSTEMI are limited. The current guideline [15] recommends drug-eluting stent (DES) over bare-metal stent (BMS) implantation if PCI is indicated in patients with CKD. In this study, we evaluated the effect of delayed hospitalization on 3-year clinical outcomes in patients with NSTEMI with or without CKD undergoing new-generation DES implantation to reflect real-world current practice.

Methods

Study population

This nonrandomized, multicenter, prospective cohort study included 13,104 patients with acute MI between November 2011 and December 2015 from the Korea Acute Myocardial Infarction Registry-National Institute of Health (KAMIR-NIH) [16]. KAMIR-NIH is a nationwide prospective multicenter registry integrated from 20 high-volume centers in the Republic of Korea. All patients aged ≥ 18 years at the time of hospital admission were included. Patients who did not receive PCI (n = = 1369, 10.4%), received unsuccessful PCI (n = = 155, 1.2%), plain old balloon angioplasty (n = 739, 5.6%), BMS or first-generation (1G)-DES (n = 563, 4.3%), or coronary artery bypass graft (CABG, n = 38, 0.3%), had STEMI (n = 5342, 40.8%), cardiogenic shock, or in-hospital death (n = 228, 1.7%), or were unavailable for follow-up (n = 157, 1.2%) were excluded (Fig. 1). Overall, a total of 4513 patients with NSTEMI who underwent successful PCI using new-generation DES were enrolled and classified into CKD (eGFR < 60 mL/min/1.73 m^2, n = 1118 [24.8%]) and non-CKD (eGFR ≥ 60 mL/ /min/1.73 m^2, n = 3395 [75.2%]) groups. Thereafter, these two groups were further sub-classified into those without delayed hospitalization (STD < 24 h, group A [n = 756] and group C [n = 2516]) or those with delayed hospitalization (STD ≥ 24 h, group B [n = 362], and group D [n = 879]) (Fig. 1). The types of new-generation DESs used are listed in Table 1. Using a web-based case report form in the internet-based Clinical Research and Trial management system (iCReaT, iCReaT Study No. C110016), the attending physicians with the assistance of trained clinical research coordinators used a web-based case report form in a clinical data management system to collect all data. Patients who registered for the study were subsequently given a unique number in sequential order. In accordance with the ethical guidelines of the 2004 Declaration of Helsinki, this study was approved by the ethics committee of each participating center and the Chonnam National University Hospital Institutional Review Board Ethics Committee (CNUH-2011-172). All 4513 patients included in the study provided written informed consent prior to enrollment. They also completed a 3-year clinical follow-up through face-to-face interviews, phone calls, or chart reviews. Event adjudication processes have been described in a previous pub-

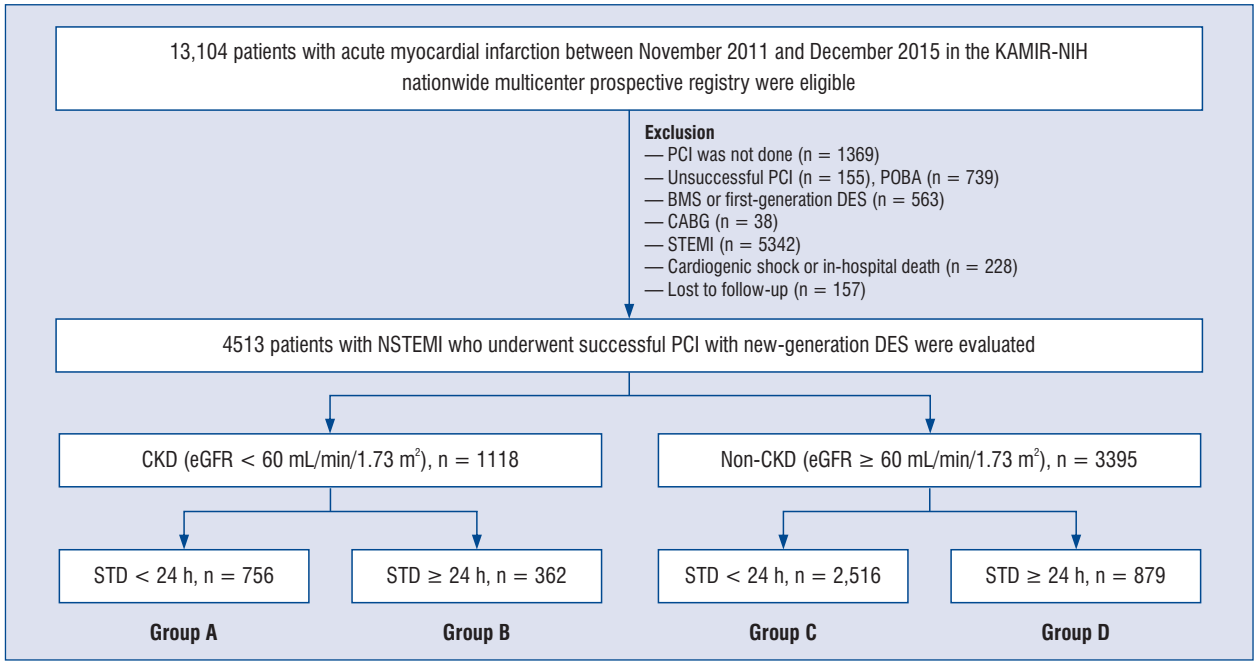

Figure 1. Flowchart. KAMIR-NIH — Korea Acute Myocardial Infarction Registry-National Institute of Health; PCI — percutaneous coronary intervention; POBA — plain old balloon angioplasty; BMS — bare-metal stent; DES — drug-eluting stent; CABG — coronary artery bypass graft; STEMI — ST-segment-elevation myocardial infarction; NSTEMI — non-STEMI; CKD — chronic kidney disease; eGFR — estimated glomerular filtration rate; STD — symptom-to-door time.

Table 1. Baseline characteristics.

Variables	CKD, n = 1118			Non-CKD, n = 3395		
	STD < 24 h (n = 756, group A)	STD ≥ 24 h (n = 362, group B)	P	STD < 24 h (n = 2516, group C)	STD ≥ 24 h (n = 879, group D)	P
Male	481 (63.6%)	189 (52.2%)	< 0.001	1980 (78.7%)	637 (72.5%)	< 0.001
Age [years]	70.1 ± 10.0	72.0 ± 10.3	0.003	61.0 ± 11.7	63.8 ± 11.7	< 0.001
LVEF [%]	51.1 ± 11.9	48.4 ± 12.5	0.001	55.5 ± 9.4	55.5 ± 10.1	0.921
BMI [kg/m^2]	23.9 ± 3.2	23.8 ± 3.5	0.758	24.3 ± 3.3	24.1 ± 3.2	0.293
SBP [mmHg]	136.6 ± 30.1	132.9 ± 25.9	0.036	136.8 ± 25.6	133.8 ± 23.2	0.002
DBP [mmHg]	79.9 ± 16.7	78.8 ± 15.6	0.256	82.6 ± 15.3	80.8 ± 13.5	0.001
STD [h]	3.7 (1.4–8.0)	72.0 (39.5-168.0)	< 0.001	3.9 (1.8–8.5)	68.3 (32.5–120.0)	< 0.001
DTB [h]	12.9 (3.6–28.7)	17.4 (4.2-40.3)	0.009	13.3 (3.9–24.2)	16.0 (3.8–24.3)	0.089
Atypical chest pain	168 (22.2%)	126 (34.8%)	< 0.001	244 (9.7%)	140 (15.9%)	< 0.001
Dyspnea	260 (34.4%)	163 (45.0%)	0.001	469 (18.6%)	202 (23.0%)	0.003
ECG on admission:						
Q-wave	89 (11.8%)	67 (18.5%)	0.003	369 (14.7%)	156 (17.7%)	0.034
ST-segment depression	236 (31.2%)	92 (25.4%)	0.049	518 (20.6%)	140 (15.9%)	0.002
T-wave inversion	150 (19.8%)	77 (21.3%)	0.579	485 (19.3%)	223 (25.4%)	< 0.001
Atrial fibrillation	47 (6.2%)	23 (6.4%)	0.930	79 (3.1%)	27 (3.1%)	0.920
Killip class 1I/III	207 (27.4%)	126 (34.8%)	0.012	240 (9.5%)	97 (11.0%)	0.213
First medical contact:						
EMS	118 (15.6%)	15 (4.1%)	< 0.001	285 (11.3%)	31 (3.5%)	< 0.001
Non-PCI center	355 (47.0%)	215 (59.4%)	< 0.001	1299 (51.6%)	505 (57.5%)	0.003
PCI center	283 (37.4%)	132 (36.5%)	0.791	932 (37.0%)	343 (39.0%)	0.312

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Table 1 (cont.). Baseline characteristics.

Variables	CKD, n = 1118			Non-CKD, n = 3395		
	STD < 24 h (n = 756, group A)	STD ≥ 24 h (n = 362, group B)	P	STD < 24 h (n = 2516, group C)	STD ≥ 24 h (n = 879, group D)	P
Hypertension	552 (73.0%)	266 (73.5%)	0.886	1126 (44.8%)	438 (49.8%)	0.010
Diabetes mellitus	361 (47.8%)	199 (55.0%)	0.025	569 (22.6%)	227 (25.8%)	0.058
Dyslipidemia	91 (12.0%)	44 (12.2%)	0.955	322 (12.8%)	97 (11.0%)	0.190
Previous MI	78 (10.3%)	39 (10.8%)	0.835	141 (5.6%)	45 (5.1%)	0.667
Previous PCI	126 (16.7%)	42 (11.6%)	0.032	202 (8.0%)	67 (7.6%)	0.772
Previous CABG	13 (1.7%)	9 (2.5%)	0.369	9 (0.4%)	2 (0.2%)	0.739
Previous HF	22 (2.9%)	14 (3.9%)	0.469	16 (0.6%)	5 (0.6%)	0.827
Previous stroke	71 (9.4%)	40 (11.0%)	0.394	107 (4.3%)	46 (5.2%)	0.257
Current smokers	176 (23.3%)	68 (18.8%)	0.089	1093 (43.4%)	319 (36.3%)	< 0.001
Peak CK-MB [mg/dL]	20.3 (5.7–62.1)	11.3 (5.0-34.5)	< 0.001	31.1 (7.8–100.4)	12.3 (4.3–43.5)	< 0.001
Peak troponin-I [ng/mL]	10.5 (2.1–21.6)	6.5 (2.0-21.6)	0.017	11.3 (2.2–23.1)	4.9 (1.3–21.4)	0.009
Blood glucose [mg/dL]	188.0 ± 101.0	179.2 ± 107.5	0.191	150.8 ± 62.0	140.3 ± 54.3	< 0.001
Serum creatinine [mg/L]	2.13 ± 2.45	2.02 ± 2.17	0.446	0.81 ± 0.18	0.79 ± 0.17	0.005
eGFR [mL/min/1.73 m^2]	37.1 ± 17.7	36.8 ± 17.5	0.779	112.3 ± 51.9	110.6 ± 48.5	0.381
Total cholesterol [mg/dL]	169.9 ± 46.3	172.9 ± 46.2	0.264	184.1 ± 42.5	179.0 ± 42.9	0.002
Triglyceride [mg/L]	130.6 ± 103.3	133.0 ± 99.3	0.710	135.3 ± 120.5	127.6 ± 87.2	0.043
HDL cholesterol [mg/L]	41.7 ± 11.6	40.8 ± 11.7	0.240	43.6 ± 11.0	42.3 ± 10.9	0.001
LDL cholesterol [mg/L]	104.0 ± 35.3	107.6 ± 35.9	0.114	117.3 ± 35.9	114.1 ± 35.5	0.022
GRACE risk score:	157.0 ± 41.4	161.5 ± 38.7	0.076	118.0 ± 34.5	123.2 ± 33.6	< 0.001
> 140	485 (64.2%)	259 (71.5%)	0.015	615 (24.4%)	262 (29.8%)	0.002
Pre-PCI antiplatelet agents:						
ASA	755 (99.9%)	360 (99.4%)	0.246	2,506 (99.6%)	874 (99.4%)	0.555
Clopidogrel	615 (81.3%)	302 (83.4%)	0.454	1,713 (68.1%)	627 (71.3%)	0.075
Ticagrelor	103 (13.6%)	38 (10.5%)	0.150	525 (20.9%)	165 (18.8%)	0.189
Prasugrel	38 (5.0%)	22 (6.1%)	0.480	278 (11.0%)	87 (9.9%)	0.376
Discharge medications:						
ASA	752 (99.5%)	358 (98.9%)	0.282	2,502 (99.4%)	869 (98.9%)	0.099
Clopidogrel	616 (81.5%)	303 (83.7%)	0.404	1,715 (68.2%)	628 (71.4%)	0.075
Ticagrelor	102 (13.5%)	38 (10.5%)	0.177	525 (20.9%)	165 (18.8%)	0.189
Prasugrel	38 (5.0%)	21 (5.8%)	0.571	276 (11.0%)	86 (9.8%)	0.342
BBs	643 (85.1%)	292 (80.7%)	0.070	2,180 (86.6%)	757 (86.1%)	0.688
ACEI or ARBs	618 (81.7%)	285 (78.7%)	0.256	2,114 (84.0%)	735 (83.6%)	0.790
Statin	694 (91.8%)	335 (92.5%)	0.724	2,433 (96.7%)	845 (96.1%)	0.452
Anticoagulant	25 (3.3%)	21 (5.8%)	0.054	34 (1.4%)	16 (1.8%)	0.330
Infarct-related artery:						
Left main	30 (4.0%)	13 (3.6%)	0.869	58 (2.3%)	30 (3.4%)	0.084
LAD	309 (40.9%)	163 (45.0%)	0.196	1,099 (43.7%)	360 (41.0%)	0.166
LCx	176 (23.3%)	70 (19.3%)	0.143	690 (27.4%)	214 (24.3%)	0.076
RCA	241 (31.9%)	116 (32.0%)	0.956	669 (26.6%)	275 (31.3%)	0.009
Treated vessel:						
Left main	41 (5.4%)	19 (5.2%)	0.903	93 (3.7%)	48 (5.5%)	0.030
LAD	432 (57.1%)	238 (65.7%)	0.006	1,440 (57.2%)	494 (56.2%)	0.607
LCx	296 (39.2%)	131 (36.2%)	0.357	967 (38.4%)	338 (38.5%)	0.992
RCA	305 (40.3%)	145 (40.1%)	0.948	899 (35.7%)	363 (41.3%)	0.004

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Table 1 (cont.). Baseline characteristics.

Variables	CKD, n = 1118			Non-CKD, n = 3395		
	STD < 24 h (n = 756, group A)	STD ≥ 24 h (n = 362, group B)	P	STD < 24 h (n = 2516, group C)	STD ≥ 24 h (n = 879, group D)	P
Extent of CAD:						
1-vesssel disease	255 (33.7%)	125 (34.5%)	0.788	1,243 (49.4%)	385 (43.8%)	0.004
2-vessel disease	270 (35.7%)	122 (33.7%)	0.547	822 (32.7%)	308 (35.0%)	0.212
≥ 3-vessel disease	231 (30.6%)	115 (31.8%)	0.679	451 (17.9%)	186 (21.2%)	0.035
ACC/AHA type B2/C lesions	635 (84.0%)	307 (84.8%)	0.792	2,116 (84.1%)	739 (84.1%)	0.984
Pre-PCI TIMI flow grade 0/1	306 (40.5%)	147 (40.6%)	0.967	986 (39.2%)	330 (37.5%)	0.399
GP IIb/IIIa inhibitor	50 (6.6%)	25 (6.9%)	0.898	231 (9.2%)	85 (9.7%)	0.686
Transradial approach	264 (34.9%)	149 (41.2%)	0.047	1,383 (55.0%)	545 (62.0%)	< 0.001
IVUS/OCT	160 (21.2%)	84 (23.2%)	0.440	668 (26.6%)	231 (26.3%)	0.984
FFR	10 (1.3%)	5 (1.4%)	0.937	66 (2.6%)	26 (3.0%)	0.629
Drug-eluting stents*:						
ZES	199 (26.3%)	82 (22.7%)	0.210	619 (24.6%)	190 (21.6%)	0.081
EES	423 (56.0%)	210 (58.0%)	0.520	1283 (51.0%)	448 (51.0%)	0.989
BES	112 (14.8%)	63 (17.4%)	0.291	541 (21.5%)	219 (24.9%)	0.039
Others	22 (2.9%)	7 (1.9%)	0.423	73 (2.9%)	22 (2.5%)	0.635
Stent diameter [mm]	3.05 ± 0.41	3.03 ± 0.40	0.411	3.09 ± 0.42	3.08 ± 0.43	0.619
Stent length [mm]	31.2 ± 14.9	32.9 ± 16.1	0.097	29.0 ± 13.3	29.2 ± 14.5	0.735
Number of stents	1.24 ± 0.48	1.28 ± 0.51	0.159	1.19 ± 0.44	1.19 ± 0.45	0.776

*Drug-eluting stents were composed of ZES (Resolute Integrity stent; Medtronic, Inc., Minneapolis, MN), EES (Xience Prime stent, Abbott Vascular, Santa Clara, CA; or Promus Element stent, Boston Scientific, Natick, MA), and BES (BioMatrix Flex stent, Biosensors International, Morges, Switzerland; or Nobori stent, Terumo Corporation, Tokyo, Japan); Values are means ± standard deviation or median (interquartile range) or numbers and percentages. The p values for continuous data were obtained from the unpaired t-test. The p values for categorical data were obtained from the chi-square or Fisher's exact test; CKD — chronic kidney disease; LVEF — left ventricular ejection fraction; BMI — body mass index; SBP — systolic blood pressure; DBP — diastolic blood pressure; STD — symptom-to-door time; DTB — door-to-balloon time; ECG — electrocardiogram; EMS — emergency medical service; PCI — percutaneous coronary intervention; MI — myocardial infarction; CABG — coronary artery bypass graft; HF — heart failure; CK-MB — creatine kinase myocardial band; eGFR — estimated glomerular filtration rate; HDL — high-density lipoprotein; LDL— low-density lipoprotein; GRACE — Global Registry of Acute Coronary Events; ASA — acetylsalicylic acid; BBs — beta-blockers; ACEIs — angiotensin converting enzyme inhibitors; ARBs — angiotensin receptor blockers; LAD — left anterior descending coronary artery; LCx — left circumflex coronary artery; RCA — right coronary artery; CAD — coronary artery disease; ACC/AHA — American College of Cardiology/American Heart Association; TIMI — Thrombolysis In Myocardial Infarction; GP — glycoprotein; IVUS — intravascular ultrasound; OCT — optical coherence tomography; FFR — fractional flow reserve; ZES — zotarolimus-eluting stent; EES — everolimus-eluting stent; BES — biolimus-eluting stent

lication by KAMIR investigators. An independent event-adjudicating committee in the KAMIR-NIH evaluated all clinical events [16].

Percutaneous coronary intervention procedure and medical treatment

According to general guidelines [17], CAG and PCI were performed via a transfemoral or transradial approach. Acetylsalicylic acid (ASA; 200–300 mg) and clopidogrel (300–600 mg), ticagrelor (180 mg), or prasugrel (60 mg) were prescribed as loading doses before PCI. After PCI, ASA (100 mg/day) was recommended in all patients, along with clopidogrel (75 mg/day), ticagrelor (90 mg twice a day), or prasugrel (5–10 mg/day) for at least 1 year. The access site, revascularization strategy, and DES selection were left to the discretion of the individual operators.

Study definitions and clinical outcomes

Non-STEMI was defined as the absence of persistent ST-segment elevation with increased levels of cardiac biomarkers in the appropriate clinical context [2, 4]. A successful PCI was defined as residual stenosis of < 30% and thrombolysis in MI flow grade 3 in the IRA. The glomerular function for eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation [18]. Based on the definition of the National Kidney Foundation [19], CKD was defined as an eGFR < 60 mL/min/1.73 m^2. The Global Registry of Acute Coronary Events (GRACE) risk score [20] was calculated for all patients. Patients with STD ≥ 24 h were included in the delayed hospitalization group based on the findings of a recent report [10]. The symptom onset time was defined as the

time of onset of the last sustained chest pain [21]. Typical chest pain was defined as substernal chest discomfort of characteristic quality and duration, triggered by exertion or emotional stress and relieved by rest or nitroglycerin [2, 4]. Atypical chest pain was defined as chest pain that was inconsistent with the characteristics of typical chest pain. The primary clinical outcome was the occurrence of major adverse cardiac and cerebrovascular events (MACCE), defined as all-cause death, recurrent MI (re-MI), and any repeat coronary revascularization, including target lesion revascularization (TLR), target vessel revascularization (TVR), non-TVR, and stroke. According to the American Heart Association/American Stroke Association guidelines, an acute cerebrovascular event resulting in death or neurological deficit for > 24 h or the presence of acute infarction demonstrated by brain imaging studies was defined as a stroke [22]. All-cause death was considered cardiac death (CD) unless an undisputed non-cardiac cause was present [23]. The secondary clinical outcome was definite or probable stent thrombosis (ST) during the 3-year follow-up period. ST was defined according to the definition provided by the Academic Research Consortium [24]. The definitions of re-MI, TLR, TVR, and non-TVR have been previously published [25].

Statistical analyses

For continuous variables, intergroup differences were evaluated using the unpaired t-test, and data are expressed as mean ± standard deviation or median (interquartile range). For categorical variables, intergroup differences were analyzed using the chi-squared test or, if not applicable, Fisher's exact test, and data are expressed as counts and percentages. Univariate analysis was performed for all variables in the groups with or without delayed hospitalization, with the p value set at < 0.05. Subsequently, a multicollinearity test [26] was performed between the included variables to confirm non-collinearity between them. The variance inflation factor values were calculated to measure the degree of multicollinearity among the variables. A variance inflation factor > 5 indicates high correlation [27]. Multicollinearity was considered when the tolerance value was < 0.1 [28] or the condition index was > 10 [27]. The variables included in the multivariable analysis were male sex, age, left ventricular ejection fraction (LVEF), body mass index, systolic blood pressure, diastolic blood pressure, DTB, atypical chest pain, dyspnea, Q-wave on electrocardiogram (ECG), ST-segment depression, T-wave inversion, Killip class II/III, use of emergency medical service, non-PCI center, hypertension, diabetes mellitus (DM), dyslipidemia, previous MI, previous PCI, previous CABG, previous heart failure, previous stroke, current smoker, levels of peak creatine kinase myocardial band (CK-MB), peak troponin-I, blood glucose, high-sensitivity C-reactive protein (hs-CRP), total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and beta-blockers. Moreover, to adjust for potential confounders, a propensity score (PS)-adjusted analysis was performed using a logistic regression model. We tested all potentially relevant variables, including baseline clinical, angiographic, and procedural factors (Table 1). The c-statistic for the PS-matched analysis in this study was 0.704. Patients in the delayed hospitalization group (STD ≥ 24 h) were matched to those in the non-delayed hospitalization group (STD < 24 h) (1:1) using the nearest available pair-matching method according to PSs. The subjects were matched using a caliper width of 0.01. This procedure yielded 2274 well-matched pairs (**Suppl. Table S1**). Various clinical outcomes were estimated using Kaplan-Meier curve analysis, and group differences were compared using the log-rank test. Statistical significance was defined as a 2-tailed p value of < 0.05. All statistical analyses were performed using the SPSS software version 20 (IBM, Armonk, NY, USA).

Results

Baseline characteristics

Baseline characteristics of the study population are summarized in Table 1. In both the CKD and non-CKD groups, the mean values of peak CK-MB and peak troponin-I were higher in the STD < 24 h group, and the mean age, mean value of hs-CRP, number of patients with high GRACE risk score (> 140), and number of patients who received the transradial approach for PCI were higher in the STD ≥ 24 h group. Additionally, in both the CKD and non-CKD groups, the number of patients with atypical chest pain, dyspnea, Q-wave on ECG, and first medical contact outside of a PCI-capable center were significantly higher in the STD ≥ 24 h group than in the STD < 24 h group.

Clinical outcomes

The rates of major clinical outcomes at 3 years are listed in Tables 2, 3, and Figure 2. Multivariable-adjusted analysis revealed that in patients with CKD, MACCE (adjusted hazard ratio [aHR]:

Table 2. Clinical outcomes of the STD < 24 hours and STD ≥ 24 hours groups in patients with CKD or non-CKD at 3 years.

Outcomes	CKD, n = 1118			Unadjusted		Multivariable-adjusted*		Propensity score-adjusted	
	STD < 24 h (n = 756, group A)	STD ≥ 24 h (n = 362, group B)	Log-rank	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
MACCE	158 (20.9)	72 (19.9)	0.656	1.065 (0.806–1.408)	0.656	1.131 (0.844–1.516)	0.409	1.555 (0.871–1.614)	0.400
All–cause death	76 (10.2)	40 (11.0)	0.637	0.912 (0.622–1.337)	0.637	1.063 (0.710–1.591)	0.768	1.005 (0.627–1.542)	0.983
Cardiac death	43 (5.7)	29 (8.0)	0.155	0.712 (0.444–1.140)	0.157	1.007 (0.610–1.661)	0.979	1.097 (0.614–1.959)	0.755
Non-cardiac death	33 (4.5)	11 (3.0)	0.292	1.440 (0.728–2.849)	0.295	1.272 (0.621–2.609)	0.511	1.184 (0.522–2.583)	0.686
Recurrent MI	34 (4.7)	16 (4.6)	0.952	1.019 (0.562–1.845)	0.952	1.192 (0.636–2.235)	0.584	1.085 (0.530–2.220)	0.823
Any repeat revascularization	83 (11.6)	32 (9.2)	0.271	1.257 (0.836–1.890)	0.272	1.209 (0.788–1.857)	0.385	1.311 (0.819–2.098)	0.259
Stroke	19 (2.6)	16 (4.6)	0.086	0.563 (0.289–1.094)	0.090	1.469 (0.735–2.938)	0.276	1.499 (0.760–3.302)	0.316
ST (definite or probable)	6 (0.8)	2 (0.6)	0.652	1.442 (0.291–7.146)	0.654	1.604 (0.301–8.457)	0.622	1.631 (0.321–9.761)	0.592
Outcomes	**Non-CKD, n = 3395**			**Unadjusted**		**Multivariable-adjusted***		**Propensity score-adjusted**	
	STD < 24 h (n = 2516, group C)	STD ≥ 24 h (n = 879, group D)	Log-rank	HR (95% CI)	P	HR (95% CI)	p	HR (95% CI)	P
MACCE	280 (11.1)	93 (10.6)	0.622	1.061 (0.839–1.341)	0.622	1.139 (0.894–1.450)	0.292	1.217 (0.920–1.610)	0.170
All-cause death	60 (2.4)	27 (3.1)	0.267	0.774 (0.491–1.219)	0.268	1.096 (0.682–1.962)	0.704	1.056 (0.606–1.839)	0.847
Cardiac death	27 (1.1)	14 (1.6)	0.224	0.672 (0.352–1.281)	0.227	1.253 (0.624–2.518)	0.526	1.026 (0.461–2.285)	0.949
Non-cardiac death	33 (1.3)	13 (1.5)	0.705	0.884 (0.465–1.679)	0.705	1.049 (0.501–2.235)	0.887	1.138 (0.526–2.460)	0.743
Recurrent MI	67 (2.7)	22 (2.5)	0.798	1.065 (0.658–1.724)	0.798	1.275 (0.775–2.098)	0.339	1.713 (0.974–3.012)	0.062
Any repeat revascularization	215 (8.6)	64 (7.4)	0.238	1.183 (0.895–1.563)	0.239	1.249 (0.937–1.665)	0.130	1.242 (0.892–1.630)	0.199
Stroke	36 (1.4)	22 (2.5)	0.033	0.566 (0.333–0.963)	0.036	1.619 (0.934–2.805)	0.086	1.502 (0.887–2.663)	0.104
ST (definite or probable)	11 (0.4)	6 (0.7)	0.373	0.638 (0.236–1.726)	0.377	1.265 (0.437–5.123)	0.665	1.231 (0.376–4.032)	0.732

*Adjusted by male sex, age, LVEF, BMI, SBP, DBP, DTB, atypical chest pain, dyspnea, Q-wave in electrocardiogram, ST-segment depression, T wave inversion, Killip class II/III, emergency medical service, non-PCI center, hypertension, diabetes mellitus, dyslipidemia, previous MI, previous PCI, previous CABG, previous heart failure, previous stroke, current smoker, peak CK-MB, peak troponin-I, blood glucose, total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol, and beta-blocker; CKD — chronic kidney disease; STD — symptom-to-door time; HR — hazard ratio; CI — confidence interval; MACCE — major adverse cardiac and cerebrovascular events; MI — myocardial infarction; ST — stent thrombosis, LVEF — left ventricular ejection fraction; BMI — body mass index; SBP — systolic blood pressure; DBP — diastolic blood pressure; DTB — door-to-balloon time; MI — myocardial infarction; PCI — percutaneous coronary intervention; CABG — coronary artery bypass graft; CK-MB — creatine kinase myocardial band; HDL — high-density lipoprotein; LDL — low-density lipoprotein

Table 3. Clinical outcomes of the CKD and non-CKD groups in both STD < 24 hours and STD ≥ 24 hours groups at 3 years.

Outcomes	STD < 24 h (n = 3272)			Unadjusted		Multivariable-adjusted*		Propensity score-adjusted#	
	CKD (n = 756, group A)	Non-CKD (n = 2516, group C)	Log-rank	HR (95% CI)	P	HR (95% CI)	p	HR (95% CI)	P
MACCE	158 (20.9)	280 (11.1)	< 0.001	2.001 (1.647–2.432)	< 0.001	1.681 (1.361–2.076)	< 0.001	1.856 (1.374–2.505)	< 0.001
All-cause death	76 (10.2)	60 (2.4)	< 0.001	4.399 (3.136–6.171)	< 0.001	3.327 (2.097–4.816)	< 0.001	3.603 (2.155–6.025)	< 0.001
Cardiac death	43 (5.7)	27 (1.1)	< 0.001	5.507 (3.403–8.911)	< 0.001	3.797 (2.241–6.434)	< 0.001	4.942 (2.431–7.845)	< 0.001
Non-cardiac death	33 (4.5)	33 (1.3)	< 0.001	3.489 (2.153–5.652)	< 0.001	2.918 (1.731–5.214)	< 0.001	2.450 (1.133–5.097)	0.023
Recurrent MI	34 (4.7)	67 (2.7)	0.006	1.775 (1.175–2.682)	0.006	1.246 (0.595–2.014)	0.502	1.288 (0.699–2.371)	0.417
Any repeat revascularization	83 (11.6)	215 (8.6)	0.014	1.370 (1.063–1.765)	0.015	1.234 (0.584–1.530)	0.114	1.348 (0.949–1.658)	0.090
Stroke	19 (2.6)	36 (1.4)	0.030	1.833 (1.052–3.196)	0.033	1.343 (0.741–2.434)	0.331	1.484 (1.036–2.584)	0.294
ST (definite or probable)	6 (0.8)	11 (0.4)	0.204	1.884 (0.697–5.095)	0.212	1.587 (0.546–4.614)	0.396	1.698 (0.406–4.743)	0.468
Outcomes	**STD ≥ 24 h (n = 1241)**			**Unadjusted**		**Multivariable-adjusted***		**Propensity score-adjusted#**	
	CKD (n = 362, group B)	Non-CKD (n = 879, group D)	Log-rank	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
MACCE	72 (19.9)	93 (10.6)	< 0.001	1.994 (1.466–2.713)	< 0.001	1.751 (1.225–2.483)	0.006	1.938 (1.232–3.047)	0.004
All-cause death	40 (11.0)	27 (3.1)	< 0.001	3.748 (2.300–6.107)	< 0.001	2.162 (1.234–3.692)	0.011	2.531 (1.255–5.102)	0.009
Cardiac death	29 (8.0)	14 (1.6)	< 0.001	5.222 (2.759–9.883)	< 0.001	2.506 (1.254–5.009)	0.009	4.882 (1.661–8.235)	0.004
Non-cardiac death	11 (3.0)	13 (1.5)	0.055	2.154 (0.965–4.808)	0.061	1.714 (0.707–4.155)	0.233	1.184 (0.429–3.265)	0.744
Recurrent MI	16 (4.6)	22 (2.5)	0.056	1.854 (0.974–3.530)	0.060	1.704 (0.828–3.506)	0.147	1.433 (0.576–3.462)	0.439
Any repeat revascularization	32 (9.2)	64 (7.4)	0.247	1.284 (0.840–1.963)	0.248	1.679 (0.776–3.441)	0.142	1.588 (0.674–2.990)	0.152
Stroke	16 (4.6)	22 (2.5)	0.056	1.855 (0.974–3.532)	0.060	1.481 (0.728–3.013)	0.278	1.070 (0.455–2.521)	0.876
ST (definite or probable)	2 (0.6)	6 (0.7)	0.835	0.844 (0.170–4.181)	0.835	1.362 (0.104–4.346)	0.721	1.937 (0.176–5.374)	0.589

*Adjusted by male sex, age, LVEF, BMI, DBP, DTB, atypical chest pain, dyspnea, ST-segment depression, atrial fibrillation, Killip class II/III, emergency medical service, non-PCI center, hypertension, diabetes mellitus, previous MI, previous PCI, previous CABG, previous heart failure, previous stroke, current smoker, peak CK-MB, blood glucose, total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol, beta-blocker, and statin. #Propensity score-adjusted analysis was performed using a logistic regression model. We tested all potentially relevant variables such as baseline clinical, angiographic, and procedural factors (Table 1). The c-statistic for the propensity score-matched analysis in this study was 0.715. Patients in the CKD were matched to those in the non-CKD group (1:1) using the nearest available pair-matching method according to propensity scores. The subjects were matched with a caliper width of 0.01. This procedure yielded 1624 well-matched pairs; STD — symptom-to-door time; CKD — chronic kidney disease; HR — hazard ratio; CI — confidence interval; MACCE — major adverse cardiac and cerebrovascular events; MI — myocardial infarction; ST — stent thrombosis, LVEF — left ventricular ejection fraction; BMI — body mass index; SBP — systolic blood pressure; DBP — diastolic blood pressure; DTB — door-to-balloon time; MI — myocardial infarction; PCI — percutaneous coronary intervention; CABG — coronary artery bypass graft; CK-MB — creatine kinase myocardial band; HDL — high-density lipoprotein; LDL — low-density lipoprotein

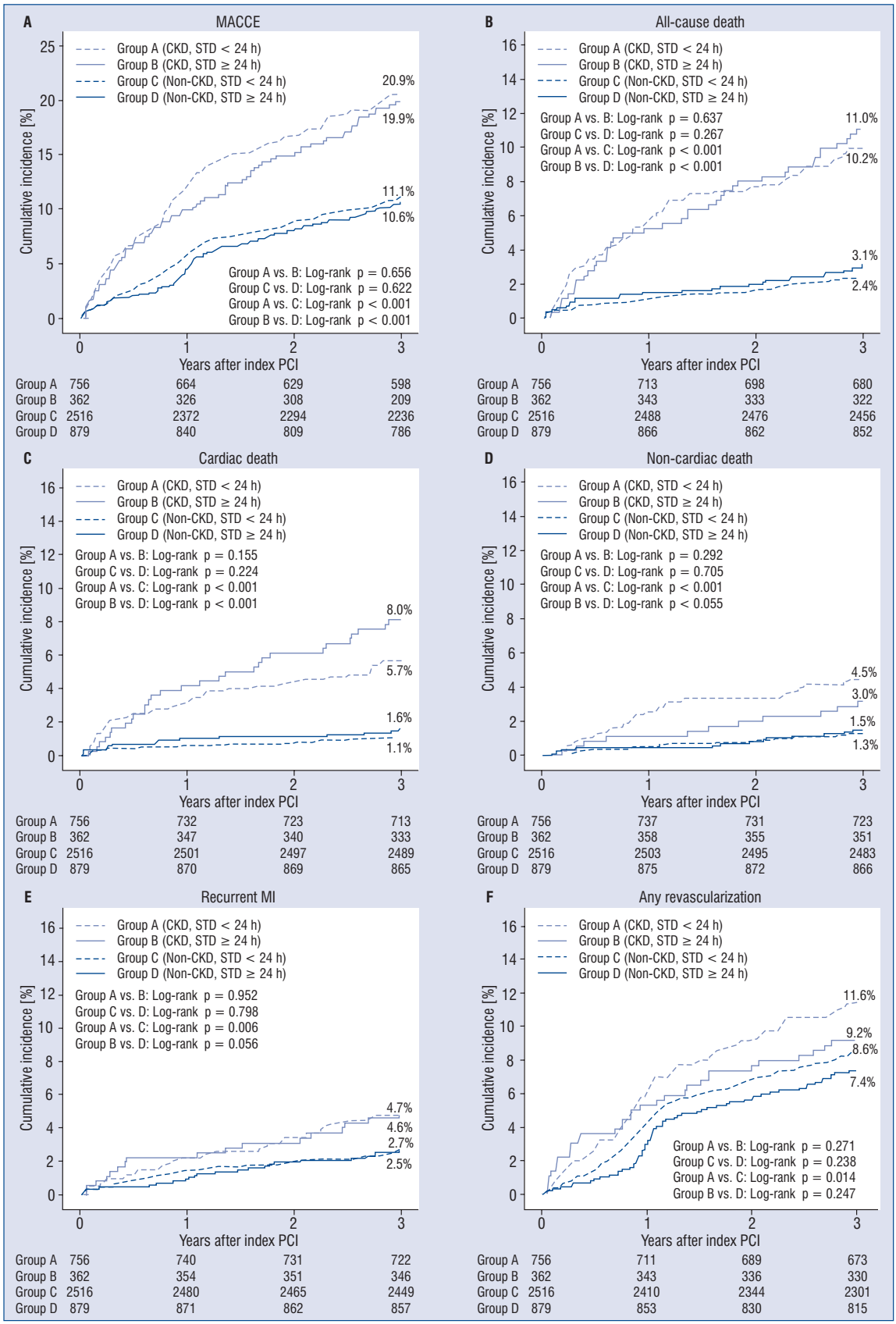

Figure 2. Kaplan-Meier curved analysis for major adverse cardiac and cerebrovascular events (MACCE) (**A**), all-cause death (**B**), cardiac death (**C**), non-cardiac death (**D**), recurrent myocardial infarction (MI) (**E**), any repeat revascularization (**F**), stroke (**G**), and stent thrombosis (**H**); CKD — chronic kidney disease; STD — symptom-to-door time; PCI — percutaneous coronary intervention.

1.131; 95% CI: 0.844–1.516; p = 0.409), all-cause death (aHR: 1.063; p = 0.768), CD (aHR: 1.007; p = 0.979), non-CD (NCD; aHR: 1.272; p = 0.511), re-MI (aHR: 1.192; p = 0.584), any repeat revascularization (aHR: 1.209; p = 0.385), stroke (aHR: 1.469; p = 0.276), and ST (aHR: 1.604; p = 0.622) rates were not significantly different between the STD < 24 h and STD ≥ 24 h groups. Furthermore, in patients without CKD, the MACCE (aHR: 1.139; 95% CI: 0.894–1.450; p = 0.292), all-cause death (aHR: 1.096; p = 0.704), CD (aHR: 1.253; p = = 0.526), NCD (aHR: 1.049; p = 0.887), re-MI (aHR: 1.275; p = 0.339), any repeat revascularization (aHR: 1.249; p = 0.130), stroke (aHR: 1.619; p = 0.086), and ST (aHR: 1.265; p = 0.665) rates were not significantly different between the STD < 24 h and STD ≥ 24 h groups. These results were confirmed by the PS-adjusted analysis, which showed that the primary and secondary clinical outcomes were not significantly different between the STD < 24 h and STD ≥ 24 h groups in both CKD and non-CKD groups (Table 2). Table 3 shows the comparison of clinical outcomes between patients with and without CKD in both the STD < 24 h and STD ≥ 24 h groups. Multivariable-adjusted analysis revealed that in both STD < 24 h and STD ≥ 24 h groups, MACCE (aHR: 1.681; p < 0.001 and aHR: 1.751; p = 0.006, respectively), all-cause death (aHR: 3.327; p < 0.001 and aHR: 2.162; p = 0.011, respectively), and CD (aHR: 3.797; p < 0.001 and aHR: 2.506; p = 0.009, respectively) rates were significantly higher in the CKD group than in the non-CKD group. Moreover, in the STD < 24 h group, the NCD rate (aHR: 2.918; p < 0.001) was significantly higher in the CKD group than in the non-CKD group. **Supplementary Figure S1** shows the subgroup analysis for MACCE in the CKD and non-CKD groups using a Cox logistic regression model. The results revealed that patients in all subgroups except for those showing significant p-for-interaction demonstrated comparable MACCE rates between the STD < 24 h and STD ≥ 24 h groups. **Supplementary Table S2** shows the independent predictors of MACCE. Reduced LVEF (< 50%) and multivessel disease were common independent predictors of MACCE in both CKD and non-CKD groups. Although STD and DBT were not significant independent predictors of MACCE, CKD (aHR: 1.404; 95% CI: 1.161–1.696; p < 0.001) was a significant predictor of MACCE in the total study population. Furthermore, in the total study population, CKD was significant independent predictor of all-cause death (aHR: 2.106; 95% CI: 1.537–2.886; p < 0.001), CD (aHR: 2.646; 95% CI: 1.713–4.085; p < 0.001), and NCD (aHR: 1.595; 95% CI: 1.002–2.539; p = 0.047; **Suppl. Table S2**).

Discussion

The main findings of this study are as follows: (1) MACCE, all-cause death, CD, NCD, re-MI, any repeat revascularization, stroke, and ST rates were not significantly different between the STD < 24 h and STD ≥ 24 h groups in multivariable--adjusted and PS-adjusted analyses in both the CKD and non-CKD groups; (2) Regardless of analyzed STD, MACCE, all-cause death, and CD rates were significantly higher in the CKD group than in the non-CKD group in multivariable-adjusted and PS-adjusted analyses; furthermore, the NCD rate was higher in the CKD group than in the non-CKD group in patients with STD < 24 h; (3) In the total study population, although STD and DTB were not significant independent predictors of MACCE and mortality, the presence of CKD was a significant independent predictor of MACCE and mortality.

Pre-hospital delay is the total amount of time taken by patients to present to the emergency department following acute symptom onset [29]. Previous research [29, 30] demonstrated that delayed hospitalization in patients with acute coronary syndrome (ACS) was associated with atypical symptoms and decreased ambulance use. In this study, in both CKD and non-CKD groups, the number of patients who presented atypical chest pain (CKD group: 34.8% vs. 22.2%, p < 0.001; non-CKD group: 15.9% vs. 9.7%, p < 0.001) was significantly higher in the STD ≥ 24 h group than in the STD < 24 h group (Table 1). Furthermore, the number of patients who used emergency medical service was significantly lower in the STD ≥ 24 h groups than in the STD < 24 h groups (CKD group: 4.1% vs. 15.6%, p < 0.001; non-CKD group: 3.5% vs. 11.3%, p < 0.001). Moreover, atypical chest pain was a significant independent predictor of MACCE in the CKD group (aHR: 1.508; 95% CI: 1.129–2.015; p = 0.005) and in the total study population (aHR: 1.322; 95% CI: 1.075–1.626; p = 0.008) (**Suppl. Table S2**), and a significant independent predictor of all-cause death (aHR: 1.779; p < 0.001) and NCD (aHR: 2.248; p = 0.001) (**Suppl. Table S2**).

According to a recent report [10], patients with NSTEMI and STD ≥ 24 h had higher long-term all--cause mortality (17.0% vs. 10.5%; p < 0.001) than those with STD < 24 h. These data are valuable in showing the clinical importance of pre-hospital

delay in patients with NSTEMI. However, approximately 15% of this study population did not receive PCI or had unsuccessful PCI; furthermore, patients who received BMS or 1G-DES and those who experienced cardiogenic shock or in-hospital death were included. To date, second-generation DES is the preferred revascularization option because it can reduce restenosis and mortality rates compared to 1G-DES during long-term follow-up [31]. However, because long-term outcomes can be affected by the occurrence of in-hospital death [32], individuals who experienced in-hospital death or cardiogenic shock should not be included in the analysis during the estimation of long-term mortality. In these aspects, their research [10] has limitations in reflecting the current real-world practice and in showing long-term prognosis of patients with NSTEMI. To overcome these limitations, we excluded patients with in-hospital death or cardiogenic shock, as shown in Figure 1.

The current European guideline suggest [15] that the target DTB should be decreased to < 60 min to achieve the lowest mortality in patients with STEMI. However, DTB was not an independent predictor of MACCE and mortality in patients with NSTEMI in our study (**Suppl. Table S2**), which is consistent with previous studies [10, 33–35]. In a meta-analysis of randomized controlled trials including 5324 patients with NSTEMI [33], reduced DTB did not reduce mortality. Bonello et al. [34] also showed that the rate of mortality and MI was not affected by the median time between randomization and CAG (range: 0.5–14.0 h and 18.3–86.0 h). In the subgroup analysis of the most recent meta-analysis including 3422 patients from 11 randomized trials [36], the all-cause death rate was lower in the revascularization group than in the medical therapy group in patients with NSTE-ACS and CKD (relative risk: 0.73; 95% CI: 0.51–1.04; p = 0.08). Because patients presenting with NSTEMI often have many comorbidities, including CKD [11, 12], an early invasive strategy may worsen the outcomes in those patients, becuase the renal function can be further reduced due to contrast dye administration and sub-optimal fluid support prior to the procedure. In a recent publication [35], consistent with previous reports [33, 34], the 2-year major clinical outcomes were similar between the early invasive and delayed invasive groups in patients with NSTEMI (n = 8241) in the four different renal function groups. Kim et al. [37] also suggested that culprit-only PCI may be a better reperfusion option for patients with NSTEMI with multivessel disease and CKD rather than multivessel PCI, including complete revascularization and incomplete revascularization, with regard to the procedure time and the risk of contrast-induced nephropathy. In our study, as shown in **Supplementary Table S2**, STD (< 24 h vs. ≥ 24 h) was not an independent predictor of MACCE, all-cause death, CD, and non-CD in both the CKD and non-CKD groups. However, the presence of CKD was an independent predictor of all-cause death (aHR: 2.106; p < 0.001), CD (aHR: 2.646; p < 0.001), and non-CD (aHR: 1.595; p = 0.047) compared to the non-CKD group. Additionally, in the total study population, CKD was an independent predictor of MACCE (aHR: 1.404; p < 0.001). Therefore, our results suggest that CKD may be a stronger determinant of worse outcomes in NSTEMI patients compared to SDT (< 24 h vs. ≥ 24 h). In patients presenting STEMI, the relative mortality was found to increase by 7.5% for every 30-min delay in reperfusion [38], and pre-hospital activation and direct cardiac catheterization laboratory transfer were related to lower 1-year mortality (adjusted odds ratio: 5.3; 95% CI: 2.2–12.4; p < 0.001) [39].

Although we could not precisely determine the causative factors for our results, several factors can be considered. First, patients with STEMI often have complete occlusion of the coronary artery, while patients with NSTEMI more often have partial or incomplete occlusion [40]. In the case of completely absent blood supply, available oxygen in the ischemic zone of the myocardium disappears within seconds, and after a certain duration of complete ischemia there is no treatment modality that can salvage ischemic myocardium [41]. A necrotic cardiomyocyte cannot be brought back to life [42]. In contrast, cardiomyocytes exposed to low residual oxygen levels may be able to maintain sufficient adenosine triphosphate levels to survive for an extended period, even if the amount of adenosine triphosphate is insufficient to allow their contraction [42]. Hence, the impact of delayed hospitalization on major clinical outcomes in the NSTEMI group may be lower than that in the STEMI group. However, in our study, the number of patients with pre-PCI Thrombolysis in Myocardial Infarction flow grade 0/1 was not significantly different between the STD ≥ 24 h and STD < 24 h groups (Table 1, **Suppl. Table S1**) or between the CKD and non-CKD groups. Second, in our study, patients with CKD had lower LVEF and higher incidence of Killip class II/III, hypertension, DM, previous MI, PCI, CABG, heart failure, and stroke, left main as IRA, 3-vessel disease, and higher mean age,

hs-CRP level, and GRACE risk scores than those with non-CKD in both the STD < 24 h and STD ≥ 24 h groups and in the total study population. Hence, these worse baseline characteristics in the CKD group may be related to worse 3-year clinical outcomes in patients with CKD, as shown in Table 3. Additionally, the number of patients presenting with atypical chest pain and dyspnea was higher in patients with CKD than in patients without CKD. Atypical chest pain was a significant independent predictor of MACCE in the CKD group and in the total study population (**Suppl. Table S2**) and a significant independent predictor for all-cause death and NCD (**Suppl. Table S2**) in our study.

Despite the limited availability of data on patients with NSTEMI and CKD [14], the number of patients with CKD has increased over the past decade and is expected to increase owing to decreased mortality and increased incidence of DM and obesity [41]. As the GFR declines, the risk of coronary artery disease and vascular calcification increases [11]. Moreover, calcification of the intima and media of the large vessels in CKD is associated with all-cause death and cardiovascular mortality [43]. Consistent with previous reports [13, 44], CKD was an independent predictor of all-cause and cardiovascular mortality in our study. Therefore, although STD could be considered an important predictor of long-term outcomes in patients with STEMI [38, 39], the obtained results underline the important effects of CKD on the long-term clinical outcomes in patients with NSTEMI. Although the population size may have been insufficient in our study, the used registry based on 20 tertiary high-volume university hospitals may provide meaningful results.

Limitations of the study

This study has some limitations. First, although the main predictors of prehospital delay include sociodemographic, clinical, situational, appraisal, and behavioral factors [29], this study may have induced some bias regarding educational level, marital status, employment status, and any other important factors that were not assessed because the used registry did not include these variables. Second, there may have been some underreported and/or missing data. Third, because the estimation of renal function was based on a single eGFR measurement at the time of presentation to the hospital, eGFR may have changed during the follow-up period. However, the follow-up results for eGFR were incomplete. This is an important source of bias in this study. Fourth, because of the limitations of the medical insurance system in Korea, the use of fractional flow reserve to estimate intermediate lesions was very low in this study (Table 1). Fifth, the 3-year follow-up period in this study was relatively short for estimating the long-term clinical outcomes.

Conclusions

In conclusion, in the era of new-generation DES, the presence of CKD appears to be a much more important determinant of MACCE and mortality rates than STD in patients with NSTEMI. ST is one of the most concerning events after DES implantation, given its grim prognosis. However, ST rates were similar between the CKD and non-CKD groups and between the STD < 24 h and STD ≥ 24 h groups in our study. Further well-designed large-scale studies are warranted to confirm these results.

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Application of homocysteine as a non-invasive and effort-free measurements for risk assessment of patients with pulmonary hypertension

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Abstract

Background: *Current guideline-recommended multiparameters used to assess the risk levels of pulmonary arterial hypertension (PAH) are invasive hemodynamic measurements or effort-dependent exercise tests. Serum natriuretic peptide is only one kind of effort-free biomarker that has been adopted for risk assessment. This study aimed to investigate the application of homocysteine as a non-invasive and effort-free measurement for the risk assessment of patients with PAH.*

Methods: *Samples of 50 patients diagnosed with PAH via right heart catheterization were obtained, and the patients were divided into low-, intermediate- and high-risk groups for further analysis. Additionally, serum N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) and homocysteine levels of monocrotaline (MCT)-induced PAH rats were analyzed at each week with progressed severity of PAH, and they were sacrificed on day 28 with pathology being assessed.*

Results: *Hyperhomocysteinemia was an independent predictor (odds ratio [OR]: 1.256; 95% confidence interval [CI]: 1.002–1.574) and showed a linear correlation with NT-proBNP. Hyperhomocysteinemia could discriminate between low/intermediate and high-risk levels in PAH with a cut-off value in 12 μmol/L. Moreover, the elevated homocysteine levels by weeks in MCT rats also demonstrated the association between homocysteine and the severity of PAH.*

Conclusions: *Homocysteine can be a non-invasive and effort-free risk assessment for patients with pulmonary hypertension. Homocysteine level had a linear correlation with NT-proBNP level, and patients with hyperhomocysteinemia had a higher risk level, higher NT-proBNP level, and decreased lower diffusing capacity for carbon monoxide. The correlation between homocysteine level and PAH severity was also demonstrated in MCT rats.* (Cardiol J 2024; 31, 2: 285–299)

Keywords: biomarker, homocysteine, pulmonary hypertension, risk assessment

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Introduction

Pulmonary arterial hypertension (PAH) is defined as mean pulmonary arterial pressure (mPAP) > 20 mmHg at rest as assessed by right heart catheterization, pulmonary arterial wedge pressure ≤ 15 mmHg, and pulmonary vascular resistance > 2 wood units, according to the classification of 2022 European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines [1]. Pathologic progressions of vascular remodeling leads to pulmonary hypertension, right-sided heart failure, and death, once compensatory mechanisms have failed [2–4].

Most of the ESC/ERS recommended multiparameters for risk assessment and outcome prediction are invasive hemodynamic measurements or effort-dependent exercise tests except serum natriuretic peptide, B-type natriuretic peptide (BNP), or N-terminal prohormone of B-type natriuretic peptide (NT-proBNP), which is only one type of effort-free biomarker that has been adopted for risk assessment [5]. However, any kind of effort-dependent exercise tests are limited by a patient's physical restriction or exercise disability, an alternative or additional biomarker could provide more information of outcomes if invasive or effort-dependent tests are not accessible or available.

There are many circulating biomarkers involved in functional pathways associated with the pathobiology of pulmonary hypertension. Homocysteine is one of these circulating biomarkers, which involved several pathological functional pathways of PAH, and was considered to be correlated with diagnosis and prognosis of PAH [6, 7]. Elevated homocysteine levels have been toxic to the vascular endothelium and is an attribute for coronary disease, cerebrovascular disease, and peripheral vascular disease [8, 9]. However, the relationship between homocysteine and pulmonary hypertension remains unclear. This study aimed to investigate the application of homocysteine as an alternative or additional non-invasive and effort-free measurement in addition to serum natriuretic peptide for risk assessment of patients with pulmonary hypertension.

Methods

Samples in this study were obtained from the Kaohsiung Veterans General Hospital Biobank with approval from the respective ethics committees of Kaohsiung Veterans General Hospital. Deidentified data of patients diagnosed with pulmonary hypertension were analyzed to establish the association between circulating biomarkers and the risk levels of pulmonary hypertension. Pulmonary hypertension was defined as a mPAP ≥ 20 mmHg at rest, as assessed by right heart catheterization according to 2022 ESC/ERS guidelines [1].

Animal model

A monocrotaline (MCT)-induced PAH rat model was used in this study, and the Institutional Animal Care and Use Committee of Kaohsiung Veterans General Hospital approved the experimental protocols. Six-week-old male Sprague-Dawley rats in 220–280 g, were purchased from BioLASCO (Ilan, Taiwan) and handled according to the IACUC guidelines. To establish the MCT-induced PAH model, Sprague-Dawley rats were injected intraperitoneally with 60 mg/kg MCT (Sigma-Aldrich, St. Louis, MO, USA) as previously described [10, 11]. At the 1st, 2nd, 3rd, and 4th weeks, rat venous blood was drawn for analysis. On day 28, the animals were sacrificed, and PAH pathology was assessed as described previously [12]. All experimental protocols were performed in accordance with the European ethical regulation (Directive 2010/63/EU) and approved by the Institutional Animal Care and Use Committee, Kaohsiung Veterans General Hospital, Taiwan (Ref. 2019-2021-A054).

Serum NT-proBNP and homocysteine level of MCT rats

Rats were treated with phosphate-buffered saline or MCT (60 mg/kg) for 7, 14, 21, and 28 days. Blood samples were collected from the tail vein of the rats. Serum NT-proBNP and homocysteine concentrations were measured using ELISA kits (MBS2881463, MyBioSource, Inc., San Diego, CA, USA for NT-proBNP; MBS703069, MyBioSource, Inc., San Diego, CA, USA for homocysteine) according to the manufacturer's instructions.

Information about hemodynamic measurements of MCT rats, histology and immunohistochemical analysis of pulmonary arteries, blood tests assay for human, multiplex immunoassay of human blood, hemodynamics and cardiopulmonary function tests of human, and risk level assessment are presented in the **Supplementary Appendix**.

Ethics statement

The Institutional Review Board (IRB) of Kaohsiung Veterans General Hospital approved this study (No. KSVGH21-CT9-04). Written informed

consent was not required for this study as the Biobank research database consisted of de-identified secondary data for research purposes. The IRB of Kaohsiung Veterans General Hospital issued a formal written waiver of the requirement for informed consent.

Statistical analyses

SPSS version 22 (IBM Corp., Armonk, NY, USA) was used for data analysis. Percentile values were used to express categorical data and were analyzed using the chi-square test. Mean (μ) and standard deviation (SD) values were used for continuous variables using the Student unpaired test. Multiplex immunoassay biomarkers were analyzed by one-way analysis of variance (ANOVA) with Bonferroni correction, and statistical significance was defined as $p < 0.05$ after verifying the equality of variances.

Univariate and multivariate forward stepwise logistic regression analyses were performed to assess predictors for the high-risk group, and the odds ratios (OR) and the associated 95% confidence intervals (CI) for significant variables were calculated, and statistically significant predictor was set at $p < 0.05$. Correlation analysis was performed to assess the correlation between the biomarkers and NT-proBNP levels. To compare NT-proBNP and homocysteine levels with increasing severity of pulmonary hypertension by weeks following MCT infusion, ANOVA with post-hoc Fisher's least significant difference test was adopted after verifying the equality of variances. In addition, statistical significance was set at $p < 0.05$.

To find the most appropriate cut-off value for selective biomarker to determine the risk level for pulmonary hypertension, a receiver operating characteristic (ROC) analysis was performed. Moreover, different biomarkers combinations and the comparison between respective predictive value of each model were illustrated. The areas under the curves (AUC) were calculated.

Results

The basic characteristics of patients with pulmonary hypertension based on the ESC/ERS guideline-recommended risk assessment are reported in Table 1 [13]. There were 3 patients in low-risk group, 24 intermediate-risk patient, and 23 patients in high-risk group. There were no disparities in sex and age between the low/intermediate-risk and high-risk groups. Biochemistry panel demonstrated worse renal function blood urea nitrogen = 15.0 ± 4.5 vs. 24.0 ± ± 13.7 mg/dL, p = 0.006; serum creatinine = 0.9 ± ± 0.2 vs. 1.2 ± 0.5 mg/dL, p = 0.030) in high-risk group. With regard to circulating biomarkers, higher homocysteine (10.6 ± 4.0 vs. 17.0 ± 7.0 μmol/L, p = 0.005, Fig. 1A), uric acid (UA; 6.0 ± ± 1.7 vs. 7.7 ± 2.5 mg/dL, p = 0.006, Fig. 1B), D-dimer (744.8 ± 579.1 vs. 1,525.5 ± 1,559.7 ng/mL, p = 0.040, Fig. 1C), and C-reactive protein (CRP; 0.7 ± 0.7 vs. 2.6 ± 2.7 mg/dL, p = 0.007, Fig. 1D) were observed in the high-risk group. Despite no significant differences of multiplex immunoassay circulating biomarkers, including angiopoietin-2, bone morphogenetic protein (BMP)-2, BMP-4, cluster of differentiation 40 (CD40), endoglin, interlukin-6, myeloperoxidase, osteopontin, and vascular endothelial growth factor (VEGF), there was an increased trend by disease severities. Furthermore, Bonferroni correction was applied for analysis of multiplex immunoassay biomarkers (**Suppl. Table S1**), and the insignificance could be attributed to the small sample size.

Hemodynamics and cardiopulmonary function tests for pulmonary hypertension risk assessment based on the ESC/ERS guidelines are also listed in Table 1. Compared to reports in low/intermediate-risk group, the high-risk group was reported to have worse World Health Organization (WHO) functional (Fc III = 11.1% vs. 73.9%, p < 0.001), worse exercise and cardiopulmonary exercise capacity (six-minute walking distance [6MWD] = = 367.7 ± 102.6 vs. 251.4 ± 143.0 m, p < 0.001; VE/VCO_2 = 32.8 ± 7.4 vs. 41.3 ± 14.9, p = 0.049), higher NT-proBNP value (NT-proBNP = 794.5 ± ± 918.5 vs. 4390.6 ± 4843.6 pg/mL, p = 0.002). Regarding hemodynamic parameters, patients in the high-risk group had worse cardiac function (cardiac output = 5.4 ± 0.6 vs. 4.1 ± 1.5 L/min, p = 0.028; cardiac index = 3.6 ± 0.5 vs. 2.4 ± 0.9 L/min/m^2, p = 0.001), worse vascular saturation (pulmonary artery saturation = 73.3 ± 4.8 vs. 50.7 ± 15.1%, p = 0.007; superior vena cava saturation = 71.3 ± ± 6.6 vs. 57.5 ± 12.0%, p < 0.001; inferior vena cava saturation = 74.5 ± 8.7 vs. 54.9 ± 14.1%, p = = 0.005), and higher pulmonary vascular resistance (6.0 ± 3.4 vs. 10.9 ± 8.6 woods, p = = 0.034) compared to the reports of patients in the low/intermediate-risk group. With regard to pulmonary function tests, forced expiratory volume in the first second (FEV_1) and FVC (FEV_1 = 1.9 ± 0.8 vs. 1.4 ± 0.5% predicted, p = = 0.024; FVC = 2.3 ± 1.2 vs. 1.7 ± 0.6 L, p = 0.020) were lower in the high-risk group than in the low/intermediate-risk group.

Table 1. Basic characteristics, hemodynamics and cardiopulmonary function tests of patients with pulmonary hypertension based on risk levels.

Variables	Low/intermediate risk (n = 27)	High risk (n = 23)	P
Female	22.0 (81.5%)	20.0 (87.0%)	0.711
Age [years]	56.4 ± 14.7	63.7 ± 15.8	0.141
Body weight [kg]	60.4 ± 12.5	68.6 ± 25.0	0.166
Body height [cm]	156.5 ± 8.6	151.0 ± 22.5	0.279
Body surface area [m^2]	1.6 ± 0.2	1.7 ± 0.2	0.521
Hematology tests:			
White blood cells [K/μL]	6.8 ± 2.2	6.8 ± 2.2	0.992
Red blood cells [M/μL]	4.5 ± 0.5	4.6 ± 0.9	0.630
Hemoglobin [g/dL]	13.3 ± 1.7	13.3 ± 1.8	0.952
Hematocrit [%]	40.1 ± 4.3	41.1 ± 6.0	0.510
Red blood cell volume distribution [%]	14.8 ± 4.8	15.9 ± 4.3	0.424
Platelet [K/μL]	250.5 ± 96.2	204.8 ± 73.2	0.069
Neutrophil [%]	62.1 ± 13.6	65.4 ± 10.9	0.349
Lymphocyte [%]	28.2 ± 11.9	23.0 ± 10.1	0.108
Neutrophil/Lymphocyte ratio	3.2 ± 3.1	3.6 ± 2.2	0.625
Prothrombin time [s]	11.1 ± 1.3	18.1 ± 22.8	0.158
International normalized ratio	1.0 ± 0.1	1.2 ± 0.6	0.120
Partial thromboplastin time [s]	31.0 ± 4.6	30.5 ± 6.9	0.779
Biochemistry panel:			
Sodium [mmol/L]	141.2 ± 3.1	139.2 ± 3.9	0.043
Blood urea nitrogen [mg/dL]	15.0 ± 4.5	24.0 ± 13.7	0.006
Serum creatinine [mg/dL]	0.9 ± 0.2	1.2 ± 0.5	0.030
Estimated GFR [mL/min/1.73 m^2]	73.6 ± 14.3	62.2 ± 26.1	0.070
Fasting plasma glucose level [mg/dL]	100.2 ± 13.9	98.1 ± 32.7	0.796
Aspartate aminotransferase [U/L	30.7 ± 20.4	27.8 ± 12.3	0.542
Alanine aminotransferase [U/L]	25.9 ± 15.2	25.2 ± 18.2	0.874
Alkaline phosphatase [U/L]	62.0 ± 32.4	79.3 ± 32.6	0.105
Total bilirubin [mg/dL]	0.7 ± 0.5	0.9 ± 0.7	0.234
Albumin [g/dL]	4.1 ± 0.6	3.8 ± 0.6	0.070
Lactate dehydrogenase [U/L]	214.7 ± 89.2	212.6 ± 34.2	0.925
Lipid profile:			
Total cholesterol [mg/dL]	178.2 ± 40.9	162.3 ± 32.1	0.146
High-density lipoprotein [mg/dL]	50.5 ± 17.5	46.5 ± 16.2	0.413
Low-density lipoprotein [mg/dL]	96.0 ± 25.7	98.6 ± 30.6	0.751
Triglyceride [mg/dL]	120.3 ± 65.7	96.4 ± 37.3	0.154
Multiplex immunoassay circulating biomarkers:			
Angiopoietin-2 [pg/mL]	6237.3 ± 4790.3	5871.0 ± 5029.6	0.793
BMP-2 [pg/mL]	14.6 ± 0.0	12.4 ± 2.1	0.074
BMP-4 [pg/mL]	4.5 ± 0.6	5.1 ± 1.2	0.084
CD40 [pg/mL]	1689.6 ± 923.9	1666.3 ± 817.7	0.926
Endoglin [pg/mL]	1319.1 ± 541.6	1411.1 ± 433.6	0.522
Interlukin-6 [pg/mL]	2.5 ± 1.6	3.6 ± 6.5	0.452
Myeloperoxidase [pg/mL]	6476.3 ± 1897.4	6345.4 ± 1753.7	0.802
Osteopontin [pg/mL]	28901.9 ± 13600.6	35805.0 ± 34042.2	0.369
VEGF [pg/mL]	34.7 ± 23.8	26.2 ± 13.8	0.141
von Willebrand factor [%]	161.9 ± 53.5	164.8 ± 60.5	0.890

→

Table 1 (cont.). Basic characteristics, hemodynamics and cardiopulmonary function tests of patients with pulmonary hypertension based on risk levels.

	Low/intermediate risk (n = 27)	High risk (n = 23)	P
World Health Organization functional class III	3.0 (11.1%)	17.0 (73.9%)	< 0.001
Six-minute walking distance [m]	367.7 ± 102.6	251.4 ± 143.0	< 0.001
Cardiopulmonary exercise testing:			
Peak oxygen consumption [mL/min/kg]	74.4 ± 28.0	65.6 ± 25.4	0.315
VE/VCO_2	32.8 ± 7.4	41.3 ± 14.9	0.049
NT-proBNP [pg/mL]	794.5 ± 918.5	4390.6 ± 4843.6	0.002
Hemodynamics:			
Heart rate [bpm]	83.5 ± 16.5	85.9 ± 13.0	0.583
Right atrial pressure [mmHg]	11.7 ± 3.8	13.9 ± 6.3	0.235
Cardiac output [L/min, Thermodilution method]	5.4 ± 0.6	4.1 ± 1.5	0.028
Cardiac index [$L/min/m^2$, Thermodilution method]	3.6 ± 0.5	2.4 ± 0.9	0.001
Cardiac output [L/min, Fick formula]	4.3 ± 1.3	3.5 ± 1.4	0.162
Cardiac index [$L/min/m^2$, Fick formula]	2.7 ± 0.8	2.1 ± 0.8	0.082
Pulmonary artery saturation [%]	73.3 ± 4.8	50.7 ± 15.1	0.007
Superior vena cava saturation [%]	71.3 ± 6.6	57.5 ± 12.0	< 0.001
Inferior vena cava saturation [%]	74.5 ± 8.7	54.9 ± 14.1	0.005
Mean arterial pressure [mmHg]	97.7 ± 12.1	98.6 ± 12.3	0.802
Mean pulmonary arterial pressure [mmHg]	36.5 ± 14.1	43.6 ± 11.7	0.082
Pulmonary arterial wedge pressure [mmHg]	8.7 ± 6.5	11.0 ± 7.0	0.238
Pulmonary vascular resistance [woods]	6.0 ± 3.4	10.9 ± 8.6	0.034
Left ventricular ejection fraction [%]	59.8 ± 4.0	58.9 ± 2.7	0.365
Peak tricuspid regurgitation peak gradient [mmHg]	51.5 ± 16.0	59.6 ± 23.3	0.154
Pulmonary function tests:			
Total lung capacity [L]	4.6 ± 1.3	4.3 ± 0.9	0.587
FEV1 [s]	1.9 ± 0.8	1.4 ± 0.5	0.024
FEV1/FVC (% predicted)	82.0 ± 7.6	83.4 ± 13.0	0.667
Diffusing capacity for carbon monoxide (% predicted)	58.3 ± 25.8	50.8 ± 25.3	0.385

Data of continuous variables were expressed as mean ± standard deviation. Changes of categorical variables were analyzed by chi-square tests and were expressed by (N, %); BMP — bone morphogenetic protein; CD40 — cluster of differentiation 40; FEV1 — forced expiratory volume in first second; GFR — glomerular filtration rate; NT-proBNP — N-terminal prohormone of B-type natriuretic peptide; VEGF — vascular endothelial growth factor; VE/VCO_2 — ventilatory equivalents for carbon dioxide

Univariate (Table 2) and multivariate (Table 3) logistic regression analyses were performed to assess the predictors in the high-risk group. Multivariate logistic regression analysis demonstrated that homocysteine (OR: 1.256; 95% CI: 1.002––1.574, Table 3) was an independent predictor of high-risk levels. Furthermore, correlation analysis was performed to assess potential biomarkers that correlate with NT-proBNP levels (Table 4). Homocysteine ($\beta = 0.75$, $p < 0.001$) and UA ($\beta = 0.44$, $p = 0.002$) levels showed a good linear correlation with NT-proBNP levels. The linear correlation between NT-proBNP/homocysteine (Fig. 1E) and NT-proBNP/UA (Fig. 1F) was shown in Figure 1.

To find the most appropriate cut-off value for homocysteine for determining the risk level for pulmonary hypertension, a ROC analysis was performed. The best cut-off value was homocysteine = 12 μmol/L, the area under the ROC curve was 0.82, with a 95% CI between 0.67 to 0.97. Hyperhomocysteinemia (homocysteine > 12 μmol/L) could discriminate high-risk levels from low/intermediate-risk levels in pulmonary hypertension, with more high-risk patients (≤ 12: 18.8%; > 12: 70.6%, p = 0.003, Fig. 1G) in patients with hyperhomocysteinemia. Patients with homocysteine > 12 μmol/L also had higher NT-proBNP (803.0 ± 1,165.4 vs. 4,057.7 ± 5,230.9 pg/mL,

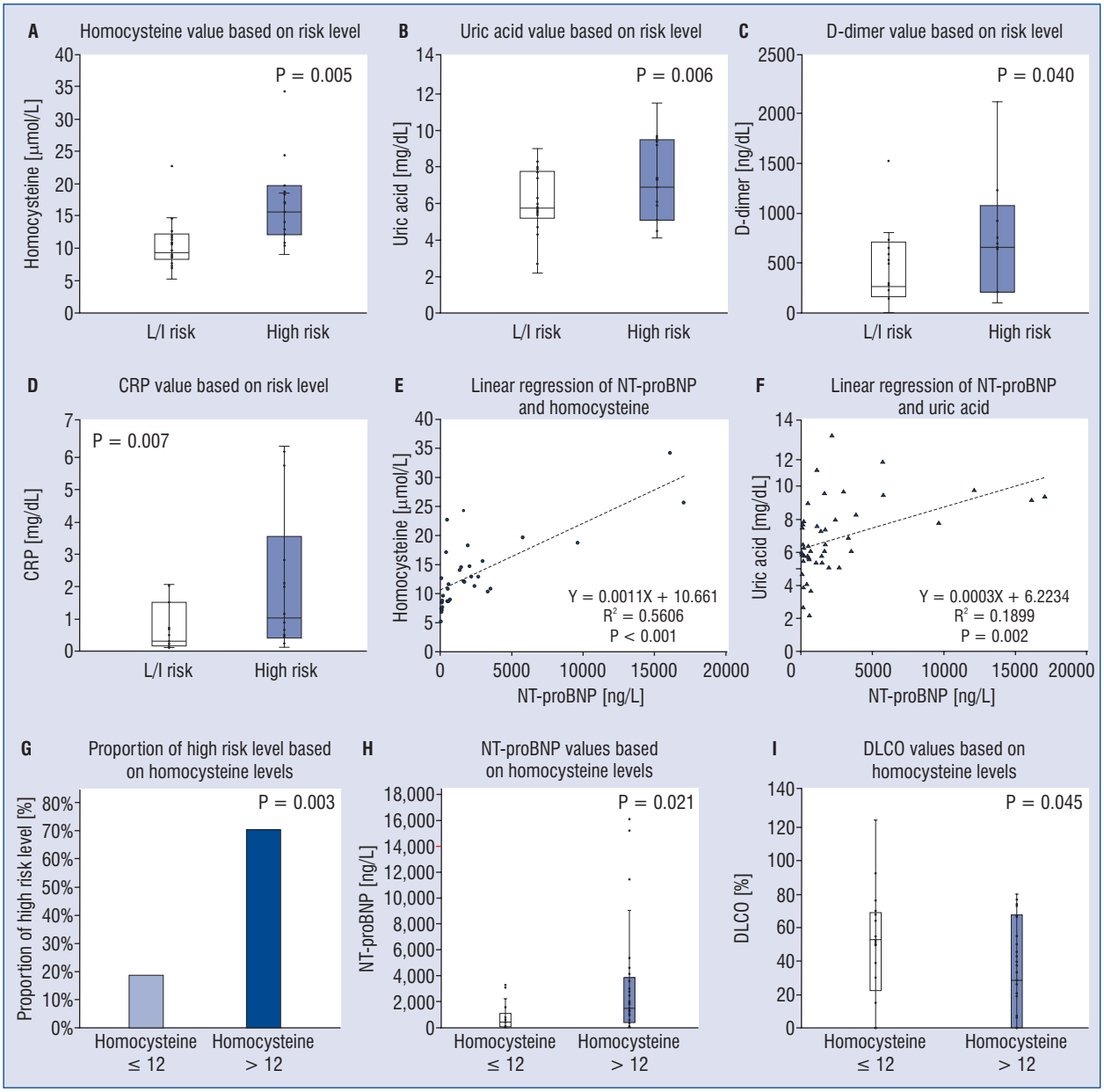

Figure 1. Circulating biomarkers of patients with pulmonary hypertension between low/intermediate (L/I) and high-risk groups and linear relationships between biomarkers and N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) were illustrated in panels **A–F**. In the high-risk group, there were higher homocysteine (10.6 ± 4.0 vs. 17.0 ± ± 7.0 µmol/L, p = 0.005, **A**), higher uric acid (6.0 ± 1.7 vs. 7.7 ± 2.5 mg/dL, p = 0.006, **B**), higher D-dimer (744.8 ± ± 579.1 vs. 1,525.5 ± 1,559.7 ng/mL, p = 0.040, **C**), and higher C-reactive protein (CRP; 0.7 ± 0.7 vs. 2.6 ± 2.7 mg/dL, p = 0.007, **D**) levels than values in L/I-risk group; **E.** Linear relationship between NT-proBNP and homocysteine; **F.** Linear relationship between NT-proBNP and uric acid; **G–I.** Panels demonstrated that patients with pulmonary hypertension in hyperhomocysteinemia groups had a higher risk level. The best cut-off value acquired from receiver operating characteristic analysis was homocysteine = 12 µmol/L; **G.** Hyperhomocysteinemia (homocysteine > 12 µmol/L) could discriminate high-risk levels from L/I risk levels in pulmonary hypertension, with more high-risk patients (≤ 12:18.8%; > 12: 70.6%, p = 0.003) in patients with hyperhomocysteinemia; **H.** Patients with homocysteine > 12 µmol/L had higher NT-proBNP (803.0 ± 1,165.4 vs. 4,057.7 ± 5230.9 pg/mL, p = 0.021); **I.** Lower diffusing capacity for carbon monoxide (DLCO) (64.6 ± 24.6 vs. 44.2 ± 25.4% predicted, p = 0.045) was reported in patients with hyperhomocysteinemia.

Table 2. Univariate logistic regression analyses of predictive factors for high-risk level in pulmonary hypertension.

Variables	B	Standard error	Odds ratio	95% confidence interval	P value
Female	0.46	0.79	1.587	0.335–7.530	0.561
Age [years]	0.04	0.02	1.039	0.993–1.086	0.100
Body surface area [m^2]	0.91	1.37	2.477	0.170–36.118	0.507
Height [cm]	0.03	0.03	0.972	0.920–1.027	0.306
Weight [kg]	0.02	0.02	1.025	0.990–1.060	0.161
Heart rate [bpm]	0.01	0.02	1.009	0.971–1.048	0.659
Mean arterial pressure [mmHg]	0.00	0.02	1.002	0.956–1.051	0.919
Hematology tests:					
White blood cells [K/μL]	0.00	0.13	1.001	0.775–1.294	0.993
Red blood cells [M/μL]	0.15	0.40	1.156	0.532–2.512	0.714
Hemoglobin [g/dL]	0.01	0.17	1.005	0.728–1.388	0.976
Red blood cell volume distribution [%]	0.05	0.07	1.047	0.919–1.192	0.493
Platelet [K/μL]	0.01	0.00	0.993	0.986–1.001	0.071
Neutrophil [%]	0.03	0.03	1.035	0.983–1.089	0.192
Lymphocyte [%]	0.06	0.03	0.947	0.893–1.003	0.063
Neutrophil/Lymphocyte ratio	0.26	0.17	1.290	0.922–1.805	0.137
Prothrombin time [s]	0.32	0.19	1.370	0.941–1.995	0.100
Partial thromboplastin time [s]	0.01	0.05	0.986	0.893–1.088	0.775
Biochemistry panel:					
Na [mmol/L]	0.20	0.11	0.822	0.667–1.011	0.064
Estimated GFR [mL/min/1.73 m^2]	0.03	0.02	0.973	0.945–1.003	0.074
Aspartate aminotransferase [U/L]	0.01	0.02	0.989	0.955–1.024	0.541
Alanine aminotransferase [U/L]	0.00	0.02	0.996	0.963–1.031	0.835
Alkaline phosphatase [U/L]	0.02	0.01	1.019	0.995–1.043	0.127
Total bilirubin [mg/dL]	0.62	0.53	1.852	0.658–5.214	0.243
Albumin [g/dL]	0.94	0.54	0.392	0.135–1.138	0.085
Lactate dehydrogenase [U/L]	0.00	0.01	1.000	0.989–1.010	0.925
Lipid profile:					
High-density lipoprotein [mg/dL]	0.01	0.02	0.986	0.952–1.022	0.441
Low-density lipoprotein [mg/dL]	0.00	0.01	1.003	0.983–1.025	0.744
Total cholesterol [mg/dL]	0.01	0.01	0.988	0.971–1.005	0.162
Triglyceride [mg/dL]	0.01	0.01	0.991	0.979–1.004	0.190
Circulating biomarkers:					
Angiopoietin-2	0.00	0.00	1.000	1.000–1.000	0.765
BMP-2	6.15	6396.08	0.002	0.000–0.000	0.999
BMP-4	0.90	0.49	2.467	0.945–6.439	0.065
CD40	0.00	0.00	1.000	0.999–1.001	0.797
Endoglin	1.00	1.00	1.000	0.999–1.002	0.449
Interlukin-6	0.07	0.09	1.067	0.900–1.266	0.453
Myeloperoxidase	0.00	0.00	1.000	1.000–1.000	0.908
Osteopontin	0.00	0.00	1.000	1.000–1.000	0.360
VEGF	0.00	0.00	1.000	1.000–1.000	0.360
Homocysteine [μmol/L]	0.26	0.10	1.293	1.054–1.586	0.014
von Willebrand factor [%]	0.00	0.01	1.001	0.988–1.014	0.886
Uric acid [mg/dL]	0.41	0.17	1.509	1.088–2.094	0.014
D-dimer [ng/mL]	0.00	0.00	1.001	1.000–1.002	0.058

→

Table 2 (cont.). Univariate logistic regression analyses of predictive factors for high-risk level in pulmonary hypertension.

Variables	B	Standard error	Odds ratio	95% confidence interval	P value
LVEF [%]	–0.07	0.09	0.935	0.790–1.106	0.431
Peak tricuspid regurgitation peak gradient [mmHg]	0.02	0.02	1.022	0.992–1.053	0.152
Pulmonary function tests:					
Total lung capacity [L]	–0.24	0.42	0.787	0.348–1.783	0.566
FEV1	–1.12	0.50	0.328	0.122–0.880	0.027
FEV1/FVC (% predicted)	0.01	0.03	1.013	0.957–1.073	0.654
Diffusing capacity for carbon monoxide (% predicted)	–0.02	0.02	0.981	0.953–1.011	0.218

BMP — bone morphogenetic protein; CD40 — cluster of differentiation 40; FEV1 — forced expiratory volume in first second; GFR — glomerular filtration rate; LVEF — left ventricular ejection fraction; VEGF — vascular endothelial growth factor

Table 3. Multivariate logistic regression analyses of predictive factors for high-risk level in pulmonary hypertension.

Variables	B	SE	OR	95% CI	P value
Homocysteine [μmol/L]	0.20	0.10	1.256	1.002–1.574	0.048
Uric acid [mg/dL]	0.30	0.20	1.338	0.834–2.147	0.227
FEV1 (L)	–1.00	0.60	0.378	0.120–1.193	0.097

CI — confidence interval; FEV1 — forced expiratory volume in first second; OR — odds ratio; SE — standard error

Table 4. The correlation between N-terminal prohormone of brain natriuretic peptide and circulating biomarkers.

Variables	Unstandardized coefficient			P value
	B	Standard error	β	
Angiopoietin-2 [pg/mL]	–0.04	0.11	–0.05	0.759
BMP-2 [pg/mL]	–287.03	442.25	–0.28	0.545
BMP-4 [pg/mL]	921.35	591.51	0.26	0.129
CD40 [pg/mL]	0.18	0.65	0.04	0.783
Endoglin [pg/mL]	0.02	1.17	0.00	0.988
Interlukin-6 [pg/mL]	–51.42	120.84	–0.06	0.672
Myeloperoxidase [pg/mL]	–0.04	0.35	–0.02	0.905
Osteopontin [pg/mL]	0.00	0.02	0.00	0.978
VEGF [pg/mL]	–18.76	36.81	–0.07	0.613
Homocysteine [μmol/L]	489.53	77.85	0.75	< 0.001
Uric acid [mg/dL]	750.24	233.61	0.44	0.002

BMP — bone morphogenetic protein; CD40 — cluster of differentiation 40; VEGF — vascular endothelial growth factor

p = 0.021, Fig. 1H) and lower diffusing capacity for carbon monoxide (DLCO) (64.6 ± 24.6 vs. 44.2 ± ± 25.4% predicted, p = 0.045, Fig. 1I).

The MCT-rat model was obtained successfully and reflected by the elevated right ventricular systolic pressure (21.4 ± 3.0 vs. 44.8 ± 9.0 mmHg, p = 0.001, Fig. 2B) and right ventricular hypertrophy (Fultons's index: 25.2 ± 2.8 vs. 49.1 ± 12.5%, p = 0.003, Fig. 2C) indicated by a significantly increased Fultons's index. MCT rats demonstrated

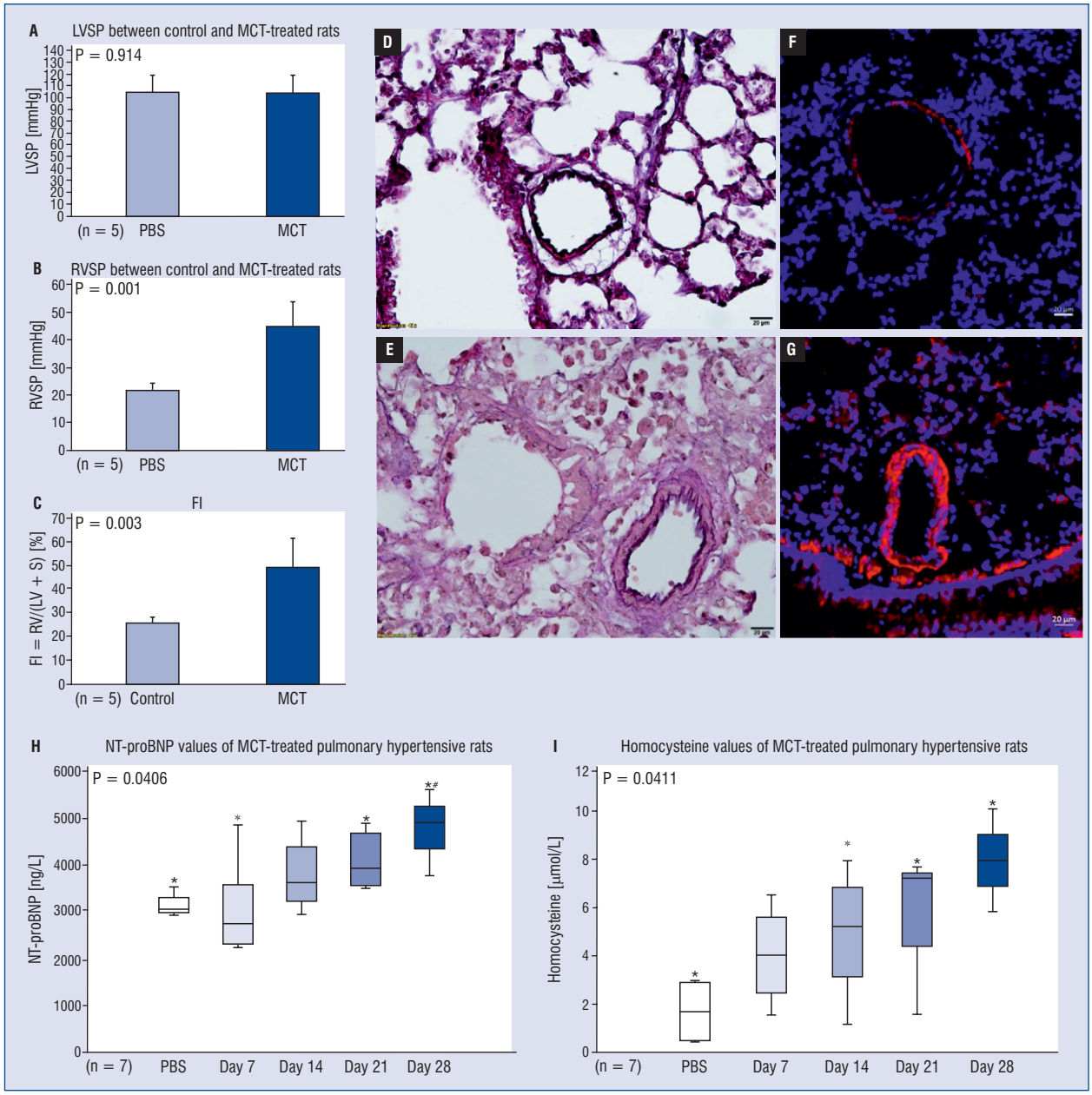

Figure 2. Hemodynamic measurements, histology, immunohistochemical analysis of pulmonary arteries in monocrotaline (MCT) rats; N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) and homocysteine levels between control and MCT-induced pulmonary hypertensive rats. Rats were treated with MCT (60 mg/kg) for 28 days (n = 7 per group), and blood sampling was obtained from the tail vein of rats. Compared to rats treated with phosphate-buffered saline (PBS), rats treated with MCT (60 mg/kg) for 28 days (n = 5 per group) had similar left ventricular systolic pressure (LVSP) (**A**), but elevated right ventricular systolic pressure (RVSP) (**B**) and elevated Fulton's index (FI) with a higher ratio of right ventricular (RV) weight to left ventricular (LV) plus septal weight (RV/LV+S) (**C**). Elastica van Gieson staining revealed increased muscularization **(E)** and occluded pulmonary arteries in MCT-induced rats compared to the control group (**D**). Immunofluorescence staining of alpha-smooth muscle actin in lung sections from MCT-treated rats (**G**) demonstrated proliferated pulmonary arterial smooth muscle cells compared to PBS rats (**F**). NT-proBNP (**H**) and homocysteine (**I**) values were elevating with the severity of pulmonary hypertension by weeks. There were significant differences of NT-proBNP (p = 0.0406) and homocysteine (p = 0.0411) values with increasing severity of pulmonary hypertension by weeks following MCT infusion; *,#: ANOVA with post-hoc least significant difference test revealed a statistical difference between the marked groups.

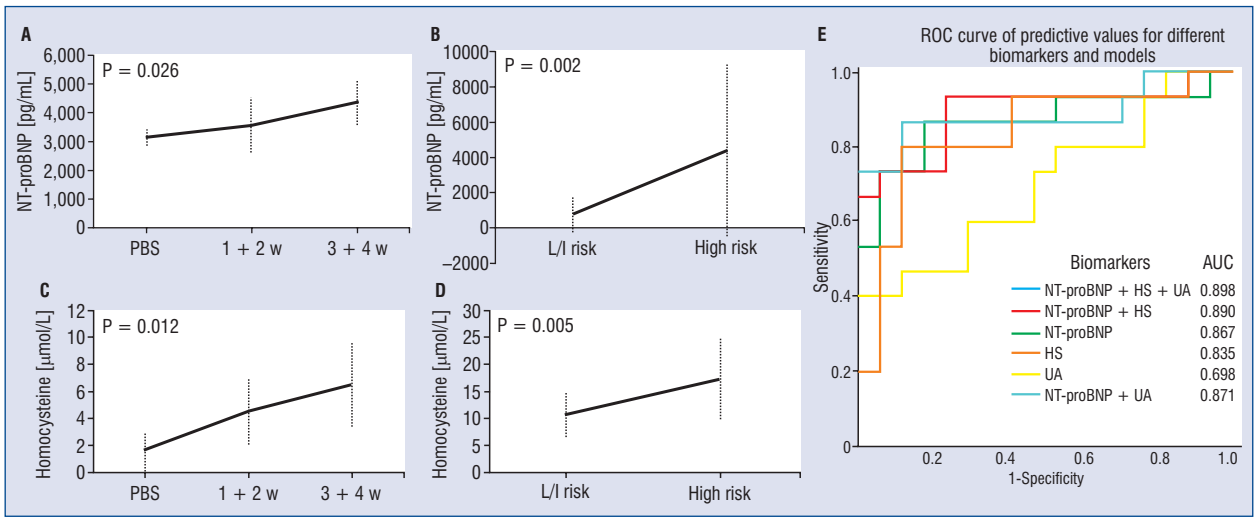

Figure 3. Comparative association of N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) and homocysteine level between monocrotaline (MCT) pulmonary arterial hypertension (PAH) rats and PAH humans by disease severity. The PAH severity progressed by weeks for MCT rats; **A.** NT-proBNP level of MCT rats by weeks demonstrated higher NT-proBNP by progressed severity (p = 0.026); **B.** NT-proBNP level of PAH humans by severity. There was a higher NT-proBNP level in the high-risk group than in the low/intermediate (L/I) risk group (p = 0.002); **C.** Homocysteine level of MCT rats by weeks. Higher homocysteine level was demonstrated in 3 and 4 weeks MCT rats compared with the values in first 2 weeks (p = 0.012); **D.** Homocysteine level of PAH humans by severity. There was higher homocysteine value of high-risk patients than in the low/intermediate (L/I) group (p = 0.005); **E.** Different biomarker combinations and the comparison between respective predictive value of each model were illustrated. The areas under the curves (AUC) were calculated. NT-proBNP + homocysteine (HS) + uric acid (UA) had strongest predictive value (AUC = 0.898), following by NT-proBNP + HS (AUC = 0.890), NT-proBNP + UA (AUC = 0.871), NT-proBNP (AUC = 0.867), HS (AUC = 0.835), and then UA (AUC = 0.698); PBS — phosphate-buffered saline; w — weeks.

the elevation of NT-proBNP (Fig. 2H) and homocysteine (Fig. 2I) levels with progressed severity of pulmonary hypertension by weeks. Comparative association of NT-proBNP and homocysteine level between MCT rats and humans by disease severity were illustrated in Figure 3A–D. In addition, different biomarker combinations and the comparison between respective predictive value of each model were illustrated in Figure 3E. NT-proBNP + homocysteine + UA had strongest predictive value (AUC = 0.898), following by NT-proBNP + homocysteine (AUC = 0.890), NT-proBNP + UA (AUC = = 0.871), NT-proBNP (AUC = 0.867), homocysteine (AUC = = 0.835), and then UA (AUC = 0.698).

Discussion

This study aimed to identify potential biomarkers correlated and comparable to the current guidelines recommending NT-proBNP. A higher homocysteine level was an independent predictor for high-risk levels, and it showed a linear correlation with NT-proBNP. Further analysis indicated that the most appropriate cut-off value of homocysteine for risk level discrimination of pulmonary hypertension was homocysteine = 12 μmol/L.

The rationale for exploring biomarkers compatible and comparable with NT-proBNP

There was no single attribution of regulators or signaling molecules has adequate capacity to estimate the risk [6, 7, 14]. Currently, both the U.S. REVEAL risk score and the ESC/ERS guidelines are the most widely used multidimensional tools for risk assessment [13]. Among these, right heart catheterization is the only test to obtain the precise hemodynamic parameters for diagnosis and therapies [5].

Surprisingly, a previous study reported that BNP or NT-proBNP had a 98% sensitivity for excluding high right atrial pressure (≥ 8 mmHg) and low cardiac index (< 2.5 L/min/m^2), and in circumstances of extreme low BNP (< 50 pg/mL) or NT-proBNP (< 300 pg/mL) level, hemodynamic measurements no longer had independent prog-

nostic predictive values [14]. Moreover, COMPERA and the SPAHR registries demonstrated that the ability of mortality prediction is excellent even when only about a third of patients are followed up under the assessment of right heart catheterization [15, 18]. Nevertheless, due to the complexity of pulmonary hypertension, any single biomarker is insufficient for the broad assessment of patients with different etiologies of pulmonary hypertension. This study aimed to explore potential biomarkers compatible and comparable with NT-proBNP for disease follow-up.

The investigations of novel biomarkers and application of homocysteine for PAH risk assessment

The investigations of novel biomarkers, such as angiopoietin-2, BMP-2, BMP-4, CD40, endoglin, interlukin-6, myeloperoxidase, and osteopontin are currently in progress [7, 19, 20]. Angiopoietin-2 is produced by vascular smooth muscle cells and is involved in vascular damage/remodeling, and expression of angiopoietin-2 was up-regulated in plexiform lesions PAH lung tissues [21]. BMP-2 and BMP-4 exert opposing roles in the hypoxic pulmonary vasculature mediated by increasing endothelial nitric oxide synthase expression and activity, and BMP-2 has suggested protective effect [22, 23]. CD40 is a type I transmembrane receptor and one of the members of the tumor necrosis factor superfamily, which is expressed on epithelial cells, fibroblasts, endothelia cells, vascular smooth muscle cells, and platelets. The expression of CD40 promotes pro-thrombotic and pro-inflammatory effects, and is associated with systemic sclerosis and PAH [24, 25]. Endoglin and VEGF are angiogenic modulatory factors [26, 27]. Interlukin-6 is associated with vascular remodeling and development of PAH, which is able to predict poor adverse outcomes within the following year [28, 29]. Myeloperoxidase is able to reduce the bioavailability of nitric oxide, which is an important anti-inflammatory and vasodilating molecule. It also predicts outcomes in patients with PAH [30]. Osteopontin is involved in tissue remodeling, inflammation, and metastasis, which is recognized in cardiomyocytes and fibroblasts. Previous studies supported its correlation with mPAP, NT-proBNP, 6MWD and function class [31–33]. Bonferroni correction was applied for analysis of multiplex immunoassay biomarkers (**Suppl. Table S1**); despite having no significant statistical difference between low-, intermediate- and high-risk groups, the increased trend by disease severity was demonstrated. The insignificance could be attributed to the small sample size.

This study demonstrated that patients in high-risk group for pulmonary hypertension had higher homocysteine, UA, D-dimer, and CRP base on univariate analysis (Table 2). However, multivariate logistic regression analysis demonstrated that homocysteine (OR: 1.256; 95% CI: 1.002–1.574, Table 3) was the only independent predictor for high-risk levels. In addition, studies in animals and in cell cultures also demonstrated that homocysteine has a variety of toxic effects on the vasculature, endothelial dysfunction, medial remodeling and adventitial inflammation [34–41] which supports the result of serum homocysteine level of MCT rats in the present study.

In comparison with angiopoietin-2, BMP-2, BMP-4, CD40, endoglin, interlukin-6, myeloperoxidase, and osteopontin, which need to be acquired by multiplex immunoassay of human blood and were not feasible in clinical tests, homocysteine is available in daily clinical care. Furthermore, homocysteine impairs endothelium-dependent vasodilatation and is an endogenous inhibitor of nitric oxide synthase. Moreover, increased homocysteine level in PAH was also reported in a previous study [42–44]. In addition, comparison between each model illustrated in Figure 3E reported higher predictive value of homocysteine (AUC = 0.835) compared to uric acid (AUC = 0.698). Therefore, homocysteine rather than other biomarkers was selected for final advanced analysis under the consideration of multivariate analysis and clinical feasibility compared to other biomarkers.

Correlation between homocysteine and NT-proBNP, and application of homocysteine for follow-up of pulmonary hypertension

Homocysteine interferes with the expression of endothelial nitric oxide synthetase, with which its multifactorial attributions increase vascular thickness and activate elastin fragmentation, which eventually leads to PAH [8, 45]. Pulmonary hypertension can develop rapidly under hypoxic situations, and hyperhomocysteinemia was reported in cyanotic PAH patients compared to non-cyanotic patients [42–44]. A low DLCO could be seen in patients with primary pulmonary hypertension and other pulmonary vascular diseases with or without the restriction of lung volumes [46]. Moreover, lower DLCO (< 45%) was demonstrated in PAH patients with lower arterial oxygen tension [47]. Low DLCO was also an index of worse prognosis, a strong and independent risk factor for survival

in patients with pulmonary hypertension [48–50]. Hyperhomocysteinemia is an index for hypoxia and low DLCO [51]. This study reported that higher homocysteine group had more high-risk level patients (≤ 12 μmol/L: 18.8%; > 12 μmol/L: 70.6%, p = 0.003, Fig. 1G), and higher NT-proBNP (803.0 ± 1,165.4 vs. 4,057.7 ± 5,230.9 pg/mL, p = 0.021, Fig. 1H). This result supported the possibility of using homocysteine for disease follow-up.

A previous study demonstrated that higher homocysteine levels were correlated with higher concentrations of NT-proBNP when the differences were assessed in comparison with the upper quartile (≥ 18 μmol/L) with the lower quartile (≤ 12 μmol/L) [52]. Hyperhomocysteinemia predicted high NT-proBNP values via a link with impaired mitochondrial fatty oxidation [52]. Furthermore, homocysteine was one of the determinants of natriuretic peptide which was analyzed by univariate analyses [52]. Association between the log of plasma concentration of homocysteine and BNP was demonstrated with a correlation coefficient of +0.297 (95% CI: +0.097–+0.474, p = 0.004) [52]. In addition, homocysteine was reported to stimulate myocardial BNP and induce adverse left ventricular remodeling [53]. However, studies describing the correlation between homocysteine and NT-proBNP through a link with pulmonary hypertension are rare. This study showed that homocysteine had a linear correlation with NT-proBNP levels (β = 0.75, p < 0.001, Fig. 1E). The 1-year mortality was < 5%, 5–20%, and > 20% if NT-proBNP values are < 200, 300–1100, > 1100 pg/mL illustrated in 2022 ESC guideline [1]. As long as the biomarker identified had a good correlation with NT-proBNP, it was able to represent the estimated 1-year mortality as well as NT-proBNP does.

With regard to the use of homocysteine for pulmonary hypertension follow-up or severity evaluation, the current study demonstrated that hyperhomocysteinemia was present in pulmonary hypertension associated with the congenital heart disease group compared to the non-pulmonary hypertension group [42]. In addition, elevated total plasma homocysteine was reported in primary pulmonary hypertension patients compared to the control group (14.7 ± 7.2 vs. 10.2 ± 5.1, p = = 0.027), with the cut-off value of 15 μmol/L [54]. Hyperhomocysteinemia is a crucial factor in the pathogenesis of primary pulmonary hypertension as well as poor renal function [54]. These results support the present study, that a higher homocysteine value was reported in the high-risk group compared to the low/intermediate-risk group, and the most appropriate cut-off value based on ROC analysis was homocysteine = 12 μmol/L. In light of the small sample size of this study and ethical consideration, the present study used MCT induced PAH rats to evaluate the accessibility and reliability of using homocysteine to predict PAH risk level. The result proved a comparative association between disease severity and homocysteine level, which were demonstrated both in rats and humans (Fig. 3A–D).

Limitations of the study

Individual differences of metabolism and increased lipid profiles may interfere with homocysteine values. In addition, the acquisition of blood samples depends on the interval between application and permission. Blood samples of the present study were stored for an average of between 2 weeks and 1 month. The half-life of each biomarker and accuracy might affect the results of measurement. However, this was restricted by experimental accessibility and was a limitation of the present study. In addition, the small sample size of this study limits the reliability of the application of homocysteine as an index of risk assessment. Further investigation is needed to validate this study's result.

Study strength

Previous studies have illustrated the correlation between hyperhomocysteinemia and high NT-proBNP value via a link with impaired mitochondrial fatty oxidation. However, the correlation between homocysteine and NT-proBNP through a link with pulmonary hypertension has been obscured. Based on previous evidence, hyperhomocysteinemia were related with hypoxia-induced pulmonary vascular constriction and pulmonary hypertension. This study demonstrated that homocysteine had a linear correlation with NT-proBNP. These results posed a potential new circulating biomarker to achieve more accurate risk assessment of pulmonary hypertension.

Conclusions

This study demonstrated that patients with higher homocysteine levels had higher risk levels, higher NT-proBNP levels, and lower DLCO. This study also delineated a linear correlation between homocysteine and NT-proBNP levels. In summary, homocysteine can help discriminate between low/ /intermediate and high-risk groups. It is a potential

biomarker that could be compatible and comparable with NT-proBNP as a non-invasive and effort-free measurement for risk assessment and disease follow-up in pulmonary hypertension.

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Conflict of interest: None declared

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Intravenous iron supplementation improves energy metabolism of exercising skeletal muscles without effect on either oxidative stress or inflammation in male patients with heart failure with reduced ejection fraction

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Abstract

Background: *Skeletal muscle dysfunction is a feature of heart failure (HF). Iron deficiency (ID) is prevalent in patients with HF associated with exercise intolerance and poor quality of life. Intravenous iron in iron deficient patients with HF has attenuated HF symptoms, however the pathomechanisms remain unclear. The aim of study was to assess whether intravenous iron supplementation as compared to placebo improves energy metabolism of skeletal muscles in patients with HF.*

Methods: *Men with heart failure with reduced ejection fraction (HFrEF) and ID were randomised in 1:1 ratio to either intravenous ferric carboxymaltose (IV FCM) or placebo. In vivo reduction of lactates by exercising skeletal muscles of forearm was analyzed. A change in lactate production between week 0 and 24 was considered as a primary endpoint of the study.*

Results: *There were two study arms: the placebo and the IV FCM (12 and 11 male patients with HFrEF). At baseline, there were no differences between these two study arms. IV FCM therapy as compared to placebo reduced the exertional production of lactates in exercising skeletal muscles. These effects were accompanied by a significant increase in both serum ferritin and transferrin saturation in the IV FCM arm which was not demonstrated in the placebo arm.*

Conclusions: *Intravenous iron supplementation in iron deficient men with HFrEF improves the functioning of skeletal muscles via an improvement in energy metabolism in exercising skeletal muscles, limiting the contribution of anaerobic reactions generating adenosine triphosphate as reflected by a lower in vivo lactate production in exercising muscles in patients with repleted iron stores.* (Cardiol J 2024; 31, 2: 300–308)

Keywords: heart failure, iron deficiency, skeletal muscles, exercise capacity, energy metabolism, physical fitness

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Introduction

Skeletal muscle dysfunction constitutes an important pathophysiological feature of heart failure (HF) and contributes to debilitating symptomatology of this disease syndrome, i.e., impaired exercise capacity and increased perception of dyspnoea, also during submaximal exercises [1–3]. Most importantly, these abnormalities translate into poor quality of life and unfavourable clinical outcomes in patients with HF [4], and therefore constitute clinically relevant targets for novel therapies.

Iron deficiency (ID) has been demonstrated to be prevalent in patients with HF [5, 6], and to be associated with impaired exercise capacity in these patients [5, 7, 8]. Most importantly, intravenous (IV) iron supplementation in iron deficient patients with HF has attenuated HF symptoms, and markedly improved exercise capacity and health related quality of life [9–13] as well as reduced the risk of recurrent HF hospitalizations [9–13].

Intriguingly, despite overwhelming evidence on clinical efficacy of IV iron repletion in patients with HF, the pathomechanisms responsible for these advantageous effects remain unclear. Being that the micronutrient critically needed for intracellular energy generation [14–16], iron is considered to play an important role in energy metabolism both within myocardial and skeletal muscle tissue [14–16]. Experimental evidence indicates that depleted intracellular iron leads to inefficient aerobic processes with adaptive anaerobic reactions within skeletal muscle tissue, and as a consequence decreases work [15–18] capacity. Recently, it has been shown that IV iron repletion in patients with HF improves skeletal muscle energetics as reflected by a shorter phosphocreatine recovery half-time on phosphorus magnetic resonance spectroscopy [19].

This paper is a complementary mechanistic study which aimed to assess whether IV iron supplementation as compared to placebo improves energy metabolism of exercising skeletal muscles in iron deficient male patients with HF, along with its effects on skeletal muscle performance, inflammation and oxidative status.

Methods

Study design

Herein, is reported a single-center, randomised (1:1), double-blind placebo-controlled study.

Caucasian outpatients with stable heart failure, reduced ejection fraction (HFrEF) and concomitant ID were examined. There following inclusion criteria of the study are: (1) male sex and age >18 years, (2) a documented history of chronic HF (established diagnosis of chronic HF according to the criteria of the European Society of Cardiology [20]) of at least 6-month duration, (3) ID defined as serum ferritin < 100 ng/mL, or serum ferritin 100–299 ng/mL with transferrin saturation (TSAT) < 20% [10, 11], (4) hemoglobin level ≥ 10 g/dL and ≤ 15 g/dL, (5) left ventricular ejection fraction ≤ 40% as assessed in echocardiography examination, not older than 6 months at the time of randomization, (6) New York Heart Association class I–III, (7) clinical stability along with unchanged HFrEF pharmacotherapy for at least 1 month preceding randomization, (8) signed informed consent form. Exclusion criteria included: (1) acute coronary syndrome or an episode of acute HF within 3 months preceding the study, (2) the therapy for anemia (including the use of erythropoiesis-stimulating agents) or/and ID (either IV or oral iron therapy) within 12 months prior to the study, (3) chronic infectious disease or symptoms of acute infection at the time of randomization, (4) a history of autoimmune, hematological or malignant disease (cancer), (5) muscular or neuro-muscular disorders, (6) dementia or significant cognitive dysfunction, or (7) simultaneous participation in any clinical trial.

Between April 16, 2014 and January 28, 2016 patients were randomly assigned in a 1:1 ratio to receive either ferric carboxymaltose (FCM) (provided by Vifor Pharma, Glattbrugg, Switzerland) or placebo (normal saline).

The trial was conducted in strict compliance with Good Clinical Practice from the International Council for Harmonisation (ICH GCP) and with the Declaration of Helsinki, and its protocol was approved by the local ethics committee (Bioethics Committee, Wroclaw Medical University, Consent No. 218/2014). All subjects gave written informed consent, before any trial-related procedure was performed.

Study procedures and visit schedule

The study intervention was an IV administration of FCM. Medication was administered as 10 or 20 mL of FCM (which is an equivalent of 500 or 1000 mg of iron, respectively) diluted in normal saline (0.9% weight/volume NaCl) to 100 mL volume. IV drop infusion was administered over at least 15 minutes. Normal saline was administered as placebo as per the instructions for active therapy. FCM dose was determined by the subject's body weight and hemoglobin value. The first dose was administered for all randomized subjects at week

0 after performing all planned procedures. The subsequent doses were administered as a part of the outpatient visits at week 6 and week 12 based on the following dosing scheme. At week 0, patients with hemoglobin ≥ 10 g/dL and ≤ 14 g/dL received 1000 mg of FCM, whereas those with hemoglobin > 14 g/dL and ≤ 15 g/dL were given 500 mg of FCM (regardless of body weight). At week 6, the study treatment was administered only to those with body weight ≥ 70 kg and hemoglobin ≥ 10 g/dL and ≤ 14 g/dL (500 mg of FCM). Additional doses of FCM were applied at week 12 for subjects in whom ID persisted, and for whom hemoglobin was ≥ 10 g/dL and ≤ 15 g/dL at those visits (500 mg of FCM, regardless of body weight).

Because FCM is a dark-brown solution that is easily distinguishable from the saline placebo, study personnel responsible for the preparation and administration of the study drug were aware of the group assignments (remained unblinded) and therefore were not involved in any study assessments. The laboratory results regarding iron status and hemoglobin were available only to the unblinded study personnel. To ensure that patients were unaware of the study treatment they were receiving, black syringes were used to administer the study drug and a curtain (or something similar) was used to shield the injection site from the patient's view, as in previous clinical trials with FCM [10, 11].

Study assessments and endpoints

The following parameters were assessed at baseline (week 0) and at the end of follow-up (week 24) (details on methodology are provided below):

- Energetic performance of exercising skeletal muscles:
  - production of lactates by exercising skeletal muscles of forearm (a difference in lactate level before and after exposure to standardised forearm exercise in peripheral blood derived from exercising muscles) (a change in lactate production between week 0 and 24 was considered as a primary endpoint of a study);
- Functional performance of skeletal muscles and global exercise capacity:
  - quadriceps strength;
  - six-minute walking test distance;
- Biomarkers related with functioning of skeletal muscles:
  - serum levels of irisin and hemojuvelin;
- Iron and anemic status assessed in peripheral blood:
  - serum ferritin, TSAT, the presence of ID,
  - hemoglobin level;
- Inflammatory status:
  - serum levels of C-reactive protein (CRP), tumor necrosis factor (TNF)-alpha, interleukin (IL)-1beta, IL-6, IL-22;
- Oxidative status:
  - serum activity of glutathione S-transferase (GST), catalase, superoxide dismutase (SOD).

Methodology

Energetic performance of exercising skeletal muscles. It was expressed as a production of lactates by exercising skeletal muscles of the forearm (a difference in lactate level before and after exposure to standardised forearm exercise in peripheral blood derived from exercising muscles, and expressed in mOsm/L.

The handgrip (forearm flexors compartment) exercise session performed by the dominant (mainly right) arm was considered as a standardised exercise load provided to this area of skeletal muscles. Briefly, the patient was requested to rhythmically handgrip the electronic dynamometer for 300 s at 50% of predetermined maximal voluntary contraction (MVC) (150 squeezes per exercise). The frequency of squeezing was driven by an electronic metronome and the real-time % of MVC curve was displayed on a large LCD monitor to help the patient to precisely follow the required grip strength and the exercise pace. Immediately after the exercise the patient performed an additional assessment of MVC to compare with its baseline (pre-exercise) value. Furthermore, before the exercise a superficial vein was catheterized (retrograde direction) in the antecubital fossa to obtain muscular blood metabolic parameters before and immediately after the handgrip exercise (standardised analysis of venous blood gases was performed to assess lactate level). Antecubital fossa veins are connected to deep veins of the forearm draining forearm flexors and metabolites detected in this area reflect, in vivo, the metabolism of exercising forearm muscles [21].

Quadricep strength. Peak quadricep torque (Nm) was measured in both lower extremities during a maximal dynamic and isometric knee extension with the hip in a 90° flexion while a patient sitting in a rehabilitation armchair type UPR 1A (Summer, Opole, Poland). Measurements were repeated at least 3 times and the highest value was recorded. Quadriceps muscle strength (N, a maximal dynamic and isometric strength) was calculated as a peak quadricep torque (Nm) and was divided

by a distance between a rotation axis and a point where lifted weights were attached (m).

Six-minute walking test. The six-minute walk test was performed in a long, straight hospital corridor, over a 30-m distance [22, 23]. Each participant was asked to walk (not run) back and forth along the corridor as briskly as possible, so that the longest possible distance was covered in 6 minutes. The participant was allowed to slow down or stop and rest, if necessary, particularly in the case of symptoms such as severe dyspnoea or fatigue. During any rest period, the participant was informed of the elapsed time and encouraged to recommence walking when the symptoms attenuated enough to allow walking. However, the test was discontinued if the symptoms persisted. The participant was also allowed to discontinue the test at will at any time. Moreover, the test was interrupted by the investigator immediately one of the following symptoms appeared: chest pain that did not resolve at rest, dyspnoea precluding continuation of walking, cramps of the lower limb muscles, balance difficulty, severe sweating, pallor, or cyanosis. Otherwise, every 2 minutes during the test, an investigator informed the participant of the amount of time left and encouraged him to continue the test. At 6 minutes, the participant was advised to stop and be seated. An investigator immediately measured post-exercise arterial blood pressure and pulse rate. The participant assessed subjective fatigue and dyspnoea levels with the modified Borg scale from 0 (none) to 10 (maximal). The distance walked was measured to the nearest whole meter.

Measurements performed in peripheral blood. In all participants venous blood samples were taken in the morning following an overnight fast. Hematological measurements were made in fresh venous blood with EDTA.

Parameters related with inflammatory status and those reflecting the functioning of skeletal muscles. The following particles were measured in either plasma or serum using a commercially available enzyme-linked immunosorbent assays (ELISA): hemojuvelin (ng/mL) (Cloud-Clone Corp., CCC, Wuhan); irisin (μg/mL) (BioVendor, Brno, Czech Republic); IL-6 (pg/mL) (R&D Systems, Minneapolis, MN, USA); IL-22 (pg/mL) (R&D Systems); IL-1β (pg/mL) (R&D Systems); TNF-α (pg/mL) (R&D Systems). The dilution of a series of serum/plasma samples were standardised in order to obtain absorption values at the middle of the standard curve. All measurements were performed in triplicate. Optical density at 450 nm was measured, with a reading time of 1 s, using a microtiter plate reader (BioTek, Synergy HTX).

Parameters reflecting oxidative stress. Activities of the following antioxidant enzymes were established using commercially available kits from Cayman Chemical Company (Ann Arbor, Michigan, USA): GST (nmol/min/mL), SOD (U/mL). All measurements were performed in triplicate according to manufacturer instructions.

Parameters related with iron and anaemic status. Hemoglobin concentration was measured using the ADVIA 2120 system (Siemens). Anemia was defined according to World Health Organization as hemoglobin concentration < 12 g/dL in women and < 13 g/dL in men. The following blood biomarkers reflecting iron metabolism were measured directly: serum ferritin (μg/L), iron (mg/dL), and total iron binding capacity (TIBC, mg/dL). TSAT was calculated as the ratio of serum iron (mg/dL) and TIBC (mg/dL) multiplied by 100 and expressed as a percentage. Serum ferritin was measured using an immunoassay based on electrochemiluminescence with the Elecsys 2010 system (Roche). Serum iron and TIBC were assessed using a substrate method with the Konelab Prime 60i system (Thermo Scientific). ID was defined as serum ferritin level < 100 μg/L or serum ferritin 100–299 μg/L in combination with a TSAT < 20% [10, 11].

Other laboratory measures. Serum level of high-sensitivity CRP (hs-CRP, mg/L) was assessed using immunonephelometry with BN II System (Siemens). Plasma level of N-terminal pro-B type natriuretic peptide (pg/mL) was measured using an immunoassay based on chemiluminescence with Dimension RxL system (Siemens). Estimated glomerular filtration rate (mL/min/1.73 m^2) was calculated using the Modification of Diet in Renal Disease equation [24].

All randomized patients were followed for the occurrence of prespecified outcomes throughout the follow-up period, regardless of whether the study participants were taking their study treatment or were compliant with study procedures. Throughout the follow-up period, all appropriate treatments for HF or other medical conditions could be initiated, altered or halted at the clinical discretion of the healthcare provider according to each patient's individual indications or contraindications.

Statistical analyses

Most continuous variables had a normal distribution, and were expressed as a mean ± the

standard error of the mean. Categorized variables were expressed as a number and percentage. The intergroup differences were tested using the Mann-Whitney U-test for unpaired samples.

The efficacy analyses were performed on the full-analysis set in accordance with the intention-to-treat principle. Treatment effect analysis was an unpaired comparison of the changes in continuous variables between the treatment arms using the Student t-test. Summary statistics include the point estimates of week 0 and 24 for continues variables, the change from baseline to week 24, and the estimates and 2-sided 95% confidence intervals for the difference between two study treatment arms.

P-value of < 0.05 was considered statistically significant. Statistical analyses were performed using the STATISTICA 13.1 data analysis software system (StatSoft).

Results

Twelve and 11 iron deficient male patients with HFrEF to a placebo arm and a IV FCM arm, were recruited, respectively. At baseline, there were no differences in clinical variables, comorbidities and applied treatment between these two study arms (Table 1). Intravenous FCM therapy as compared to placebo reduced the exertional production of lactates in exercising skeletal muscles (a change in lactates at week 0 and 24 in a placebo arm: 3.8 ± ± 0.2 and 2.5 ± 0.2, a change in lactates at week 0 and 24 in a IV FCM arm: 3.6 ± 0.3 and 1.6 ± 0.3; $p < 0.05$ for a difference between these study arms), which was associated with a numerical increase in quadricep strength and six-minute walking distance (Table 2, Fig. 1). These effects were accompanied by a significant increase in both serum ferritin and TSAT in the IV FCM arm (serum ferritin at week 0 and 24: 83 ± 18 and 325 ± 66; $p < 0.001$, TSAT at week 0 and 24: 20.6 ± 1.8 and 28.3 ± 1.6; $p < 0.05$), which was not demonstrated in the placebo arm (serum ferritin at week 0 and 24: 85 ± 14 and 96 ± 21; $p > 0.05$, TSAT at week 0 and 24: 19.0 ± ± 2.1 and 19.2 ± 2.5; $p > 0.05$). There were no changes in hemoglobin, biomarkers reflecting either functioning of skeletal muscles (irisin, hemojuvelin), inflammation (CRP, TNF-α, IL-β, IL-6, IL-22) or oxidative stress (GST, catalase, SOD) in both study arms throughout the study (Table 2).

Table 1. Baseline characteristics, comorbidities, and heart failure treatment among men with heart failure with reduced ejection fraction included in two study arms: placebo vs. intravenous ferric carboxymaltose.

	Placebo (n = 12)	IV FCM (n = 11)
Demographics and clinical measures		
Age [years], mean ± SEM	68 ± 3	63 ± 5
Male gender	12 (100%)	11 (100%)
Caucasian race	12 (100%)	11 (100%)
Body mass index [kg/m^2]	28.3 ± 1.3	28.1 ± 1.3
Ischemic etiology of HF	11 (92%)	9 (81%)
NYHA functional class		
II	8 (67%)	8 (73%)
III	4 (33%)	3 (27%)
LVEF [%]	30 ± 2	30 ± 2
Comorbidities		
Coronary artery disease	11 (92%)	9 (81%)
Paroxysmal atrial fibrillation	1 (8%)	2 (18%)
Diabetes mellitus	6 (50%)	3 (27%)
Dyslipidaemia	8 (67%)	6 (55%)
COPD	1 (8%)	0 (0%)
Peripheral artery disease	3 (25%)	2 (18%)
Arterial hypertension	5 (42%)	8 (73%)
Treatment		
ACEI or ARB	11 (92%)	11 (100%)
MRA	9 (75%)	8 (72%)
Beta-blocker	11 (92%)	11 (100%)
Digoxin	1 (8%)	0 (0%)
Ivabradine	2 (17%)	2 (18%)
Diuretic	5 (42%)	6 (54%)
Statin	12 (100%)	10 (91%)
ICD/CRT-D	11 (92%)	4 (36%)

Data is presented as mean plus/minus standard error of mean (SEM) for continues variables, numbers with % for categorized variables. IV FCM — intravenous ferric carboxymaltose; HF — heart failure; NYHA — New York Heart Association; LVEF — left ventricular ejection fraction; COPD — chronic obstructive pulmonary disease; ACEI — angiotensin converting enzyme inhibitors; ARB — angiotensin II antagonists; MRA — mineralocorticoid receptor antagonists; ICD/CRT-D — implantable cardioverter-defibrillator/ /cardiac resynchronization therapy with defibrillator function

Discussion

In the present study it was demonstrated that intravenous iron supplementation in iron deficient men with HFrEF improves energy metabolism in skeletal muscles. Intravenous therapy with FCM resulted in a significant increase in serum ferritin and TSAT, and the restoration of iron stores in the body was accompanied by a smaller in vivo production of lactates by exercising skeletal muscles, indicating the lower contribution of anaerobic processes generating adenosine triphosphate (ATP) in this tissue.

Table 2. The effect of intravenous ferric carboxymaltose vs. placebo on muscle energetics assessed in vivo, skeletal muscle functioning, and biomarkers related with functioning of skeletal muscles, iron status, inflammatory and oxidative status in men with heart failure with reduced ejection fraction.

	Baseline		End of study		Treatment effect (95% CI)
	Placebo (n = 12)	IV FCM (n = 11)	Placebo (n = 12)	IV FCM (n = 11)	
Energetic performance of exercising skeletal muscles					
Lactate [mOsm/L] baseline	1.4 ± 0.1	1.3 ± 0.2	1.6 ± 0.2	1.3 ± 0.1	0.1 (–0.3 to 0.4)
Lactate [mOsm/L] change after exercise	3.8 ± 0.2	3.6 ± 0.3	2.5 ± 0.2***	1.6 ± 0.3**	–0.8 (–1.6 to 0.0)*
Functional performance of skeletal muscles and global exercise capacity					
Quadriceps strength	87 ± 4	84 ± 4	89 ± 5	95 ± 6	7 (–1 to 15)
6MWT	463 ± 31	474 ± 15	475 ± 24	492 ± 14*	6 (–25 to 37)
Biomarkers related with functioning of skeletal muscles					
Hemojuvelin [ng/mL]	3.52 ± 0.10	3.36 ± 0.06	3.11 ± 0.08***	3.44 ± 0.29	0.41 (–0.23 to 1.05)
Irisin [ng/mL]	1.32 ± 0.16	1.58 ± 0.18	1.20 ± 0.12	1.01 ± 0.08*	–0.32 (–0.9 to 0.26)
Iron status and anaemic status assessed in peripheral blood					
Ferritin [ng/mL]	85 ± 14	83 ± 18	96 ± 21	325 ± 66***	231 (115 to 346)***
Ferritin < 100 ng/mL	8 (67)	9 (82)	8 (67)	0 (0)***	–
Transferrin saturation [%]	19.0 ± 2.1	20.6 ± 1.8	19.2 ± 2.5	28.3 ± 1.6 **	7.4 (1.8 to 13.1)*
Transferrin saturation < 20%	8 (67)	6 (55)	7 (58)	1 (9)	–
Iron deficiency [%]	12 (100)	11 (100)	11 (92)	3 (27)***	–
Hemoglobin [g/dL]	13.6 ± 0.3	13.6 ± 0.3	13.6 ± 0.3	13.8 ± 0.3	0.2 (–0.5 to 0.8)
Inflammatory status					
High sensitive CRP [mg/L]	3.4 ± 0.9	2.3 ± 0.7	3.3 ± 1.1	3.2 ± 0.9	1.0 (–1.2 to 3.2)
TNF-alfa [pg/mL]	0.50 ± 0.00	7.05 ± 5.12	1.07 ± 0.38	0.50 ± 0.00	–7.13 (–18.57 to 4.32)
IL-1beta [pg/mL]	0.10 ± 0.05	0.05 ± 0.00	0.07 ± 0.02	0.18 ± 0.13	0.16 (–0.15 to 0.47)
IL-6 [pg/mL]	5.62 ± 1.99	3.15 ± 0.94	3.70 ± 1.08	5.71 ± 1.88	3.43 (–2.16 to 9.02)
IL-22 [pg/mL]	52.75 ± 16.45	51.63 ± 7.38	48.92 ± 7.20	46.75 ± 4.33	–16.96 (–38.69 to 4.77)
Oxidative status					
GST [nmol/min/mL]	2.76 ± 037	2.05 ± 0.51	2.65 ± 0.26	2.76 ± 0.36	0.61 (–0.78 to 1.99)
Catalase [nmol/min/mL]	49.27 ± 6.69	45.64 ± 8.19	55.43 ± 6.10	40.38 ± 5.12	–12.01 (–39.08 to 15.06)
SOD [U/mL]	0.41 ± 0.07	0.29 ± 0.04	0.28 ± 0.06	0.23 ± 0.06	0.01 (–0.16 to 0.18)

Data is presented as mean ± standard error of mean for continues variables, numbers with percent for categorized variables; CI — confidence interval; IV FCM — intravenous ferric carboxymaltose; 6MWT — six-minute walk test; CRP — C-reactive protein; TNF — tumor necrosis factor; IL — interleukin; GST — glutathione S-transferase; SOD — superoxide dismutase; *p < 0.05; **p < 0.01; ***p < 0.001

There is enormous evidence demonstrating that IV iron supplementation improves quality of life and exercise capacity in patients with HF among all other approved symptomatic therapies [9, 10, 25]. Importantly, these effects seem to be independent on the effects of erythropoiesis [26, 27]. It is suggested that iron incorporated in iron-depleted myocardial and skeletal muscles and acting locally improves energy metabolism. There is substantial experimental evidence demonstrating, in vitro, that iron supplementation improves the function of cardiomyocytes and skeletal myocytes, and these effects are partially due to better function of mitochondria in these tissues [28–31].

The current study provides complementary evidence to data published by Charles-Edwards et al. [19]. The authors demonstrated that intravenous repletion of iron deficiency by iron isomaltoside enhanced skeletal muscle energetics in iron deficient patients with HF, as reflected by shorter PCr recovery half-times (PCr $t_{1/2}$) on phosphorus magnetic resonance spectroscopy [19]. In the present study another measure was applied allow-

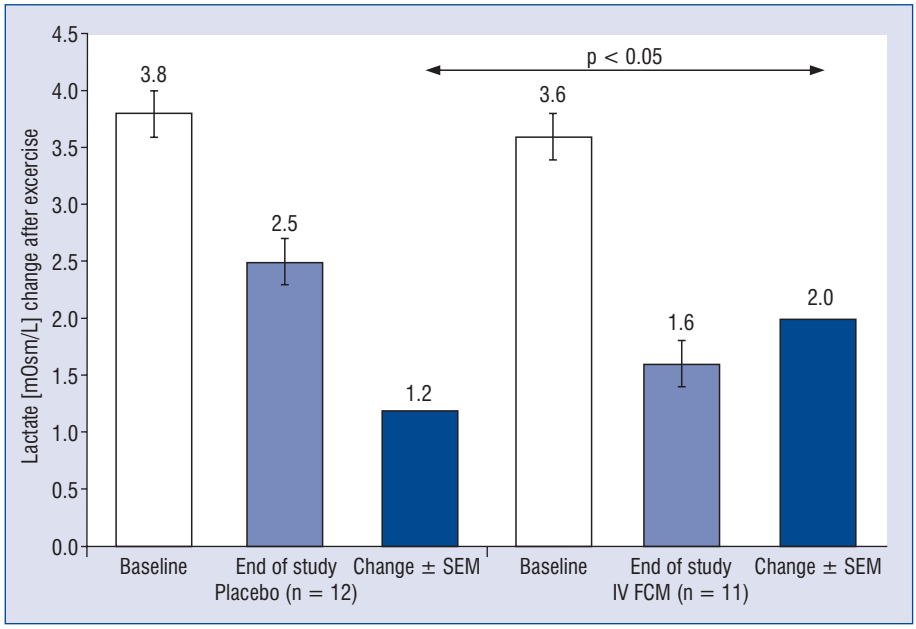

Figure 1. Reduction in exertional in vivo lactate production in skeletal muscles in men with heart failure with reduced ejection fraction due to intravenous iron therapy as compared to placebo; IV — intravenous; FCM — ferric carboxymaltose; SEM — standard error of mean.

ing assessment in vivo energetics of exercising skeletal muscles [21]. Lactates were measured in antecubital fossa veins that are connected to deep veins of the forearm draining forearm flexors and metabolites detected in this area reflect in vivo, the metabolism of exercising forearm muscles.

Limitations of the study

This was a relatively small mechanistic study including a small number of subjects in both study arms. Moreover, the study was limited only to men and patients with HFrEF.

Due to the small group of respondents, in order to maintain the homogeneity of the group, only men were included in the study.

Taking into account the influence of hormones on skeletal muscles the decision was dictated by the exclusion of hormonal variability among both sexes.

It was fully agreed that further studies in larger and more diverse populations are warranted to confirm and generalize these findings.

Nevertheless, the methodology applied used previously to investigate directly in vivo energetics of skeletal muscles in HF.

Conclusions

Intravenous iron supplementation in men with HFrEF improves the functioning of skeletal muscles via an improvement in energy metabolism in exercising skeletal muscles, limiting the contribution of anaerobic reactions generating ATP as reflected by a lower in vivo lactate production in exercising muscles in patients with repleted iron stores.

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Bivalirudin versus heparin in contemporary percutaneous coronary interventions for patients with acute coronary syndrome: A systematic review and meta-analysis

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Abstract

Background: *Bivalirudin is associated with fewer major bleeding events than heparin in patients undergoing percutaneous coronary intervention (PCI), but confounding effects of concomitant glycoprotein IIb/IIIa inhibitors, routine femoral artery access, and less potent effects of clopidogrel limits meaningful comparisons. The present study is a systematic review and meta-analysis to compare bivalirudin to heparin in contemporary practice.*

Methods: *The Cochrane Library, PubMed, EMBASE, and Ovid MEDLINE databases were searched for relevant studies, including comparisons between bivalirudin and heparin in the current medical era from inception to December 23, 2021. Studies reporting incidences of major adverse cardiac events (MACE) and net adverse clinical events (NACE) in patients undergoing PCI and meeting the inclusion criteria were retained. Data extraction was performed by three independent reviewers.*

Results: *The meta-analysis included 8 studies. Compared to heparin, bivalirudin during PCI was associated with a lower NACE risk, lower all-cause death, and similar MACE risk, with a pooled risk ratio of 0.82 (95% confidence interval [CI] 0.69–0.97, p = 0.02), 0.83 (95% CI 0.74–0.94, p = 0.002), and 0.93 (95% CI 0.78–1.10, p = 0.38), respectively. Moreover, the reduction in NACE was mainly attributed to reduced bleeding (22% reduction in the risk of major bleeding, 95% CI 0.63–0.97, p = 0.03).*

Conclusions: *These findings suggest that bivalirudin use during PCI reduced the risk of NACE and all-cause death but did not reduce the risk of MACE compared with heparin use in PCI. More studies specifically designed for anticoagulation strategies and a personalized anticoagulation regimen to comprehensively balance bleeding and ischemia risks are required.* (Cardiol J 2024; 31, 2: 309–320)

Keywords: percutaneous coronary intervention, bivalirudin, heparin, contemporary practices, mortality

Introduction

Primary percutaneous coronary intervention (PCI) is the optimum reperfusion strategy for patients presenting with acute myocardial infarction [1]. In the procedural phase, anticoagulant drugs combined with antiplatelet therapy are the accepted standard for preventing adverse ischemic events [2]. Bivalirudin is a direct thrombin inhibitor, working via the highly specific inhibition of thrombin. It can

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prolong activated clotting time to prevent thrombus formation during catheterization, and its inhibition of thrombin is reversible and short-lived [3, 4]. Earlier studies, such as the HORIZONS-AMI [5] and EUROMAX [6] trials, showed that anticoagulation with bivalirudin, compared to heparin plus glycoprotein IIb/IIIa inhibitors (GPI), reduced the risk of death and bleeding but increased the incidence of acute stent thrombosis. Subsequently, the HEAT-PPCI trial [7] revealed that the bleeding risks of bivalirudin and heparin were comparable, but increased rates of acute stent thrombosis were observed in the bivalirudin group. In view of this, the BRIGHT trial [8] proposed the concept of the "antithrombosis empty window period" within 4 hours after PCI because of the short--term antithrombotic effect of bivalirudin and the delayed pharmacodynamic effects of clopidogrel and demonstrated that the use of bivalirudin with a median 3-hour post-procedure PCI-dose infusion resulted in a decrease in bleeding events, without significant differences in major adverse cardiac, cerebral events, or stent thrombosis.

However, significant advances have occurred in pharmacological therapy and PCI technology in the past 20 years. For example, the recent preferred use of radial-artery access and bailout GPI is associated with fewer major bleeding complications [9–11]. Moreover, the current recommended use of potent $P2Y_{12}$ inhibitors in patients with acute coronary syndrome (ACS) undergoing PCI and in chronic coronary syndrome patients with PCI and a high ischemia risk may also confound clinical outcomes [12–14]. According to the current practice, it is unclear whether bivalirudin performs better than heparin in PCI, especially in ACS patients. Thus, this study aimed to review the outcome of bivalirudin versus heparin use in PCI according to the current practice.

Methods

Search strategy

This meta-analysis was performed in compliance with the PRISMA statement [15]. The study protocol was registered with PROSPERO (ID: CRD42022302633) at onset. PubMed, Embase, Ovid MEDLINE, and Cochrane Library databases were systematically searched for relevant studies from January 1, 2000 until December 23, 2021. The following medical subject heading terms and keywords were used to identify relevant articles: "bivalirudin" or "angiomax" or "hirulog" or "antithrombin", and "coronary stenting" or "percutaneous coronary intervention" or "PCI" or "angioplasty" or "coronary angioplasty" or "stents". Both randomized controlled trials (RCTs) and cohort studies were included, excluding other study designs (cross-sectional and case-control studies). The references of studies were also checked for suitable articles. No language restriction was applied.

Study selection

Several assessments were performed, followed by the removal of duplicate articles after the initial screening. The titles and abstracts of relevant publications were further screened for suitability before full article retrieval. Additionally, meeting abstracts, editorials, and reviews were also checked and excluded from the analysis [16]. Studies included were those that: 1) compared bivalirudin with heparin in PCI; 2) were published in peer-reviewed journals with available full texts; 3) reported cardiovascular clinical outcomes; 4) reported the bailout use of GPI; 5) included the use of radial-artery access and potent $P2Y_{12}$ inhibitors; and 6) included mainly patients with ACS. Trials with the routine use of GPI, exclusive use of femoral-artery access, or clopidogrel were excluded. Three investigators (ZXC, JYZ, and FBL) independently reviewed all retrieved studies, and differences were resolved via consensus.

Data extraction and quality assessment

Study data, including the first author's name, study design, location of study, sample size, clinical baseline characteristics, post-procedure infusion of bivalirudin, types of major adverse cardiac events (MACE), types of net adverse clinical events (NACE), frequency of patients in the bivalirudin and heparin groups, and incidence of mortality, were independently extracted by three investigators (JYZ, ZXC, CL). The definitions of MACE and NACE endpoints differed slightly between studies, but MACE basically included death, myocardial infarction (MI), and stroke, while NACE basically included MI, death from any cause, stroke, and major bleeding (see Table 3). The study quality was evaluated according to the Newcastle-Ottawa Quality scale. High-quality studies were defined as studies with a modified Newcastle-Ottawa score of ≥ 5 (maximum, 9).

Statistical analysis

Risk ratios of NACE, MACE, and particular events were estimated for each study between the bivalirudin and heparin groups. The heterogeneity

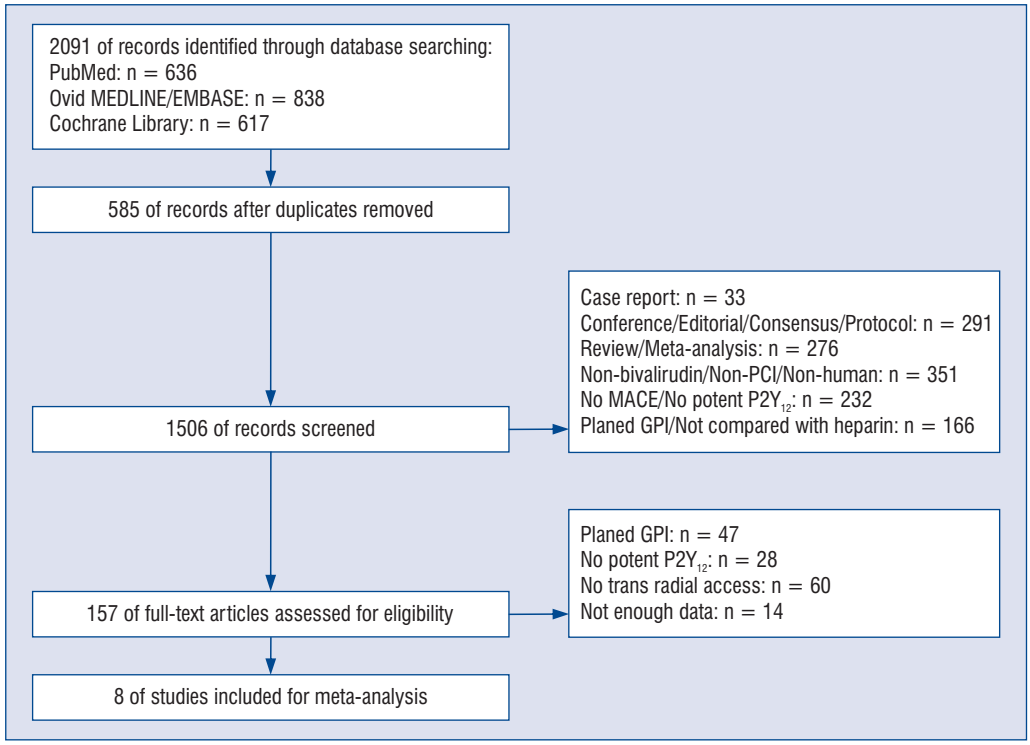

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) flow diagram of the study selection. PCI — percutaneous coronary intervention; DAPT — dual antiplatelet therapy; GPI — glycoprotein IIb/IIIa inhibitors; MACE — main adverse cardiac events.

of the effect measure was assessed by the Q and I^2 statistics. A random-effects model (DerSimonian and Laird method) was applied if heterogeneity was detected ($p < 0.10$ or $I^2 \geq 25\%$); otherwise, a fixed-effects model (Mantel-Haenszel) was used. Subgroup analyses were conducted by the study design (randomized vs. cohort) and by bivalirudin infusion strategies during PCI (extended vs. non-extended). Sensitivity analyses, excluding one study at a time, were performed to clarify whether the results were due to a study with an extreme result. Publication bias was assessed using the Begg adjusted rank correlation test and Egger regression asymmetry test. A p-value of < 0.05 was considered statistically significant. R version 4.1.2 software were used for the statistical analyses.

Results

Study selection

Six hundred thirty six publications were identified in PubMed, 617 publications in the Cochrane Library, and 838 publications in EMBASE and Ovid MEDLINE combined. Of these 2091 studies, 585 were duplicates. Eight of the remaining studies [6, 7, 17–22] met the inclusion criteria. Details of the search strategy are shown in Figure 1.

Study characteristics and quality assessment

Of the 8 included studies [6, 7, 17–22], 4 were randomized trials or prespecified subgroup analyses of randomized trials, whereas the others were retrospective or prospective cohort studies. Five of the included studies reported the NACE rates between the bivalirudin and heparin groups [6, 17–19, 21], while 7 reported MACE rates [6, 7, 17–21]. Three of the included studies had subgroups or cohorts with extended post-procedure infusion of bivalirudin [6, 18, 21]. The mean risk-of--bias score in the Newcastle-Ottawa scale was 8.3, and all included studies were high quality (score > 5). For the quality assessment of RCTs, the scale mainly included the following: (1) generation of random sequence (selection bias); (2) concealment of distribution sequence (selection bias); (3) blind method for research object and implementer (implementation bias); (4) blind method for result evaluation (measurement bias); (5) incomplete result (loss of follow-up bias); (6) selective report

(report bias); and (7) other bias. The general characteristics and definitions of outcome events in the included studies are summarized in Tables 1–3.

Risk of NACE in ACS patients undergoing PCI with bivalirudin vs. heparin

Five of the studies with NACE as the outcome provided the number of patients with bivalirudin and heparin. The effects of bivalirudin were heterogeneous among these studies, with a pooled risk ratio of 0.82 (95% confidence interval [CI] 0.69–0.97, p = 0.03, Fig. 2). This suggests that patients with ACS undergoing PCI with bivalirudin had an 18% reduction in NACE risk compared to those using heparin during the procedure. This calculation also revealed a significant reduction in bleeding in the bivalirudin group compared to the heparin group, with a pooled risk ratio of 0.78 (Fig. 2). The subgroup of patients that received an extended bivalirudin infusion after PCI had a 27% reduction in NACE risk compared to those using heparin during PCI, with a pooled risk ratio of 0.73 (95% CI 0.55–0.98, p < 0.01, Fig. 3).

Risk of MACE in ACS patients undergoing PCI with bivalirudin vs. heparin

Seven of the studies with MACE as the outcome provided the number of patients with bivalirudin or heparin during PCI. The effects of bivalirudin were heterogeneous among these studies, with a pooled risk ratio of 0.93 (95% CI 0.78–1.10, p = 0.38). Patients with ACS undergoing PCI with bivalirudin showed a reduced risk of all-cause mortality (Fig. 2) compared to those that used heparin during the procedure. However, the risk of cardiac death, MI, ischemic stroke, or stent thrombosis was similar between the two groups.

A subgroup analysis was performed of post--procedure bivalirudin infusions compared with heparin use during the procedure; bivalirudin demonstrated superior performance in the subgroup. Bivalirudin resulted in a decrease in NACE, greater decrease in major bleeding events, and lower risk of stent thrombosis (Fig. 3) compared with the group that did not use post-procedure bivalirudin infusion. In this subgroup, bivalirudin still reduced the risk of all-cause death and cardiac death (**Suppl. Fig. 1**) in patients undergoing PCI.

Furthermore, a subgroup analysis was performed of all RCT studies, which showed similar results as those above, including a decrease in NACE, without an increase in MACE or stent thrombosis events (**Suppl. Fig. 2**).

Stratified analysis and publication bias

To explore the study heterogeneity, stratified analyses across several key study characteristics and clinical factors was performed. Examining RCTs and non-randomized studies separately showed similar conclusions compared to when both study types were combined. The Egger weighted regression and Begg rank correlation approaches found no evidence of publication bias in the reporting of the findings.

Discussion

This systematic review and meta-analysis examined the effectiveness and safety of bivalirudin compared with heparin in contemporary PCI. According to available research, this is the first meta-analysis in the current medical era to assess this topic in this population. The present findings indicated that patients with ACS using bivalirudin during PCI had an 18% reduction in NACE risk compared to those using heparin. The reduction in NACE was mainly attributed to a reduction in bleeding. In addition, bivalirudin use in patients with ACS undergoing PCI did not show an increased risk of MACE, including stent thrombosis, compared to those with heparin use during PCI. Moreover, compared with the subgroup of non-extended bivalirudin infusion, the extended infusion subgroup showed reduced all-cause death and cardiac death when the heparin group was used as a control, which was most likely due to the reduced incidence of ischemic cardiovascular events in the early postprocedural period.

These results demonstrate that using bivalirudin is feasible and favorable in patients with ACS undergoing PCI because it does not increase MACE while reducing bleeding events. However, the proportion of transradial access, potency of the $P2Y_{12}$ inhibitors administered, type of stent, and use of extended infusion after PCI varied among the included studies. These factors may lead to the fluctuation of the benefit difference between bivalirudin and heparin. Moreover, age, sex, combined hypertension, combined diabetes, renal insufficiency, and lesion characteristics may also contribute to the different outcomes for patients undergoing PCI with bivalirudin or heparin. Because these heterogenous factors may confound the results, more studies comparing bivalirudin and heparin alone in contemporary clinical practice are needed to illustrate the best anticoagulation regimens during PCI.

Table 1. Baseline characteristics of the included studies.

Research, year	Study type	Quality score	Setting	Type of patients	Study design	Bolus after procedure
Zhang, 2020	Cohort study	7	The First Affiliated Hospital of Zhengzhou University	High-bleeding--risk ACS	Retrospective	Bivalirudin for up to 4 h after the procedure
Chen, 2020	Cohort study	8	The First Affiliated Hospital of USTC	STEMI	Retrospective	
HEAT-PPCI, 2014	RCT	8	Liverpool Heart and Chest Hospital (UK)	STEMI	Prospective	
MATRIX, 2018	RCT	9	78 hospitals in Italy, the Netherlands, Spain, and Sweden	ACS	Prospective	Full dose for up to 4 h or at a reduced dose of 0.25 mg/kg/h for at least 6 h
VALIDATE-SWEDEHEART, 2017	RCT	9	Uppsala Clinical Research Center	STEMI and NSTEMI	Prospective	
NCDR CathPCI, 2017	Cohort study	8	More than 1,800 sites across the United States	STEMI	Prospective	
SWEDEHERT, 2016	Observational registry study	8	Swedish Coronary Angiography and Angioplasty Register (SCAAR)	STEMI	Prospective	
EUROMAX, 2014	Pre-speciedanalysis	9	Nine European countries	STEMI	Prospective	The infusion of bivalirudin should be continued for at least 4 h after PCI at a dose of be 0.25 mg/kg/h; however, continuation of the full dose (1.75 mg/kg/h) used during PCI was also permitted

ACS — acute coronary syndrome; DAPT — dual antiplatelet therapy; PCI — percutaneous coronary intervention; RCT — randomized controlled trial; STEMI — ST-segment elevation myocardial infarction

Table 2. Baseline characteristics of the included studies.

Research, year	Age, years	Male, n (%)	Hypertension, n (%)	Diabetes, n (%)	Dyslipidemia, n (%)	CKD, n (%)	Previous PCI, n (%)
Zhang, 2020							
Bivalirudin (n = 361)	69.4 ± 10.1	213 (59.0%)	242 (67.0%)	130 (36.0%)	–	99 (27.4%)	92 (25.5%)
Heparin (n = 462)	66.4 ± 11.0	252 (54.5%)	302 (65.4%)	188 (40.7%)	–	133 (28.8%)	120 (26.0%)
Chen, 2020							
Bivalirudin (n = 412)	80.34 ± 4.54	257 (62.4%)	–	–	–	–	–
Heparin (n = 260)	78.73 ± 3.92	157 (60.4%)	–	–	–	–	–
HEAT-PPCI, 2014							
Bivalirudin (n = 905)	62.9 (53.7, 74.0)	647 (71.5%)	362 (40%)	114 (13%)	327 (37%)	–	76 (8%)
Heparin (n = 907)	63.6 (54.0, 73.8)	663 (73.1%)	388 (43%)	136 (15%)	342 (38%)	–	54 (6%)
MATRIX, 2018							
Bivalirudin (n = 3610)	65.4 ± 11.9	2731 (75.7%)	2264 (62.7%)	824 (22.8%)	1596 (44.2%)	48 (1.3%)	536 (14.8%)
Heparin (n = 3603)	65.4 ± 11.9	2764 (76.7%)	2222 (61.7%)	793 (22.0%)	1558 (43.2%)	47 (1.3%)	504 (14.0%)
VALIDATESWEDEHEART, 2017							
Bivalirudin (n = 3004)	68 (59, 75)	2229 (74.2%)	1557 (51.8%)	491 (16.3%)	953 (31.7%)	–	456 (15.2%)
Heparin (n = 3002)	68 (60, 75)	2177 (72.5%)	1548 (51.6%)	508 (16.9%)	936 (31.2%)	–	426 (14.2%)
NCDR CathPCI, 2017							
Bivalirudin (n = 29660)	60.3 ± 12.3	22,201 (74.9%)	19,456 (65.6%)	7,553 (25.5%)	17,009 (57.4%)	–	5,331 (18.0%)
Heparin (n = 37708)	60.4 ± 12.4	28,294 (75.0%)	24,707 (65.5%)	9,432 (25.0%)	21,742 (57.7%)	–	6,917 (18.3%)
SWEDEHERT, 2016							
Bivalirudin (n = 16891)	67.7 ± 12	11841 (70.1%)	7432 (44%)	2415 (14.3%)	3547 (21%)	/	1351 (8%)
Heparin (n = 3724)	68.7 ± 12	2530 (68%)	1748 (47%)	543 (14.6%)	893 (24%)	–	398 (10.7%)
EUROMAX, 2014							
Bivalirudin (n = 1089)	61 (52, 71)	814 (21.9%)	459 (42.2%)	127 (11.7%)	398 (36.6%)	147 (14.7%)	97 (8.9%)
Heparin (n = 460)	62 (53, 73)	356 (77.4%)	243 (52.8%)	80 (17.4%)	417 (37.6%)	165 (16.5%)	51 (11.1%)

CKD — chronic kidney disease; PCI — percutaneous coronary intervention

The main factors influencing the effect of periprocedural anticoagulation (bivalirudin or heparin) are discussed below.

Bailout uses of GPI

Bivalirudin is associated with fewer major bleeding events than heparin in patients undergoing PCI, but the confounding effect of concomitant GPI limits a meaningful comparison. Anantha--Narayanan et al. [23] performed a systematic review and meta-analysis to compare bivalirudin and heparin with and without adjunctive GPI in PCI. The study included 26 comparison groups (22 original studies and 4 subgroup analyses) with

Table 3. Baseline characteristics of the included studies.

Research, year	Previous MI, n (%)	Current smoking, n (%)	Transradial access, n (%)	Potent $P2Y_{12}$, n (%)	Outcome measurement	NACE	MACE or MACCE
Zhang, 2020							
Bivalirudin (n = 361)	89 (24.7%)	104 (28.8%)	333 (92.2%)	229 (63.4%)	30 days	All-cause death, recurrent MI, ischemia-driven target vessel revascularization, stroke, and BARC 2–5 bleeding events	MI, death from any cause, or stroke
Heparin (n = 462)	107 (23.2%)	128 (27.7%)	405 (87.7%)	315 (68.2%)			
Chen, 2020							
Bivalirudin (n = 412)	32 (7.8%)	86 (20.9%)	347 (84.2%)	–	1 year		All-cause death, recurrent MI, ischemia-driven target vessel revascularization, and stroke
Heparin (n = 260)	27 (10.4%)	41 (15.8%)	234 (90.0%)	–			
HEAT-PPCI, 2014							
Bivalirudin (n = 905)	122(14%)	–	727 (80%)	801(89.0%)	28 days	All-cause mortality, MI, stroke, or BARC 3 or 5	All-cause mortality, cerebro-vascular accident, reinfarction, or additional unplanned target lesion revascularization
Heparin (n = 907)	93 (10%)	–	744 (82%)	819(91.0%)			
MATRIX, 2018							
Bivalirudin (n = 3610)	530 (14.7%)	1307 (36.2%)	1676 (46.4%)	713 (19.8%)	1 year	Death from any cause, MI, or major bleeding	All-cause mortality, MI, or stroke
Heparin (n = 3603)	501 (13.9%)	1302 (36.1%)	1688 (46.8%)	690 (19.2%)			
VALIDATESWEDEHEART, 2017							
Bivalirudin (n = 3004)	490 (16.3%)	716 (23.8%)	2708 (90.1%)	2916 (97.1%)	30 days		
Heparin (n = 3002)	484 (16.1%)	710 (23.7%)	2716 (90.5%)	2927 (97.5%)			
NCDR CathPCI, 2017							
Bivalirudin (n = 29660)	4,894 (16.5%)	–	29660 (100%)	14521 (47.7%)	30 days		Death, MI, stroke
Heparin (n = 37708)	6,384 (16.9%)	–	37708 (100%)	15777 (51.1%)			
SWEDEHERT, 2016							
Bivalirudin (n = 16891)	2010 (11.9%)	5219 (30.9%)	10641 (63%)	–	1 year		Death, MI, stroke
Heparin (n = 3724)	617 (16.6%)	1038 (27.9%)	2269 (61%)	–			
EUROMAX, 2014							
Bivalirudin (n = 1089)	80 (7.4%)	–	510 (47.7%)	578 (60.5%)	30 days	Death, MI, IDR, stroke, or major bleeding	Death, MI, IDR, or stroke
Heparin (n = 460)	48 (10.4%)	–	245 (54.1%)	194 (50.9%)			

IDR — ischemia-driven revascularization; BARC — Bleeding Academic Research Consortium; MACE — major adverse cardiac event; MI — myocardial infarction; NACE — net adverse cardiac event; ST — stent thrombosis

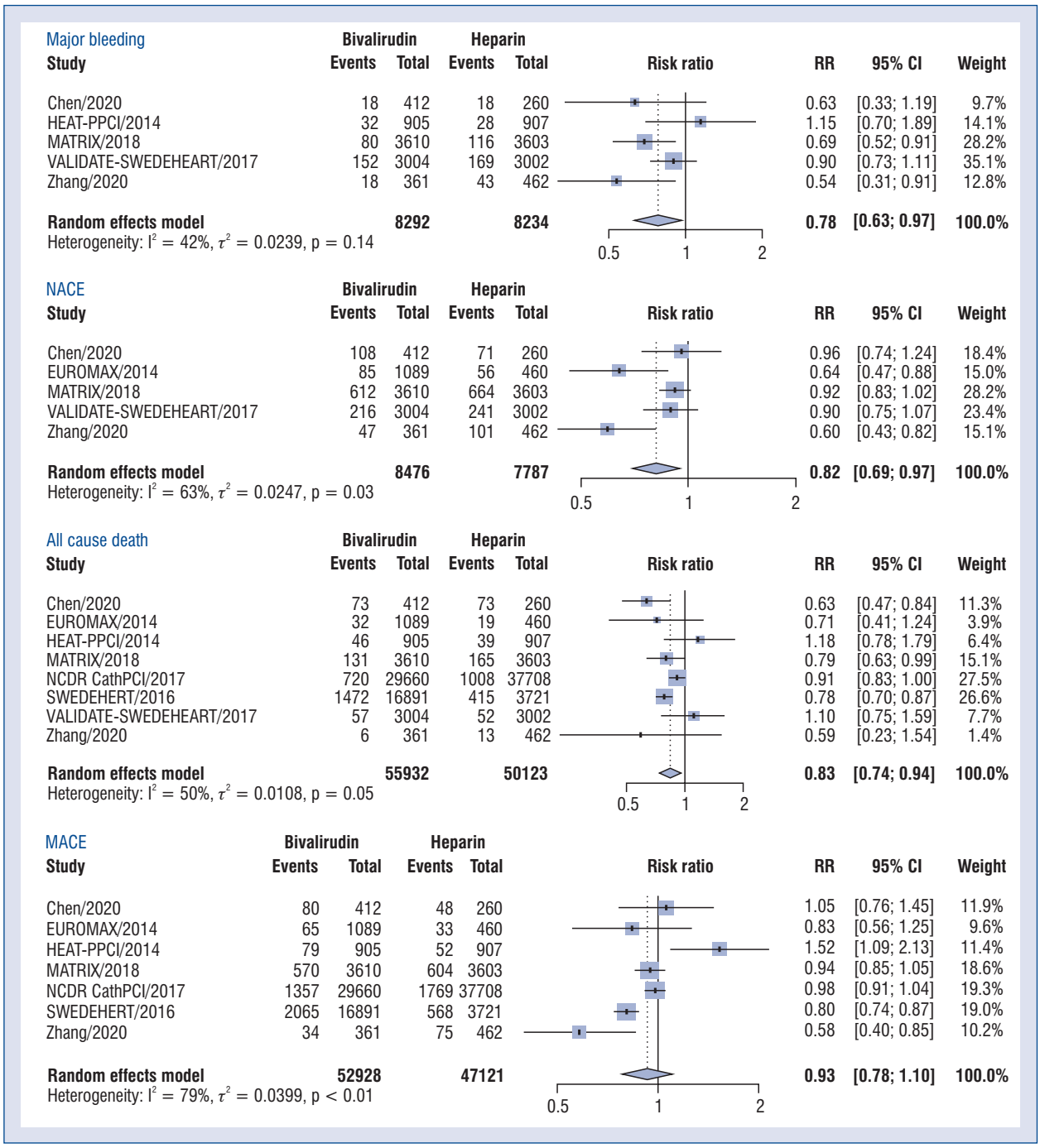

Figure 2. Pooled relative risks of net adverse clinical events (NACE), all-cause death, main adverse cardiac events (MACE), and major bleeding in patients receiving bivalirudin vs. heparin during percutaneous coronary intervention. Major bleeding was defined as a bleeding event of the Bleeding Academic Research Consortium (BARC) type 2, 3, and 5 or BARC 3 and 5 according to the included studies; RR — risk ratio.

53,364 patients and demonstrated that bivalirudin use is associated with a lower risk of major bleeding regardless of GPI use in the heparin arm. This persisted even after retaining studies with GPI use in the bivalirudin arm, which was expected to bias the results towards the null. The prespecified analysis from the EUROMAX trial yielded a similar conclusion [24], which illustrates that bivalirudin reduces major bleeding compared to that using heparin therapy with bailout or routine GPI. The trial also indicated that routine GPI was not superior to bailout GPI regarding MACE or stent

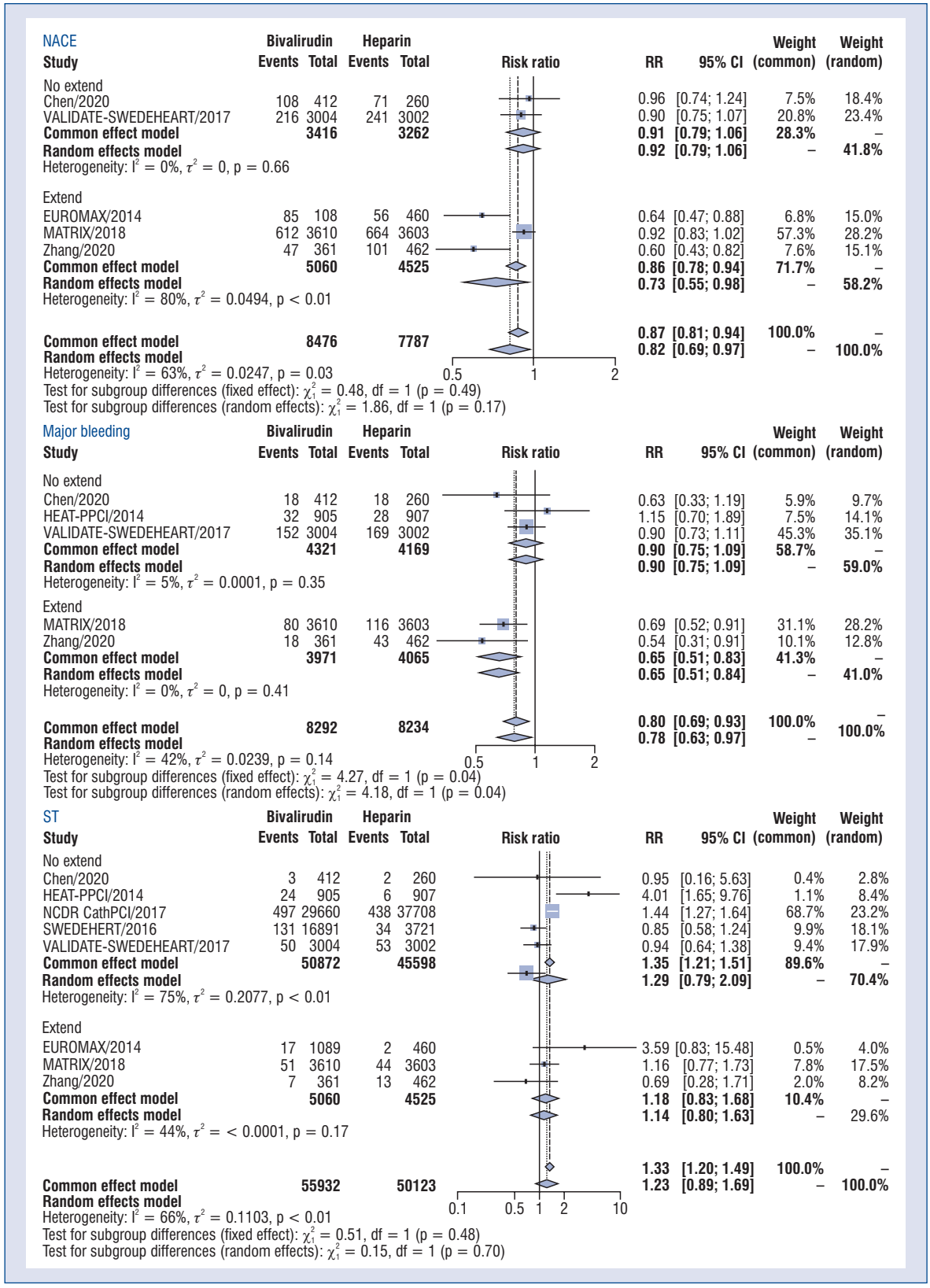

Figure 3. Pooled relative risks of net adverse clinical events (NACE), stent thrombosis (ST), and major bleeding in patients receiving bivalirudin vs. heparin in the extended infusion subgroup. Major bleeding was defined as a bleeding event of the Bleeding Academic Research Consortium (BARC) type 2, 3, and 5 or BARC 3 and 5 according to the included studies; RR — risk ratio.

thrombosis. Bailout GPI is still a relevant choice currently because routine GPI use does not appreciably prevent ischemic events, such as MACE and stent thrombosis.

Preferred transradial coronary interventions

In the era of femoral artery access, several studies have shown that bivalirudin reduced the risk of bleeding in patients compared to that of heparin. However, it is unclear if the bleeding benefit of bivalirudin remains relevant considering the current increase in the use of transradial access. MacHaalany et al. [9] conducted research involving all-comers and demonstrated no additional benefit in terms of the bleeding risk with the use of bivalirudin compared with the use of heparin when PCI was performed via radial access. Moreover, a study conducted by Jovin et al. [20] with patients from the NCDR CathPCI database in whom PCI was predominantly performed via radial access showed that the risk of bleeding did not significantly differ between the bivalirudin and heparin groups. These results illustrated that the ability of bivalirudin to prevent bleeding is attenuated among patients that undergo PCI via transradial access [25]. However, with the bailout use of GPI and the emergence of the bivalirudin extended infusion strategy, the advantages of bivalirudin have been rediscovered. In a meta-analysis by Kheiri et al. [26] that included 10 RCTs with 16,328 patients for whom transradial access during PCI was exclusively performed, the use of bivalirudin was significantly associated with a reduction in short-term NACE (30-day) compared with heparin. Moreover, in the BRIGHT study, the majority of the patients (79%) had radial access, and bivalirudin still exhibited a bleeding benefit [8]. This finding is consistent with the results of the current study, which suggests that although theoretically possible, the advantage of bivalirudin in reducing bleeding might be attenuated by transradial access, and it may still benefit patients in the contemporary medical setting.

Post-procedure bivalirudin infusion

In the present study, subgroup analysis showed that patients had better outcomes with respect to MACE, cardiac death, and stent thrombosis, when extended infusion strategy of bivalirudin was chosen. A single-center study by Frere et al. [27] prospectively enrolled 30 patients undergoing PCI for non-ST elevation ACS to investigate the antithrombotic efficacy of bivalirudin compared to unfractionated heparin during PCI. The study showed that an optimal inhibition of platelet reactivity was obtained 4 h after the PCI procedure. Another reason that patients with STEMI require a post-procedure PCI-dose of bivalirudin is that morphine and early gastrointestinal mucosal edema in STEMI inhibit the effect of $P2Y_{12}$ inhibitors [28]. Previous post hoc analyses have suggested that a prolonged infusion of high-dose bivalirudin after the procedure may prevent early stent thrombosis [16, 17]. As noted earlier, the BRIGHT trial proposed the concept of an "antithrombosis empty window period" within 4 hours after surgery because of the short antithrombotic effect of bivalirudin and the delayed pharmacodynamic effects of clopidogrel. The study demonstrated no significant differences in major adverse cardiac or cerebral events or stent thrombosis between the bivalirudin group with a median 3-h post-procedure PCI-dose infusion and those with heparin and GPI, while bivalirudin resulted in a decrease in bleeding events [8]. Moreover, Fahrni et al. [29] conducted a meta-analysis to compare the effect of prolonged PCI-dose bivalirudin infusion on clinical outcomes in patients undergoing primary PCI. The study included 6 RCTs comprising 17,294 patients and showed that prolonging the bivalirudin infusion at the PCI dose (1.75 mg/kg/h) for 3 h eliminated excess risk of acute stent thrombosis and maintained bleeding benefits [30]. Valgimigli et al. [21] reported outcomes of the MATRIX trial, where 3,610 patients were assigned to receive bivalirudin with or without prolonged post-PCI bivalirudin infusion. The results showed that a post-PCI full-dose bivalirudin infusion was associated with improved outcomes when compared with a no or low-dose post-PCI infusion or heparin. These findings suggest that the infusion of bivalirudin after PCI is effective in reducing the incidence of stent thrombosis in the early postoperative period without increasing the patient's risk of bleeding. However, these studies mostly occurred in the era without potent $P2Y_{12}$ inhibitors, radial artery access, or routine GPI.

The BRIGHT-4 study is a randomized controlled clinical trial that aimed to compare the treatment of post-PCI bivalirudin high-dose infusion with heparin monotherapy. The study found that the treatment of post-PCI bivalirudin high--dose infusion can reduce the relative risk of primary endpoint events by 31% (3.06% vs. 4.39%, $p = 0.0070$) compared with heparin monotherapy, including a 25% relative risk reduction in all-cause mortality (2.96% vs. 3.92%, $p = 0.0420$) and a 79% relative risk reduction in major bleeding (0.17% vs.

0.80%, p = 0.0014) within 30 days [32]. This study mainly used the potent $P2Y_{12}$ inhibitor ticagrelor, with the majority using the radial artery approach and without routine use of GPI, all of which suggest that the BRIGHT-4 study is more in line with contemporary clinical practices. Although the results of the BRIGHT-4 study were not yet published at the time of this meta-analysis, the conclusion of the present study is almost identical to the conclusion of the BRIGHT-4 study. Both studies suggest that bivalirudin has great value and prospects in today's clinical context. Therefore, based on the data included in this meta-analysis and the conclusion of the BRIGHT-4 study, it is believed herein, that in the next version of the guidelines, although the recommendation of bivalirudin may not replace heparin as the routine anticoagulant used in PCI due to the long-term experience with heparin and its simpler administration method, the recommendation level of bivalirudin may increase.

Limitations of the study

There were some limitations to the current study. First, the meta-analysis included both RCTs and cohort studies, which enhanced the heterogenicity of the studies, as observational data are subject to possible observable and unobservable confounding factors. Second, definitions for MACE and NACE were not consistent across studies, and this might have resulted in measurement bias because some studies reported NACE with major bleeding alone, whereas some included only minor bleeding. Third, the proportions of GPI, novel $P2Y_{12}$ inhibitors, and radial access differed among studies, which also contributed to the heterogeneity of this study. Finally, because the BRIGHT-4 study was not published before December 2021, when the search was completed for this meta-analysis, the BRIGHT-4 study was not included in this study.

Conclusions

Previous studies revealed that bivalirudin reduced the incidence of major bleeding in patients with ACS undergoing PCI compared to those receiving heparin, but it increased the risk of postoperative stent thrombosis. The meta-analysis, herein, revealed that bivalirudin is favorable in PCI in contemporary practice because it did not increase the risk of MACE and reduced the risks of NACE and all-cause death. In the contemporary medical era, with the use of new $P2Y_{12}$ antagonists and post-procedure bivalirudin infusion, the efficacy and safety of bivalirudin is reiterated. In conclusion, bivalirudin may be a better choice for patients with ACS during PCI compared with heparin alone in current medical practice.

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Advancements in artificial intelligence-driven techniques for interventional cardiology

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Abstract

This paper aims to thoroughly discuss the impact of artificial intelligence (AI) on clinical practice in interventional cardiology (IC) with special recognition of its most recent advancements. Thus, recent years have been exceptionally abundant in advancements in computational tools, including the development of AI. The application of AI development is currently in its early stages, nevertheless new technologies have proven to be a promising concept, particularly considering IC showing great impact on patient safety, risk stratification and outcomes during the whole therapeutic process. The primary goal is to achieve the integration of multiple cardiac imaging modalities, establish online decision support systems and platforms based on augmented and/or virtual realities, and finally to create automatic medical systems, providing electronic health data on patients. In a simplified way, two main areas of AI utilization in IC may be distinguished, namely, virtual and physical. Consequently, numerous studies have provided data regarding AI utilization in terms of automated interpretation and analysis from various cardiac modalities, including electrocardiogram, echocardiography, angiography, cardiac magnetic resonance imaging, and computed tomography as well as data collected during robotic-assisted percutaneous coronary intervention procedures. Thus, this paper aims to thoroughly discuss the impact of AI on clinical practice in IC with special recognition of its most recent advancements. (Cardiol J 2024; 31, 2: 321–341)

Keywords: artificial intelligence (AI), interventional cardiology (IC), cardiac modalities, augmented and/or virtual realities, automatic medical systems

Introduction

Artificial intelligence (AI), and in particular machine learning (ML), allows for the processing and analysis of huge amounts of medical data in real time, and will prove to be revolutionary for healthcare systems. AI is developing very fast particularly in the field of cardiology, ranging from electrocardiography (ECG) interpretation to clinical decision support systems for cardiac interventional procedures [1, 2]. According to recent updates of medical devices approved by the United States Food and Drug Administration (FDA) for general use, the majority of AI/ML-enabled devices are authorized in radiology, followed by the cardiovascular area. The latter is most prominently represented by interventional cardiology (IC), which is a subspecialty of cardiology that

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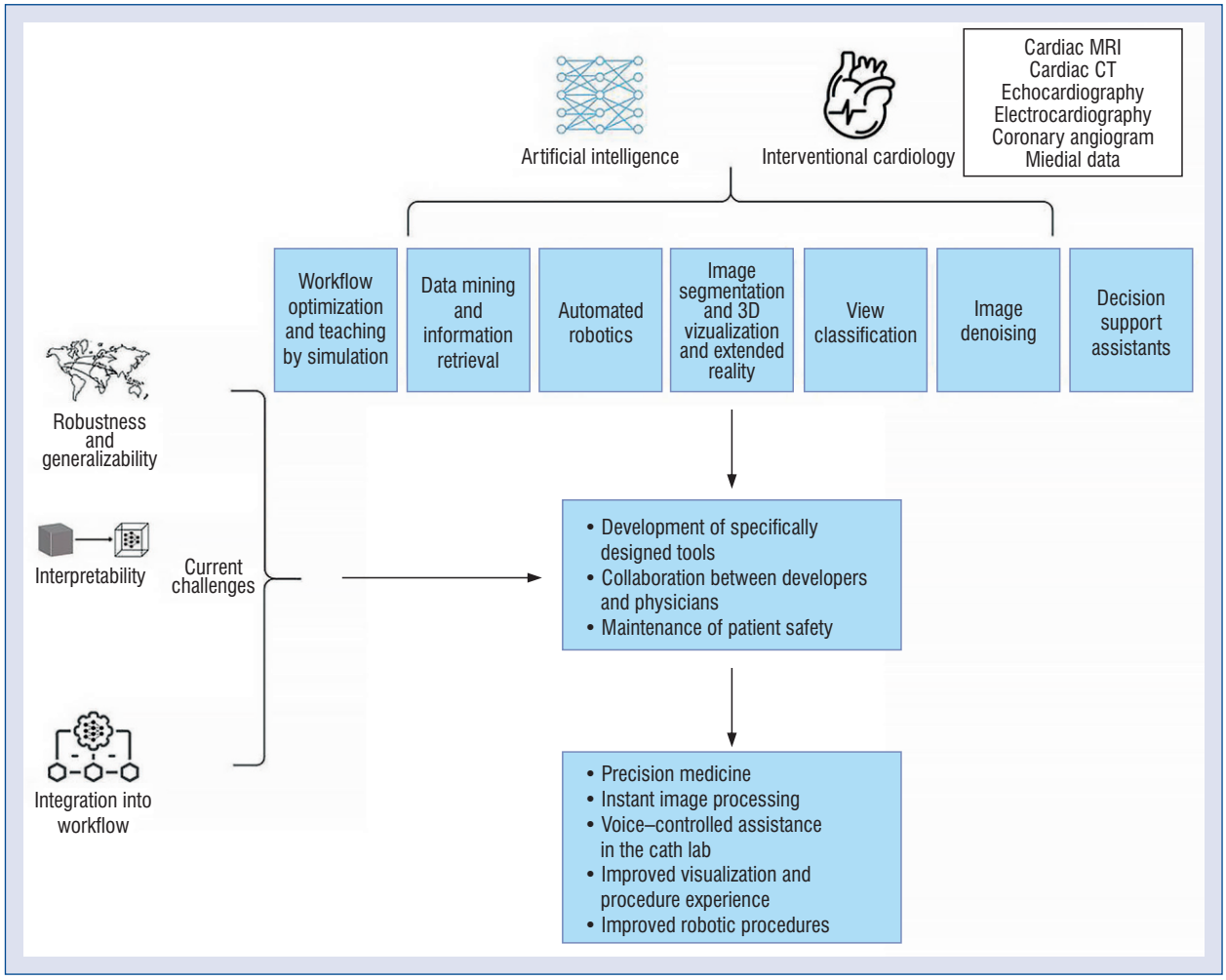
provides catheter-based treatment of structural heart diseases. The steady growth in the number of FDA-approved devices highlights the potential of embedding them into routine clinical practice. AI/ML-based devices empower cardiologists to implement a complex approach to heart diseases in numerous ways such as earlier establishment of diagnosis, patient risk stratification before targeted interventions, and general improvement in quality of care. The potential use of AI in IC may cover each step of the therapeutic process, including in-hospital first-line assessment of chest pain [3] and/ /or cardiogenic shock, periprocedural planning the intervention's strategy for better navigation and guidance as well as predicting periprocedural risks [4], and potential patient outcomes. The specific nature of IC provides clinicians with many imaging modalities, including both anatomic and functional assessment of structural heart diseases. Therefore, AI is considered a promising technological tool expected to have a significant impact on imaging reconstruction, analysis, and interpretation, leading to an increase in the availability and quality of healthcare data and further progress in analytic techniques in the future. The utilization of AI in clinical practice has been proven to be valuable, particularly regarding echocardiography examination [5], angiographic assessment of coronary artery stenoses [6], including lesion characteristics [7], assessment of cardiac perfusion via single photon emission computed tomography imaging [8], and in cardiac magnetic resonance (CMR) imaging [9]. The aforementioned studies suggest that in the future AI may be capable of providing both clinicians and patients with automated diagnosis based on the interpretation of imaging examination independent of an imaging specialist.

The potential of AI application in the IC field is presented in the Central illustration. For example, in the international research project CEREBRIA-1 (Machine Learning vs Expert Human Opinion to Determine Physiologically Optimized Coronary Revascularization Strategies) it was established that in the case of the treatment of patients with stable coronary artery disease, ML-based algorithms gave similar indications to those of an international team of medical doctors. Thus, when during specialized treatment the medical unit does not always have specialist knowledge that allows it to effectively interpret the ECG data, AI algorithms such as the AI-based triage algorithm (DELTAnet) [10] can be an effective support tool. In IC progress has also been made. Here, one can distinguish two main lines of research and potential applications of AI: virtual (medical image processing, decision making), and physical, such as robotic interventional procedures [11]. AI gives opportunities for improvements in the field of computer vision and image processing that can be applied to robotic interventions [12]. However, autonomous robotic vascular procedures remain a challenge [11]. On the other hand, in [13] an AI-supported approach in ultrasound-guided cardiac interventions to identify, localize and track the critical structures and lesions and validate the algorithm's performance was proposed. It turned out that the proposed model for identifying and locating heart structures successfully exceeded the abilities of experts (medical doctors).

The majority of imaging modalities in IC such as echocardiography, CMR, angiography, and computed tomography (CT) provide two-dimensional (2D) data that can be easily converted using various three-dimensional (3D) modeling techniques into physical objects with accurate representations of the heart and correct anatomical features [14]. Consequently, multi-modality image integration in cardiology contributes to a better understanding of structural cardiac anatomy, leading to a precise patient-tailored approach for interventional procedures. Indeed, here lies another promising potential combination of AI and other new technologies for example 3D modeling enhanced by immersive technologies. Immersive technologies, such as virtual reality, augmented reality, and mixed reality, have revolutionized the way we interact with digital environments. These technologies create highly engaging and interactive experiences by blending virtual components with the real world or by completely immersing the user in a virtual environment. AI plays a crucial role in enhancing these immersive experiences. By integrating AI, immersive technologies can become more interactive and responsive to user actions and behaviors immersive technologies and AI, the potential fusion of these technologies may contribute to a more thorough understanding of different aspects of cardiac anatomy during procedures [15]. They may also influence the selection of the appropriate device and procedural technique, due to better preprocedural planning and real-time intraprocedural visualization for complex anatomical and geometrical relations [16].

However, AI is a very general term. Also, the AI application field is wild. This paper concentrates on the algorithms taking into account the type of neural networks that have been applied in IC in particular. It presents and discusses the neural



Central illustration. Artificial intelligence workflow in interventional cardiology: a basic schema; CT — computed tomography; MRI — magnetic resonance imaging, 3D — three-dimensional.

networks and learning algorithms that have been used in the analysis of medical data and shows further directions of development of the AI-driven approach.

Review methodology

The methodology of this systematic review is based on the PRISMA Statement [17]. Recent publications, reports, protocols, and review papers from Scopus and Web of Science databases have been considered. The keywords 'Artificial Intelligence, Machine Learning, Extended Reality, Mixed Reality, Virtual Reality, Metaverse, cardiology, interventional cardiology, segmentation, segmentation algorithms, classification algorithms, ethics, AI ethics' and their variations were identified. In the first step, features of the material such as title and abstract were evaluated taking into account exclusion criteria (for example criterion 1, PhD thesis and materials not related to cardiology, was removed from the procedure whereas criterion 2, full-text papers in English, including electronic publications before printing, was considered). Subsequently, articles and technical reports meeting the criteria were retrieved and analyzed. The documents used in this study were selected based on the procedure presented in Figure 1. Finally, 100 documents were taken into account.

Application of artificial intelligence

Various neuronal networks have been used in the field of medicine. They differ not only in architecture but above all in the type of neuron model applied. And consequently, the number of parameters that need to be optimized. Also, depending on the type of neural network, different

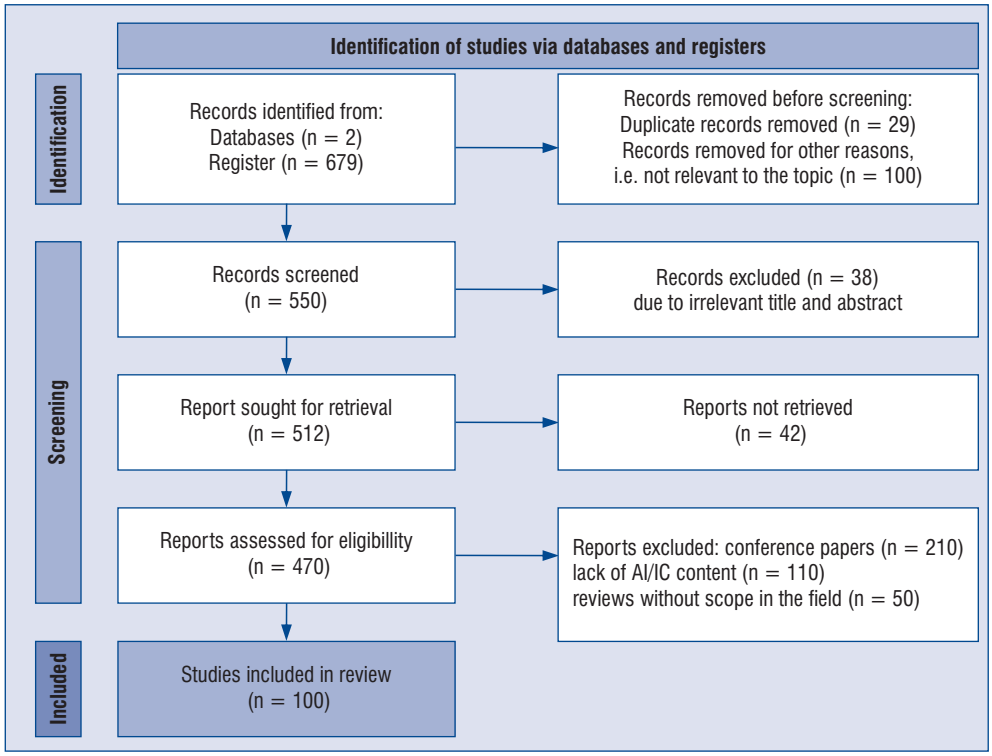


Figure 1. The scheme of the methodology of literature review; AI — artificial intelligence; IC — interventional cardiology.

training algorithms may provide obtaining higher accuracies of the predicted results.

Artificial Neural Networks (ANNs)

The first type of AI solution in cardiology is based on Artificial Neural Networks (ANNs). These are an interconnected group of nodes (artificial neurons) that model connections of biological neurons as weights between nodes. ANNs find applications in IC, including echocardiography and cardiac CT, contributing to the automation and improvement of the assessment of cardiovascular diseases as well as significantly enhancing the diagnosis and treatment of cardiovascular diseases [18]. These neural networks provide a computational tool that can automate the analysis of echocardiography and cardiac CT images, increase accuracy, and reduce the detection time of heart conditions such as vessel constrictions or congenital defects [19]. ANNs also aid in the identification of important cardiac structures in medical images, making the work of doctors and radiologists easier [20]. One of the key advantages of ANNs is their ability to learn from vast amounts of data, predicting outcomes based on patterns. Another advantage is automation. They can automatically extract features and process data, which is extremely valuable in medical image analysis, imaging studies, and ECG data analysis. This automation can significantly expedite and simplify diagnostic and research work. Neural networks adjust weights and model parameters to minimize prediction errors based on training data. This allows the model to extrapolate its capabilities and is also known for its ability to detect subtle patterns and relationships in data. This can help identify the risk of heart diseases and other conditions at an earlier stage, improving healthcare quality and reducing diagnosis time. However, it's important to note that ANNs also have limitations. Their complex architecture and operation require a large amount of training data to achieve high accuracy. There is also a risk of overfitting, where the model may learn irrelevant noise in the data (a model learns the training data too well, including its noise and random fluctuations, this issue leads to a model that performs exceptionally on the training data but poorly on new, unseen data). Additionally, interpreting results obtained through neural networks can be challenging due to their intricate structure [21]. ANNs have been successfully applied for the automatic measurement of ejection fraction and left ventricular longitudinal strain based on biplanar images of the left ventricle with high accuracy, as much as 98% [22]. ANNs

have also been used to automatically differentiate hypertrophic cardiomyopathy from physiological cardiac hypertrophy in athletes [23]. In addition to echocardiography, ANNs have played a role in analyzing ECG data for the detection of electrolyte imbalances. Notably, ANNs have been effective in identifying moderate to severe hypokalemia and hyperkalemia based on ECG patterns. These AI-based systems can contribute to the early diagnosis of electrolyte disturbances, which can lead to various cardiac complications.

Recurrent Neural Networks (RNNs)

The second type of neural network that can be applied in cardiology includes Recurrent Neural Networks (RNNs). These allow for the managing and interpreting of data that have a naturally sequential character, such as natural language or time series. Their structure enables the "remembering" and integration of information from previous stages of the sequence, making them especially useful in analyzing complex medical data such as ECG recordings, echocardiogram data, or continuous monitoring of a patient's health condition [5]. In IC, RNNs can be applied to analysis of the patterns and trends in the patient's medical data. As a consequence, RNNs can predict potential outcomes of interventions, assisting in planning more effective treatment plans, for example, predicting the prognosis of patients with adult congenital heart disease, and pulmonary hypertension [24]. One interesting solution based on RNNs is that of DeepHeart [25]. This employs semi-supervised sequence learning based on data from popular wearable devices (Fitbit, Apple Watch, or Android Wear) to predict cardiovascular risk more effectively than traditional biomarkers. RNNs also play an important role in the automatic selection of myocardial inversion time, a key factor in assessing heart conditions. This automation streamlines the diagnostic process, making it more efficient and accurate [26]. Moreover, the adaptability of RNNs allows them to process data from various sensors to predict conditions such as diabetes, high cholesterol, high blood pressure, and sleep apnea [27].

Convolutional Neural Networks (CNNs)

Another solution that has emerged as a transformative force in the field of IC, a branch of medicine focused on the catheter-based treatment of heart diseases regards Convolutional Neural Networks (CNNs). These enable the processing and interpreting of complex cardiovascular images, significantly enhancing the accuracy of diagnoses and the effectiveness of treatments [28]. Convolutional Layers, serving as the foundation of CNNs, are instrumental in extracting features from input images, such as angiograms or echocardiograms. By utilizing a diverse array of filters, these layers efficiently identify patterns and features that are key indicators of heart diseases. This identification and analysis process is crucial in diagnosing and understanding various cardiac conditions. Pooling Layers also play a vital role in reducing the complexity of the data processed by convolutional layers. This process involves retaining only the most essential features, thereby streamlining the data while preserving the critical diagnostic information. The ability to simplify image data without losing important details is a significant advantage in the precise analysis of cardiac images. Fully Connected Layers are responsible for the critical tasks of classification or regression, based on the features extracted by the convolutional and pooling layers. In the context of IC, this means accurately identifying specific cardiac conditions, predicting patient outcomes, and providing valuable insights for procedural planning. Thus, CNNs improve both diagnostic accuracy and the effectiveness of treatment strategies [29]. As CNNs continue to evolve, their impact on IC is expected to grow, paving the way for more sophisticated and personalized patient care [30]. For example, CNNs can be successfully applied to the analysis of aortic valves during transcatheter aortic valve implantation procedures [1]. It has been found that the proposed approach ensured a higher degree of accuracy, thereby increasing the likelihood of successful outcomes. In this paper [31] employed CNNs to classify views in transthoracic echocardiograms. This AI-based solution ensured a more precise interpretation of cardiac imaging, which is essential for administering the correct treatment to patients. A significant advancement has also been made in the segmentation of heart chambers [32]. Moreover, an important element in interventional surgery also comprises the education of future medical staff. Indeed, Akinyemi et al. [33] describes the application of CNNs to a system enabling the identification of operators' activities.

Spiking Neural Networks (SNNs)

Recently, more complex, brain-inspired neural networks such as Spiking Neural Networks (SNNs) are beginning to be used in medicine [34], his approach provides a good computational tool to analyze dynamic data and time-dependent information

and offers a highly useful solution for applications such as temporal sequences or patterns. In IC, SNNs have found an application that could expand in the future in the analysis of ECG signals. ECG signals are inherently temporal and contain complex patterns that describe various cardiac conditions. SNNs are a good choice for this task because they can analyze these signals with a high degree of precision, identifying subtle anomalies that might be overlooked by more traditional methods. This capability is crucial for the early detection and classification of arrhythmias, which can assist in rapid intervention and better outcomes for patients [35]. In turn, [36] applied SNNs to the classification of various cardiac arrhythmias. This solution allows for more targeted and effective treatment strategies for different types of arrhythmias. Similarly, [37] emphasizes the precision of SNNs in cardiac analysis, particularly in their ability to classify heartbeats with high accuracy. Their work is especially significant in identifying conditions such as Ventricular Ectopic Beats, a type of arrhythmia that can be challenging to detect. This highlights the adaptability of SNNs to a wide range of cardiac data, proving their versatility and effectiveness in various clinical contexts. Moreover, the building and training of a deep spiking neural network, as outlined in research [38], expanded this scope by classifying ECG signals for a broad range of heart-related conditions.

Deep Neural Networks (DNNs)

All these networks can be considered as Deep Neural Networks (DNNs), namely networks that have multiple layers between input and output layers. They are exceptionally effective in deciphering complicated patterns contained in extensive data sets, making them indispensable tools in modern medical analysis and decision-making processes [39]. By processing vast amounts of medical data, including diagnostic images and patient records, DNNs can uncover subtle patterns and indicators that might be missed by traditional analysis methods [40]. The most significant advantages of DNNs include their ability to model complex relationships thanks to their structural depth, enabling efficient pattern and feature recognition in data. The flexibility of DNNs allows for their application in a wide range of uses, from computer vision and image analysis to natural language processing, and even robotics and automation. Automatic feature extraction from data is another notable advantage, eliminating the need for manual feature determination and selection, particularly beneficial in complex or multi-dimensional data sets. Another DNN type that is applied in dimensionality reduction and unsupervised learning is the autoencoder, which can effectively encode input data into a smaller dimension form, aiding in data compression or multidimensional data visualization. For example, based on DNNs, (Fully Connected Neural Networks [FNN]), a comprehensive method for representing entire raw Electronic Health Records (EHR) of patients using the Fast Healthcare Interoperability Resources (FHIR) format has been developed [41]. This approach enables accurate prediction of multiple medical events across various centers without the need for site-specific data harmonization. In the field of IC, FNNs have been applied to assess the severity of coronary artery stenoses [42]. Then, [43] showed how a DNN model successfully reclassified hemodynamically insignificant stenosis, showing performance comparable to computational fluid dynamics-based CT-fractional flow reserve methods. Additionally, the combination of Fuzzy C-Means Clustering with DNN has been applied to the diagnosis of coronary artery disease using CMR imaging data [44]. Other important and interesting DNN applications in IC include the development of autoencoder for effectively reconstructing output data from input datasets, thus creating a 3D segmentation of the heart, which serves as a data source for a supervised noise-reducing autoencoder [45]. On the other hand, Generative Adversarial Networks (GANs) find applications in generating new data similar to training data. They consist of a generator (learning part) and a discriminator (the part that learns how to distinguish the generator's fake data from real data). GANs are particularly valued for generating realistic images, applicable in computer graphics, augmented reality, and other fields requiring synthetic yet realistically appearing data [46]. GANs were utilized to transform low-dose cardiac CT images into standard-dose images, contributing to improved diagnostic quality [47]. Moreover, GANs have been applied to reduce noise in coronary CT angiography images, showcasing the multifunctionality of DNNs in enhancing cardiac imaging techniques and diagnostic efficiency in IC [48].

Summary

Table 1 summarizes a comparison of the neural networks that are applied in IC [24, 28, 31, 36–38, 42–44, 49–78]. Thus, all types of neural networks suffer from the overfitting issue that appears when the network loses its generalization. In this context, it is extremely important to prepare a good quality and appropriate quantity of data sets.

Table 1. A comparison of the neural networks that are applied in interventional cardiology.

Network type	Type of evaluation metrics	Application field	Data sets — training/testing/validation sets [%] or training/testing sets [%]	Input parameters	Out parameters	References
ANN	Accuracy 92.00%	Automatic detection of arrhythmia on ECG	MIT-BIH arrhythmia database, ECG recording *50/50*	ECG records	Classification of three different cardiac conditions (normal, RBBB, and paced beats)	Isin, Ozdalili, 2017 [49]
RNN	Diagnosis, accuracy 97.00% Patient presentation at a MDT 90.20%	Estimating prognosis and guiding therapy in ACHD and pulmonary hypertension	Dataset, which consists of 10,019 adult patients under follow-up at the Royal Brompton Hospital London, from 2000 to 2018 *The division of data into training, testing, or validation sets is not specified*	Clinical and demographic data, ECG parameters, cardiopulmonary exercise testing, and selected laboratory markers	Categorization of diagnostic group, disease complexity, NYHA class, need for discussion at MDT meetings	Diller at al., 2019 [24]
RNN	Accuracy 91.00%	Classification of arrhythmia-based ECG records	The heart disease dataset collected from Kaggle consists of 303 records *The division of data into training, testing, or validation sets is not specified*	ECG signals	Classification of heart arrhythmias	Bavani, 2021 [50]
RNN	Accuracy 85.40%	Classification of arrhythmia based on ECG recordings	MIT-BIH arrhythmia database, ECG recordings *The division of data into training, testing, or validation sets is not specified*	ECG signals	Classification of ECG arrhythmia	Singh et al., 2018 [51]
RNN	Accuracy 95.00%	Real-time detection of AF from short--time single lead ECG traces	MIT-BIH AFDB and MIT-BIH NSRDB *The division of data into training, testing, or validation sets is not specified*	ECG signals	Classification of ECG traces NSR and AF	Sujadevi et al., 2018 [52]
CNN	Accuracy 91.70%	Recognition of different standard echocardiographic views	A total of 834,267 images from 15 views *80/10/10*	Echocardiographic images from various echocardiographic views, including parasternal long axis, RV inflow, basal short axis, etc.	Multi-category classification of 15 echocardiographic views	Madani et al., 2018 [31]

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Table 1 (cont.). A comparison of the neural networks that are applied in interventional cardiology.

Network type	Type of evaluation metrics	Application field	Data sets — training/testing/validation sets [%] or training/testing sets [%]	Input parameters	Out parameters	References
CNN	Accuracy AlexNet: 78.90% GoogLeNet: 79.50% ResNet-152: 82.10%	Detection and classification of MDE patterns on MRI	1995 MDE images from 200 patients *The division of data into training, testing, or validation sets is not specified*	MDE images classified into 7 categories	Classification of MDE patterns	Ohta et al., 2019 [53]
CNN	Accuracy 85.70%	Identifying asymptomatic LV systolic dysfunction using ECG recordings	Patients at the Mayo Clinic 625,326 patients screened *40/10/50*	12-lead ECG data paired with TTE data	Classification of EF as ≤ 35% or > 35%	Attia et al., 2019 [54]
CCNN	Accuracy 99.01%	Automatic detection of STEMI using ECG recordings	Dataset of 667 STEMI ECGs and 7571 control ECGs training set (5697 ECGs) *70/30*	12-lead ECG data with preprocessing and data-expanding techniques	STEMI detection and classification	Zhao et al., 2020 [55]
CNN combined with GAN	Accuracy 98.30%	Classification of arrhythmia using ECG recordings	ECG recordings from the MIT-BIH arrhythmia dataset *The division of data into training, testing, or validation sets is not specified*	Single lead ECG recordings	Classification of ECG heartbeats into 15 different arrhythmia classes	Shaker et al., 2020 [56]
CNN	Accuracy 91.33%	Detection of cardiac arrhythmias based on ECG signal analysis	1,000 ECG signal from the MIT-BIH arrhythmia database *The division of data into training, testing, or validation sets is not specified*	Long-duration raw ECG signals, specifically 10-second signal fragments, without QRS detection and segmentation	Classification of the ECG signals into 17 different cardiac arrhythmia disorders	Yıldırım et al., 2018 [57]
CNN	Accuracy 94.03%	Classification of heartbeats in different categories in ECG signals	The study used 109,449 single lead/ /beat ECG signals from 47 subjects. The signals are from the PhysioBank MIT-BIH arrhythmia database *The division of data into training, testing, or validation sets is not specified*	Single lead ECG signals	Classification of heartbeats into 5 AAMI classes: non-ectopic, supraventricular ectopic, ventricular ectopic, fusion, and unknown beats	Acharya, 2017 [58]

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Table 1 (cont.). A comparison of the neural networks that are applied in interventional cardiology.

Network type	Type of evaluation metrics	Application field	Data sets — training/testing/validation sets [%] or training/testing sets [%]	Input parameters	Out parameters	References
CNN-attention-LSTM	Accuracy 93.75%	Reduction of false arrhythmia alarms in ICUs using single-lead ECG segments	The study used a training set of 750 recordings from the PhysioNet computing in cardiology challenge 2015 *The division of data into training, testing, or validation sets is not specified*	Single-lead ECG segments, along with other biosignals like photoplethysmogram and arterial blood pressure waveform	Classification of ICU alarms into 'true' or 'false' categories, specifically targeting 5 types of life-threatening arrhythmia alarms	Mousavi et al., 2020 [59]
CNN-LSTM	Accuracy 98.10%	Automated diagnosis of arrhythmia using ECG signals	The study used 16,499 ECG segments from the MIT-BIH arrhythmia database *The division of data into training, testing, or validation sets is not specified*	Modified limb lead II ECG signals, segmented with 99 samples to the left of the first R peak and 160 samples to the right of the last identified uninterrupted R peak	Classification of ECG segments into 5 arrhythmia classes (normal, LBBB, RBBB, APB, PVC)	Oh et al., 2018 [60]
CNN	Accuracy 96.00%	MI detection via ECGs	The study used actual ECG datasets from the PTB diagnostic database, with a focus on generalized anterior MI *The division of data into training, testing, or validation sets is not specified*	Multilead ECG data, with preprocessing involving fuzzy information granulation and beat segmentation	Detection of MI	Liu et al., 2018 [61]
CNN	Accuracy Class-based MI detection: 99.95% Patient-specific MI detection: 98.79%	MI detection and localization using 12-lead ECG	The study used 12-lead ECG signals from the PTB diagnostic ECG database, from 290 subjects *The division of data into training, testing, or validation sets is not specified*	12-lead ECG signals, including 5 types of MI and healthy controls, sampled at 1 kHz with 16-bit resolution	Automated detection and localization of MI using ECG data	Liu et al., 2018 [61]
CNN	Accuracy 95.11%	Automated detection of CAD using ECG signals	ECG signals from the Fantasia database (for normal) and St.-Petersburg Institute of Cardiology Technics 12-lead arrhythmia database (for CAD), sampled at 257 Hz *The division of data into training, testing, or validation sets is not specified*	Two and five-second durations of ECG signal segments, preprocessed using discrete wavelet transform and Z score normalization	Diagnosis of CAD using ECG signal	Acharya et al., 2017 [62]

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Table 1 (cont.). A comparison of the neural networks that are applied in interventional cardiology.

Network type	Type of evaluation metrics	Application field	Data sets — training/testing/validation sets [%] or training/testing sets [%]	Input parameters	Out parameters	References
CNN	Sensitivity of 91.24% Specificity of 95.37% PPV of 90.5% Pearson coefficient of 0.983	Automatic quantification of calcium score in ECG-triggered non-contrast enhanced cardiac CT images	The study included 152 exams from a screening study *40/15/45*	Non-contrast enhanced CT images with slice thickness of 3.0 mm, acquired with various in-plane resolutions	Segmentation and classification of candidate lesions as coronary or non-coronary, and quantification of calcium score	Santini et al., 2017 [63]
CNN	Sensitivity of 97.2% for coronary calcification detection, and an accuracy of 84.4% for risk category assignment	Automatic detection and quantification of CAC in low-dose chest CT scans of heavy smokers	The study included 1028 heavy smokers aged between 50 and 75, scanned between 2004 and 2006 at 3 medical centers *The division of data into training, testing, or validation sets is not specified*	Low-dose chest CT scans without contrast enhancement, acquired using different CT scanners	Identification of CAC and subsequent cardiovascular risk categorization based on Agatston scores	Zreik et al. [64]
CNN	AUC of 0.74 ± 0.02 Specificity at sensitivity levels of 0.60, 0.70, and 0.80 was 0.77, 0.71, and 0.59, respectively	Identification of patients with functionally significant coronary artery stenosis using deep learning analysis of the LV myocardium in CCTA scans	Retrospectively collected CCTA scans of 166 patients (59.2 ± 9.5 years, 128 males) from 2012 to 2016 *20 images were used to train the LV myocardium encoder, and classification was evaluated in the remaining 126 CCTA scans with 50 10-fold cross-validation experiments*	CCTA scans, segmented LV myocardium, divided into spatially connected clusters	Classification of patients according to the presence of functionally significant coronary artery stenosis	Zreik et al., 2018 [64]
CNN	Frame-wise AUC: 0.971 Frame-wise accuracy: 0.934 Clip-wise accuracy: 0.965 External validation frame-wise AUC: 0.925 (single model), 0.956 (ensemble model)	Lesion detection, localization, and classification in coronary angiography	452 right coronary artery angiography movie clips *The division of data into training, testing, or validation sets is not specified*	Key frames extracted from coronary angiography movie clips	Classification of areas narrowed by over 50%, visualization of stenotic locations	Moon et al., 2021 [65]
CNN	Cardiac phase detection accuracy 98.80%, sensitivity was 99.30%, and specificity was 97.60% End-diastolic frame prediction had a precision of 98.40% and a recall of 97.90%	End-diastolic frame detection in coronary angiographies	The networks were trained on 56,655 coronary angiographies from 6820 patients and evaluated on 20,780 coronary angiographies from 6261 patients *The division of data into training, testing, or validation sets is not specified*	Coronary angiography images	Cardiac phase labels for each frame and detection of end-diastolic frames	Ciusdel et al., 2020 [66]

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Table 1 (cont.). A comparison of the neural networks that are applied in interventional cardiology.

Network type	Type of evaluation metrics	Application field	Data sets — training/testing/validation sets [%] or training/testing sets [%]	Input parameters	Out parameters	References
CNN	Accuracy 95.00%	Lesion detection in X-ray coronary angiography	The study used a synthetic dataset of 10,000 images *80/20*	X-ray coronary angiography images	Detection and classification of coronary artery stenosis	Ovalle-Magallanes et al., 2020 [67]
CNN	Recall of CTO detection: 89.3% Sensitivity and specificity of CTO classification: 94.5% and 89.1%, respectively F1 Score: 0.89 Area under the curve: 0.98	Lesion detection, localization, and classification in coronary angiography images	A total of 2059 cases (326 cases in blunt and 1732 cases in tapered morphology), with data augmentation techniques applied *The division of data into training, testing, or validation sets is not specified*	Coronary angiography images	Detection and classification of CTO lesions	Liu et al., 2019 [68]
CNN	F1 Score: 0.96 Mean average precision: 0.95 (Faster-RCNN Inception ResNet V2), 0.83 (SSD MobileNet V2), 0.94 (RFCN ResNet-101 V2)	Detection and localization of coronary artery	The study used clinical angiography data of 100 patients *The division of data into training, testing, or validation sets is not specified*	Stenoses Coronary angiography images	Detection and localization of coronary artery stenoses	Danilov et al., 2021 [69]
CNN	For segment prediction, the recognition accuracy 98.40%, and the recognition sensitivity 85.20% For detecting lesion morphologies, the F1-scores ranged from 0.80 to 0.85	Lesion detection, localization, and classification in coronary angiography images	The study used 20,612 angiograms from 10,073 patients *65/35*	Angiograms in DICOM format with various angiographic views	Identification of coronary artery segments and recognition of lesion morphology including stenotic lesion, total occlusion, calcification, thrombosis, and dissection	Du et al., 2020 [28]
CNN	Accuracy 97.42%	ECG signal processing and arrhythmia classification	ECG signals from MIT-BIH arrhythmia database *50/50*	Two-dimensional grayscale images of segmented ECG heartbeats	Classification of 5 different arrhythmia types	Izci et al., 2019 [70]

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Table 1 (cont.). A comparison of the neural networks that are applied in interventional cardiology.

Network type	Type of evaluation metrics	Application field	Data sets — training/testing/validation sets [%] or training/testing sets [%]	Input parameters	Out parameters	References
CNN	Accuracy 93.75%	ECG signal classification for heart conditions	ECG signals from MITDB (47 subjects), NSRDB (18 subjects), BIDMC congestive HF database (15 subjects) 162 recordings used from PhysioNet databases *The division of data into training, testing, or validation sets is not specified*	ECG signals	Classification of ECG signals into 3 categories: congestive HF, arrhythmia, normal heartbeats	Kaouter et al., 2019 [71]
CNN	Accuracy 96.67%	ECG arrhythmia classification	ECG signals from MITDB (54 subjects) Total 1000 non-overlapping frames representing various cardiac issues and normal conditions, from 45 subjects (19 women, 26 men) *The division of data into training, testing, or validation sets is not specified*	Images of ECG signals	Diagnosis of 17 types of arrhythmia	Al-Huseiny et al., 2020 [72]
CNN	Accuracy 93.40%	Heartbeat and MI classification	MITDB (47 subjects), PTBDB (290 subjects) *The division of data into training, testing, or validation sets is not specified*	ECG signals	Classification of heartbeats and MI	Kachuee et al., 2018 [73]
CNN	Accuracy 85.99%	Heartbeat diseases classification, AF detection	PhysioNet/CinC Challenge 2017 (8,528 ECG records) *Division of data into training, testing, or validation sets is not specified*	Single lead ECG recordings of variable length	Classification of normal sinus rhythm, AF, other abnormal rhythms, and noise	Kamaleswaran et al., 2018 [74]
CNN	Accuracy 99.78%	Classification of MI	Physiobank (PTB) ECG database: 52 normal subjects, 148 MI patients *Division of data into training, testing, or validation sets is not specified*	12-lead ECG signals	Diagnosis of MI	Baloglu et al., 2019 [75]
SNN	Accuracy 95.60 ± 0.5 [%]	ECG signal processing and arrhythmia classification	MIT-BIH dataset ECG signals encoded into spike trains using delta modulators *Division of data into training, testing, or validation sets is not specified*	ECG signals that are encoded into spike trains using delta modulators	Classification of ECG signals into different arrhythmia classes	Corradi et al., 2019 [36]

Table 1 (cont.). A comparison of the neural networks that are applied in interventional cardiology.

Network type	Type of evaluation metrics	Application field	Data sets — training/testing/validation sets [%] or training/testing sets [%]	Input parameters	Out parameters	References
SNN	Accuracy 97.16 [%]	ECG signal processing and classification, specifically for arrhythmia detection	PhysioNet MIT-BIH arrhythmia database *60/40*	Input encoding of ECG signals into spike trains using delta modulators	Classification of heartbeats into various categories, focusing on the detection of VEBs and normal heartbeats	Kovács, Samiee, 2022 [37]
SNN	Accuracy 97.90%	ECG signal processing for cardiac arrhythmia detection	The MIT-BIH ECG arrhythmia database *The division of data into training, testing, or validation sets is not specified*	ECG signal	Classification of ECG signals for arrhythmia detection	Amirshahi, Hashemi, 2019 [76]
SNN	Accuracy 84.80%	ECG classification that is used for diagnosing arrhythmias and other heart-related conditions	2017 PhysioNet/CinC Challenge 8,528 single-lead ECG records with varying lengths from 9 to 60 seconds *90/10*	The ECG signals are subjected to zero padding to standardize signal length	Classification results of the ECG signal into the 4 categories (normal, AF, other, noise)	Feng et al., 2022 [38]
SNN	Accuracy 95.60 ± 0.5 [%]	ECG signal processing and arrhythmia classification	MIT-BIH dataset ECG signals encoded into spike trains using delta modulators *Division of data into training, testing, or validation sets is not specified*	ECG signals that are encoded into spike trains using delta modulators	Classification of ECG signals into different arrhythmia classes	Corradi et al., 2019 [36]
DNN	Accuracy 83.20%	Determination of the severity of coronary artery stenoses	Data from 125 lesions in 87 patient-specific anatomical models from CT data *The division of data into training, testing, or validation sets is not specified*	Patient-specific anatomical models from CT data	Prediction of FFR values	Itu et al., 2016 [42]
DNN	Accuracy 74.60%	Improvement in the performance of CCTA by correctly reclassifying hemodynamically nonsignificant stenosis	122 consecutive patients were initially included, with exclusions leading to a final sample *The division of data into training, testing, or validation sets is not specified*	CCTA data	Detection of functionally important CAD	Coenen et al., 2015 [43]

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Table 1 (cont.). A comparison of the neural networks that are applied in interventional cardiology.

Network type	Type of evaluation metrics	Application field	Data sets — training/testing/validation sets [%] or training/testing sets [%]	Input parameters	Out parameters	References
DNN	Accuracy 99.91% with 10 clusters (5 clusters for healthy subjects, 5 clusters for sick subjects)	Diagnosing CAD using CMRI dataset	CMRI dataset with labeled and unlabeled data *The division of data into training, testing, or validation sets is not specified*	CMRI data	Diagnosis of CAD	Joloudari et al., 2022 [44]
DNN	Accuracy Inter-patient: 93.10% For reduced rhythm classes: 92.24% For merged rhythm classes: 96.13%	Detection of different rhythm classes from an ECG database	New ECG database with 50,977 single lead beats, classified into 5 AAMI classes *Division of data into training, testing, or validation sets is not specified*	ECG data from all 12 leads	Detection of cardiac arrhythmias	Xu et al., 2018 [77]
DNN	The AUROCs for DEHF were 0.843 (internal validation) and 0.889 (external validation) for HFrEF; and 0.821 (internal validation) and 0.850 (external validation) for HF with mid-range to reduced EF	HF identification using ECG	55,163 ECGs from 22,765 patients at 2 hospitals *Division of data into training, testing, or validation sets is not specified*	ECG records	Identification of HFrEF (EF ≤ 40%), and HF with mid-range to reduced EF (≤ 50%)	Kwon et al., 2018 [78]

AAMI — Association for the Advancement of Medical Instrumentation; ABP — arterial blood pressure; ACHD — adult congenital heart disease; AF — atrial fibrillation; AFDB — Atrial Fibrillation Database; ANN — Artificial Neural Networks; APB — Atrial Premature Beat; AUC — area under the receiver operating characteristic curve; BIDMC — Beth Israel Deaconess Medical Center; CAC — coronary artery calcifications; CAD — coronary artery disease; CCTA — coronary computed tomography angiography; CMRI — cardiac magnetic resonance imaging; CNN — Convolutional Neural Networks; CT — computed tomography; CTO — chronic total occlusion; DEHF — deep-learning algorithm for ECG-based HF identification; DNN — Deep Neural Networks; ECG — electrocardiogram; EF — ejection fraction; FFR — fractional flow reserve; GAN — Generative Adversarial Networks; HF — heart failure; HFrEF — heart failure with reduced ejection fraction; ICUs — intensive care units; LBBB — left bundle branch block; LSTM — long short-term memory; LV — left ventricle; MDE — myocardial delayed enhancement; MDT — multidisciplinary team; MI — myocardial infarction; MIT-BIH — MIT-BIH Massachusetts Institute of Technology - Beth Israel Hospital; MITDB — MIT-BIH Arrhythmia Database; MRI — magnetic resonance images; NSR — normal sinus rhythm; NSRDB — Normal Sinus Rhythm Database; NYHA — New York Heart Association; PPV — positive predictive value; PTB — Physikalisch-Technische Bundesanstalt; PTBDB — Physikalisch-Technische Bundesanstalt Diagnostic ECG Database; PVC — Premature Ventricular Contraction; RBBB — right bundle branch block; RNN — Recurrent Neural Networks; RV — right ventricle; SNN — Spiking Neural Networks; STEMI — ST-segment elevated myocardial infarction; TTE — transthoracic echocardiogram; VEBs — ventricular ectopic beats

Ethical implications of ai in interventional cardiology

It is trivially true that all human systems are important for well-being, but the heart and circulatory function are clearly of prime significance. Any use of AI in cardiac interventions must thus be subjected to rigorous ethical scrutiny to ensure that it is in conformity with correct practice on at least two levels. The first is the set of institutional ethical norms established on the central level by international bodies and national government and on the local level by clinical institutions such as hospitals. The second concerns the detailed sets of ethical practices that need to be taken into account when AI is being implemented, such as ethical risk points [79]. Naturally, many aspects of ethical challenges, norms, and practices will be common across all areas of medicine. On the level of practical ethics, these include the collection and categorization of data, the data journey (as data are transferred, interpreted, and potentially adapted between systems and departments [80] and the ownership of and access to data.

However, there are certain specific characteristics of cardiological intervention that set it apart when it comes to the application of artificial technology, and each has its own ethical dimension. Notably, cardiological interventions are often made when the patient is at serious risk of dying. In that case, ethical decisions may have to be made concerning when or whether to attempt resuscitation. Legal implications need to be taken into account as well as the views of relatives, especially if they are holders of powers of attorney. It has already been pointed out that physicians may be reluctant to take certain actions because of this background [81]. AI now adds another layer of complication especially where the system makes recommendations as to courses of action: questions arise such as where the liability lies [82]. Indeed, just as a cardiac event may occur quickly, so too should treatment be given immediately. Emerging digital twin technology based on AI promises to be able to analyze complex datasets quickly, build cardiac models, and suggest treatment pathways. As described by Coorey et al. [83] a digital twin in cardiology is a digital representation of the physical system that is updated in real-time as the system changes. The ambition would be to create a perfect model with two interfaces: the first between the physical and its digital model, and the second between the nexus and the social plane (including, at least, physicians, the patient, caregivers, and others). Indeed, AI is increasingly being deployed in cardiology in terms of real-time data exchange, detection of conditions, severity assessment, and disease prognosis [84]. Then, Monzelum et al. (2022) [85] developed a cardiac arrest risk prediction score in an innovative clinical predictive model called The Cardiac Arrest Cardio-Oncology Score (CACOS), with the intention of providing early predictions and improving resource allocation and health outcomes. Aqel et al. [86] has also pointed out that AI will be particularly useful in predicting and managing sudden cardiac arrest, thus leading to better patient outcomes. The question next arises as to the relationship between a person and their digital twin: many issues of ownership, control, and decision-making arise [87]. For example, will the individual (now a patient) own the digital twin and be able to make decisions in advance as to its use? Will those decisions be linked to covenants in a life insurance policy? Whereas these can be discussed over a long time period with some diseases, at a moment of cardiac arrest it is difficult to see how these can be considered fully on the spot without specific easily accessible ethical protocols previously put in place to cater to the interaction with AI.

In addition, good regulation of AI is clearly needed regarding health care, with special reference to significant practices such as IC. However, the regulatory landscape is in its infancy at present. All stakeholders need to be able to interpret and explain AI and trust it: Explainable AI (XAI) and Trustworthy AI (TAI) are needed [88]. Regulation is being developed on the national and international level, although it is partial in extent and overlap [89]. The European Union has formulated a tool called the Assessment List for Trustworthy Artificial Intelligence (ALTAI) [90] and is working on extensive legislation [91]. Further suggestions have been made for rules and an assessment list for TAI by Floridi [92]. However, the general challenge for regulators in AI is to keep up with developments in a technological field that is developing extremely rapidly [93].

Future approach: Application of extended reality and 3D visualization supported by AI

Integrating AI into immersive technologies is crucial for handling the complexity of medical data, especially when combining multiple data modalities and if its possible 3D representation of these data. AI's ability to process and analyze complex, multi-layered data efficiently makes it essential for real-time processing in digital immersive en-

vironments, ensuring seamless user experiences. With increasing quality and resolution in medical imaging, 3D reconstruction of organs comes within clinical reach [94]. Medical imaging provides many 1D (ECG) and 2D views of the 3D heart (CT/MRI/ECHO DICOM), leaving the 3D interpretation to medical experts. Recent developments enable the 3D reconstruction of organs with many available segmentation tools [95]. Although segmentation software provides such capabilities, for clinical practice and education these are too complex to be used [96]. To train medical students and staff to deal with these advanced medical imaging-based reconstructions, an easy-to-use tool accompanied by educational material needs to be developed and tied to the clinical educational field of IC [97].

Complex cardiac procedures, such as implantation of the aortic valve (transcatheter aortic valve implantation procedures), complex ablation cases, patent foramen ovale, and surgical procedures on hearts with genetic defects, require advanced (functional) imaging and combination with anatomical and electrical behavior. 3D visualization in these anatomical complex examples is very difficult, whereas present research results create the opportunity to obtain a digital 3D view.

Recent developments enable the 3D reconstruction of organs with many available segmentation tools. Although segmentation software provides these capabilities, for clinical practice and education such tools are too complex to be used. An easy-to-use tool and educational material need to be developed to educate medical students and staff to effectively use these advanced medical imaging-based reconstructions. These 3D reconstructions provide many advantages in clinical evaluation, diagnosis, and preprocedural planning [15]. However, there are no standard clinical tools available to provide 3D segmentation alongside medical imaging. Such an approach brings 3D segmentation a step closer to the clinical workflow and thus improves clinical diagnostic, prognostic, and procedural planning.

The teaching of the latest technological development in cardiac treatment combining imaging data with 3D segmentation needs to be improved. The 3D educational medical imaging tool aims to provide a 3-D viewing tool that is easy to use by many students and professionals to promote the teaching of complex cardiac patient treatment. To ensure the embedding of the software in the clinical curriculum, the project will also build up educational clinical cases in which this educational tool will play an important role.

One of the primary benefits of using computer-generated 3D models extended by immersive technologies in cardiac anatomy is the ability to provide educators with a highly realistic and interactive learning experience. In particular, the visualization of something you cannot see, the electrical processes of the heart, is educationally powerful and challenging. Incorporating the outcomes of the spatial relationship of cardiac structures with educational content will provide a new dimension in the future of clinical cardiac education.

All strategy connecting with multimodality cardiac imaging refers to non-invasive imaging of the heart using ultrasound, magnetic resonance imaging, CT, or other imaging methods as well as ECGs. These cardiac techniques are referred to for everyday practice in preprocedural planning and educational approaches [98]. The teaching of these applications is brought to a higher level through the use of 3D visualization with the incorporation of non-invasive imaging of ECG output enhanced by immersive technologies in terms of a new digital educational tool with a multimodality approach and can be enriched with the use of artificial intelligence for the segmentation process.

Artificial intelligence facilitates personalization by analyzing user behavior, enhancing engagement in various applications. It plays a key role in integrating diverse data streams like visual, sensor, and user input data, ensuring a coherent and functional environment. AI also enables more intuitive interactions through technologies like natural language processing and gesture recognition. As digital applications expand, AI ensures scalability and adaptability to new data types and volumes. Additionally, AI contributes to error reduction and quality assurance, critical in precision-dependent applications. In summary, AI's role in immersive technologies is not just beneficial but fundamental to the development and enhancement of them.

Discussion and conclusions

Artificial intelligence application in medicine, in particular in IC represents a significant advancement in the field, offering potential improvements in patient care, diagnosis, treatment, and procedural outcomes [99]. AI has to be taken into account in the process of integration into everyday practice regarding key ways and approaches such as enhanced diagnostic accuracy [100]. AI can analyze raw medical data and images with high precision, aiding in the detection and assessment of cardiovascular diseases. It can provide an alternavtive

to identifying patternes and anomalies that might be missed by the human eye. AI can process large datasets to predict the outcome of cardiac interventions, such as the likelihood of complications or success of a procedure. Moreover, one of the big developments for use in IC concerns AI-driven robotic systems that can aid in performing precise movements during procedures such as coronary angioplasty, potentially improving outcomes and reducing physician fatigue. Indeed, such systems can give decision support, offering recommendations based on patient data, which may help in choosing the most appropriate interventional strategies. Based on patient datasets and clinical information, AI can assist in remote patient monitoring, analyzing data from wearable devices to detect signs of heart failure and arrhythmias. It can also improve post-procedural care, ensuring patients adhere to medications and lifestyle changes. AI gives a wide spectrum of opportunities, but its limitations also need to be considered, especially data dependency. AI systems require large amounts of data for training. The quality and quantity of this data are crucial. Poor or biased data can lead to inaccurate or biased outcomes. Another very important issue is lack of transparency, which can be a significant issue. AI, especially with its deep learning models, often operates as a "black box", making it difficult for non-specialists to understand how it arrives at certain conclusions or decisions in fields that require trust and explain ability.

To summarize, the combination of AI and IC has great promise to increase the efficiency and accuracy of cardiovascular imaging technologies combined with reducing costs of the whole process. However, their full integration and clinical application is still a challenge. In Table 1 the comparison of the neural networks that are applied in IC is shown. It turns out that the most commonly used neural networks in IC are CNNs that enable the processing of ECG output to classify heart diseases with high accuracy. However, calculations using traditional neural networks, including CNNs, are very time and energy-consuming. Yet AI, inspired by the structure of the brain, in its deployment of particular SNNs, is becoming a promising, energy-saving alternative to traditional ANNs. Furthermore, the difference in the performance of ANNs compared to SNNs translates into the application potential of SNNs. To fully exploit the potential of SNNs, including the ability to detect abnormalities in biomedical signals and design more specialized neural networks, their learning mechanisms need to be improved. Another important issue is connected with the fact that the majority of researchers have so far used ready-made AI solutions in the field of medicine, without going into the principles of their operation. In other words, they have treated them as the contents of a black box, whereas, in order to be better understood and used, the application of AI-based methods requires clarification of their structures and principles of operations. AI-based algorithms can be adapted to fit data, in the hope that the used data is a good representation of the population it is meant for and, that the resulting algorithm can classify new data correctly. A major problem is still how the algorithm came to its conclusion, at best it can identify the parts of the input data that were used to come to that conclusion, but it will not be able to explain underlying mechanisms. Considering that AI is applied in such an important field as human health and life, it is necessary to ensure that operators who are using AI know the principles on which the results are obtained. Additionally, this knowledge will help in their correct interpretation, which is especially of huge importance in the context of efficient disease treatment. Another issue is connected with the quality and availability of datasets, namely, access to electronic health records (EHRs). This is also connected with the risk of biases in medical data. Also, the internet segmentation of medical data may include errors. On the other hand, taking into account ethical considerations and the regulatory landscape, AI raises numerous ethical concerns, including the inextricable connection of ethical risk points to technical risk points. Indeed, any future AI-based system must meet the ethical, technical, and legislative issues raised. Thus, the first condition in this field has been done by formulating guidelines for AI-based systems. Additionally, in some countries, patients must give informed consent to sharing their medical data with AI algorithms and the AI-assisted diagnosis process, which is good practice.

In the future, AI-driven simulations will be utilized for training interventional cardiologists, providing them with a safe environment to practice complex procedures and enhance their skills. These simulations will allow cardiologists to engage in intricate medical procedures in a controlled setting. This scientific advancement will highlight the role of AI in augmenting the education and training of medical professionals, focusing on skill enhancement and proficiency in complex cardiac interventions. Integrating AI into immersive technologies is crucial for transforming cardiology, simplifying complex 3D medical data analysis,

and enhancing education and clinical practice with personalized, interactive, and efficient solutions. Additionally, novel approaches will involve the use of immersive technologies such as mixed reality or virtual reality, integrated with AI, for conducting remote multidisciplinary heart team meetings. AI will play a crucial role in facilitating these remote consultations and diagnostics, effectively bridging geographical obstacles. This will enable advanced IC care and expert consultations to be accessible remotely. The integration of AI and these cutting-edge technologies will be transformative, significantly improving healthcare delivery by gathering interdisciplinary teams from various locations, thereby expanding the reach and quality of cardiac care.

Artificial intelligence's transformative role in IC, enhances diagnostic accuracy, procedural outcomes, remote monitoring, and education, while acknowledging the need for ethical considerations and a deeper understanding of AI mechanisms in healthcare is evidence-based on presented PRISMA Statement methodology.

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Advances in myocarditis management in the light of the latest research and recent guidelines of the European Society of Cardiology

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Abstract

Myocarditis remains an unknown disease with varying clinical manifestations, often leading to heart failure. The latest 2021 and 2022 guidelines of the European Society of Cardiology (ESC) are the first official European documents updating knowledge on the diagnosis and treatment of myocarditis since the 2013 ESC expert consensus statement. These guidelines and new studies allow standardization and improvements to the management of myocarditis. In this review, we discuss the most important aspects of myocarditis diagnosis, therapies and follow-up based on current knowledge. (Cardiol J 2024; 31, 2: 342–351)

Keywords: cardio-immunology, heart failure, inflammatory cardiomyopathy, immunosuppression, endomyocardial biopsy, personalized medicine

Introduction

Myocarditis/inflammatory cardiomyopathy remains an understudied disease with various clinical manifestations, often leading to heart failure (HF). Moreover, an increase in morbidity and mortality from myocarditis has been recorded in recent years [1, 2]. Myocarditis significantly increases the risk of HF, serious arrhythmias, conduction abnormalities, sudden cardiac death (SCD), anxiety, depression, and it reduces the quality of life [3]. Myocarditis occurs mainly in young adults (18–40 years old) and children; thus, it affects people who study, work or lead active family lives [4].

In recent years, there was a lack of a unified approach to the diagnosis of myocarditis, especially as demonstrated by the COVID-19 pandemic. All cases resembling myocarditis were diagnosed as myocarditis without a confirmation by endomyocardial biopsy (EMB) or autopsy [5].

Recent (2021 HF, 2022 cardio-oncology, 2022 prevention of SCD) guidelines of the European Society of Cardiology (ESC) are the first official documents updating the knowledge on the management of myocarditis since the 2013 ESC expert consensus statement [6–9]. These guidelines and new research allow standardization and improvements to the diagnosis and treatment of myocarditis. In the following paper, a summary is presented of the most important aspects in the management of myocarditis based on current knowledge (Central illustration) [6].

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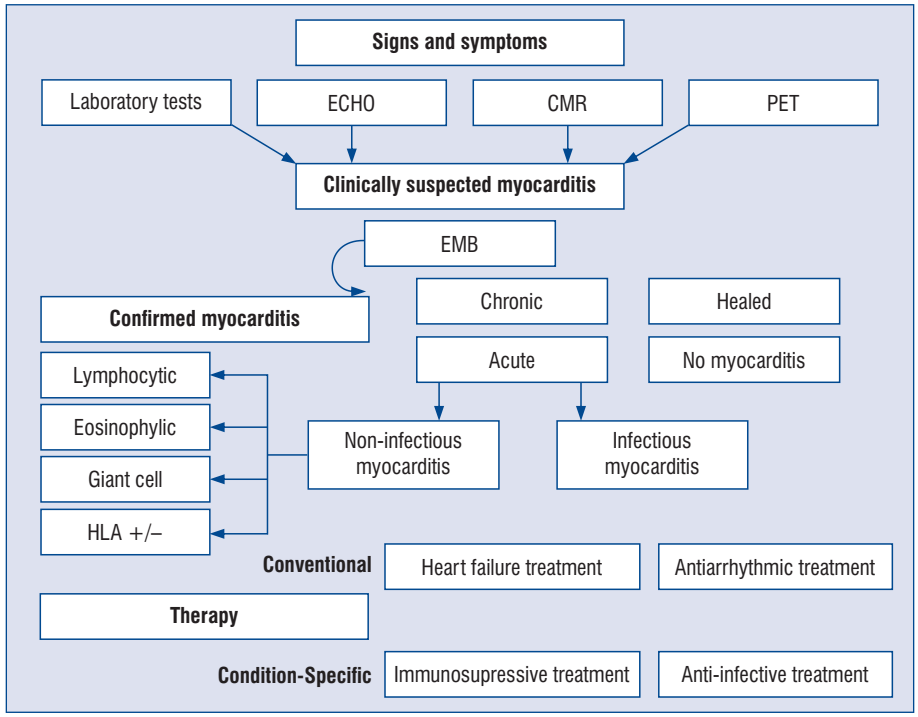

Central illustration. Personalized diagnostics and treatment of myocarditis; CMR — cardiac magnetic resonance; ECHO — echocardiography; EMB — endomyocardial biopsy; HLA — human leukocyte antigen; PET — positron emission tomography.

Table 1. Myocarditis etiologies.

Etiology	Examples
Infections	Viral: adenoviruses, echoviruses, enteroviruses (e.g., Coxsackieviruses), herpes viruses (human cytomegalovirus, Epstein-Barr virus, human herpesvirus 6), hepatitis C virus, human immunodeficiency virus (HIV), influenza A virus, parvovirus B19, SARS-CoV-2
	Bacterial, fungal, protozoal, rickettsial, spirochetal, helminthic
Autoimmune	Hypereosinophilic syndrome, Kawasaki disease, lupus erythematous, rheumatoid arthritis, scleroderma, ulcerative colitis, celiac disease, Churg-Strauss syndrome, Crohn's disease, dermatomyositis
Hypersensitivity reactions to drugs	Penicillin, ampicillin, cephalosporins, tetracyclines, sulfonamids, antiphlogistics, benzodiazepines, clozapine, loop and thiazide diuretics, methyldopa, smallpox vaccine, tetanus toxoid, tricyclic antidepressants
Toxic reactions to drugs	Immune checkpoint inhibitors, amphetamines, anthracyclines, catecholamines, cocaine, cyclophosphamide, 5-fluorouracil, phenytoin, trastuzumab
Others	Arsenic, copper, iron, radiotherapy, thyreotoxicosis

Etiology based management

The etiology of myocarditis is often unclear, nonetheless, knowing the causative factor frequently determines patient outcome. The leading causes of myocarditis are infectious agents, systemic diseases, drugs, and toxins (Table 1). The immunohistological assessment characterizes inflammatory processes by the type of infiltrating cells into lymphocytic, eosinophilic, giant cell myocarditis or cardiac sarcoidosis. To date, infectious etiology should always be assessed during heart tissue examination. However, continuing evidence suggest that in the majority of cases cardiomyocyte injury is caused by immune-mediated reactions activated by viruses, and not by direct virus cell-

Table 2. Recommended diagnostic tests in patients with suspected myocarditis.

Clinical manifestation	Chest pain, dyspnea, signs of left and/or right heart failure, and/or arrhythmias or sudden cardiac death
Diagnostic tests	
ECG	Novel ST-T abnormalities, atrial or ventricular arrhythmias, atrio-ventricular blocks, QRS abnormalities
Laboratory tests	Increased troponins with dynamic fluctuations
	C-reactive protein or erythrocyte sedimentation rate often increased but non-specific
	Raised concentrations of brain natriuretic peptides and circulating cytokines
	Diagnostic tests for specific infective factor
	Viral serology — low efficacy due to high rate of IgG antibodies against cardiotropic viruses in the general population
	Anti-heart autoantibodies — may help personalize diagnosis, treatment, and therapy monitoring. So far, it has been used in a limited number of centers [69, 70]
Echocardiography	New regional wall motion abnormalities or global ventricular dysfunction
	Elevated wall thickness caused by myocardial edema, pericardial effusion, intracardiac thrombi
CMR	Inflammation, edema, and fibrosis detection through T1 and T2 mapping, extracellular volume assessment and LGE
ICA or CTCA	To rule out significant coronary artery disease
EMB	Necessary for definite diagnosis and personalized treatment. May be useful in treatment monitoring
Cardiac PET	May be useful in patients with suspected systemic autoimmune disease or cardiac sarcoidosis and with contraindications to CMR

Definition of suspected myocarditis: clinical manifestation + ≥1 obligatory positive test and no coronary artery disease, valvular, congenital heart disease or other disease that could explain the symptoms; CMR — cardiac magnetic resonance; CTCA — computed tomography coronary angiography; ECG — electrocardiography; EMB — endomyocardial biopsy; ICA — invasive coronary angiography; LGE — late gadolinium enhancement; PET — positron emission tomography

injury. This may be attributed to molecular mimicry between viruses and cardiac antigens [10].

Autoimmune/immune-mediated myocarditis may occur i.e., during antineoplastic treatment, due to previous infection (without the presence of the infectious agent) or in the course of autoimmune disorders with extra-cardiac presentations, e.g., sarcoidosis, hypereosinophilic syndrome, scleroderma, granulomatosis with polyangiitis and systemic lupus erythematous (Table 1) [6]. In some cases, cardiac involvement may be the only manifestation of an autoimmune disorder [11].

Novel cardio-oncology ESC guidelines define cancer-therapy-related cardiovascular toxicity for example immune checkpoint inhibitors-associated myocarditis [8]. Immune checkpoint inhibitor-myocarditis most often appears in the first 12 weeks of the therapy; however, it can also appear after 20 weeks [12].

Moreover, research suggests that there may be a genetic liability to myocarditis. For example, a genetic alteration in the desmosome may predispose one to the spread of an infectious agent and development of the disease [13]. In patients with HF and left ventricle (LV) dysfunction and EMB proven myocarditis, about 30% of patients had pathogenic variants of cardiomyopathy causing genes like *Titin* [14]. The search for the etiology of the disease is a key element that provides the opportunity to implement disease-directed treatment [15].

Diagnostics of myocarditis

Clinically suspected vs. true myocarditis

The clinical presentation of patients with myocarditis is diverse. It ranges from asymptomatic cases, chest pain and palpitations with transient electrocardiogram (ECG) changes, to life-threatening cardiogenic shock and ventricular arrhythmias. The diagnosis is made based on the clinical picture and preliminary abnormalities in additional tests (Table 2). Recent HF guidelines highlight that myocarditis should be suspected when there is a clinical presentation and ≥ 1 mandatory diagnostic test (by preference cardiac magnetic resonance [CMR]) comes out positive (Table 2). CMR should be performed to assess cardiac function, structure,

and tissue characterization in every patient with suspected myocarditis [6].

A combination of methods including CMR, and troponin levels improves the diagnostic accuracy [16]. It is also necessary to rule out significant coronary artery disease or extra-cardiac causes of symptoms (by invasive coronary angiography or computed tomography) [6].

Patients with clinically suspected acute myocarditis usually present with recent symptoms (i.e. chest pain, palpitations) and signs of acute myocardial injury (electrocardiographic changes, elevated troponin levels). Elevated cardiac troponin levels are an important sign of myocyte injury and should always be assessed. However, troponin elevation is not always present in patients with clinically suspected myocarditis, especially in the chronic stage of the disease [17]. Other biomarkers of cardiac injury or inflammation (e.g., C-reactive protein level) are not specific and, therefore, their testing is not recommended.

Patients with suspected chronic myocarditis usually present with signs of chronic HF. Additionally, myocarditis may cause raised concentrations of brain natriuretic peptides, circulating cytokines and markers related to extracellular matrix degradation, but these biomarkers have no clinical utility in the diagnosis of myocarditis. Despite recent advances in non-invasive methods, true myocarditis may only be confirmed by EMB or autopsy [6].

Electrocardiogram

Electrocardiogram is usually abnormal in patients with HF as well as with myocarditis [18]; however, the changes are not specific for myocarditis.

Myocarditis may be suggested mainly by concave and diffuse ST-T segment elevation, as well as atrial and ventricular arrhythmias. Atrioventricular and/or intraventricular conduction abnormalities may reflect e.g., laminopathy, Lyme disease, cardiac sarcoidosis, giant cell myocarditis and/or diffuse and advanced inflammatory processes [19].

Echocardiography

Echocardiography should be performed in every patient to exclude other, non-inflammatory causes of symptoms, evaluate cardiac morphology, and function, and assess potential complications (fluid, thrombi, valvular regurgitations). Additionally, echocardiography (ECHO) is the best imaging tool for non-invasive monitoring of the course of the disease. Modern techniques such as speckle tracking echocardiography (STE) may identify patients with subclinical myocardial dysfunction at an early stage of the disease. Therefore, STE should be recommended in the diagnostic process of suspected acute myocarditis, especially in patients with initially preserved LV ejection fraction (LVEF). STE has high sensitivity and may be correlated with EMB results and novel CMR techniques [20]. Moreover, STE may be used for the prognosis of a worse myocardial function in long-term follow-up [21].

Cardiac magnetic resonance

Cardiac magnetic resonance imaging with diagnostic requirements defined by the Lake Louise Criteria (LLC) updated in 2018 is the non-invasive test of choice [22]. CMR enables the assessment of cardiac morphology and function. It also offers a unique opportunity for myocardial tissue characterization, necessary for differential diagnosis. The LLC are based on the following CMR features: tissue edema, hyperemia, necrosis, or fibrosis, which vary along with either acute or chronic phases of myocarditis. Updated LLC criteria include a new CMR technique, i.e. parametric T1 and T2 mapping [23]. According to novel LLC, the diagnosis of myocarditis requires at least one T1-based criterion (presence of late gadolinium enhancement [LGE] in non-ischemic pattern distribution, increased myocardial T1 relaxation times or extracellular volume values) and at least one T2-based criterion (visible myocardial edema [hyperintensity in T2 weighted short tau-inversion recovery], increased myocardial T2 relaxation times, or T2 signal intensity ratio) [24].

The updated CMR LLC include parametric mapping as the reference noninvasive method for the diagnosis and prognosis of myocarditis [22, 23]. Novel CMR mapping techniques generate pixel-wise, quantitative maps of the myocardium. Therefore, quantitative parametric mapping improves sensitivity in showing inflammation, edema, and fibrosis in contrast to typical T1 and T2 imaging CMR techniques [25, 26].

Its prognostic role is also an additional advantage of CMR. The presence of LGE is associated with a worse prognosis and higher risk of all-cause mortality, HF hospitalization, arrhythmias, and SCD [27]. Grun et al. [28] have shown that the presence of LGE was associated with 8.4–12.8--fold increased all-cause and cardiac mortality in a group of 202 patients with EMB-proven viral myocarditis over 4.7 years of follow-up. Primary LGE is a prominent predictor of outcomes, i.e., all-cause mortality, cardiovascular death, SCD,

cardiac transplantation, appropriate implantable cardioverter-defibrillator (ICD) shock, and reoccurrence of myocarditis, regardless of LVEF [28]. Another study, (n = 1,672 patients with dilated cardiomyopathy [DCM]) have demonstrated a 1.5--fold increased risk for all-cause mortality, heart transplantation, or left ventricular assist device implantation in patients with LGE presence over a median follow up of 2.3 years [29].

The location of LGE is also of importance. The non-ischemic LGE pattern in epicardial, midwall regions or insertion points has been linked with the diagnosis of myocarditis [30]. The patients with acute myocarditis and LGE in the midwall layer of the anteroseptal myocardial segment have a worse prognosis in contrast to other patterns of presentation [31]. One of the studies has shown LGE involvement in midwall and septal regions to be associated with a higher risk of major adverse cardiac events [32]. Another study from Mahrholdt et al. [33] has also confirmed that LGE involvement of the septal wall predicts persistent LV dysfunction, although LGE involvement of the lateral wall is associated with superior outcome during follow-up.

A favorable outcome and recovery involve a complete resolution of inflammation or persistence of both LGE and edema, contrary to the persistence of LGE and disappearance of edema which are associated with a worse prognosis [34]. Moreover, persistent LGE identifies patients not completely responding to treatment and it may be a changing factor for intensified medical treatments or procedures such as ICD implantation [35].

A follow-up CMR a few months after the acute/ /initial episode of myocarditis may have a prognostic value and is recommended particularly in patients willing to return to physical activity. A possible reduction of LGE extent, resolution of inflammation and changes in LVEF should be assessed. Reduced LVEF and high degree of LGE at admission are negative prognostic factors. Therefore, patients with decreased LVEF at baseline should be closely monitored with follow-up CMR at 3 to 6 months due to the possibility of LV dysfunction [36].

Some CMR limitations should be considered in clinical evaluation. CMR has an especially high diagnostic value in acute myocarditis, but its sensitivity in chronic myocarditis is significantly limited. What is more, failure to fulfill the LCC criteria does not exclude myocarditis just as a confirmation of myocarditis on CMR images does not allow for the assessment of the etiology of myocarditis, viral status, and definitive confirmation of myocarditis.

Nuclear techniques

Single-photon emission computed tomography may be performed to determine myocardial viability, inflammation, and infiltration [6].

18F-2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) is a novel imaging technique which may improve diagnostic accuracy. It can determine the inflammation of the myocardial tissue by increased glucose uptake in the inflamed areas. Since CMR accuracy is low in chronic myocarditis, FDG-PET may be applicable in those cases, and be complementary to CMR [37].

Endomyocardial biopsy

Endomyocardial biopsy is a gold standard and provides a definitive diagnosis of myocarditis. The EMB allows for the assessment of the specific histotype, immunologic and virologic status of the myocardium with immunohistochemistry and polymerase chain reaction analysis [38].

The latest ESC HF guidelines recommend EMB in patients with severe cardiac impairment and/or serious ventricular arrhythmias or atrioventricular blocks [6]. In patients not responding to standard HF and antiarrhythmic therapy in a short time, EMB should be performed for a better insight of the HF mechanism and the diagnosis of possible ongoing myocarditis (Table 3). Therefore, an approach with the use of EMB allows for a personalized and specific treatment due to the identification of disease etiology, particularly in case of giant cell myocarditis, eosinophilic myocarditis, cardiac sarcoidosis, and systemic inflammatory disorders. EMB can be repeated in case of unexplained progression of HF or to monitor response to treatment (Table 3) [6].

At least 5–7 samples should be obtained to ensure the best accuracy and precise immunohistologic and molecular evaluation. There is no preference regarding left or right ventricular EMB. However, if possible, biventricular EMB should be performed. Biventricular EMB provides an improved diagnostic and prognostic accuracy, especially in the detection of suspected cardiac sarcoidosis or giant cell myocarditis [6]. The latest ESC guidelines on the management of ventricular arrhythmias and prevention of SCD recommended a novel approach using mapping--guided biopsy to provide the diagnosis in patients with focal myocardial involvement in CMR [9]. Endocardial electroanatomic mapping may be beneficial for targeted EMB, particularly in patients with suspected cardiac sarcoidosis or giant cell-myocarditis [9].

Table 3. Recommendations for endomyocardial biopsy in patients with suspected myocarditis [6, 38].

Recommendations for endomyocardial biopsy	Class of recommendation
In case of acute/fulminant myocarditis with progression or persistent cardiac dysfunction and/or malignant ventricular arrhythmias and/or atrioventricular block without expected response to standard treatment during first < 1–2 weeks	I
In patients with exacerbation of heart failure despite optimal treatment when there is a suspicion of specific diagnosis which can be confirmed in myocardial samples	IIa
Endomyocardial biopsy is especially recommended in patients with acute and/or chronic heart failure and suspected giant cell-, eosinophilic-, immune checkpoint inhibitor-related and/or lymphocytic myocarditis, vasculitis, sarcoidosis, systemic lupus erythematosus, and other auto-immune conditions	I

Of note, EMB rate of major complications is lower than 1% if it is performed by experienced cardiologists. Biventricular EMB is also a safe procedure with a low complication rate [39].

Treatment options

For the first time, the latest ESC HF guidelines offer a detailed approach to patients with myocarditis. Treatment of myocarditis should be based on clinical presentation, disease stage and if known — disease etiology [6]. Around 50% of cases of acute myocarditis resolve spontaneously in weeks after onset, 25% of cases transform into permanent heart dysfunction and approximately 25% deteriorate or progress to DCM with a need for heart transplantation or other form of ventricular support [40, 41]. Factors such as symptomatic HF, presence of ventricular arrhythmias, atrioventricular and/or bundle branch block, low LVEF at baseline, and fulminant course of the disease predict a worse prognosis [42]. As highlighted by the current guidelines, individual therapy of myocarditis should be based on EMB findings [6]. This applies to immunosuppressive or anti-infective treatment, as well as to the monitoring of therapy.

Supportive treatment

The main goal of treatment is the optimal management of HF and arrhythmias according to standard recommendations from appropriate guidelines. According to the ESC guidelines, standard HF therapy with angiotensin converting enzyme inhibitors or angiotensin receptor neprilysin inhibitors, beta-blockers, mineralocorticoid receptor antagonists and sodium glucose co-transporter type 2 inhibitors should be initiated when baseline LVEF is decreased [6]. Patients after myocarditis with improved ejection fraction (EF) meaning patients with previous HF with reduced EF and now with an EF more than 40% should continue HF therapy [43].

Moreover, hemodynamically unstable patients with acute/fulminant myocarditis (FM) should be treated in experienced intensive cardiac care units with respiratory and mechanical circulatory support, if necessary [6]. Patients with FM and deteriorating cardiac function may require diuretics, inotropes, and vasopressors. In case of cardiogenic shock unresponsive to initial treatment, temporary mechanical ventilation, veno-arterial extracorporeal membrane oxygenation or the Impella heart pump should be considered [44]. Heart transplant or left ventricular assist device implantation should be under consideration when transient mechanical circulatory support must be continued for more than 2 or 3 weeks [45, 46].

Prevention of SCD

In patients with myocarditis, it is recommended to assess individually the indications for ICD or cardiac resynchronization therapy (CRT). ICD implantation in primary SCD prevention is not advised in the acute phase of myocarditis. The decision should be delayed for 3 to 6 months. Of note, in patients with a high risk of arrhythmias and/or serious left ventricular dysfunction a wearable cardioverter defibrillator may be beneficial as a bridge to an implanted device, cardiac transplantation, or resolution after immunosuppressive treatment [6]. Although, if sustained ventricular tachycardia or ventricular fibrillation is hemodynamically not tolerated, ICD implantation should be considered even in the acute phase of myocarditis [47, 48]. In patients with chronic myocarditis or post-myocarditis if ventricular tachycardia is recurrent, the administration of amiodarone or catheter ablation (when amiodaron is not effective or not tolerated) and/or ICD implantation should be considered [9].

Anti-cancer treatment related myocarditis

The management pathway of suspected/ /confirmed myocarditis related to antineoplastic treatment should be based on its interruption, hospital admission and detailed diagnostic workup. In patients with suspected immune checkpoint inhibitor-associated myocarditis treatment with methylprednisolone intravenously for the first 3–5 days and then orally under clinical, ECG, ECHO and cardiac troponin surveillance is recommended [49]. During recovery, a multidisciplinary approach should be applied to review the continuation of the antineoplastic treatment. Complete recovery is defined as a total resolution of acute symptoms, normalization of biomarkers, or decrease in cardiac troponin by 50% from the highest level, and improvement of LVEF after the end of immunosuppressive therapy [50]. LGE or increased T1 signal on CMR may be present but the absence of acute edema should be confirmed [51].

Immunosuppression

For the first time, the new ESC HF guidelines have suggested considering immunosuppressive treatment in EMB-proven cases. Immunosuppression with duration tailored to the disease activity (usually for at least 6–12 months) is recommended in EMB-proven myocarditis, particularly giant cell or eosinophilic myocarditis, cardiac sarcoidosis, and myocarditis (especially FM) triggered by systemic autoimmune diseases [6]. Despite the growing doubts about the role and importance of viruses in myocarditis, it is still not recommended to start immunosuppression in patients without ruling out the presence of a virus in EMB [6, 52]. However, in case of acute HF and/or life-threatening arrhythmias during FM, some experts suggest that empirical therapy with intravenous corticosteroids may be considered without delay when immune etiology is suspected [53]. Giant cell myocarditis is the most aggressive form of autoimmune myocarditis; therefore, high-dose immunosuppression should be administered right after the diagnosis [54]. Eosinophilic myocarditis requires the discontinuation of the responsible agent, and it often responds well to high-dose steroid therapy [55].

There is also promising data on immunosuppressive therapy with prednisone and azathioprine in chronic lymphocytic myocarditis [56]. A significant increase in LVEF and a decrease in LV dimensions and volumes was observed in some single-center studies [57]. Recently, Chimenti et al. [58] published a 20-year follow up of the TIMIC (Tailored IMmunosuppression in virus-negative Inflammatory Cardiomyopathy) trial that confirmed the lasting benefit of immunosuppressive therapy. However, further, randomized controlled studies are needed to explain the efficacy and safety of the immunosuppressive therapy in myocarditis. At present a multicenter, double blind randomized trial (IMPROVE-MC) on combined 12-month therapy of azathioprine with prednisone is ongoing in Poland [59, 60].

Anti-infection therapy

To date, there is no antiviral therapy that has a proven effect. Nonetheless, targeted antiviral therapy is recommended in confirmed cases of human immunodeficiency virus, cytomegalovirus, or human herpes virus 6 based on viral load and replication activity [6]. In one of the studies treatments with interferon beta in EMB-diagnosed viral myocarditis improved LVEF, quality of life and symptoms based on New York Heart Association class [61, 62].

Viral serology has low efficacy in the diagnosis of myocarditis because the presence of circulatory IgG antibodies against cardiotropic viruses in the general population without viral heart disease is high. Further, a lack of a correlation between virus serology and EMB results has been proven [63].

When other curable infectious diseases, i.e., Lyme disease are diagnosed, specific treatment should be administered [6].

Immunomodulation

The intravenous immunoglobulin (IVIG) treatment is non-established in myocarditis although it has been linked to improvement of LV function in DCM [64]. A recently published meta-analysis of the pediatric population has shown that IVIG treatment improved LVEF and decreased in-hospital mortality with fine tolerance [65]. In contrast, another meta-analysis did not prove an increase in LVEF [66]. Based on current data, IVIG is not routinely recommended as a treatment option in myocarditis or DCM [6].

Return to physical activity and long-term monitoring

Consequently, the assessment of exercise related SCD risk, by means of ECG, imaging studies, exercise stress test and Holter monitoring, is recommended following myocarditis recovery [6]. The assessment should be performed in planned time frames with follow-up at 3–6 months after the acute phase of the disease and then annually for at

least 4 years [6, 67, 68]. Moderate to high-intensity training should be abandoned for at least 6 months till symptoms, increased troponins, or clinically significant ECG/CMR/ECHO abnormalities are persistent. Patients with vast LGE areas (> 20%) and decreased LVEF should not participate in training of a moderate to high intensity. A follow-up EMB to reveal evidence of the resolution of inflammation and healed myocarditis may be considered [6]. Patients with previous myocarditis are at an increased risk for the recurrence of the disease.

Conflict of interest: None declared

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Large-bore SOFIA catheter for bailout thrombus aspiration in STEMI

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Routine thrombus aspiration in primary percutaneous coronary intervention is not recommended in the current European and American guidelines [1, 2]. The Japanese Cardiological Society recommendations state that selective or bailout manual aspiration thrombectomy may be considered in patients with ST-segment elevation myocardial infarction (STEMI) [3]. Despite downgrading in the guidelines, thrombus aspiration still has a role in STEMI interventions, albeit limited to heavy thrombus burden, unsuccessful reperfusion or distal embolization [4–6]. However, the task of large clot extraction usually calls for a large-bore catheter [7–9]. The lumen of 6 F (French) coronary aspiration devices, limited by the extra channel for rapid exchange wire, is often too small to evacuate large thrombus. Seven and eight F aspiration catheters are available, although they are less likely to be used with radial access, while femoral crossover will certainly prolong the door-to-balloon time and bring about higher risk of access site complications, particularly in patients typically receiving GP IIB/IIIA inhibitors due to the high thrombus burden. Therefore, guiding catheters that were traditionally used for extraction of proximally lodging clots are sometimes still utilised, while guide extension catheters have been employed to reach thrombus in medial and distal segments. After using a so called intermediate or distal access catheter Sofia (Microvention, Terumo) for thrombectomy in stroke interventions, being satisfied with its performance, we decided to resort to it in bailout situations in STEMI patients.

An 81-year-old male patient with a history of arterial hypertension, diabetes mellitus type 2, and chronic renal insufficiency was admitted due to the inferior wall STEMI. In angiography, the right coronary artery (RCA) occlusion was found (Fig. 1A). Six F 4.0 Judkins Right guide (Launcher by Medtronic) was used for intervention. After balloon inflation, partial recanalization revealed massive thrombus in the middle to distal RCA (Fig. 1B). Due to the clot size, based on our previous experience, a 5 F 125cm long neurointerventional catheter Sofia was used. Its excellent trackability allowed us to smoothly deliver it wirelessly even without an extra backup guiding catheter (Suppl. Video 1). Two passes were needed to completely evacuate the thrombus, with contact aspiration first performed in the middle and subsequently in the distal segment of the RCA (Fig. 1C). To maintain constant negative pressure, two 50 ml vacuum locking syringes were attached through a three-way stopcock. After the thrombectomy, TIMI 3 flow was achieved with a residual 50% stenosis (Fig. 1D). Two days later, deferred drug-eluting stent implantation was performed to avoid the no-reflow phenomenon.

Sofia is available as a 115 or a 125 centimetre long catheters with a straight tip, compatible with

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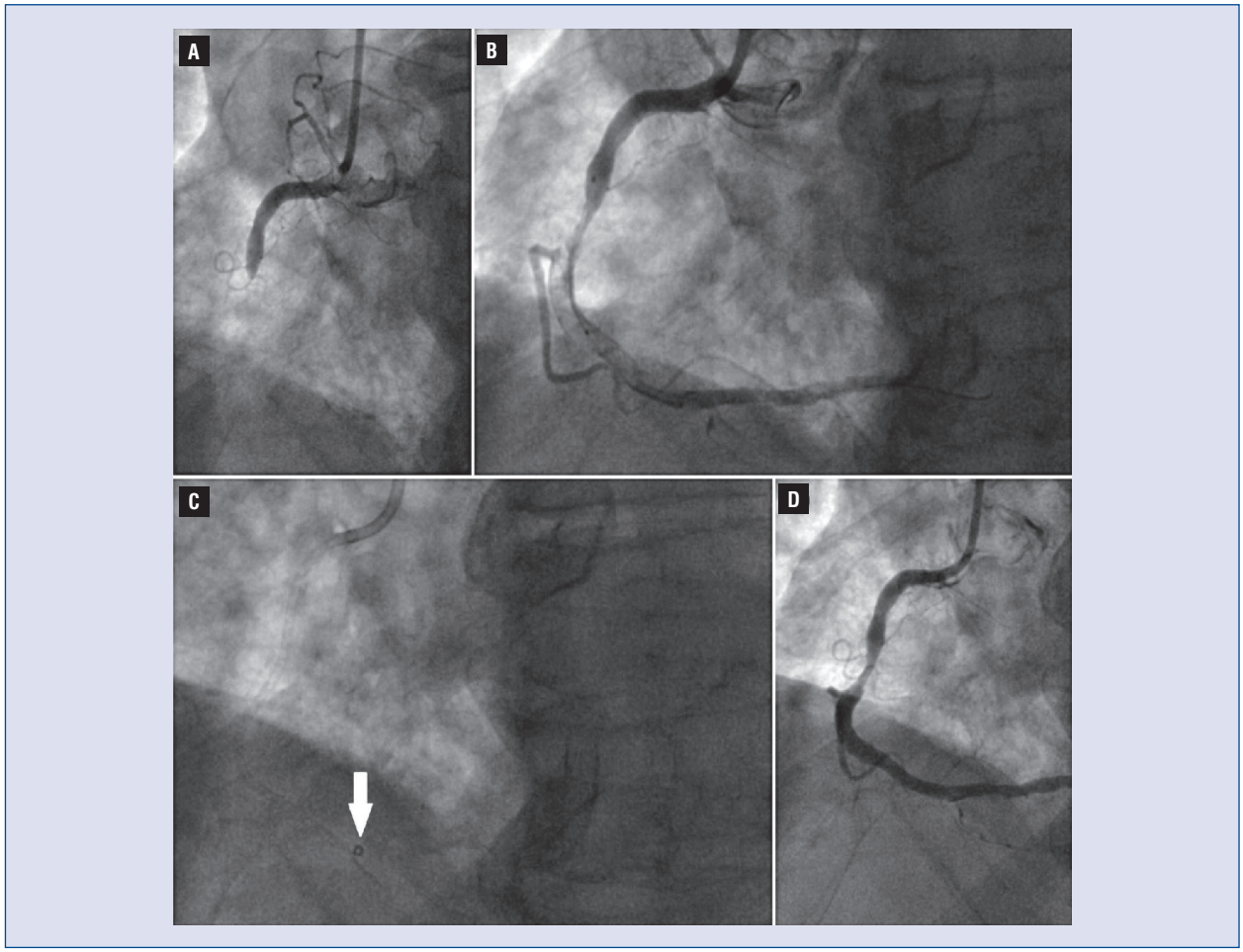

Figure 1. Aspiration thrombectomy performed with 5 F Sofia. Acute occlusion of mid-RCA (**A**). Large thrombus revealed after balloon inflation (**B**). Distal aspiration with Sofia (*arrow*) (**C**). Culprit lesion revealed after thrombus extraction (**D**).

6 F guides with an inner diameter of at least 0.070" (Figure 2 — Sofia setup). Sofia's distal 17 cm are very soft (even flaccid), flexible and hydrophilic, yet with a good kink resistance and pushability due to hybrid braid and coil reinforcement. The aspiration technique is intuitive, the same as with conventional aspiration catheters; however, a few caveats should be taken into account. Sofia is not a monorail catheter. It can be advanced and removed wirelessly (our preferred technique, offering larger aspiration lumen), but when vessel wiring is to be maintained upon withdrawal, a 300cm long guidewire is needed. For very distal aspiration, Sofia's working length can be increased by 9 cm by direct insertion of the catheter into the guide without a Y connector.

With the outer diameter roughly the same as that of the 6 F coronary aspiration devices (1.70 mm Sofia vs. 1.72 mm Hunter by IHT Dynamics), Sofia offers a 60% larger extraction lumen than the latter (1.52 mm^2 Sofia vs. 0.95 mm^2 Hunter). To provide a similar extraction area, one would have to use 7 or even 8 F coronary devices (7F Pronto V4 by Teleflex: 1.45 mm^2, 8 F Eliminate by Terumo: 1.58 mm^2). Sofia's aspiration area is comparable to 6 F guide extension catheters (1.52 mm^2 Sofia vs. 1.58 mm^2 Telescope by Medtronic), with better trackability and continuous suction lumen [10]. Sofia is also much more flexible and hydrophilic than guide extension catheters, and understandably so, as the latter have been designed for providing additional support to guiding catheters. In fact, Sofia is so extremely trackable that it can and often is advanced wirelessly in stroke interventions. Originally a neurointerventional catheter, Sofia has an atraumatic tip and flexibility necessary to navigate tortuous intracranial arteries.

We believe that the use of such large-bore aspiration catheters with greater aspiration capacity may be a game changer in the coronary

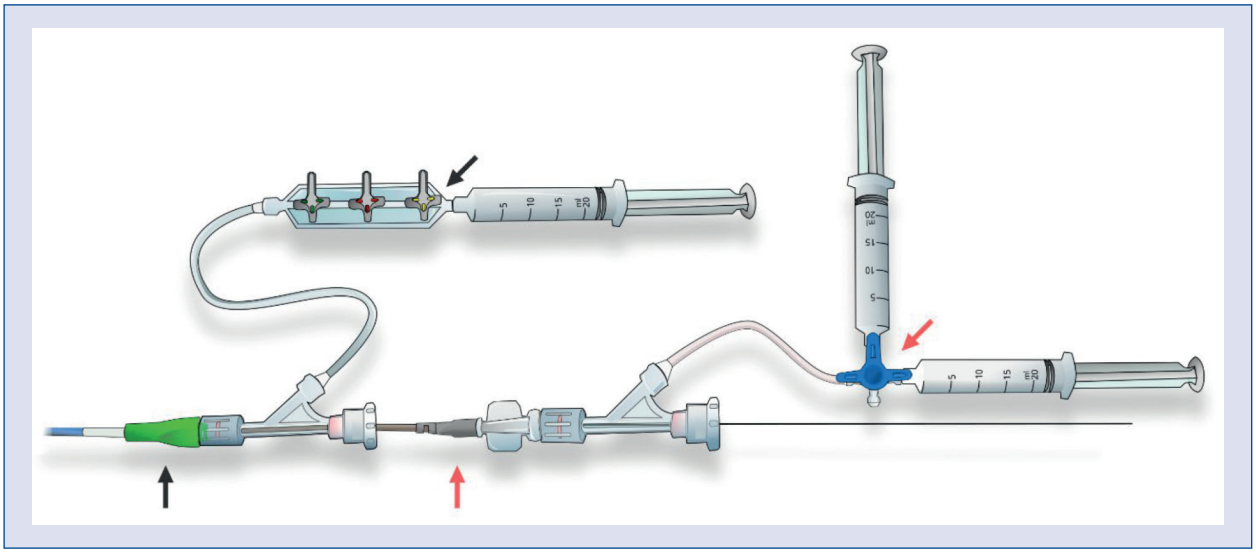

Figure 2. Author's typical setup for coronary thrombus aspiration with Sofia. Black vertical arrow — guide catheter; red vertical arrow — Sofia; black diagonal arrow — aspiration through the guide; red diagonal arrow — two vacuum locking syringes for aspiration through Sofia.

thrombectomy, significantly improving its efficacy, with the potential to reduce cerebral and coronary embolic complications due to the catheter's ability to generate greater suction force and accommodate entire chunks of clot without their fragmentation [9–12]. Our preliminary experience of massive thrombus aspiration with Sofia as a rescue or last resort technique are promising, with complete or near-complete clot clearance in all cases, and no coronary dissection or clot loss observed thus far.

Conflict of interest: None declared.

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VIA MEDICA

IMAGE INCARDIOVASCULAR MEDICINE

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First use of the Impella 5.5 in a patient with cardiogenic shock to bridge to heart transplantation in Poland

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A 46-year-old male with blood pressure (BP) 85/46 mmHg was admitted due to cardiogenic shock as a result of antero-lateral ST-segment elevation myocardial infarction treated by percutaneous coronary intervention of the left anterior descending artery in a remote hospital 2 days prior. Laboratory findings revealed N-terminal-proB-type natriuretic peptide 13,868 pg/mL, troponin I 338,068 pg/mL, and lactates 2.9 mmol/L. Echocardiography showed enlargement of both ventricles, a 10% of left ventricular (LV) ejection fraction, and LV thrombus, necessitating inotropic support with noradrenaline 4 mL/h, milrinone 9 mL/h, and vasopressin 1 mL/h (figure 1). The Shock Team decided to implement an intra-aortic balloon pump (IABP Teleflex), after which BP increased to 123/62 mmHg, and right heart catheterization revealed a mean pulmonary artery pressure of 36 mmHg, pulmonary capillary wedge pressure of 25 mmHg, cardiac index of 2.34 mL/min/1.73 m^2, cardiac power of 0.75 W, and pulmonary artery pressure index of 1.6. The control echocardiography did not show LV thrombus; thus, the IABP was replaced with the Impella CP (Abiomed). Despite transitory improvement, hemolysis and thrombocytopenia were observed. As that time, the Impella 5.5 became available, and the Shock Team decided to upgrade the device to an axillary Impella 5.5, which was performed using a double device technique (Suppl. Video 1). Two days later, signs of hemolysis and thrombocytopenia ceased, and the patient's condition improved, gaining full mobilization. After 17 days on Impella 5.5 support, uneventful orthotopic HTx (*heart transplantation*) was performed. The postoperative course was uncomplicated. After 4 months the patient was doing well with full physical activity. The Impella 5.5 provides maximal hemodynamic support with reduced risk of complications and with minimally invasive implantation.

Article information

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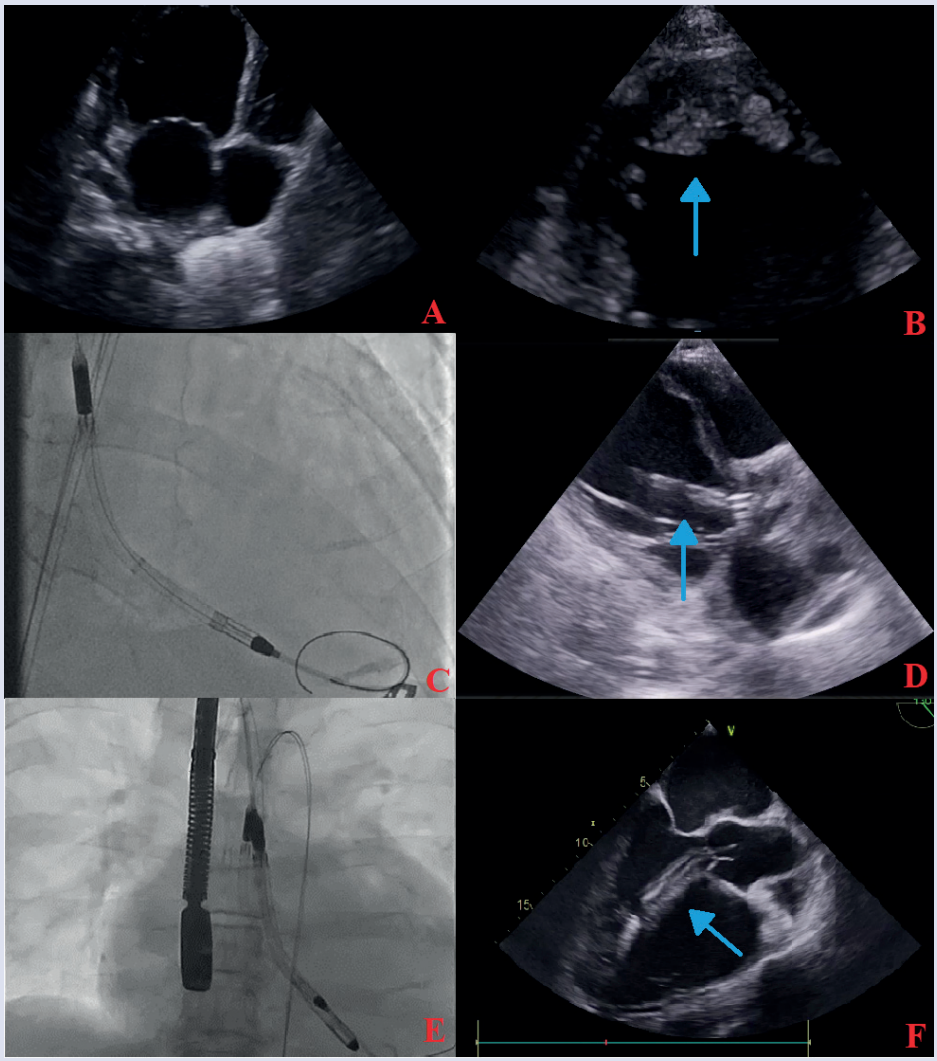

Figure 1. A. Transthoracic echocardiography, dilated left ventricle (diastolic diameter 72 mm); **B.** Clots in the apex of the left ventricle; **C.** Fluoroscopy, Impella CP implanted through right femoral access; **D.** Transthoracic echocardiography, Impella CP; **E.** Fluoroscopy, Impella 5.5 implanted through axillary access with Impella CP still in left ventricle (double device technique); **F.** Transthoracic echocardiography, Impella 5.5.

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Laser for a complex PCI with ISR, undilatable, and uncrossable lesions

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A 72-year-old woman was referred to our center with recurrent chest tightness over the previous year which had exacerbated 1 week prior. The patient had a history of self-made polyurethane-covered stent (PU-CS) implantation 6 months prior because of a proximal left anterior descending (LAD) perforation after high-pressure post-dilatation. Diagnostic angiography revealed in-stent restenosis (ISR) at the PU-CS site, stent under-expansion at the middle LAD (undilatable with a 2.75 mm noncompliant balloon inflated at 24 atmospheres for 60 s), and tight stenosis with a heavily calcified lesion at the middle circumflex (uncrossable with a 1.25 mm compliance balloon). Optical coherence tomography (OCT) revealed excessive neointimal proliferation at the ISR site and under-expanded stent struts with circumferential peri-stent calcification. Laser debulking was used to pretreat the three lesions with a 0.9 mm coronary laser atherectomy catheter (X-80 Vitesse RX, Spectranetics®) with saline flush. After laser, repeat OCT revealed a lamellar flap neointima at the PU-CS site. The OCT imaging after laser treatment in the middle circumflex region revealed calcified nodules and suspicious thrombi. The three different types of lesions were successfully fixed using one procedure (Fig. 1, Suppl. Video 1), and the patient's outcome was uneventful during nine-month follow-up. The unique OCT images of ISR may be attributed to the altered proliferation pattern of the covered stent, in which neointimal hyperplasia proceeds from the edges toward the center with minimal transgraft tissue penetration. The combined use of laser and OCT has unique advantages in terms of plaque modification and procedural success in complex coronary lesions.

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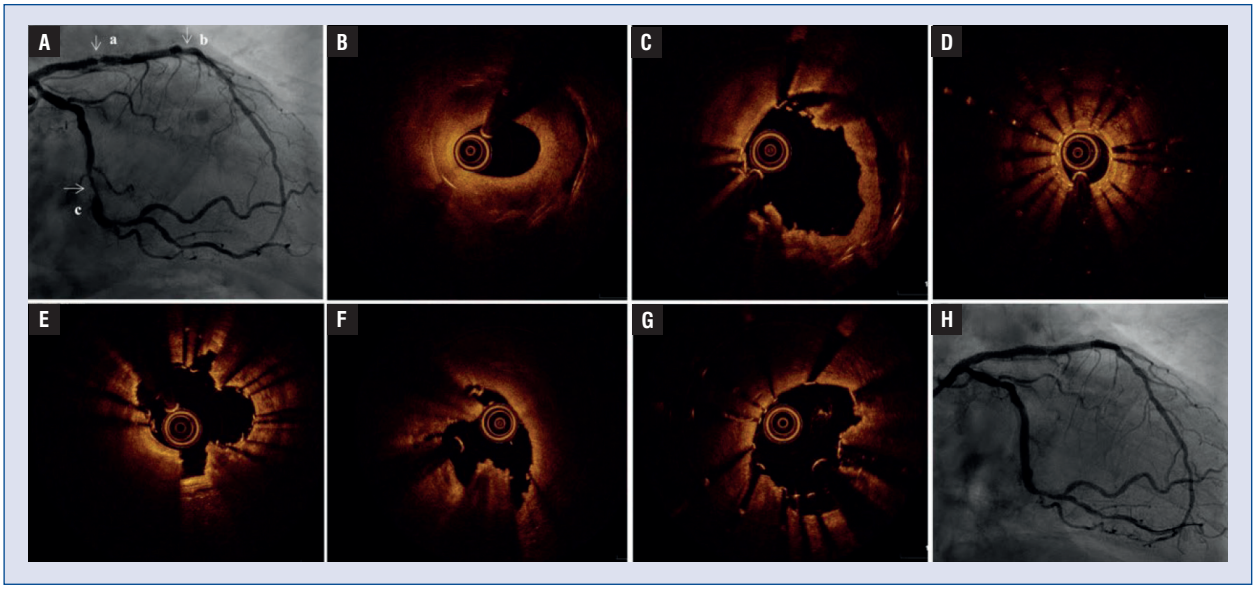

Figure 1. Representative images for the application of the laser atherectomy technique in a complex PCI. **A.** Diagnostic angiography demonstrates ISR at the PU-CS site (a), stent under-expansion at the middle segment of the LAD (b), and tight stenosis with a heavily calcified lesion at the middle circumflex (c); The PU-CS is made by a commercial drug-eluting stent covered with polyurethane-membrane cutting from 3M™ Tegaderm™ Transparent Film Dressing; **B.** OCT reveals excessive neointimal proliferation in the ISR site; **C.** After laser debulking, repeated OCT demonstrates lamellar flap neointima at the PU-CS site and a drug-coated balloon is deployed at the ISR site; **D.** OCT reveals under-expanded stent struts with circumferential peri-stent calcification at the middle segment of the LAD; **E.** OCT reveals optimal cross-sectional areas are obtained with the adjuvant of laser atherectomy and a non-complaint balloon dilatation for the under-expansion site; **F.** The OCT imaging after laser atherectomy at the middle circumflex reveals calcified nodules and suspicious thrombi; **G.** After a drug-eluting stent is implanted and a non-compliant balloon is sequentially dilatated at the middle circumflex, OCT reveals satisfactory result; **H.** Excellent angiographic results after the PCI procedure. PCI — percutaneous coronary intervention; ISR — in-stent restenosis; PU-CS — polyurethane-covered stent; LAD — left anterior descending; OCT — optical coherence tomography.

VIA MEDICA

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Stent-assisted coil embolization of large coronary artery aneurysm under intravascular ultrasound guidance

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A 57-year-old male who with a history of coronary artery bypass surgery two years prior presented with chest pain. Angiography revealed totally occluded distal left internal mammary artery graft to the left anterior descending artery (LAD), patent vein grafting to the right coronary artery, and a 90% stenosis of proximal LAD with a 6 × 9 mm sized coronary aneurysm (CAA) (Fig. 1A). After a heart team discussion, angioplasty with drug-eluting stents and stent-assisted coil embolization were planned to prevent coil dislodgement, as intravascular ultrasound (IVUS) demonstrated a wide-necked CAA (Fig. 1B). A microcatheter (Rebar® 2.4F/153cm, Medtronic) was advanced inside the CAA over a 0.014" wire (VersaTurn, Abott) after careful wiring into the CAA (Fig. 1C). Resolute onyx 3.5 × 26 mm (Medtronic) was then placed over proximal LAD, deploying it not above nominal pressure in order to avoid damage of the microcatheter, now jailed under the stent struts (Fig. 1D) and two detachable coils (Concerto 5 mm × 15 cm, 4 mm × 10 cm, Medtronic) were released inside the CAA through the microcatheter. After retrieval of the microcatheter, high-pressure stent postdilation was performed. A postprocedural IVUS and final angiography confirmed complete embolization of the CAA (Fig. 1E–F, Suppl. Video 1). The patient was discharged without complications the following day and 12-month angiographic follow-up results remained favorable (Suppl. Video 1). CAAs are unusual anomalies with undefined standards of treatment. The stent-assisted coil embolization, as described, could be a beneficial option for managing concomitant coronary artery disease and CAA.

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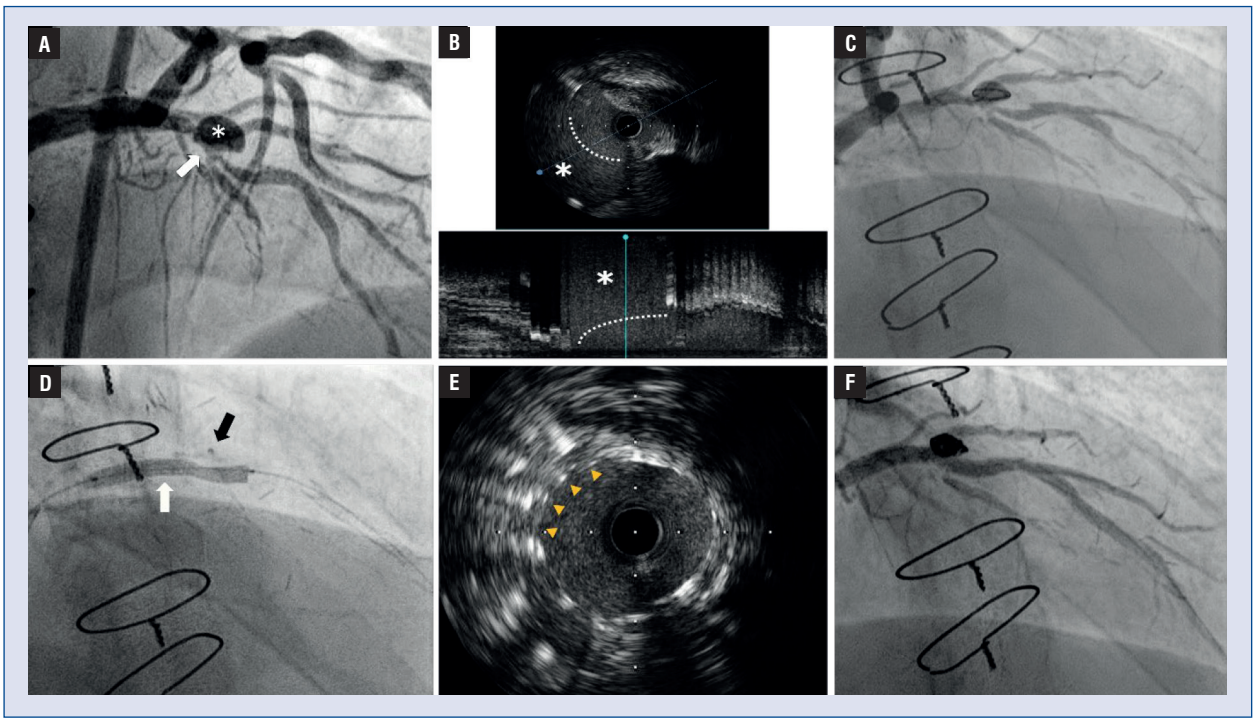

Figure 1. A. Baseline coronary angiogram showing severe stenosis of the proximal LAD (*white arrow*) with a large coronary artery aneurysm (CAA) (*asterisk*); **B.** Intravascular ultrasound (IVUS) showing CAA (asterisk) with wide-neck (*white dotted line*); **C.** Careful wiring into the CAA; **D.** Stenting at proximal LAD (*white arrow*) with the microcatheter (*black arrow*) jailed under the stent strut; **E.** Post-IVUS showed well-apposed stent struts (*yellow arrowheads*) and multiple hyperechogenic coils packed in the CAA outside the stent struts; **F.** Final angiography showing complete embolization of the CAA.

VIA MEDICA

IMAGE IN CARDIOVASCULAR MEDICINE

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Acute eosinophilic myocarditis mimicking inferior myocardial infarction presenting with delayed hypereosinophilia

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A 39-year-old male, who had a history of mugwort allergy and had had a recent antigen exposure, was hospitalized due to chest pain. The laboratory examinations showed elevated troponin T concentration and an electrocardiogram indicated inferior-wall ischemia (Fig. 1A). Transthoracic echocardiography showed a severe hypokinesis in inferior left ventricular wall and pericardial effusion (Fig. 1B; Suppl. Video 1). The coronary angiography showed no obstructive coronary artery diseases. Stress myocardial perfusion scintigraphy revealed a fixed perfusion defect of the inferior wall of the left ventricle, but no significant myocardial ischemia (Fig. 1C). The peripheral eosinophil count was normal at admission, but was increased up to 35% (eosinophilic count: 3,955/μL) on the 11th day in hospital. The histopathological examinations of the right ventricular myocardium obtained by endomyocardial biopsy demonstrated myocardial inflammation with eosinophilic infiltration (Fig. 1D). A blood examination showed a total IgE level of 1,280 IU/mL (normal range: < 170 IU/mL), and a multiple allergen simultaneous test revealed a serum mugwort-specific IgE level of 132 lumi-count (normal range: < 1.39 lumi-count). These findings led to a diagnosis of eosinophilic myocarditis (EM), and the administration of oral prednisolone was started. Thereafter, the peripheral eosinophilia resolved and his chest pain, cardiac function and pericardial effusion improved. Our observations suggested that EM may present with regional ST-segment elevations in electrocardiography and a focal asynergy in echocardiography, which are similar to acute myocardial infarction. Furthermore, this case highlights the importance of recognition that hypereosinophilia in peripheral blood may not necessarily be evident in the initial stage of EM.

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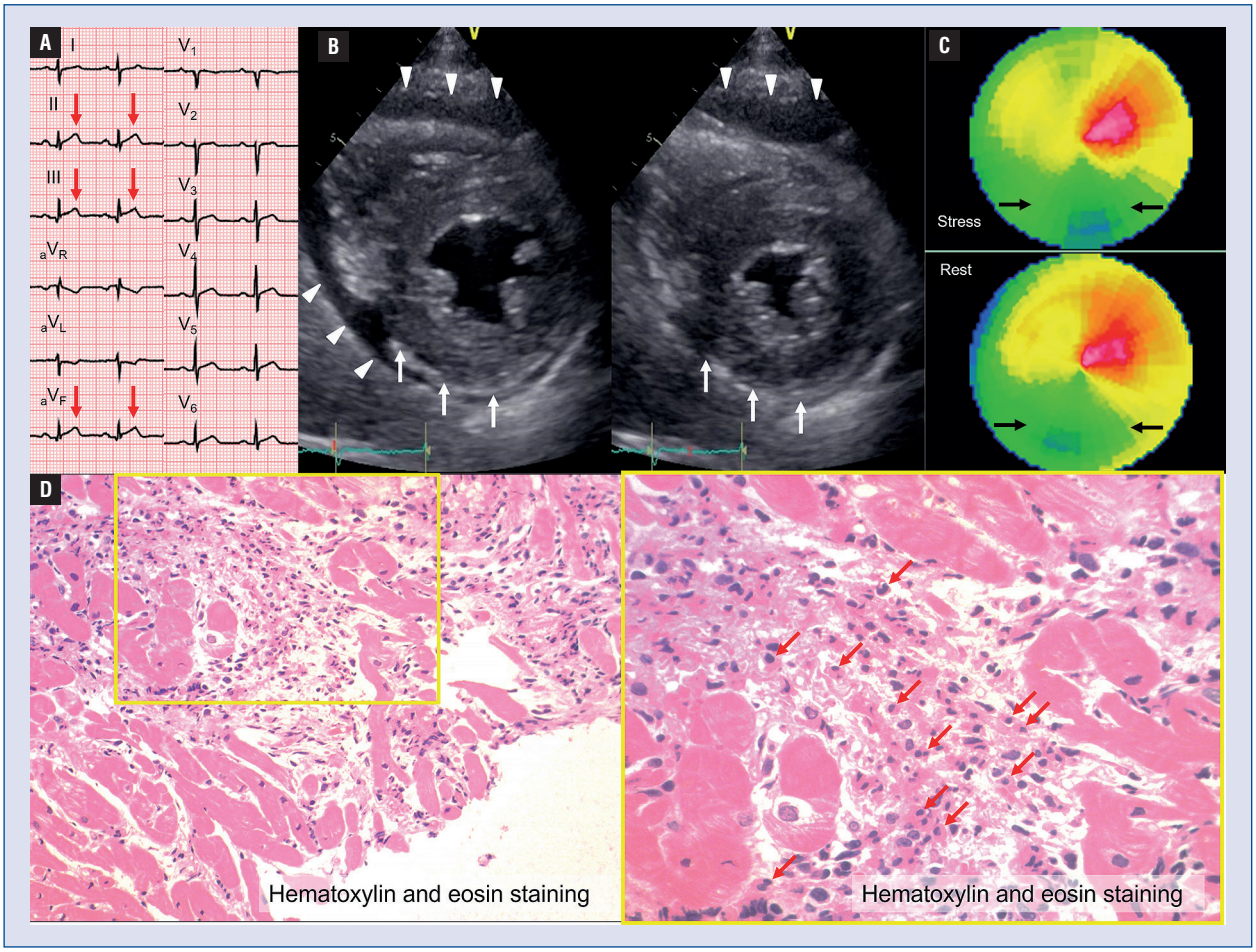

Figure 1. A. A twelve-lead electrocardiogram showed ST-segment elevations in leads II, III and $_aV_F$ (*red arrows*). **B.** Echocardiogram (*parasternal short axis*) showing a severe hypokinesis in the inferior left ventricular wall (*white arrows*) and pericardial effusion (*white arrowheads*). **C.** Stress myocardial perfusion scintigraphy using technetium-99m (99mTc) tetrofosmin revealed a fixed perfusion defect of the inferior wall of the left ventricle (*black arrows*). **D.** The histopathological examinations of endomyocardial biopsy specimen from the right ventricular septum showing myocardial inflammation with eosinophilic infiltration (*red arrows*).

VIA MEDICA

LETTER TO THE EDITOR

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Should dual antiplatelet treatment be guided by lipoprotein(a) concentration?

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This letter accompanies the article on page 365

Lipoprotein(a) (Lp(a)) is a low-density lipoprotein-like molecule, composed of the apolipoprotein (a) (apo(a)), which is attached to the apolipoprotein B-100 by a single disulfide bond [1]. It is recognized as an independent risk factor for cardiovascular events. Lp(a) favors initiation of atherogenesis by modulating recruitment of inflammatory cells in the vessel wall, increases atherosclerotic plaque vulnerability by provoking local inflammation, and adversely affects discrete key points in primary and secondary hemostasis as well as in fibrinolysis [1]. Due to the high degree of homology between apo(a) and plasminogen, Lp(a) potentiates thrombosis through inhibiting plasminogen activation and fibrin degradation, and promoting endothelial plasminogen activator inhibitor expression, tissue factor pathway inhibitor activity. The role of Lp(a) in platelet activation and aggregation is a matter of debate, as the results of in vitro experimental studies are inconsistent and in-depth clinical studies are lacking.

Recently Cui et al. [2] reported secondary analysis of a single-center, prospective registry demonstrating that extended (> 1 year) dual antiplatelet therapy (DAPT) was associated with lower risk of ischemic cardiovascular events in patients with acute coronary syndrome (ACS) treated with percutaneous coronary intervention (PCI) with elevated Lp(a) levels, but not in individuals with normal Lp(a) level. The extended DAPT was not associated with increased risk of clinically relevant bleeding and did not differ between the two groups with different Lp(a) levels. This study is the first one evaluating the effect of Lp(a) concentrations on the clinical outcomes of extended DAPT in ACS patients after PCI [2]. The present study has several limitations, including the specific Asian ethnicity of the patients, but it provides a strong rationale for more complex assessment of lipid parameters including Lp(a) in all currently ongoing and planned clinical trials aimed at assessing DAPT modification, especially de-escalation and prolonged treatment [3–7]. To understand the mechanism of influence of these factors on platelet reactivity and on the efficacy of antiplatelet drugs, multilevel pharmacodynamic and pharmacokinetic studies are necessary [8–10].

Conflict of interest: None declared

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VIA MEDICA

LETTER TO THE EDITOR

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Lipoprotein(a): an important consideration for DAPT therapy after PCI

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This letter accompanies the article on page 363

The interest in the letter is much appreciated for the study assessing the effect of extended dual antiplatelet therapy (DAPT) on clinical outcomes in invasively treated acute coronary syndrome (ACS) patients with different lipoprotein(a) [Lp(a)] concentrations [1]. Previous in vivo and in vitro studies revealed that Lp(a) has a pro-aggregatory effect through proteinase-activated receptor 1 (PAR1) via thrombin-mediated activation and CD36 via OxPL-mediated activation [2–3] and an anti-aggregatory effect through platelet-activating factor acetylhydrolase (PAFAH), collagen and αIIbβ3 integrin [4–5]. Although the net in vivo effect of Lp(a) on overall platelet function remains unknown, the preponderance of evidence suggests a net pro-aggregatory effect. For example, Zhu et al. reported that high plasma Lp(a) levels were significantly associated with increased platelet aggregation determined by thromboelastography in patients undergoing percutaneous coronary intervention (PCI) [6].

According to available research, for the first time, it was demonstrated that DAPT with aspirin plus clopidogrel > 1 year was significantly associated with lower risk of ischemic events without increasing the risk of clinically relevant bleeding in ACS patients with elevated Lp(a) levels after PCI, whereas the beneficial effect of extended DAPT was not detected in individuals with normal Lp(a) levels. Notably, there are two points to declare. First, clopidogrel, rather than ticagrelor or prasugrel, was predominantly used as a $P2Y_{12}$ inhibitor for the DAPT regimen. Second, the conclusions drawn from the study may not be generalized to other than Asian ethnicities. Therefore, studies using a more potent $P2Y_{12}$ inhibitor or in non-Asian ethnicities are needed to evaluate the prognostic effect of extended DAPT in ACS patients with elevated Lp(a) levels after PCI. In addition, further studies evaluating the role of aspirin and $P2Y_{12}$ inhibitors on platelet function will help us understand why prolonged DAPT had different effects in patients with different Lp(a) concentrations.

We totally agree with what was indicated in the letter which said that more complex assessment of lipid parameters including Lp(a) should be performed in clinical trials aimed at assessing DAPT modification, especially de-escalation and prolonged treatment. For example, the ongoing ELECTRA-SIRIO 2 (Evaluating Safety and Efficacy of Two Ticagrelor-based De-escalation Antiplatelet Strategies in Acute Coronary Syndrome — a randomized clinical trial) is being conducted to assess the influence of ticagrelor dose reduction with or without the continuation of aspirin versus DAPT with standard dose ticagrelor in reducing clinically relevant bleeding and maintaining antiischemic efficacy in ACS patients [7]. In addition to

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the main results of the study, we also expect what role Lp(a) plays.

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