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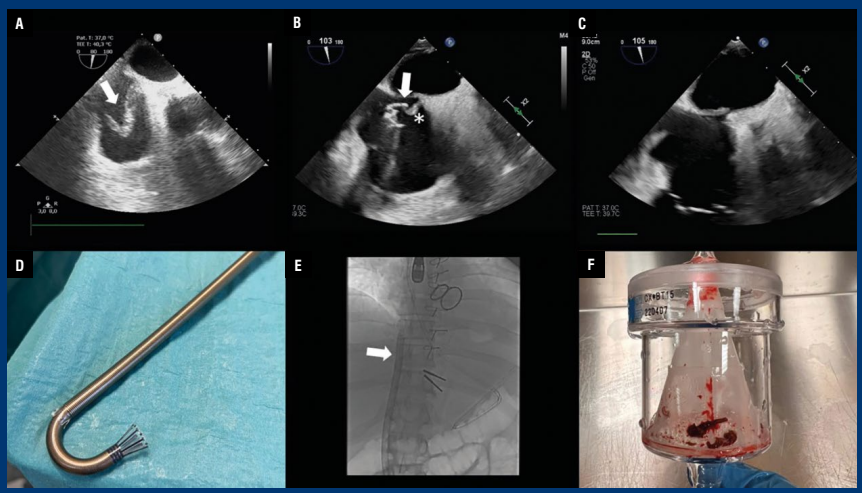

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The impact of first wave of the SARS-CoV-2 2019 pandemic in Poland on characteristics and outcomes of patients hospitalized due to stable coronary artery disease

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Abstract

Background: *An investigation of baseline characteristics, treatment, and outcomes in patients with stable coronary disease after the first wave of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic may provide valuable data and is beneficial for public health strategy in upcoming years.*

Methods: *A multi-institutional registry, including 10 cardiology departments, was searched for patients admitted from June 2020 to October 2020. The baseline characteristics (age, gender, symptoms, comorbidities), treatment (non-invasive, invasive, surgical), and hospitalization outcome (mortality, myocardial infarction, stroke, composite endpoint — major adverse cardiac and cerebrovascular events [MACCE]) were evaluated. The comparison was made to parameters presented by patients from the same timeframe in 2019 (June–October). Multivariable analysis was performed.*

Results: *Number of hospitalized stable patients following lockdown was lower (2498 vs. 1903; $p < 0.0001$). They were younger (68.0 vs. 69.0; $p < 0.019$), more likely to present with hypertension (88.5% vs. 77.5%; $p < 0.0001$), diabetes (35.7% vs. 31.5%; $p = 0.003$), hyperlipidemia (67.9% vs. 55.4%; $p < 0.0001$), obesity (35.8% vs. 31.3%; $p = 0.002$), and more pronounced symptoms (Canadian Cardiovascular Society [CCS] III and CCS class IV angina: 30.4% vs. 26.5%; $p = 0.005$). They underwent percutaneous treatment more often (35.0% vs. 25.9%; $p < 0.0001$) and were less likely to be referred for surgery (3.7% vs. 4.9%; $p = 0.0001$). There were no significant differences in hospitalization outcome. New York Heart Association (NYHA) class IV for heart failure was a risk factor for both mortality and MACCE in multivariate analysis.*

Conclusions: *The SARS-CoV-2 2019 pandemic affected the characteristics and hospitalization course of stable angina patients hospitalized following the first wave. The hospitalization outcome was similar in the analyzed time intervals. The higher prevalence of comorbidities raises concern regarding upcoming years.* (Cardiol J 2023; 30, 3: 337–343)

Key words: COVID-19, coronavirus, lockdown, coronary artery disease, pandemic

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic spread across the globe and affected life in many aspects. By October 2021 over 239 million people had suffered from infection, including only confirmed cases [1]. As such, the healthcare system in many counties remains in jeopardy. The effect of increased mortality, not only from the infection itself but also from other diseases, became apparent. According to the Polish National Primary Statistical Department, there were over 67,000 more deaths in 2020 than in 2019 in Poland, which highly exceeds the number of deaths from the infection itself [2].

Circulatory diseases, particularly heart conditions, remain the main cause of mortality and morbidity in developed countries. The investigation of the impact of the lockdown on cardiological care is of the highest priority because rapid intervention in this area is required to prevent a great number of deaths and hospitalizations. In Poland, as well as in other countries, several analyses have already been performed. However, they include mainly acute coronary syndrome (ACS) cases — their incidence and course during the pandemic [3–6]. As such, some additional analyses, considering mainly stable coronary disease, should be performed because those patients stand as a major proportion of cases referred to interventional cardiology departments. Furthermore, the investigation may provide valuable data and is beneficial for public health strategy in upcoming years

The aim of the report is to investigate the patient profile, the number of hospitalizations, and the outcomes in patients with stable coronary disease referred to invasive cardiology department for diagnosis and treatment after the first wave of the SARS-CoV-2 2019 pandemic.

Methods

Multi-institutional registry

The report contains data from the invasive cardiology network in Poland, which includes 10 departments. The data regarding patient hospitalization are processed with the medical management software. Because scheduled hospitalizations were limited during the lockdown, the data from June to October 2019 and June to October 2020 were imported to investigate the potential effect of the first wave of the pandemic on patients with stable coronary artery disease (CAD).

Selected parameters

The following data from the database were included in the analysis: the patient's unique hospitalization number, hospitalization department, data of admission and discharge, discharge characteristics, primary diagnosis (initial and after diagnostic process), other diseases, performed procedures, anamnesis, treatment, patient condition, hospitalization course, and complications (death, myocardial infarction, stroke, surgical intervention, cardiac surgery procedure). The composite endpoint comprised major adverse cardiac and cerebrovascular events (MACCE) including death, myocardial infarction, and stroke.

Local Research Ethics Board consent

No Research Ethics Board consent was required for the study. The report is retrospective, the data is a readily available dataset, and no intervention to patients was performed. The National Code on Clinical Trials has reported that ethical approval is not necessary for real retrospective studies (National Code on Clinical Researches, 2011).

Statistical analysis

The continuous data are presented as mean ± standard deviation or median (interquartile range). Categorical data are shown as numbers (percentage). The Shapiro-Wilk test was used to determine normal distribution in continuous data. In cases where normal distribution was confirmed, Student's t-test was used for analysis. In cases where normal distribution was rejected, the Mann-Whitney U test was used for continuous data investigation. The χ^2 test was used for categorical data inquiry. Cox proportional hazards regression model was used for multivariable analysis. Goodness of fit of each multivariate analysis model was verified using the χ^2 test. The data were analyzed using MedCalc v.18.5 software (MedCalc Software, Ostend, Belgium). The p-value of ≤ 0.05 was considered as statistically significant.

Data presentation

The data were divided into categories and presented as number of admissions, information regarding patient condition on admission, demographical data (age and gender), data regarding comorbidities, symptom characteristics, hospitalization course, and hospitalization outcome, including mortality analysis.

Table 1. Baseline patient characteristics.

	2019 (June–October)	2020 (June–October)	P
Hospitalizations due to stable CAD/ /overall CAD hospitalizations	2498/5299 (47.2%)	1903/4523 (42.1%)	**< 0.0001**
Age	69.0 (62.0–75.0)	68.0 (62.0–74.0)	**0.019**
Male gender	1541(61.7%)	1221 (64.2%)	0.093
Arterial hypertension	1885 (75.5%)	1684 (88.5%)	**< 0.0001**
Hyperlipidemia	1384 (55.4%)	1293 (67.9%)	**< 0.0001**
Diabetes	786 (31.5%)	679 (35.7%)	**0.003**
Obesity	783 (31.3%)	682 (35.8%)	**0.002**
Active smoking	422 (16.9%)	359 (18.9%)	0.089
History of stroke	141 (5.6%)	80 (4.2%)	**0.033**
Peripheral artery disease	224 (8.9%)	146 (7.7%)	0.125
CCS III + CCS class IV for angina	662 (26.5%)	578 (30.4%)	**0.005**
CCS IV class for angina	79 (3.2%)	56 (2.9%)	0.675
Symptoms for HF (NYHA II–IV class)	1237 (49.5%)	906 (47.6%)	0.209

Data are presented as number (percentage) and median (interquartile range); CAD — coronary artery disease; CCS — Canadian Cardiovascular Society; HF — heart failure; NYHA — New York Heart Association class for heart failure

Table 2. Treatment during hospitalization.

Treatment during hospitalization	2019 (June–October) N = 2498	2020 (June–October) N = 1903	P
Non-invasive treatment	149 (7.8%)	86 (4.5%)	**0.0346**
Coronary angiography	1549 (62.0%)	1110 (58.3%)	**0.0134**
Percutaneous revascularization	647 (25.9%)	667 (35.0%)	**< 0.0001**
Patients referred for CABG	108 (4.9%)	40 (3.7%)	**0.0001**

Data are presented as number (percentage); CABG — coronary artery bypass grafting

Results

The number of patients hospitalized due to stable CAD was significantly lower in June–October 2020 (following the first lockdown) than in the same period in 2019.

Although the patients presented with the same age and gender, the comorbidity characteristics varied. Significantly higher numbers of patients with arterial hypertension, obesity, diabetes, and hyperlipidemia were noted after the first wave of coronavirus pandemic (Table 1).

Regarding symptom characteristics, a significantly higher number of patients presented with Canadian Cardiovascular Society (CCS) III and CCS class IV of angina after the lockdown than in June–October 2019. However, the number of patients admitted with the most severe angina (CCS IV) was similar (Table 1).

The treatment was very different in June–October 2020 than in June–October 2019. Fewer patients were treated non-invasively, while a greater number of patients qualified for invasive treatment. Notably, a significantly fewer cases were referred for coronary artery bypass grafting procedure (Table 2).

When considering hospitalization outcome, there were no significant differences in mortality, infarction rate, stroke rate, and composite endpoint rate (Table 3).

Cox proportional-hazards regression model revealed no impact of the hospitalization period on mortality (Figs. 1, 2). New York Heart Association (NYHA) class IV for heart failure was the risk factor for mortality (Fig. 1).

Regarding the composite endpoint, NYHA class IV for heart failure was associated with higher risk of MACCE (Figs. 3, 4).

Table 3. Hospitalization outcome.

Hospitalization outcome	2019 (June–October) N = 2498	2020 (June–October) N = 1903	Odds ratio	P
Death	5 (0.2%)	1 (0.05%)	0.2	0.19
Myocardial infarction	2 (0.08%)	2 (0.1%)	1.3	0.78
Stroke	2 (0.08%)	3 (0.2%)	1.9	0.45
MACCE	9 (0.4%)	6 (0.3%)	0.9	0.79

Data are presented as numbers (percentage); MACCE — major adverse cardiac and cerebrovascular events (death, myocardial infarction, stroke)

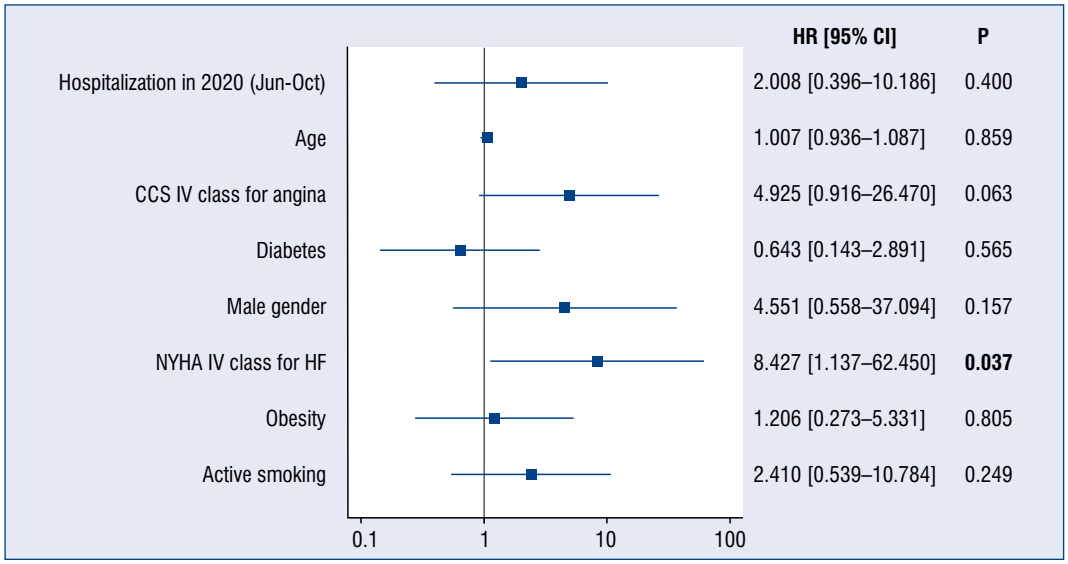

Figure 1. Forest plot of risk ratios for mortality (Cox proportional hazards regression model). Markers represent point estimates of risk ratios. Horizontal bars indicate 95% confidence intervals (CI); CCS — Canadian Cardiovascular Society score for angina; HF — heart failure; HR — hazard ratio; MACCE — major adverse cardiac and cerebrovascular events (death, myocardial infarction, stroke); NYHA — New York Heart Association for heart failure.

Discussion

The effect of the pandemic on healthcare has been touched on in many reports. It is clear that many patients did not receive proper healthcare throughout the pandemic, mainly because of healthcare system paralysis, but also due to fear of contact with potentially infected patients in both public and private hospitals. In fact, the fear of coronavirus disease 2019 (COVID-19) is a reason for patients not attending medical care when experiencing any kind of symptoms, representing multiple diseases [7–11]. It must be underlined that patients with pre-existing cardiovascular disease are especially prone to coronavirus infection and may undergo adverse outcomes due to the infection [12–15].

Not surprisingly, people admitted to hospital following the lockdown had more comorbidities, often untreated or treated inadequately. This is a worldwide phenomenon [16–21]. Furthermore, the pandemic and the lockdown heavily affected people's daily routine. It is important to mention that physical activity has an effect in both the prevention and treatment of CAD [22, 23]. Avoidance of physical exercise, an unhealthy diet, and mental and social problems largely impacted populational health. As a result, a higher number of patients with non-communicable diseases may be expected. Consequently, the long-term outcome in most of those cases is uncertain.

Because patients presented with very different baseline characteristics, the treatment was also different in both time intervals. It seems that despite a decrease in the number of patients hospitalized for stable CAD, the number of percutaneous interventions was even higher in the period following the first wave of the pandemic. This leads to the opposite conclusion to the one reported by other

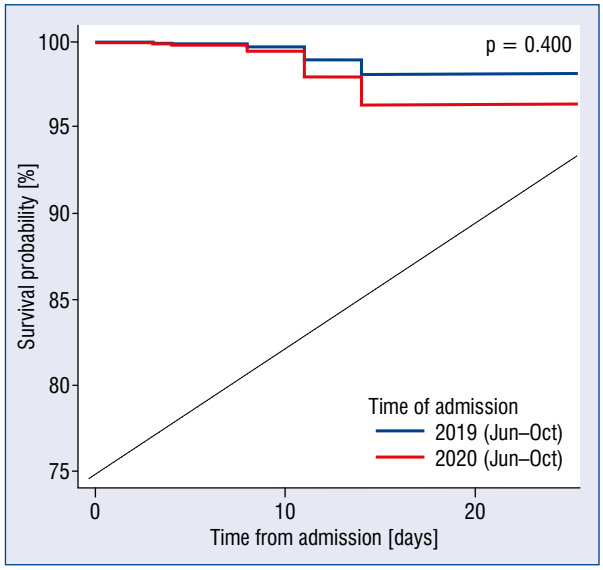

Figure 2. Cox proportional hazards cumulative survival curves with respect to different hospitalization timeframes adjusted for age, Canadian Cardiovascular Society Class IV class for angina, diabetes, male gender, New York Heart Association IV class for heart failure, obesity, and active smoking.

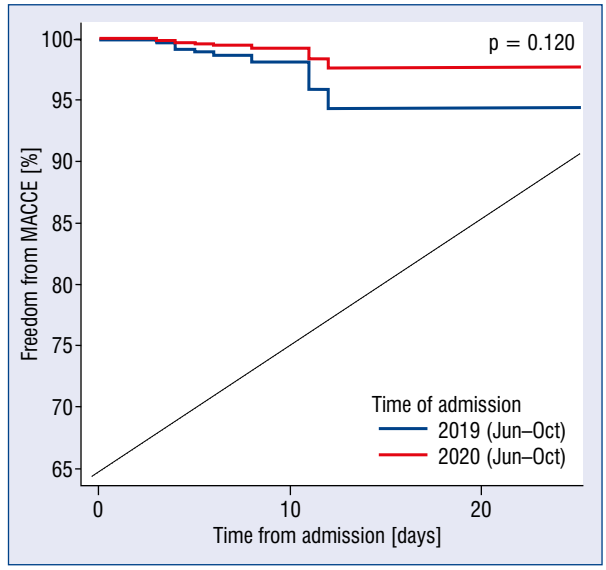

Figure 4. Cox proportional hazards freedom from major adverse cardiac and cerebrovascular events (MACCE) (death, myocardial infarction, stroke) curves with respect to different hospitalization timeframes adjusted for age, Canadian Cardiovascular Society Class IV class for angina, diabetes, male gender, New York Heart Association (NYHA) IV class for heart failure, obesity, and active smoking.

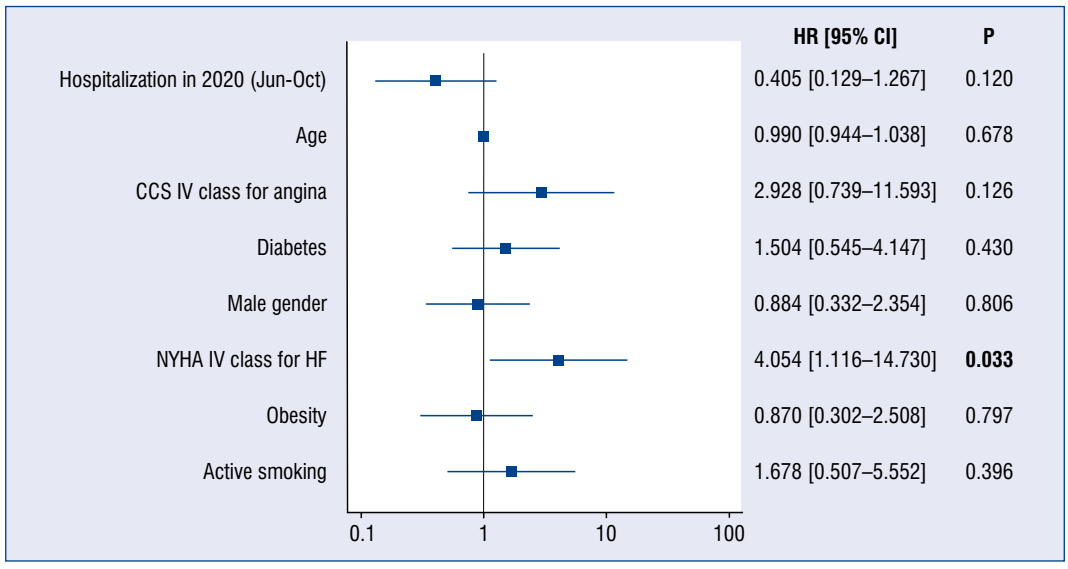

Figure 3. Forest plot of risk ratios for major adverse cardiac and cerebrovascular events (death, myocardial infarction, stroke) (Cox proportional hazards regression model). Markers represent point estimates of risk ratios. Horizontal bars indicate 95% confidence intervals (CI); CCS — Canadian Cardiovascular Society score for angina; HF — heart failure; HR — hazard ratio; NYHA — New York Heart Association for heart failure.

authors [24–26]. However, there are significant differences regarding study methodology. First, our investigation refers to patients admitted following the first wave, which describes the impact of clinical care limitation. In this situation, following lockdown withdrawal, a great number of hospi-

talizations should be expected due to the greater number of patients with severe symptoms and long lines of patients awaiting diagnostic and therapeutic processes. This effect is probably strongly limited by fear of hospitalization and potential infection, particularly in the elderly. Importantly, the analyzed timeframe refers to a time during which vaccination was not available.

The changes of treatment in time intervals need to be discussed in light of recently published results of the 'Ischemia' trial, which did not find evidence that an initial invasive strategy in stable CAD, as compared with an initial conservative strategy, reduced the risk of ischemic cardiovascular events or death from any cause over a median of 3.2 years [27]. However, it must be noted that both the 'Ischemia' trial and the guidelines for myocardial revascularization [28] underline the importance of adequate medical treatment to prevent symptoms and improve survival. Importantly, the trial was conducted during normal healthcare accessibility, prior to the pandemic. During the pandemic, each case needed to be assessed individually, taking into consideration limited accessibility to both basic healthcare (general practice) and cardiovascular care. Furthermore, the patients admitted following lockdown had more pronounced symptoms than patients admitted in the corresponding timeframe in 2019 (Table 1). The perspective of future waves of the pandemic and upcoming lockdowns also played a role in the decision-making process.

It should be emphasized that some authors already point out the consequences of postponing elective percutaneous revascularization procedures in stable patients [26].

The decrease in the number of patients referred for surgical treatment may also be associated with limited healthcare accessibility. Firstly, avoidance of multiple hospitalizations was strongly required during the pandemic, which might have affected the heart-team decisions in borderline cases to operate in favor of percutaneous treatment. Secondly, the decisions might have been affected by the perspective of an upcoming second wave of the pandemic, taking into consideration the next lockdown. This could interrupt both diagnostic and therapeutic processes and pose an even greater threat for patients. In this scenario, multiple hospitalizations, including staged intervention, complicated diagnostic processes, coronary artery bypass grafting, and longer rehabilitation following surgery, are not advantageous. Furthermore, the potential of coronavirus infection increases the perioperative risk significantly. Global reports present similar reductions in elective surgical procedures [29].

Regarding the hospitalization outcome, there were no significant changes in the analyzed timeframes. This may seem surprising, but it must be remembered that the report contains stable CAD cases. As such, the true impact of the pandemic, including the adverse outcome of the development and lack of control of non-communicable diseases, may yet become visible in a long-term observation. Furthermore, it may be speculated that the most severe cases with initially stable coronary disease underwent an ACS, which excluded them from this study. There are reports that the incidence of ACS cases is much higher (which includes our institutional experience). Those cases develop mostly on the basis of pre-existing stable CAD, which was treated in earlier stages prior to the pandemic. From this perspective, the similar number of deaths in the analyzed timeframes may be related to shifting the most complicated and most severe cases directly to the ACS cohort in 2020.

Similar conclusions can be drawn from the multivariable analysis. There was no direct impact of the hospitalization period on the risk of mortality or MACCE in the stable patient cohort. Importantly, NYHA class IV for heart failure was a risk factor for mortality and MACCE.

Limitations of the study

This report is a retrospective dataset analysis, and most of the limitations are associated with this methodology. What is more, the investigation represents only part of the picture, because due to the delay in diagnosis and treatment, some patients might have suffered from ACS during the first wave of the pandemic or just following the first wave, which excluded them from the report and might have affected the comparison regarding the most severe cases. Furthermore, the true long-term outcome in those patients is yet unknown because they presented with higher incidence of non-communicable diseases, which may have an impact on the incidence of ACS cases in the future as well as on mortality and morbidity.

Conclusions

In conclusion, the SARS-CoV-2 2019 pandemic affected the characteristics and hospitalization course of stable angina patients hospitalized following the first wave. The hospitalization outcome was not significantly affected in this group of cases. However, the high incidence of non-communicable

diseases in hospitalized patients is disturbing because an increase in acute cerebrovascular events is to be expected in forthcoming years. Consequently, a great effort should be made to provide cardiovascular care and both primary and secondary prophylaxis to avoid a dramatic rise in the incidence of acute cardiovascular events.

Conflict of interest: None declared

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Comparison of reorganized versus unaltered cardiology departments during the COVID-19 era: A subanalysis of the COV-HF-SIRIO 6 study

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Abstract

Background: *Since the beginning of the coronavirus disease 2019 (COVID-19) pandemic, numerous cardiology departments were reorganized to provide care for COVID-19 patients. We aimed to compare the impact of the COVID-19 pandemic on hospital admissions and in-hospital mortality in reorganized vs. unaltered cardiology departments.*

Methods: *The present research is a subanalysis of a multicenter retrospective COV-HF-SIRIO 6 study that includes all patients (n = 101,433) hospitalized in 24 cardiology departments in Poland between January 1, 2019 and December 31, 2020, with a focus on patients with acute heart failure (AHF).*

Results: *Reduction of all-cause hospitalizations was 50.6% vs. 21.3% for reorganized vs. unaltered cardiology departments in 2020 vs. 2019, respectively ($p < 0.0001$). Considering AHF alone respective reductions by 46.5% and 15.2% were registered ($p < 0.0001$). A higher percentage of patients was brought in by ambulance to reorganized vs. unaltered cardiology departments (51.7% vs. 34.6%; $p < 0.0001$) alongside with a lower rate of self-referrals (45.7% vs. 58.4%; $p < 0.0001$). The rate of all-cause in-hospital mortality in AHF patients was higher in reorganized than unaltered cardiology departments (10.9% vs. 6.4%; $p < 0.0001$). After the exclusion of patients with concomitant COVID-19, the mortality rates did not differ significantly (6.9% vs. 6.4%; $p = 0.55$).*

Conclusions: *A greater reduction in hospital admissions in 2020 vs. 2019, higher rates of patients brought by ambulance together with lower rates of self-referrals and higher all-cause in-hospital mortality for AHF due to COVID-19 related deaths were observed in cardiology departments reorganized to provide care for COVID-19 patients vs. unaltered ones.* (Cardiol J 2023; 30, 3: 344–352)

Key words: acute heart failure, COVID-19, hospital admission, in-hospital mortality

Introduction

On December 31, 2019 the World Health Organization (WHO) was informed of 44 pneumonia cases of unknown cause in the city of Wuhan, China. The first case of the coronavirus disease 2019 (COVID-19) in the United States of America was reported on January 20, 2020. Four days later the first patient in Europe was diagnosed with COVID-19. On March 11, 2020 due to the spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the WHO declared COVID-19 a pandemic.

Soon after healthcare systems across the globe became paralyzed. The usual medical care

pathways were replaced with new temporary solutions to provide treatment for patients infected with SARS-CoV-2. In the majority of Polish hospitals, additional beds dedicated to COVID-19 patients were made available either within pre-existing departments or emerging as new or transformed separate wards. Some hospitals were entirely transformed into multidisciplinary COVID-19 hospitals or new temporary hospitals were created. In Madrid, Spain, after reaching 100% hospital bed capacity, additional beds were provided in physical therapy gyms, corridors, libraries and tents located outside of the main hospital buildings [1]. In the Rizoli Institute, Italy, separate care pathways were created for COVID-19 patients who were hospitalized in newly established wards [2]. The enormous surge of COVID-19 patients at the very beginning of the pandemic in Italy provoked a 72% increase in the number of intensive care unit beds [3]. In Lombardy, Italy, entire hospitals were transformed to provide care for COVID-19 patients only. Many hospital wards, like stroke units, were closed or converted to treat COVID-19 patients, leaving as few as 11 out of 36 stroke units in the region of Lombardy to provide emergency care for stroke patients. According to the French "plan blanc", the number of intensive care unit beds was doubled with reallocation of all resources to fight the pandemic [3]. All routine consultations were cancelled or postponed. During the first few weeks, whole wards were converted to treat COVID-19 patients, then separate areas were created for COVID-19 patients. In Denmark, organizational changes included: upscaling intensive care unit capacity, deferral of all non-acute diagnostics and treatment, as well as intensive care medical training for healthcare professionals of other specialties [4]. All these revolutionary, large-scale reorganizations of healthcare systems have brought to light shortcomings in the treatment of other medical conditions. Reports from many countries showed a decrease in hospital admissions due to various cardiovascular causes, including life-threatening emergencies [5–11].

In the previously published impact of COVID-19 pandemic on acute Heart Failure admissions and mortality: multicenter (COV-HF-SIRIO 6) study, it was demonstrated that a reduction in hospital admissions for acute heart failure (AHF) during the COVID-19 pandemic compared with the pre-COVID era and a concurrent increase in in-hospital AHF mortality [12].

The aim of the subanalysis of the COV-HF--SIRIO 6 study was to identify differences in hospital admissions and mortality among AHF patients hospitalized in cardiology departments reorganized to provide care for COVID-19 patients vs. cardiology departments that remained unaltered.

Methods

Study design

The present retrospective study analyzed hospital records of consecutive patients hospitalized in 24 cardiology departments in Poland from January 1, 2019 to December 31, 2020. Out of all cardiology departments included in the study, those reorganized to provide care for COVID-19 patients were compared with cardiology departments that remained unaltered. Cardiology departments were considered reorganized if an official warrant from the local authorities was issued to allocate separate areas for hospitalization of COVID-19 patients. Reorganized cardiology departments provided additional beds to hospitalize COVID-19 patients in rooms separated from other patients. In unaltered cardiology departments patients with confirmed or suspected SARS-CoV-2 infection were not admitted, as no additional beds to hospitalize COVID-19 patients were created inside of these wards. The focus herein, was on hospital admissions and mortality in patients with AHF (International Statistical Classification of Diseases and Related Health Problems codes for heart failure I50.x). In order to diagnose AHF, criteria determined by the 2016 European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic heart failure were used [13]. The COV-HF-SIRIO 6 study was conducted in accordance with the Declaration of Helsinki and was approved by the Local Ethics Committee (study approval reference number KB 353/2021).

Statistical analysis

Statistical analysis was performed using the Statistica version 13.0 (TIBCO Software Inc, California, USA). Continuous variables were expressed as means with standard deviations. Due to the non-normal distribution of the investigated data as demonstrated by the Shapiro-Wilk test, non-parametric tests were chosen. Comparisons of continuous variables between the two groups were performed with the Mann-Whitney unpaired rank sum test. Comparisons between year 2019 and 2020 were performed with the Wilcoxon signed test. Categorical variables are presented as numbers and percentages and were compared using the χ^2 test. Results were considered significant at $p < 0.05$.

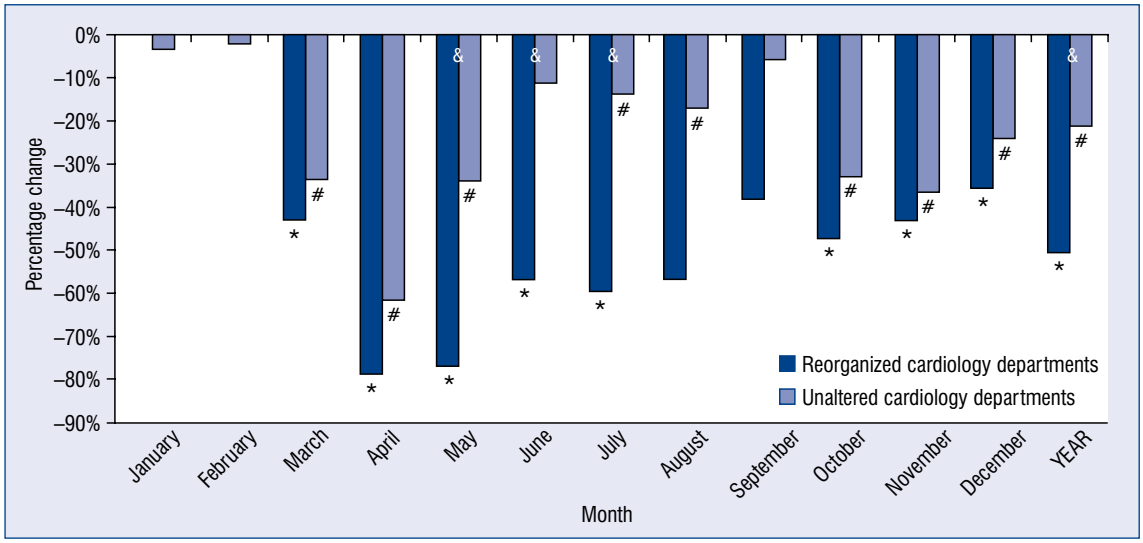

Figure 1. Reduction of all-cause hospitalizations during the COVID-19 pandemic in 2020 vs. 2019; *p < 0.05 for the comparison 2020 vs. 2019 in reorganized cardiology departments; #p < 0.05 for the comparison 2020 vs. 2019 in unaltered cardiology departments; &p < 0.05 for the comparison reorganized vs. unaltered cardiology departments in 2020.

Results

General findings

During the study period, a total of 101,433 patients were hospitalized in 24 cardiology departments in Poland. Initially, after the outbreak of the COVID-19 pandemic in March 2020, 5 out of the 24 cardiology departments included in the analysis were reorganized to provide care for COVID-19 patients, the rest remained unaltered. At the very peak of the pandemic in November 2020, the number of reorganized departments grew to 14 out of the 24 cardiology departments to provide care for COVID-19 patients (**Suppl. Table 1**). Most departments designated beds for COVID-19 patients inside of the existing wards in areas separated from other patients. The number of additional beds for COVID-19 patients closely followed the peaks of the pandemic, beginning with 66 beds in March 2020, reaching up to 264 beds in November 2020 (**Suppl. Table 1**). Four of the investigated cardiology departments were completely transformed to provide care only for COVID-19 patients in November and December 2020 (**Suppl. Table 1**).

Number of hospitalizations

The total number of hospitalizations in reorganized cardiology departments was reduced by 50.6% (from 14,674 hospitalizations in 2019 to 7,254 hospitalizations in 2020; p < 0.0001). In unaltered cardiology departments the total number of hospitalizations was reduced by far less — 21.3% (from 44,501 hospitalizations in 2019 to 35,004 hospitalizations in 2020; p < 0.0001) (Fig. 1). 239 patients were identified with concomitant AHF and COVID-19 — 90.0% of them hospitalized in reorganized cardiology departments (**Suppl. Table 1**). The number of hospital admissions for AHF decreased by 46.5% (from 2,585 in 2019 to 1,383 in 2020; p < 0.0001) in reorganized cardiology departments, and by only 15.2% (from 7,268 in 2019 to 6,163 in 2020; p < 0.0001) in unaltered cardiology departments (Fig. 2).

Mode of hospital referral for AHF

The analysis of the structure of hospital admissions for AHF revealed a significantly higher percentage of patients brought in by ambulance to reorganized vs. unaltered cardiology departments since the beginning of the COVID-19 pandemic (Fig. 3). The difference was most prominent in March 2020 accounting for a 61.7% vs. 32.8% proportion of AHF patients brought in by ambulance to reorganized vs. unaltered cardiology departments, respectively. Simultaneously, the percentage of self-referrals was lower in reorganized vs. unaltered cardiology departments (45.7% vs. 58.4%; p < 0.0001).

Length of hospital stay

The length of hospital stay for AHF was longer in reorganized cardiology departments (9.4 days in 2020 vs. 7.9 days in 2019; p < 0.01), but constant

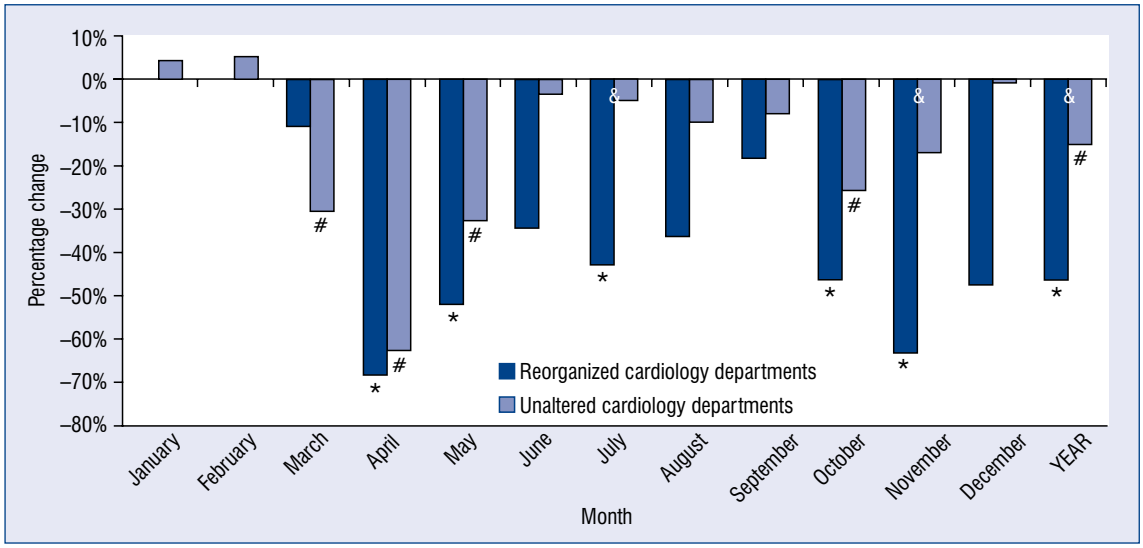

Figure 2. Reduction of acute heart failure hospitalizations during the COVID-19 pandemic in 2020 vs. 2019; *p < 0.05 for the comparison 2020 vs. 2019 in reorganized cardiology departments; #p < 0.05 for the comparison 2020 vs. 2019 in unaltered cardiology departments; &p < 0.05 for the comparison reorganized vs. unaltered cardiology departments in 2020.

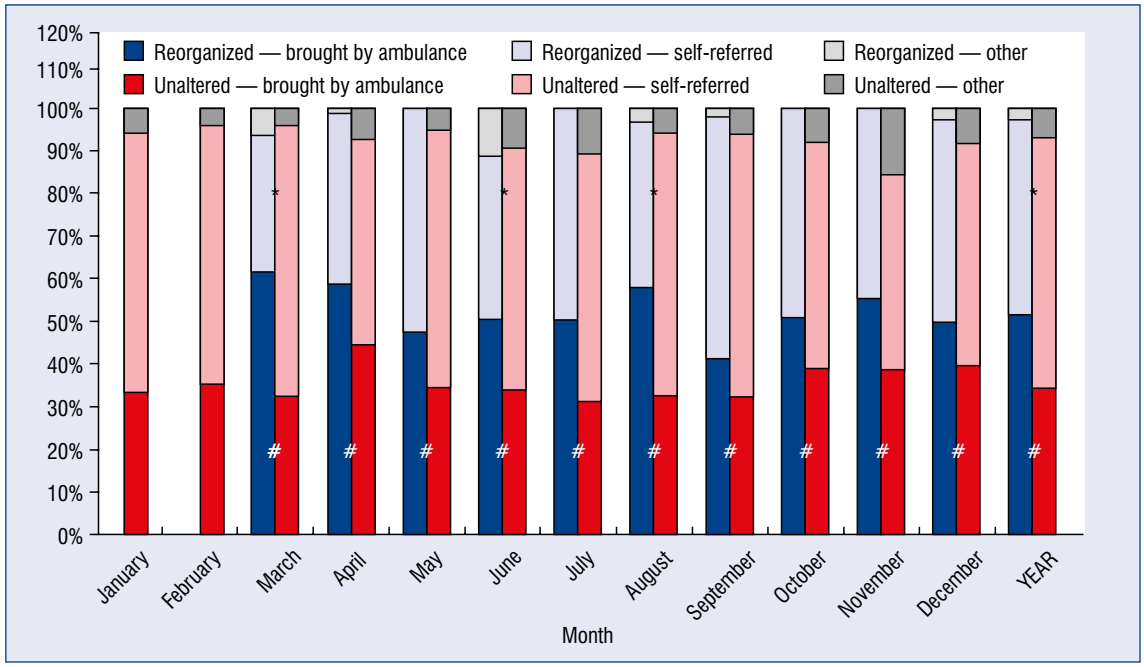

Figure 3. Modes of hospital admissions in reorganized vs. unaltered cardiology departments during the COVID-19 pandemic; *p < 0.05 for the comparison of self-referred patients in reorganized vs. unaltered cardiology departments; #p < 0.05 for the comparison of patients brought in by ambulance in reorganized vs. unaltered cardiology departments.

in unaltered cardiology departments (7.8 days in 2020 vs. 7.6 days in 2019; p = 0.84; p = 0.47 for the comparison of reorganized vs. unaltered cardiology departments in 2020; **Suppl. Table 2**).

In-hospital mortality

During the COVID-19 pandemic in 2020, the rate of all-cause in-hospital mortality in AHF patients was higher in reorganized vs. unaltered car-

diology departments (10.9% vs. 6.4%; $p < 0.0001$; Table 1). The difference was most spectacular in November 2020 with a mortality rate reaching up to 26.9% in reorganized vs. 9.1% in unaltered cardiology departments ($p < 0.0001$). However, when AHF patients with concomitant COVID-19 were excluded, the differences in all-cause in-hospital mortality rates vanished (6.9% vs. 6.4%; $p = 0.55$), except at the very peak of the pandemic in November 2020, when the mortality rate for AHF excluding COVID-19 patients was 19.4% in reorganized vs. 8.6% in unaltered cardiology departments ($p = 0.007$; Table 1).

Discussion

The COVID-19 pandemic overwhelmed healthcare systems worldwide. Organizational challenges of reallocation of available resources together with postponement of all non-urgent medical care have negatively affected treatment of other medical conditions. The present subanalysis was performed with over 100,000 patients included in the COV-HF-SIRIO 6 study to assess the impact of reorganization of cardiology departments in order to provide care for COVID-19 patients on hospital admission and mortality rates in patients with AHF. In Polish reorganized vs. unaltered cardiology departments, the following was found: i) greater reduction in hospital admissions in 2020 vs. 2019; ii) higher percentage of patients brought by ambulance and lower percentage of self-admissions; and iii) higher all-cause in-hospital mortality for AHF due to COVID-19 related deaths.

At the very beginning of the COVID-19 pandemic, reports from many countries showed reduced rates of hospital admissions for AHF [14–20]. Based on linear extrapolation, Moayedi et al. [21] predicted an incoming surge of AHF patients following the first wave of the COVID-19 pandemic in the province of Ontario, Canada. In the COV-HF-SIRIO 6 subanalysis even greater reductions in all-cause and AHF hospital admissions were found in reorganized vs. unaltered cardiology departments in 2020 vs. 2019. Without any increase in the AHF admissions in 2020 vs. 2019.

Regarding modes of hospital admissions, a significantly higher percentage of patients brought in by ambulance and lower percentage of self-referrals to reorganized vs. unaltered cardiology departments was found. This contradicts other reports from the very beginning of the COVID-19 pandemic showing reductions in the number of emergency medical team interventions [22, 23]. The reluctance to seek medical care is one of the potential causes of a 35% increase in the number of cardiovascular community deaths in comparison with the pre-COVID-19 era in a large, retrospective analysis of 587,225 cardiovascular deaths in England and Wales [24]. Interestingly, the authors reported no excess of in-hospital cardiovascular deaths during the COVID-19 pandemic. A similar analysis including 397,042 cardiovascular deaths in the United States revealed an increased number of deaths due to ischemic heart disease (ratio of the relative change in deaths per 100,000 in 2020 vs. 2019: 1.11; 95% confidence interval [CI] 1.04–1.18) or hypertensive disease (1.17; 95% CI 1.09–1.26), but not for heart failure [25].

Multiple studies have documented increases in-hospital mortality for concomitant AHF and COVID-19 [26–30]. However, only scarce data on in-hospital mortality for AHF without concomitant SARS-CoV-2 infection during the COVID-19 pandemic are available. In a single center report from the United Kingdom, a 27% reduction of hospital admissions due to AHF was reported during the first peak of the COVID-19 pandemic as compared with the first months of 2020 [31]. The length of hospital stay was similar in both groups, but the 30-day mortality for AHF was significantly higher during the COVID-19 pandemic vs. before accounting 21% vs. 11%, respectively (risk ratio: 1.9; 95% CI 1.09–3.3). In a previous subanalysis of the COV-HF-SIRIO-6 multicenter study, longer hospitalizations were found (9.6 vs. 6.6 days; $p < 0.001$) and higher in-hospital mortality (10.7% vs. 3.2%; $p < 0.001$) was found for AHF during the COVID-19 pandemic in larger vs. smaller cardiology departments [32]. As reported in a retrospective study including 13,484 patients hospitalized in a German network of 67 hospitals, in-hospital mortality for AHF was higher during the COVID-19 pandemic vs. time-related period in 2019 (7.3% vs. 6.0%; $p = 0.02$) [33]. According to a retrospective analysis from two referral centers in London, the number of hospital admissions due to AHF was reduced by 29.4% from January to June 2019 vs. a time-related period in 2020 (725 vs. 519) [34]. Due to organizational issues, patients with AHF were more frequently treated in general wards than in cardiology departments ($p = 0.04$) during the COVID-19 pandemic. No significant changes regarding the length of hospital stay were found in 2020 vs. 2019 (7 vs. 6 days; $p = 0.22$). The reported post-discharge mortality was higher in 2020 vs. 2019 ($p < 0.01$). In the subanalysis of the COV-HF-SIRIO 6 study, the in-hospital all-cause mortality was higher in reorganized vs. unaltered cardiology

Table 1. All-cause in-hospital mortality in reorganized vs. unaltered cardiology departments in 2020.

Month	Reorganized cardiology departments				Unaltered cardiology departments				P (including COVID-19 patients)	P (excluding COVID-19 patients)
	Mortality rate for AHF including concomitant COVID-19		Mortality rate for AHF excluding concomitant COVID-19		Mortality rate for AHF including concomitant COVID-19		Mortality rate for AHF excluding concomitant COVID-19			
	N	%	N	%	N	%	N	%		
1	–	–	–	–	–	–	45	5.7%	–	–
2	–	–	–	–	–	–	47	6.6%	–	–
3	2	1.6%	2	1.6%	38	8.8%	38	8.9%	0.0052	0.0067
4	9	12.0%	4	6.4%	23	12.0%	22	11.8%	0.9962	0.2233
5	8	8.6%	5	6.0%	20	5.6%	20	5.6%	0.2804	0.8915
6	7	6.5%	6	6.0%	28	5.7%	28	5.7%	0.7452	0.9185
7	3	3.4%	3	3.6%	26	4.6%	25	4.5%	0.7947	0.9475
8	3	3.2%	2	2.3%	21	4.2%	21	4.2%	0.8714	0.5561
9	11	6.1%	9	5.1%	24	5.7%	24	5.7%	0.8669	0.7766
10	25	12.8%	7	5.2%	33	9.9%	32	9.9%	0.2909	0.0949
11	50	26.9%	25	19.4%	15	9.1%	14	8.6%	< 0.0001	0.0071
12	33	14.0%	17	9.1%	10	5.1%	10	5.2%	0.0023	0.1344
Year	151	10.9%	80	6.9%	330	6.4%	326	6.4%	< 0.0001	0.5452

AHF — acute heart failure; COVID-19 — coronavirus disease 2019

departments (10.9% vs. 6.4%; p < 0.0001), but did not differ after exclusion of COVID-19-related deaths (6.9% vs. 6.4%; p = 0.55).

Limitations of the study

Several limitations of this study need to be acknowledged. Firstly, the COV-HF-SIRIO 6 study included a substantial part, but not all, Polish cardiology departments. Secondly, the data were collected retrospectively from hospital electronic databases and the information on the detailed characteristics of the study participants and clinical course of AHF is missing. Finally, readmissions were not analyzed, nor any follow-up of the study participants beyond hospital discharge.

Conclusions

The outbreak of the COVID-19 pandemic became a major challenge for healthcare systems worldwide, including cardiology departments. Our study indicates that the COVID-19 pandemic has led to: greater reduction in hospital admissions in 2020 vs. 2019, higher percentage of patients brought by ambulance together with lower percentage of self-admissions and higher all-cause in-hospital mortality for AHF due to COVID-19 related deaths in Polish cardiology departments recognized to provide care for COVID-19 patients vs. unaltered ones.

Conflict of interest: None declared

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Predictors of vessel quantitative flow ratio loss in patients with severely calcified lesions after rotational atherectomy

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Abstract

Background: *Previous studies have established that moderately to severely calcified lesions (MSCL) are associated with high rates of major adverse cardiovascular events, even when drug-eluting stents are implanted after rotational atherectomy (RA). Yet, the changes in coronary function indexes during follow-ups have never been investigated. The quantitative flow ratio (QFR), a novel coronary function index, has been increasingly adopted in daily practice in recent years.*

Methods: *A total of 111 MSCL patients were retrospectively enrolled in this study. The vessel QFR (QFRv) loss was defined as post-percutaneous coronary intervention QFRv minus follow-up QFRv. The study subjects were divided into high QFRv loss ($n = 51$) and low QFRv loss ($n = 60$) groups according to the binary method. The obtained predictors of QFRv loss were then analyzed.*

Results: *The results showed that the final burr-to-vessel ratio (B to V ratio) in the high QFRv loss group decreased significantly compared to the low QFRv loss group ($p < 0.01$). The univariate and multivariate regression analyses indicated that the final B to V ratio was an excellent predictor of QFRv loss. The cut-off value of the final B to V ratio for QFRv loss prediction was 0.50 (sensitivity: 50.98%, specificity: 68.33%, and area under the curve: 0.627 [95% confidence interval: 0.530–0.717], $p < 0.05$). Additionally, the target vessel failure incidence in the high QFRv loss group was higher than in the low QFRv loss group ($p < 0.01$).*

Conclusions: *An increased burr-to-vessel ratio can prevent QFRv loss in patients with MSCLs after RA, an effect that might be closely associated with a low target vessel failure incidence.* (Cardiol J 2023; 30, 3: 353–360)

Key words: percutaneous coronary intervention, rotational atherectomy, calcification, quantitative flow ratio

Introduction

Moderately to severely calcified lesions (MSCLs) in the coronary artery are usually a tricky lesion type during percutaneous coronary intervention (PCI). Accumulative data have shown that [1, 2] rotational atherectomy (RA) represents an effective method for MSCLs [3]. The concept of RA has been significantly improved from the original debulking to the current modifications,

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with greater emphasis on the creation of post-RA new surgical accesses for further balloon inflation and stent implantation [4].

The ROTAXUS trial revealed that, compared with stenting without RA, a routine CCL lesion preparation using RA before drug-eluting stent (DES) implantation did not decrease the primary 9-month endpoint of angiographic late lumen loss. However, the results also showed that the two studied groups had similar in-stent binary restenosis, target lesion revascularization, definite stent thrombosis, and major adverse cardiovascular events rates [5]. Subsequently, several follow-up studies were conducted on post-RA patients [5–8]. However, the changes in coronary physiological function indexes during follow-up have never been investigated because fractional flow reserve (FFR) measurement requires an invasive and complex procedure.

Recently, the quantitative flow ratio (QFR), a novel index for coronary physiological function assessment, has been increasingly adopted in daily practice as well as clinical trials [9–11]. QFR assessment is a high-quality angiographic image-based, noninvasive, and simple process that is easy to complete by computer analysis [9]. Additionally, it has been demonstrated that QFR is not significantly different from FFR and possesses an accuracy of 93.3% [9, 10]. Therefore, in this study, we retrospectively analyzed and compared the vessel QFR (QFRv) changes during PCI and follow-up time, aiming to find their predictive values for therapeutic optimization in patients with MSCL after RA.

Methods

Study population

A total of 279 patients with coronary artery calcification lesions, who underwent PCI after RA in Nanjing First Hospital, were retrospectively selected and enrolled in this study from January 2009 to September 2019. The inclusion criteria were as follows: (1) patients who met the indications for RA, (2) those who had coronaey angiography (CAG) images before PCI, immediately after PCI, and during the follow-up time, and (3) those who had high-quality CAG images with which the QFR value could be measured. The exclusion criteria were as follows: (1) incomplete CAG images, (2) no post-RA DES implant, (3) CAG images not adequate to measure the QFR value, (4) those with severe complications during RA (such as perforation and slow flow and no reflow after RA), (5) PCI history > 3 months, and (6) expected survival time < 12 months.

Vessel QFR loss was calculated (post-PCI QFRv — follow-up QFRv) and patients were divided into high QFRv (HQ) loss (QFRv loss > 0.01, n = 51) and low QFRv (LQ) loss (loss ≤ 0.01, n = 60) groups according to the median of QFRv loss (0.01).

Procedural protocol

To all patients 300 mg of clopidogrel (or 180 mg of ticagrelor), and a dose of intracoronary nitroglycerin were administered before the intervention. CAG was performed with 6-French catheters without a side hole using a conventional technique and a transradial approach. CAG images were obtained from multiple projections. A target vessel was defined as a coronary artery with MSCL-related myocardial ischemia. MSCL was graded based on CAG findings [12] or using intravascular ultrasound findings [13].

The technical aspects of the PCI procedure were determined by the practicing interventional doctor. The operation procedures and drugs used for PCI and RA were carried out according to the relevant guidelines and recommendations of the United States and Europe.

QFR computation

Offline QFR analysis was performed by a professional technician according to the previously described procedure and using AngioPlus QFR software (Pulse Medical Imaging Technology, Shanghai, China) (Fig. 1). The QFR was measured by two experienced researchers with a QFR reading license, and the number of measured cases was > 50. Additionally, its computation was performed offline in an independent laboratory according to the measurement procedures established by the FAVOR study [9]. The software automatically identified the morphology of the target vessel. Manual adjustments were made for low-resolution images, and the required QFR values were calculated through frame recording and with the contrast agent. The quantitative coronary angiography (QCA) data of each vessel were provided by software. The following QFR parameters were obtained for each target vessel: the lesion length, the minimal lumen diameter (MLD), the diameter stenosis (DS), the blood flow velocity, and the QFRv in selected vessels.

Study endpoints

The QFR of the entire target vessel was defined as QFRv, which was measured from the proxi-

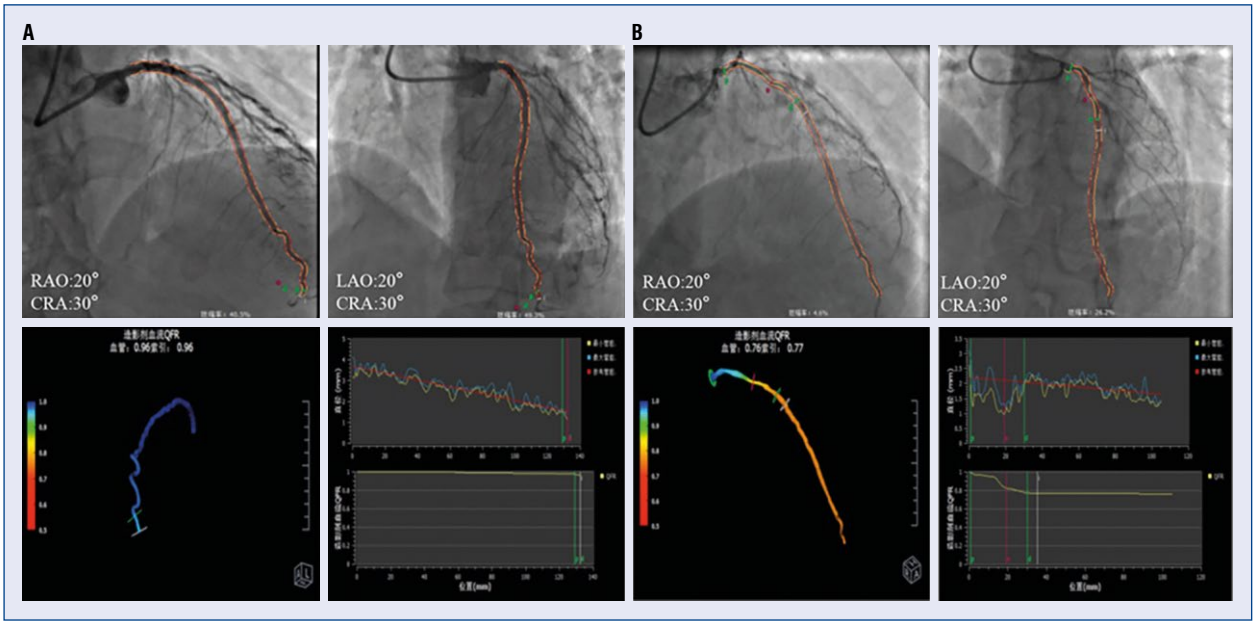

Figure 1. Vessel quantitative flow ratio (QFRv) loss analysis of a case; **A.** The post-percutaneous coronary intervention QFRv was calculated as 0.96; **B.** The follow-up QFRv was calculated as 0.77. QFRv loss in this case was 0.19 (0.96–0.77); CRA — cranial; LAO — left anterior oblique; RAO — right anterior oblique.

mal to the distal end of the vessel. The primary endpoint of this study was the analysis of the QFRv loss, expressed as the difference between the post-PCI QFRv and the follow-up QFRv. The secondary endpoint was the assessment of the target vessel failure (TVF), encompassing parameters such as cardiac death, target vessel myocardial infarction, and clinically driven target vessel revascularization [14]. The two reasons for the second CAG follow-up were as follows: (1) TVF driven and (2) CAG reexamination required by some of the patients. The period from the first CAG to the second was recorded as the follow-up time. Myocardial infarction was defined according to the European Society of Cardiology guideline [15].

Statistical analysis

Categorical variables were expressed in percentages and compared by the χ^2 test. Meanwhile, continuous variables were expressed as means with standard deviation or medians with quartile ranges and compared using the t-test (homogeneity of variance) or the rank sum test (heterogeneity of variance). Univariate and multivariate regression analysis were used to determine the predictive factors of QFRv loss. The receiver operating characteristic curve (ROC) was used to evaluate the variables' predictive ability of QFRv loss. SPSS 24.0 (SPSS Institute Inc.) software was used for all statistical analyses. The statistical significance was set at $p < 0.05$.

Results

Basic clinical data and TVF comparison between the LQ loss and the HQ loss groups for MSCL patients after RA

Finally, 111 patients, including 36 females and 75 males, were enrolled in this study, with an average age of 70.07 ± 7.36 years. The mean follow-up time of all patients was 382.8 ± 93.2 days. The incidence rates of diabetes, male gender, and TVF were significantly lower in the LQ loss group compared to the HQ loss group ($p < 0.01$ or $p < 0.05$). Additionally, the final burr-to-vessel ratio (B to V) of the LQ loss group was higher than that of the HQ loss group ($p < 0.01$) (Table 1). These results indicated that a higher QFRv loss was associated with male gender, diabetes, low final B to V, and high TVF in moderate to severe post-RA cases during the follow-up period.

QCA and QFRv data comparison between the LQ loss and the HQ loss groups in post-RA MSCL patients

The pre-PCI MLD and the MLD during the follow-up period, as well as the QFRv in the LQ loss group, were significantly higher compared to

Table 1. Basic clinical data and target vessel failure (TVF) between low QFRv (LQ) loss and high QFRv (HQ) loss groups in patients with moderately to severely calcified lesion after rotational atherectomy.

Variables	LQ loss group (Q loss ≤ 0.01, n = 60)	HQ loss group (Q loss > 0.01, n = 51)	P
Age [years]	70.18 ± 7.69	69.94 ± 7.02	0.864
Male	35 (58.33%)	40 (78.43%)	0.024
CV risk factors:			
Hyperlipidemia	38 (63.33%)	38 (74.51%)	0.207
Hypertension	42 (70.00%)	38 (74.51%)	0.598
Diabetes	17 (28.33%)	24 (47.06%)	0.042
Current smoker	23 (38.33%)	25 (49.02%)	0.257
Clinical diagnosis:			0.970
SAP	13 (21.67%)	9 (17.65%)	
UAP	38 (63.33%)	33 (64.71%)	
NSTEMI	5 (8.33%)	4 (7.84%)	
STEMI	4 (6.67%)	3 (5.88%)	
Medical treatment:			
Dual anti-platelet therapy	60 (100.00%)	51 (100.00%)	–
Statin therapy:			0.757
Atorvastatin	30 (50.00%)	27 (52.94%)	
Rosuvastatin	29 (48.33%)	21 (41.18%)	
Simvastatin	1 (1.67%)	3 (5.88%)	
ACEI/ARB	34 (56.67%)	26 (50.98%)	0.549
Disease vessel number:			0.824
Single-vessel disease	14 (23.33%)	11 (21.57%)	
Multi-vessel disease	46 (76.67%)	40 (78.43%)	
Lesion location:			1.000
LAD	49 (81.67%)	42 (82.35%)	
RCA	8 (13.33%)	7 (13.73%)	
LCX	3 (5.00%)	2 (3.92%)	
Initial burr size [mm]	1.43 ± 0.17	1.45 ± 0.19	0.539
Final burr size [mm]	1.53 ± 0.15	1.52 ± 0.21	0.782
Pre-PCI distal RVD [mm]	2.8 (2.5,3.4)	3.0 (2.4,3.2)	0.264
Final B to V	0.56 ± 0.05	0.53 ± 0.07	0.007
TVF	3 (5.00%)	21 (41.18%)	< 0.001

ACEI — angiotensin-converting enzyme inhibitors; ARB — angiotensin receptor antagonist; B to V — burr to vessel ratio; CV — cardiovascular; LAD — left anterior descending coronary artery; LCX — left circumflex coronary artery; NSTEMI — non-ST-segment elevation myocardial infarction; PCI — percutaneous coronary intervention; Q — QFRv; QFRv — vessel quantitative flow ratio; RCA — right coronary artery; RVD — reference vessel diameter; SAP — stable angina pectoris; STEMI — ST-segment elevation myocardial infarction; UAP — unstable angina pectoris

those of the HQ loss group ($p < 0.01$ or $p < 0.05$). Meanwhile, the DS of the LQ loss group was significantly lower than that of the HQ loss group during the follow-up period ($p < 0.01$) (Table 2). These results revealed that a lower MLD and a higher DS during the follow-up period could result in high QFRv loss in moderate to severe post-RA cases.

Regression and ROC analyses of QFRv loss predictors in patients with MSCL after RA

As shown by the univariate regression analysis, the final B to V represented an excellent predictor of QFRv loss in our post-RA patients ($p < 0.05$) (Table 3). The results of multivariate regression analysis showed that the final B to V was a better predictor of QFRv loss than the other

Table 2. Quantitative coronary angiography (QCA) vessel quantitative flow ratio (QFRv) and data between low QFRv (LQ) loss and high QFRv (HQ) loss groups in patients with moderately to severely calcified lesions after rotational atherectomy.

Variables	LQ loss group (Q loss ≤ 0.01, n = 60)	HQ loss group (Q loss > 0.01, n = 51)	P
Pre-PCI:			
Lesion length [mm]	58.50 (40.95, 71.90)	64.90 (49.20, 77.80)	0.064
MLD [mm]	1.1 (0.9, 1.2)	0.9 (0.8, 1.0)	0.031
DS [%]	58.4 (52.0, 65.8)	60.2 (53.3, 64.5)	0.962
FV [m/s]	0.14 (0.09, 0.17)	0.15 (0.10, 0.17)	0.320
QFRv	0.56 (0.41, 0.68)	0.57 (0.41, 0.68)	0.711
Post-PCI:			
Total stent length [mm]	60.00 (46.00, 76.50)	66.00 (51.00, 79.00)	0.252
Stent number	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	0.149
MLD [mm]	2.1 (1.8, 2.4)	2.1 (1.7, 2.4)	0.279
DS [%]	23.6 (18.5, 29.9)	25.3 (21.9, 32.8)	0.140
FV [m/s]	0.20 (0.14, 0.25)	0.21 (0.16, 0.27)	0.454
QFRv	0.93 (0.89, 0.96)	0.92 (0.90, 0.98)	0.260
Follow-up:			
MLD [mm]	2.1 (1.7, 2.2)	1.6 (1.1, 2.3)	0.002
DS [%]	26.90 (22.03, 32.03)	33.20 (24.50, 57.50)	< 0.001
FV [m/s]	0.14 (0.12, 0.19)	0.15 (0.11, 0.20)	0.932
QFRv	0.95 (0.92, 0.98)	0.83 (0.72, 0.93)	< 0.001

DS — diameter stenosis; FV — flow velocity; MLD — minimal luminal diameter; PCI — percutaneous coronary intervention

Table 3. Predictors of vessel quantitative flow ratio (QFRv) loss analyzed by univariate and multivariate regression in patients with moderately to severely calcified lesions after rotational atherectomy.

Variables	Univariate regression OR (95% CI)	P	Multivariate regression OR (95% CI)	P
Age [years]	1.004 (0.943–1.070)	0.890		
Male [%]	0.682 (0.244–1.911)	0.682		
Diabetes [%]	0.707 (0.278–1.798)	0.467		
Multi-vessel disease	0.672 (0.205–2.196)	0.510		
Total stent length [mm]	1.018 (0.996–1.039)	0.104		
Lesion length [mm]	1.011 (0.991–1.031)	0.533		
Pre-PCI MLD [mm]	0.181 (0.029–1.119)	0.066		
Pre-PCI DS [%]	1.020 (0.975–1.066)	0.623		
Pre-PCI QFRv	0.193 (0.016–2.331)	0.195		
Final B to V	0.852 (0.779–0.933)	0.001	0.858 (0.781–0.943)	0.001
Post-PCI MLD [mm]	0.412 (0.140–1.213)	0.107		
Post-PCI DS [%]	1.067 (1.005–1.133)	0.033	0.998 (0.996–1.001)	0.147

B to V — bur-to-vessel ratio; CI — confidence interval; DS — diameter stenosis; MLD — minimal lumen diameter; OR — odds ratio; PCI — percutaneous coronary intervention

assessed factor (post-PCI DS) ($p < 0.01$) (Table 3). The ROC analysis at the follow-up time also showed that the cutoff value of the final B to V was 0.50, with a sensitivity of 50.98%, a specificity of 68.33%, a Youden index of 0.193, and an area under the curve (AUC) of 0.627 (95% confidence interval [CI]: 0.530–0.717) ($p < 0.05$ or $p < 0.01$) (Fig. 2). These results showed that an increased final B

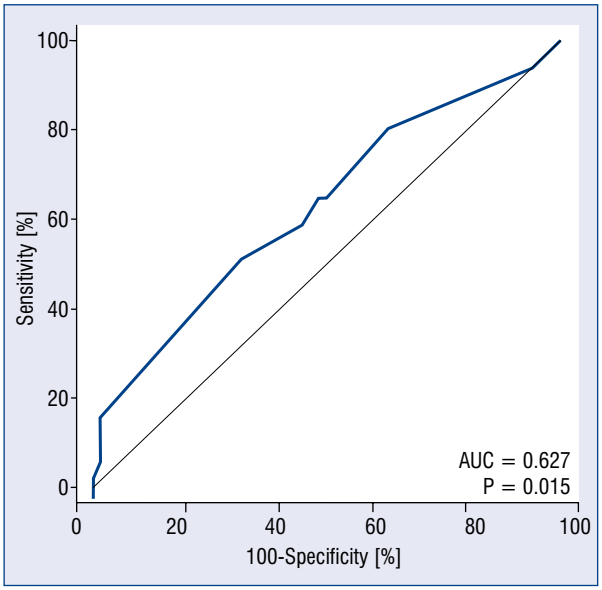

Figure 2. Receiver operating characteristic curve data of burr-to-vessel ratio (B to V) for predicting vessel quantitative flow ratio loss in patients with moderately to severely calcified lesions after rotational atherectomy; AUC — area under the curve.

to V could reduce QFRv loss in patients with MSCL after RA at the follow-up time.

Discussion

This study explored, for the first time, the possibility of utilizing QFRv loss as a viable parameter reflecting coronary physiological function in post-RA MSCL patients. Indeed, the loss of post-follow-up coronary physiological function has never been studied before, mainly because FFR determination requires an expensive pressure wire, and the measuring process is complex, which makes it difficult for researchers to quantify the data changes related to coronary physiological function during follow-up [16]. Previous studies have shown that FFR measured immediately after PCI in patients without RA was lower than a certain value that correlated with the occurrence of clinical adverse events [17–20]. It became easier to conduct coronary physiological function measurements during the follow-up period with the emergence of non-invasive and simple QFR determination methods [9]. In the present study, we found that an increased burr-to-vessel ratio could decrease QFRv loss in MSCL patients after RA during the follow-up, which might be closely associated with low TVF incidence. It is worth noticing that this is the first mention of such findings.

The upfront RA before contemporary DES in severe calcified lesion cases is feasible in modern PCI, and it is associated with a higher success rate [21]. A randomized trial comparing small (burr-to-vessel ratio of ≤ 0.7) and large (burr-to-vessel ratio of > 0.7) burrs revealed that the smaller ones achieved similar immediate lumen enlargement and late target vessel revascularization as the larger burrs, with fewer complications [22]. The European expert consensus document recommends a burr-to-vessel ratio of 0.6, while the North American expert consensus document recommends a burr-to-vessel ratio of 0.4–0.6 [23, 24]. Unfortunately, there are no current data on the relation between burr-to-vessel ratio and coronary physiological functions. The present study found that increasing the burr-to-vessel ratio (≥ 0.50) could reduce QFRv loss during the follow-up period.

Current accumulative data have shown a significant association between post-PCI without RA low FFR value and a higher clinical adverse event risk at mid- and long-term follow-ups [19, 20, 25]. Our study also reflected that the incidence rate of TVF in the LQ loss group was significantly lower compared to the HQ loss group, indicating that a lower QFRv loss might be closely associated with a lower TVF incidence. Additionally, Nozue et al. [26] reported that DS was significantly determinant for coronary computed tomography angiography-derived fractional flow reserve (FFRCT). Moreover, Chen et al. [27] revealed, after adjusting, through QRF, the low-density lipoprotein cholesterol goal for coronary physiology, that the goal-achievement group exhibited lower DS with a better change in QFR and a lower incidence of major adverse cardiovascular events at 1-year follow-up [27]. Interestingly, our study's DS follow-up was also lower in the LQ loss patients compared to their HQ loss counterparts. In summary, these findings indicated that there might be a close correlation between angiographic stenosis and coronary physiological functions.

Limitations of the study

This study's shortcomings are as follows: (1) its retrospective (not prospective) nature — fewer than 50% of patients had a follow CAG; (2) the sample size was relatively small; and (3) the potential impacts of long-term inclusion-related variations in treatment strategies and guideline changes on the outcomes.

Conclusions

In conclusion, high burr-to-vessel ratio (≥ 0.50) had a high predictive value for low QFRv loss in patients with MSCL after RA, which may be closely associated with low occurrence of TVF. It implies that the benefit of increased burr size is reflected in reduced coronary physiological dysfunction and TVF occurrence in these patients.

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Conflict of interest: None declared

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Long-term outcome of rotational atherectomy according to burr-to-artery ratio and changes in coronary artery blood flow: Observational analysis

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Abstract

Background: *Rotational atherectomy (RA) has been proven to be efficient for the treatment of calcified and diffuse coronary artery lesions. However, the optimal burr-to-artery ratio (BtAR) remains unidentified as well as an influence of change in blood flow on long-term outcome. Aim of our study was to examine the association between long-term outcome, and both BtAR and change in coronary flow during RA.*

Methods: *We conducted a retrospective study including patients who underwent RA. Two independent observers calculated BtAR, pre- and postprocedural corrected Thrombolysis in Myocardial Infarction (TIMI) frame count (cTFC) for artery treated with RA. The long-term outcome was defined as all-cause mortality.*

Results: *Receiver operating characteristic curve analysis of BtAR determined threshold of 0.6106 for all-cause mortality detection with sensitivity 50.0%, specificity 90.8%, and area under the curve 0.730 ($p < 0.001$). Kaplan-Meier survival analysis showed that the all-cause mortality rate in the group with the BtAR > 0.6106 is significantly higher compared to the patients with lower BtAR (hazard ratio [HR] 3.76, 95% confidence interval [CI] 1.51–9.32; $p < 0.001$). Kaplan-Meier survival analysis revealed that the all-cause mortality rate in the group with impairment in coronary flow was significantly higher compared to group with cTFC difference ≤ 0 after RA (HR 3.28, 95% CI 1.56–9.31; $p = 0.02$).*

Conclusions: *Burr-to-artery ratio > 0.6106 is associated with worse prognosis of patients treated with RA. Patients showing post-RA impairment in blood flow in the target artery have worse prognosis.*
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Key words: rotational atherectomy, burr-to-artery ratio, corrected Thrombolysis in Myocardial Infarction frame count, mortality

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Introduction

Over the past decades rotational atherectomy (RA) has been proven to be a safe and efficient method for treatment of calcified and diffuse coronary artery lesions [1–4]. Nevertheless, this strategy is still uncommonly used, with an application rate as low as 0.8–3.1% of total percutaneous coronary interventions (PCI) in Europe [1]. In the Polish PCI registry, this value was even lower and amounted only 0.44% of PCI procedures [5, 6]. As demonstrated by previous studies, patients undergoing RA are significantly older than those treated with standard PCI [1]. Therefore, ageing of the population of cardiovascular patients should prompt resurgence of interest in RA that may even grow in the next years. Despite technological progress including the introduction of very high pressure and low-profile balloons, laser and orbital atherectomy, RA still occupies the first place among plaque modification techniques [4].

The technique of performing RA has evolved over the years. Although more aggressive debulking strategy with bigger burr sizes and burr-to-artery ratio (BtAR) > 0.7 was preferred in the past, the current guidelines recommend an opposite approach called "plaque modification strategy" based on using smaller burrs, with BtAR 0.5–0.6 [1, 2]. Previous studies showed that smaller burr sizing (BtAR < 0.7), compared with a more aggressive strategy, was related with similar procedural and angiographic success rates, but was burdened with less angiographic complications and lower creatine kinase-myocardial band release during the procedure [7, 8]. There are only scarce literature data comparing both strategies in terms of long-term outcomes.

The incidence of coronary artery flow impairment in patients treated with RA is higher than after standard PCI [9–11]. There are several underlying mechanisms of this phenomenon, such as microcirculatory vasospasm, enhanced platelet activation and aggregation, and microvascular embolization of atherosclerotic debris [9, 12]. The occurrence of slow-flow in coronary arteries is usually associated with poor technique and inadequate burr size [1]. Administration of intracoronary nitrates, verapamil, sodium nitroprusside, or adenosine can improve the blood flow during the procedure [9, 12–14]. Previous studies showed that the occurrence of slow-flow is correlated with worse long-term prognosis [15]. However, significant slow-flow, defined as postprocedural grade 0 or 1 according to Thrombolysis in Myocardial Infarction (TIMI) scale, is infrequent and occurs in 0.0–2.6% of cases [2]. The TIMI scale is an inaccurate and operator-dependent method, nevertheless, it is still commonly used for assessment of postprocedural coronary blood flow and even despite clear slowing of the blood flow is often judged as TIMI 3 [16]. In our study, we focused on BtAR as a key difference between debulking and plaque modification strategies and on difference in post-RA coronary flow in the target vessel. The aim of our study was to examine whether BtAR and coronary flow after the procedure are associated with long-term outcomes in patients undergoing RA.

Methods

Study design and patients

This is a retrospective, double-center study including patients who underwent RA at the Department of Cardiology and Internal Medicine of the University Hospital No. 1 in Bydgoszcz and at the Department of Cardiology and Structural Heart Diseases of the Medical University of Silesia in Katowice between January 2005 and February 2017. During that time period a total of 232 RA procedures were performed. Procedural success was defined as success in facilitating stent delivery with residual stenosis < 50% and without severe procedural complication (e.g., inability to insert guiding catheter/rotablator burr through the stenotic lesion or occurrence of severe dissection/perforation). The procedures assessed as unsuccessful were not included in the further analysis. 52 cases were excluded and 180 patients were eventually enrolled with stenosis treated with RA for the analysis. The exclusion criteria were more than one RA procedure in a single patient (n = 6), unsuccessful passage of the burr through the stenotic lesion (n = 7) or inability to calculate BtAR due to technical issues (n = 39). The analysis of coronary blood flow changes was performed, with data limited to the center in Bydgoszcz. 21 patients were excluded, (12 patients) due to inability to calculate the corrected TIMI frame count (cTFC) before and after the procedure, or administration of glycoprotein IIb/IIIa inhibitors during RA (9 patients). The need for performing RA in each case was evaluated by the operator based on two main indications: presence of uncrossable lesions and inability to sufficiently dilate the lesion with a balloon. In cases when more than one burr size was used the largest size was included in the analysis. All study participants received pharmacotherapy according to the recommendations of the European Society of Cardiology valid at the time of the procedure. Clinical and procedural data were collected from patient medical records. Follow-up data

Table 1. Baseline clinical characteristics of the study population including division according to burr-to--artery-ratio (BtAR) threshold.

	All patients enrolled in the study (n = 180)	BtAR ≤ 0.6106 (n = 152)	BtAR > 0.6106 (n = 28)	P
Male sex	117 (65.0%)	97 (63.8%)	20 (71.4%)	0.58
Age	71.8 (9.0)	72.0 (9.0)	70.6 (9.1)	0.45
Hypertension	136 (75.6%)	119 (78.3%)	17 (60.7%)	0.08
Diabetes	96 (53.3%)	85 (55.9%)	11 (39.3%)	0.16
Prior MI	91 (50.6%)	78 (51.3%)	13 (46.4%)	0.79
Body mass index	28.2 (4.6)	28.3 (4.4)	27.8 (4.1)	0.62
Ejection fraction	50 (39.75–55.0)	50 (39.5–55.0)	43 (39.0–51.0)	0.37

Mean values (standard deviation), median (interquartile range), or number (%); MI — myocardial infarction

were collected from the Polish National Health Fund database. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by the Ethics Committee of Nicolaus Copernicus University in Torun, Collegium Medicum in Bydgoszcz (approval number KB 56/2020). The primary clinical endpoint was defined as all-cause mortality.

Angiograms

Two independent observers in both centers trained in angiogram assessment and blinded to other clinical data, calculated BtAR. The definition and calculation method of BtAR was similar as reported in previous studies [17]. The measurements from both observers were then averaged to give the final result. The cTFC was defined as the number of frames required for contrast dye to reach the first standard distal coronary landmark and was evaluated using the technique described by Gibson et al. [16]. The difference between the postprocedural and preprocedural cTFC was evaluated to reflect the changes in coronary artery blood flow. Both preprocedural and postprocedural cTFC were examined directly before and after RA, respectively. All angiograms were registered at 12.5 frames/s. All disputable issues and disagreements were resolved by a third independent observer. The primary angiographic endpoint was defined as post-RA cTFC. The angiograms were analyzed using OsiriX Lite software (Pixmeo SARL) and CAAS QCA software (Pie Medical Imaging BV).

Statistical analysis

The statistical analysis was performed using the Statistica 13.0 package (StatSoft, Tulsa, USA) and MedCalc 15.8 (MedCalc Software, Ostend, Belgium). Continuous variables were presented as medians with interquartile ranges or means with standard deviation (SD). Categorical variables were expressed as the number of patients presenting the given feature and the percentage of patients in the analyzed group. The optimum cut-off points for the association between BtAR and all-cause mortality was determined using receiver operator characteristics curve analysis. The Shapiro-Wilk test demonstrated that the continuous variables investigated were not normally distributed. Therefore, comparisons of continuous variables between the two groups were analyzed with the Mann-Whitney unpaired rank sum test. Categorical variables were compared using the χ^2 test and with the Yates' correction if required. The survival analyses were performed with the Kaplan-Meier method and the log-rank test. Aforementioned calculations were made for a 6-year time period (from the procedure to patient's death) because after that time period the number of patients remaining in the analysis group was very limited and could potentially increase the risk of calculation bias. Differences were considered significant at $p < 0.05$.

Results

Baseline characteristics

The mean age (SD) in the study group was 71.8 (9.0) years with a prevalence of men (65.0%). The mean BtAR (SD) was 0.4951 (0.1158). A total of 28 (15.6%) patients died with a mean (SD) of 745.2 (848.1) days from the procedure to death. Detailed characteristics of the study population is presented in Table 1.

Burr-to-artery ratio

The optimal BtAR cut-off point for prediction of all-cause mortality was 0.6106 (sensitivity

Table 2. Angiographic characteristics of the study population including division according to burr-to--artery-ratio (BtAR) threshold.

	All patients enrolled in the study (n = 180)	BtAR ≤ 0.6106 (n = 152)	BtAR > 0.6106 (n = 28)	P
Duration of the procedure [min]	80.0 (60.0–110.0)	80.0 (60.0–110.0)	66.0 (58.5–98.5)	0.31
Contrast volume [mL]	200.0 (150.0–250.0)	200.0 (150.0–250.0)	210.0 (155.0–260.0)	0.32
Location of treated stenosis:	70 (38.9%)	62 (40.8%)	8 (28.6%)	0.86
LAD				
RCA	57 (31.7%)	50 (32.9%)	7 (25.0%)	0.54
Cx	39 (21.6%)	29 (19.1%)	10 (35.7%)	0.09
OM	14 (7.8%)	11 (7.2%)	3 (10.7%)	0.80
Burr size [mm]	1.5 (1.25–1.5)	1.5 (1.25–1.5)	1.5 (1.25–1.75)	0.006
Minimum stent diameter [mm]	2.75 (2.5–3.0)	2.75 (2.5–3.0)	2.5 (2.25–3.0)	0.03
Maximum stent diameter [mm]	3.0 (2.5–3.5)	3.0 (2.75–3.5)	2.5 (2.5–3.5)	0.02
Average stent diameter [mm]*	3.0 (2.5–3.25)	3.0 (2.67–3.25)	2.5 (2.5–3.0)	0.01
Usage of glycoprotein IIb/IIIa inhibitors	16 (8.9%)	12 (7.9%)	4 (14.3%)	0.47
Total stent length [mm]	38.0 (22.0–52.0)	38.0 (23.0–52.0)	42.0 (18.0–59.0)	0.74
Catheter size [Fr]:				0.009
6	66.7%	66.5%	67.8%	
7	27.2%	29.6%	14.3%	
8	6.1%	3.9%	17.9%	

Values are median (interquartile range) or number (%); *In case of implantation more than one stent in target vessel an average diameter for all implanted stents was calculated; LAD — left anterior descending artery; RCA — right coronary artery; Cx — circumflex coronary artery; OM — obtuse marginal artery

50.0%, specificity 90.8%, area under curve 0.730; p < 0.001). Based on this BtAR threshold, the patients were divided into two groups, with the majority of them (84.4%) falling into the BtAR ≤ 0.6106 group. Both groups did not differ in terms of baseline clinical characteristics (Table 1). Duration of the procedure and location of stenosis were similar in both groups (Table 2). For patients with BtAR ≤ 0.6106 smaller burrs (median burr size 1.5 [1.25–1.5] vs. 1.5 [1.25–1.75], p = 0.006), larger stents (minimum stent diameter [mm]: 2.75 [2.5–3.0] vs. 2.5 [2.25–3.0], p = 0.03; maximum stent diameter [mm]: 3.0 [2.75–3.5] vs. 2.5 [2.5–3.5], p = 0.02; median stent diameter [mm]: 3.0 [2.67–3.25] vs. 2.5 [2.5–3.0], p = 0.01) and smaller catheters were used (catheter size [Fr]: 6 [66.5%], 7 [29.6%], 8 [3.9%] vs. 6 [67.8%], 7 [14.3%], 8 [17.9%], p = 0.009).

The Kaplan-Meier survival analysis (Fig. 1) showed a significantly higher all-cause mortality rate in the group with BtAR > 0.6106 compared with the patients with a lower BtAR (hazard ratio [HR] 3.76, 95% confidence interval [CI] 1.51–9.32; p < 0.001).

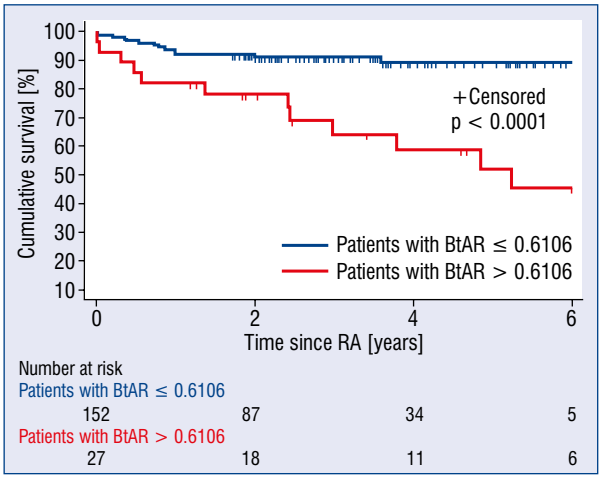

Figure 1. Survival after rotational atherectomy (RA) by burr-to-artery ratio (BtAR) after division into two groups.

Changes in coronary artery blood flow

A total of 62 patients for whom the cTFC was evaluated were divided into two groups based on the difference between the postprocedural and preprocedural values of cTFC. Patients showing impairment

Table 3. Baseline clinical and angiographic characteristics of the study population regarding corrected Thrombolysis in Myocardial Infarction frame count (cTFC) difference.

	All patients enrolled in the study (n = 62)	cTFC difference ≤ 0 (n = 38)	cTFC difference > 0 (n = 24)	P
Male sex	38(61.3%)	21 (55.3%)	17 (70.8%)	0.22
Age	71.1 (9.0)	72.7 (8.9)	68.5 (8.8)	0.07
Arterial hypertension	42 (67.7%)	25 (65.8%)	17 (70.8%)	0.84
Diabetes type 2	33 (53.2%)	17 (44.7%)	16 (66.7%)	0.12
Prior MI	30 (48.4%)	16 (42.1%)	14 (58.3%)	0.26
Body mass index	28.3 (4.5)	29.3 (4.7)	26.7 (3.9)	0.04
Ejection fraction	42.5 (38.0–49.)	40 (35.5–49.25)	47 (41.25–49.0)	0.17
Duration of the procedure [min]	65.0 (50.0–90.0)	65.0 (55.0–90.0)	60.0 (50.0–90.5)	0.56
Contrast volume [mL]	182.0 (140.0–270.0)	182.0 (145.0–261.0)	180.0 (137.5–278.0)	0.79
Location of treated stenosis:				
LAD	9 (14.5%)	7 (18.4%)	2 (8.3%)	0.47
RCA	23 (37.1%)	14 (36.8%)	9 (37.5%)	0.96
Cx	20 (32.6%)	13 (34.2%)	7 (29.2%)	0.68
OM1	7 (11.3%)	4 (10.5%)	3 (12.5%)	0.86
OM2	3 (4.8%)	0 (0%)	3 (12.5%)	0.28
Burr size [mm]	1.25 (1.25–1.5)	1.25 (1.25–1.5)	1.5 (1.25–1.5)	0.12
Minimum stent diameter [mm]	2.5 (2.5–3.0)	2.5 (2.375–3.0)	2.625 (2.5–3.0)	0.57
Maximum stent diameter [mm]	3.0 (2.5–3.5)	3.0 (2.5–3.5)	3.0 (2.5–3.5)	0.21
Average stent diameter [mm]*	2.8 (2.5–3.0)	2.775 (2.5–3.0)	3.0 (2.5–3.25)	0.27
Total stent length [mm]	38.5 (20.0–51.5)	40.5 (23.0–53.0)	38.0 (19.5–50.0)	0.79
Catheter size [Fr]:				
6	71.0%	71.0%	70.8%	0.42
7	22.6%	23.7%	20.8%	
8	6.4%	5.3%	8.3%	
Burr-to-artery ratio	0.5364 (0.4668–0.6476)	0,5177 (0.4561–0.6476)	0,5637 (0.4940–0.6449)	0.24

Mean values (standard deviation), median (interquartile range) or number (%); *In case of implantation more than one stent in target vessel an average diameter for all implanted stents was calculated; MI — myocardial infarction; LAD — left anterior descending artery; RCA — right coronary artery; Cx — circumflex coronary artery; OM1 — first obtuse marginal artery; OM2 — second obtuse marginal artery

in blood flow in the target artery (cTFC difference > 0) had a lower body mass index (mean [SD], 26.7 [3.9] vs. 29.8 [4.7], p = 0.04) with no other baseline or procedural differences in comparison to patients presenting cTFC difference ≤ 0 (Table 3).

The Kaplan-Meier survival analysis (Fig. 2) revealed a significantly higher all-cause mortality rate in the group with impaired post-RA coronary artery blood flow (cTFC difference > 0) compared with patients with preserved coronary flow with cTFC difference ≤ 0 (HR 3.28, 95% CI 1.56–9.31; p = 0.02).

Discussion

The main finding of this study is that BtAR higher than 0.6106 and impaired postprocedural coronary flow (cTFC difference > 0) are associated with almost 4-times and over 3-times higher risk of mortality in those groups, respectively.

The increase in mortality found in cases with higher BtAR can be explained by a higher complication rate associated with a more aggressive debulking strategy [7]. Other potential causes of this phenomenon include higher debris production, increased platelet activation and aggregation, microvascular embolization resulting in heart systolic dysfunction [18]. The optimal BtAR remains unidentified, however the current guidelines recommend the burr size of < 0.7 [1] or < 0.6 [2] of the vessel diameter. Recently published studies reflecting implementation of recommendations into clinical practice reported the BtAR < 0.6

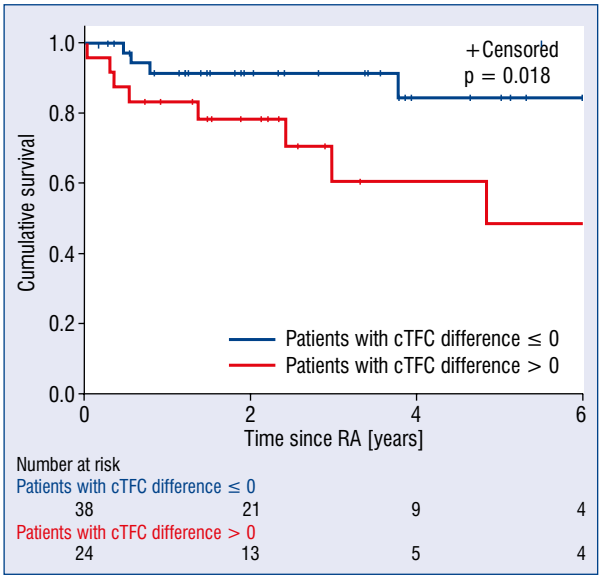

Figure 2. Survival after rotational atherectomy (RA) by changes in coronary blood flow; cTFC — corrected Thrombolysis in Myocardial Infarction frame count.

[3, 19, 20] or even < 0.5 [21, 22] for the overall study population. The mean BtAR (SD) calculated for all patients in the present study was 0.50 (0.12). The beneficial effect of RA performed with lower BtAR has been demonstrated in previously published studies [7, 17, 20]. One of the earliest studies regarding RA, by Kaplan et al. [17], revealed that the need for vessel revascularization is decreased in patients with BtAR 0.6–0.85. Randomized CARAT trial [7] revealed that RA performed with smaller burrs (BtAR ≤ 0.7) provided similar procedural success, but with a lower angiographic complication rate, in comparison to a more aggressive strategy. Cuenza et al. [20] reported significantly higher BtAR in patients who developed major adverse events. In the current study, patients with higher BtAR had worse long-term prognosis, thus supporting the need for less aggressive treatment. Despite benefits of a smaller burr sizing, evidence regarding the lower limit of optimal BtAR range is very scarce. Brown et al. [23] demonstrated that RA performed even with BtAR < 0.5 can provide low complication and high success rates. Therefore, in order to find the optimal burr size, it is recommended to start RA with the smallest possible burr size and increase it until a favorable result is achieved [1, 2].

In order to overcome the subjectivity and imprecision of the TIMI scale, the cTFC difference was used as a more precise and objective tool for assessment of coronary blood flow [16]. It was found that impairment of coronary blood flow was correlated with higher mortality.

Several studies [24–30] investigated the influence of preprocedural or postprocedural blood flow in the target artery on short and long-term outcome, but the majority focused on patients with myocardial infarction for whom RA is rather the last interventional option [19]. According to available research, this is the first study to evaluate the association between a change in coronary blood flow during RA and long-term outcomes.

The results of the GUSTO IIb [31] and RAPPORT [32] trials showed that patients with suboptimal coronary blood flow (TIMI ≤ 2) after primary PCI had worse prognosis (with mortality rates of TIMI 3 vs. TIMI ≤ 2 of 1.5% and 10.2%, respectively, p < 0.001) during 30 days of observation. De Luca et al. [25] noted that in high-risk patients treated with primary PCI due to acute myocardial infarction the preprocedural TIMI flow grade 3 was an independent predictor of 1-year survival. Mehta et al. [26] reported a strong association between final TIMI grade ≤ 2 and both in-hospital and 1-year adverse events, although they noticed that TIMI ≤ 2 which occurred less commonly after primary PCI. A study by Ndrepepa et al. [27] revealed an association between postprocedural TIMI flow grade and 1-year mortality in patients with acute coronary syndrome treated with PCI, however no correlation was found between preprocedural TIMI score and mortality.

Gibson et al. [28] demonstrated lower 90-minute cTFC after thrombolysis administration to be a predictor of improved in-hospital and 1-month clinical outcomes [28] and 2-year survival [29]. Importantly, the authors noticed that among patients with normal coronary blood flow (TIMI grade 3, cTFC ≤ 40), there may be lower- and higher-risk subgroups [28]. Although thrombolytic therapy is currently not recommended for patients with myocardial infarction as a primary strategy, this finding should be taken into consideration regarding the results of the present study, since normal flow after RA was observed in the vast majority of patients (98.4% and 93.5% according to the TIMI scale or cTFC, respectively). French et al. [30] showed that the cTFC (3 weeks after myocardial infarction) is an independent predictor of 5-year survival, however no relationship was found regarding 10-year survival. The authors reported also that the cTFC method, although yielding additional prognostic information, was not superior to TIMI flow grade.

Limitations of the study

Several limitations of the present study should be noted. The main limitation of the present study is its retrospective design. On the other hand, the use of objective quantitative data as the BtAR and the mortality hard endpoint can mitigate potential confounding arising from a retrospective design. The next limitation is a relatively low number of patients included in the final analysis. Nevertheless, it should be underlined that RA is remains a rarely performed procedure, especially in Poland. Therefore this study showed results of one of the largest Polish cohorts of patients who underwent this procedure. Another limitation, potentially influencing the results, is the extended duration of study period, possibly resulting in heterogeneity of the study population with regard to the evolution of available procedural techniques and pharmacotherapy over the last decade. Furthermore, only all-cause mortality data were able to be retrieved, which rendered a complementary analysis of cardiovascular deaths impossible. Finally, the cTFC parameter difference introduced in the current study, although prognostically useful, is time-consuming to calculate and therefore its use in everyday practice may be limited.

Conclusions

This is the first study to evaluate the association between long-term outcome of patients treated with RA and BtAR as well as changes in coronary blood flow. The BtAR higher than 0.6106 and impairment of blood flow assessed with the cTFC difference were associated with worse survival.

Conflict of interest: None declared

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Angiography-based coronary flow reserve: The feasibility of automatic computation by artificial intelligence

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Abstract

Background: *Coronary flow reserve (CFR) has prognostic value in patients with coronary artery disease. However, its measurement is complex, and automatic methods for CFR computation are scarcely available. We developed an automatic method for CFR computation based on coronary angiography and assessed its feasibility.*

Methods: *Coronary angiographies from the Corelab database were annotated by experienced analysts. A convolutional neural network (CNN) model was trained for automatic segmentation of the main coronary arteries during contrast injection. The segmentation performance was evaluated using 5-fold cross-validation. Subsequently, the CNN model was implemented into a prototype software package for automatic computation of the CFR (CFR_{auto}) and applied on a different sample of patients with angiographies performed both at rest and during maximal hyperemia, to assess the feasibility of CFR_{auto} and its agreement with the manual computational method based on frame count (CFR_{manual}).*

Results: *Altogether, 137,126 images of 5913 angiographic runs from 2407 patients were used to develop and evaluate the CNN model. Good segmentation performance was observed. CFR_{auto} was successfully computed in 136 out of 149 vessels (91.3%). The average analysis time to derive CFR_{auto} was 18.1 ± 10.3 s per vessel. Moderate correlation ($r = 0.51$, $p < 0.001$) was observed between CFR_{auto} and CFR_{manual}, with a mean difference of 0.12 ± 0.53.*

Conclusions: *Automatic computation of the CFR based on coronary angiography is feasible. This method might facilitate wider adoption of coronary physiology in the catheterization laboratory to assess microcirculatory function.* (Cardiol J 2023; 30, 3: 369–378)

Key words: artificial intelligence, convolutional network, coronary flow reserve, X-ray angiography, coronary heart disease

Introduction

Myocardial ischemia can be due to epicardial or microvascular disease, which are the two main leading pathophysiological mechanisms. Fractional flow reserve (FFR) has consistently proven to be the most stable and accurate parameter to assess the hemodynamic severity of epicardial coronary stenosis. Guidance of percutaneous coronary interventions (PCI) by FFR results in significant improvement of outcomes in different clinical scenarios [1–3].

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Conversely, coronary microvascular dysfunction has been classically relegated to a secondary role due to different factors, among them the complexity of its assessment. Coronary flow reserve (CFR), defined as hyperemia-to-rest flow ratio, depends on both epicardial and microvascular vessels, thus being one of the parameters used to estimate microvascular dysfunction. CFR can be non-invasively assessed by positron emission tomography [4], or invasively by means of Doppler wire [5] or thermodilution [6, 7]. However, all these methods are scarcely available in most cardiology departments, being restricted to few expert centers. Nonetheless, the evidence on the prognostic impact and clinical relevance of microvascular dysfunction is currently increasing [8, 9] and subsequently, the need to increase the availability of a method to assess coronary microcirculatory function. Discordance between FFR and CFR assessment occurs in up to 32% of cases [10], because they offer clinically relevant complementary information. Patients without epicardial disease (normal FFR) but microvascular dysfunction (low CFR) have a significantly worse prognosis than those with both normal FFR and CFR [8]. Furthermore, a recent study has challenged the paradigm of revascularization in lesions with low FFR but preserved CFR [9]. This evidence is, however, hardly pervading clinical practice, due to the limited availability of current methods to assess CFR [11].

Image-based computational methods of physiology have substantially contributed to reducing costs and to expanding physiology guidance in PCI. FFR can be accurately estimated by different computational methods based on coronary computed tomography angiography [12], coronary angiography [13, 14], optical coherence tomography [15–17], or intravascular ultrasound [18]. Nonetheless, the feasibility of computational methods for the assessment of microcirculatory function has been limited, although some pioneer approaches have recently been proposed, with varying success [19, 20]. In the current study, we aimed to propose a novel automatic computational approach to estimate CFR based on coronary angiography, dubbed CFR_{auto}, and evaluated its potential to improve the availability of microvascular assessment for clinical decision-making in a cost-effective manner.

Methods

Study sample

A search of the database of the Corelab (CardHemo, Med-X Research Institute, Shanghai Jiao Tong University, Shanghai, China) was performed, looking for patients with coronary angiography performed at rest or/and under maximal hyperemia. The exclusion criteria were as follows: 1) Patients with chronic total occlusion; 2) Patients with prior coronary bypass grafting of the interrogated vessels; 3) Angiographic images with significant overlap or foreshortening. Data of all patients with coronary angiography performed only at rest were used for the development and validation of the convolutional neural network (CNN) model. The remaining patients with coronary angiography performed both at rest and under maximal hyperemia were used for independent validation of the CFR_{auto}. Figure 1 shows the flow diagram of the study, explaining the use of the different datasets for CNN model development and CFR_{auto} validation. The study protocol was approved by the institutional review board, and all patients had previously provided informed consent for enrolment into the institutional database for potential future investigations.

Vessel segmentation in the CNN

Data annotation. Lumen contours of the three main epicardial coronary arteries with coronary stenosis, namely the left anterior descending (LAD), left circumflex (LCx), and right coronary artery (RCA), in all patients were semi-automatically annotated by experienced analysts, trained in quantitative coronary angiography (QCA) and regularly audited at the core laboratory.

Development of the CNN model. An adapted CNN model in U-shape [21] was applied for segmentation of the main epicardial coronary arteries. The model consisted of a contracting path for high-level feature extraction and an expansion path to produce a full-resolution segmentation image. Details of the architecture of the original U-Net have been described previously [21]. The U-Net was modified to optimize the segmentation of the vessel: two additional down-sampling layers were implemented on the U-Net structure to enlarge the receptive field and thus avoid discontinuity of detected centerlines. Moreover, the number of feature maps per layer was reduced to accelerate the computation speed (Fig. 2).

For the CNN training process, a combination of dice and focal losses was used as the loss function [22, 23]. Dice loss is widely used for image segmentation, with excellent results, while focal loss can be useful in cases of smaller vessel area with respect to the image size. The Adam optimization algorithm [24] was used to facilitate CNN

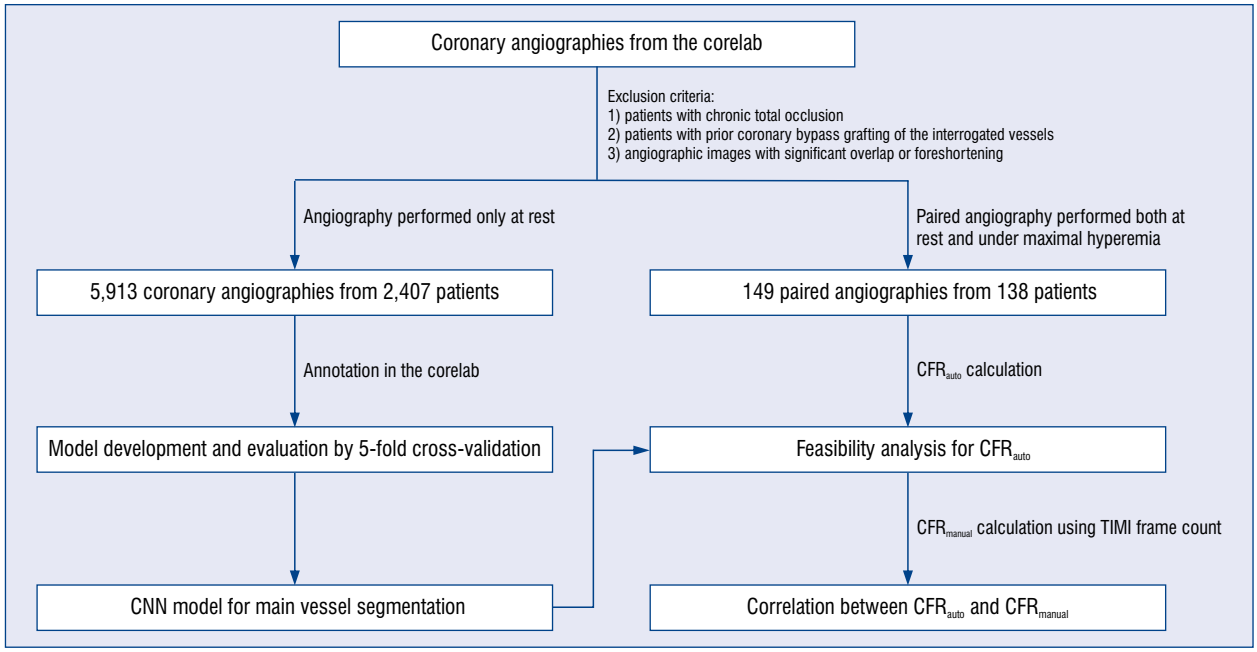

Figure 1. Flow diagram of the study; CFR — coronary flow reserve; CNN — convolutional neural network; TIMI — Thombolysis in Myocardial Infarction.

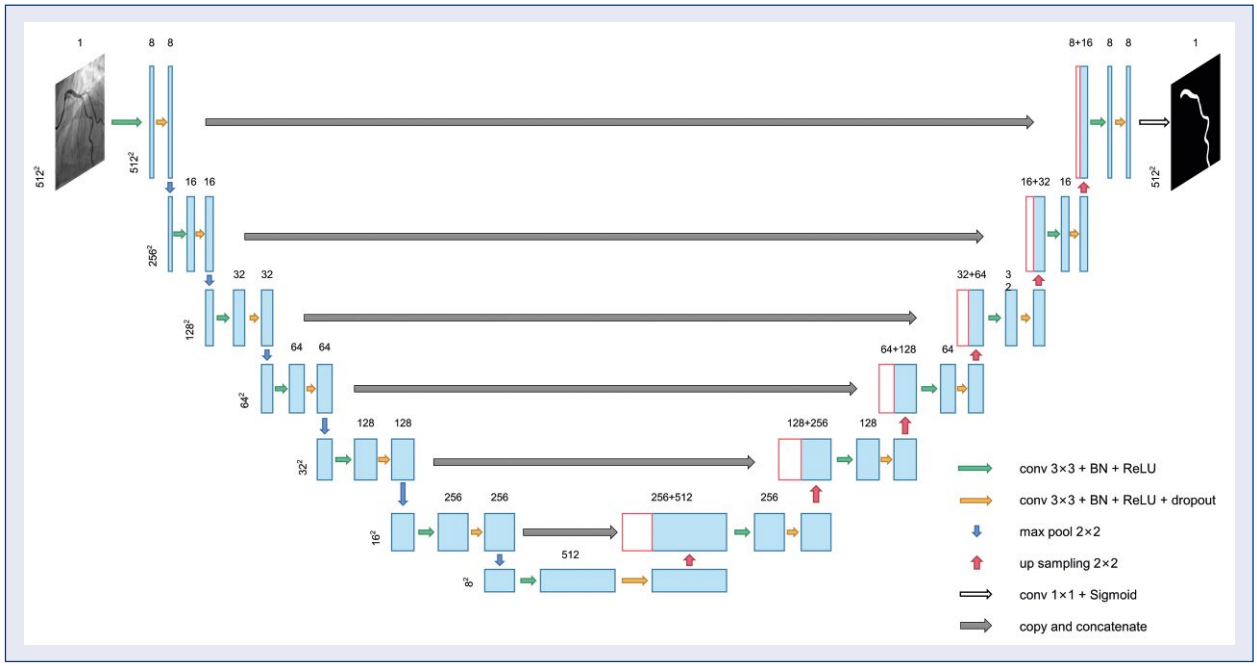

Figure 2. The structure of the proposed convolutional neural network for vessel segmentation.

convergence. The whole training process has 70 epochs in total, with a learning rate of 2×10^{-4} at the first 30 epochs. At the 31st and 61st epochs, the learning rate decreased to 0.4 times that of the previous learning rate. This setting facilitates CNN convergence while preventing overfitting.

The CNN model for LAD, LCx, and RCA segmentation was separately trained using the corresponding datasets. Model performance was evaluated by 5-fold cross-validation using evaluation metrics of dice similarity index, precision, recall, and F1 score.

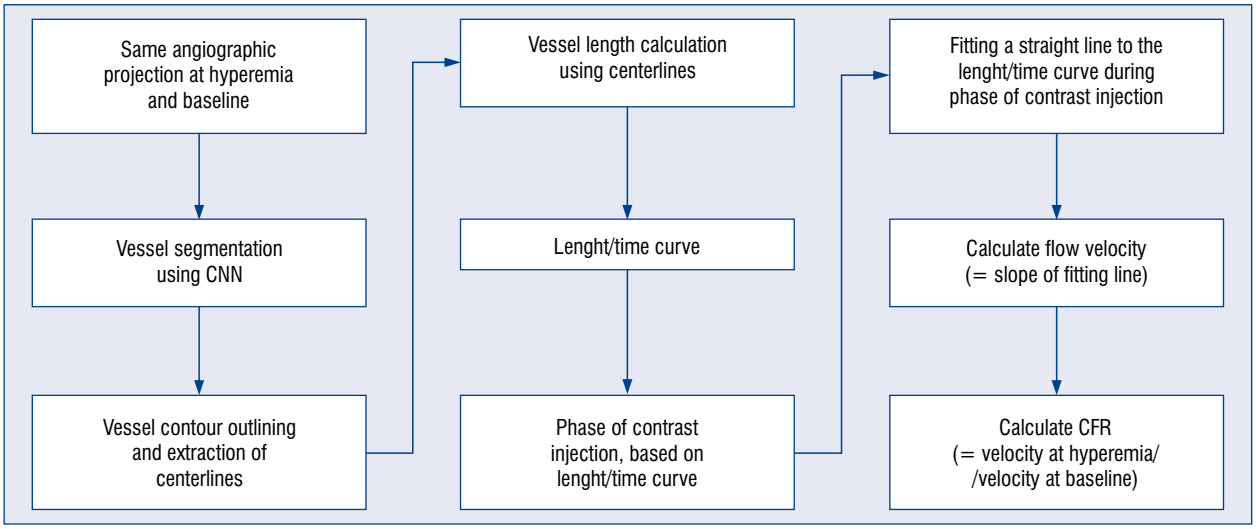

Figure 3. Workflow diagram describing the entire process of the proposed method; CFR — coronary flow reserve; CNN — convolutional neural network.

Automatic CFR computation

The developed CNN model was integrated into a prototype software package (FlowPlus; Pulse Medical Imaging Technology, Shanghai, China) for automatic CFR calculation. Two loops of the same angiographic projection, at hyperemia and at baseline, should be uploaded into the software in the DICOM format. The trained CNN model automatically segmented the vessel and subsequently delineated the vessel contour and centerlines. The length of the vessel was calculated for each frame according to the length of the centerline. Considering the frame rate, the curve of vessel length variation over time (length/time curve) could be easily derived. The phase of contrast injection was then automatically calculated as the period of the curve in which the length progressively increases. The flow velocity could then be easily calculated by fitting a straight line to the length/time curve during the phase of contrast injection, using the least-square method. The slope of this fitting line defined the rate of length change over time, and hence the flow velocity [25]. At this point, CFR could be derived as the quotient between hyperemic and rest flow velocities (Fig. 3).

Validation of the automatic CFR computation

The automatically computed CFR (CFR_{auto}) was validated on a different sample of patients, other than the one used for the development of the CNN model, considering manually calculated CFR (CFR_{manual}) as reference. A manual Thrombolysis in Myocardial Infarction (TIMI) frame count [26] was performed by experienced QCA analysts on the same angiography loops as the automatic count in all patients. TIMI frame count method needs to count the frames the contrast take from to point contrast just enter the vessel to the point of maximal filling of the vessel, then use the frame rate to obtain the filling time. Finally, the manually measured vessel length was used to calculate the flow velocity. Coronary flow velocities at hyperemia and baseline were then calculated, and subsequently the CFR_{manual} was derived, following the same rationale as previously described. The main difference between CFR_{auto} and CFR_{manual} is the way the flow velocities are derived; in CFR_{auto} CNN was used to automatically obtain flow velocities, while in CFR_{manual} the flow velocity was manually calculated by counting frames. The agreement and correlation between CFR_{auto} and CFR_{manual} were then evaluated.

Statistical analysis

Continuous variables were presented as mean ± standard deviation or median (Q1–Q3) if a Gaussian distribution could not be assumed. The correlation between CFR_{auto} and CFR_{manual} was evaluated using Pearson's correlation test and linear regression analysis, taking CFR_{manual} as the standard reference. The proportional bias (slope from 1) and constant bias (the deviation of the intercept from 0) were evaluated in the linear regression. The agreement between CFR_{auto} and CFR_{manual} as continuous variables was assessed using Bland-Altman analysis and the intraclass correlation coefficient for the absolute value (ICCa). A two-sided p-value ≤ 0.05 was considered to indicate a statistically significant

difference. Statistical analysis was performed using the MedCalc 18.2.1 (MedCalc Software Ltd, Acacialaan 22, 8400 Ostend, Belgium) software package.

Results

Baseline demographic data

Altogether, 137,126 images of 5913 coronary angiographic runs from 2407 patients were used for the development of the CNN model, comprising 2543 LAD, 1538 LCx, and 1832 RCA runs. The independent sample was used to assess the feasibility of the CFR_{auto} and its agreement with the CFR_{manual}, which consisted of 149 paired angiographies from 138 patients. Clinical and lesion characteristics of the independent sample are presented in Tables 1 and 2, respectively.

Table 1. Baseline clinical characteristics (n = 138).

Age [years]	63.7 ± 9.2
Male	108 (78.2)
Body mass index [kg/m^2]	26.7 (24.2–29.5)*
Hypertension	79 (57.2%)
Diabetes mellitus	37 (29.1%)*
Cardiovascular history:	
Prior myocardial infarction	38 (27.5%)
Prior PCI	50 (36.2%)
Prior CABG	5 (3.6%)

Values are mean ± standard deviation, number (%) or median (interquartile range). *Body mass index missing in 4 patients, diabetes mellitus missing in 11 patients; CABG — coronary artery bypass surgery; PCI — percutaneous coronary intervention

Table 2. Baseline lesion characteristics (n = 149).

Index artery:	
Left anterior descending artery	85 (57.0%)
Left circumflex artery	34 (22.8%)
Right coronary artery	30 (20.1%)
Percent diameter stenosis [%]	46.3 ± 8.2
Minimum lumen diameter [mm]	1.52 ± 0.36
Reference vessel diameter [mm]	2.82 ± 0.46

Values are number (%) and mean ± standard deviation.

Segmentation performance of the CNN

The segmentation performances of the proposed CNN model were good in all epicardial coronary arteries by 5-fold cross-validation, with mean dice coefficients values of 0.780 ± 0.007, 0.722 ± ± 0.005, and 0.758 ± 0.003 for LAD, LCx, and RCA, respectively (Table 3). Figure 4 shows paradigmatic examples of the segmentation results for different vessels during contrast injection. Figure 5 shows some unsuccessful CFR_{auto} computations.

Feasibility of automatic CFR analysis

CFR_{auto} computation was successful in 136 out of 149 vessels (feasibility 91.3%). Unsuccessful CFR_{auto} computations were due to poor visualization of contrast dye flowing (n = 7), missegmentation of the catheter (n = 4), interposition of other anatomic structures (n = 1), and unusual angiographic view (n = 1).

Correlation and agreement analysis

The average value of CFR_{auto} was 1.49 ± ± 0.54. Moderate correlation ($r = 0.51$, $p < 0.001$) was observed between CFR_{auto} and CFR_{manual}, with a slope 0.511 and an intercept 0.857 in the linear regression (Fig. 6A). CFR_{auto} showed moderate agreement with CFR_{manual} (mean difference = 0.12 ± ± 0.53, $p < 0.001$, ICCa = 0.50; 95% confidence interval [CI] 0.36–0.62) (Fig. 6B). Inter- and intraobserver variability in CFR_{manual} calculation were 0.09 ± 0.74 and 0.03 ± 0.42, with ICCa values of 0.62 (95% CI 0.41–0.76) and 0.71 (95% CI 0.54–0.83), respectively.

Analysis time of automatic CFR computation

The average analysis time for computation of CFR per vessel was 18.1 ± 10.3 s on an off-the-shelf workstation equipped with a 6-core Intel i7-8750H processor (Intel Corporation, Santa Clara, CA, USA; 2.2 GHZ), NVIDIA GeForce GTX 1050Ti graphics card (NVIDIA, Santa Clara, CA, USA), and 16 GB of RAM.

Table 3. Segmentation performance of the proposed model on left anterior descending (LAD), left circumflex (LCx), and right coronary artery (RCA) vessels using 5-fold cross-validation.

	Dice	Precision	Recall	F1
LAD	0.780 ± 0.007	0.763 ± 0.004	0.919 ± 0.004	0.834 ± 0.002
LCx	0.722 ± 0.005	0.748 ± 0.004	0.849 ± 0.005	0.796 ± 0.003
RCA	0.758 ± 0.003	0.777 ± 0.006	0.893 ± 0.004	0.831 ± 0.002

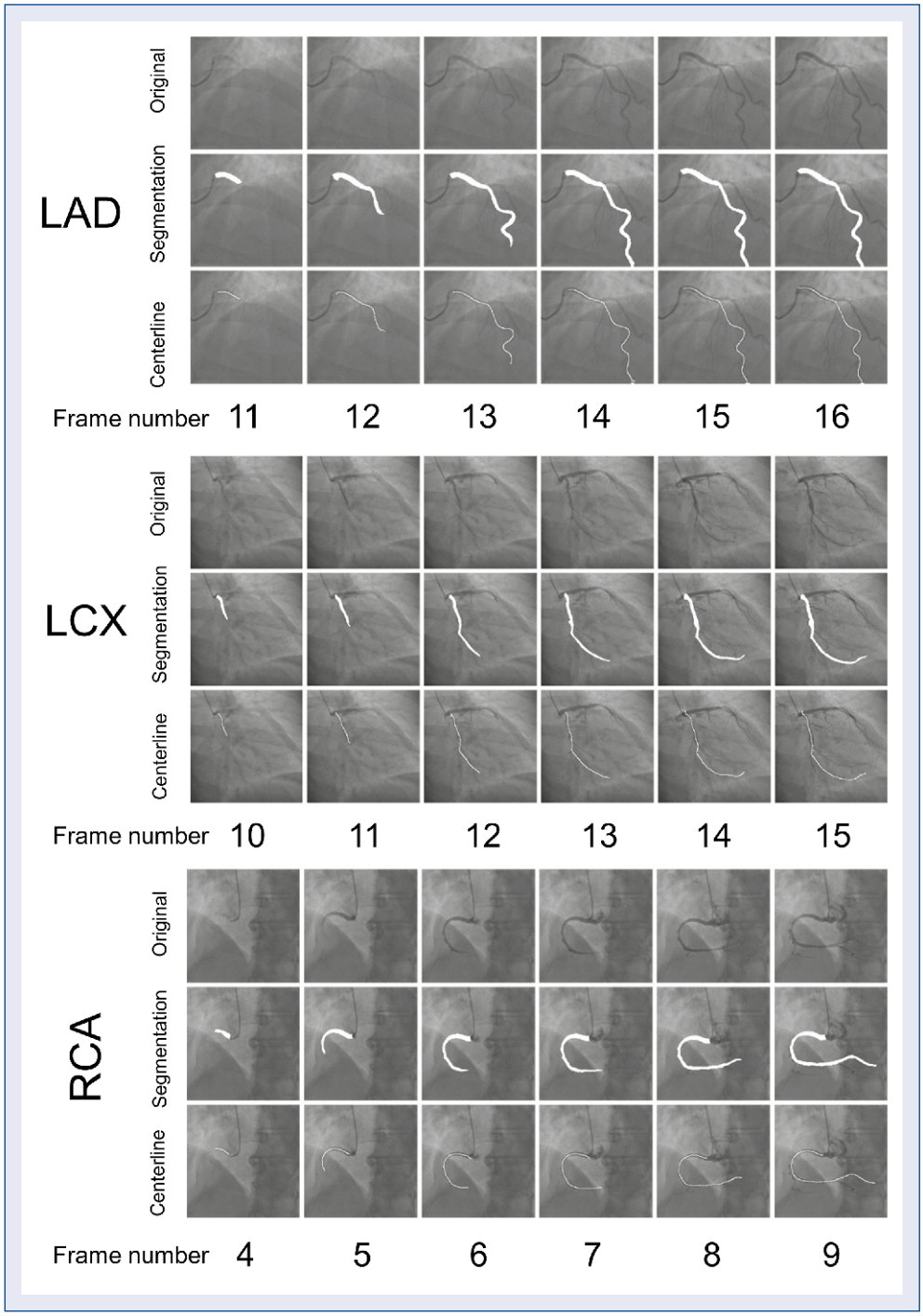

Figure 4. Segmentation results of left anterior descending (LAD), left circumflex (LCx), and right coronary artery (RCA). The first row of each group is the original image, the second row is the segmentation result, and the third row is the extracted vessel centerline. The white area is the segmentation mask and centerline mask.

Discussion

To the best of our knowledge, this is the first study validating a novel method based on artificial intelligence for automatic CFR computation from coronary angiography. The key findings of the present study are as follows: 1) The CNN model showed good performance in segmentation of the main coronary arteries from angiographic loops, 2) Automatic CFR calculation from coronary angiography is feasible in 91.3% of cases; 3) Automatic CFR computation showed moderate agreement

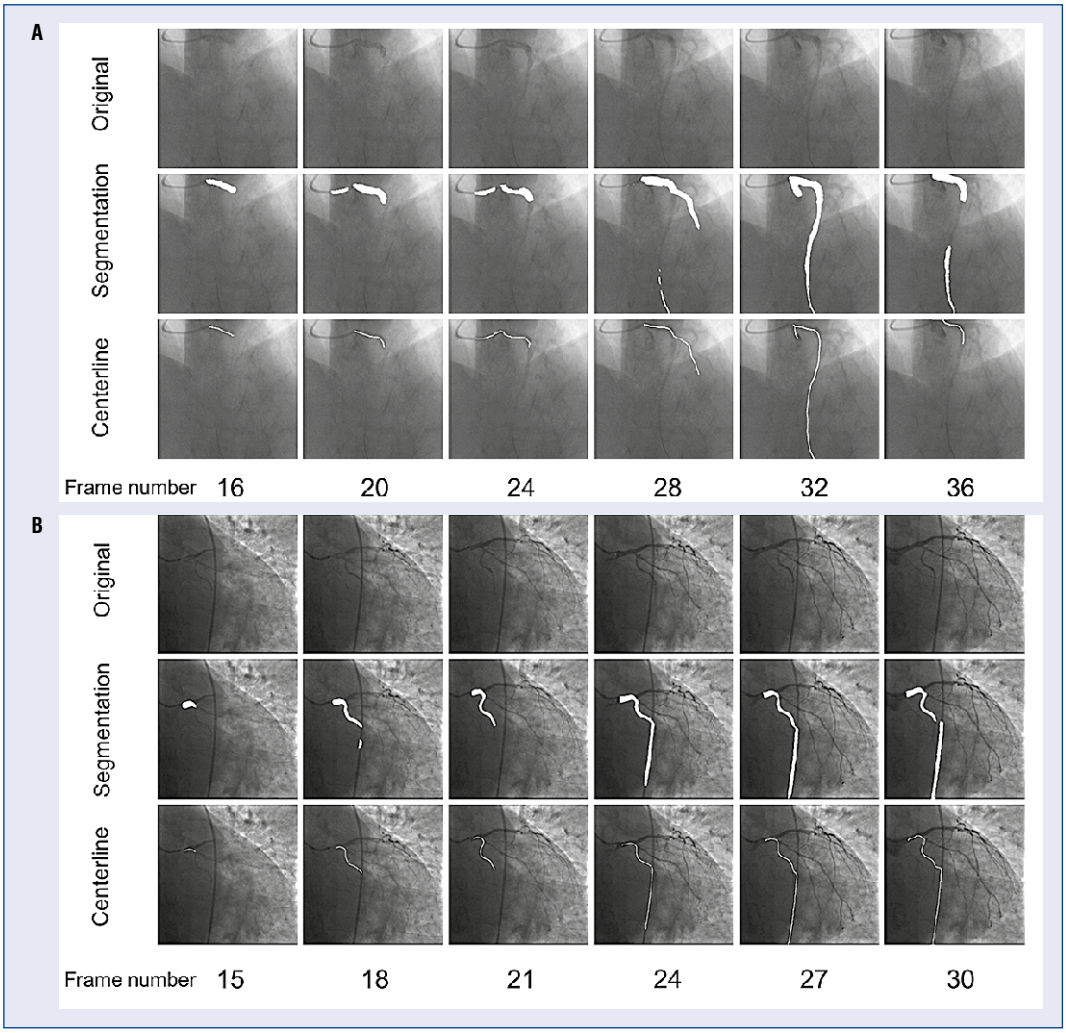

Figure 5. Paradigmatic cases of unsuccessful automatic coronary flow reserve computations. The first row of each group is the original image, the second row is the segmentation result, and the third row is the extracted vessel centerline. Common mechanisms for failure are poor visualization of contrast dye (**A**), and mis-segmentation of the catheter (**B**) or of other anatomic structures.

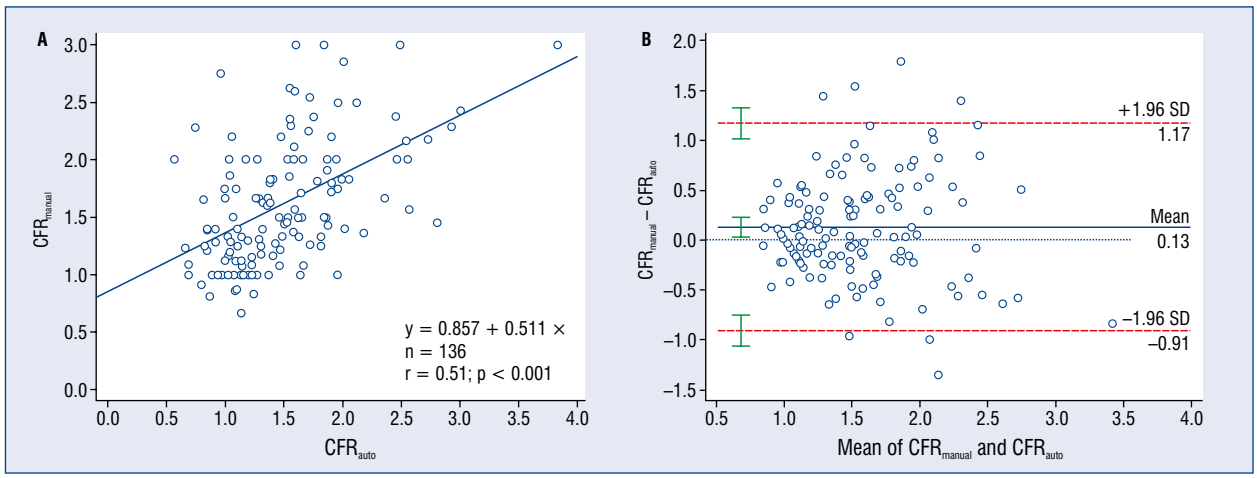

Figure 6. Correlation and agreement between automatic coronary flow reserve (CFR_{auto}) and frame-counting CFR (CFR_{manual}).

with conventional manual CFR calculation based on TIMI frame count.

Physiology-guidance has consistently proved to result in better clinical outcomes than classical anatomic-guidance for the treatment of epicardial coronary disease in different clinical scenarios [1–3, 27, 28]. Nonetheless, patients with microvascular disease have historically been neglected because of the scarce availability of methods to assess microcirculatory function. The access to positron emission tomography, Doppler wire, or thermodilution remains limited in most cardiology departments worldwide, so patients with microvascular dysfunction are often denied a diagnosis. The cases are instead considered non-cardiologic and are referred for endless gastroenterological or psychiatric studies, thus resulting in considerable frustration and depression, together with unnecessary costs for the health systems. The evidence on the prognostic relevance of microcirculatory dysfunction is currently compelling [8], and therefore the need to generalize its evaluation is as unmet. A cost-effective angiography--based method to estimate CFR could exponentially increase the availability of microvascular assessment, without additional wiring or prolongation of the procedure. Some groups have proposed angiography-based computational methods to assess the index of microvascular resistance (IMR), a parameter to specifically appraise the microcirculatory function, finding acceptable agreement with thermodilution [19]. Our study follows a similar approach, although it focuses on CFR and developing a model of artificial intelligence to simplify the calculation in the cathlab. The high feasibility of the proposed method (91.3%) suggests a broad practical applicability. In this first step, the CNN model focused on CFR calculation, a parameter depending on both epicardial and microvascular functions, although other parameters to assess microvascular dysfunction, like IMR, could similarly be derived in future studies following a similar rationale.

The applications of artificial intelligence in the field of coronary artery segmentation from angiography are expanding. Different CNN architectures have been proposed to segment the entire coronary tree [29, 30] or the main vessel [31]. Of note, our segmentation task is unique because all frames of the angiographic run covering the entire contrast injection were segmented. At early phases of the contrast injection, the main vessels appear short in length and the definition of the borders is poorer than at phases of complete filling, thus increasing the segmentation difficulty and potentially affecting the evaluation of the overall segmentation performance.

For all procedures involving artificial intelligence, the first mandatory step is the validation vs. the same procedure manually performed by expert human operators. Thus, the current study validated an automatic method to calculate CFR, based on artificial intelligence, vs. the same manual computational method. This was not a validation of the computational method vs. an invasive standard, as previous studies have done [19, 20]. This kind of validation will be pursued in future studies once the CNN model has been fine-tuned, and it may provide interesting complementary information. It might help to understand the moderate agreement between manual and automatic methods for CFR calculation, notwithstanding the excellent performance of the CNN model for the segmentation of the vessels. The correlation between CFR_{auto} and CFR_{manual} is moderate. However, it is important to note that the manual computational method based on frame count is not the clinical standard for CFR measurement. The reproducibility of CFR_{manual} is only moderate, as indicated by the inter- and intra-observer ICCa of 0.62 (95% CI 0.41–0.76) and 0.71 (95% CI 0.54–0.83), respectively. Moreover, the values found in linear regression with a slope and an intercept that considerably deviated from 1 and 0, respectively, do not permit us to rule out proportional or constant bias. This may be because the manual operators tend to count frames outside the steady perfusion period, especially at hyperemia and at high flow velocities, resulting in higher flow velocities and CFR values than the automatic method, especially at the high extreme of the scale. However, the CNN model might be more consistent, accurate, and reproducible than the corresponding manual method, as in other CNN models [32]. Therefore, we consider that the variability of CFR_{manual} played a major role in the moderate correlation between CFR_{auto} and CFR_{manual}. The validation of the method vs. an invasive standard might show that the CNN models outperform the manual calculation or otherwise unravel details of the workflow that might eventually deserve further attention.

Limitations of the study

The CNN model focused exclusively on the calculation of CFR, a parameter that depends on both epicardial and microvascular function. Other parameters, like IMR, are more specific to assessing microvascular dysfunction, and they could be similarly derived in future studies, following a similar rationale. As in other computational meth-

ods of physiology, this approach loses accuracy in some anatomical scenarios, such as chronic total occlusions or bypass grafts, and might have limited feasibility in cases of extreme foreshortening or vessel overlap, which were excluded from the current study [13–15, 17, 33].

Conclusions

Automatic CFR computation using coronary angiography was feasible and showed a moderate agreement with the manual computational method based on frame count. Image-derived CFR calculation may facilitate wider adoption of coronary physiology and the assessment of microvascular function in routine clinical practice.

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Angio-computed tomography reveals differences in the anatomy of renal arteries in resistant hypertension patients qualified for renal denervation versus pseudo-resistant hypertensive subjects

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Abstract

Background: *Renal denervation is a novel therapeutic option in resistant hypertension (RHT). The anatomy of renal arteries and the presence of additional renal arteries are important determinants of the effect of the procedure. The aim of this study was to assess the anatomy of renal arteries using angio-computed tomography in patients with RHT, who were qualified for renal denervation.*

Methods: *We analyzed angio-computed tomography scans of the renal arteries of 72 patients qualified for renal denervation. We divided the study population into two groups: a resistant hypertension group (RHT) and a pseudo-resistant hypertension group (NRHT). The biochemical and endocrine diagnostic procedures were performed to rule out secondary hypertension. We analyzed the morphology, the diameters, and the number of additional renal arteries.*

Results: *In both groups, we found additional renal arteries (ARN). ARN were more frequent in RHT than in patients with non-resistant hypertension (48.4% vs. 24.3%; $p < 0.05$). They were present more often on the left side (18 left side vs. 7 right side). The ARNs were longer than main renal artery — left side 41.7 ± 12.1 mm vs. 51.1 ± 11.8 mm, right side 49.2 ± 14.5 mm vs. 60 ± ± 8.6 mm, respectively ($p < 0.05$). The diameters of ARN were similar in both groups. In the group of patients with RHT the number of ARN was significantly higher ($p < 0.04$).*

Conclusions: *The ARNs occur more often in patients with RHT. It seems that there is no connection between the resistance of hypertension and the diameters of renal arteries.* (Cardiol J 2023; 30, 3: 379–384)

Key words: renal denervation, renal artery anatomy, resistant hypertension

Introduction

Resistant hypertension (RHT) is defined as an in-office blood pressure (BP) of at least 140 mmHg systolic (SBP) and/or 90 mmHg diastolic (DBP) in patients on maximal doses of three or more antihypertensive medications, including a diuretic [1]. Several studies estimate that RHT occurs in 10–15% of patients with hypertension [2–4]. The definition excludes secondary hypertension, white-coat hypertension, and other causes of uncontrolled BP, such as poor adherence or non-optimal medi-

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cation regimen and dosing. The latter situation is referred to as pseudo-resistant hypertension.

There are few data on the pathogenesis and causes of true-resistant hypertension. A possible explanation is that renal artery anatomy and/or function differ between patients with RHT and healthy individuals [5, 6]. One novel approach to the treatment of RHT is renal artery denervation (RDN). Although the safety of this technique has been demonstrated in several trials, its effectiveness is still being evaluated [7–10]. The anatomy of renal artery is crucial for the effect of the procedure.

Renal arteries arise from the abdominal aorta at the level of the L1/L2 vertebra. The right renal artery is usually longer than the left due to the position of the aorta, inferior vena cava, and right kidney. At the level of the renal hilum, renal arteries usually divide into five segmental arteries that supply independent renal segments. To qualify for RDN, patients must undergo an angiogram or angio-computed tomography (CT) of the renal arteries to assess their diameters and exclude abnormalities.

Studies suggest that several factors impact the efficacy of RDN [5, 6, 11]. After the unsatisfying results of the SYMPLICITY HTN-3 trial, even more effort was put into identifying the perfect candidates for RDN, who would gain the most from the procedure. The aim of this study was to assess renal artery anatomy using angio-CT in patients with RHT, who qualified for RDN.

Methods

This was a single-center study to assess the anatomy of renal arteries in patients initially diagnosed with RHT, who were referred for RDN. The group of 72 patients initially screened for eligibility for renal denervation, after exclusion of secondary hypertension and optimization of pharmacological treatment (including supervised drug administration), was dived into two groups:

— True-resistant hypertension group (RHT; n = 31) — resistant hypertension (defined as SBP > 140 mmHg and/or DBP > 90 mmHg despite three or more antihypertensive medications, including a diuretic, at a maximum tolerable dose);
— Non-resistant hypertension (pseudo-resistant hypertension; NRHT; n = 41) — patients in whom improving adherence or pharmacotherapy adjustment (dose increase and/or adding another antihypertensive agent) normalized the BP values.

Blood pressure measurements were obtained by taking the average of three office-based measurements and 24-hour ambulatory BP monitoring. Biochemical and endocrine diagnostic procedures were performed to rule out secondary hypertension. In all patients the following conditions were excluded: renal artery stenosis, Cushing disease, pheochromocytoma, primary hyperaldosteronism, hyperthyroidism, and coarctation of the aorta. Transthoracic echocardiography was performed using a Vivid E9 ultrasound system equipped with an M5S-D transducer (GE Healthcare).

Computed tomography scans were taken using a 64-row multi-slice CT scanner (Toshiba). CT data were analyzed on a Vitrea post-processing workstation (Vital Images) using two- and three-dimensional viewing modes and evaluated by two observers who reached a consensus.

The main renal artery was defined as the largest artery arising from the aorta to the kidney; other arteries were defined as additional renal arteries. We counted the number of additional renal arteries and measured the length, area of the ostium, diameter of the ostium (in anterior-posterior and superior-inferior axes), area of branching, and diameter of branching (in anterior-posterior axis and superior-inferior axis) of the main and additional renal arteries. Statistical analysis was performed using STATISTICA software. Values were expressed as mean (standard deviation) in the case of normal distribution or median (Q1;Q3) in the case of non-normal distribution. To compare quantitative variables the t-test (normal distribution) and U-Mann-Whitney test (non-normal distribution) were used.

Within the group with confirmed RHT, 15 patients who fulfilled the criteria and had no additional renal arteries underwent RDN using the Simplicity (Medtronic, USA) system. Clinical inclusion criteria for RND were as follows: age of 18+ years, uncontrollable treatment-resistant hypertension (defined as SBP > 160 mmHg despite three or more antihypertensive medications, including a diuretic, at a maximum tolerable dose, or ≥ 150 mmHg in patients with type 2 diabetes), main renal arteries with diameter > 4 mm, and trunk length of the main artery > 20 mm. The results of long-term follow-up were previously published [12].

The study was approved by the Ethics Committee and conformed to the Declaration of Helsinki. Informed written consent was obtained from all patients enrolled in the study.

Table 1. Baseline characteristics of the study groups.

Characteristics	Resistant hypertension (n = 31)	Non-resistant hypertension (n = 41)
Age (years ± SD)	66 ± 8.5	62 ± 12
Male	15 (48.3%)	21 (51.2%)
Body mass index [kg/m^2]	30.9 ± 4.1	29.8 ± 3.5
Medical history		
Type 2 diabetes	10 (32.3%)	14 (34.1%)
Left ventricular ejection fraction [%]	60.3 ± 5.5	60.7 ± 4.3
Family history of hypertension	22 (70.9%)	26 (63.4%)
No. of antihypertensive medication	5.03 ± 0.8	4.3 ± 0.6
Mean office systolic/diastolic BP [mmHg]	202 ± 31.5/107 ± 14.2	180.8 ± 19.9/104 ± 13.9
Mean 24 hours ambulatory systolic/diastolic BP [mmHg]	150.8 ± 12.9/87.2 ± 12.8	148.8 ± 10.7/85.8 ± 10.3

BP — blood pressure; SD — standard deviation

Results

Baseline characteristics of studied groups are presented in Table 1. Patients did not differ with regard to age, sex distribution, body mass index, and medical history of hypertension and diabetes. Mean office SBP values were non-significantly lower in the non-resistant group (202 ± 31.5 vs. 180.8 ± 19.9; p = NS); mean office DBP and ambulatory BP monitoring values were similar. The number of used antihypertensive drugs was higher in true RHT, but NRHT patients declared on average 4.3 medications.

The diameters of the main and additional renal arteries did not differ significantly between groups (Table 2). The right main renal artery was significantly longer than the left main renal artery in both groups (48.1 vs. 40.3 mm and 50.3 vs. 42.7 mm, respectively; $p < 0.05$).

Additional renal arteries (Figs. 1A–C) were observed more frequently in patients with RHT (15 patients, 48.4%) than in patients with NRHT (10 patients, 24.3%; $p < 0.05$). Moreover, patients with RHT had more additional renal arteries than patients with NRHT ($p < 0.04$). Additional renal arteries were present more often on the left side than on the right side (18 vs. 7 arteries, respectively; $p < 0.05$), were longer than main renal arteries (left side: 51.1 ± 11.8 vs. 41.7 ± 12.1 mm and right side: 59.9 ± 8.6 vs. 49.2 ± 14.5 mm, respectively; $p < 0.05$), and had smaller branching and ostium areas (Table 3).

We assessed the eligibility of all study patients for RDN using the SYMPLICITY and SPYRAL systems. The SYMPLICITY system requires that the main renal arteries be > 20 mm in length and > 4 mm in diameter; in our study, 52 (72%) patients had this anatomy. The SPYRAL system requires that the main renal arteries be > 20 mm in length and > 3 mm in diameter; in our study, 62 (86%) patients had this anatomy.

We also analyzed the relationship between the main renal artery anatomy and the outcome of RDN — data published previously [12]. We found no correlations between the anatomy or diameters of the main renal arteries and the efficacy of RDN at 24-month follow-up.

Discussion

Awareness of renal artery anatomy before RDN is crucial for the safety and success of the procedure. Von Achen et al. [13] reported that the anatomy of renal arteries impacts the outcomes of RDN. In the present study, the dimensions of the main renal arteries were similar between patients with and without resistant hypertension. However, additional renal arteries were longer and had smaller diameters than the main renal arteries, consistent with an earlier report [14].

In our population, we found that additional renal arteries were more common in patients with RHT than in patients with NRHT, which is similar to the result of a previous study [11]. Lauder et al. [14] showed that renal artery anatomy differs between hypertensive and normotensive subjects (accessory renal arteries in 22% vs. 9%, respectively) but does not differ between patients with poor and good BP control. Also, VonAchen et al. [13] reported that the presence of additional renal arter-

Table 2. The diameters of main and additional renal arteries in resistant and non-resistant hypertension subjects.

Characteristics	Resistant hypertension (n = 31)	Non-resistant hypertension (n = 41)	P
Right renal artery [mm]			
Length — mean (SD)	48.1 (15.2)	50.3 (14.1)	NS
Area of the ostium — median (Q1;Q3)	30.9 (22.6;42.3)	33.2 (28.3;39.8)	NS
AP ostium — median (Q1;Q3)	6.4 (5.2;7.9)	6.9 (5.7;7.8)	NS
SI ostium — median (Q1;Q3)	5.2 (4.6;7.0)	5.5 (4.6;6.9)	NS
Branching area — median (Q1;Q3)	22.7 (19.6;29.3)	26.2 (18.7;34.9)	NS
AP branching — mean (SD)	5.38 (1.46)	5.56 (1.53)	NS
SI branching — mean (SD)	4.85 (1.42)	5.07 (1.36)	NS
Left renal artery [mm]			
Length — mean (SD)	40.3 ± 10.7	42.7 ± 13.1	NS
Area of the ostium — median (Q1;Q3)	30.3 (24.7;47)	34.9 (27.8;48)	NS
AP ostium — mean (SD)	6.5 (1.8)	6.7 (2)	NS
SI ostium — mean (SD)	5.82 (2.1)	6.2 (1.9)	NS
Branching area — median (Q1;Q3)	22.4 (18.8;25.1)	24.1 (17.5;31.2)	NS
AP branching — mean (SD)	5.2 (1.1)	5.25 (1.4)	NS
SI branching —– median (Q1;Q3)	4.6 (4;5.4)	4.8 (4;6.3)	NS
Right additional renal arteries [mm] — mean (SD)	**N = 4**	**N = 3**	
Length	59.55 (10.6)	60.1 (9.1)	NS
Area of the ostium	11.8 (1.9)	13.2 (3.7)	NS
AP ostium	3.35 (1)	3.6 (1)	NS
SI ostium	2.85 (0.5)	3.3 (0.5)	NS
Branching area	9.9 (0.2)	11 (4.3)	NS
AP branching	3 (0.6)	2.9 (0.9)	NS
SI branching	2.6 (0.3)	3 (0.4)	NS
Left additional renal arteries [mm] — mean (SD)	**N = 11**	**N = 7**	
Length	52.9 (12.9)	49.9 (11.6)	NS
Area of the ostium	11.6 (3.2)	15.3 (6.03)	NS
AP ostium	4.1 (0.64)	4.4 (2.2)	NS
SI ostium	3 (0.58)	3.5 (1.7)	NS
Branching area	12.8 (4.3)	12.45 (2.5)	NS
AP branching	3.9 (0.8)	3.7 (0.9)	NS
SI branching	3.4 (1.1)	3 (0.78)	NS

AP — anterior posterior dimension; SI — superior inferior dimension; SD — standard deviation

ies is twice as common in patients with RHT than in healthy individuals. In our observation, additional renal arteries were more frequent in the RHT group than in patients with NRHT. Considering that the accessory renal arteries are a potential cause of renovascular hypertension [15], identifying them reveals a potential cause, while proper anatomy assessment makes it a therapeutic target at least in a fraction of patients with RHT.

These additional renal arteries had obviously different anatomy and diameters compared to those of main renal arteries, and not all additional renal arteries were eligible for RDN. Our findings also suggest that the SPYRAL system for RDN may be suitable for a larger number of patients due to the smaller dimensions of the catheter.

The ablation of additional renal arteries has been suggested to increase the efficacy of RDN [6].

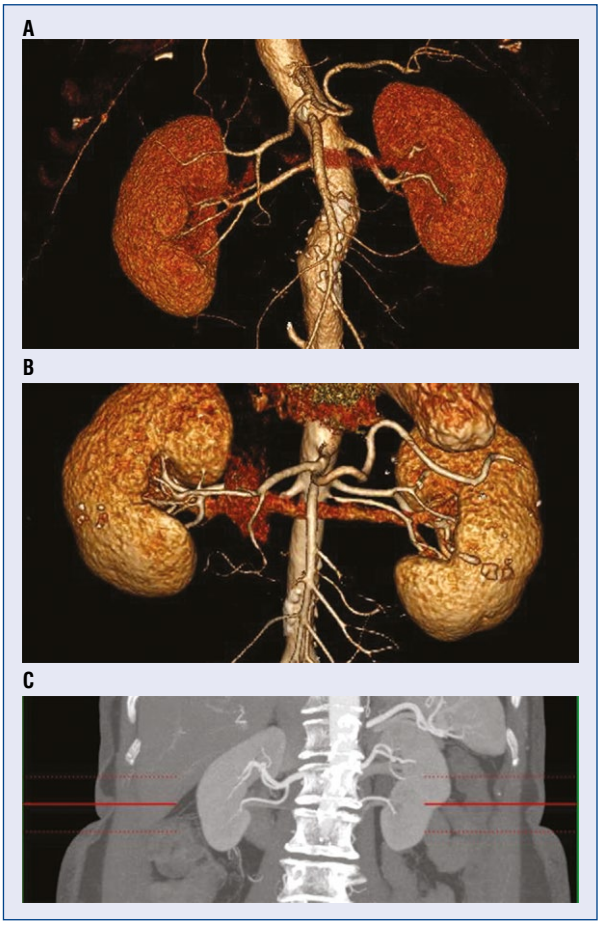

Figure 1. A–C. Additional renal arteries in patients from our study group.

However, denervation of additional renal arteries is not always possible due to their small diameter. Therefore, further development of catheters may enable the targeting of almost all accessory renal arteries in the future [16, 17].

In contrast to our study and the above-cited reports, Lauder et al. [14] do not report a significant difference between in the frequency and the number of additional renal arteries in RHT. This may be caused by several factors, one of which being the modality. Commonly used renal artery angiography is more likely to miss small additional renal arteries with non-typical ostium location than angio-CT. Our report is the first to present the use of angio-CT for renal artery assessment in a highly selective group of true-resistant vs. pseudo-resistant hypertension.

Our results suggest that the efficacy of RDN could be improved by treating patients with favorable renal artery anatomy, and attempting to denervate all renal arteries, including additional arteries.

Limitations of the study

The major limitation of the study is a low number of analyzed cases and a lack of healthy (non-hypertensive) control subjects for comparison of the results. However, the number of RHT (and pseudo-RHT) patients qualified for RDN and is low, even in high reference centers.

Table 3. Comparison of the diameters of main and additional renal arteries.

Characteristics	Main renal arteries	Additional renal arteries	P
Right side [mm] — mean (SD)			
Length	49.2 (14.5)	59.9 (8.64)	0.057
Area of the ostium	34.77 (12.82)	12.8 (3.23)	**< 0.001**
AP ostium	6.63 (1.77)	3.53 (0.95)	**< 0.001**
SI ostium	5.75 (1.86)	3.18 (0.53)	**< 0.001**
Branching area	25.9 (10.23)	10.7 (3.52)	**< 0.001**
AP branching	5.48 (1.49)	2.92 (0.83)	**< 0.001**
SI branching	4.98 (1.38)	2.89 (0.44)	**< 0.001**
Left side [mm] — mean (SD)			
Length	41.68 (12.1)	51.05 (11.8)	**0.004**
Area of the ostium	37.1 (14.59)	13.87 (5.34)	**< 0.001**
AP ostium	6.62 (1.92)	4.3 (1.76)	**< 0.001**
SI ostium	6.01 (2.03)	3.34 (1.39)	**< 0.001**
Branching area	24.88 (9.93)	12.59 (3.22)	**< 0.001**
AP branching	5.25 (1.3)	3.79 (0.89)	**< 0.001**
SI branching	4.93 (1.52)	3.19 (0.92)	**< 0.001**

AP — anterior posterior dimension; SI — superior inferior dimension; SD — standard deviation

Conclusions

Additional renal arteries occur more often in patients with resistant hypertension. The additional renal arteries have different anatomy and diameters in comparison to the main renal arteries.

Conflict of interest: None declared

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Impact of the initial clinical presentation on the outcome of patients with infective endocarditis

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Abstract

Background: *Infective endocarditis (IE) is a life-threatening disease. Despite advancements in diagnostic methods, the initial clinical presentation of IE remains a valuable asset. Therefore, the impact of clinical presentation on outcomes and its association with microorganisms and IE localization were assessed herein.*

Methods: *This retrospective study included 183 patients (age 68.9 ± 14.2 years old, 68.9% men) with definite IE at two tertiary care hospitals in Belgium. Demographic data, medical history, clinical presentation, blood cultures, imaging data and outcomes were recorded.*

Results: *In-hospital mortality rate was 22.4%. Sixty (32.8%) patients developed embolism, 42 (23%) shock, and 103 (56.3%) underwent surgery during hospitalization. Shock at admission predicted embolism during hospitalization (odds ratio [OR] 2.631, 95% confidence interval [CI] 1.119–6.184, p = 0.027). A new cardiac murmur at admission predicted cardiac surgery (OR 1.949, 95% CI 1.007––3.774, p = 0.048). Methicillin resistant Staphylococcus aureus predicted in-hospital mortality and shock (p = 0.005, OR 6.945, 95% CI 1.774–27.192 and p = 0.015, OR 4.691, 95% CI 1.348–16.322, respectively). Mitral valve and aortic valve IE predicted in-hospital death (p = 0.039, OR 2.258, 95% CI 1.043–4.888) and embolism (p = 0.017, OR 2.328, 95% CI 1.163–4.659), respectively.*

Conclusions: *In this retrospective study, shock at admission independently predicted embolism during hospitalization in IE patients. Moreover, a new cardiac murmur at admission predicted the need for cardiac surgery. This emphasizes the importance of a comprehensive initial clinical evaluation in combination with imaging and microbiological data, in order to identify high-risk IE patients early.*
(Cardiol J 2023; 30, 3: 385–390)

Key words: infective endocarditis, clinical presentation, cardiac surgery, in-hospital mortality

Introduction

Despite improvements in medical and surgical therapy, infective endocarditis (IE) remains a deadly disease, with a vast array of potential complications [1, 2]. While imaging, particularly echocardiography, is the main diagnostic tool in patients with suspected IE [2], the initial clinical presentation remains a valuable asset. However, clinical presentation of IE can be highly variable and

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non-specific, influenced by predisposing conditions, causative microorganisms and IE localization [3, 4]. This could cause a diagnostic delay with increased complications and mortality [5]. Therefore, the present study sought to assess the impact of initial clinical presentation on outcome of IE patients during hospitalization and its association with microorganisms and IE localization.

Methods

Patients with definite IE diagnosed by the modified Duke criteria [2] were retrospectively included in a comprehensive database from 2015 to 2018. This study was conducted at two tertiary care hospitals in Belgium: UZ Brussel and AZ Maria Middelares Gent.

Demographic data, medical history, clinical presentation at admission, blood cultures, imaging data and outcomes were recorded. Transthoracic and transoesophageal echocardiography had been performed in all patients.

Admission data was defined as data from the first 24 hours of hospitalization.

Outcomes during hospitalization (more than 24 h after admission) included: in-hospital mortality, embolic events (cerebro-vascular and non-cerebro-vascular, diagnosed with imaging modalities), shock (cardiogenic or septic) and cardiac surgery.

Cardiac surgery was performed following current guideline recommendations [2].

Statistical analysis

Continuous variables were expressed as mean ± standard deviation. Categorical variables were expressed as percentages. Comparison of continuous variables was done with the Student t-test or Mann–Whithney U test. Comparison of binomial variables was done with a χ^2 or the Fisher exact test. In order to evaluate potential predictors of outcomes, a multivariate logistic regression modeling was used. Variables with a p-value < 0.10 in the univariate analysis along with variables of known clinical importance were included in the multivariate analysis. Statistical significance was considered for a p-value < 0.05. Statistical analyses were conducted using IBM SPSS Statistics (Version 26.0.0, SPSS, Chicago, IL, USA).

Ethical approval

The study was approved by the local Ethics Committee of both hospitals and was carried out in accordance with the ethical principles for medical research involving human subjects established by the Helsinki Declaration, protecting the privacy of all participants, as well as the confidentiality of their personal information.

Table 1. Baseline and demographic characteristics.

	Total (n = 183)
Age [year]	69.0 ±14.2
Male	68.9%
Medical history	
Previous endocarditis	11 (6.0%)
Heart failure	25 (13.7%)
Coronary artery disease	43 (23.5%)
Atrial fibrillation	41 (23.3%)
Cardiac device	25 (13.7%)
Arterial hypertension	86 (47.0%)
Diabetes mellitus	16 (8.7%)
Previous stroke	24 (13.1%)
Chronic kidney disease	40 (21.9%)
Cancer	23 (12.6%)
Valve disease	93 (50.8%)
History of cardiac surgery/ /invasive interventions	86 (47.0%)
History of non-cardiac invasive intervention in the last 6 months	28 (15.3%)
Medication	
Anticoagulants	50 (27.3%)
Acetylsalicylic acid	62 (33.9%)

Results

Baseline population characteristics

One hundred eighty-three patients with definite IE (age 69 ± 14.2 years old, 68.9% males) were included. 51% of patients had previous valvular heart disease. Baseline characteristics are shown in Table 1.

At admission, clinical presentation consisted primarily of fever, general non-wellbeing and dyspnea. 61 (33.3%) patients presented with a new cardiac murmur at admission. 28 (15.3%) patients presented with shock and 33 (18%) patients had embolic events at admission. Initial clinical presentation can be found in Table 2.

Microbiological data are presented in Table 3. An average of 3.5 ± 2.3 antibiotic therapies was used per patient.

Echocardiography at admission showed native aortic valve IE in 56 (30.6%) and aortic valve prosthesis IE in 37 (20.2%) patients, among the 51 (27.8) patients with aortic valve prosthesis.

Table 2. Clinical presentation at admission.

	Total (n = 183)
Fever	114 (62.3%)
General non-wellbeing	56 (30.6%)
Dyspnea	38 (20.8%)
Cough	14 (7.7%)
Acute pulmonary edema	4 (2.2%)
Chest pain	6 (3.3%)
Embolic events	33 (18.0%)
Dizziness	6 (3.3%)
Syncope	8 (4.4%)
Other	57 (31.1%)
Shock:	28 (15.3%)
Cardiogenic shock	10 (5.4%)
Septic shock	18 (9.8%)
Congestive heart failure	15 (8.2%)
New cardiac murmur	61 (33.3%)
Osler noduli	4 (2.2%)
Janeway lesions	7 (3.8%)
Roth spots	2 (1.1%)
Splinter hemorrhages	5 (2.7%)
Conjunctival hemorrhages	2 (1.1%)

Table 3. Microbiological data.

	Total (n = 183)
Staphylococcus aureus	45 (24.6%)
Methi – S Staphylococcus aureus	34 (18.6%)
Methi – R Staphylococcus aureus	11 (6%)
Coagulase negative Staphylococcus	27 (14.8%)
Methi – S Staphylococcus CN	13 (7.1%)
Methi – R Staphylococcus CN	14 (7.7%)
Streptococcus viridans	50 (27.3%)
Enterococcus	21 (11.5%)
Streptococcus gallolyticus	21 (11.5%)
Other	17 (9.3%)
Coxiela burnetii IgG anti phase I > 1:800	1 (0.5%)
Blood culture negative	5 (2.7%)

Methi – S — methicillin sensitive; Methi – R — methicillin resistant; CN — coagulaso-negative

Native mitral valve IE was found in 70 (38.2%) patients and prosthetic mitral valve IE in 10 (5.4%) patients, among them 14 (7.6%) patients had a mitral valve prosthesis. 23 (12.5%) patients had multivalvular endocarditis.

Predictors of outcome

Univariate analysis is shown in Supplemental material (**Suppl. Table 1**). Multivariate analysis can be found in Table 4.

In-hospital mortality. In-hospital mortality rate was 22.4% (41 patients). Clinical presentation at admission was not predictive for in-hospital mortality. However, by multivariate analysis, both Methicillin resistant *Staphylococcus aureus* (MRSA) and mitral valve IE were independent predictors for in-hospital mortality (p = 0.005, odds ratio [OR] 6.945, 95% confidence interval [CI] 1.774–27.192 and p = 0.039, OR 2.258, 95% CI 1.043–4.888, respectively).

Embolic events. Sixty (32.8%) patients developed embolic events during hospitalization. Shock at admission independently predicted embolism (OR 2.631, 95% CI 1.119–6.184, p = 0.027). When adjusted by IE localization, aortic valve IE was also an independent predictor of embolic events (OR 2.328, 95% CI 1.163–4.659, p = 0.017).

Shock. Forty-two (23%) patients developed cardiogenic shock (16 patients) or septic shock (26 patients) during hospitalization. Initial clinical presentation was not predictive for shock. When

Table 4. Multivariate independent predictors of outcomes.

Outcomes	Predictor	Odds ratio	95% CI	P
In-hospital mortality	Age	1.035	1.004–1.067	0.028
	MRSA	6.945	1.774–27.192	0.005
	Mitral valve IE	2.258	1.043–4.888	0.039
Embolic events	Shock at admission	2.631	1.119–6.184	0.027
	Aortic valve IE	2.328	1.163–4.659	0.017
Shock	MRSA	4.691	1.348–16.322	0.015
Surgery	New cardiac murmur	1.949	1.007–3.774	0.048

MRSA — Methicillin resistant *Staphylococcus aureus*; IE — infective endocarditis; CI — confidence interval

adjusted for microorganisms, MRSA IE independently predicted shock during hospitalization (OR 4.691, 95% CI 1.348–16.322, p = 0.015).

Cardiac surgery. Surgery was performed in 103 (56.3%) patients. The presence of a new cardiac murmur at admission independently predicted the need for cardiac surgery (OR 1.949, 95% CI 1.007–3.774, p = 0.048).

Discussion

This retrospective study showed that: 1) A new cardiac murmur at admission independently predicted cardiac surgery; 2) Shock at admission was an independent predictor of embolic events during hospitalization; 3) MRSA infection was an independent predictor of in-hospital mortality and shock during hospitalization; 4) Mitral valve IE was an independent predictor of in-hospital mortality; 5) Aortic valve IE independently predicted embolic events during hospitalization.

In-hospital mortality

In-hospital mortality (22.4%) was comparable to previous studies, but remains unacceptably high despite optimal medical and surgical management [1, 6–8]. In this study, the initial clinical presentation was not predictive for in-hospital mortality, while previous studies found congestive heart failure and embolic events at admission to be predictive of in-hospital death [7–11]. Other recent studies found in-hospital development of heart failure and septic shock to be predictive of in-hospital mortality [12]. However, in this current analysis only the initial presentation at admission was considered.

When adjusting for causative microorganisms, MRSA was predictive of in-hospital mortality. Previously, *S. aureus* has been identified as a predictor of in-hospital mortality, but no distinction between MRSA and Methicillin-susceptible *Staphylococcus aureus* (MSSA) was made [5, 7, 8, 11]. Nonetheless, another previous, prospective study showed a statistically non-significant increased mortality in MRSA vs. MSSA IE [13].

Moreover, mitral valve IE was associated with increased in-hospital mortality, as previously described by Murdoch et al. [5]. Patient characteristics may be responsible for the worse outcome in mitral valve IE [14]. However, in this study, no association was found between mitral valve IE and characteristics such as causative microorganisms, age or other complications. Furthermore, other studies did not find a significant difference in mortality between aortic and mitral valve IE [15].

In the ESC-EORP European endocarditis registry, in hospital mortality was associated with the Charlson index, creatinine > 2 mg/dL, congestive heart failure, cerebral complication, perivalvular abscess, vegetation length and unperformed cardiac surgery (when indicated) by multivariate analysis [1]. No such associations were found in this retrospective series.

Embolic events

32.8% of IE patients developed an embolic event during hospitalization, which is higher than in the ESC-EORP European endocarditis registry (20.5%) [1] and the ICE cohort (23%) [5]. An initial presentation with shock (septic or cardiogenic) at admission was an independent predictor of embolic events. In shock, systemic inflammation, circulatory changes and hypercoagulopathy may be underlying contributors to the development of embolic events [16–18]. Shock-induced atrial fibrillation could also predispose to embolization [19]. Previous data have shown that septic shock increases the risk of stroke [18, 20]. In the Embolic Risk French calculator proposed by Hubert et al. [21], shock has not been analyzed as a possible predictor of embolic risk. Future research might be helpful to determine whether shock at admission could be incorporated into an adapted embolic risk calculator.

Additionally, aortic valve IE independently predicted embolic events during hospitalization, as also found in the ESC-EORP European endocarditis registry [1]. In contrast, Hubert et al. [21] and Thuny et al. [22] found embolic risk to be independent of valve localization. Vilacosta et al. [23] found embolization to be associated with mitral valve IE when vegetation size exceeds 10 mm. However, in this series there was no significant difference in vegetation size between aortic and mitral valve IE (13.4 ± 6.7 mm vs. 13.5 ± 5.8 mm, p = 0.949). Another study showed that embolism was more frequently seen in mitral prosthetic than aortic prosthetic valve thrombosis [24]. In this series, aortic valve prosthesis IE (20.2%) was more common than mitral valve prosthesis IE (5.4%).

In the ESC-EORP European endocarditis registry, in-hospital embolic events were also associated with staphylococcal infection [1]. A microbiological association could not be confirmed in this study. Thus, it remains uncertain why aortic valve IE was predictive of embolism in this series.

Shock

23% of IE patients developed shock (septic or cardiogenic) as a complication during hospitalization, compared to 16% in the ESC-EORP European endocarditis registry [1]. Other studies have shown a lower incidence for isolated septic shock [8, 25]. In this study, initial clinical presentation was not predictive of shock. In contrast, MRSA bacteriemia was an independent predictor of shock during hospitalization. Similarly, Olmos et al. [25] showed *S. aureus* to be and independent predictor of septic shock, without distinguishing between MRSA and MSSA. Shock has previously been identified as a common complication of MRSA bacteremia [26]. Severe shock has been shown to be more frequent in *S. aureus* IE compared to other pathogens [27].

Cardiac surgery

Cardiac surgery was performed in 56% of IE patients, which is comparable to previously reported operative rates [1, 5, 11, 28]. In this study, a new cardiac murmur at admission was predictive of surgery. The presence of a new cardiac murmur in IE patients may reflect important turbulence due to valvular damage. This finding confirms that a thorough physical examination at admission remains invaluable despite the readily availability of imaging modalities such as echocardiography in current clinical practice. Detection of a new clinical murmur could help in the identification of patients eligible for early surgery, in dialogue with the endocarditis "Heart Team" [2]. Therefore, advanced investigations should be considered as a supplement, but not a replacement of a careful clinical examination.

Limitations of the study

This is a retrospective study with a limited number of patients. Therefore, larger prospective clinical studies are warranted to confirm the present findings.

Conclusions

In this retrospective study, shock at admission independently predicted embolism during hospitalization in IE patients. Moreover, a new cardiac murmur at admission predicted the need for cardiac surgery. These findings emphasize the importance of a comprehensive initial clinical evaluation, in spite of the availability of medical imaging and microbiological information, for an early identification of IE patients at high-risk of complications or a need for surgery.

Conflict of interest: None declared

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Increased risk of adverse events in patients with low-on clopidogrel platelet reactivity after percutaneous coronary intervention: A systematic review and meta-analysis

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Abstract

Background: *Clinical evidence has been controversial regarding the influence of low platelet reactivity (LPR), ischemic and bleeding outcomes among patients receiving coronary stent implantation. Hence, the present study performed a meta-analysis to systematically evaluate the significance of LPR on adverse cardiovascular events.*

Methods: *MEDLINE, EMBASE and CENTRAL databases were searched up to November 2020 for relevant studies including patients with acute coronary syndrome undergoing percutaneous coronary intervention. LPR was the exposed arm while the non-LPR group represented the control. The primary outcome of interest was bleeding risk including major and minor bleeding events. Secondary outcomes included all-cause mortality, repeated revascularization, nonfatal myocardial infarction, and stent thrombosis. Study-level outcomes were evaluated in random-effect models.*

Results: *A total of 20 studies with 19,064 patients were included. Pooled analysis showed that LPR was associated with an increased bleeding risk (relative risk [RR] 2.80, 95% confidence interval [CI] 1.95–4.02, $p < 0.01$). Patients with LPR had a lower risk of non-fatal myocardial infarction (RR 0.59, 95% CI 0.38–0.91, $p < 0.05$) and of serious vascular events (RR 0.50, 95% CI 0.30–0.84, $p < 0.01$).*

Conclusions: *Low platelet reactivity is associated with an increased bleeding risk of patients who underwent coronary stent implantation. The results suggest possible benefits of this marker in risk stratification, with potential improvement in risk prediction. There are potential advantages using combinations with other factors in prediction models, however, they require further study. PROSPERO registration number: CRD42019136393).* (Cardiol J 2023; 30, 3: 391–400)

Key words: low platelet reactivity, acute coronary syndrome, percutaneous coronary intervention, bleeding risk, clopidogrel

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Introduction

Dual antiplatelet therapy consisting of acetylsalicylic acid and adenosine diphosphate (ADP) receptor antagonist is essential for patients undergoing percutaneous coronary intervention (PCI) [1]. Clopidogrel used to be the gold standard therapy before the introduction of new P2Y12 inhibitors, such as prasugrel and ticagrelor, which have demonstrated their clinical advantages in large randomized controlled trials (RCTs) involving acute coronary syndrome (ACS) patients [2, 3]. Both prasugrel and ticagrelor provide more effective inhibition of platelet function than acetylsalicylic acid, however, their use was followed by an increased bleeding risk [2, 3].

Platelet function testing assesses individual response to antiplatelet drugs and platelet reactivity (PR) strongly relates to clinical outcomes after ACS [4–6]. Numerous studies have shown a relationship between high platelet reactivity (HPR) and thrombotic events [7–9]. Recent studies have also found that platelet function testing and/or genetic testing may provide important information guiding antiplatelet therapy [10, 11].

With the use of more effective agents, the prevalence of HPR has decreased and an increasing proportion of patients have very low on-treatment ADP reactivity. However, the clinical significance of low platelet ractivity (LPR) is less well established and it is not routinely measured. The effect of LPR was investigated in some studies raising a signal of increased bleeding risk which remains debated, partly due to contradictory results [12–14]. The objective herein, was to perform a systematic review and meta-analysis aimed at assessing the impact of LPR on efficacy and safety outcomes after PCI.

Methods

Search strategy

A systematic review and meta-analysis were performed with reference to the PRISMA guideline [15]. The National Library of Medical Publications (MEDLINE); including its subset, PubMed, the Excerpta Medica Database (EMBASE) and Cochrane Library databases were searched for relevant articles with no restriction of time in November 2020 by using a search strategy that combined the following: Medical Subject Headings and free-text search terms: "acute coronary syndrome" OR "ACS" AND "PCI" OR "percutaneous coronary intervention" AND "platelet reactivity" OR "thrombocyte reactivity". No language restriction was used. The PICO format was adapted to set the inclusion criteria. The PICO items selected were the following: (P) patients with ACS and/or undergoing PCI and receiving dual antiplatelet therapy consisting of acetylsalicylic acid and clopidogrel, prasugrel or ticagrelor, (I) LPR (C) non-LPR or HPR based on the measurement of on-treatment PR defined by an ADP-specific platelet function assay and (O) major adverse cardiac events (MACE) and bleeding. The non-LPR group consisted of HPR or HPR plus normal platelet reactivity (NPR) where data was given for NPR. The clinical outcomes of interest evaluated at the longest available follow-up of ADP-receptor inhibitor treatment were (a) major bleeding events (defined using the trials internal definitions using Bleeding Academic Research Consortium [BARC] 3–5 or Thrombolysis in Myocardial Infarction [TIMI] major criteria), and (b) minor bleeding events (BARC 1–2 or TIMI minor) [16], (c) definite/probable stent thrombosis, (d) non-fatal myocardial infarction (MI) (type 1, 4a, 4b), (e) a composite endpoint of the reported serious vascular events that included cardiovascular death, non-fatal MI or non-fatal stroke, (f) repeated target vessel revascularization, and (g) all-cause mortality.

Studies that assessed responsiveness to clopidogrel, which was the difference between baseline and posttreatment PR (inhibition of platelet aggregation), were excluded from the analysis. The reference lists in the articles were also checked to capture all relevant articles published within the topic of interest.

Data extraction

Observational studies and cohorts — regardless of their prospective/retrospective design — were identified. Two investigators (A.B. and A.K.) independently screened the retrieved titles, abstracts and studies for eligibility and relevant full texts were systematically retrieved for further assessment. Disagreements between reviewers were solved by consensus. The retrieved studies were examined to exclude duplicate or overlapping data. Unpublished data and meeting abstracts were not considered for the present analysis because results could not be considered as certain and definitive.

Risk of bias

The methodological qualities of the studies were assessed using the Prediction model Risk Of Bias Assessment Toll (PROBAST) for assessing the quality of cohorts and the Newcastle-Ottawa Scale with reference to observational studies [17, 18].

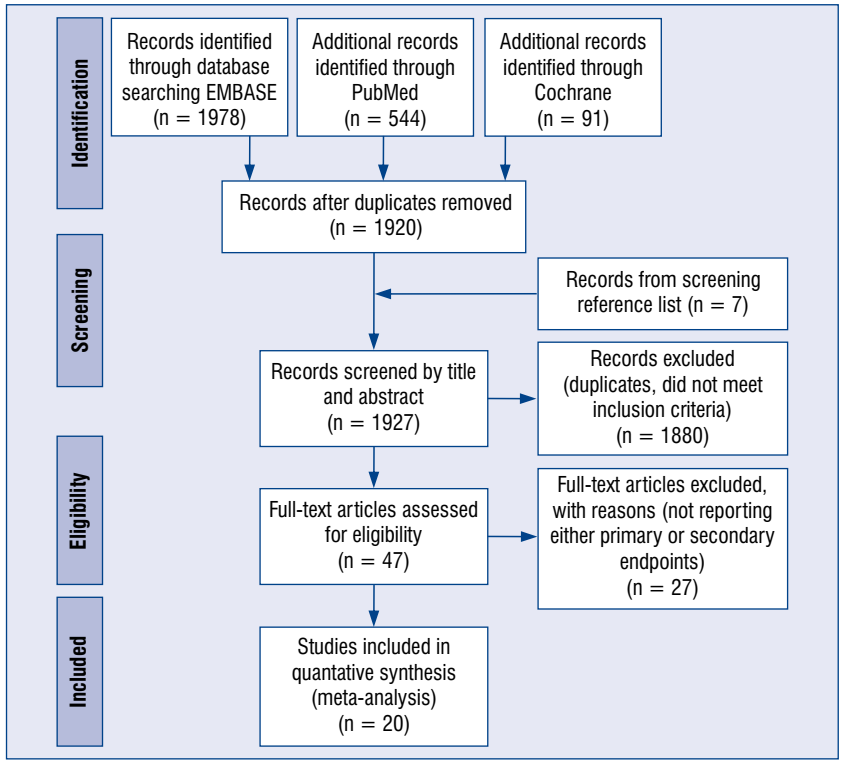

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Publication bias was estimated using funnel plots. Visual evaluation and Egger's regression intercept were used to the check for asymmetry.

Statistical analysis

Statistical computations were performed using R (v 4.0.03) package 'dmetar' designed for the evaluation of meta-analyses and OpenMeta [Analyst] open source statistical softwares. A random-effect model was applied at all the analyses with DerSimonian-Laird estimation to derive risk ratios (RR) on dichotomous outcomes and weighted mean difference on continuous data with a 95% confidence interval [CI]. Heterogeneity was tested with the χ^2 heterogeneity statistic for which a p-value < 0.1 was considered potentially heterogenous. Consistency was assessed using I^2 statistics [19]. Sensitivity analyses were carried out omitting one study at a time and calculating the effect size with the 95% CI to investigate the influence that a single study has on the final estimation regarding LPR with increased bleeding risk.

Ethical approval

Ethical or board review approval was not required for this meta-analysis.

Results

Search results and effect of LPR on the clinical outcomes

Twenty studies, involving 19,064 patients met the inclusion criteria. The process of the literature search and bias assessment is summarized in Figure 1 and for online **Supplementary Figure S4**.

Table 1 describes the main characteristics of the included studies [7, 13, 20–36]. Based on pooled results of the random-effects model meta-analysis, LPR was associated with a significantly increased risk for major and minor bleeding events compared to non-LPR (RR 2.80, 95% CI 1.95–4.02, $p < 0.01$) (Fig. 2).

Patients with LPR had significantly lower risk of non-fatal MI and of serious vascular events (RR 0.59, 95% CI 0.38–0.91, $p < 0.05$ and RR 0.50, 95% CI 0.30–0.84, $p < 0.01$, respectively; Fig. 3). The risk for stent trombosis was 45% lower in the case of LPR, however, this difference did not reach the level of statistical significance (RR 0.55, 95% CI 0.27–1.11, $p = 0.10$; Fig. 3). Even though the mortality of LPR patients was numerically higher the difference between the two groups remained insignificant (RR 1.57, 95% CI 0.69–3.57, $p = 0.28$;

Table 1. Detailed characteristics of studies included in the meta-analysis.

First author	Kabbani [20]	Patti [21]	Sibbing [7]	Tsukahara [22]	Huczek [23]	Patti [24]	Bonello [25]	Cuisset [26]	Mangiacapra [27]	Cuisset [13]
Publication year	2003	2008	2010	2010	2011	2011	2012	2012	2012	2013
Acronym	–	ARMYDA--PRO	ISAR	–	–	ARMYDA--BLEEDS	–	–	ARMYDA--PROVE	POBA
Design	P, O, single center	P, O, single center	P, O, single center	R, O, single center	P, O, single center	P, O, single center	P, O, multicenter	P, O, single center	P, O, multicenter	P, O, single center
Clinical setting	SCAD	ACS, DES	CAD	DES, ACS	ACS	SA, NSTEMI, MI	ACS	ACS	SA	NSTEMI, STEMI
Number of patients	112	160	2533	184	374	310	301	107	732	1542
Platelet function test	Flow cytometry	VerifyNow	MEA	WBA-neo	VerifyNow	VerifyNow	VASP	VASP	VerifyNow	VASP
Selected cut-off for LPR	pGP IIb/IIIa act ≤ 24.9%	lowest quartile	188 AU × min	PATI > 28 μmol/L	PRU ≤ 150	Lowest quartile	PRI < 16%	PRI < 20%	PRU ≤ 178	PRI ≤ 10%
LPR, n (%)	56 (50)	40 (25)	975 (38.5)	46 (25)	124 (33)	77 (24.8)	84 (27.9)	23 (21.5)	248 (33.9)	69 (4.5)
Clopidogrel (LD/MD, mg)	300/75	600/75	600/75	300/75	600/75	600/75	–	600/75	600/75	600/75, 600/150, 60 LD
Prasugrel (LD/MD, mg)	–	–	–	–	–	–	60 LD	10 MD	–	10 MD
Definition of bleeding	NR	BARC	TIMI	BARC	TIMI	BARC	TIMI	BARC	TIMI	BARC
End point	MI, UREV, RREV	MACE, MI, TVR	Bleeding	ST, bleeding	Bleeding, D, MI	Major bleeding	ST, bleeding	ST, MI, TVR, bleeding	D, MI, TVR, bleeding	Bleeding, ST
Follow-up, months	12	1	1	16	1	1	12	1	1	6
Age (mean ± SD)	62.5	66 ± 9	67.5 ± 10.5	68 ± 9	66.6 ± 11.3	66.5	58.1	60.5 ± 10	66 ± 10	64 ± 12.5
Female, n (%)	47 (41.9)	31 (19)	599 (23.6)	52 (28.3)	144 (38.5)	67 (21.6)	34 (11.3)	16 (14.9)	196 (26.8)	70 (4.5)
Diabetes mellitus, n (%)	29 (25.9)	55 (34)	725 (28.6)	88 (47.8)	74 (19.8)	115 (37)	70 (23.3)	107 (100)	216 (29.5)	462 (30.0)
Smoking, n (%)	NR	NR	334 (13.2)	77 (42)	180 (48.1)	NR	154 (51.2)	40 (37.4)	145 (19.8)	NR
Hypertension, n (%)	NR	NR	2295 (90.6)	140 (76.0)	251 (67.1)	NR	122 (40.5)	63 (58.9)	570 (77.8)	886 (57.4)
DES, n (%)	NR	41 (26)	2533 (100)	184 (100)	16 (4.3)	95 (30.6)	NR	NR	201 (27.5)	894 (58.0)
PCI approach (%)	NR	NR	NR	Femoral: 18	Radial: 88 Femoral: 12	Femoral: 100	NR	NR	Femoral: 96 Radial: 4	Radial: 91 Femoral: 9

→

Table 1 (cont.). Characteristics of the studies included in the meta-analysis.

First author	Mangiacapra [28]	Alfredsson [29]	Li [30]	Jin [31]	Deharo [32]	Mangiacapra [14]	Su Nam [33]	Aradi [34]	Mshelbwala [35]	Nakamura [36]
Publication year	2014	2015	2016	2017	2017	2018	2019	2019	2020	2020
Acronym	–	APACHE	–	–	TOPIC	–	–	TROPICAL--ACS	–	PENDULUM
Design	P, O, multicenter	O, single center	R, O, single center	O, single center	RCT, single center	P, O, single center	R, O, single center	RCT, multicenter	R, O, single center	P, O, multicenter
Clinical setting	SCAD, NSTEMI	NSTEMI, STEMI	ACS	ACS	ACS	SCAD	SA, ACS	ACS	ACS	ACS, non-ACS
Number of patients	800	113	512	278	646	500	814	2527	252	6267
Platelet function test	VerifyNow	MEA	VerifyNow	LTA	VASP	VerifyNow	VerifyNow	MEA	VerifyNow	VerifyNow
Selected cut-off for LPR	PRU ≤ 178	AUC × min ≤ 468	PRU ≤ 85	Lowest quartile	PRI < 20%	PRU < 178	PRU < 85	ADP ≤ 18 U	PRU ≤ 208	PRU ≤ 85
LPR, n (%)	272 (34.0)	93 (82.3)	46 (8.9)	61 (21.94)	305 (47.2)	160 (32.0)	71 (8.7)	484 (19.2)	144 (57.1)	677 (10.8)
Clopidogrel (LD/MD, mg)	600/75	600/75	300/75 600/75	300/75	75 MD	600/75	600/75	600/75	600/75	300/75
Prasugrel (LD/MD, mg)	–	–	–	–	60/10	–	–	60/10	NR	20/3.75
Ticagrelor (LD/MD, mg)	–	–	–	–	180/90	-	–	–	NR	–
Definition of bleeding	TIMI	TIMI	BARC	TIMI	BARC	TIMI	BARC	BARC	BARC	BARC
Endpoint	Bleeding, ST, TVR, D	D, MI, stroke, bleeding	Bleeding	Bleeding, entry-site complication	Bleeding, stroke, D, UREV	MI, ST, RREV, bleeding	All-cause death	D, MI, TVR, bleeding	MACE	MACCE, bleeding
Follow-up, months	1	6	12	6	11.9	60	48	12	12	12
Age (mean ± SD)	67 ± 10	66 ± 12.5	65.6 ± 7.75	61.35 ± 9.79	60.1 ± 10.2	67 ± 9.8	62.3 ± 11.94	58.7 ± 10.47	61.1 ± 10.5	70 ±10.7
Female, n (%)	210 (26.3)	33 (29.2)	93 (18.2)	57 (20.5)	114 (17.6)	109 (21.8)	257 (31.6)	535 (21.2)	101 (40.1)	1358 (21.7)
Diabetes mellitus, n (%)	236 (29.5)	14 (12.4)	113 (22.1)	70 (25.2)	177 (27.4)	156 (31.2)	256 (31.4)	513 (20.3)	121 (48.0)	2767 (44.2)
Smoking, n (%)	NR	30 (26.5)	NR	121 (43.5)	286 (44.3)	100 (20.0)	468 (57.5)	NR	177 (70.2)	1346 (21.5)
Hypertension, n (%)	NR	41 (36.3)	NR	158 (56.8)	313 (48.5)	407 (81.4)	509 (62.5)	NR	217 (86.1)	4892 (78.0)
DES, n (%)	231 (28.9)	45 (39.8)	NR	NR	585 (90.6)	338 (67.6)	788 (96.8)	NR	234 (93.0)	6267 (100)
PCI approach (%)	Femoral: 100	NR	NR	Femoral: 12.23	Femoral: 4 Radial: 96	Femoral: 96 Radial: 4	NR	Brachial: 1 Femoral: 40 Radial: 59	NR	Femoral: 26.0 Brachial: 4.3 Radial: 72.1

ACS — acute coronary syndrome; ADP — adenosine diphosphate; AUC — area under the curve; BARC — Bleeding Academic Research Consortium Criteria; D — death; DES — drug-eluting stent; GP — glycoprotein; LD — loading dose; LPR — low platelet reactivity; LTA — light transmission aggregometry; MD — maintenance dose; MEA — multiplate electrode aggregometry; MACE — major adverse cardiac events; MACCE — major adverse cardiac and cerebrovascular events; MI — myocardial infarction; NR — not reported; NSTEMI — non ST segment elevation myocardial infarction; O — observational study; P — prospective; PCI — percutaneous coronary intervention; PRI — VASP-P-derived platelet reactivity index; PRU — platelet reaction units; R — retrospective; RCT — randomized controlled trial; RREV — repeated revascularization; SA — stable angina; SCAD — stable coronary artery disease; SD — standard deviation; ST — stent thrombosis; STEMI — ST segment elevation myocardial infarction; TIMI — Thrombolysis In Myocardial Infarction; TVR — target vessel revascularization; UREV — urgent revascularization; VASP — vasodilator-stimulated phosphoprotein

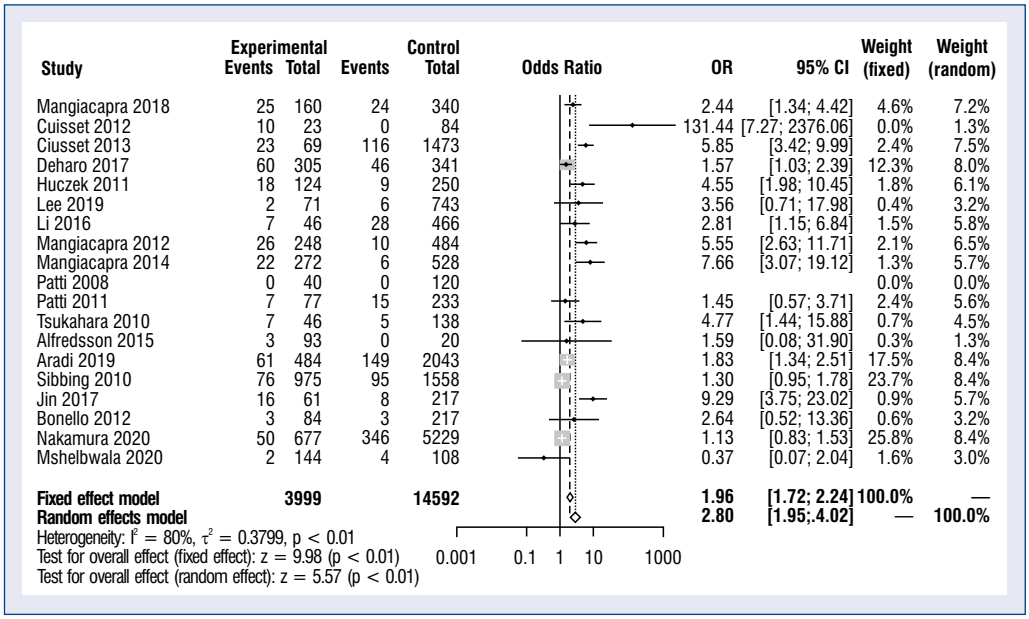

Figure 2. Principal pooled analysis. Forest plots of major and minor bleeding risk in studies following percutaneous coronary intervention with low platelet reactivity (LPR) versus without LPR. The grey rectangles are proportional with the study weight. The diamond represents the cumulative odds ratio (OR) and confidence interval (CI).

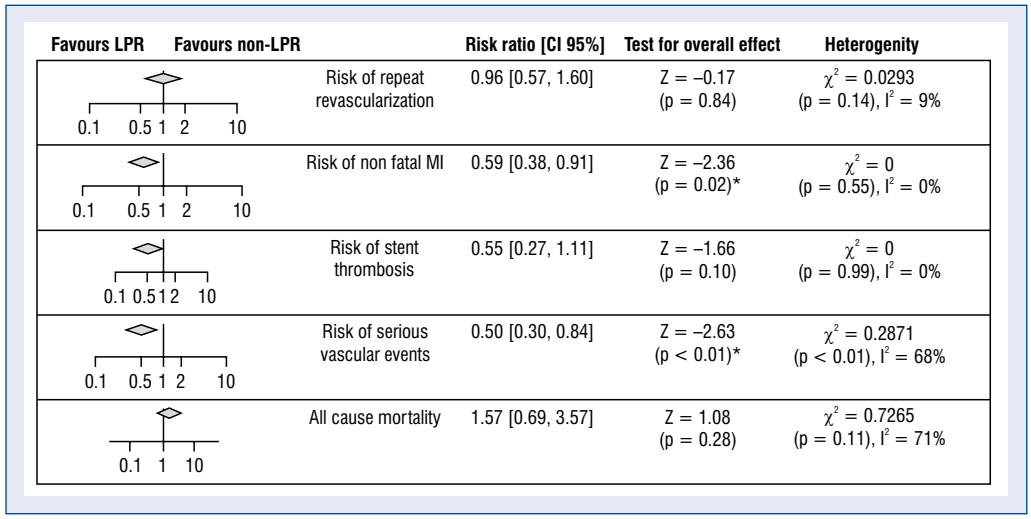

Figure 3. Summary of the outcomes of the secondary endpoints. The diamond represents the cumulative risk ratio and confidence interval (CI) of all patient groups. *Mean difference (95% CI); LPR — low platelet reactivity; MI — myocardial infarction.

Fig. 3). No significant difference was found regarding repeated revascularization (RR 0.96, 95% CI 0.57–1.60, p = 0.84; Fig. 3). Body mass index was significantly lower in the LPR group (standardized mean difference –0.18, 95% CI –0.32 to –0.05, p < 0.01; **Suppl. Fig. S1**).

Heterogeneity and subgroup analyses

The rate of LPR demonstrated a mean prevalence of 27% (95% CI for mean 20–35%, range 4.5––82%). Overall heterogeneity concerning major and minor bleeding events was considerable (I^2 = 80%, p < 0.01). To find possible determinants of the

observed heterogeneity, the prevalence of LPR and bleeding events was analyzed according to the following grouping factors: type of platelet function device, definition of bleeding events and amount of clopidogrel loading dose (LD).

The analysis confirmed that all the selected ADP-specific assays were able to predict the occurrence of bleeding events and the higher risk of patients with LPR was consistent regardless of the clinical presentation. Noticeably, considerable heterogeneity was observed in the results between studies using VASP-P and Verify Now assays; however, the Multiplate assay showed more homogenous findings (**Suppl. Fig. S2**). Subgroup analysis was also performed to assess the potential influence of different clopidogrel LD regimes. Despite the different types of clopidogrel loading dose, heterogeneity remained high (**Suppl. Fig. S2).**

When bleeding events were divided into major and minor events separately the heterogeneity was reduced considerably for major bleeding (I^2 = 34%) while heterogeneity remained high for minor bleeding (I^2 = 82%; **Suppl. Fig. S3**).

Publication bias

Based on visual estimation of the funnel plot for bleeding events, no major asymmetry suggestive for publication bias was found. Furthermore, Egger's regression test confirms no small-study effect (**Suppl. Fig. S4**). Analysis of bias showed high quality of the source information with low probability of possible bias (**Suppl. Fig. S4**).

Discussion

The key finding of this meta-analysis is that patients with LPR after PCI are at a higher risk of bleeding. LPR detected by an ADP-specific laboratory assay is also associated with a lower risk of non-fatal MI. The composite endpoint of serious vascular events demonstrated lower risk with LPR. All-cause mortality did not differ significantly between LPR and non-LPR patient groups. Importantly, despite the differences in the methodology, patient selection and cut-off definition among studies, the increased risk of bleeding was homogenously reflected.

To date, this is the first meta-analysis of studies testing the role of LPR on bleeding and ischemic events in patients who underwent PCI.

In the first study reporting on the impact of enhanced response to clopidogrel treatment including 2,533 patients with coronary artery disease undergoing planned PCI, LPR was found to be associated with a two-fold higher risk for in-hospital major bleeding events [7]. Further reports suggested that LPR is a marker for a higher risk of bleeding events also among prasugrel-treated patients [25, 26].

Some recent studies, however, do not necessarily support that optimal PR does denote the same range in every patient population. In the TRILOGY ACS trial involving ACS patients without PCI, the relationship between LPR and risks of major bleeding was missing. Among medically managed non-ST-segment elevation ACS patients receiving prolonged dual antiplatelet therapy, platelet reactivity unit values were not significantly associated with the long-term risk of major bleeding events, suggesting that LPR does not independently predict serious bleeding risk [37].

Aimed at assessing the potential influence of different clopidogrel LD regimes, a subgroup analysis was performed. The results showed no association between different LDs of clopidogrel and rate of bleeding events. These findings are in line with a recent meta-analysis that compared the use of different LDs of clopidogrel and found that these are not associated with an increased risk for major bleeding within 30 days. However, it also suggested that the administration of 600 mg LD of clopidogrel is associated with a lower risk of MACE [38]. This observation is further supported by a retrospective study of patients with stable coronary artery disease which shows no difference between different LD groups in terms of major bleeding and hemoglobin drop post PCI [39].

When interpreting data from platelet function studies, the complex mechanisms of bleeding should be considered. Besides the potential impact of platelet inhibition, several clinical factors also influence the risk of these events. Residual PR, as an independent risk factor also has several associations with patient characteristics and these may also influence the expressed risk. HPR is more frequently encountered in obese and diabetics, while LPR may more likely arise in patients with advanced age and lower body weight [40, 41]. A significant association of LPR was revealed with lower body mass index in the current analysis. These characteristics may also impact the prognosis and when analyzed in multivariate models, the magnitude of risk, as in cases of ischemic risk with HPR, this risk is considerably reduced [42].

Importantly, periprocedural bleeding risk is substantially influenced by the access site selection, being significantly higher with transfemoral interventions. Bleeding avoidance strategies like

routine use of the transradial approach may interfere with this risk by reducing bleeding and improving outcomes among high-risk ACS patient [43]. In the present analysis, the rate of transradial approach reached 59% (reported in 8 studies including 8,667 [45%] patients). However, since this data was not presented in a considerable proportion of studies this impedes the further analysis of potential impact of access site selection.

The findings herein, are partly in line with the results of a previous meta-analysis published in 2015 including 17 trials with a total of 20,839 patients validating standardized cut-off points for platelet function testing. In that study thienopyridine-treated patients with HPR were associated with 2.73-fold higher risk for stent thrombosis ($p < 0.00001$) and a 1.5-fold higher risk for mortality ($p < 0.05$) compared with those with optimal PR following PCI, meanwhile patients with LPR were associated with a 2-fold increased risk for major bleeding complications without any further reduction in the risk of stent thrombosis [38]. In the present study, there was no significant difference between LPR and non-LPR groups in case of mortality, stent thrombosis or repeated revascularization. However, the risk of serious vascular events resulted in a significant difference favoring the LPR group. Regarding risk of non-fatal MI, the event rate was significantly lower in the LPR group.

However, there are some limitations that may impact the interpretation of the current results. Observational studies were included that are usually unbalanced regarding baseline clinical characteristics of the patients. These studies could reflect the real-world practice better, meanwhile due to a lack of monitoring drug compliance, underreporting negative results and incomplete follow-up, their interpretation may be more difficult and might carry ascertainment biases. To balance possible confounding factors, data were pooled with logarithmic transformation according to the random-effect model via generic inverse weighting with the intent of methodical compensation of these factors.

It should be mentioned that the patients were not treated uniformly regarding the LDs of clopidogrel and that platelet function assessments were performed at different time points after PCI with different devices and cut-offs for LPR that may have contributed to heterogeneity. There are multiple tests in the field with a real-gold standard evidently missing. Considering the plethora of available platelet function tests, the aim to restrict the analyses to those that implement a method based on ADP dependent in vitro platelet activation was used in order to best assess the efficacy of ADP receptor dependent activation pathway. From this perspective, acceptable methodologies were not restricted based on the final readout of the method. The use of different P2Y12 inhibitors may also have influenced residual platelet reactivity. Due to a lack of patient-level data, subgroup analyses were not done to identify drug related efficacy. It is also important to note that different definitions of bleeding may have contributed to heterogeneity. The aim to collect data according to the two most widely used and standardized definitions, the TIMI bleeding and BARC criteria were used.

Conclusions

In conclusion, this meta-analysis supports that LPR is associated with important clinical outcomes of patients who underwent coronary stent implantation. The possible benefit of this marker in risk stratification or improvement of risk prediction, if combined with other factors in prediction models remains to be established by further studies.

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Mindfulness-based emotional regulation for patients with implantable cardioverter-defibrillators: A randomized pilot study of efficacy, applicability, and safety

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Abstract

Background: *The efficacy of mindfulness-based interventions to reduce anxiety or improve quality of life (QoL) in patients with cardiac pathologies is well established. However, there is scarce information on the efficacy, applicability, and safety of these interventions in adult patients with an implantable cardioverter-defibrillator (ICD). In this study, we examined their efficacy on QoL, psychological and biomedical variables, as well as the applicability and safety of a mindfulness-based intervention in patients with an ICD.*

Methods: *Ninety-six patients with an ICD were randomized into two intervention groups and a control group. The interventions involved training in mindfulness-based emotional regulation, either face-to-face or using the "REM Volver a casa" mobile phone application (app).*

Results: *The sample presented medium-high QoL baseline scores (mean: 68), low anxiety (6.84) and depression (3.89), average mindfulness disposition (128), and cardiological parameters similar to other ICD populations. After the intervention, no significant differences were found in the variables studied between the intervention and control groups. Retention was average (59%), and there were no adverse effects due to the intervention.*

Conclusions: *After training in mindfulness-based emotional regulation (face-to-face or via app), no significant differences were found in the QoL or psychological or biomedical variables in patients with an ICD. The intervention proved to be safe, with 59% retention.* (Cardiol J 2023; 30, 3: 401–410)

Key words: quality of life, implantable cardioverter-defibrillator, emotional regulation, mindfulness, anxiety

Introduction

Stress, anxiety, and depression are some of the psychological disorders associated with pathologies of the cardiovascular system, affecting cognitive performance and quality of life (QoL) [1–3].

Mindfulness is a complementary intervention in the treatment of problems such as anxiety,

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which has demonstrated psychological benefits [2, 4–7]. It has also been shown to be effective in cardiovascular diseases [4, 8], facilitating greater emotional stability [9–12] and improving mood in patients with heart disease [3, 8, 13].

The implanted cardioverter-defibrillator (ICD) is a first-line treatment in patients who have had poorly tolerated ventricular tachyarrhythmias or who have had resuscitated cardiac arrest. It also plays a fundamental role in the primary prevention of sudden cardiac death in patients with heart disease and risk of developing malignant ventricular arrhythmias. After ICD implantation, many of these patients suffer not only from the fear of arrhythmias and their possible consequences, but also (and especially) from the shocks that the ICD can deliver to treat arrhythmias [14, 15].

In patients with heart disease, Younge et al. [1] obtained positive results in the physiological parameters (exercise capacity and heart rate) assessed after an online mindfulness-based intervention. However, there is scarce information on the influence of this type of intervention in patients with ICDs. Salmoirago-Blotcher et al. [12, 16, 17] conducted mindfulness-based interventions in this type of patient. Their results showed a significant increase in participants' levels of mindfulness but did not have a significant effect on anxiety symptoms. In addition, they did not study the effect on QoL or the biomedical variables of the patients.

The main objective of this pilot study was to analyze the efficacy, applicability, and safety of a mindfulness-based intervention administered face-to-face or through an application (app) on QoL, psychological, and biomedical variables in a sample of patients with an ICD. The secondary objective was to describe the baseline characteristics of QoL, psychological, and biomedical variables in this population.

Methods

Design and study population

A randomized controlled clinical trial was conducted with a pre-post design.

The study population consisted of patients with heart disease and an ICD treated in the Arrhythmia Unit of the Cardiology Department of a Spanish university hospital. In total, 340 patients met the inclusion criteria, which were as follows: being over 18 years of age; having an ICD that had been implanted 3 months ago or more; having sufficient knowledge of Spanish; ownership of a mobile phone and the ability to use mobile apps; and sufficient availability and physical condition to attend face-to-face training in emotional regulation.

The exclusion criteria were as follows: being over 75 years of age; being on the waiting list for a heart transplant or other heart-related surgery; being a current mindfulness practitioner or having been one during the last 5 years; or having a severe mental disorder in an acute period.

The sample size was calculated to detect a difference greater than or equal to 10 units in the QoL variable, considering an alpha risk of 0.05 and beta of 0.2, in a bilateral contrast, as well as a standard deviation of 20 points and a loss rate of 20%. The estimated number of patients was 237, to be distributed into three groups of 79 patients each.

Patients were recruited by telephone and were randomized using the Excel function [=RANDBETWEEN (1;3)]. The participants were randomly distributed into three groups: two for the intervention (face-to-face group and app group) and a non-intervention control group.

Measuring instruments

- SF-36 (Short Form): Health-related QoL survey [18];
- HADS (Hospital Anxiety and Depression Scale): Scale designed to assess the presence of anxiety or depression in the medical patient [19];
- STAXI (State-Trait Anger Expression Inventory): Questionnaire that assesses the expression of anger, both as a personality trait and with respect to the state at the time of measurement [20];
- FFMQ (Five Facet Mindfulness Questionnaire): This questionnaire explores five factors of mindfulness disposition [21].

Variables

The main outcome variable was QoL, assessed by the SF-36 questionnaire. We assessed the degree of applicability based on recruitment and retention figures, as well as the safety of both interventions in terms of adverse effects reported by participants. In each session, we asked about the possible occurrence of any psychological discomfort or the existence and degree of negative adverse effects. Any discomfort, harm, or increase in negative psychological symptoms (anxiety, depression, anger) arising directly from the intervention was considered a negative adverse effect [22, 23].

The secondary variables considered were anxiety, depression, anger, mindfulness disposition, and the following biomedical variables: type

of baseline heart disease of the patient, functional class (FC), left ventricular ejection fraction (LVEF), indication for ICD implantation, time since implantation, history of ICD therapies, and pharmacological treatment and its changes during the intervention period. The information provided by the ICD itself was also analyzed: therapies — both appropriate and inappropriate, non-sustained ventricular tachycardias, mean heart rate, and daily activity of the patient. The data provided by the ICD were compared by considering the 2 months before and the 2 months after the intervention. Ninety-two percent of the patients had remote ICD monitoring.

The independent variable was participation in a mindfulness-based emotional regulation program, either in person or through an app.

The study protocol was approved by the hospital's Clinical Research Ethics Committee.

Trial registration: ClinicalTrials.gov, identifier NCT04235881.

Interventions

Face-to-face group. A face-to-face 8-week group training program was conducted, with a maximum of 25 participants, based on the mindfulness-based stress reduction program designed by Kabat-Zinn. It included all the elements of the original training program, except that the sessions were 2 hours long and the 7-hour silent practice day was not carried out. The program was taught by 2 accredited mindfulness-based stress reduction teachers.

App group. The intervention was carried out using the "REM Volver a casa" ("REM coming back home") mobile phone application. This application was developed to deliver a user-led 8-week mindfulness-based emotional regulation training program. It was designed by teachers accredited in standardized mindfulness program.

Control group. During the face-to-face and app training period, no intervention was carried out with the participants assigned to the control group. Once the post-intervention data collection was completed, the patients in the control group were offered the mindfulness-based emotional regulation program using the "REM coming back home" app.

Statistical analysis

In the descriptive analysis, the absolute frequency (n) and relative frequency (%) were calculated for qualitative variables. For quantitative variables, the normality of the distributions of the variables was tested using the Kolmogorov-Smirnov goodness-of-fit test, expressed as median and interquartile range (IQR). For the analysis of group independence, the Kruskal-Wallis H test was used for quantitative variables, and the χ^2 test (chi-square with Fisher's exact test) was used for categorical variables.

The efficacy of the intervention was analyzed by comparisons between the three study groups. An additional analysis was also chosen, pooling the two intervention groups and comparing the overall group with the control group. The tool used was the Mann-Whitney U test.

For the analysis of drop-out and retention of the study participants, we used the χ^2 test (chi-square) for categorical variables and the Mann-Whitney U test for quantitative variables.

For all tests, the p-values for all results were bilateral; a value of < 0.05 indicated statistical significance.

Statistical analyses were performed using SPSS, version 20 (IBM Corp., United States).

Results

A total of 251 patients were randomized, of whom 96 started the study and 57 completed it (Fig. 1).

Baseline characteristics

The sample, 74% male, had a median age of 60 years (49–67). The median age was higher in the face-to-face group (65 [53–71]) than in the app group (59 [47–64; $p = 0.013$]) or the control group (56 [46–67; $p = 0.052$]), and it was higher in men (61 [51–68]) than in women (53 [46–61; $p = 044$]). Almost half (49%) of the participants in the app group had a university education, compared to just over a third (36%) in the face-to-face group.

Regarding baseline heart disease, half (52%) of the participants had ischemic heart disease with previous myocardial infarction; slightly fewer than half (41%) had non-ischemic cardiomyopathy, mainly dilated, and a minority (7%) had primary electrical disease. Median LVEF was 31% (25–50). 45.8% were in FC II and 14.6% were in FC III. Fewer patients in FC III were found in the face-to-face group (2.8%) than in the app (17.1%) and control (31.6%) groups. In slightly more than half (56%) of participants, the implant was performed as primary prevention; in 44% it was performed as secondary prevention. The mean time from implantation to completion of the study was 2.9 ± ± 2.14 years.

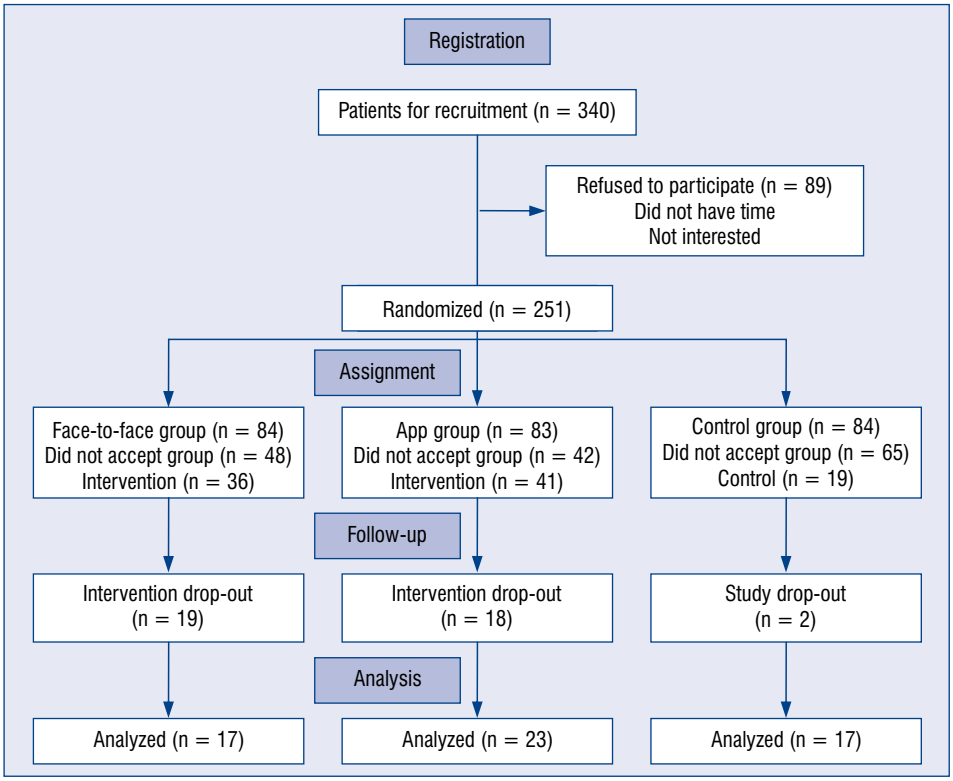

Figure 1. Study flowchart.

Twenty-three percent of the study participants had shocks in the period between implantation and the completion of the study (mean time of 2 years).

Quality of life scores were medium-high (73 [65–90]), low anxiety (6 [4–9]) and depression (3 [1–5.5]), and average in mindfulness disposition (128 [118–139]).

Except for the age variable and FC, there were no statistically significant differences between the groups (Table 1).

Results of the intervention

No significant differences were found between the intervention and control groups for QoL, anxiety, anger, or depression scores or biomedical variables (appropriate or inappropriate therapies, non-sustained ventricular tachycardias, mean heart rate, or mean daily activity). However, for the general health dimension of the QoL variable, the difference corresponding to the contrast between the face-to-face group and the control group was significant (Table 2).

In the comparison between the two intervention groups grouped together (face-to-face and app) and the control group, statistical significance was not reached in any of the variables (Table 3). The comparison test between secondary studies (n = 10) vs. university studies (n = 24) only reported statistically significant differences ($p = 0.040$) in the mental health dimension of the QoL variable. Due to the low number of patients, no comparisons were made with other educational levels.

Applicability

Recruitment reached almost 74% of potential participants. After randomization and allocation of participants to the study groups, the drop-out rate was 62%. Subsequently, during the intervention, the drop-out rate was 40%. Retention was average in the face-to-face (47%) and app (56%) groups, with no significant difference between them ($p = 0.497$). In the control group, retention was high (89%), with a significant difference compared to the face-to-face ($p = 0.003$) and app ($p = 0.017$) groups. Female retention (80%) was higher than male retention (52%; $p = 0.018$). Apart from group type and sex, no other variables related to drop-out or retention in the study were identified.

Safety

During the sessions, participants in the face-to-face group reported no negative adverse effects, such as anxiety, stress, low mood, or other psychological distress. Nor did the app group participants indicate psychological distress in their individual practices.

Table 1. Study variables.

	Participant characteristics: baseline data (n = 96)			Test H (o, χ^2)	P value
	Face-to-face group (n = 36)	Application group (n = 41)	Control group (n = 19)		
Sociodemographic					
Age [years]	65 (53–71)	59 (47–64)	56 (46–67)	(2) = 7.170	0.028*
Sex:				χ^2 = 0.464	0.869
Female	9 (25.0%)	12 (29.3%)	4 (21.1%)		
Male	27 (75.0%)	29 (70.7%)	15 (78.9%)		
Educational level:				χ^2 = 3.672	> 741
None	4 (11.1%)	4 (9.7%)	2 (10.5%)		
Primary	8 (22.2%)	7 (17.1%)	4 (21.1%)		
Secondary	11 (30.6%)	10 (24.4%)	8 (42.1%)		
University	13 (36.1%)	20 (48.8%)	5 (26.3%)		
Cardiology/implantable cardioverter-defibrillator					
Functional class:				χ^2 = 10.118	0.034*
I	15 (41.7%)	15 (36.6%)	8 (42.1%)		
II	20 (55.5%)	19 (46.3%)	5 (26.3%)		
III	1 (2.8%)	7 (17.1%)	6 (31.6%)		
IV	0 (0.0%)	0 (0.0%)	0 (0.0%)		
Prevention:				χ^2 = 4.285	> 127
Primary	25 (69.4%)	19 (46.3%)	10 (52.6%)		
Secondary	11 (30.6%)	22 (53.7%)	9 (47.4%)		
Pathology:				χ^2 = 1.046	0.927
No heart disease	2 (5.5%)	4 (9.8%)	1 (5.4%)		
Ischemic	20 (55.6%)	21 (51.2%)	9 (47.3%)		
Non-ischemic	14 (38.9%)	16 (39.0%)	9 (47.3%)		
Shocks:				χ^2 = 1.728	0.440
No	30 (83.3%)	31 (75.6%)	13 (68.4%)		
Yes	6 (16.7%)	10 (24.4%)	6 (31.6%)		
Implant years	3.0 (2.0–3.4)	3.0 (2.5–3.9)	3.0 (2.4–3.6)	0.368	
LVEF	33 (28–49)	34 (30–50)	28 (25–50)	(2) = 2.834	0.242
Mean heart rate	65.5 (62.5–70)	65.0 (65–70)	65.0 (60–70)	(2) = 0.495	0.781
NSVT	0 (0–1)	0 (0–1)	0 (0–0)	(2) = 0.677	0.713
Daily activity [h]	3 (2–3.4)	3 (2.5–3.9)	3 (2.4–3.6)	(2) = 0.641	0.726
Quality of life					
Physical functioning	70.0 (60.0–85.0)	85.0 (65–95)	80.0 (60–95)	(2) = 3.427	0.180
Role physical	100 (62.5–100)	100 (50–100)	100 (25–100)	(2) = 0.209	0.901
Bodily pain	72.0 (60.5–84.0)	72 (62–90)	74 (51–84)	(2) = 0.513	0.774
General health	48.5 (31.0–59.5)	52.0 (37–72)	52.0 (40–77)	(2) = 1.703	0.427
Vitality	52.5 (47.5–75.0)	65.0 (55–80)	55.0 (30–75)	(2) = 3.536	0.171
Social functioning	87.5 (62.5–100)	87.5 (62.5–100)	75.0 (50–100)	(2) = 1.383	0.501
Role emotional	100.0 (0.0–100)	100 (33.3–100)	100 (0–100)	(2) = 1.528	0.466
Mental health	74.0 (58.0–84.0)	76.0 (60–88)	64 (48–84)	(2) = 1.441	0.487
Physical component summary	75.65 (57.3–87)	82.3 (66.7–89)	78 (45.3–93)	(2) = 0.738	0.691
Mental component summary	80.2 (47.6–93.3)	86.5 (62.6–96)	71.1 (39.5–94)	(2) = 1.516	0.469
Overall	51.0 (45.5–65.5)	58.5 (46.0–76)	51.0 (35–73.5)	(2) = 2.345	0.310

→

Table 1 (cont.). Study variables.

	Participant characteristics: baseline data (n = 96)			Test H (o, χ^2)	P value
	Face-to-face group (n = 36)	Application group (n = 41)	Control group (n = 19)		
Psychological variables					
Anxiety	6.0 (4.0–10.0)	6.0 (3.0–8.0)	7.0 (5.0–10.0)	(2) = 1.788	0.409
Depression	3.5 (2.0–5.0)	2.0 (1.0–5.0)	3.0 (1.0–6.0)	(2) = 0.837	0.658
Anger (state)	15.0 (15–19)	15.0 (15–16)	15.0 (15–17)	(2) = 1.068	0.586
Anger (trait)	18.0 (14–22)	17.0 (15–21)	19.0 (15–21)	(2) = 0.378	0.828
Anger Expression Index	29.0 (21–36)	28.0 (19–33)	25.0 (19–35)	(2) = 0.551	0.759
Mindfulness total	128 (118–140)	127 (119–136)	124 (109–141)	(2) = 0.760	0.684

Data are shown as median (interquartile range) or number (%). Test: Kruskal-Wallis H, unless specified. χ^2 (chi-square); *P value for alpha = 0.05; LVEF — left ventricular ejection fraction; NSVT — non-sustained ventricular tachycardia

Discussion

To our knowledge, this study is the first randomized clinical trial to study the applicability and efficacy of 2 mindfulness-based interventions: face-to-face and app-based, in adult patients fitted with an ICD, to improve QoL, psychological, and biological variables.

As with other studies [24, 25], the baseline characteristics of our sample showed medium-high values in most of the scales of the QoL variable. The cardiological biomedical characteristics of the population in this study were also similar to those found in other ICD patient populations, such as those of the Spanish Society of Cardiology's ICD Registry [26]. These data, together with the absence of symptoms of anxiety, depression, and anger, suggest that having an ICD, not recently implanted, does not entail lower QoL. In addition, the data would justify the absence of significant changes in the scores obtained after the intervention [27].

Numerous studies have shown that ICD shocks are the main determinant of poorer QoL, increased anxiety, and psychological disturbances [28–30]; in our study, only 23% of the included patients had experienced a previous ICD shock. In addition, some studies have shown that in the early post-ICD implantation period, there is a greater deterioration in QoL and emotional impairment [31]. In our sample, the proportion of patients who had been implanted less than a year ago was small (28%).

The small sample size probably explains why some trends towards favorable changes in the intervention groups compared to the control group did not reach statistical significance, except for the improvement in the general health dimension of the QoL variable in the face-to-face group compared to the control group.

Educational level does not seem to affect the results of mindfulness training. However, a higher educational level (university) could have a favorable effect on mental health, an effect that was found in the comparison between the levels of secondary and university studies.

In patients with cardiovascular disease, several studies, reviews, and meta-analyses have shown that this type of intervention has a moderate effect on outcomes relating to psychological variables and unclear effects on biological variables [32]. A recent systematic review and meta-analysis [33] showed an improvement in psychological variables as well as in systolic, although not diastolic, blood pressure. However, the QoL of patients was not analyzed in this review and patients with ICDs were not included. On the other hand, the effect obtained by Salmoirago-Blotcher et al. [16] on anxiety symptoms did not reach statistical significance in the overall group; it was only reached if patients who performed all sessions were considered.

Dash et al. [34], in a pilot study on the effect of meditation in 25 heart failure patients with ICDs, demonstrated a reduction in episodes of atrial fibrillation and sustained ventricular tachycardia. However, we used a rough analysis of these episodes, not adjusted for the number of episodes per patient, which is a major methodological limitation.

Regarding the lack of effect of the intervention on biomedical variables, in the study by Toise et

Table 2. Pre-post differences in each group and contrast between groups.

	Face-to-face group (n = 17)	Application group (n = 23)	Control group (n = 17)	Face-to-face Control (p)	Application Control (p)	Face-to-face Application (p)
Cardiology/implantable cardioverter-defibrillator						
Mean heart rate	0.0 (–5.0 to 0.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.552	0.792	0.668
NSVT	0.0 (–3.0 to 0.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.257	0.668	0.098
Daily activity	0.2 (0.1 to 0.7)	0.2 (0.0 to 1.0)	0.3 (0.0 to 0.5)	0.594	0.424	0.934
Quality of life						
Physical functioning	0.0 (0.0 to 5.0)	0.0 (–5.00 to 5.0)	5.0 (–5.0 to 20.0)	0.540	0.097	0.245
Role physical	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.708	0.866	0.730
Bodily pain	0.0 (–10.0 to 6.0)	0.0 (0.0 to 12.0)	0.0 (–6.0 to 6.0)	0.919	0.208	0.571
General health	5.0 (5.0 to 15.0)	5.0 (–5.0 to 12.0)	0.0 (–5.0 to 5.0)	0.049*	0.162	0.431
Vitality	0.0 (–5.0 to 15.0)	5.0 (–5.0 to 10.0)	10.0 (0.0 to 10.0)	0.586	0.598	0.825
Social functioning	0.0 (0.0 to 12.5)	0.0 (0.0 to 12.5)	0.0 (0.0 to 25.0)	0.496	0.148	0.487
Role emotional	0.0 (0.0 to 33.4)	0.0 (0.0 to 33.3)	0.0 (0.0 to 0.0)	0.540	0.633	0.705
Mental health	4.0 (0.0 to 16.0)	4.0 (0.0 to 12.0)	4.0 (–4.0 to 8.0)	0.786	0.628	0.989
Physical component summary	0.3 (–7.3 to 7.3)	2.3 (–1.7 to 10.0)	0.0 (–1.6 to 11.0)	0.357	0.671	0.632
Mental component summary	2.7 (0.0 to 9.5)	2.7 (0.0 to 16.6)	1.3 (–1.4 to 12.7)	0.540	0.661	0.837
Overall	0.0 (0.0 to 20.0)	5.0 (–2.5 to 12.5)	5.0 (0.0 to 6.0)	0.865	0.537	0.837
Psychological variables						
Anxiety	–1.0 (–3.0 to 0.0)	0.0 (–2.0 to 1.0)	–2.0 (–2.0 to 0.0)	0.973	0.186	0.201
Depression	–1.0 (–1.0 to 1.0)	0.0 (–2.0 to 1.0)	–1.0 (–2.0 to 0.0)	0.394	0.095	0.494
Anger (state)	0.0 (–1.0 to 0.0)	0.0 (0.0 to 0.0)	0.0 (–1.0 to 0.0)	1.000	0.869	0.904
Anger (trait)	–1.0 (–4.0 to –1.0)	1.0 (–3.0 to 2.0)	–1.0 (–2.0 to 0.0)	0.413	0.417	0.151
Anger Expression Index	0.0 (–4.0 to 2.0)	–2.0 (–12.0 to 5.0)	–2.0 (–4.0 to 1.0)	0.474	0.945	0.641
Mindfulness total	0.0 (–3.0 to 9.0)	5.0 (–4.0 to 11.0)	5.0 (–4.0 to 12.0)	0.444	0.921	0.366

Data are shown as median (interquartile range). Test: Mann-Whitney U; *P value for alpha = 0.05; NSVT — non-sustained ventricular tachycardia

Table 3. Pre-post differences in each group and contrast between joined intervention group and control group.

	Participants with intervention vs. control group		Test U	P value
	Intervention group (n = 40)	Control group (n = 17)		
Cardiology/implantable cardioverter-defibrillator				
Mean heart rate	0.0 (–5.0 to 0.0)	0.00 (0.00 to 0.00)	334.0	0.901
NSVT	0.0 (–1.0 to 0.0)	0.00 (0.00 to 0.00)	322.5	0.716
Daily activity	0.2 (0.0 to 0.9)	0.30 (0.00 to 0.50)	297.0	0.451
Quality of life				
Physical functioning	0.0 (–5.0 to 5.0)	5.0 (–5.0 to 20.0)	262.0	0.166
Role physical	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	323.5	0.727
Bodily pain	0.0 (–3.0 to 11.0)	0.0 (–6.0 to 6.0)	292.5	0.395
General health	5.0 (0.0 to 13.5)	0.0 (–5.0 to 5.0)	232.5	0.058
Vitality	5.0 (–5.0 to 12.5)	10.0 (0.0 to 10.0)	304.5	0.532
Social functioning	0.0 (0.0 to 12.5)	0.0 (0.0 to 25.0)	271.0	0.197
Role emotional	0.0 (0.0 to 33.3)	0.0 (0.0 to 0.0)	307.0	0.492
Mental health	4.0 (0.0 to 12.0)	4.0 (–4.0 to 8.0)	314.0	0.647
Physical component summary	1.0 (–3.4 to 8.7)	0.0 (–1.6 to 11.0)	297.5	0.458
Mental component summary	2.7 (0.0 to 15.85	1.3 (–1.4 to 12.7	305.5	0.546
Overall	2.5 (–1.25 to 13.8)	5.0 (0.0 to 6.0)	312.0	0.624
Psychological variables				
Anxiety	–0.5 (–2.0 to 0.0)	–2.0 (–2.0 to 0.0)	293.5	0.411
Depression	0.0 (–1.5 to 1.0)	–1.0 (–2.0 to 0.0)	255.5	0.133
Anger (state)	0.0 (–1.0 to 0.0)	0.0 (–1.0 to 0.0)	334.5	0.917
Anger (trait)	–1.0 (–4.0 to 2.0)	–1.0 (–2.0 to 0.0)	335.0	0.930
Anger Expression Index	–1.0 (–6.0 to 5.0)	–2.0 (–4.0 to 1.0)	316.0	0.675
Mindfulness total	4.0 (-4.0 to 10.0)	5.0 (-4.0 to 12.0)	294.0	0.637

Data are shown as median (interquartile range). Test: Mann-Whitney U; NSVT — non-sustained ventricular tachycardia

al. [15], the number of device therapies was lower in the intervention group than in the control group (2014 study). We believe that the absence of differences in our study is mainly due to a short pre- and post-intervention analysis time window and better scheduling of screening and therapies in ICDs.

Despite the high recruitment rate (74%), which is much higher than that reported in other studies (Salmoirago-Blotcher et al. [16] — 13%; Frizelle et al. [35] — 28%), the sample was greatly reduced due to the high number of dropouts. The patients explained the dropouts as being due to difficulties in participating or a preference for a group other than the assigned group. The dropouts from the control group (77%) correspond to patients who did not want to be part of this group or did not want to wait a long time to receive training through the application for mobile terminals. It is noteworthy that only 3% of the patients with FC III were in the face-to-face group, probably because the greater physical demands of this format led them to refuse to participate. On the other hand, some patients assigned to the mobile phone app group gave technical difficulties with the use of the mobile phone as a reason for dropping out.

The mean retention rate (59%) was far from that reported by Salmoirago-Blotcher et al. [16] (93%) or that of the systematic review conducted by Scott-Sheldon [33] (81%). The lack of explicit follow-up during the intervention may have been the reason for failure to achieve higher retention.

Clinical implications

The neutral results of this pilot study, in terms of the effects of the intervention in an unselected population of patients fitted with ICDs, suggest that it would probably be more efficient to use it in patients with higher levels of anxiety, depression, or stress and poorer QoL, ideally after the onset of ICD shocks.

We did not obtain results that would lead us to think about a better response to training in patients who have suffered ICD discharges. Only 8 patients with shock underwent mindfulness training. Hence, it was not possible to obtain conclusive results regarding training when comparing 8 patients with shocks vs. 32 without shocks. No statistically significant differences were found in the analysis (U Mann-Whitney).

The low retention rate observed in the study and the current low incidence of shocks in patients with ICDs suggest that future studies in this field should be designed as multi-center studies in order to achieve adequate sample sizes.

Finally, it is demonstrated that the app intervention is feasible and can be used for this type of training.

Limitations of the study

The main limitation of our study was the low number of patients in each group, which meant we were unable to draw conclusive results. Other studies with a much smaller size, such as the 45 participants in the study by Salmoirago-Blotcher et al. [16], found significant results for the anxiety variable.

The high dropout rate in both intervention branches could be an expression of the fact that patients with ICDs do not find this type of tool useful.

Another limitation was that patients with ICD shocks (the main predictor of QoL impairment and anxiety in these patients) or with recent implantation were under-represented.

Finally, a lack of information on attendance at the sessions, or on the use of the app, means that we cannot provide data on treatment compliance.

Conclusions

After patients with an ICD completed an 8-week mindfulness training program, either face-to-face or through an app, no significant differences were found in QoL, psychological, or biomedical variables.

The intervention program, both face-to-face and via app, was well accepted by participants, with a retention rate of 59% and no adverse effects reported.

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Sodium restriction in patients with chronic heart failure and reduced ejection fraction: A randomized controlled trial

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Abstract

Background: *Sodium restriction is recommended for patients with heart failure (HF) despite the lack of solid clinical evidence from randomized controlled trials. Whether or not sodium restrictions provide beneficial cardiac effects is not known.*

Methods: *The present study is a randomized, double-blind, controlled trial of stable HF patients with ejection fraction ≤ 40%. Patients were allocated to sodium restriction (2 g of sodium/day) vs. control (3 g of sodium/day). The primary outcome was change in N-terminal pro-B-type natriuretic peptide (NT-proBNP) at 20 weeks. Secondary outcomes included quality of life and adverse safety events (HF readmission, blood pressure or electrolyte abnormalities).*

Results: *Seventy patients were enrolled. Median baseline sodium consumption was 3268 (2225–4537) mg/day. Adherence to the intervention based on 24-hour urinary sodium was 32%. NT-proBNP and quality of life did not significantly change between groups ($p > 0.05$ for both). Adverse safety events were not significantly different between the arms ($p > 0.6$ for all). In the per protocol analysis, patients who achieved a sodium intake < 2500 mg/day at the intervention conclusion showed improvements in NT-proBNP levels (between-group difference: –55%, 95% confidence interval –27 to –73%; $p = 0.002$) and quality of life (between-group difference: –11 ± 5 points; $p = 0.04$). Blood pressure decreased in patients with lower sodium intake (between-group difference: –9 ± 5 mmHg; $p = 0.05$) without significant differences in symptomatic hypotension or other safety events ($p > 0.3$ for all).*

Conclusions: *Adherence assessed by 24-hour natriuresis and by the nutritionist was poor. The group allocated to sodium restriction did not show improvement in NT-proBNP. However, patients who achieved a sodium intake < 2500 mg/day appeared to have improvements in NT-proBNP and quality of life without any adverse safety signals. ClinicalTrials.gov Identifier: NCT03351283.* (Cardiol J 2023; 30, 3: 411–421)

Key words: heart failure, sodium intake, NT-proBNP, quality of life

Introduction

Given the primacy of sodium in the pathophysiology of heart failure (HF), it is intuitive that sodium restriction should be a primary goal of treatment [1–6]. However, despite being recommended by international guidelines, sodium restriction lacks solid clinical evidence from well-powered randomized controlled trials [7, 8]. In fact, most of the evidence comes either from trials assessing the effect of sodium restriction in non-HF populations such as patients with hypertension or from observational studies [9, 10]. Notably, available evidence has shown conflicting results making it difficult to support specific recommendations for sodium restriction in HF [11–19].

Traditionally, it would be expected that sodium restriction can lead to a negative sodium balance resulting in an improved volume status. However, severe sodium restriction might not be desirable because detrimental effects such as higher activation of the renin–angiotensin–aldosterone system and worse outcomes have been reported in clinical trials as well as in a large observational study [17, 19]. Therefore, a gap in knowledge would be whether a non-severe sodium restriction could provide beneficial cardiac effects compared to a standard cardiac diet of ~3 g of sodium/day.

Thus, in the present randomized, controlled trial the effect of sodium restriction (2 g of sodium/day) was tested vs. a control group (3 g of sodium/day) in stable HF patients with reduced ejection fraction. Hypothesized herein, was that patients randomized to sodium restriction will show improved cardiac parameters such as B-type natriuretic peptide (BNP) levels and cardiac-related quality of life.

Methods

Study design

This was a randomized, double-blind, parallel-group trial in stable chronic HF patients with reduced ejection fraction. The study was registered in 2017 (ClinicalTrials.gov Identifier: NCT03351283).

Population

From January 2018 to November 2019, we assessed the eligibility of consecutive patients with chronic HF and reduced ejection fraction (≤ 40%) who attended our tertiary care center. Inclusion criteria were: 1) treatment with both an

angiotensin-converting-enzyme inhibitors (ACEI) or angiotensin-receptor-blockers (ARB), and a beta-blocker; 2) stable medical treatment defined as no change in medications for the prior 4 weeks; 3) age ≥ 18 years; 4) systolic blood pressure equal or greater than 90 mmHg; 5) highly motivated patients willing to participate. Excluded patients were those with: 1) a history of a HF admission in the prior month or with a New York Heart Association class III or IV; 2) an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 assessed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation; 3) serum sodium < 130 mmol/L; 4) hemoglobin < 10 g/dL; 5) patients scheduled to any intervention with the aim of improving their cardiovascular function (for example percutaneous coronary intervention, coronary artery bypass grafting, etc.); 6) valvular heart disease equal or greater than moderate degree; 7) dementia; 8) cancer or any other condition compromising life expectancy within the following 12 months. The study was approved by the Ethics Committee of the documented hospital and all participants provided written informed consent. The study was terminated when the target subject recruitment was achieved.

Intervention and adherence

Patients were randomized to either sodium restriction (goal of 2 g of sodium/day) vs. a control group (3 g of sodium/day). A 24-hour urinary collection was collected the day before randomization to estimate baseline sodium intake. During the visit for randomization, a qualified nutritionist estimated dietary sodium intake using a standardized 24-hour food diary to obtain the dietary consumption of each patient. A thorough nutritional analysis of the subjects' diets was obtained using the Food Processor® SQL Nutrition Analysis Software (version 7.9; ESHA Research). The nutritionist then calculated and provided multiple written diets (menus) each containing either 2 g (sodium restriction group) or 3 g of sodium (control). For this study the control group would be provided with menus of 3 g of sodium/day as this is the upper boundary recommended by international guidelines [20]. During the initial visit, the nutritionist did a comprehensive explanation of each of the diets and educated the patients and their families with regards to hidden salt and the importance of following the provided diet. Diets were individually tailored to each patient to have appropriate macronutrients and calorie content. The nutritionist elaborated individualized menus following a comprehensive dietary approach so diets with either 2 or 3 g of sodium/day but had similar caloric and nutrient contents, which has been shown to be feasible [21]. Following randomization, patients were seen at 6 and 12 weeks where the nutritionist estimated dietary sodium intake with the food frequency questionnaire. Based on estimated sodium intakes, the nutritionist went over the diets with the patient to improve adherence. At the end of the intervention (week 20), another 24-hour urine collection was collected to estimate final sodium intake. The estimated sodium intakes from the 24-hour food dairy were used for advice, and the 24-hour urine collection was used to assess adherence. Completeness of 24-hour urine collections was determined on the basis of volume, with a threshold of ≥ 250 mL [22]. Adherence was defined as a urinary sodium excretion < 2500 mg in the sodium restriction group, and a sodium excretion between 2500 and 3500 mg/day in the control group.

Outcomes

The primary outcome was change in N-terminal pro-B-type natriuretic peptide (NT-proBNP) from baseline to the end of the 20-week intervention. Secondary outcomes were 1) change in quality of life quantified by the Minnesota Living with Heart Failure Questionnaire (MLHFQ), 2) change in eGFR, and 3) survival free of the composite of mortality and hospitalization. Safety end points included hyponatremia (serum sodium < 130 mmol/L), hyperkalemia (serum potassium > 5.5 mmol/L), hypotension (systolic blood pressure < 90 mmHg) and worsening renal function (defined as an absolute increase in creatinine ≥ 0.3 mg/dL).

Sample size

Sample size was calculated with Stata SE version 16.0. Based on the study of Paterna et al. [11] mean ± standard deviation of BNP after 180 days of a diet with ~2800 mg of sodium/day was 555 ± 175 pg/mL vs. 745 ± 305 pg/mL with a diet of ~1800 mg sodium/day. For a significance level of alpha = 0.05, and a statistical power of 0.80, the minimum sample size was calculated as 29 patients per group. Assuming a 20% dropout rate the final sample size was estimated to be 70 patients.

Randomization

The www.randomization.com website was used to generate a simple sequential randomization plan. The nutritionist was responsible for the randomization as he was the investigator who allocated participants to the intervention and followed them during the entire study.

Blinding

Investigators involved in the assessment of outcomes as well as participants were blinded throughout the study. Participants received menus but they did not know if the menus aimed to have a sodium restriction with a goal of 2 g of sodium/day or 3 g of sodium/day. Baseline measurement of main variables (NT-proBNP, quality of life, eGFR, etc.) were assessed before randomization.

Statistical methods

Continuous variables were presented as mean ± ± standard deviation or median (quartile 1, quartile 3), according to the observed distribution. Baseline between-group differences were assessed with the Student t test or the Mann-Whitney test, as appropriate. Categorical variables were presented as absolute or relative frequencies, and between-group differences were assessed with the Pearson χ^2 test. Changes from baseline to the end of the intervention were assessed with the paired Student t test or the Wilcoxon signed-rank test. Endpoints were estimated as changes from baseline to the end of the intervention and were compared with the Student t test or Mann-Whitney test. Survival-free of the composite outcome was assessed with the log-rank test and the Kaplan-Meier method. Analyses were done by intention to treat with all available data. For the per protocol analysis, patients were divided into two groups based on 24-hour urinary sodium excretion at the end of the intervention: those who achieved < or ≥ 2500 mg of sodium/day. This cutoff value was chosen because this is the midpoint between 2000 and 3000 mg, which were the targets of the intervention. The goal of the per-protocol analyses was to describe if sodium restriction (2 g of sodium/day) could provide beneficial cardiac effects compared to patients who did not achieve sodium restriction. Specifically, it was not our intention to compare a specific 2-g sodium arm vs. a specific 3-g sodium arm but rather a sodium restriction group (2 g) vs. a group that did not achieve this restriction. Sensitivity analyses were done using 2750 or 3000 mg of sodium/day as cutoff values, as well as with multivariable linear regression with each of the three cutoff values adjusting for age, sex, and changes in medications during the study (ACEI or ARB, and loop diuretics). For linear regression, skewed variables were log transformed to approximate normal distribution. P values < 0.05 were considered statistically significant. Stata SE version 16.0 (StataCorp, College Station, TX) was used for statistical analysis.

Results

Patient characteristics

Ninety-nine patients were assessed for eligibility, seventy of whom were randomized (**Suppl. Fig. 1**). Seven patients in the sodium restriction group and 6 patients in the control group refused to continue participating. Therefore, 57 (81%) patients completed the 20-week intervention. Two thirds were male and ischemic heart disease was the predominant etiology. Mean sodium consumption at baseline (based on 24-hour sodium urinary excretion) was 3582 ± 1806 mg/day and was not significantly different between groups. Table 1 summarizes baseline characteristics of randomized patients. Except for gender and use of aldosterone antagonist, the groups were comparable.

Adherence to intervention

At baseline, estimated sodium consumption was not statistically different between groups (sodium restriction group: 3305 ± 1989; control group: 3911 ± 1533; p = 0.21). Based on 24-hour recalls at 6 and 12 weeks, estimated sodium consumption was not significantly different between groups (p > 0.10 for both). Sodium consumption at the end of the intervention (based on 24-hour urinary collection) showed a near significant association to be lower in the sodium restriction group (sodium restriction group: 3003 ± 1244 mg/day; control group: 3755 ± 1797 mg/day; mean difference 752, 95% confidence interval [CI] 64 to 1568 mg/day, p = 0.07). However, the change in sodium intake was not significantly different between groups (sodium restriction group: –57 ± 1948 mg/day; control group: –426 ± 1571 mg/day; p = 0.50). Adherence to the intervention based on 24-hour urinary sodium was 32% and was similar between the 3-g compared to the 2-g group (28% vs. 35%, respectively; p = 0.55).

Outcomes. Intention-to-treat analysis

In the overall population NT-proBNP did not significantly change from baseline to the end of the intervention (median change in NT-proBNP –29 pg/mL [interquartile range –267 to 211 pg/mL], p = 0.69). No significant changes were observed between groups (p = 0.88) (Table 2, Fig. 1). Quality of life quantified by the MLHFQ improved from baseline to the end of the intervention in the overall population (change –9.3 ± ± 19.9, p < 0.001). A near significant associa-

Table 1. Baseline characteristics of patients.

	Total population (n = 70)	Sodium restriction (n = 37)	Control (n = 33)	P
Demographics				
Age [years]	60 ± 12	61 ± 12	58 ± 13	0.32
Male	47 (67%)	20 (54%)	27 (82%)	0.014
Past medical history				
Diabetes	26 (37%)	14 (38%)	12 (36%)	0.90
Hypertension	34 (49%)	19 (51%)	15 (45%)	0.62
Dyslipidemia	36 (51%)	17 (46%)	19 (58%)	0.33
Ischemic heart disease	51 (73%)	23 (62%)	28 (85%)	0.058
LVEF [%]	30 ± 7	29 ± 8	32 ± 7	0.11
Physical exam and functional class				
Systolic blood pressure [mmHg]	111 ± 15	110 ± 16	112 ± 15	0.64
Body mass index [kg/m^2]	28.1 ± 4.7	27.3 ± 4.6	29.0 ± 4.8	0.12
NYHA class I	31 (44%)	16 (43%)	15 (45%)	0.85
NYHA class II	39 (56%)	21 (57%)	18 (55%)	0.85
MLHFQ (points)	38 (19, 58)	35 (12, 54)	40 (27, 59)	0.15
Laboratory data				
Serum sodium [mmol/L]	141 ± 4	141 ± 3	142 ± 4	0.51
eGFR [mL/min/1.73 m^2]	64 ± 25	67 ± 25	62 ± 24	0.37
NT-proBNP [pg/mL]	762 (363, 2683)	1402 (378, 3387)	540 (350, 1704)	0.14
Urinary sodium excretion [mg/day]	3268 (2225, 4537)	3259 (1645, 4209)	3419 (2990, 4605)	0.12
Medication				
Loop diuretic dose (mg of furosemide equivalent/day)	20 (0, 40)	40 (0, 40)	20 (0, 40)	0.64
Loop diuretics	50 (70%)	27 (73%)	23 (70%)	0.76
ACEI, ARB or ARNI	66 (94%)	35 (95%)	31 (94%)	> 0.99
Beta-blocker	63 (90%)	34 (92%)	29 (88%)	0.70
Aldosterone antagonist	51 (73%)	31 (84%)	20 (61%)	0.029

Continuous data is shown as mean ± standard deviation, or median (quartile 1, quartile 3). ACEI — angiotensin converting enzyme inhibitor; ARB — angiotensin receptor blocker; ARNI — angiotensin receptor neprilysin inhibitor; eGFR — estimated glomerular filtration rate; LVEF — left ventricular ejection fraction; MLHFQ — Minnesota Living with Heart Failure Questionnaire; NT-proBNP — N-terminal pro-B-type natriuretic peptide; NYHA — New York Heart Association

tion was found to be an improvement in quality of life in the control group (p = 0.052) (Table 2, Fig. 1). No significant changes were observed for blood pressure, serum sodium, serum potassium, serum creatinine and weight between groups (p ≥ 0.14 for all). Fourteen patients experienced a HF readmission and 1 patient died. Out of the 15 events, 8 occurred in the sodium restriction group and 7 in the control group. Survival free of HF readmission or death was not significantly different between groups (p = 0.89). The proportion of hyponatremia, hyperkalemia, hypotension, and worsening renal function was also similar between groups (Table 3).

Per-protocol analysis

Based on 24-hour urinary sodium excretion, 36% of patients achieved a sodium intake < 2500 mg/day at the end of the intervention. In the group with < 2500 mg/day, sodium intake statistically changed from baseline to the end of the intervention: mean change –1076 mg (95% CI –354 to –1798, p = 0.006), while in the group with ≥ 2500 mg/day, the change was not statistically significant: mean change +263 (95% CI –437 to +963, p = 0.45). The between groups difference was statistically different: 1339 mg (95% CI 2398 to 280 mg/day); p = 0.01 (Fig. 2). NT-proBNP levels (p = 0.01) and quality of life (p = 0.04) improved in the group

Table 2. Changes in endpoints from baseline to the end of the intervention. Intention to treat analysis.

Intention to treat	Sodium restriction				Control				Between-group difference: sodium restriction vs. control	
	Baseline	Week 20	Within group change	P	Baseline	Week 20	Within group change	P	Estimate	P
NT-proBNP [pg/mL]*	1403 (378, 3387)	882 (452, 3847)	–35 (–165, 176)	0.88	540 (350, 1704)	569 (262, 1500)	–25 (–165, 176)	0.52	3% (–38%, 70%)	0.91
MLHFQ (points)	34 ± 4	29 ± 4	–5 ± 4	0.19	47 ± 5	32 ± 4	–15 ± 3	< 0.001	9 ± 2.6	0.052
SBP [mmHg]	110 ± 3	112 ± 3	2 ± 3	0.51	110 ± 3	110 ± 3	0 ± 4	0.95	2 ± 5	0.72
Serum sodium [mmol/L]	141 ± 0.5	142 ± 0.5	1 ± 0.6	0.038	142 ± 0.6	142 ± 0.6	0 ± 0.6	0.62	1.6 ± 0.9	0.08
Serum potassium [mmol/L]	4.7 ± 0.1	4.6 ± 0.1	–0.1 ± 0.1	0.37	4.6 ± 0.1	4.7 ± 0.1	0 ± 0.1	0.75	–0.2 ± 0.2	0.38
Serum creatinine [mg/dL]	1.12 ± 0.06	1.16 ± 0.06	0.04 ± 0.05	0.35	1.18 ± 0.07	1.20 ± 0.06	0.02 ± 0.03	0.32	0.02 ± 0.06	0.72
Weight [kg]	71.3 ± 2.6	71.7 ± 2.7	0.4 ± 0.9	0.64	81.4 ± 3.0	80.5 ± 3.0	–0.9 ± 0.6	0.16	1.3 ± 1.1	0.25

Data is shown as median (interquartile range) or mean ± standard error (SE). *For the between-group difference of NT-proBNP, statistical test was performed on the log scale because of skewness. Estimate is presented on the percent scale. Because confidence intervals (CIs) are asymmetrical and thus SEs are not useful, 95% CIs is presented. SBP — systolic blood pressure; MLHFQ — Minnesota Living with Heart Failure Questionnaire; NT-proBNP — N-terminal pro-B-type natriuretic peptide

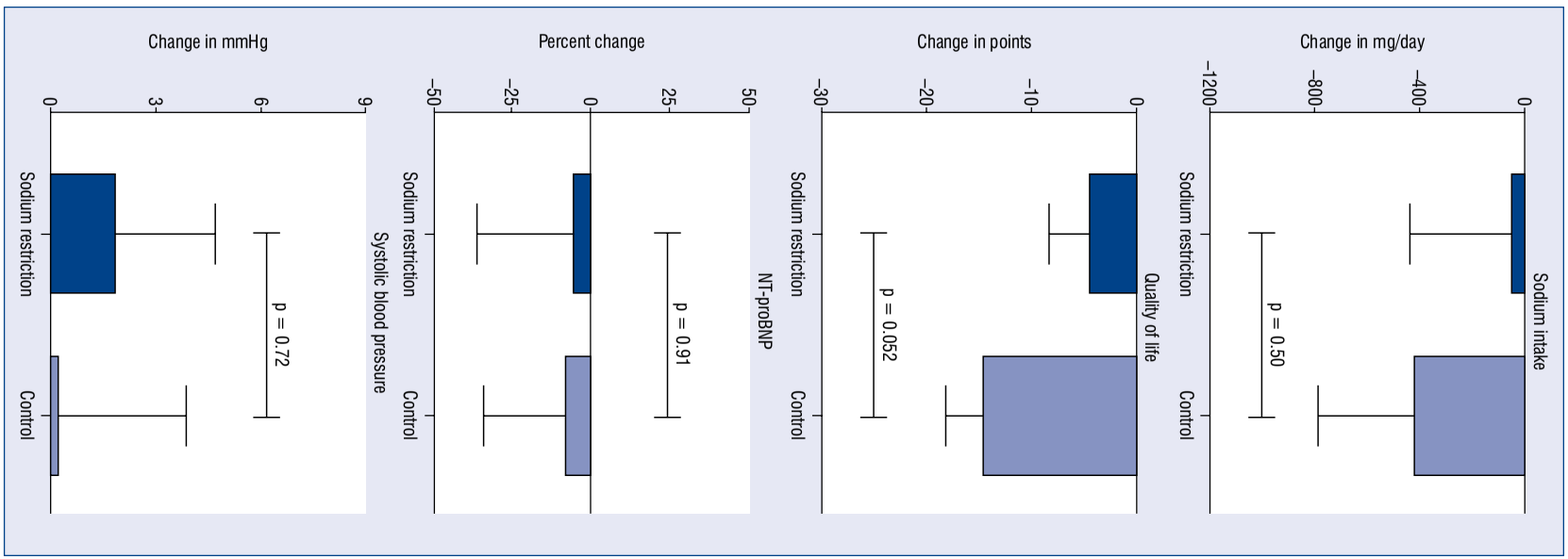

Figure 1. Intention to treat analysis. Bars show the mean change in parameter. Error bars show standard error of the mean; NT-proBNP — N-terminal pro-B-type natriuretic peptide.

Table 3. Safety parameters.

	Intention to treat			Per protocol		
	Sodium restriction (n)	Control (n)	P	< 2500 mg sodium/ /day (n)	≥ 2500 mg sodium/ /day (n)	P
Serum sodium < 130 mmol/L	0	0	—	0	0	—
Serum potassium > 5.5 mmol/L	1	0	> 0.99	1	0	0.35
Systolic blood pressure < 90 mmHg	2	2	> 0.99	1	2	> 0.99
Worsening renal function (> 0.3 mg/dL)	3	1	0.62	2	2	0.61

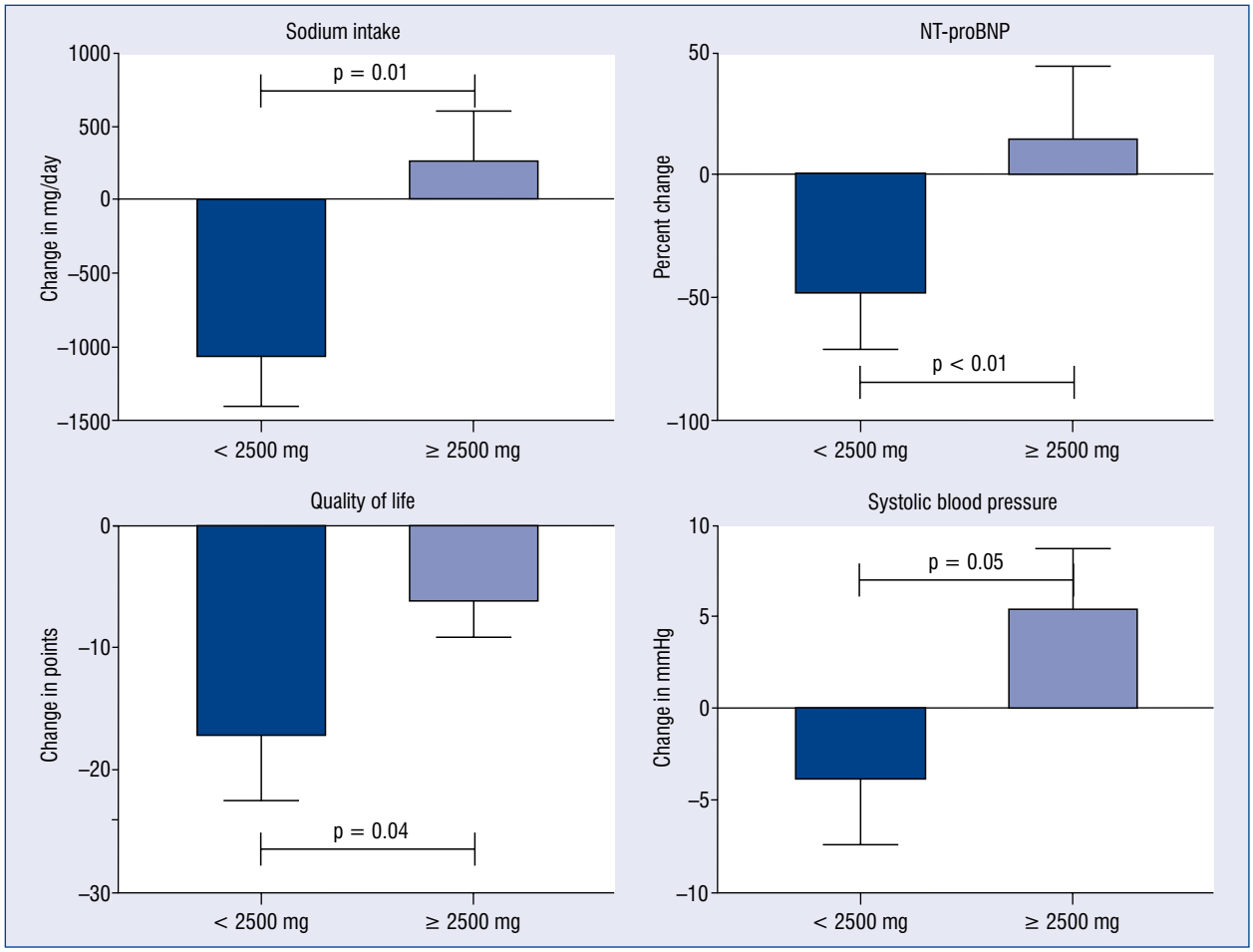

Figure 2. Per protocol analysis. Bars show mean change in parameter. Error bars show standard error of the mean; NT-proBNP — N-terminal pro-B-type natriuretic peptide.

with < 2500 mg/day compared to the group with ≥ 2500 mg/day (Fig. 2, Table 4). Likewise, blood pressure decreased in the patients with lower sodium consumption compared to the other group ($p = 0.05$). No significant changes were observed for serum sodium, potassium, creatinine and weight between groups ($p > 0.10$ for all) (Fig. 2, Table 4). The proportion of hyponatremia, hyperkalemia, hypotension, and worsening renal function was similar between groups (Table 3). In sensitivity analysis, similar results were observed for NT-proBNP levels and quality of life in favor of the group with lower sodium intake when using cutoff values of 2750 or 3000 mg, and after adjusting for

Table 4. Changes in endpoints from baseline to the end of the intervention. Per protocol analysis.

Per protocol	< 2500 mg sodium				≥ 2500 mg sodium/day				Between-group difference: < 2500 mg vs. ≥ 2500 mg	
	Baseline	Week 20	Within group change	P	Baseline	Week 20	Within group change	P	Estimate	P
NT-proBNP [pg/mL]*	1448 (336, 3961)	579 (169, 2345)	–205 (–1123, 0)	0.02	582 (367, 2501)	750 (311, 1982)	–12.5 (–116, 467)	0.44	–55% (–27%, –73%)	0.002
MLHFQ (points)	46 ± 6	28 ± 6	–17 ± 5	0.003	39 ± 4	32 ± 4	–6 ± 3	0.02	–11 ± 5	0.04
SBP [mmHg]	112 ± 3	108 ± 4	–4 ± 3	0.26	110 ± 3	115 ± 3	5 ± 3	0.09	–9 ± 5	0.05
Serum sodium [mmol/L]	142 ± 0.5	142 ± 0.7	0 ± 0.7	0.55	141 ± 0.5	142 ± 0.5	1 ± 0.6	0.07	–1 ± 1	0.12
Serum potassium [mmol/L]	4.7 ± 0.1	4.8 ± 0.1	0.1 ± 0.2	0.61	4.6 ± 0.1	4.6 ± 0.1	0 ± 0.1	0.95	0.1 ± 0.2	0.61
Serum creatinine [mg/dL[	1.14 ± 0.09	1.23 ± 0.08	0.09 ± 0.07	0.24	1.16 ± 0.06	1.17 ± 0.06	0.01 ± 0.03	0.76	0.08 ± 0.07	0.25
Weight [kg]	71.4 ± 3.4	70.4 ± 3.1	–1.0 ± 0.9	0.28	78.9 ± 2.8	78.3 ± 2.9	–0.6 ± 0.6	0.36	–0.4 ± 1.1	0.70

Data is shown as median (interquartile range) or mean ± standard error (SE). *For the between-group difference of NT-proBNP, statistical test was performed on the log scale because of skewness. Estimate is presented on the percent scale. Because confidence intervals (Cis) are asymmetrical and thus SEs are not useful, 95% CIs is presented. SBP — systolic blood pressure; MLHFQ — Minnesota Living with Heart Failure Questionnaire; NT-proBNP — N-terminal pro-B-type natriuretic peptide

covariables with the three different cutoff values (**Suppl. Table 1**).

Discussion

There are scarce data from randomized trials to support an appropriate level of sodium restriction in patients with HF. The current main findings are: 1) A nutritional intervention aimed to reduce sodium intake did not reduce NT-proBNP levels; however, 2) Patients who achieved < 2500 mg of sodium/day showed improvements in NT-proBNP levels and quality of life; 3) Sodium intake within the limits of the present study appeared to be safe as very few safety issues were noted; 4) Even in highly motivated patients with a tight follow-up, adherence to sodium restriction was remarkably low.

In the Geriatric Out-of-Hospital Randomized Meal Trial in Heart Failure (GOURMET) and Prevent Adverse Outcomes in Heart Failure by Limiting Sodium Pilot Study (PROHIBIT), 4 weeks and 12 weeks of interventions aimed at reducing sodium intake, respectively, were not associated with reductions in BNPs [23, 24]. Conversely, in the Study of Dietary Intervention Under 100 MMOL in Heart Failure (SODIUM-HF), sodium restriction for 6 months did result in a significant reduction of BNP levels [25]. In the present study, a 20-week intervention did not show improvements in NT-proBNP levels, likely due to poor adherence. However, patients who achieved a sodium intake < 2500 mg/day did show improvement in NT-proBNP levels. Importantly, length of interventions was notably different among the 4 mentioned studies. Shorter interventions (2 weeks in GOURMET and 12 weeks in PROHIBIT) were not associated with improvements in NT-proBNP levels. Conversely, longer interventions (6 months in the SODIUM-HF and 20 weeks in the per-protocol analysis of the present study) did show a potential benefit. Therefore, one might hypothesize that the effect of sodium restriction on natriuretic peptides may be possible in the long-term.

Regarding quality of life, a statistically significant improvement was observed in the group that achieved < 2500 mg of sodium/day compared to that of the control group. This finding is consistent with the GOURMET, PROHIBIT, and SODIUM-HF studies, in which interventions aimed to reduce sodium intake showed improvement in quality of life despite somehow different interventions: food was provided in the first two, and written menus in the last one [23–25]. Therefore, it is likely that sodium restriction could have improved quality

of life, and these beneficial effects may appear as soon as 4 weeks in the GOURMET study and may continue for up to 6 months (SODIUM-HF and the present study).

Importantly, neither in the present study nor in the other 3 randomized trials an increased risk of adverse outcomes was observed in patients allocated to sodium restriction [23–25]. These findings contrast with the study performed by Italian investigators where patients with intensive restriction compared to moderate sodium restriction (1800 mg vs. 2800 mg of sodium/day, respectively) showed higher risk of hospital readmission [11]. Notably, in that study patients were treated with higher doses of loop diuretics (250 mg to 500 mg of furosemide per day) compared to the present study (~20 mg of furosemide per day) or the PROHIBIT trial (~50 mg of furosemide equivalents per day). Given that loop diuretics strongly enhance neurohormonal activation [26, 27], and lower sodium chloride intake also stimulates the renin–angiotensin–aldosterone system [28, 29], it is possible that these differences drove the outcomes in that study. Another remarkable difference is that in the present study, the GOURMET, and PROHIBIT trials most patients were taking ACEI/ARBs, while in the Italian study only 30% were taking captopril. The effect of sodium restriction in patients with or without ACEI/ARB was reported in the HART study (A Self-management Intervention for Mild to Moderate Heart Failure) where worse outcomes with sodium restriction were observed only in patients who were not receiving ACEI/ARB [19].

Another remarkable observation in the present study is that it is very hard for patients with HF to adhere to diet interventions that aim to decrease sodium intake. This finding is consistent with a previous trial where very few patients achieved a sodium consumption < 2000 mg/day even with dietitian education, or even in the PROHIBIT study where adherence was ~50% despite having food provided [24, 30]. The SODIUM-HF trial will provide unique information to understand if diet interventions aiming to decrease sodium intake can improve clinical outcomes [31].

With regards to medication, it was noted that 70% of the population were receiving loop diuretics which has been shown to potentially affect the accuracy of 24-hour urine collections likely because in stable HF patients loop diuretics are key to maintaining sodium homeostasis as demonstrated in a recent study where loop diuretic omission resulted in a 50% reduction in natriuresis [32, 33]. Importantly, in the present study the use of aldosterone antagonists was higher in the sodium restriction group at baseline, and although all patients were taking ≤ 25 mg of spironolactone, which is not typically considered a natriuretic dose, some potential natriuretic or cardiac effect of these drugs cannot be negated and thus a possible influence on the observed results. Interestingly, serum sodium actually increased in the sodium restriction group; however, the magnitude of the change was not clinically relevant (1 mmol/L during the 20-week intervention) and the between-group difference did not reach statistical significance ($p = 0.08$).

Limitations of the study

This was a single-center study with a relatively small sample size; thus, results should be interpreted cautiously. Namely, the present study might be underpowered to detect a smaller difference of change in NT-proBNP levels. Baseline sodium intake was not excessively high; therefore, results may not be extrapolated to patients with higher sodium intake. Assessments of sodium intake 4 times during a 20-week period and do not consider whether there were large fluctuations between these times. Adherence was assessed by 24-hour urinary collections, which may not be a reproducible method, and completeness of urine collections was determined on volume alone, which may be an insensitive method [34]. In addition, adherence to the intervention was poor. Food was not provided but patients were asked to follow written diets, which decreases adherence to the intervention. However, in the rigorously conducted PROHIBIT study diet compliance was ~50% in support of the notion that diet interventions are extremely challenging [24]. NT-proBNP showed a near statistical association to be lower in the control group at baseline, and thus some impact cannot be ruled out on the results because the primary outcome was a change in NT-proBNP. Finally, there were more men in the control group which could have potentially affected adherence to the intervention and consequently the observed results.

Conclusions

Adherence to an intervention aimed to reduce sodium intake was poorly assessed both with the 24-hour urinary sodium excretion and by the nutritionist; thus, this study shows the challenges of this type of intervention and suggests its limited usefulness in future studies. No significant improvement in NT-proBNP levels were observed in patients

allocated to an intervention aiming to reduce sodium intake. However, patients who achieved a sodium intake < 2500 mg/day at the end of the 20-week intervention did show improvements in NT-proBNP levels and quality of life without any adverse safety signal.

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Pseudo-discordance mimicking low-flow low-gradient aortic stenosis in transcatheter aortic valve replacement patients with severe symptomatic aortic stenosis

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Abstract

Background: *While the combination of a small aortic valve area (AVA) and low mean gradient is frequently labeled 'low-flow low-gradient aortic stenosis (AS)', there are two potential causes for this finding: underestimation of mean gradient and underestimation of AVA.*

Methods: *In order to investigate the prevalence and causes of discordant echocardiographic findings in symptomatic patients with AS and normal left ventricular (LV) function, we evaluated 72 symptomatic patients with AS and normal LV function by comparing Doppler, invasive, computed tomography (CT) LV outflow tract (LVOT) area, and calcium score (CaSc).*

Results: *Thirty-six patients had discordant echocardiographic findings (mean gradient < 40 mmHg, AVA ≤ 1 cm^2). Of those, 19 had discordant invasive measurements (true discordant [TD]) and 17 concordant (false discordant [FD]): In 12 of the FD the mean gradient was > 30 mmHg; technical pitfalls were found in 10 patients (no reliable right parasternal Doppler in 6). LVOT area by echocardiography or CT could not differentiate between concordants and discordants nor between TD and FD (p = NS). CaSc was similar in concordants and FD (p = 0.3), and it was higher in true concordants than in TD (p = 0.005). CaSc positive predictive value for the correct diagnosis of severe AS was 95% for concordants and 93% for discordants.*

Conclusions: *Discordant echocardiographic findings are commonly found in patients with symptomatic AS. Underestimation of the true mean gradient due to technical difficulties is an important cause of these discrepant findings. LVOT area by echocardiography or CT cannot differentiate between TD and FD. In the absence of a reliable and compete multi-window Doppler evaluation, patients should undergo CaSc assessment.* (Cardiol J 2023; 30, 3: 422–430)

Key words: aortic stenosis, echocardiography, aortic valve, valvular disease, calcium

Introduction

Severe aortic stenosis (AS) is defined by an aortic valve (AV) area (AVA) ≤ 1.0 cm^2 and a mean gradient ≥ 40 mmHg [1, 2]. These parameters conflict in a high proportion of patients who present with an AV area ≤ 1 cm^2, but a mean gradient < 40 mmHg, even when systolic left ventricu-

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lar (LV) function appears normal [3]. While this discordance is frequently attributed to possible low-flow low-gradient severe AS with preserved LV function, the list of potential sources for discrepancies includes several causes: possible underestimation of Doppler flow velocity and derived mean gradients, echocardiographic underestimation of an elliptical LV outflow tract (LVOT) area [4–6], or small body size with transvalvular flow that is below average, but adequate

Notwithstanding the long list of potential root causes, studies of the syndrome of low flow low gradient severe AS frequently lack a comprehensive approach employing both independent imaging modalities and independent hemodynamic assessment to systematically and reliably rule them out. We therefore sought to investigate the prevalence of a discrepant echocardiographic constellation and the distribution of its individual root causes by comparing Doppler data to invasive hemodynamic data as well as computed-tomographic findings in patients with severe symptomatic AS and normal LV ejection fraction (LVEF).

Methods

Patients with symptomatic AS and LVEF > 50%, who underwent a complete echocardiographic, computed tomography (CT), and hemodynamic evaluation before transcatheter AV replacement at Sheba Medical Center from 2011 to 2019, were included in this study.

All patients underwent a full cardiac CT scan including quantification of AV calcification.

The study was authorized be the Sheba Medical Center Helsinki Committee.

Echocardiographic evaluation

Echocardiographic studies were performed utilizing commercially available machines according to current American Society of Echocardiography guidelines [7]. LVEF was measured using the Simpson method, and valve area was calculated by the continuity equation. Pressure gradients were assessed from continuous wave transvalvular velocity tracings. Stroke volume (SV) was calculated as the product of the time velocity integral (VTI) and cross-sectional area of the LVOT and indexed to body surface area. All studies were performed by specialized echocardiography technologists and reported by a trained echocardiographer. For the purpose of this study, all original recordings were carefully re-evaluated by an experienced echocardiographer (R.K.).

Hemodynamic evaluation

Right heart catheterization was performed in all patients, recording pulmonary arterial pressure and capillary wedge pressure. Mean pressures were averaged from three cardiac cycles. Cardiac output was determined using the Fick method, and SV was calculated as cardiac output divided by heart rate. Left heart catheterization with retrograde passage of the stenotic AV was performed. Pressure gradients were measured from simultaneous LV and aortic pressure recordings or pullback tracings with electronic alignment of the recorded ventricular and aortic pressure curves, and AVA was calculated using the Gorlin equation.

CT acquisition protocol

An electrocardiogram (ECG)-gated non-contrast calcium score (CaSc) scan was followed by a contrast-enhanced scan utilizing a 256-slice scanner (Brilliance iCT, Philips Healthcare; collimation 96 × 0.625 mm, gantry rotation time of 330 ms, pitch value 0.2), with injection of 70 to 85 mL of a nonionic contrast agent at a flow rate of 3.5 mL/s followed by a 30-mL saline chase bolus (5 mL/s). Automated peak enhancement detection in the descending aorta was used for timing of the scan, and the data acquisition was automatically initiated at a threshold level of 100 Hounsfield units. Acquisition was performed during an inspiratory breathhold while the ECG was recorded simultaneously to allow retrospective gating of the data.

Calcium score analysis

Calcium score quantification was performed using dedicated software ("Heartbeat CS", IntelliSpace Portal, version 7V, Philips) implementing the Agatston method [8–10]. Briefly, lesion-specific scores were calculated as the product of the area of each calcified focus and peak CT Hounsfield units value and summed to obtain a total CaSc carefully excluding nonvalvular calcification of surrounding structures.

Definitions, stepwise analysis, and statistical methods

Patients with discordant echocardiographic findings (mean gradient < 40 mmHg despite AVA ≤ 1 cm^2), who were confirmed to have a mean gradient < 40 mmHg on invasive measurements, were defined as true discordant (TD). Patients with discordant echocardiographic findings, who had an invasive mean gradient ≥ 40 mmHg, were defined as false discordant (FD).

The clinical, echocardiographic, hemodynamic, and CT characteristics of concordants were

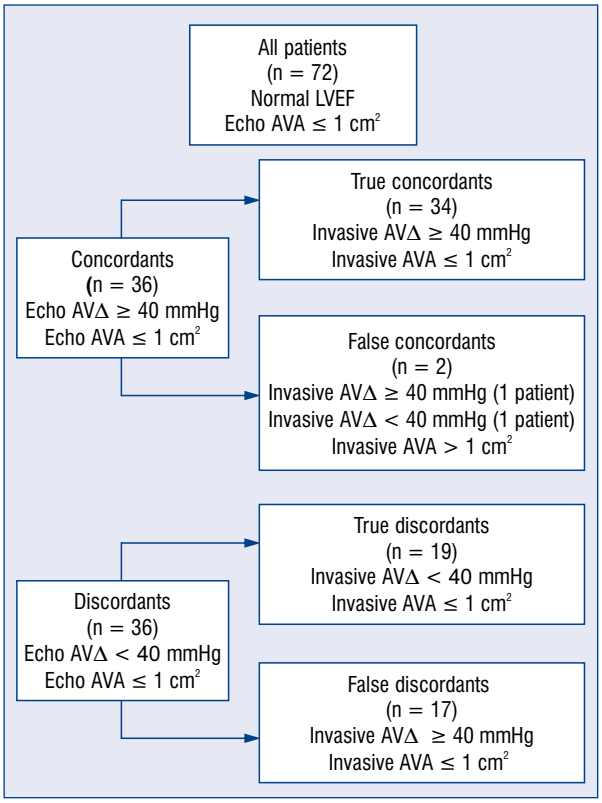

Figure 1. Patient population; AVA — aortic valve area; LVEF — left ventricular ejection fraction.

compared to discordants as a whole, as well as separately to FD and to TD. Finally, FD and TD were compared. Results are presented as mean ± standard deviation, and the different groups were compared by unpaired two-sample t-test.

Non-parametric data were expressed as percentages and were compared by χ^2-square test.

The positive predictive value of CaSc for the prediction of severe AS by invasive measurement was calculated for patients with concordant and discordant echocardiographic findings, respectively.

Results

Seventy-two patients had an echocardiographic AVA < 1.0 cm^2; their mean age was 81.6 ± 6.9 years, and 41 were females (57%). The flow chart in Figure 1 shows the patient distribution across the sub-groups defined by the pre-specified criteria. Clinical characteristics, and echocardiographic, invasive hemodynamic, and CT measurements of the whole patient population and the concordant and discordant groups are shown in Table 1.

Thirty-six patients had concordant echocardiographic findings (mean gradient > 40 mmHg and AVA ≤ 1 cm^2) compatible with high-gradient severe AS (concordants, Table 1), Systolic blood pressure was similar at echocardiography and the invasive evaluation (139 ± 29 mmHg and 134 ± ± 30 mmHg). Two patients with high echocardiographic mean gradients had an invasively measured AVA > 1 cm^2, and one of them had lower invasive gradient (related to significant pressure recovery) and was hence "false concordant". Consequently, the positive predictive value of concordant findings per echo for concordant findings at cardiac catheterization was 94.4%.

Thirty-six patients showed discordant findings on echocardiography, (mean gradient < 40 mmHg and an AVA ≤ 1 cm^2, discordants). Their systolic blood pressure was similar at echocardiography and the invasive evaluation (137 ± 27 mmHg and 136 ± 27 mmHg). Overall, when compared to concordants, discordants showed similar clinical characteristics (Table 1) and showed no significant difference in LVOT area. However, discordants had lower mean gradient, larger AVA, lower CaSc, and smaller SV index with values ≤ 35 mL/m^2 being significantly more prevalent (p = 0.006).

Nineteen of the discordant patients had an invasive hemodynamic mean gradient < 40 mmHg (TD), and 17 discordant patients showed hemodynamic mean gradients ≥ 40 mmHg (FD) (Table 2). Consequently, discordant findings per echocardiography had only a 52.7% positive predictive value for discordant findings at cardiac catheterization.

True discordants differed from the true concordant mainly in echocardiographic Doppler parameters, with smaller LVOT VTI, smaller AV VTI with lower mean gradients, lower SV indices, and slightly larger AVA (Table 2). Their invasive hemodynamic AVA was similar, their mean gradients were lower, and their CaSc were lower (p = 0.005); SV index ≤ 35 mL/m^2 was significantly more prevalent among TD than in TC (p = 0.01).

False discordants differed from TC only in their echocardiographic Doppler parameters with lower LVOT VTI, lower AV VTI, lower mean gradients, slightly larger AVA, and a lower SV index (Table 2). On invasive evaluation, TC and FD had similar AVA, similar mean gradients, and a similar CaSc indicating similar disease severity (Table 2). SV index ≤ 35 mL/m^2 was significantly more prevalent among FD than in TC (p = 0.04).

When compared to FD, TD had lower mean echocardiographic gradients and similar AVA and SV index. On invasive evaluation their gradients were significantly lower, and their AVA was simi-

Table 1. Baseline clinical, echocardiographic, invasive hemodynamic, and computed tomography characteristics: Concordants vs. discordants.

	All (n = 72)	Concordant (n = 36)	Discordant (n = 36)	P
Clinical				
Age [years]	81.6 ± 6.9	81.3 ± 7.9	81.8 ± 5.8	0.7
Gender (% female)	41 (57%)	20 (54%)	19 (56%)	0.9
Body surface area [m^2]	1.8 ± 0.21	1.79 ± 0.21	1.81 ± 0.22	0.7
Hypertension	56 (80%)	29 (85%)	27 (74%)	0.4
Diabetes mellitus	32 (45%)	16 (47%)	16 (43%)	0.7
Coronary artery disease	35 (49%)	18 (53%)	17 (46%)	0.55
Echocardiography				
LVEDD [cm]	4.5 ± 0.6	4.5 ± 0.6	4.5 ± 0.6	0.8
LVMI [g/m^2]	133 ± 49	136 ± 58	128 ± 35.6	0.6
LVEF [%]	61.0 ± 4.8	61 ± 5.3	61 ± 4.4	0.96
LVOT area [cm^2]	3.3 ± 0.5	3.4 ± 0.5	3.2 ± 0.46	0.2
LVOT VTI [cm]	22.8 ± 4.6	24.5 ± 4.2	21.3 ± 4.4	0.005
AV VTI [cm]	97.3 ± 20.3	113 ± 14.1	82.2 ± 12	< 0.0001
Mean gradient [mmHg]	41 ± 14	52 ± 11.0	29.5 ± 5.5	< 0.0001
AVA [cm^2]	0.77 ± 0.17	0.71 ± 0.17	0.82 ± 0.14	0.002
Stroke volume index [mL/m^2]	42 ± 10.4	46.1 ± 9.8	38.2 ± 9.7	0.001
Invasive hemodynamic				
Mean gradient [mmHg]	45.9 ± 13.4	51.3 ± 13	40.3 ± 11.6	0.0003
AVA [cm^2]	0.68 ± 0.21	0.65 ± 0.17	0.66 ± 0.9	0.9
Computed tomography				
LVOT area [cm^2]	4.24 ± 1.12	4.3 ± 1.1	4.2 ± 1.1	0.6
Ellipticity index	1.27 ± 0.09	1.25 ± 0.08	1.27 ± 0.09	0.4
Calcium score [AU]	2347 ± 1196	2678 ± 1151	1984 ± 1155	0.02

AV — aortic valve; AVA — aortic valve area; LVEDD — left ventricular end diastolic diameter; LVEF — left ventricular ejection fraction; LVMI — left ventricular mass index; LVOT — left ventricular outflow tract; VTI — velocity time integra

lar. CaSc tended to be lower, implying less severe valvular disease. The prevalence of SV index ≤ 35 mL/m^2 was similar between TD and FD (p = 0.8).

There was no difference between non-invasively and invasively determined mean gradients in echocardiographically TC patients (as well as TD), nor was there a difference in invasive mean gradients between TC and FD (Fig. 2A). While echocardiographic AVA was slightly smaller in TC when compared to TD and FD, there were no significant differences in mean invasive AVA across groups (Fig. 2B).

After a thorough review of the echocardiographic examinations of the 17 FD we found that a reliable right parasternal view was missing in 6 patients, LVOT VTI tracings were suboptimal in 3 patients, and inadequate due to poor imaging quality in 1 case. Seven of the 17 patients had an echocardiographic mean gradient > 35 mmHg, 5 had a mean gradient > 30 mmHg, and only 5 of them had a gradient between 25 and 29 mmHg.

Calcium score levels had a positive predictive value of 95% for the correct diagnosis of severe AS (likely) in concordants and of 93% in discordants.

Discussion

The main findings of this study are as follows: 1) In a selected group of symptomatic patients with severe AS and discordant echocardiographic findings (with a mean gradient > 30 mmHg), who underwent full hemodynamic evaluation, technical errors leading to underestimation of the true aortic gradient (pseudo-discordance) are almost as common as true low flow low gradient severe AS; 2) CT assessment of LVOT area was not helpful in differentiating between true and false discord-

Table 2. Baseline clinical, echocardiographic, invasive hemodynamic, and computed tomography characteristics.

	False discordant (n = 17)	True discordant (n = 19)	True concordant (n = 34)	P*	P**	P***
Clinical						
Age [years]	82.8 ± 4.5	81.4 ± 6.6	81.7 ± 7.9	0.8	0.5	0.4
Gender (% female)	6 (37.5%)	14 (74%)	18 (53%)	0.02	0.37	0.05
Body surface area [m^2]	1.84 ± 0.22	1.80 ± 0.23	1.79 ± 0.21	0.9	0.5	0.6
Hypertension	12 (69%)	15 (79%)	29 (85%)	0.8	0.4	0.84
Diabetes mellitus	8 (44%)	8 (42%)	16 (47%)	1	0.8	1
Coronary artery disease	10 (56%)	7 (37%)	18 (53%)	0.4	0.9	0.3
Echocardiography						
LVEDD [cm]	4.5 ± 0.5	4.6 ± 0.6	4.5 ± 0.6	0.7	0.9	0.6
LVMI [g/m^2]	132 ± 35	128 ± 40	138 ± 60	0.5	0.7	0.7
LVEF [%]	62 ± 4	59.7 ± 4.2	61 ± 5.4	0.4	0.46	0.09
LVOT area [cm^2]	3.3 ± 0.4	3.1 ± 0.5	3.3 ± 0.5	0.25	0.8	0.38
LVOT VTI [cm]	21.7 ± 43	21.2 ± 4.5	24.3 ± 4.3	0.02	0.05	0.8
AV VTI [cm]	84.8 ± 10.7	80.6 ± 12.5	113 ± 14.4	< 0.0001	< 0.0001	0.3
Mean Δ [mmHg]	32 ± 6	27.5 ± 4.9	51.8 ± 11.5	< 0.0001	< 0.0001	0.01
AVA [cm^2]	0.85 ± 0.14	0.83 ± 0.15	0.71 ± 0.17	0.006	0.004	0.8
Stroke volume index [mL/m^2]	39.2 ± 8.5	37.8 ± 102	45.9 ± 10	0.008	0.02	0.63
Invasive hemodynamic						
Mean Δ [mmHg]	51 ± 6.6	31.9 ± 6.4	52.2 ± 12.9	< 0.0001	0.5	< 0.0001
AVA [cm^2]	0.66 ± 0.25	0.69 ± 0.19	0.65 ± 0.17	0.4	0.9	0.6
Computed tomography						
LVOT area [cm^2]	4.4 ± 1.4	4.11 ± 0.9	4.2.9 ± 0.8	0.5	0.8	0.5
Ellipticity index	1.27 ± 0.11	1.26 ± 0.08	1.2 ± 0.08	0.6	0.5	0.5
Calcium score [AU]	2369 ± 1076	1707 ± 1141	2724 ± 1159	0.005	0.3	0.1

All abbreviations as in the main text and in Table 1; *Compares concordants and true discordants; **Compares concordants and false discordants; ***Compares true discordants and false discordants

ance; 3) Without an adequate transvalvular velocity recording from all echocardiographic windows the diagnosis of low gradient severe AS cannot be definitively established, and CT determination of the CaSc should be mandatory (Fig. 3).

These findings are in full agreement with the current guidelines stating that in patients older than 70 years, who have typical symptoms, AVA < 0.8 cm^2, and a high CaSc (> 1200 AU in women, and > 2000 AU in men, respectively) are associated with a very high probability of true severe AS [1, 2]. The findings have important implications for the diagnosis of true paradoxical low flow low gradient severe AS. Establishing its presence echocardiographically remains an exclusion diagnosis and is confounded by several factors that may lead to spuriously discordant findings.

Underestimation of peak velocity and Doppler-derived gradients. In many cases, heavily calcified valves may not allow the maximal envelope velocity to be obtained from an apical window, even when the angle alignment is optimal and the recorded signal appears to be of diagnostic quality. The use of multiple interrogation windows is paramount — in particular, the use of a right (or suprasternal) window, which allows sampling the velocity of the approaching jet without interposition of a calcified valve that may filter out the maximum signal. Previous studies have shown that relying solely on the apical view may lead to a significant underestimation of the peak and mean gradients in between 20% and 50% of cases [11, 12].

Underestimation of AVA by the continuity equation. In clinical practice, application of the

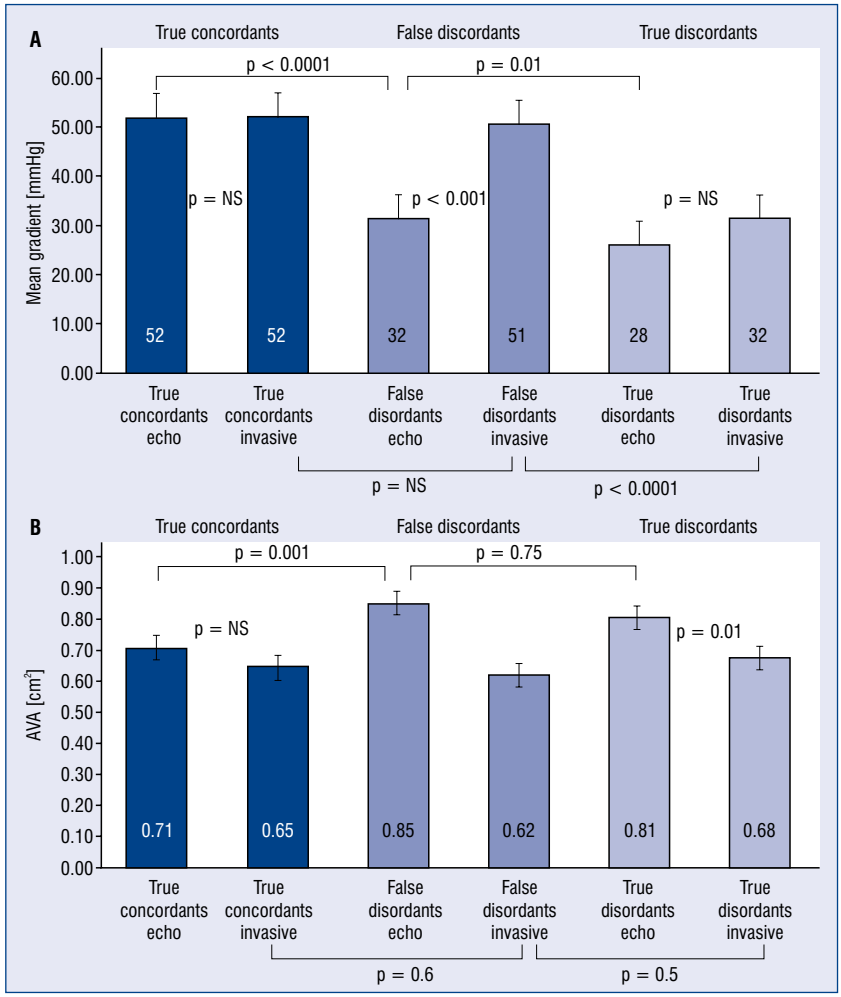

Figure 2. All patients with aortic valve area (AVA) ≤ 1 cm^2 (n = 70); **A.** Mean gradient [mmHg]; **B.** AVA [cm^2].

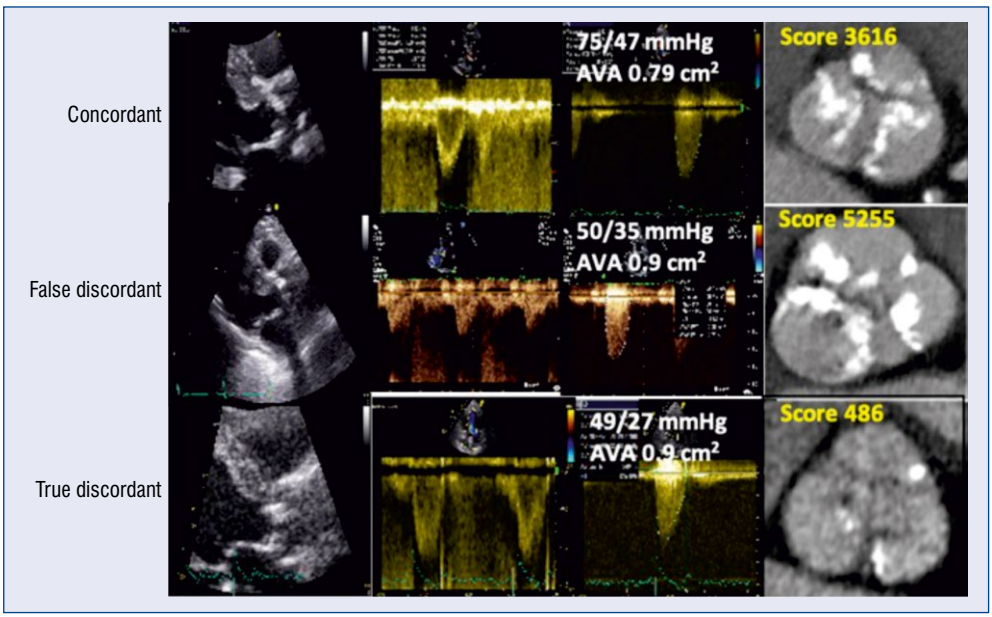

Figure 3. Three typical patients; AVA — aortic valve area.

continuity equation relies on calculation of the LVOT area by a single diameter assuming circularity. However, the LVOT area has been shown to be elliptic by both echocardiography [4] and CT studies [5, 13], so underestimation of the true valve area is possible. We therefore assessed the anatomic LVOT area in the three-dimensional CT data set.

Small body size. Patients with small body size may show valve areas ≤ 1.0 cm^2 even with non-severe AS, and they have smaller than expected gradients due to a lower cardiac output, which simply reflects their smaller perfused muscle mass.

We sought to determine the distribution of the root causes by first validating the hemodynamic severity of the lesion by cardiac catheterization, and then by assessing the lesion severity by an additional imaging modality independent of both echocardiography and cardiac catheterization (CaSc), and finally by determining the true LVOT area by CT to assess the potential impact of the circularity assumption for the determination of AVA in each patient individually [14].

Contrary to our expectation, underestimation of the gradients by echocardiography was the most common cause of misclassification. Even though all the echocardiographic studies were performed in the high-volume laboratory of an academic tertiary referral center by experienced echocardiography technologists using state-of-the-art equipment, Doppler acquisition from the right parasternal view was unreliable in six patients, and Doppler tracings were retrospectively identified to be of suboptimal quality in another 4, explaining the misclassification in 59% of the FD patients. The fact that valve calcification, potentially obscuring the maximum velocity signals from an apical window, tended to be particularly high in patients in whom gradients were underestimated (Fig. 3) further supports this assessment. The main reason for this finding is probably related to the nature of the studied patient population, which consisted of elderly and highly symptomatic individuals, many of whom had multiple comorbidities and had difficulty in changing body position during the echocardiographic examination. This, however, is typical for the patient population routinely referred for echocardiographic evaluation of valvular heart disease to date; hence, the findings are of wider clinical relevance. Even though underestimation of the LVOT diameter is considered to be responsible for most of the AVA underestimation encountered in clinical practice [4–6], a CT assessment of the LVOT area did not help in differentiating between concordants and discordants in this study. As expected, the LVOT area assessed by CT was elliptical and larger than the echocardiographically estimated LVOT area. However, because the LVOT was consistently found to be elliptical in all patients, with a similar distribution across the diverse sub-groups, the eccentricity index did not facilitate distinguishing between TD and FD.

Comparison with previous studies

Discordance in echocardiographic measures of severe AS (velocity, gradient, and valve area) has been reported in up to 40% of patients, the most common constellation encountered in clinical practice being a low mean gradient (< 40 mmHg) despite a small AVA (≤ 1 cm^2) [15–17]. Several studies attempted to elucidate the clinical importance of these findings by serial echocardiographic and clinical follow-up:

Maes el al. [18] studied 205 patients with a working diagnosis of "paradoxical low flow low gradient severe AS". Eighty-two percent increased their gradient during follow up and 50% progressed to high-gradient severe AS [18]. Among the 1131 patients evaluated in this study, only 34 were excluded due to poor image quality. Tribouilloy retrospectively evaluated the echocardiograms of 59 patients who were followed up with serial echocardiograms during 2 years [19]. No patient was excluded for poor imaging quality. Mean Doppler gradient increased in 82% of these patients during follow-up, fulfilling the criteria of severe high gradient AS in 41%. Zusman et al. [20] retrospectively evaluated a group of 303 patients with symptomatic normal-flow low-gradient severe AS and concluded that these patients may benefit from intervention when compared to clinical treatment. No patient was excluded based on imaging quality. Only 61 patients had a second echocardiographic examination, and 13 of those showed increased gradients [20]. In a similar study Kang et al. [21] evaluated a group of 284 patients with normal flow low gradient severe AS, of whom 186 were followed clinically. Again, no patient was excluded due to poor imaging. Of note, 145 of the 186 patients followed up clinically increased their gradients on subsequent echocardiographic examinations [21].

The observed increase in gradients during serial echocardiographic examinations in these studies is compatible with the hypothesis that in many patients low flow low gradient AS with normal LV function may represent an intermediate stage of AS, between moderate and high gradient AS, rather than a more advanced stage of the disease [19],

a conclusion further supported by the study by Slimani et al. [22], which demonstrated that patients with paradoxical low flow low gradient severe AS less frequently display reduced longitudinal deformation, LV hypertrophy, or myocardial fibrosis than patients with high gradient severe AS [22].

The most conclusive and practical approach to the diagnostic conundrum of discordant echocardiographic findings appears to be assessment of the aortic valve CaSc by CT. This is compatible with the findings by Shen et al. [23], who evaluated the effects of age and AV anatomy on the relationship between AV calcification and the echocardiographic parameters of AS severity in 200 patients with severe AS and preserved LV function. The authors concluded that in elderly patients AV calcification appears to be the main factor significantly associated with the severity of AS, and CaSc evaluation should be used for the differential diagnosis of severe AS with discordant echocardiographic findings [23]. The results of the present study expand their findings by first comparing echocardiographic results to invasive measurements (to discriminate between true and false discordant findings) and then by evaluating LVOT anatomy and degree of valve calcification quantitatively per CT across patient groups, enabling a proper root cause analysis of this relationship.

Finally, current guidelines [1] recommend AV replacement in patients with symptomatic severe AS or with LVEF < 50%, while intervention is not indicated in patients with symptomatic moderate AS and LV dysfunction [24]. In order to clarify whether a more aggressive approach is necessary in these patients, the Transcatheter Aortic Valve Replacement to UNload the Left ventricle in patients with ADvanced heart failure (TAVR UNLOAD) trial aims to randomize 300 patients into two arms: transcatheter aortic valve replacement combined with optimized heart failure therapy versus optimal heart failure therapy alone [25]. The primary endpoint will be a composite of all-cause death, disabling stroke, heart failure hospitalizations, symptomatic AV disease, or non-disabling stroke.

Limitations of the study

The main limitations of this study are the highly selected population, limited sample size, and the fact that the echocardiographic and invasive studies were not performed simultaneously. However, such simultaneous recordings are unlikely to have improved agreement between invasive and non-invasive data because the time difference between the studies was not long (79 ± 70 days), and obtaining an adequate right parasternal window uniformly requires patients to lie fully turned to the right, which is not practical during cardiac catheterization. In addition, the study group consisted exclusively of symptomatic patients, increasing the pre-test probability for severe AS. However, this is the group of clinical interest because asymptomatic patients rarely undergo invasive hemodynamic investigations.

Finally, the inclusion of all consecutively studied patients in this investigation, without retrospective exclusion of patients with more challenging signal quality, should not be seen as a weakness but as a strength of the study. It allowed us to reliably analyze the true root causes of discordant findings in routine echocardiography. Such information is important to overcome selection bias, which may lead to underestimation of pseudo-discordance in clinical practice.

Conclusions

Discordant echocardiographic findings are commonly found in patients with symptomatic AS. In patients with pseudo-discordance underestimation of the true mean gradient due to technical difficulties is an important root cause for these discrepant findings. LVOT area by echocardiography or CT cannot differentiate between TD and FD. Low gradient severe AS can only be diagnosed when a reliable Doppler recording from all echocardiographic windows is available. Otherwise, a CaSc determination by computerized tomography is required.

Conflict of interest: None declared

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Distinctive characteristics of His bundle potentials in patients with atrioventricular nodal reentrant tachycardia

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Abstract

Background: *His bundle (HB) potentials vary in amplitude and duration in patients with and without slow pathways. The aim of this study was to determine the characteristics of HB potentials and to elucidate whether they can provide clues for identification of slow pathway (SP).*

Methods: *The present research prospectively studied the electrophysiological findings of 162 patients with symptomatic atrioventricular nodal reentrant tachycardia (AVNRT) due to slow-fast or fast-slow type and atrioventricular reentrant tachycardia (AVRT). Maximal HB potential (HBmax, HB with the highest amplitude) among HB cloud was recorded in both groups. For AVNRT patients, the following were measured: (1) AH interval at the "jump" during programmed atrial stimulation (A2H2, taken as a reflection of SP conduction time); (2) Distance from HBmax to the successful SP ablation site (HBmax-ABL) and from HBmax to the ostium of coronary sinus (HBmax-CSO).*

Results: *HBmax was 0.29 ± 0.10 mV in AVNRT patients, whereas it was 0.17 ± 0.05 mV in AVRT group ($p < 0.0001$). Likewise, the HBmax duration was 22 ± 5 ms in AVNRT group and 16 ± 3 ms in AVRT group ($p < 0.0001$). The area under the receiver operating characteristic curve of HBmax amplitude in AVNRT patients was 0.86 and the optimal HBmax cut-off to predict AVNRT was ≥ 0.22 mV with a sensitivity of 0.78 and specificity of 0.84. HBmax-CSO was positively correlated with HBmax-ABL, and HBmax-ABL was positively correlated with A2H2.*

Conclusions: *HBmax amplitudes were higher and durations longer in patients with AVNRT, as compared to those with AVRT. Moreover, the distance between HBmax and successful ablation site was positively correlated with the SP conduction time and with the distance from HBmax to the CSO.*
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Key words: tachycardia, atrioventricular nodal reentry, slow pathway, His bundle, catheter ablation

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Introduction

Since its introduction in 1992, catheter ablation of the slow pathway (SP) has been considered the first-line treatment in symptomatic patients with atrioventricular (AV) nodal reentrant tachycardia (AVNRT) [1]. The procedure is usually performed using fluoroscopy but three-dimensional (3D) mapping can provide further help by identifying the anatomical structures that are relevant for the ablation [2]. In some patients with AVNRT it is also possible to record SP potentials in the perinodal region [3]. High-resolution mapping of the Triangle of Koch may increase the overall safety and efficacy of the ablation procedure [4].

The possibility to record His bundle (HB) potentials in humans was reported more than 5 decades ago [5]. In patients with AV conduction disturbances, the site of the block can be determined by recording the time delay between the HB signal and the earliest ventricular activation on surface electrocardiogram. The amplitude and duration of the HB signal depend on multiple factors, such as the type of catheter used, interelectrode spacing and orientation of the catheter tip. Despite widespread use of HB potentials in daily electrophysiology practice, detailed assessments of their signal characteristics in AVNRT patients are lacking. The aim of this study is to determine the distinctive features of the HB potentials, and elucidate if they provide clues for identification of patients with SP, an electrical prerequisite for the development of AVNRT.

Methods

Study patients

Electrophysiological findings of consecutive patients with symptomatic AVNRT due to slow-fast type or fast-slow type reentry and AV reentrant tachycardia (AVRT) due to an accessory pathway were studied between December 2018 to September 2020. The study data was prospectively collected in the Catheter Ablation Registry at the University Heart Center Zurich, which was approved by the Institutional Ethical Committee.

Electrophysiological study findings

All electrophysiological studies were performed in the fasting, non-sedated state. After local anesthesia, multielectrode catheters were introduced percutaneously through the right femoral vein and positioned in high right atrial, right ventricular and HB positions, followed by measurements of basic electrophysiological parameters. AV nodal effective refractory period (AVNERP) was measured at progressively shortening intervals following 8 drive trains at 600 ms. An atrio-His (AH) jump, suggestive of the presence of an SP, was identified, if there was a 50 ms or more increase in H1H2 interval by using 10 ms decrements of A1A2. The longest conduction time of the fast pathway (A1H1) was measured as the last premature extrastimulus coupling interval before an AH jump. The shortest conduction time of the slow pathway (A2H2) was defined as the first premature extrastimulus coupling interval after an AH jump. All measurements were performed under baseline conditions without administration of isoprenaline.

If a tachycardia was not inducible at baseline, isoproterenol was administered. Various stimulation techniques were used in both groups to ensure the induction and reproducibility of the clinical tachycardia. V-A-V response during ventricular entrainment was used to exclude an atrial tachycardia.

Mapping and catheter ablation

After diagnosis of AVNRT or AVRT, a 7-Fr quadripolar, steerable radiofrequency ablation catheter (Navistar 4 mm, Biosense Webster, Irvine, CA, USA) was introduced into the right atrium. Prior to mapping, calibration for respiratory compensation was performed. The filter settings for bipolar signals were set at the 16–500 Hz range. Using the ablation catheter, anatomical locations showing HB potentials were extensively searched and tagged point-by-point using the CARTO 3D electroanatomical mapping system (Biosense Webster, Irvine, CA, USA) to determine the His cloud (Fig. 1). For each patient, there was a minimum of 8 points that determined the His cloud. The HB signal with the maximal amplitude was labeled as HBmax. Every point was double-checked by offline analysis to confirm correct annotation. 3D mapping hallmarks of HBmax, the central point of the coronary sinus ostium (CSO), and the site of SP ablation (ABL) in the standard right anterior oblique view (RAO 30°) were annotated for distance identification. The amplitude and duration of HBmax between the two groups were measured using endocardial tracings at a recording speed of 400 mm/s.

For SP ablation, the inferior/posterior aspect of the interatrial septum adjacent to the CSO was targeted. The local signal typically showed a small, low frequency atrial and a sizeable, high-frequency ventricular deflection, and rarely an SP potential, but no HB signal, as described by previous publications [6–8]. The ablation site was selected if there was adequate safety distance from the lowest HB

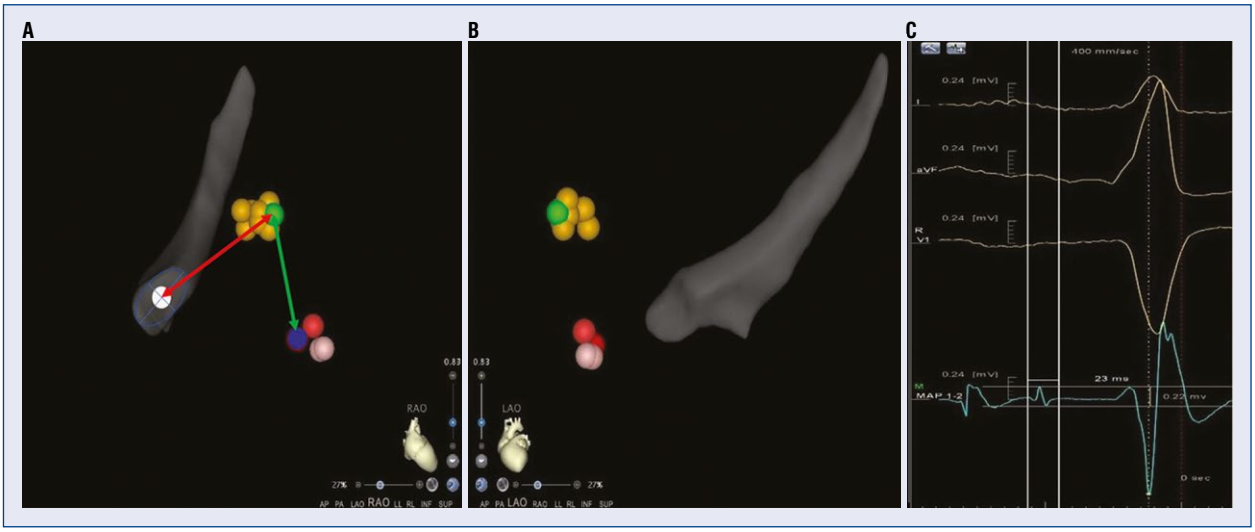

Figure 1. Anatomical hallmarks (His cloud, coronary sinus and ablation points) are shown on a CARTO 3D electroanatomical map in (**A**) right anterior oblique (RAO, 30°) and (**B**) left anterior oblique (LAO, 60°) views and endocardial electrograms with a recording speed of 400 mm/s are shown in (**C**). HB — bundle of His; HBmax — maximal His potential; CSO — ostium of coronary sinus; ABL — ablation site. The maximal HB potential (HBmax) was marked as a green point within the His cloud (multiple yellow points). The best site with induction of slow junctional beats among various ablation points (in red) was labeled as ABL (blue point). The center of CSO was also marked (white point). The red arrow line indicates the distance between HBmax and CSO. The green arrow line indicates the distance between HBmax and the slow pathway ablation site. Due to CSO variability, its center was determined as the intersection of the longest diameter and the shortest diameter.

point. The site of SP ablation (ABL, blue point in 3D map) with best response showing slow junctional beats during ablation was identified for each patient. AVRT patients were ablated along either the right or left AV valvular annulus, depending on the location of the accessory pathway.

Radiofrequency energy was applied with an overall period of 60–120 s on the ablation site with a power setting in the range of 30–50 W for both groups. The endpoint for AVNRT ablation was non-inducibility of the tachycardia. For patients with an AH jump (with or without an echo beat) after ablation, the SP ablation sites were often multiple. Since this study also aims at the SP ablation site, patients who had a residual SP were excluded from analysis. For AVRT patients, abolishing antegrade and/or retrograde accessory pathway conduction was considered as the endpoint of the procedure. Electrophysiologic study was repeated at least 20 min after last ablation to confirm the success of the procedure. In order to prevent thromboembolic complications, intravenous heparin was administered during the procedure and subcutaneous unfractionated heparin was given post-operatively during bed rest. Patients who underwent ablation of left-sided accessory pathways were prescribed acetylsalicylic acid for 4–6 weeks. All patients were discharged from the clinic either on the same day of the procedure or on the day after. They were followed up at our cardiac arrhythmia clinic or by the referring physicians after discharge.

Statistical analysis

Data were expressed as means ± standard deviation. For continuous variables, data were expressed as median (interquartile range), and Kruskal–Wallis test was performed to examine the difference among groups. Mann–Whitney U test was used to test the difference in continuous variables between groups. The correlations between measurements were examined by linear regression analysis. For the HBmax measurements that significantly differed between AVNRT and AVRT groups, receiver operating characteristic (ROC) curve analysis was used to compare the predicted accuracy and determine cut-off values with optimal performance. Statistical significance was set at $p < 0.005$.

Results

Patient characteristics

A total of 162 patients were finally enrolled in the study. Of these, 112 (57 ± 22 years; 45 males)

Table 1. Electrophysiologic parameters in AVNRT and AVRT patients.

Parameters	AVNRT		AVRT		P
	Prior ablation	Post ablation	Prior ablation	Post ablation	
N	N = 112, 45 male		N = 50, 29 male		< 0.005*
Age [years]	57 ± 22		33 ± 12		> 0.005*
AVBCL [ms]	369 ± 75	398 ± 45	363 ± 74	366 ± 70	> 0.005*
					< 0.005[1#]
					> 0.005[2#]
VABCL [ms]	374 ± 56	380 ± 51	365 ± 19	367 ± 43	> 0.005*
					< 0.005[1#]
					> 0.005[2#]
A1H1 interval [ms]	159 ± 38	NA	NA	NA	
A2H2 interval [ms]	250 ± 48 (n = 107)[@]	NA	NA	NA	
HV interval [ms]	45 ± 6	45 ± 5	NA	43 ± 4	< 0.005*
					< 0.005[#]
Tachycardia CL [ms]	388 ± 58	NA	372 ± 65	NA	< 0.005*

Data were presented as median (lower to upper quartile; range) or mean ± standard deviation. AVNRT — atrioventricular nodal reentrant tachycardia; AVRT — atrioventricular reentrant tachycardia; AVBCL — atrioventricular block cycle length; VABCL — ventriculoatrial block cycle length; A1H1 — fast pathway conduction time; A2H2 — slow pathway conduction time; HV — conduction time from His Bundle to earliest ventricular activation on surface electrocardiogram; CL — cycle length; NA — no relevant measurement available; *Compared between AVNRT and AVRT groups prior or post-ablation; #Compared within group prior or post-ablation; 1#In AVNRT group; 2#In AVRT group; @Note that the Pearson correlation analysis related to A2H2 was performed in 107 typical AVNRT patients, excluding 5 patients fast-slow type AVNRT who had no observed antegrade slow pathway conduction

had AVNRT and the remaining 50 had AVRT (33 ± 12 years; 29 males). No patients were enrolled in the latter group if they had evidence for the presence of concomitant dual AV nodal physiology. Eight patients had coronary artery disease (6 in AVNRT group). Four patients had sick sinus syndrome with an implanted pacemaker, one had dilated cardiomyopathy and one had valvular heart disease, all of whom in the AVNRT group. In the remaining 121 patients (74 AVNRT, 47 AVRT), there was no evidence of an underlying structural heart disease. All patients had normal systolic left ventricular function (left ventricular ejection fraction [LVEF] > 50%), except for one AVNRT patient with cardiomyopathy having an LVEF of 36%. All antiarrhythmic drugs were discontinued prior to electrophysiological study latest on the previous day prior to the procedure. In the AVNRT group, 5 fast-slow type AVNRTs were identified and 107 slow-fast AVNRTs were diagnosed prior to ablation. In the AVRT group, 12 Wolff-Parkinson-White syndrome patients were found to have pre-excited electrocardiogram at baseline. For concealed accessory pathways, 16 patients demonstrated anterograde concealment, 16 demonstrated retrograde concealment, and 6 demonstrated both anterograde and retrograde concealment. Regarding the localization of the accessory pathways around the mitral and tricuspid annuli, there were 6 accessory pathways in the right anterior septum, 4 in the right mid-septum, 9 in the right posterior septum, 10 in the right sided free wall (4 right posterior or right posterolateral, 3 right lateral, 3 right anterior), 4 in the left posterior septum, 1 in the left mid-septum, 16 in the left lateral free wall (13 left lateral or left anterolateral, 3 left posterior or left posterolateral).

The catheter ablation procedure was acutely successful and uneventful in all patients in both AVNRT and AVRT cohorts. Twelve-lead surface electrocardiography parameters and electrophysiological measurements prior to and after ablation in patients of both groups were shown in Table 1.

HB potential characteristics in AVNRT patients compared with AVRT patients

There were significant differences in HBmax amplitude and duration between the AVNRT (slow-fast and fast-slow type) and AVRT groups after adjusting for age and gender, as shown in Figure 2. The HBmax amplitude was 0.29 ± 0.10 mV in AVNRT patients, whereas it was 0.17 ± 0.05 mV in the AVRT group ($p < 0.0001$). Likewise, the HBmax duration was 22 ± 5 ms in the AVNRT group

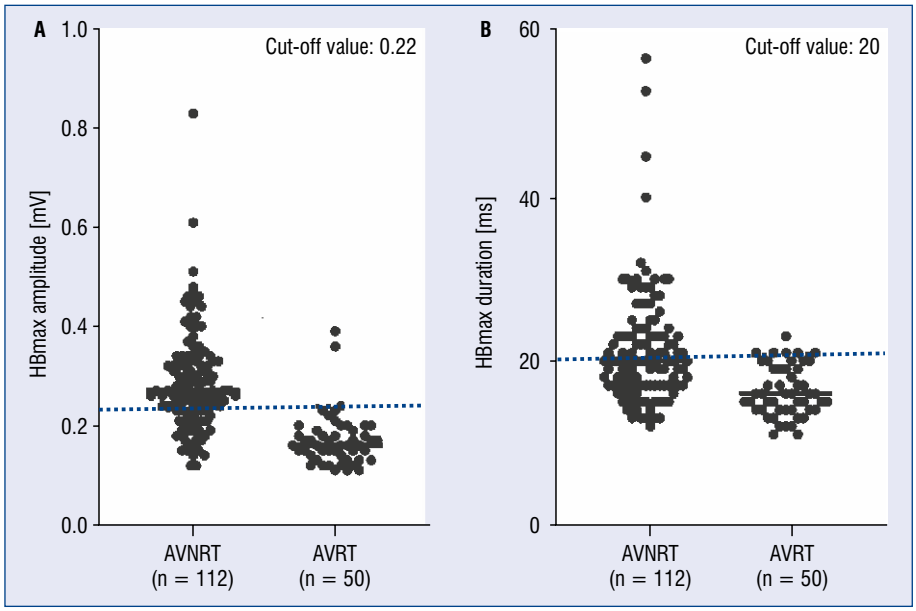

Figure 2. Scatterplot of cut-off values of maximal His potential (HBmax) amplitude (**A**) and HBmax duration (**B**) in AVNRT patients; AVNRT — atrioventricular nodal reentrant tachycardia; AVRT — atrioventricular reentrant tachycardia.

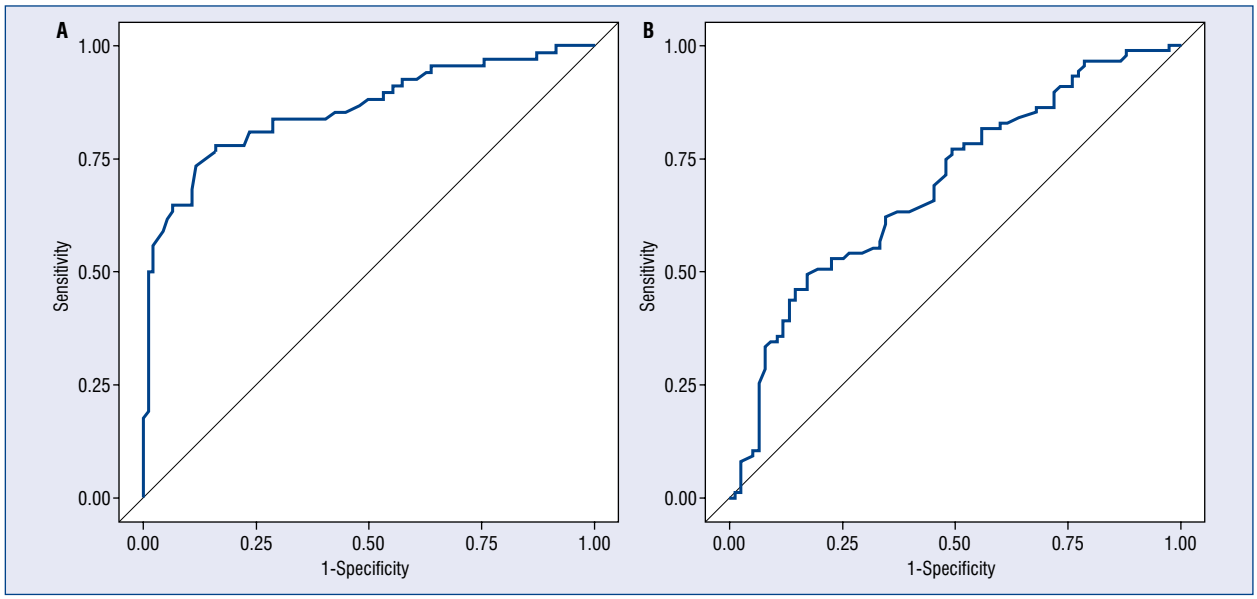

Figure 3. Receiver operating characteristic curve analysis for the optimal cut-off values of maximal His potential (HBmax) amplitude (**A**) and HBmax duration (**B**).

and 16 ± 3 ms in the AVRT group ($p < 0.0001$). Moreover, in five AVNRT patients with fast-slow type reentry, HBmax amplitude was 0.36 ± 0.09 mV and duration was 24 ± 2.8 ms, which were significantly different than those values in AVRT patients ($p < 0.0001$).

It was then sought to define the diagnostic value of HBmax amplitude and duration for discrimination of AVNRT due to SP from AVRT. After adjusting for age and gender, linear logistic regression analysis revealed that HBmax amplitude and duration were independent predictors for AVNRT (Fig. 3). The area under the ROC curve (AUC) of HBmax amplitude in AVNRT patients was 0.86, and the optimal cut-off to predict AVNRT was equal to or greater than 0.22 mV with a sensitivity of 0.78

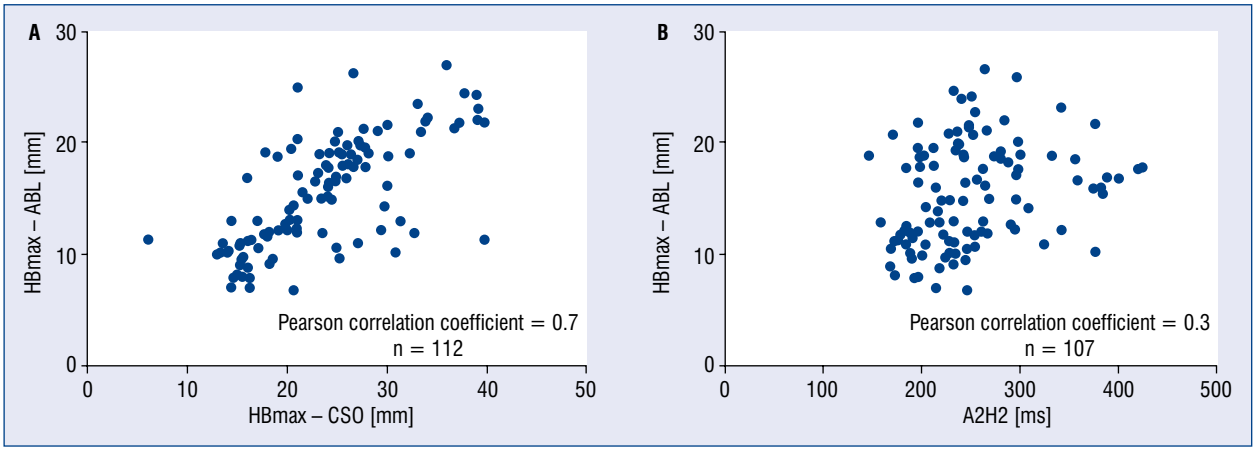

Figure 4. Pearson correlations between the distance maximal His potential (HBmax) site from the successful ablation site and coronary sinus ostium (CSO) (**A**), and the distance HBmax site from the successful ablation site and slow pathway conduction (A2H2) (**B**); ABL — ablation site.

and specificity of 0.84 (Fig. 2). Meanwhile, the AUC of HBmax duration was 0.69, and the optimal cut-off to predict AVNRT was equal to or greater than 20 ms with a sensitivity of 0.49 and specificity of 0.83.

Electrophysiological and anatomical correlations of HBmax in AVNRT patients

Three-dimensional CARTO maps showed 15.4 ± 4.9 mm distance between the successful ablation site and the HBmax recording site. The distance between the center of the CSO and the HBmax recordings site was 23.5 ± 5.6 mm. The mean A2H2 interval with an SP conduction was 250 ± 48 ms. The distance between HBmax and CSO was positively correlated with the distance between HBmax and the successful ablation site ($r^2 = 0.7174$, 95% confidence interval [CI] 0.6101 to 0.7989, $p = 0.0004$), in accordance with the previous publication (Fig. 4) [9]. The HBmax distance from the successful ablation site was positively correlated with the shortest SP conduction time (A2H2) ($r^2 = 0.3368$, 95% CI 0.1515 to 0.4993, $p < 0.00001$), but it was not correlated with HBmax amplitude or duration. The distance between HBmax and CS ostium was not correlated with A2H2. Likewise, it was neither correlated with HBmax amplitude nor HBmax duration.

Ablation procedure and follow up

Ablation was successfully performed in all patients enrolled. No significant cardiac adverse effects occurred during energy application, and all had preserved AV conduction. The overall duration of each study was 1–3 hours. No patient had tachycardia recurrence or apparent electrocardiography parameter changes with a mean post-ablation period of 6 months.

Discussion

Main findings

The present study had several findings: First, it was demonstrated that HBmax amplitudes were higher and HBmax durations were longer in patients with AVNRT, as compared to those measurements in patients with AVRT. These measurements might be helpful for primary evaluation of the two arrhythmic conditions with a relatively high sensitivity and specificity. Second, the distance between HBmax and successful ablation site was positively correlated with the SP conduction time and with the distance from HBmax to the CSO. These findings may be helpful in choosing the optimal SP site for ablation.

The higher HBmax amplitudes and longer HBmax durations were not only observed in patients with typical AVNRT but were also observed in patients with atypical AVNRT due to fast-slow type reentry, as compared to those measured in patients with AVRT. On the other hand, these measurements were not significantly different in patients with left-sided, right-sided, or septal accessory pathways. The differential diagnosis of atypical AVNRT from AVRT could be challenging since extra electrophysiologic maneuvers were often required, such as parahisian pacing and ventricular entrainment [10, 11]. The HBmax measurements might provide primary clues for

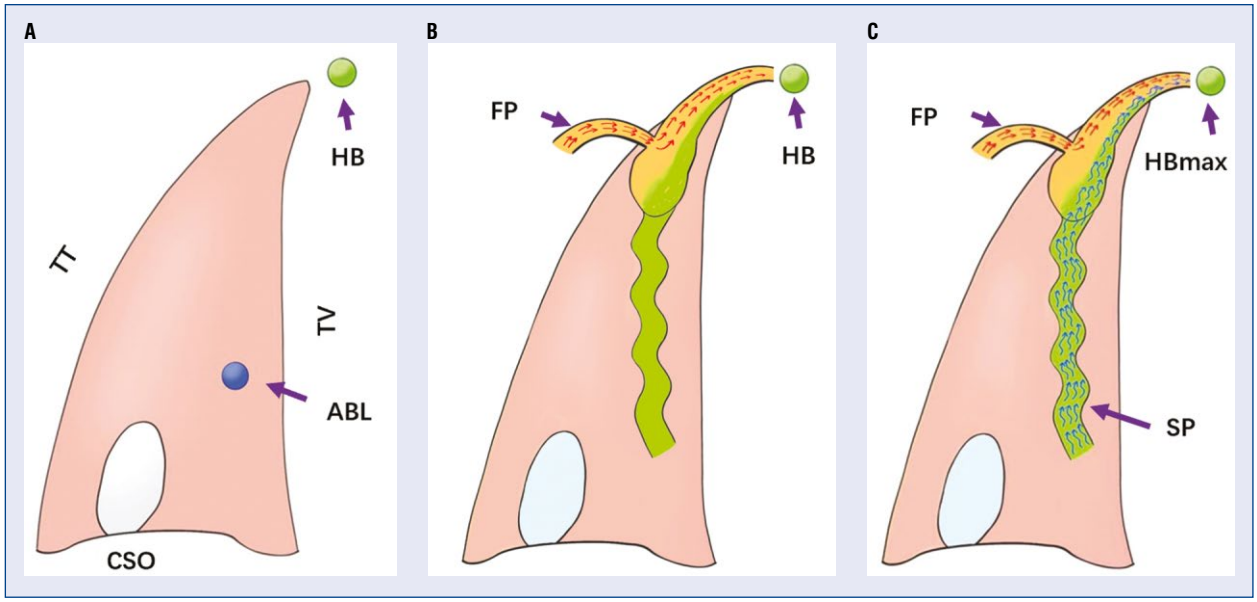

Figure 5. Schematic illustration of dual pathway anterograde conduction. The schematic represents the Koch's triangle and adjacent area; **A.** Triangle of Koch in the right anterior oblique projection and the location of HBmax and ABL hallmarks; **B.** Fast pathway conduction of sinus activity to distal HB in patients without dual atrioventricular conduction; **C.** The dual pathway conduction of sinus activity to distal HB through longitudinal dissociation in patients with atrioventricular nodal reentrant tachycardia. The red arrows represent fast pathway conduction, and the blue curved arrows represent slow pathway conduction. The yellow area represents Cx43(–) cells, and the green area the Cx43(+) cells; TT — tendon of Todaro; TV — tricuspid valve; CSO — ostium of coronary sinus; ABL — successful ablation site; HB — His bundle; HBmax — maximal His bundle recording site; FP — fast pathway; SP — slow pathway.

dual AVN physiology and lead to corresponding electrophysiological study protocol priority for mechanism identification.

Distinctive HB potential in AVNRT patients

It has been known for more than 30 years that longitudinal dissociation within the posterior AV nodal region is the main mechanism, which gives rise to localized reentry and AVNRT [12]. Despite this, the signal characteristics of the HB potentials in human beings with an SP have not been scrutinized in depth to date. Only previous observations from rabbit AVNRT models show an augmentation of the HB signal amplitude during pacing with short premature coupling intervals [13]. The current study, using electroanatomical 3D mapping of the AV nodal and HB region, fills the knowledge gap for patients with AVNRT and is in line with previous observations from animal models. In the present study, particular attention was paid to obtaining a complete representation of the HB cloud by taking 8 or more annotation points along the area of HB that showed distinct HB potentials. The observed augmentation of the HBmax signal (especially its amplitude) in patients with AVNRT possibly reflects an electrical region that represents the continuation of two distinct electrical pathways joining together into an enhanced HB deflection. Clearly, this also necessitates proper orientation of the fibers at the bipolar recording site of the His catheter. This illustration is shown in the form of a schematic diagram in Figure 5.

The presence of an SP may also be manifested in some occasions during sinus rhythm. Intermittent occurrence of prolonged PR intervals, which may arise following ectopic beats, may suggest an SP [14]. Ablative elimination of the SP in such patients will restore physiological AV conduction over the fast pathway. Moreover, dual AV nodal non-re-entrant tachycardia, which is characterized by double antegrade conduction from a single sinus nodal activity simultaneously via the slow and fast AV nodal pathways into the ventricle, has been described [15, 16]. Furthermore, SP potentials prior to the HB deflection can also be detected by electrophysiological catheter during sinus rhythm on some occasions [3].

Meanwhile, immunobiological study on human AV junction demonstrates differential Cx43(+) myocyte distribution, with rightward nodal extensions and HB much more than leftward nodal extensions and compact node (Fig. 5) [17]. These observations provide further proof of the unique

conduction properties of different parts of AV junctional area, which contribute to longitudinal dissociation and reentrant arrhythmias.

HBmax electrophysiology correlates with related anatomy in AVNRT patients

The positive correlation between SP conduction time and the distance from HBmax to successful ablation site, as observed in our study, may simply imply a longer conduction time for the SP wavefront to perpetuate due to a longer anatomical distance. This finding is in line with the findings of Dagres et al. [18] who demonstrated that SP with longer conduction intervals was more often ablated in a more inferior area of the Koch's triangle.

The observed difference in tachycardia cycle length between AVNRT and AVRT in the current study is in line with previous observations in adult patients [19]. In contrast, tachycardia cycle length of the two arrhythmic conditions does not differ in pediatric patients [20]. This discrepancy is explained as the conduction of both fast and slow pathways is faster in children than in adults. The adult patients in the study herein, did not manifest a correlation between age and SP conduction time or the distance from HBmax to CSO.

Limitations of the study

The present study has some limitations. HBmax in this study was observed during sinus rhythm before any electrophysiological maneuvers or medication induction was introduced. This could only give us a preliminary assessment of possible differential diagnosis of dual AVN physiology or AVNRT. Whereas the fundamental evaluation and step-by-step electrophysiological study can never be underestimated. Moreover, since the focus herein was on the effective ablation site compared to other anatomical structures within the triangle of Koch, patients with multiple SPs were excluded. Therefore, we could not comment on whether observations would hold true in patients with slow--slow type reentry.

Conclusions

HBmax amplitudes are higher and HBmax durations are longer in patients with AVNRT, as compared to those in AVRT. These features may provide preliminary clues to differentiate the two arrhythmic conditions with relatively high sensitivity and specificity. Moreover, the distance between HBmax and successful ablation site is positively correlated with the SP conduction time and with the distance from HBmax to the CSO. These findings are helpful in determining the presence of an SP and in optimizing SP ablation.

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Conflict of interest: None declared

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Comparison of long-term clinical outcomes among zotarolimus-, everolimus-, and biolimus-eluting stents in acute myocardial infarction patients with renal impairment

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Abstract

Background: *It is important to determine the best drug-eluting stent (DES) for acute myocardial infarction (AMI) in patients with renal impairment. In this studythe outcomes of everolimus-eluting stents (EESs), zotarolimus-eluting stents (ZESs) and biolimus-eluting stents (BESs) were evaluated.*

Methods: *From the Korea Acute Myocardial Infarction-National Institutes of Health registry, a total of 1,470 AMI patients with renal impairment undergoing percutaneous coronary intervention (PCI) were enrolled (816 with EES, 345 with ZES, and 309 with BES). Renal impairment was defined as creatinine clearance < 60 mL/min/1.73 m^2 estimated by the Cockcroft-Gault method. Major adverse cardiac and cerebrovascular events were determined as the composite of all-cause death, non-fatal myocardial infarction (MI), cerebrovascular accident, any revascularization, rehospitalization and stent thrombosis. All clinical outcomes were analyzed.*

Results: *The baseline characteristics of the patients revealed no significant difference between the three groups, except for Killip classification > 2, beta-blockers, lesion type, vascular approach, staged PCI, left main coronary artery (LMCA) complex lesions, LMCA PCI, and the number and length of implanted stents. In the Kaplan-Meier analysis, similar clinical outcomes were derived from the unadjusted data between the three DES groups. However, after the inverse probability of treatment weighting, a statistically significant difference was found in non-fatal MI, which implied a higher incidence of non-fatal MI in the ZES group than in the other two DES groups.*

Conclusions: *In AMI patients with renal impairment, there was no significant difference between the three stent groups in terms of long-term clinical outcomes, except for non-fatal MI.* (Cardiol J 2023; 30, 3: 440–452)

Key words: myocardial infarction, renal insufficiency, drug-eluting stents, zotarolimus, everolimus, biolimus

Introduction

The incidence of acute coronary syndrome (ACS) with concomitant acute myocardial infarction (AMI), is gradually rising, leading to serious socioeconomic problems. Risk factors for coronary artery disease (CAD) such as diabetes, hypertension, and chronic kidney disease (CKD) are similarly increasing. Among these risk factors, CKD is an independent risk factor for cardiovascular disease [1, 2]. In patients with end-stage kidney disease (ESKD), the incidence of cardiovascular diseases is 8.8–10 times higher than the general population [3, 4].

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Acute myocardial infarction, a medical emergency, is a type of ACS that requires rapid revascularization. The advent of coronary stents, utilized for the treatment of coronary stenosis, has contributed to a decrease in both, restenosis and the likelihood of emergency coronary artery bypass grafting (CABG) [5, 6]. After 2002, the emergence of drug-eluting stents (DESs), including the sirolimus-eluting stents (SESs) and paclitaxel-eluting stents significantly reduced the incidence of restenosis and the need for repeat revascularization compared with balloon angioplasty. The use of first-generation DES (1G-DES) has reduced the rate of target lesion revascularization (TLR) and CABG as a treatment option after stent implantation [7, 8]. However, there is an increasing concern about stent thrombosis, one of the most catastrophic phenomena of percutaneous coronary intervention (PCI), which manifests as ST-segment elevation myocardial infarction (STEMI) and/or sudden cardiac arrest requiring repeat revascularization [9]. Newer generation durable polymer-coated DESs using zotarolimus or everolimus, called second-generation drug-eluting stents (2G-DESs), were developed to ameliorate polymer biocompatibility, leading to a significant reduction in in-stent restenosis, stent thrombosis, the duration of dual antiplatelet therapy (DAPT), and bleeding complications [10, 11]. In addition, biolimus-eluting stents (BESs), which use a biodegradable polymer, have been developed to treat long-term vascular complications related to durable polymers. Studies have shown that BES reduce late stent thrombosis compared with 1G-DES [12]. In addition, it exhibited similar safety and efficacy characteristics compared with those of other 2G-DESs [13, 14].

It has been established that cardiovascular disease is a leading cause of morbidity and mortality among CKD patients. CKD progresses through supply-demand mismatch, ischemic preconditioning, collateralization of blood vessels, and a high prevalence of left ventricular hypertrophy, leading to the development of CAD [2, 15].

In this study, the focus was on the differences in clinical outcomes between DESs in AMI patients. There is a paucity of clinical data on the difference in the outcomes between the three stent groups (zotarolimus-eluting stents [ZESs], everolimus-eluting stents [EESs], and BESs) in patients with AMI and renal impairment (AMI-RI). This clinical study aimed to elucidate the clinical differences between these three types of stents in patients with AMI and concomitant renal impairment undergoing PCI.

Methods

Study population

The study population was extracted from the Korea Acute Myocardial Infarction Registry-National Institutes of Health (KAMIR-NIH), a nationwide, multicenter, online observational cohort study. The KAMIR-NIH consecutively enrolled AMI patients at 20 major cardiovascular institutes between 2011 and 2015. Among 13,104 AMI patients, a total of 4,692 AMI-RI patients were initially screened. The exclusion criteria included patients who: (a) had a prior myocardial infarction (MI); (b) died during index hospitalization; (c) underwent no PCI or unsuccessful and/or partial revascularization during the index PCI; (d) underwent PCI without stent implantation or with stents other than the EES, ZES, or BES; (e) underwent CABG as a revascularization strategy; (f) underwent thrombolysis; and (g) received overlap implantations of two or three types of EES, ZES, or BES. After excluding 3,222 patients, a total of 1,470 patients were included in the study. These patients were classified into three groups as follows: (a) AMI-RI patients undergoing PCI with EES implantation (n = 816), (b) AMI-RI patients undergoing PCI with ZES implantation (n = 345), and (c) AMI-RI patients undergoing PCI with BES implantation (n = 309) (Fig. 1). Follow-up data of these patients were obtained mainly through regularly scheduled outpatient visits. The present study was conducted according to the ethical principles of the Declaration of Helsinki, the best-known policy statement of the World Medical Association, which was revised in 2013 [16]. Similarly, the study protocol of the KAMIR-NIH registry was also approved by the ethics committee of each participating center [17]. Written informed consent was secured from all participants.

Definition and clinical endpoints

Kidney function was determined by the creatinine clearance (CrCl) calculated using the Cockcroft-Gault formula [18], and it was based on the serum creatinine level upon admission. In this study, renal impairment was determined as CrCl < 60 mL/min/1.73 m^2 based on the serum creatinine level at the time of admission.

Acute myocardial infarction was defined according to current guidelines [19, 20], which include the typical rise and/or fall of biochemical markers of myocardial necrosis with at least one of the following: (a) clinical symptoms indicative of myocardial ischemia, (b) development of pathological Q-waves

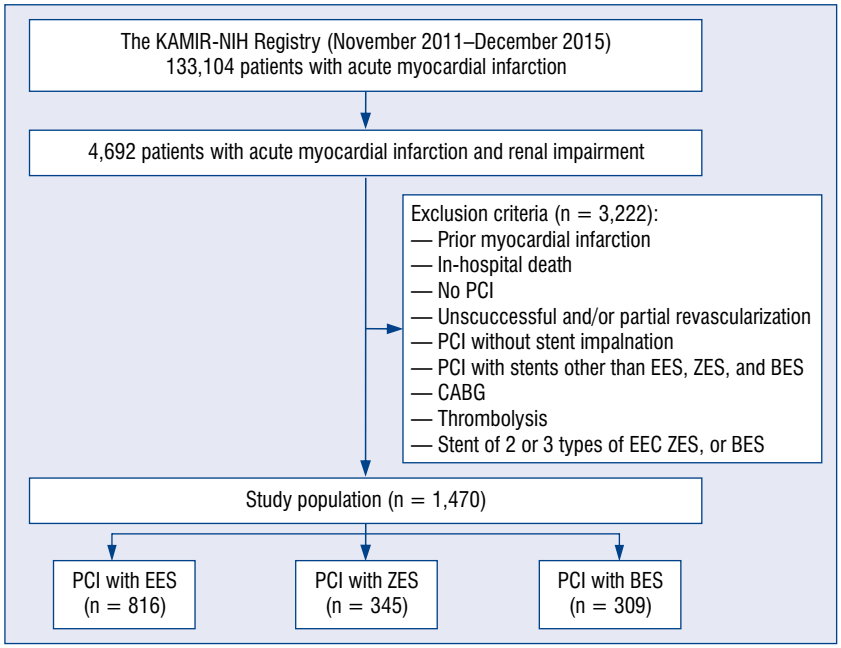

Figure 1. Flow chart for the selection of study participants; BES — biolimus-eluting stent; CABG — coronary artery bypass graft; EES — everolimus-eluting stent; KAMIR-NIH — Korea Acute Myocardial Infarction Registry-National Institutes of Health; PCI — percutaneous coronary intervention; ZES — zotarolimus-eluting stent.

in the 12-lead electrocardiogram (ECG) results, (c) ECG changes indicative of ischemia (elevation or depression of the ST-segment), and (d) imaging modalities suggesting MI (i.e., new loss of viable myocardium or new-onset regional wall motion abnormality). STEMI was defined as AMI with new-onset ST-segment elevation of at least 1 mm (0.1 mV) in 2 or more contiguous leads, or new-onset left bundle branch block observed on ECG [21]. To quantitatively evaluate the left ventricle, left ventricular ejection fraction (LVEF) was examined using 2-dimensional echocardiography. The Killip classification, introduced in 1967, is defined as follows: Killip class I, no chronic heart failure; Killip class II, third heart sound and rales; Killip class III, overt pulmonary edema; and Killip class IV, cardiogenic shock [22]. Significant stenosis of the left main coronary artery (LMCA) was defined as an — at least — 50% reduction in the intraluminal diameter of the LMCA. Unprotected left main disease was defined as the presence of significant stenosis in the LMCA with no patent bypass graft to the left anterior descending coronary artery or left circumflex coronary artery. LMCA complex lesions were defined as the presence of significant stenosis in the LMCA with the presence of added epicardial coronary artery stenosis. Significant stenosis of other epicardial coronary arteries was defined as a reduction of at least 70% in the intraluminal diameter of the epicardial coronary artery. The degree of coronary flow was quantitatively classified according to the Thrombolysis In Myocardial Infarction (TIMI) flow grade.

Clinical follow-up was performed after the commencement of the study. The primary endpoint was major adverse cardiac and cerebrovascular events (MACCE), defined as the composite of all-cause death (cardiac and non-cardiac death), non-fatal MI, cerebrovascular accident (CVA), any revascularization using PCI or CABG, rehospitalization, and stent thrombosis. The secondary endpoints were net adverse clinical events (NACE), all-cause mortality, non-fatal MI, any revascularization, CVA, rehospitalization, and stent thrombosis. NACE was defined as a composite of all-cause death, non-fatal MI, and any revascularization. Any revascularization was defined as any repeat PCI or CABG of any part of the epicardial coronary arteries overall. Rehospitalization was defined as post-index admission due to angina and/ /or heart failure.

Statistical analysis

All data analysis was performed using both STATA version 15.0 (StataCorp, College Station, Texas, United States of America) and SPSS ver-

sion 25.0 (SPSS Inc., Armonk, New York, USA). Continuous variables were expressed as means ± standard deviation and analyzed using the Student t-test and the analysis of variance test. Discrete (categorical) variables were represented as percentages with numbers and analyzed using the Pearson chi-squared test, the Fisher two-by--two exact test, or linear by linear association. All results were considered statistically significant at $p < 0.05$.

To control for differences in baseline characteristics and potential confounding factors, the propensity score weighting method, called the inverse probability of treatment weighting (IPTW), was applied [23]. The propensity score was constructed by a multiple logistic regression model using a total of 41 covariates. Participants with missing data in these covariates or whose follow-up period after hospital discharge was estimated as 0 days were excluded from IPTW adjustment.

Unadjusted and IPTW-adjusted survival analyses were performed using the Kaplan-Meier analysis to determine the incidence of clinical outcomes, and log-rank (Mantel-Cox) tests were performed to evaluate differences among the treatment groups (i.e., EES, ZES, and BES groups).

Results

Baseline clinical and procedural characteristics

Baseline clinical characteristics are summarized in Table 1. Before IPTW adjustment, a significant baseline difference was observed between the three groups in terms of the Killip classification at admission. Although the proportion of Killip classification > 2 in the ZES group was similar to that in the EES group, the BES group had a lower Killip classification than the other two groups. For discharge medications, there was a significant difference in the use of beta-blockers. The BES group received a relatively low prescription of this medication compared with the EES group. Although the EES group had a higher proportion of patients with DAPT ≥ 12 months than the ZES group, the net difference was similar between the three groups.

In coronary angiography and procedural characteristics (Table 2), some differences were observed between the three groups. The BES group had a relatively lower incidence of pre-procedural TIMI flow grade 0–I and stent number ≥ 3. The incidence of thrombus aspiration was higher in the ZES group than in the EES group. The incidence of RCA PCI was higher in the ZES group than in the other two groups. The ZES group had a higher proportion of STEMI patients compared to the EES group. Nonetheless, the net difference between the three groups was similar for these variables. Meanwhile, the overall difference was found in terms of the American Heart Association and the American College of Cardiology lesion type, vascular approach, staged PCI, LMCA complex lesions, LMCA PCI, stent number, total stent length, and total stent length > 60 mm.

After IPTW adjustment, baseline clinical and procedural characteristics were balanced between the three DES groups (**Suppl. Tables 1, 2**).

Long-term follow-up clinical outcomes

After hospital discharge, follow-up was conducted with a median delay of 1,088 days. Clinical outcomes of MACCE, NACE, all-cause mortality, non-fatal MI, any revascularization, CVA, rehospitalization and stent thrombosis were determined. Kaplan-Meier analysis was performed to describe the crude (unadjusted) and IPTW-adjusted survival curves, and the pair-wise log-rank test results for these comparisons are shown in Figures 2 and 3. Before IPTW adjustment, there were no significant differences in any clinical outcomes between the three DES groups. However, after IPTW, a significant difference was found between these groups in terms of non-fatal MI. In the ZES group, the incidence of non-fatal MI was higher than in the other two groups. The number of patients at risk is shown in Table 3.

Discussion

This study demonstrates that except for non--fatal MI, there was no significant difference among the three stent groups concerning long-term MACCE, NACE, all-cause mortality, any revascularization, CVA, rehospitalization and stent thrombosis. Regarding non-fatal MI, despite the significant difference not derived from unadjusted raw data analysis, IPTW-adjusted analysis showed that the ZES group had a higher incidence of non-fatal MI than the other two groups ($p = 0.005$).

Chronic kidney disease is a major health issue, with an increasing prevalence worldwide [24]; similarly, it is a debilitating medical condition, culminating in ESKD requiring dialysis or kidney transplantation, and is recognized as an independent cardiovascular risk factor [2, 25]. Among patients with renal impairment, cardiovascular events such as CAD, are the main cause of mortality [25, 26]. CKD

Table 1. Baseline clinical characteristics.

Characteristics	EES group (n = 816)	ZES group (n = 345)	BES group (n = 309)	P (EES vs. ZES)	P (EES vs. BES)	P (ZES vs. BES)	P
Male gender	467 (57.2%)	194 (56.2%)	174 (56.3%)	0.754	0.781	0.984	0.744
Age [years]	72.90 ± 9.33	72.86 ± 8.37	73.81 ± 8.41	0.951	0.136	0.152	0.275
Age ≥ 65 years	674 (82.6%)	294 (85.2%)	268 (86.7%)	0.273	0.094	0.578	0.076
Killip classification > 2	155 (19.0%)	68 (19.7%)	39 (12.6%)	0.777	**0.012**	**0.014**	**0.031**
BMI [kg/m^2]	22.44 ± 3.15	22.86 ± 3.13	22.38 ± 3.19	**0.036**	0.761	0.050	0.073
BMI ≥ 25 [kg/m^2]	144 (17.7%)	76 (22.0%)	59 (19.1%)	0.083	0.579	0.355	0.363
Previous history:							
Hypertension	524 (64.2%)	209 (60.6%)	196 (63.4%)	0.241	0.807	0.454	0.614
Diabetes mellitus	274 (33.6%)	119 (34.5%)	112 (36.2%)	0.764	0.400	0.640	0.413
Dyslipidemia	78 (9.6%)	31 (9.0%)	31 (10.0%)	0.760	0.811	0.648	0.912
Prior heart failure	12 (1.5%)	7 (2.0%)	9 (2.9%)	0.493	0.111	0.465	0.123
Prior CVA	74 (9.1%)	29 (8.4%)	29 (9.4%)	0.717	0.870	0.660	0.955
Smoking	343 (43.1%)	147 (44.0%)	134 (44.4%)	0.775	0.702	0.927	0.691
Family history of CAD	29 (3.6%)	12 (3.5%)	7 (2.4%)	0.943	0.298	0.385	0.362
CrCl [mL/min/1.73 m^2]	41.84 ± 13.88	43.19 ± 13.27	43.55 ± 12.83	0.126	0.060	0.722	0.095
LVEF < 40% (%)	128 (16.1%)	46 (13.9%)	35 (11.8%)	0.351	0.078	0.440	0.067
Discharge medications:							
Acetylsalicylic acid	815 (99.9%)	345 (100.0%)	309 (100.0%)	1.000	1.000	–	0.765
P2Y12 inhibitors	814 (99.8%)	344 (99.7%)	309 (100.0%)	1.000	1.000	1.000	0.714
Calcium channel blockers	58 (7.1%)	21 (6.1%)	21 (6.8%)	0.528	0.855	0.712	0.749
Beta-blockers	690 (84.6%)	280 (81.2%)	245 (79.3%)	0.153	**0.035**	0.548	**0.029**
ACEI or ARBs	653 (80.0%)	267 (77.4%)	247 (79.9%)	0.312	0.973	0.428	0.779
Statins	758 (92.9%)	315 (91.3%)	284 (91.9%)	0.350	0.574	0.781	0.504
Fibrates	2 (0.2%)	2 (0.6%)	1 (0.3%)	0.587	1.000	1.000	0.791
Oral anticoagulants	37 (4.5%)	13 (3.8%)	9 (2.9%)	0.557	0.220	0.545	0.217
Duration of DAPT:				**0.004**	0.832	**0.013**	0.609
< 12 months	312 (38.2%)	163 (47.2%)	124 (40.1%)				
12–24 months	140 (17.2%)	62 (18.0%)	50 (16.2%)				
24–36 months	114 (14.0%)	30 (8.7%)	26 (8.4%)				
≥ 36 months	250 (30.6%)	90 (26.1%)	109 (35.3%)				
Duration of DAPT (< 12 vs. ≥ 12 months):				**0.004**	0.561	0.067	0.220
< 12 months	312 (38.2%)	163 (47.2%)	124 (40.1%)				
≥ 12 months	504 (61.8%)	182 (52.8%)	185 (59.9%)				

Values are presented as mean ± standard deviation or number (%). ACEI — angiotensin-converting enzyme inhibitors; ARB — angiotensin II receptor blocker; BES — biolimus-eluting stent; BMI — body mass index; CAD — coronary artery disease; CrCl — creatinine clearance; CVA — cerebrovascular accident; DAPT — dual antiplatelet therapy; EES — everolimus-eluting stent; LVEF — left ventricular ejection fraction; ZES — zotarolimus-eluting stents

Table 2. Coronary angiography and procedural characteristics.

Characteristics	EES group (n = 816)	ZES group (n = 345)	BES group (n = 309)	P (EES vs. ZES)	P (EES vs. BES	P (ZES vs. BES)	P
AHA/ACC lesion type:				0.429	**< 0.001**	**0.005**	**< 0.001**
Type A	3 (0.4%)	10 (2.9%)	6 (1.9%)				
Type B1	103 (12.6%)	46 (13.3%)	54 (17.5%)				
Type B2	346 (42.4%)	128 (37.1%)	151 (48.9%)				
Type C	364 (44.6%)	161 (46.7%)	98 (31.7%)				
AHA/ACC type B2 or C	710 (87.0%)	289 (83.8%)	249 (80.6%)	0.145	**0.007**	0.287	**0.006**
Vascular approach:				0.930	**0.006**	**0.017**	**0.014**
Femoral approach	594 (72.8%)	252 (73.0%)	199 (64.4%)				
Non-femoral approach	222 (27.2%)	93 (27.0%)	110 (35.6%)				
Significant coronary stenosis	798 (97.8%)	340 (98.6%)	298 (96.4%)	0.398	0.201	0.081	0.308
GPIIb/IIIa inhibitor use	101 (12.4%)	44 (12.8%)	37 (12.0%)	0.859	0.854	0.763	0.922
Thrombus aspiration	157 (19.3%)	90 (26.2%)	62 (20.1%)	**0.009**	0.762	0.066	0.360
Image-guided PCI:	143 (17.5%)	61 (17.7%)	59 (19.1%)	0.949	0.540	0.641	0.582
IVUS use	138 (16.9%)	58 (16.8%)	55 (17.8%)	0.967	0.724	0.739	0.763
OCT use	7 (0.9%)	4 (1.2%)	6 (1.9%)	0.741	0.129	0.529	0.172
Pre-procedural TIMI 0–I	460 (56.4%)	225 (65.2%)	149 (48.2%)	**0.005**	**0.014**	**< 0.001**	0.126
Infarct-related artery:				0.085	0.347	0.533	0.204
LMCA	22 (2.7%)	7 (2.0%)	2 (0.6%)				
LAD	395 (48.4%)	159 (46.1%)	146 (47.2%)				
LCX	124 (15.2%)	39 (11.3%)	55 (17.8%)				
RCA	275 (33.7%)	140 (40.6%)	106 (34.3%)				
Multivessel PCI (not IRA-only PCI):	193 (23.7%)	74 (21.4%)	60 (19.4%)	0.415	0.129	0.520	0.115
Staged PCI	85 (10.4%)	26 (7.5%)	18 (5.8%)	0.127	**0.017**	0.383	**0.010**
LMCA complex lesions (multivessel lesion or ULMD)	32 (3.9%)	9 (2.6%)	5 (1.6%)	0.268	0.053	0.382	**0.038**
Territories of revascularization:							
LMCA PCI	36 (4.4%)	12 (3.5%)	5 (1.6%)	0.465	**0.026**	0.136	**0.027**
LAD PCI	519 (63.6%)	221 (64.1%)	189 (61.2%)	0.883	0.450	0.445	0.519
LCX PCI	247 (30.3%)	94 (27.2%)	102 (33.0%)	0.301	0.375	0.108	0.582
RCA PCI	368 (45.1%)	179 (51.9%)	133 (43.0%)	**0.034**	0.536	**0.024**	0.976
Multivessel disease	275 (33.7%)	116 (33.6%)	96 (31.1%)	0.980	0.402	0.486	0.447
STEMI diagnosis	397 (48.7%)	184 (53.3%)	141 (45.6%)	0.145	0.365	**0.049**	0.651
Stent profiles:							
Stent number	1.57 ± 0.84	1.61 ± 0.89	1.42 ± 0.75	0.472	**0.006**	**0.005**	**0.012**
Stent number ≥ 3	109 (13.4%)	54 (15.7%)	27 (8.7%)	0.304	**0.034**	**0.007**	0.111
Total stent length [mm]	32.04 ± 15.92	30.45 ± 15.72	25.68 ± 11.61	0.119	**< 0.001**	**< 0.001**	**< 0.001**
Total stent length > 60 mm	68 (8.3%)	16 (4.6%)	6 (1.9%)	**0.026**	**< 0.001**	0.056	**< 0.001**
Mean stent diameter [mm]	3.08 ± 0.41	3.09 ± 0.39	3.05 ± 0.39	0.646	0.282	0.186	0.417

Values are presented as mean ± standard deviation or number (%). AHA/ACC — The American Heart Association and the American College of Cardiology; BES — biolimus-eluting stent; EES — everolimus--eluting stent; GPIIb/IIIa — glycoprotein IIb/IIIa complex; IRA — infarct-related artery; IVUS — intravascular ultrasound; LAD — left anterior descending coronary artery; LCX — left circumflex coronary artery; LMCA — left main coronary artery; PCI — percutaneous coronary intervention; RCA — right coronary artery; STEMI — ST-segment elevation myocardial infarction; OCT — optical computed tomography; TIMI — Thrombolysis In Myocardial Infarction; ZES — zotarolimus-eluting stent; ULMD — unprotected left main disease

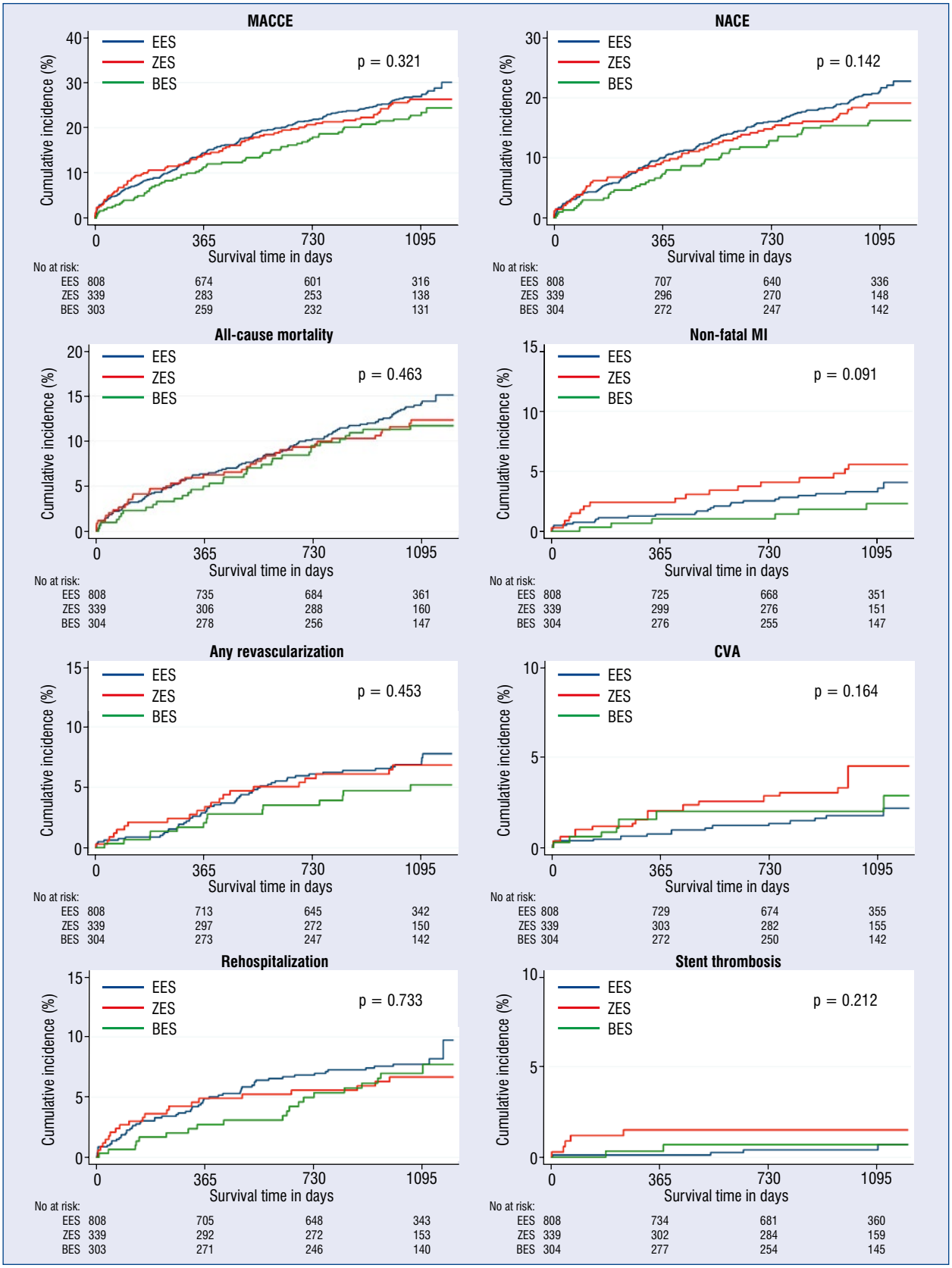

Figure 2. Kaplan-Meier survival analyses of long-term follow-up clinical outcomes (MACCE, NACE, and all-cause mortality, non-fatal MI, any revascularization, CVA, rehospitalization, and stent thrombosis), stratified according to stent types (before inverse probability of treatment weighting); CVA — cerebrovascular accident; MACCE — major adverse cardiac and cerebrovascular events; MI — myocardial infarction; NACE — net adverse clinical events.

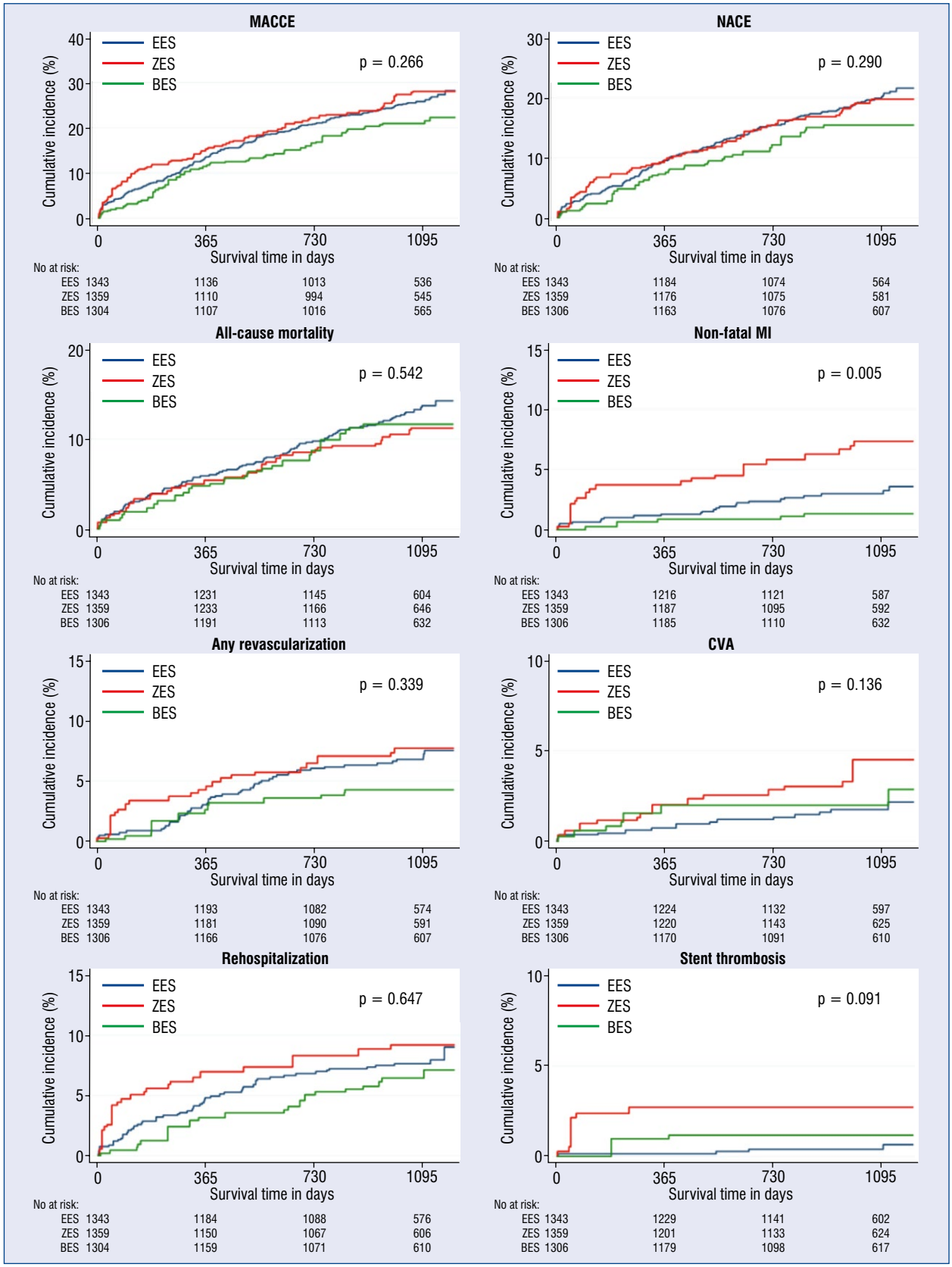

Figure 3. Kaplan-Meier survival analyses of long-term follow-up clinical outcomes (MACCE, NACE, and all-cause mortality, non-fatal MI, any revascularization, CVA, rehospitalization, and stent thrombosis), stratified according to stent types (after inverse probability of treatment weighting); CVA — cerebrovascular accident; MACCE — major adverse cardiac and cerebrovascular events; MI — myocardial infarction; NACE — net adverse clinical events.

patients tend to have a higher risk of experiencing cardiovascular events than patients with normal kidney function [27, 28]. Furthermore, the 2-year mortality rate after AMI is approximately 50% in ESKD patients, which is much higher than the mortality rate after AMI in the general population [29]. Some large-scale studies demonstrated that reduced kidney function was independently associated with an increased risk of mortality and cardiovascular events in patients with reduced LVEF [30, 31]. A similar trend was observed between kidney function and cardiovascular events in an AMI setting [25].

Although the mechanism underlying the development of cardiovascular disorders by renal impairment is still not well understood, it may be explained by several factors related to renal impairment. The progression of renal impairment is closely related to systemic inflammation and oxidative stress, which are responsible for the clinical manifestations of numerous complications, including atherosclerosis, vascular calcification (calciphylaxis), anemia, heart failure, and derangements in calcium-phosphate homeostasis (mineral and bone disorders) [32–34]. Additionally, CKD is associated with an increased risk of thrombosis [35]. In CKD patients, clinically relevant thrombosis often presents as venous thromboembolism, vascular access-associated thrombosis, and right atrial thrombosis [35]. Similarly, thrombosis may occur within arteries, presenting as CAD, CVA, or peripheral artery disease [36]. These factors are directly and/or indirectly associated with cardiovascular disorders and may contribute to the development of cardiovascular events in patients with renal impairment. Meanwhile, the prevalence of coronary risk factors tends to be high in CKD patients [37, 38]. In the present study, the proportion of patients with hypertension and diabetes mellitus increased with the worsening of the CrCl (**Suppl. Table 3**). Because these coronary risk factors, including hypertension and diabetes mellitus, are equally recognized as predictors of renal impairment, they may worsen kidney function, subsequently increasing the influence of such risk factors [25]. This synergistic effect is also reflected in the present study, as lower CrCl caused lower LVEF with increasing incidence of the two aforementioned coronary risk factors (**Suppl. Table 3**).

Several clinical studies have compared the clinical outcomes of implanted coronary stents in patients with AMI who underwent PCI. DES implantation showed better clinical outcomes than the bare-metal stent in reducing MI and mortality after PCI [39, 40]. Some studies compared 2G-DES and BES in AMI patients. Kim et al. [41] compared the 2-year clinical outcomes of 2G-DES with those of BES in AMI patients with dyslipidemia after PCI and found similar results. Choe et al. [42] reported that BES shows clinical outcomes similar to those of new-generation DES. An article about the network meta-analysis of the efficacy and safety of coronary stents in patients with STEMI showed comparable results regarding the risk of primary outcomes between the DES groups, including the ZES, EES, and BES groups [40].

Similarly, there are published papers comparing stents in patients with AMI and renal impairment. Hachinohe et al. [43] reported that ZES results in a higher frequency of major adverse cardiovascular events (MACE) due to the increased TLR rate compared with SES in AMI patients with concomitant CKD. Ahmed et al. [44] compared the ZES and EES in STEMI patients with CKD undergoing PCI, and their results showed similarities with the risk of 12-month MACE and death in patients with STEMI and CKD undergoing PCI.

Unlike these studies comparing two stent groups among AMI-RI patients, the current study is the first to compare clinical outcomes between three DES groups in selected AMI-RI patients undergoing PCI. This study highlights that the use of ZES is associated with the occurrence of non-fatal MI compared with the use of the other two DESs. In addition, clinical findings herein, were based on a longer follow-up period than in previously published articles that were mentioned earlier.

Nonetheless, it is still unclear why this significant result was derived regarding non-fatal MI. It was mainly driven by the difference between ZES and EES groups, or between ZES and EES groups. In a comparative study evaluating 5-year efficacy of both EES and Resolute ZES in PCI-treated ACS patients, Resolute ZES demonstrated worse long-term outcomes than EES [45]. The authors of this study emphasized that the clinical differences between the two stent types were mainly driven by the polymer characteristics, not by the antiproliferative agents. Because the fluoropolymer, a highly fluorinated bilayer copolymer, coated with EES platform has high biocompatibility, reduces platelet adhesion and thrombus formation, these characteristics seems to influence better long-term outcomes in EES compared to Resolute ZES. Meanwhile, unlike both ZES and EES, which have durable polymers, BES has biodegradable polymers. In the BIOSTEMI trial, biodegradable polymer DES was statistically superior to durable polymer DES among STEMI patients [46]. Similarly, in the present study, BES showed relatively

Table 3. Unadjusted and adjusted clinical outcomes.

Clinical outcomes	Overall patients				Inverse probability of treatment weighting analysis			
	EES (n = 808*)	ZES (n = 339*)	BES (n = 304*)	P	EES (n = 1343**)	ZES (n = 1359**)	BES (n = 1306**)	P
MACCE	217 (26.9%)	86 (25.4%)	69 (22.7%)	0.321	344 (25.6%)	367 (27.0%)	274 (21.0%)	0.266
NACE	167 (20.7%)	62 (18.3%)	47 (15.5%)	0.142	266 (19.8%)	257 (18.9%)	194 (14.9%)	0.290
All-cause mortality:	111 (13.7%)	40 (11.8%)	34 (11.2%)	0.463	175 (13.0%)	145 (10.7%)	145 (11.1%)	0.542
Cardiac death	65 (8.0%)	25 (7.4%)	14 (4.6%)	0.151	104 (7.7%)	92 (6.8%)	67 (5.1%)	0.407
Non-cardiac death	46 (5.7%)	15 (4.4%)	20 (6.6%)	0.521	71 (5.3%)	53 (3.9%)	78 (6.0%)	0.516
Non-fatal MI	26 (3.2%)	17 (5.0%)	6 (2.0%)	0.091	39 (2.9%)	92 (6.7%)	16 (1.2%)	**0.005**
Any revascularization	53 (6.6%)	21 (6.2%)	14 (4.6%)	0.453	87 (6.5%)	97 (7.1%)	52 (3.9%)	0.339
Cerebrovascular accident	17 (2.1%)	14 (4.1%)	9 (3.0%)	0.164	23 (1.7%)	55 (4.1%)	28 (2.2%)	0.136
Rehospitalization	60 (7.4%)	21 (6.2%)	21 (6.9%)	0.733	98 (7.3%)	118 (8.7%)	83 (6.4%)	0.647
Stent thrombosis	4 (0.5%)	5 (1.5%)	2 (0.7%)	0.212	6 (0.5%)	36 (2.7%)	15 (1.1%)	0.091

Values are presented as number (%).

BES — biolimus-eluting stent; EES — everolimus-eluting stent; MACCE — major adverse cardiac and cerebrovascular events; MI — myocardial infarction; NACE — net adverse clinical events; ZES — zotarolimus-eluting stent

*Number of patients represents the number in the study population excluding those whose follow-up period was 0 days after hospital discharge.
**Number of patients represent the number in the synthetic pseudo-population generated by the inverse probability of treatment weighting. The propensity score was constructed by a multiple logistic regression model using a variety of clinical variables, such as sex, age ≥ 65 years, Killip classification > 2, body mass index, hypertension, diabetes mellitus, dyslipidemia, prior heart failure, prior cerebrovascular accident, smoking, family history of coronary artery disease, creatinine clearance, left ventricular ejection fraction < 40%, discharge medications (acetylsalicylic acid, P2Y12 inhibitors, calcium channel blockers, beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, statins, fibrates, and oral anticoagulants), The American Heart Association and the American College of Cardiology lesion type (type A or B1 versus type B2 or C), vascular approach (femoral vs. non-femoral approach), significant coronary stenosis, glycoprotein IIb/IIIa complex inhibitor use, thrombus aspiration, image-guided percutaneous coronary intervention (PCI), pre-procedural Thrombolysis In Myocardial Infarction 0–I, infarct-related artery, multivessel PCI, staged PCI, left main coronary artery (LMCA) complex lesions, multivessel disease, territories of revascularization (LMCA PCI, left anterior descending coronary artery PCI, left circumflex coronary artery PCI, and right coronary artery PCI), ST-segment elevation myocardial infarction diagnosis, stent number, total stent length, mean stent diameter, and the duration of dual antiplatelet therapy ≥ 12 months.

good clinical outcomes (MACCE, NACE, cardiac death, non-fatal MI, any revascularization, and re-hospitalization), although many of them were not statistically insignificant. Additionally, the statistical process should be considered in interpreting these results. In total, 110 patients (patients with a follow-up of 0 days or patients with any missing value in 41 covariates) were excluded from the IPTW-adjusted analysis. Thus, selection bias may have occurred in this process, causing disparities in non-fatal MI outcomes before and after IPTW (p-value of 0.091 before IPTW, and 0.005 after IPTW).

Limitations of the study

There are several limitations to be considered when interpreting the results of this study. First, the contributing institutions in the KAMIR-NIH registry tended to be tertiary centers with a higher volume of patients than average medical institutes. Thus, the mortality rates and treatment practice patterns could not be generalized to all medical institutions treating STEMI patients. Second, the information concerning hemodialysis in the KAMIR-NIH registry was not considered, making it impossible to separate hemodialysis patients from non-hemodialysis patients. Third, detailed stent information such as stent material, stent linker type, strut thickness, and polymer coating, to account for the heterogeneity of each DES, were not included in the analysis. Moreover, the KAMIR--NIH registry does not include several important angiographic profiles and lesion characteristics such as the presence of bifurcation lesion, chronic total occlusion, overlapping stents, use of shockwave intravascular lithotripsy and the use of rotational atherectomy. Fourth, considering the timing of data collection, older types of DESs, which are no longer used in routine clinical practice, could undoubtedly also be included in the analysis. Fifth, this study was based on an observational registry; however, it was a non-randomized study. Hence, although statistical adjustment using the propensity score weighting method was conducted to overcome this limitation, a large-scale multicenter randomized controlled trial is needed in the future.

Conclusions

In summary, there were no differences in the long-term clinical outcomes between the ZES, EES, and BES groups in AMI-RI patients undergoing PCI, except for non-fatal MI. Unlike EES, ZES may be a predictor of non-fatal MI.

Acknowledgments

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Conflict of interest: None declared

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COVID-19-induced coagulopathy: Experience, achievements, prospects

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Abstract

The presence of coagulopathy as part of the systemic inflammatory response syndrome is a characteristic feature of severe coronavirus disease 2019 (COVID-19). Hematological changes (increased D-dimer [DD], prolonged activated partial thromboplastin clotting time [APTT] and prothrombin time [PT], high fibrinogen levels) have been observed in hospitalized patients with COVID-19, which characterize the risk of thrombotic events. Against the background of COVID-19 there is endothelial dysfunction, hypoxia and pulmonary congestion, mediated by thrombosis and microvascular occlusion. Up to 71.4% of patients who died from COVID-19 had disseminated intravascular coagulation syndrome, compared with only 0.6% of survivors. The main manifestation of COVID-19-associated coagulopathy is a significant increase in DD without a decrease in platelet count or prolongation of APTT and PT, indicating increased thrombin formation and the development of local fibrinolysis. An increase in DD levels of more than 3–4 times was associated with higher in-hospital mortality. Therefore, COVID-19 requires assessment of the severity of the disease for further tactics of thromboprophylaxis. The need for continued thromboprophylaxis, or therapeutic anticoagulation, in patients after inpatient treatment for two weeks using imaging techniques to assess of thrombosis assessment. (Cardiol J 2023; 30, 3: 453–461)

Key words: coronavirus disease 2019 (COVID-19) infection, COVID-19-induced coagulopathy, SARS-CoV-2

Introduction

Since 2019, the outbreak of the then new coronavirus disease 2019 (COVID-19), which first originated at Wuhan, located in the Chinese province of Hubei, has spread around the world, and on 11 March 2020, the World Health Organization (WHO) announced the new COVID-19 as a pandemic [1, 2].

The number of confirmed cases and deaths from COVID-19 disease started to grow each day [3]. Mortality rates vary from country to country and depend on the capacity and effectiveness of the health care system. Since the beginning of

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the pandemic, Iran has been and is still considered a high-risk area with a much higher mortality rate than most cases in China [4–6].

The clinical spectrum of infection with the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is different, ranging from the absence of any symptoms to lethal septic shock. 81% of all reported cases of COVID-19 by children and adults had a mild course of the disease, 14% — severe (eg, shortness of breath or oxygen saturation ≤ 93%) and 5% — critical condition (respiratory failure, septic shock, death) [7, 8].

The transition from mild to severe in patients with COVID-19 may be caused by cytokine storms and increased hypercoagulation with a significant risk of thromboembolic complications, affecting mainly venous, but are also registered in the arterial system [9–11].

The presence of comorbidities (cardiovascular, obesity, diabetes) that contribute to the development of coagulopathy, including those caused by sepsis, increased levels of D-dimer (DD), C-reactive protein (CRP), troponins and other markers of disseminated intravascular coagulation (DIC) in more than 6 times from the reference, is associated with a worse prognosis in hospitalized patients with severe coronavirus COVID-19, reaching 42% of in-hospital mortality [7].

A new term for COVID-induced coagulopathy (CIC) has been introduced to describe changes in blood clotting in patients with COVID-19 [12]. Characteristic laboratory data of CIC are observed, namely, elevated levels of DD and fibrin degradation products, which indicate an enhanced thrombotic state with high fibrin turnover. However, other CIC markers remain relatively unchanged.

Initial anticoagulant therapy, especially by direct injection, reduces mortality by 48% after 7 days and by 37% after 28 days and achieves a significant improvement in inhaled oxygen/O_2 (PaO_2/FiO_2) by mitigating microthrombi and associated pulmonary coagulopathy [13].

Most protocols for the prevention of venous thromboembolism (VTE) with the use of therapeutic (full) doses of anticoagulants have been introduced in many countries [14–23], mainly for hospitalized adult patients. However, there are a limited number of publications on thromboprophylaxis in pediatric patients [23–26].

The present study offers a practical approach to CIC in patients with COVID-19, based on experience in the current literature and of our own experience in the treatment of patients hospitalized in local institutions.

Epidemiology

Since the outbreak of COVID-19 in December of 2019, which originated in the city of Wuhan, in the Chinese province of Hubei, this disease has spread around the world [7, 27]. On February 11, 2020, the International Coronavirus Taxonomy Study Group officially named the new coronavirus that causes COVID-19 "SARS-CoV-2", and on March 11, 2020, the WHO announced a new COVID-19 pandemic [4–6, 8, 12, 14, 25, 28], which had its epicenter on the Asian continent (China), which later moved to the European (mainly to Italy and Spain), and then — to the Americas, first to the United States, and is now present in the United States and Latin America (Mexico and Brazil).

SARS-CoV-2 is a single-stranded RNA coronavirus that enters the cell mainly through binding to the type 2 angiotensin-converting enzyme (ACE-2) receptor, which is abundant in the alveolar clitoris, lungs, cardiac myocytes, vascular endothelium and other cells [29]. SARS-CoV-2 is transmitted mainly by inhalation of viral particles and entry into the respiratory tract. This virus can survive up to 24–72 hours on the surfaces of various objects indoors, which contributes to its spread [9, 19, 27, 30, 31].

Respiratory viral infection caused by COVID-19 is usually asymptomatic or with mild symptoms including fever, cough, fatigue, shortness of breath, diarrhea, headache and myalgia (up to 81.4% of patients). Severe cases are characterized by an increase in respiratory failure with a respiratory rate > 30 per minute, a decrease in saturation < 93% at rest, PaO_2/FiO_2 < 300 mmHg and infiltration > 50% of the lungs within 24–48 hours (up to 13.9% of patients) and may progress to the development of a critical condition (up to 4.7% of patients), demonstrating rapid deterioration and development of acute respiratory distress syndrome, septic shock, metabolic acidosis and coagulopathy, including cytokine storm [8, 12, 14–19, 32–36].

These clinical manifestations and paraclinical signs change with the further development of the pandemic worldwide, and also depend on the severity of the infection.

Coagulopathy

The most persistent hemostatic changes in COVID-19 are thrombocytopenia and increased DD [37], which are associated with the development of liver failure due to active inflammation in the lungs,

intestines, myocardium, resulting in frequent use of ventilation requiring intensive care. In some cases this disease leads to the death of patients. Elderly patients with comorbidities with higher levels of DD had a higher risk of nosocomial mortality [20–22]. Given the clinical consequences of elevated DD levels, even in the absence of other serious symptoms, inpatient treatment should be considered, as this indicates an increase in thrombin levels and a higher risk of COVID-induced complications.

Blood clotting profile studies should be performed in hospitalized patients with suspected or confirmed COVID-19, including DD, activated partial thromboplastin clotting time (APTT), prothrombin time (PT), platelet count (PLT), and fibrinogen levels (Fib). Changes in these parameters may occur 7–11 days after the onset of symptoms or 4–10 days after hospitalization. It is important to repeat the study of these indicators to detect coagulopathy (DD, APTT, PT, Fib, PLT) in patients with severe COVID-19 at least every 2–3 days [9, 21, 38–44].

The combination of thrombocytopenia, prolonged prolongation of APTT and PT, increased DD indicates the development of DIC, the manifestations of which differ from those observed in septic processes of other etiologies, where thrombocytopenia is more pronounced and does not reach DD values observed in COVID-19. Recent evidence suggests that COVID-19-associated coagulopathy is a combination of low-grade DIC and pulmonary thrombotic microangiopathy, which has a significant effect on organ dysfunction in patients with the most severe condition [20, 45].

The presence of coagulopathy as part of the systemic inflammatory response syndrome is a common sign of severe COVID-19. Importantly, hematological changes in coagulation tests (elevated DD-dimer, prolonged APTT and PT, thrombocytopenia, and/or low fibrinogen levels) were observed in hospitalized patients with COVID-19, characterizing thrombotic events rather than hemorrhagic events. That is, COVID discoagulopathy causes thrombotic complications, in particular, VTE). Against the background of CIC, and hence endothelial dysfunction, there is hypoxia and pulmonary congestion, mediated by thrombosis and microvascular occlusion (including cerebrovascular events, limb ischemia, etc.) [9, 16, 21, 23–25, 46].

In patients who died of COVID-19, fibrin and thrombin deposition occurred predominantly in the pulmonary microcirculatory tract, which contributed to the development of acute respiratory distress syndrome and coagulopathy. In addition, hypoxia due to severe COVID-19 exacerbated thrombosis not only due to increased blood viscosity but also through a signaling pathway dependent on the transcription factor induced in the development of hypoxia [16, 23, 26, 47–52].

SARS-CoV-2 infection develops endothelial disease with profound microcirculatory changes, in which there is excessive thrombin formation and impaired fibrinolysis, similar to endothelial dysfunction in coagulopathy caused by sepsis (SIC). The receptor for viral adhesion is ACE-2 on endothelial cells, and virus replication causes inflammatory cell infiltration, endothelial apoptosis, and microvascular prothrombotic events. Viral inclusions in endothelial cells and infiltration by mononuclear and polymorphonuclear cells with evidence of endothelial apoptosis were observed in postmortem analysis of SARS-CoV-2 infection. Impaired microcirculation contributes to the development of severe clinical consequences in patients with COVID-19 [9, 16, 53, 54]. Other abnormalities that may be relevant in the context of coagulopathy are decreased fibrinogen levels, increased lactate dehydrogenase, and, in some patients, marked increases in serum ferritin levels [26, 55, 56].

Another important feature of COVID-19 infection is the development of an acute procoagulant response in elevated levels of FVIII, von Willebrand, and fibrinogen, which are associated with an increased risk of thrombosis. In severe stages of the disease there is an increase in inflammatory cytokines (tumor necrosis factor [FNO-α] and interleukins [IL]: 1 and 6). IL-6 induces the expression of tissue factor in macrophages, which initiates the activation of coagulation and thrombin formation [32]. FNO-α and IL-1 are major mediators of endogenous coagulation inhibition. Severely compromised patients with COVID-19 may experience a cytokine storm characterized by high concentrations of proinflammatory cytokines and chemokines [18, 20, 32].

The International Society for Thrombosis and Hemostasis (ISTH) has proposed a new category for the detection of early-stage DIC associated with sepsis, called SIC. This indicator can be used in patients with COVID-19, and in those who meet these criteria, it is optimal to use anticoagulants.

Up to 71.4% of patients who died from COVID-19 had an ICE, compared with only 0.6% of survivors. The main change in this coagulopathy is a marked increase in DD without a decrease in PLT, or a prolongation of APTT and PT, indicating

the process of thrombin formation and local rather than systemic fibrinolysis. The highest level of hospital mortality was found in patients with DD values more than 3–4 times [24, 26, 28, 38, 39].

Given the occurrence of signs of coagulation system dysfunction in COVID-19, it is proposed to assess the severity of the disease (COVID-19--associated hemostatic abnormalities — CAHA--score) [28, 30, 41, 57–59]:

— **Stage 1 CAHA:** The patient has mild symptoms and can be cared for at home or in hospital. At this stage, pulmonary microthrombi may be missed on computed tomography;
— **Stage 2 CAHA:** The patient may develop more severe symptoms and need resuscitation. Computed tomography scans of these patients may reveal lung filling defects due to blood clots or embolism. They may also have asymptomatic deep vein thrombosis in the lower extremities, which means significant activation of coagulation;
— **Stage 3 CAHA:** The patient's clinical condition is deteriorating, which requires the maintenance of a higher level of intensive care. Extensive pulmonary thrombi and systemic thrombosis, including DIC, have been reported.

Thus, there is a need to identify an increased risk of thrombotic events at an early stage and to prevent thrombotic events and organ damage as much as possible.

Deterioration of laboratory parameters associated with blood coagulation indicates the progression of the severity of COVID-19 infection and suggests the need for greater and more aggressive intensive care, while improvement in these parameters along with improvement or clinical stability indicates an adequate evolution [24].

Thromboprophylaxis

Hospitalized patients with COVID-19 have both internal and external risk factors for thrombosis, including old age, obesity, immobilization, neurological disease, cancer, intensive care, previous cases of thromboembolism or thrombophilia [42].

Pharmacological thromboprophylaxis should be considered in all hospitalized patients with COVID-19 if there are no contraindications (active bleeding or severe thrombocytopenia). Different scales (Padua, Caprini, IMPROVE) can be used to assess risk. The dose should be adjusted according to renal function. Although existing protocols should be followed when selecting the drug, the WHO recommends the use of unfractionated or low molecular weight heparins (LMWH) and, if contraindicated, mechanical thromboprophylaxis should be considered. Pharmacological thromboprophylaxis is recommended once a day, as it reduces the risk of skipping additional doses and is associated with less impact on medical personnel during its use. If LMWH is not available, unfractionated heparin may be considered, keeping in mind that this requires more frequent injections. Patients with more severe infections may require higher doses of thromboprophylaxis due to their hypercoagulable state. The use of direct anticoagulants for thromboprophylaxis is not recommended in this context due to the possible interactions that may occur with the various drugs and treatments available and studied for the treatment of COVID-19 [5, 20, 21, 42].

Some of the non-anticoagulant properties of LMWH include the potential for binding to inflammatory cytokines, inhibition of neutrophil chemotaxis and leukocyte migration, neutralization of positively charged complement factor C5a, and sequestration of acute phase proteins [18, 44].

In view of the above it is suggested that LMWH, administered in the early stages of SARS--CoV-2 infection may have a positive effect not only in preventing thrombosis, but also in reducing systemic and pulmonary inflammation and limiting viral invasion [12, 19], among others. Non-anticoagulant properties of heparin: antiviral action (experimental models), reduction of collagen deposits and antiarrhythmic action (animal models), modulation of endothelial dysfunction, improvement of microvascular dysfunction and alleviation of pulmonary coagulopathy [33, 42].

Patients who remain fully immobilized may benefit from drug thromboprophylaxis due to periodic pneumatic compression. This therapy should also be considered if there is severe thrombocytopenia (platelets from 25 G/L to 50 G/L) [8, 34, 35, 42].

According to the authors [8, 27, 42], long-term outpatient thromboprophylaxis (14 to 45 days) should be considered in patients at high risk of deep vein thrombosis, regardless of COVID-19 infection, including reduced mobility, previous thromboembolic events, comorbidities (eg. active cancer) and elevated DD levels of more than 2 times). Thromboprophylaxis is not recommended for patients in quarantine due to a mild form of COVID-19 but with significant comorbidities, or patients without COVID-19 but functionally limited in quarantine. These patients should be advised to stay active at home.

Pharmacological thromboprophylaxis in adult patients with COVID-19

The results of studies on the prevention of deep vein thrombosis in adult patients in critical condition with COVID-19-associated pneumonia have been published [10, 35, 36].

Histopathological examinations revealed diffuse lesions of the alveoli with deep inflammation, thrombosis and thrombotic microangiopathy of small vessels and capillaries of the lungs. In extrapulmonary organs, endothelial cell damage and diffuse microvascular thrombosis have also been reported, indicating thrombotic microangiopathy, which may explain the acute onset of multiorgan failure [10, 35, 36].

According to current guidelines, patients with stage 1 CAHA should receive LMWH in the absence of contraindications [35, 41]. Several trials are currently underway for patients with treatment disorders corresponding to stage 2 CAHA to determine whether a full dose of anticoagulants compared to prophylactic can help prevent the development of coagulopathy and ischemia in the extrapulmonary circulation. After the detection of blood clots, the standard practice is to treat such patients with anticoagulants in a therapeutic dose [35, 41, 42]. Intensification of antithrombotic therapy (prevention of double-dose LMWH) in stage 2 CAHA can be performed in combination with several other experimental measures, such as thrombolysis, which may be effective in patients in stage 3 CAHA [41].

The developed guidelines provide guidance to physicians caring for both COVID-19 patients and patients with chronic thrombotic conditions requiring ongoing treatment. Recently, there has been published work focusing on anticoagulant strategies for the prevention and treatment of deep vein thrombosis in patients with proven SARS--CoV-2 infection who are in outpatient treatment and hospitalized for the prevention or treatment of thrombosis [35, 42].

Pharmacological thromboprophylaxis in pediatric and adolescent patients with COVID-19

Rare deaths of children from COVID-19 infection have been reported in worldwide [60]. Most often diagnosed with asymptomatic disease, or with mild or moderate severity [46, 61]. As in adults, the risk of serious illness and death in children is higher in people with comorbidities [47, 62]. In general, the experience of monitoring infants and children with COVID-19 in hospitals is limited [63].

From the standpoint that a significant number of clinical issues deserve further study and clarification, we have prepared general recommendations for thromboprophylaxis childrens regimens.

Outpatients with mild COVID-19 should not be prescribed pharmacological thromboprophylaxis, but it is important to encourage increased mobility of the child and to control adequate hydration in the presence of fever or vomiting. Given the rapid deterioration reported in many adult patients with mild symptoms, regular monitoring of DD, Fib, PLT, PT and APTT every 48 hours for 5–7 days may be recommended. Patients with DD levels above 300 ng/mL have a high risk of thrombosis and should receive LMWH prophylaxis with continuous assessment of deep vein thrombosis.

Patients with moderate COVID-19 who require hospitalization should receive anticoagulant therapy [64] using prophylactic doses of LMWH.

Intensification of anticoagulant therapy is recommended in case of severe COVID-19 (DD > > 500 ng/mL, serum ferritin > 500 ng/mL, worsening of clinical signs of disease). Especially when the patient is in critical condition (DD > 2500 ng/mL, PLT > 450 G/L and CRP > 100 mg/dL; Table 1).

Coagulation should be closely monitored during treatment to prevent excessive anticoagulant therapy and bleeding [65, 66]. Anti-Xa levels and ARTT ratios are good ways to determine the effectiveness of LMWH in patients with confirmed deep vein thrombosis. After reaching the desired level, the test can be repeated every 6–7 days. If an invasive procedure is required, it is recommended to skip two doses of LMWH before the procedure [26].

In patients with renal insufficiency, unfractionated heparins of 75 IU/kg intravenous infusion over 10 minutes (maximum 5000 IU) as the loading dose are the anticoagulants of choice. This should be followed by a continuous maintenance intravenous infusion (maximum initial rate of 1300 IU/h). The recommended infusion rate is 28 IU/kg/h in infants and children under 12 months of age, 20 IU/kg/h in children 1 to 15 years of age, and 18 IU/kg/h in children 16 years of age and older.

For patients already receiving anticoagulant therapy, the proposed algorithm approach is illustrated in Figure 1.

Transferring a patient from an inpatient setting to an outpatient setting is the next step, including reassessing anticoagulant therapy and ensuring

Table 1. Anticoagulant prophylaxis with Enoxaparin for patients with moderate, severe and critical form of COVID-19, which require hospitalization.

	Profile dose	Prophylactic intensified dose	Treatment dose
Target anti-Xa	0.2–0,4 U/mL	0.4–0.8 U/mL	0.6–1.1 U/mL
≤ 2 months	0.75 mg/kg, every 12 h	1.0 mg/kg, every 12 h	1.5 mg/kg, every 12 h
From 2 months till ≤ 18 years:			
< 40 kg	0.5 mg/kg, every 12 h	0.75 mg/kg, every 12 h	1.0 mg/kg, every 12 h
> 40 kg	40 mg, 1 time a day	60 mg, every 12 h	40 mg, every 12 h

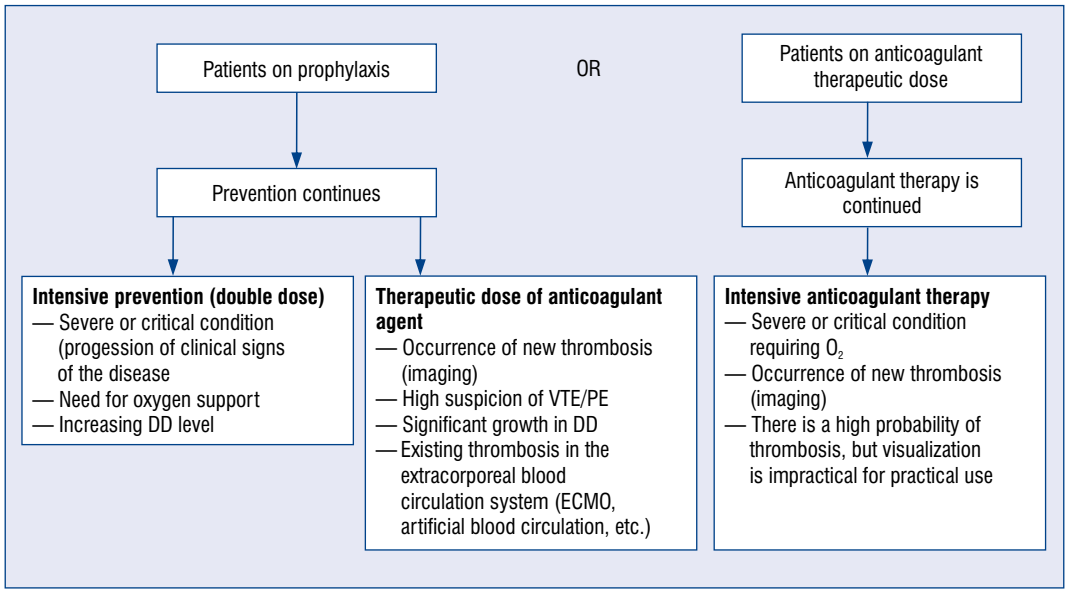


Figure 1. Algorithm for the use of anticoagulants in coronavirus disease 2019 (COVID-19) patients with ≤ 18 years who have already taken an anticoagulant. Heparin resistance in COVID-19: if the heparin dose is > 25 IU/kg/day and there is no activated partial thromboplastin clotting time prolongation anti-Xa monitoring at the level of 0.3–0.7 IU/mL; DD — D-dimer; ECMO — extracorporeal membrane oxygenation; PE — pulmonary embolism; VTE — venous thromboembolism.

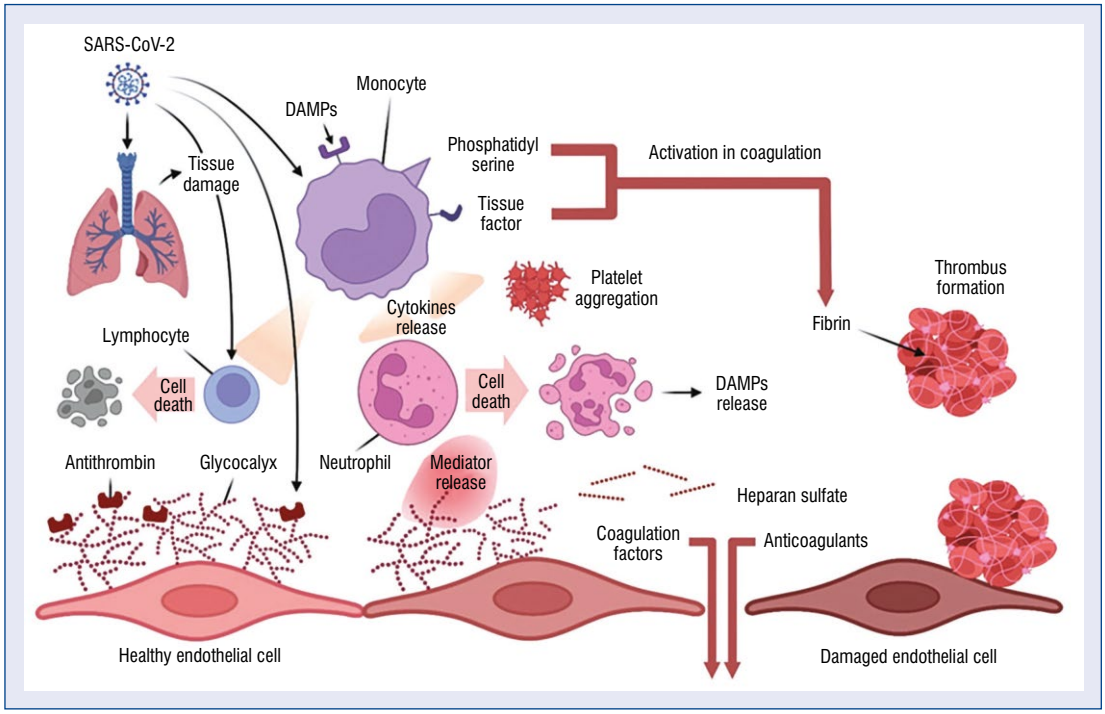
adequate communication between physicians, the patient, family members, or caregivers. The use of thromboprophylaxis in patients with COVID-19 after inpatient treatment should be considered if the stratification of deep vein thrombolism risk indicates a persistently increased risk of co-morbidity due to comorbidities, as well as a concentration twice or more above the upper control range. This is evidenced by studies suggesting thromboprophylaxis or therapeutic anticoagulation in patients after inpatient treatment. At least 2 weeks of anticoagulant therapy and imaging studies to assess thrombosis are recommended, as well as extended anticoagulant therapy [49].

Conclusions

Severe complications and a high number of deaths due to COVID-19 have once again drawn the attention of experts to the prevention and treatment of thrombotic and thromboembolic diseases.

The direct and indirect effects of COVID-19 are associated with the development of a cytokine storm, which accelerates the onset of systemic inflammatory response syndrome and promotes thrombotic events (Central illustration).

Antiviral and pathogenetic agents of COVID-19 (lopinavir/ritonavir, remdesivir, tocilizumab, sarylumab, fingolimod, chloroquine/hydroxychloroquine, interferon, azithromycin) may have



Central illustration. Mechanism of thrombus formation during COVID-19 infection; DAMP — danger/damage associated molecular patterns; SARS-CoV-2 — severe acute respiratory syndrome coronavirus 2.

drug interactions with antiplatelet agents and/or anticoagulants.

At the same time, recommendations for social distancing may adversely affect the treatment of patients without COVID-19 who have thrombotic events, and fear of developing COVID-19 or complications may result in some patients not receiving or discontinuing anticoagulant therapy.

Some clinical issues deserve further research and refinement to better understand the specific features, needs and concerns of critically ill children and adults with COVID-19 infection, especially those who already have comorbidities.

Protocols for thromboprophylaxis, in particular the use of anticoagulants or additional considerations for the treatment of covid-induced coagulopathy, should be used in accordance with the latest national and international guidelines.

Conflict of interest: None declared

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REVIEW ARTICLE

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Catheter-directed therapy to treat intermediate- and high-risk pulmonary embolism: Personal experience and review of the literature

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Abstract

Pulmonary embolism (PE) is the third leading cause of cardiovascular death in the western world. Prompt recognition, risk stratification, and individualized treatment are crucial to improve outcomes in patients with PE. Anticoagulation alone is a sufficient therapeutic option in low-risk patients, whereas primary reperfusion with systemic thrombolysis (ST) is usually chosen in high-risk patients. The choice of treatment in intermediate-risk patients is complex and depends on the clinical presentation. Catheter-directed therapy (CDTh) includes all therapies delivered via a catheter placed in the branches of the pulmonary arteries directly into the thrombus. Because ST bears a high risk of major bleeding and numerous patients have contraindications to ST, CDTh is an alternative to ST in intermediate- and high-risk PE patients. CDTh includes local thrombolysis using low-dose alteplase, ultrasound-assisted thrombolysis, and mechanical fragmentation and aspiration of the thrombi, as well as their combinations. In this review article, we have summarized devices and technical details for CDTh, discussed the efficacy and safety of CDTh in comparison to ST in previous clinical trials, and outlined future research directions regarding CDTh, both based on the literature and our personal experience from the local PE Response Team of the Center for the Management of Pulmonary Embolism (CELZAT) in Warsaw.
(Cardiol J 2023; 30, 3: 462–472)

Key words: pulmonary embolism, catheter-based therapy, interventional cardiology, review

Introduction

Pulmonary embolism (PE) is the third leading cause of cardiovascular death in the western world, associated with 5–10% in-hospital mortality [1]. PE is frequently a complication of deep vein thrombosis (DVT), referred to as venous thromboembolism (VTE) [2]. The symptoms of PE range from shortness of breath, through severe dyspnea, chest pain, and hemoptysis, to the clinical picture of cardiogenic shock. Because these symptoms are unspecific, clinical scores have been proposed to evaluate the risk of PE, such as the Wells score and the Geneva score. These scores include the main risk factors for VTE, including previous DVT or PE, immobilization, surgery, especially after pelvis

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and femoral neck fracture, or active malignancy. Other risk factors for VTE are states of overall hypercoagulability such as pregnancy, antiphospholipid state, or genetic mutations of proteins C and S [3, 4]. All these factors contribute to blood flow stasis, vessel wall damage, and/or hypercoagulability, which are known as the Virchow triad [5].

Besides unspecific symptoms, stratification of the risk of early mortality also poses a clinical challenge in PE patients. The Pulmonary Embolism Severity Index (PESI) or simplified PESI (sPESI), which are scores based on clinical presentation and the patient's history, are useful to determine the risk of PE-associated mortality. PESI class III–V or sPESI ≥ 1 denotes intermediate- or high-risk patients. In addition, right ventricle (RV) dysfunction on transthoracic echocardiography (TTE) or computed tomography pulmonary angiography (CTPA), and elevated biomarkers of cardiac injury are indicative of intermediate- or high-risk PE. Signs of hemodynamic instability with PE confirmation on CTPA and/or evidence of RV dysfunction on TTE are sufficient to classify a patient into the high-risk PE category [6–8]. Currently, hemodynamic instability, which delineates acute high-risk PE, is defined as one of the following clinical manifestations at presentation: (i) cardiac arrest; (ii) obstructive shock (systolic blood pressure [SBP] < 90 mmHg or the need for vasopressor therapy, and end-organ hypoperfusion); or (iii) persistent hypotension (SBP < 90 mmHg or a drop ≥ 40 mmHg for more than 15 min). Altogether, patients with high-risk PE present with clear signs of hemodynamic instability, whereas intermediate-/high-risk patients are hemodynamically stable but have signs of RV dysfunction or myocardial necrosis.

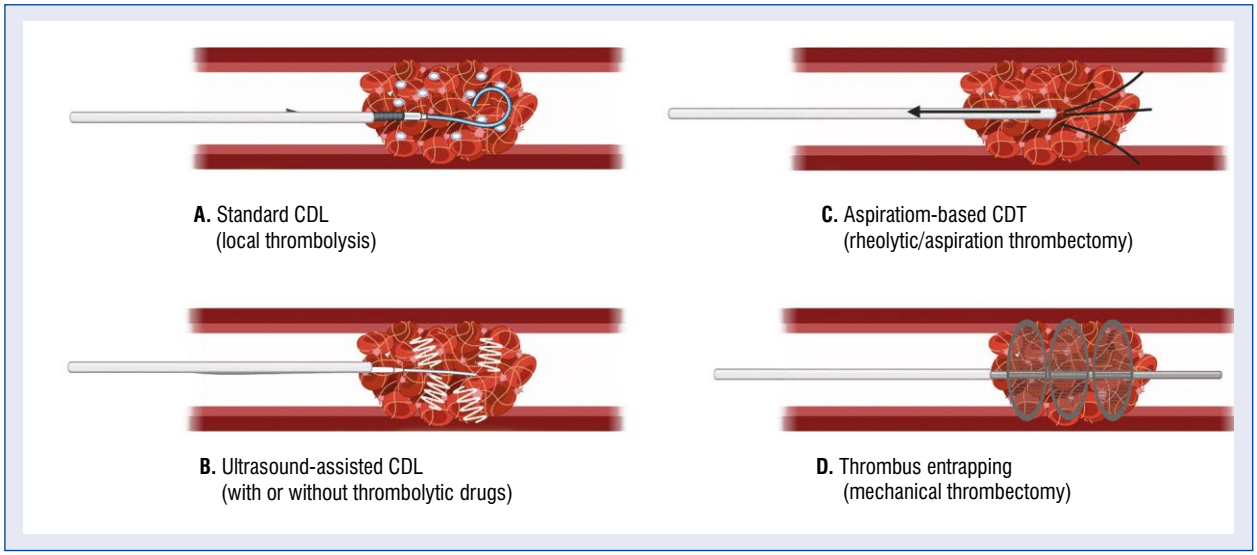
Prompt recognition, risk stratification, and individualized treatment are crucial to improve outcomes in patients with PE. Anticoagulation alone is a sufficient therapeutic option in low-risk patients, whereas systemic thrombolysis (ST) is usually chosen in high-risk patients. The choice of treatment in intermediate-risk patients is complex and depends on the clinical presentation. Moreover, in numerous patients, the hemodynamic status changes over time, requiring adjustment of therapy [9, 10].

Whereas ST decreases RV overload, thus improving the hemodynamic state in patients with PE, the high doses of thrombolytic agents administered during ST, delivered in a short time frame (50–100 mg tissue plasminogen activator [TPA] over 15 min – 2 h), bear a high risk of major bleeding (9.9%), including intracranial hemorrhage (1.7%) [11, 12]. Hence, the net clinical benefit of ST is hampered by the associated complications. Numerous patients have contraindications to ST, such as active internal bleeding, recent ischemic stroke, intracranial surgery or arterial puncture, history of previous intracranial hemorrhage, low platelet count, or coagulation disturbances at presentation [13, 14].

Catheter-directed therapy (CDTh) and surgical embolectomy are alternatives to ST in intermediate- and high-risk PE patients with hemodynamic deterioration despite anticoagulation and in patients in whom thrombolysis is contraindicated or has failed. Whereas surgical embolectomy is an invasive procedure carried out with cardiopulmonary bypass and requiring the incision of the pulmonary arteries to remove the thrombi, CDTh is a less invasive approach to interventional PE treatment. CDTh includes all therapies that are delivered via a catheter placed in the branches of the pulmonary artery (PA) directly into the thrombus. CDTh ranges from local catheter-directed thrombolysis (CDL) using low-dose alteplase, through ultrasound-assisted thrombolysis, to mechanical fragmentation and aspiration of the thrombi, known as catheter-directed thrombectomy (CDT), as well as combinations of these methods [15, 16]. Preliminary data suggest that CDTh has a procedural success rate of above 80%, defined as hemodynamic stabilization, correction of hypoxemia, and survival to hospital discharge. In addition, the rate of major bleeding complications might be reduced in CDTh, compared with ST. However, a clear mortality benefit of CDTh remains to be demonstrated [16–19]. In this review article, we have summarized devices and technical details for CDTh, discussed the efficacy and safety of CDTh in comparison to ST in the main clinical trials, and outlined future research directions to investigate whether CDTh is a viable alternative to ST in intermediate- and high-risk PE patients, or in those with contraindications to ST. The presented information is based both on the literature and our personal experience, gathered during the interdisciplinary consultation of the PE patients within the local PE Response Team of the Center for the Management of Pulmonary Embolism (PERT CELZAT) in Warsaw.

Devices and technical details for CDTh

Although CDTh emerged about two decades ago, evidence-based data on its efficacy and safety are scarce. Numerous devices have been approved for CDTh of PE and are mentioned in the guidelines, but no device is specifically recommended, so the choice of the device for CDTh is at the operator's discretion [20].



Central illustration. Devices approved for catheter-directed therapy (CDTh) in pulmonary embolism; **A.** Standard catheter-directed thrombolysis (CDL); **B.** Ultrasound-assisted CDL (EKOS™ Endovascular System); **C.** Aspiration--based catheter directed thrombectomy (CDT) (AngioJet™, Penumbra Indigo® System, AngioVac System); **D.** Thrombus entrapping using mesh discs (FlowTriever Infusion Aspiration System).

Catheter-directed therapy can be used with or without thrombolysis (catheter-directed thrombolysis; CDL or CDT). CDL includes standard local thrombolysis and ultrasound-assisted thrombolysis. CDT comprises rheolytic thrombectomy, aspiration thrombectomy, and mechanical thrombectomy. There are also combinations of thrombolysis- and thrombectomy-based techniques [7]. Devices approved for CDTh in PE are shown in the Central illustration. The pros and cons of currently available CDTh are shown in Table 1.

Devices

Standard CDL

Standard CDL (Central illustration A) is based on local administration of the low-dose alteplase, compared to the high dose administered during ST (1 mg/h up to a total of 24 mg of TPA vs. 50–100 mg of TPA, respectively). Standard CDL is performed using a multi-hole infusion catheter such as the Uni-Fuse™ (AngioDynamics, Lanthan, US), advanced through a venous access site (jugular or common femoral vein) towards the right atrium, RV, and placed in the PA, in the vicinity of the thrombus [13, 21, 22].

Ultrasound-assisted thrombolysis

Ultrasound-assisted thrombolysis (USAT; Central illustration B) is another method of CDL. During USAT, ultrasound waves are used for thrombus fragmentation, thus accelerating local TPA dispersion and facilitating thrombolysis [23]. USAT requires a specialized type of catheter with small ultrasound transducers such as the EKOS™ Endovascular System (Boston Scientific, Bothell, WA, USA) [24]. Although initially considered more efficient than standard thrombolysis, in the SUNSET sPE trial, patients with sub-massive PE treated with USAT had similar 48-h clearance of pulmonary thrombus compared with those undergoing standard CDL, using comparable mean lytic doses and durations of lysis [25].

Rheolytic CDT

Rheolytic thrombectomy (Central illustration C) is based on the Bernoulli principle, in which high velocity retrograde-directed saline jets are used to create a low-pressure area for thrombus aspiration at the distal part of the catheter [26]. The aspiration is facilitated by the local pulse spray of a thrombolytic drug. Rheolytic CDT can be performed using an AngioJet™ (Boston Scientific, Marlborough, MA, USA) [27]. Although initially promising and effective in peripheral arteries and veins [28], when used in the pulmonary arteries, AngioJet™ was associated with bradycardia, pulmonary vasospasm, and worsening hypoxia, as well as increased mortality [28]. These side effects have been attributed to the release of adenosine from disrupted platelets. Therefore, the Food and Drug

Table 1. Pros and cons of current Food and Drug Administration (FDA)-approved catheter-directed therapies (CDTh) in pulmonary embolism.

Name of technique	Pros	Cons	Example of device	Ref.
Catheter-directed thrombolysis (CDL)				
Standard CDL	Can be performed using a multi-hole infusion catheter Enables to decrease the dose of thrombolytic drug, compared to systemic thrombolysis	Risk of hemorrhagic complications inherent to administration of thrombolytic drug	UniFuse® (AngioDynamics) Cragg-McNamara® (ev3 Endovascular)	[7, 20]
Ultrasound-assisted CDL	Ultrasound facilitates penetration of the thrombolytic agent over a shorter duration	Requires a specialized catheter No difference compared to standard CDL	EKOS™ Endovascular System (Boston Scientific)	[23, 26]
Without thrombolysis				
Rheolytic thrombectomy	Easy to apply Enables clot fragmentation and aspiration without the need to administer thrombolysis	High incidence of bradycardia, hemoptysis, renal failure Black box warning by FDA regarding its use in pulmonary embolism	AngioJet™ (Boston Scientific)	[30]
Aspiration thrombectomy	Easy to apply Enables clot fragmentation and aspiration without the need to administer thrombolysis	Provides inconsistent suction and requires experience to operate the syringe	(Penumbra Indigo® System, Penumbra)	[31–33]
Vacuum thrombectomy	Limited blood loss due to a centrifugal pump reinfusing blood into a venous canula	Size and stiffness of the apparatus limit its maneuverability	AngioVac System (Angio Dynamics)	[34–36]
Mechanical thrombectomy	Rotator drive unit attached to a wire which rotates at ~4000 RPM, enabling de-clotting Retractable nitinol disks that mechanically retrieve the clot, additional vacuum provided by an aspirator	Potential fatigue of the sinuous wire may occur with prolonged activation Kinking of the device may limit its maneuverability	Cleaner XT™ (Argon Medical)* FlowTriever Infusion Aspiration System (Inari Medical)	[37]

*The Cleaner XT™ Rotational Thrombectomy System is registered for mechanical de-clotting of dialysis fistulae and peripheral vasculature, but its use in patients with pulmonary embolism remains off-label.

Administration has issued a "black box" warning for AngioJet™ [29].

Aspiration thrombectomy

During aspiration thrombectomy, an end-hole catheter is placed inside the thrombus. Using a syringe, negative pressure (vacuum) is applied, and the thrombus is manually aspirated [30]. While easy to apply, it provides inconsistent suction and requires experience to operate the syringe. To circumvent these disadvantages, another system available on the market (Penumbra Indigo® System, Penumbra, Alameda, CA, USA) implements automatic suction, ensuring consistent and labor-free suction through an 8F catheter [31, 32]. This system also uses a retractable separator that moves back and forth, thus facilitating thrombus fragmentation [33]. The short-term (48 h) safety

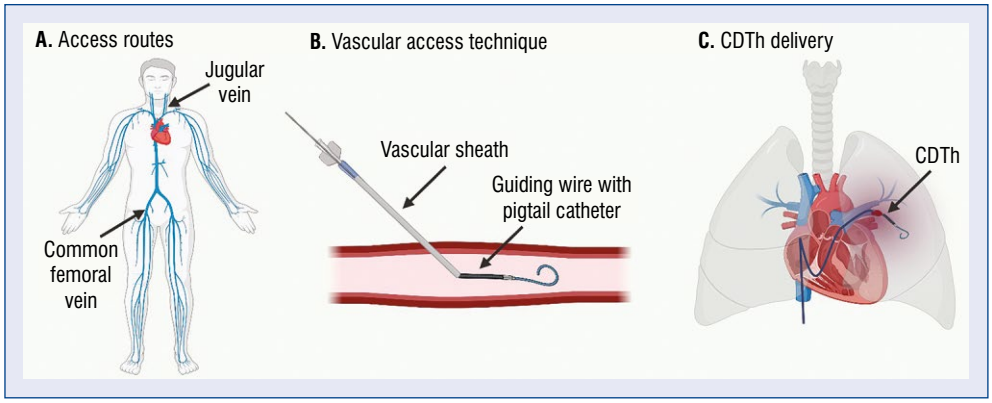


Figure 1. Common steps of catheter-directed therapy (CDTh) in pulmonary embolism; **A.** Access routes; **B.** Vascular access technique; **C.** CDTh delivery.

and efficacy of the Penumbra Indigo® System was confirmed in the EXTRACT-PE study [31]. An ongoing multicenter STRIKE-PE study is evaluating the long-term (90 days) safety and efficacy of this system in patients with PE (NCT04798261).

AngioVac

Aspiration methods are all burdened with blood loss due to suction. A potential solution to this problem is the AngioVac System (Angio Dynamics, Latham, NY, USA). It is an aspiration-based method, in which the blood that has been sucked out is at the same time administered into a venous access port. Although mitigating the blood loss, this device requires a cardiovascular pump and a perfusionist to operate on it [34–36].

FlowTriever

Finally, there is a new device called the FlowTriever Infusion Aspiration System (Inari Medical, Irvine, CA, USA). Instead of a simple, large-bore catheter, the FlowTriever removes the thrombus by ensnaring it between 3 retractable mesh disks that are unfolded out of the catheter. Once the thrombus is trapped, the 3 disks are re-sheathed and removed together with the clotting material [37].

Technical details

Although the devices for CDTh vary, the procedures consist of common steps. These steps have been summarized in Figure 1.

Before the procedure, it is important to check whether no left bundle branch block is present because manipulations of the catheters in the right heart chambers can cause a right bundle branch block, resulting in a complete heart block. In addition, it is crucial to exclude right heart mobile thrombi, which are contraindications performing CDTh.

First, a venous access must be obtained, which is based on the operator's preference. The femoral common vein and the internal jugular vein are both common access sites (Fig. 1A). The disadvantage of the femoral vein is that the thrombus can be present there due to DVT, which might complicate the procedure. Furthermore, if an inferior vena cava filter has previously been inserted, for example in patients with recurrent PE, it may cause problems with advancement of the catheter [38]. Therefore, ultrasound guidance during venipuncture is useful. If the clot is bilateral and a thrombolysis-based technique is used, it is advisable to use two sheaths, one for each catheter, which are subsequently placed in the right and left PA.

Following insertion of the vascular sheath, a guidewire is advanced via the inferior vena cava towards the right atrium and RV, and further into the PA (Fig. 1B, C). Because advancing the catheters via the right heart chambers may damage the chordae of the tricuspid valve, it is common to start the procedure using a pigtail catheter [39].

After advancing the catheter the PA pressure should be measured. Normal mean PA pressure ranges between 8 and 20 mmHg [36]. After the placement of the catheter, the next steps vary depending on the device used. As an example, we will use a standard CDL. The catheter is placed in the vicinity of the pulmonary embolus and low doses of thrombolytic agent are administered (usually TPA at the rate of 0.5–1.0 mg/h over the course of 12–24 h). The continuous infusion of unfrac-

tionated heparin is also used to achieve 2.5-fold prolongation of the activated partial thromboplastin time to prevent peri-sheath thrombus formation. After the procedure, the patient should be admitted to the intensive care unit and monitored for any major bleeding events, especially intracranial hemorrhage. The procedure is deemed a clinical success if the pressure in the PA drops and signs of RV strain decrease. The catheter may then be removed at bedside [19].

To perform a CDT procedure, similar steps are applied. Through a venous access, a thrombectomy catheter is advanced using a guidewire into the PA. After the catheter has been placed in the vicinity of the thrombus, clot is fragmented and aspired manually or with the help of vacuum force, without the need to administer thrombolysis. This process can be facilitated using retractable separators, available in some devices [30, 31].

Efficacy and safety of CDTh in clinical trials

Currently, percutaneous CDTh should be performed with high-risk PE patients who are unsuitable candidates for thrombolysis due to contraindications or failure of previous therapy, as well as in low- or intermediate-risk PE as an alternative to rescue thrombolytic therapy for patients with hemodynamic deterioration on anticoagulation treatment (class IIa recommendations, based on expert opinion) [7]. However, it is still unclear which therapeutic approach to choose for patients suffering from intermediate- or high-risk PE on anticoagulation treatment, whose hemodynamic status is not improving or is worsening [40]. These recommendations are based on 5 main clinical trials, which aimed to evaluate the outcomes in PE patients treated with CDTh. Despite the differences in study designs and methods to evaluate RV strain (RV/LV ratio, PA pressure, RV dilatation) [40], all these trials concluded that CDTh improved the hemodynamic status in patients with PE and may be associated with less bleeding events than ST, although no direct head-to-head comparisons between CDTh and ST are available. Because all these studies were single arm and conducted in relatively small groups of patients (59–150), their results should be interpreted with caution and require confirmation in future randomized trials. Evidence regarding the efficacy and safety of CDTh in patients with PE is summarized in Table 2.

SEATTLE II trial

The SEATTLE II study was a single-arm, multicenter trial to evaluate the efficacy safety of

Table 2. Efficacy and safety of catheter-directed therapy vs. systemic thrombolysis in patients with pulmonary embolism.

	SEATTLE II	PERFECT	ULTIMA	OPTALYSE PE	FLARE	EXTRACT-PE
Patients (number)	150	101	30	101	106	119
Mean age [years]	59	60	63	60	55	59
Mean BMI [kg/m^2]	35.6	31.0	31.0	35.8	35.8	36.7 women 31.7 men
RV/LV index change	1.55 → 1.13	NA	1.28 → 0.99	Arm 1: 1.47 → 1.07 Arm 2: 1.43 → 1.08 Arm 3: 1.49 → 1.02 Arm 4: 1.51 → 1.03	1.56 → 1.15	1.47 → 1.03
Decrease in SPAP [mmHg]	51.4 → 37.5	51.7 → 37.23	52.0 → 39.7	NA	29.8 → 27.8	NA
Bleeding events (number, %)	17 major (11%) 0 minor (0%)	0 major (0%) 13 minor (12%)	0 major (0%) 3 minor (10%)	4 major (3.9%) NA	1 major (0.9%) NA	2 major (1.7%)
Mortality (number, %)	4 (3%)	6 (9%)	0 (0%)	1 (1%)	1 (0.9%)	3 (2.5%)

BMI — body mass index; LV — left ventricle; NA — not available; RV — right ventricle; SPAP — systolic pulmonary artery pressure

ultrasound-assisted, catheter-directed fibrinolysis using the EKOS™ Endovascular System. To classify PE as massive (31 patients), patients had to present signs of syncope, systolic hypotension, or cardiogenic shock. Sub-massive PE (119 patients) was diagnosed in patients with PE, normotension, and RV disfunction. Other inclusion criteria were proximal PE, PE symptoms for less than 14 days, and an RV/LV index greater than 0.9. Patients with stroke or transient ischemic attack, head trauma, massive surgery during the last 7 days, major bleeding, or coagulation disorders were excluded from the study. All 151 patients (mean age 59 years, 51% female) received unfractionated heparin to achieve activated partial thromboplastin time between 40 and 60 s. The doses of thrombolytic drugs were as follows: 1 mg/h for 24 h with a unilateral catheter or 1 mg/h per catheter for 12 h with bilateral catheters. PA pressure was measured at the start of the procedure (after 24 h in patients with unilateral PE and after 12 h in patients with bilateral PE). The primary safety outcome (major bleeding within 72 h of procedure initiation) occurred in 17 (11%) patients, including 1 severe bleeding event and 16 moderate bleeding events, according to GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) scale [41]. The primary efficacy outcome showed a decrease in the RV/LV diameter ratio within 48 h of procedure initiation, measured with computed tomography, from 1.55 at baseline to 1.13 after 48 h from initiation ($p < 0.0001$). The mean PA systolic pressure (51.4 mmHg vs. 36.9 mmHg) and mean Miller angiographic obstruction index score (22.5 vs. 15.8; also decreased at 48 h after CDL initiation; $p < 0.0001$ for both). Three patients died during hospitalization, and one died during 30 days after discharge.

Altogether, SEATTLE II showed that ultrasound-assisted CDL reduced RV dilation, pulmonary hypertension, and anatomic thrombus burden, and was associated with moderate bleeding risk in patients with acute-massive and sub-massive PE.

PERFECT trial

The PERFECT TRIAL evaluated the efficacy and safety of CDTh in 101 patients with acute PE (mean age 60 years, 52% female), either massive ($n = 28$), defined as acute PE with hypotension (SBP < 90 mmHg), or sub-massive ($n = 73$), defined as acute PE with increased RV strain, but without hypotension [42]. Massive PE was treated using pharmacomechanical methods excluding the AngioJet™ device. For treatment of sub-massive PE, standard CDL or USAT were used. The thrombolytic agent was either urokinase (100,000 IU/h) or TPA (0.5–1.0 mg/h). All patients were administered a low dose of heparin (300–500 IU/h) to prevent peri-sheath thrombosis. The primary efficacy endpoints were defined as meeting the following criteria: decrease in PA pressure and/or right heart strain, stabilization of hemodynamic parameters (SBP > 90 mmHg without pressor support), and in-hospital survivability. Safety endpoints were measured in bleeding events and procedure-related complications. Twenty-four of 28 (85.7%) patients with massive PE and 71/73 (97.3%) with sub-massive PE were treated with clinical success. Seventy-eight of 82 (89.1%) patients had a PA pressure decrease (51.2 mmHg before treatment vs. 37.2 mmHg after the procedure). Fifty-seven of 64 (89.1%) patients monitored with follow-up echocardiography showed improvement in RV function. In terms of safety outcomes, there were no major procedure-related complications, no major hemorrhages, and no hemorrhagic strokes. Thirteen of 101 (95%) patients had a minor bleeding event. All of them were self-limited. Six patients died: 4 due to massive PE and 2 due to sub-massive PE.

The PERFECT trial showed that CDTh leads to a decrease in PA pressure and right heart strain and is not associated with major bleeding events. Similar outcomes were observed in patients treated with standard CDL and USAT-assisted CDL, questioning the superiority of USAT over CDT in patients with massive and sub-massive PE.

ULTIMA trial

The ULTIMA trial compared the efficacy and safety of USAT and anticoagulation alone in 59 patients with intermediate-risk acute PE (mean age 63 years). Patients were randomized to receive either USAT, along with local administration of 20 mg of TPA on top of anticoagulation (30 patients), or to receive unfractionated heparin alone (29 patients). All patients suffered from acute PE for less than 14 days and had an RV/LV dilatation ratio > 1.0. The exclusion criteria were age < 18 and > 80 years, major bleeding or high bleeding risk, PE symptoms for > 14 days, low image quality in echocardiographic study, and no possibility to assess the RV/LV dilatation ratio. Patients with signs of cardiogenic shock (SBP < 90 mmHg) were also excluded from the trial. The main outcome measure was the change in RV/LV dilatation ratio between baseline and 24 h after the initiation of USAT or administration of heparin. Mean PA

pressure was measured before the procedure and after 24 h. A 90-day follow-up was scheduled, including echocardiography. Safety outcomes included bleeding, hemodynamic decompensation, and death during 90 days after the procedure. In the USAT group the mean RV/LV dilatation ratio decreased from 1.28 at baseline to 0.99 after 24 h. In contrast, hardly any decrease was observed in the heparin group — from 1.20 at baseline to 1.17 at 24 h. Mean PA systolic pressure decreased from 52.0 mmHg to 39.7 mmHg after 18 h in the USAT group (no invasive PA pressure measurement was performed in the heparin group). There were no deaths in the USAT group and 1 death in the heparin group, unrelated to PE. No patient suffered from hemodynamic decompensation or major bleeding events. Minor bleeding occurred in 3 patients from the USAT group and in one patient from the heparin group [43].

To conclude, USAT resulted in a greater short-term reduction in the RV/LV dilatation ratio than anticoagulation alone. However, the differences between the two groups at 90 days were no longer significant, leaving the question regarding the long-term benefits of USAT unanswered.

OPTALYSE PE trial

The OPTALYSE PE trial aimed to study the lowest optimal TPA dose and delivery using USAT for the treatment of acute PE. A total of 101 patients (18–75 years of age) presenting symptoms of acute, intermediate-risk PE were enrolled. All patients suffered from PE for less than 14 days, had normal SBP (defined as > 90 mmHg), and a RV/LV diameter ratio > 0.9. The exclusion criteria were head injury, active or recent major bleeding, stroke or transient ischemic attack, low platelet count, and hematocrit < 30%. Those who had had major surgery up to 7 days before enrolment were also excluded from the trial. All patients received therapeutic anticoagulation with unfractionated heparin. Patients were randomized into 4 arms: 2 mg/h TPA for 2 h (total 4 mg TPA for unilateral PE and 8 mg TPA for bilateral PE); 1 mg/h TPA for 4 h (total 4 mg TPA for unilateral PE and 8 mg TPA for bilateral PE); 1 mg/h TPA for 6 h (total 6 mg TPA for unilateral PE and 12 mg TPA for bilateral PE); and 2 mg/h TPA for 6 h (total 12 mg TPA total for unilateral PE and 24 mg TPA for bilateral PE). The primary efficacy endpoint was the change in the RV/LV diameter ratio measured at baseline and 48 h after the procedure. The secondary efficacy endpoint was the change in the modified Miller score, measured at baseline and 48 h after the procedure. The safety outcomes were major bleeding events within 72 h after the procedure, symptomatic recurrent PE, and mortality. A decrease in RV/LV diameter ratio was observed in all arms (0.40, 0.35, 0.42, and 0.48 decrease, respectively). The modified Miller score decreased by 5.5% in arm 1, 9.2% in arm 2, 14.0% in arm 3, and 25.7% in arm 4. No major bleeding events occurred in arm 1. In other arms, 5 bleeding events occurred in 4 patients. One patient died within 30 days, and the estimated 12-month mortality was 2% [44].

In conclusion, a decrease of RV/LV diameter ratio was registered in all 4 infusion regimens. There was no evidence of one regimen being superior in efficacy and safety to the other.

FLARE trial

The FLARE trial evaluated the safety and efficacy of percutaneous mechanical thrombectomy using the FlowTriever System (Inari Medical, Irvine, CA, USA) in 106 patients with acute, intermediate-risk PE, aged 18–75 years, with a PE duration < 14 days. Patients had to be hemodynamically stable (SBP > 90 mmHg, heart rate < 130 beats/min) and have a RV/LV ratio > 0.9. Among the exclusion criteria were contraindication to anticoagulant therapy, thrombolytic therapy within 30 days of the trial and active cancer. The decrease in RV/LV ratio during the initial 48 h after treatment was the main efficacy endpoint. Safety endpoints were defined as major bleeding, mortality, and device- or treatment-related adverse effects. Two out of 106 patients received additional thrombolytic drugs due to a large thrombus burden. In total, 101 patients received anticoagulation before the procedure. The mean decrease in RV/LV ratio at 48 h was 0.38. Four patients experienced 6 major adverse effects [37]. It was concluded that the use of the FlowTriever System for percutaneous mechanical thrombectomy seems to be safe and effective in patients with acute intermediate-risk PE.

EXTRACT-PE trial

The Extract-PE trial evaluated the safety and efficacy of the Indigo Aspiration System (Penumbra, Alameda, CA, USA) for the treatment of acute PE without the use of thrombolytic drugs. It enrolled 119 patients > 18 years old (44.5% women), who presented with symptoms of acute, sub-massive PE for less than 14 days. The inclusion criteria comprised also SBP > 90 mmHg and RV/LV ratio > 0.9. Exclusion criteria were as follows: TPA administration within 14 days of

baseline, major trauma within 14 days, active cancer, cardiovascular or pulmonary surgery within 7 days, and pulmonary hypertension. The main efficacy endpoint was the change in RV/LV ratio from baseline to 48 h after the procedure. The main safety endpoints were the rates of major adverse effects such as major bleeding, device-related death, and other device-related adverse effects within 48 h after the procedure. Secondary safety endpoints consisted of all-cause mortality, procedure-related adverse effects, and the recurrence of PE symptoms within 30 days. The mean RV/LV dilatation ratio decreased from 1.47 at baseline to 1.04 at 48 h after the procedure (0.43 reduction). A 4.3-mmHg reduction in PA pressure was observed immediately after thrombus aspiration. An overall 4.7-mmHg decrease in PA pressure was measured after the procedure. During the initial 48 h, 2 patients experienced serious adverse effects. One patient suffered from major bleeding and one from both device-related hemoptysis and major bleeding, which led to the patient's death. During the 30-day observation period, 2 patients died due to progression of pre-existing diseases. Three patients experienced procedure-related adverse effects [31]. The authors concluded that the use of the Indigo Aspiration System led to a reduction in the RV/LV ratio and was associated with a low rate of major adverse events in intermediate-risk PE patients and may be considered for use in this subpopulation.

Conclusions and future directions

Catheter-directed therapies are emerging and promising methods to treat both high-risk PE, if ST is contraindicated or has failed, or low- or intermediate-risk PE in the case of hemodynamic deterioration despite anticoagulation. Previous trials have consistently shown that CDTh leads to a significant decrease in PA pressure and right heart strain, thus improving hemodynamic status. They seem to be associated with fewer bleeding events compared to ST, which clearly indicates that CDTh might be a similarly efficient and safer option compared to ST and may therefore lead to a breakthrough in the treatment of acute PE. The low doses of thrombolytic drugs seem safer than systemic therapy, even in patients with contraindications to thrombolysis, which might improve outcomes. Furthermore, CDT may be used without administration of thrombolytic drugs, as a mechanical way of clot debulking, which further decreases the bleeding risk. Based on our experience in the last 5 years, there were 235 PERT activations, including 80 (34.0%) activations in intermediate-/high-risk patients and 21 (8.9%) activations in high-risk patients. CDTh was used in 11 (4.7%) patients and included aspiration thrombectomy in 5 patients (Penumbra Indigo® System, Penumbra), mechanical thrombectomy in 2 patients (Cleaner XT™, Argon Medical), and the combined use of different techniques in 4 patients (aspiration or mechanical thrombectomy along with catheter-directed thrombolysis).

The trials that addressed the efficacy and safety of CDTh evaluated imaging surrogates as endpoints but did not provide firm evidence regarding improved outcomes, including mortality. In addition, the single-arm design of most trials, without a control group receiving ST or treated with surgical pulmonary embolectomy, as well as the use of different CDTh methods evaluated in previous studies, complicate the interpretation of the results. Finally, different inclusion criteria and endpoints make it difficult to compare the studies and objectively determine the results of treatment with CDTh. Altogether, more randomized trials are urgently needed to draw firm conclusions considering the potential superiority of CDTh over ST, as well as to form new recommendations regarding the most efficient and safe method of CDTh and to identify the target groups of patients who might especially benefit from catheter-directed treatment [39].

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Flecainide in clinical practice

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Abstract

Flecainide, similar to encainide and propafenone, is IC class antiarrhythmic, inhibiting Nav1.5 sodium channels in heart muscle cells and modulates cardiac conduction. Despite its over 40-year presence in clinical practice, strong evidence and well-known safety profile, flecainide distribution in Europe has not always been equal. In Poland, the drug has been available in pharmacies only since October this year, and previously it had to be imported on request. Flecainide can be used successfully in both the acute and chronic treatment of cardiac arrhythmias. The main indication for flecainide is the treatment of paroxysmal supraventricular tachycardias, including atrial fibrillation, atrioventricular nodal re-entrant tachycardia, atrioventricular re-entrant tachycardia and ventricular arrhythmias in patients without structural heart disease. Beyond that, it may be used in some supraventricular tachycardia in children and for sustained fetal tachycardia. Many studies indicate its efficacy comparable to or better than previously used drugs such as propafenone and amiodarone, depending on the indication. This review aims to highlight the most important clinical uses of flecainide in the light of the latest scientific evidence and to provide an overview of the practical aspects of treatment, including indications, off-label use, contraindications, areas of use, monitoring of treatment and most common complications, taking into account special populations: children and pregnant women. (Cardiol J 2023; 30, 3: 473–482)

Key words: flecainide, atrial fibrillation, cardioversion, supraventricular arrhythmias, ventricular arrhythmias

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Introduction

The Food and Drug Administration officially approved flecainide on October 31, 1985. Since then, major steps have been taken in diagnosing and managing supraventricular and ventricular arrhythmias; therefore, antiarrhythmic drugs play an essential role in contemporary clinical practice. To select the most appropriate treatment for a particular patient, fully understanding the advantages and limitations of loose molecules is necessary. In this article, we look at flecainide's pharmacological and clinical profiles.

Like, encainide and propafenone, flecainide is a class IC antiarrhythmic drug. Its main mechanism of action relies on strong inhibition of the Nav1.5 sodium channel, which is responsible for fast inward sodium flow during the 0 phase of action potential and rapid depolarization of the heart muscle. Despite the long-term clinical experience using flecainide in different patient subpopulations, its availability across European Union and European Economic Area countries was not always equal (Fig. 1). The drugs containing flecainide were previously imported to Poland from abroad as a targeted import on special demand and a doctor's recommendation; since October 2022, flecainide has been available on the Polish market. This review highlights the main application areas of flecainide, considering the latest guidelines and scientific evidence.

Flecainide: Scope of use

Flecainide is used in paroxysmal supraventricular tachycardias (SVT), including atrial fibrillation (AF), atrioventricular re-entrant tachycardia (AVRT), and atrioventricular nodal re-entrant tachycardia (AVNRT) in patients without structural heart disease. Flecainide is also used to prevent life-threatening sustained ventricular tachycardia (VT) and some channelopathies [1]. Additionally, the off-label use includes sustained fetal tachycardia (maternal/transplacental administration), premature ventricular beats (PVCs), and pharmacological cardioversion of AF. The main contraindications for treatment with flecainide are ischemic heart disease, hypertension with left ventricular hypertrophy (LVH), congestive heart failure, hypertrophic cardiomyopathy, degree 2 and 3 atrioventricular blocks, complete bundle branch block and significant liver and kidney disease (Table 1) [1]. The issue of the structural definition of heart disease in the context of the use of this drug is still under debate, and further studies are needed to determine flecainide's level of safety, allowing for a better understanding and differentiation of this term, especially in the context of ischemic heart disease. The current contraindica-

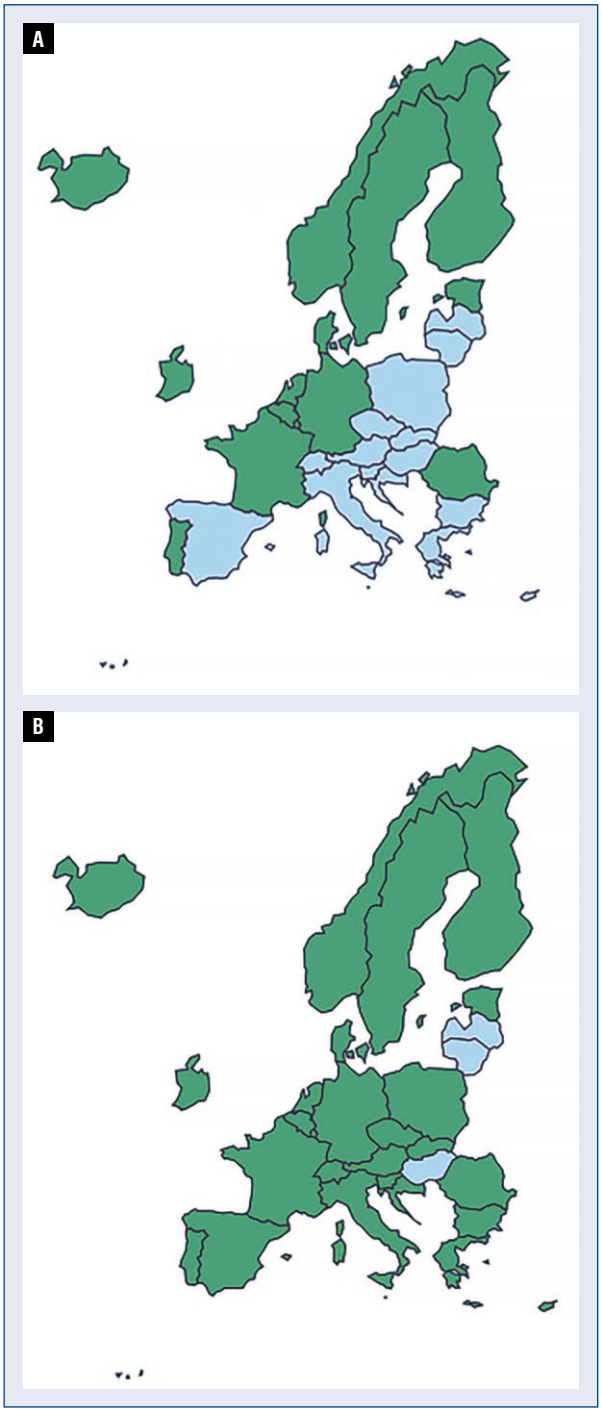


Figure 1. Flecainide availability across European Economic Area countries in 2018 (**A**) and 2022 (**B**). Source: National registers appointed by the European Medicines Agency.

Table 1. Flecainide indication and contraindications.

Flecainide indications	Flecainide contraindications
Atrial fibrillation/atrial flutter in patients who do not have structural heart disease	Ischemic heart disease
Pharmacological cardioversion of atrial fibrillation or flutter	Hypertrophic cardiomyopathy
Paroxysmal supraventricular tachycardia	Hypertension with left ventricular hypertrophy
Atrioventricular nodal re-entrant tachycardia	Congested heart failure
Atrioventricular re-entrant tachycardia	High-degree atrioventricular block
Wolff-Parkinson-White syndrome	Complete bundle branch block
Sustained ventricular tachycardia	Structural heart disease
Premature ventricular beats	Sick sinus syndrome
Sustained fetal tachycardia (maternal/transplacental administration)	Cardiogenic shock
	Acquired/congenital QT prolongation with a history of torsades de pointes
	Concurrent intake of ritonavir

tions for using flecainide in patients with structural heart disease are based on a prematurely interrupted CAST study and left much confusion. CAST was terminated 2 years after the start of enrollment due to increased mortality and sudden cardiac death in flecainide's group. That might have an impact not only on further contraindications but also on the underutilization of this drug, even in fields with strong clinical evidence of flecainide's safety [2–4].

Focus on atrial fibrillation

Emergency treatment

Flecainide may be successfully used in the pharmacological cardioversion of AF, and it is recommended for the cardioversion of new-onset AF in patients without structural heart disease [4–6]. Flecainide is characterized by a relatively high success rate in restoring sinus rhythm and a short median time to restore the rhythm, which makes this substance a reasonable alternative to propafenone and amiodarone [4, 7–9]. Martínez-Marcos et al. [7] compared these three substances administered intravenously in the single-blind trial and showed that flecainide was superior to others, with a 90% conversion rate in the first 12 hours to 72% and 64% for propafenone and amiodarone, respectively. Similar conclusions have been shown by Boriani et al. [8], a study in which they compared different drug protocols on AF conversion rate to sinus rhythm. Flecainide was administered per os and had a comparable conversion rate to orally and intravenously administered propafenone groups after 8 hours (75%, 76%, 75%, respectively).

The European Society of Cardiology (ESC) guidelines recommend considering flecainide for the induction of electrical cardioversion [5], although it is good to clarify that in evidence — Climent et al. [10] showed that flecainide does not significantly increase the rate of successful cardioversion and does not prevent AF relapses after the procedure. Moreover, 35% higher effectiveness of the first shock, compared to the placebo, was present in the subgroup of patients with successful cardioversion and not in the total study population. Some studies report that flecainide dose before cardioversion reduces energy requirements. On the other hand, studies show increased energy requirements in patients receiving flecainide's treatment. However, different methods were used to compare those results [11] reliably. Still, more research is needed to evaluate the role of this substance in cardioversion premedication. Nevertheless, it seems that flecainide does not reduce the effectiveness of electrical cardioversion and may have potential benefits without significant adverse effects in patients with persistent AF.

In selected patients, it is worth considering flecainide in the "pill in the pocket" strategy after evaluating the effectiveness and safety of such therapy in a hospital setting. Despite a lower conversion rate, this strategy may be preferred as it allows early conversion at a lower cost burden to the healthcare system with relatively low risk for a patient. It has been shown that if taken within 10 min from the onset of symptoms, the success rate of sinus rhythm recovery reaches 94% within 4 hours without needing further medical interven-

tion. The incidence rate of side effects remains low, at 7%. Only 1 in 165 patients in the study needed emergency room treatment due to atrial flutter (AFL). Others presented milder symptoms such as nausea, asthenia and vertigo [12]. The current ESC guidelines state that the "pill in the pocket" strategy with flecainide should be considered in everyday clinical practice (class IIa with confidence level B).

Long-term rhythm control

European Society of Cardiology guidelines recommend flecainide or propafenone for the long-term control of heart rhythm in AF patients with normal left ventricular function and no structural heart disease (defined as significant LVH and myocardial ischemia). These recommendations are strongly supported by several studies confirming flecainide's efficiency and safety profile [13–15]. The 2019 review of the Cochrane Antiarrhythmic Drugs database, based on four randomized controlled trials with over 511 participants, confirmed the effectiveness of chronic treatment with flecainide acetate compared to placebo or no treatment (relative risk [RR] 0.65). Flecainide, similar, to the previous 2015 review of Cochrane, had a better risk ratio than propafenone (RR 0.67) and was only second to amiodarone (RR 0.52) [13]. PITAGORA — randomized trial, on 127 patients paced for sinus node diseases in a mean follow-up of 20 months which showed that, among IC class agents, only flecainide was non-inferior to amiodarone in the management of atrial arrhythmias with comparable 1-year freedom from atrial tachyarrhythmia episodes. The findings of this study may apply to clinical practice; however small group count (37 randomized to flecainide) remains a significant limitation. In line with the new ESC guidelines, in patients with AF treated with flecainide for long-term heart rhythm control, concomitant use of an atrioventricular node blocking agent should be considered to avoid the transition to 1:1 conduction of AFL (class IIA recommendation) (Table 2).

Other supraventricular arrhythmias

Although electrical cardioversion remains the gold standard in acute settings and catheter ablation in the chronic treatment of supraventricular arrhythmias, flecainide might be considered in some cases where first-line treatment is unavailable or has no effect.

Flecainide may be considered in the acute treatment of focal atrial tachycardia in hemodynamically stable patients when adenosine, followed by beta-blockers or calcium channel blockers, are ineffective [16]. When ablation cannot be performed as a chronic treatment, it can be considered among non-dihydropyridine calcium channel blockers, beta-blockers, or propafenone. Treatment with flecainide was successful in 86% of patients with acute (intravenous) drug administration and 95% with chronic atrial tachycardia treatment [17]. An intravenous flecainide may effectively stop AVNRT and AVRT. It was effective in 14 (100%) patients with AVNRT and 11 (92%) patients with AVRT [18]. Flecainide is effective towards accessory pathways. Therefore, it can be considered in antidromic AVRT when vagal nerve manoeuvre and adenosine fail [16]. In 1986, Kim et al. [19] showed that, following intravenous or oral treatment with flecainide, recurrent SVT was non-inducible in 6 patients with recurrent atrioventricular tachycardia and three with recurrent atrioventricular node tachycardia. In these 9 patients, intravenous flecainide prevented the induction of recurrent SVT by inhibiting retrograde conduction in the reentry loop. Twelve patients continued treatment with oral flecainide for 16 months after hospital discharge in the same study. Tachycardia recurred in three of whom arrhythmia remained inducible after treatment with flecainide and in one of whom SVT was not inducible [19]. This indicates that flecainide is an antiarrhythmic agent worth considering in treating AVRT and AVNRT patients. In the chronic treatment of antidromic AVRT, flecainide should be considered, mainly when ablation is contraindicated or not feasible. Flecainide may also be considered in pre-excited AF (class IIB recommendation) (Table 3). Nevertheless, it is not recommended as first-line antiarrhythmics in patients with congenital heart disease, ventricular dysfunction, severe fibrosis, and sinus rhythm recovery in supraventricular macroreentry arrhythmias. Flecainide causes prolongation of AFL cycle length; however, it has a poor conversion rate, therefore, dofetilide is the first choice in hemodynamically stable patients [20].

Ventricular arrhythmias

Flecainide can be used in a provocation test to diagnose the Brugada type 1 pattern on the ECG as an alternative for ajmaline, but with much longer observation times (4 and 24 h vs. 0.5 and 4 h). Beyond diagnostics, flecainide is widely used in managing patients with ventricular arrhythmias, with its main application in catecholaminergic polymorphic ventricular tachycardia (CPVT). Several

Table 2. Recommendations with flecainide mentioned by European Society of Cardiology in the 2020 Guidelines for management of atrial fibrillation (adapted from: [5]).

Recommendations	Class of recommendation	Level of evidence
Recommendations for long-term antiarrhythmic drugs		
Flecainide or propafenone is recommended for long-term rhythm control in AF patients with normal left ventricle function and without structural heart disease, including significant LVH and myocardial ischemia	I	A
In AF patients treated with **flecainide** for long-term rhythm control, concomitant use of an atrioventricular nodal-blocking drug (if tolerated) should be considered	IIa	C
Recommendations for the management of AF during pregnancy		
Acute management		
Ibutilide or **flecainide** i.v. may be considered for termination of AF in stable patients with structurally normal hearts	IIb	C
Long-term management (oral administration of drugs)		
Flecainide, propafenone, or sotalol should be considered to prevent AF if atrioventricular nodal-blocking drugs fail	IIa	C
Recommendations for cardioversion		
For pharmacological cardioversion of recent-onset AF, i.v. vernakalant (excluding patients with recent ACS or severe HF) or **flecainide** or propafenone (excluding patients with severe structural heart disease) is recommended	I	A
Pre-treatment with amiodarone, **flecainide**, ibutilide, or propafenone should be considered to facilitate the success of electrical cardioversion	IIa	B
In selected patients with infrequent and recent-onset AF and no significant structural or ischemic heart disease, a single self-administered oral dose of **flecainide** or propafenone ('pill in the pocket' approach) should be considered for patient-led cardioversion, but only following efficacy and safety assessment	IIa	B

ACS — acute coronary syndrome; HF — heart failure; AF — atrial fibrillation; LVH — left ventricular hypertrophy

studies showed it reduces (24%) or reverses (42%) episodes of CPVT in patients without conventional therapy [21, 22]. Moreover, in patients on optimal beta-blocker therapy, after adding flecainide, CPVT suppression exceeded 85%; therefore, it should be considered as an addition to beta-blockers or alone if there are any contraindications for beta-blocker therapy [21, 23]. It is also highly recommended in CPTV patients after sudden cardiac arrest as a part of therapeutic intervention with implantable cardioverter-defibrillator implantation and beta-blockers (class I recommendation) [22, 24, 25]. 2022 ESC guidelines introduced changes and new concepts, including flecainide and its role in idiopathic PVC/VT and Andersen-Tawil syndrome (Table 4) [25].

An important consideration for clinical practice use

Before starting flecainide therapy, it is essential to rule out any contraindications. To rule out contraindications for the initiation of treatment, it is necessary to perform a 12-lead electrocardiogram (ECG), and it is also recommended to perform a cardiac stress test to exclude potential myocardial ischemia and an echocardiogram to assess the function of the left ventricle. An important parameter to be assessed before and during treatment is the width of the QRS complex, especially as flecainide should be viewed as a drug with a narrow therapeutic window [26]. During flecainide therapy, prolongation of QT and an increase in QRS between 12% and 20% can be expected. In cases of QRS width an increase of more than 25% from the baseline value bundle branch block or other blocks over 120 ms, ESC guidelines suggest discontinuing the treatment. Some authors propose reducing the dosage by half, and then, if the targeted QRS width still cannot be achieved, therapy should be discontinued (Central illustration) [5, 9, 25]. During flecanide treatment, a range of other adverse, proarrhythmic events with an incidence between

Table 3. Recommendations on using flecainide by European Society of Cardiology in 2019 Guidelines on supraventricular tachycardia (adapted from: [16]).

Recommendations	Class of recommendation	Level of evidence
Recommendations for the therapy of atrioventricular re-entrant tachycardia due to manifest or concealed accessory pathways		
Acute therapy — Hemodynamically stable patients		
In antidromic AVRT, i.v. ibutilide or procainamide or i.v. **flecainide** or profanenone or synchronized direct current cardioversion should be considered if vagal manoeuvres and adenosine fail	IIa	B
Chronic therapy		
Propafenone or **flecainide** may be considered in patients with AVRT and without ischemic or structural heart disease, if ablation is not desirable or feasible	IIb	B
Recommendations for the therapy of focal atrial tachycardia		
Acute therapy — Hemodynamically stable patients		
Adenosine (6–18 mg i.v. bolus) should be considered	IIa	B
Beta-blockers (i.v. esmolol or metoprolol) should be considered in the absence of decompensated heart failure, if adenosine fails	IIa	C
Verapamil or diltiazem (i.v.) should be considered for hemodynamically stable patients in the absence of hypotension or HFrEF, if adenosine fails	IIa	C
If the above measures fail, the following may be used:	IIb	C
• i.v. ibutilide		
• or i.v. **flecainide** or propafenone		
• or i.v. amiodarone		
Chronic therapy		
Beta-blockers or non-dihydropyridine calcium channel blockers (verapamil or diltiazem in the absence of HFrEF), or propafenone or **flecainide** in the absence of structural or ischemic heart disease, should be considered if ablation is not desirable or feasible	IIa	C
Recommendations for the acute therapy of pre-excited atrial fibrillation		
Hemodynamically stable patients		
Flecainide or propafenone (i.v.) may be considered	IIb	B
Recommendations for the therapy of supraventricular tachycardia in pregnancy		
Chronic therapy		
Flecainide or propafenone should be considered for prevention of SVT in patients with WPW syndrome, and without ischemic or structural heart disease	IIa	C
Flecainide or propafenone in patients without ischemic or structural heart disease should be considered if atrioventricular nodal blocking agents fail to prevent SVT	IIa	C

i.v. **flecainide** and propafenone are contraindicated in patients with ischemic or structural heart disease. They also prolong the QTc interval but much less than class III agents
AVRT — atrioventricular re-entrant tachycardia; HFrEF — heart failure with reduced ejection fraction; SVT — supraventricular tachycardia; WPW — Wolff-Parkinson-White

< 1% to 13%, may occur. This includes bradycardia, additional ventricular contractions, atrioventricular block, SVT, bundle branch block and AF, drug-induced Brugada, hypotension, 1:1 AFL, worsening heart failure, dizziness, tremor and nausea [4, 26, 27]. Lavalle et al. [4] proposed a practical guide for managing adverse events due to flecainide.

Safety in special populations

Pregnancy

Flecainide could be safely used in any supraventricular arrhythmia in pregnant women [5, 16]. Heart rhythm control is the preferred strategy in AF pregnant patients. Electrical car-

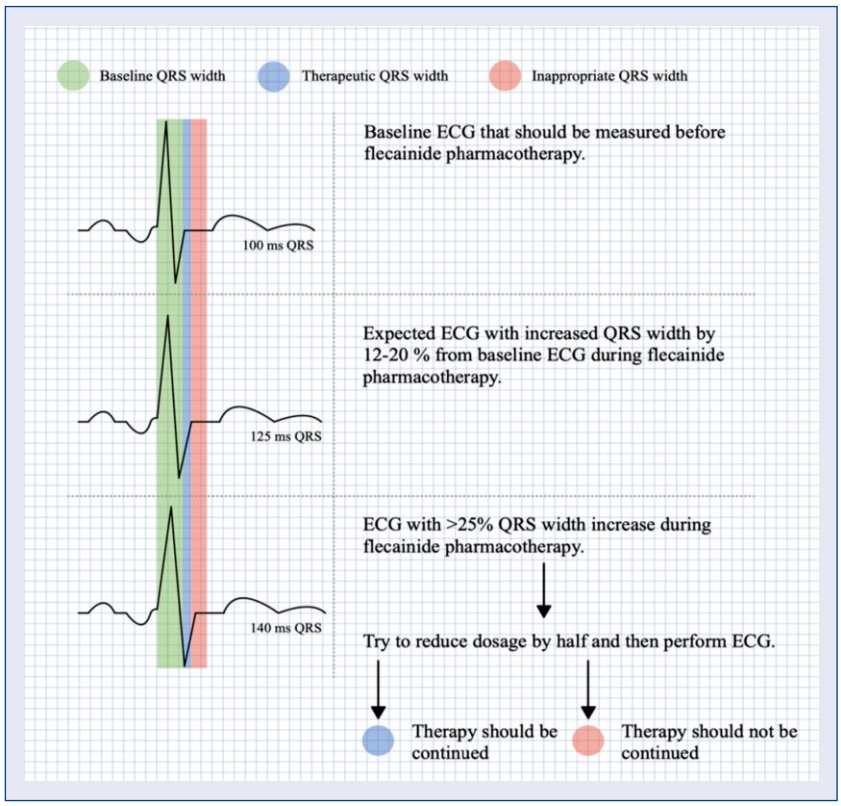
Table 4. Comprehensive recommendations for the use of flecainide as in the 2022 European Society of Cardiology Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death (adapted from: [25]).

Recommendations	Class of recommendation	Level of evidence
Recommendations for management of patients with Andersen–Tawil syndrome		
Beta-blockers and/or **flecainide** with or without acetazolamide should be considered in patients with Andersen–Tawil syndrome to treat ventricular arrhythmia	IIa	C
Recommendations for the management of patients with catecholaminergic polymorphic ventricular tachycardia		
ICD implantation combined with beta-blockers and **flecainide** is recommended in CPVT patients after aborted cardiac arrest	I	C
LCSD should be considered in patients with diagnoses of CPVT when the combination of beta-blockers and **flecainide** at therapeutic dosage are either not effective, not tolerated, or contraindicated	IIa	C
ICD implantation should be considered in patients with CPVT who experience arrhythmogenic syncope and/or documented bidirectional/polymorphic VT while on the highest tolerated beta-blocker dose and on **flecainide**	IIa	C
Flecainide should be considered in patients with CPVT who experience recurrent syncope, polymorphic/bidirectional VT, or persistent exertional PVCs, while on beta-blockers at the highest tolerated dose	IIa	C
Recommendations for the management of patients with idiopathic premature ventricular complexes/ventricular tachycardia		
Beta-blockers, non-dihydropyridine CCBs, or **flecainide** should be considered when catheter ablation is not available, desired, or is particularly risky in symptomatic patients with idiopathic VT/PVCs from the RVOT or the left fascicles	IIa	B
Catheter ablation or **flecainide** should be considered in symptomatic patients with idiopathic VT/PVCs from an origin other than the RVOT or the left fascicles	IIa	C
Recommendations for the prevention of sudden cardiac death and management of ventricular arrhythmia during pregnancy		
For acute conversion of hemodynamically tolerated SMVT during pregnancy, a beta-blocker, sotalol, **flecainide**, procainamide, or overdrive ventricular pacing should be considered	IIa	C
Recommendations for the acute management of sustained ventricular tachycardia and electrical storm		
In patients presenting with a hemodynamically tolerated SMVT in the absence of significant SHD, **flecainide**, ajmaline, or sotalol may be considered	IIb	C

CCB — calcium channel blockers; CPVT — catecholaminergic polymorphic ventricular tachycardia; ICD — implantable cardioverter-defibrillator; LCSD — left cardiac sympathetic denervation; PVCs — premature ventricular beats; RVOT — right ventricular outflow tract; SHD — structural heart disease; SMVT — sustained monomorphic ventricular tachycardia; VT — ventricular tachycardia

dioversion is recommended in hemodynamically unstable pregnant women; however, intravenous flecainide might be considered in hemodynamically stable women without structural heart disease [16].

In a series of cases, Chauvaue et al. [28] demonstrated the safe use of intravenous 100 mg flecainide to restore sinus rhythm in pregnant women and then followed by 200–300 mg of oral flecainide daily until delivery without complications for fetus growth and delivery. Similar case reports have been presented by Lewis and Currie [29], who performed successful pharmacological cardioversion on 38-year-old women in the 27th week of pregnancy. No evidence of congenital abnormality was observed [29]. Flecainide, despite limited evidence, is considered safe for the fetus and should be considered for managing fetal arrhythmia. In 1991 Allan et al. [30] conducted 12 successful rhythm conversions in 14 hydropic fetuses, with 1 case of spontaneous intrauterine death. In most cases, the time to conversion was under 48 hours. In the comparison of flecainide, sotalolol, and digoxin in



Central illustration. An important considerations for clinical practice use of flecainide; ECG — electrocardiogram.

SVT and AFL management on 159 fetuses, flecainide was superior to other drugs, with a 59% conversion rate and median 4 days to conversion in SVT; however, contrary, sotalol was more efficient than flecainide and digoxin in AFL patients [31].

Children

Flecainide is recommended as one of the first lines in some SVT in infants and children without structural heart disease and preserved ventricular function. It might be considered in symptomatic idiopathic VT and ion channelopathies such as long QT syndrome and catecholaminergic VT [32]. A retrospective cohort study on 175 children, including those with congenital heart disease and cardiomyopathy, showed that flecainide was well-tolerated. No significant difference in proarrhythmic effect was found in children with and without congenital heart disease. There was no cardiac arrest in this cohort; however, one death related to respiratory syncytial virus infection was reported [33]. In 2020 Vaquer et al. [34] reported 3 cases of flecainide intoxication in infants. Flecainide as a drug with a narrow therapeutic window, potential proarrhythmic effects, and interactions with dairy products, should be administered with caution and under ECG and plasma level monitoring, especially in the first 48–72 hours and in patients under 1 year old.

Summary

Flecainide, used in reference to the current state of the art and under proper supervision, can be seen as a highly effective and safe drug for arrhythmia management. The risk of side effects, in particular the proarrhythmic effect, can be minimized by diligently examining the patient for contraindications to treatment, using the drug according to current recommendations and guidelines, gradual dose increase under the supervision of a doctor in the hospital, and regular monitoring of the effects treatment with the use of ECG.

Conflict of interest: None declared

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VIA MEDICA

STUDY PROTOCOL

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Study design and rationale for comparison of the incidence of slow flow following rotational atherectomy to severely calcified coronary artery lesions between short single session and long single session: The randomized ROTASOLO trial

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Background

Severely calcified coronary artery disease is still the Achilles' heel in percutaneous coronary intervention (PCI) [1], although there were many developments in devices and techniques over the last two decades [2–6]. Rotational atherectomy (RA) has been a cornerstone for the treatment of severely calcified coronary artery disease for more than 20 years [7–9]. However, unique complications occur in PCI with RA [10–12]. Among unique complications, slow flow is the most common complication following RA [13–15]. The severity of slow flow varies widely from transient thrombolysis in myocardial infarction (TIMI) grade 2 flow to persistent TIMI grade 0 flow (no flow), which would be associated with serious periprocedural myocardial infarction (PMI) [16, 17]. Previous retrospective studies reported that slow flow following RA was positively associated with lesion length, angulation, and burr-to-artery ratio, and was inversely associated with reference diameter, systolic blood pressure just before RA, and primary RA strategy [13]. Moreover, the maximum number of reverberations in intravascular ultrasound (IVUS) and the greater arc of calcification at minimum lumen area were also associated with slow flow following RA [18]. Although the clinical expert consensus document from the Japanese Association of CardioVascular Intervention and Therapeutics recommends appropriate burr size, short ablation time, and avoiding excessive speed down [19], the methods to prevent slow flow have not been established. The present retrospective study showed that a short single session was inversely associated with slow flow [13]. Thus, it was hypothesized that the short single session strategy would prevent the occurrence of slow flow following RA irrespective of total ablation time. This paper describes the study design and rationale for "Comparison of the Incidence of Slow Flow Following ROTAtional Atherectomy to Severely Calcified Coronary Artery Lesions between ShOrt Single Session Versus LOng Single Session: The Randomized ROTASOLO Trial" [UMIN000047231].

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Methods

Study design

The design of the ROTASOLO trial, which is currently ongoing, is an open-label randomized study to compare the incidence of slow flow following RA between the short single session strategy and the long single session strategy. The short single session strategy was defined as repeating short single session (no more than 15 s) RA until the burr crosses the target lesion, whereas the long single session strategy was defined as repeating long single session (20–30 s) RA until the burr crosses the target lesion. The trial will include 300 patients undergoing RA at the following 3 hospitals: (1) Saitama Medical Center, Jichi Medical University, (2) JCHO Saitama Medical Center, and (3) Nerima-Hikarigaoka Hospital in Japan. The planned enrollment period is 36 months. The primary outcome will be assessed immediately after RA in each procedure. The study was approved by the Institutional Review board of Saitama Medical Center, Jichi Medical University [S21–105], JCHO Saitama Medical Center [22–17], and Nerima-Hikarigaoka Hospital [22051201].

Inclusion criteria for the participation in the ROTASOLO trial are as follows: (1) patients with ischemic heart disease including acute coronary syndrome and chronic coronary syndrome who undergo PCI using RA, (2) patients who gave written informed consent, (3) angiographically severe calcification in target lesions, and (4) and intravascular imaging shows over 180-degree superficial calcification/calcified nodule, intravascular imaging devices cannot cross the lesion due to severe stenosis, or an intravascular imaging device (typically optical coherent tomography [OCT]) cannot provide valid images due to severe stenosis. Meanwhile, the exclusion criteria are as follows: (1) less than 20 years-old, and (2) contraindication in instructions-for-use of Rotablator.

Randomization

Pre-screening will be performed by investigators according to the findings of coronary angiography and/or computed tomography (CT)-angiography. If the patients are considered suitable for PCI with RA, investigators would explain the detail of the study. Each patient would provide written informed consent. Then, investigators would make a tentative registration for the study via REDCap (Research Electronic Data Capture; Vanderbilt University) [20, 21]. The ROTAPRO (Boston Scientific, Marlborough, MA) would be used for all RA procedures. During PCI, investigators would check all inclusion and exclusion criteria for the study. First, the operators would try intravascular imaging (IVUS or OCT) to the angiographically severe calcified lesions. After intravascular imaging, the operators would decide the initial burr size and the type of RotaWire (Floppy type or Extra-Support type) before randomization. After the operators decide the initial burr size and the type of RotaWire, patients would be centrally randomized at a 1:1 ratio using REDCap. The randomization was done using random permuted blocks, with block sizes ranging from 2 to 6, and was stratified according to center. The trial flow diagram is shown in Figure 1.

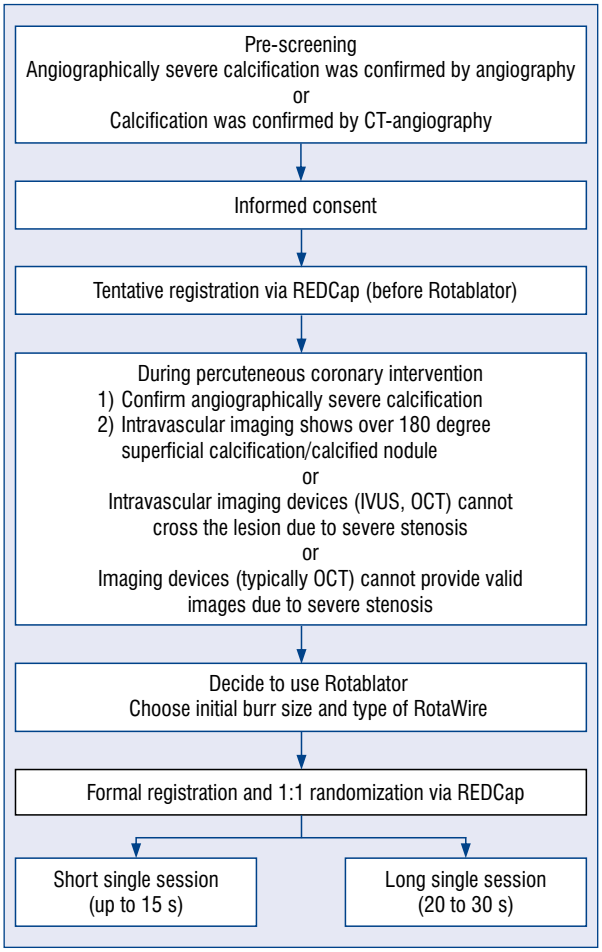

Figure 1. The trial flow diagram; CT — computed tomography; IVUS — intravascular ultrasound; OCT — optical coherence tomography.

The RA burr would be advanced over the wire to a position proximal to the lesion. The rotational speed would be set at the conventional range (140,000–190,000 rpm) with the burr proximal to the lesion. Techniques regarding RA would

Table 1. The detail of timing when to evaluate slow flow just after rotational atherectomy (RA).

Situation	Timing when we evaluate slow flow
The first burr crossed the target lesion (full RA). No second burr was used.	Just after the first burr crossed the target lesion.
The first burr crossed the target lesion (full RA). The second burr was used for burr size-up. The second burr crossed the target lesion (full RA).	Just after the first burr crossed the target lesion.
The first burr could not cross the target lesion. The second burr was used for burr size-down. The second burr crossed the target lesion (full RA).	Just after the second burr crossed the target lesion.
The first burr could not cross the target lesion, but switch to balloon dilatation (halfway RA). No further RA.	Just after the first burr attempt.
The first burr could not cross the target lesion. The second burr was used for burr size-down. However, the second burr also could not cross the target lesion (halfway RA).	Just after the second burr attempt.
The first burr could not cross the target lesion, but switch to balloon dilatation (halfway RA). However, balloon did not work. Then, switch to RA again. The second burr could cross the target lesion.	Just after the second burr crossed the target lesion.
The first burr could not cross the target lesion. The second burr was used for burr size-up. The second burr crossed the target lesion (full RA).	Just after the second burr crossed the target lesion.

Full RA means that the burr could cross the target lesion. Halfway RA means that RA was tried, but the burr could not cross the target lesion. Even if the burr could not reach to the midpoint of the target lesion, RA attempts that eventually could not cross the target lesion would be classified as halfway RA.

be consistent with those that were recommended by the clinical expert consensus document on RA from the Japanese Association of Cardiovascular Intervention and Therapeutics [19]. In the short single session group, operators would control the single session time up to 15 s. In the long single session group, operators would control the single session time from 20 s to 30 s. In both groups, operators can add sessions until the first burr crosses the target lesion. If the operator decides to use the second burr (i.e., burr size-up) after the first burr crosses the target lesion, operators can set the single session time freely. In other words, operators do not need to follow the short or long single session strategy after the first burr crosses the target lesion. The console of ROTAPRO clearly display each run time, which is open to the main- and sub-operators. Clinical engineers in catheter rooms call the time of each session. The time of each session in this study is recorded before the first burr crosses the target lesion.

Primary outcome

The primary outcome was slow flow just following RA. Although slow flow is usually defined as TIMI grade ≤ 2 [22], this TIMI grade ≤ 2 was not adopted in the current study as the definition of slow flow in the ROTASOLO trial, because the borderline between TIMI grade 2 and TIMI grade 3 is sometimes ambiguous. Furthermore, the TIMI flow grade is a subjective parameter. In the ROTASOLO trial, slow flow just after RA was defined as ([initial TIMI-frame count before RA] × 1.1 minus [TIMI-frame count just after RA]) less than 0. Absence of slow flow was defined as ([initial TIMI-frame count before RA] × 1.1 minus [TIMI frame count just after RA]) not lower than 0. For the present TIMI-frame count evaluation, the frame rate was set as 15 frames per second (15 fps). Initial TIMI-frame count before RA was multiplied 1.1-fold, because TIMI frame count would be influenced by not only slow flow, but also injection speed, the dose of contrast media, the depth of guide-catheter, and the presence of guidewire. In other words, if the TIMI-frame count just after RA is slightly higher than the TIMI-frame count before RA, it may be a margin of error rather than slow flow caused by RA. Therefore, initial TIMI--frame count before RA × 1.1 was compared with TIMI-frame count just after RA.

If ≥ 2 burrs are used for RA, slow flow will be evaluated only after the first burr crosses the lesion. Once the first burr crossed the lesion, slow flow would not be evaluated for this study after the second burr crosses the lesion. If the first burr could not cross the lesion and the second burr (typically smaller burr) could cross the lesion, slow flow would be evaluated for this study after

the second burr crosses the lesion. If halfway RA is performed [23], slow flow will be evaluated just after halfway RA. In other words, slow flow just after RA is evaluated only one time per PCI. The detail of timing when slow flow is evaluated just after RA is shown in Table 1. Secondary outcomes are PMI and complications such as vessel perforation.

Definitions of variables

All clinical information and study outcomes will be collected as electronic data capture (EDC) via REDCap. Patient characteristics include age, sex, height, body weight, hypertension, diabetes mellitus, dyslipidemia, current smoker, creatinine level at admission, hemodialysis, peritoneal dialysis, history of heart failure requiring hospitalization, use of statin, use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers/ /angiotensin receptor neprilysin inhibitor, and use of beta-blockers. Lesion characteristics include type of lesion, presence of visible thrombus, chronic total occlusion, in-stent lesion, target vessel, ostial lesion, reference diameter, lesion length, and lesion angle. Procedure characteristics include use of balloon before RA, guide catheter size, use of intra-aortic balloon pumping, use of veno-arterial extracorporeal membrane oxygenation, type of RotaWire, number of used burrs, initial burr size, maximum burr size, initial burr to artery ratio, maximum burr to artery ratio, total run time, mean single run time, mean rotational speed, blood pressure before RA, heart rate before RA, use of halfway RA, and type of final procedure. Study outcomes include final TIMI-flow grade, type III vessel perforation, burr entrapment, PMI, and in-hospital death. Hypertension was defined as a systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg, or medical treatment for hypertension [24]. Diabetes mellitus was defined as a hemoglobin A1c level > 6.5% or treatment for diabetes mellitus [24]. Dyslipidemia was defined as a total cholesterol level > 220 mg/dL, a low-density lipoprotein cholesterol level > 140 mg/dL, or treatment for hyperlipidemia [24]. Creatine kinase and creatine kinase-myocardial band (CK-MB) at the day after RA will be collected. PMI was defined as CK-MB ≥ 10 upper limit of normal [25]. The reference diameter and lesion length will be calculated by quantitative coronary angiography [13]. The burr-to-artery ratio was defined as the burr size divided by the reference diameter [13].

Sample size calculations and statistical methods

Sample size calculations were based on previously published data. The present retrospective study includes 513 lesions treated with RA, the incidence of slow flow was 14.7% in lesions that received short single session (no more than 15 s), whereas the incidence of slow flow was 28.8% in lesions that received long single session (20–30 s) [13]. If the cut-off of the probability of a type-I error (α) was set as 5% (0.05) and the cut-off of the probability of a type-II error (β) as 20% (0.2), a total of 266 lesions would be needed to detect the difference between the two groups. It was anticipated that substantial cases would be excluded by this strict imaging criteria, a total of 300 patients were chosen as the sample size for the ROTASOLO study. The primary outcome (incidence of slow flow) will be compared between the short single session group and the long single session group using the Fisher exact test.

Monitoring and auditing

The ROTASOLO study will be monitored via REDCap by the Center for Clinical Investigation in Jichi Medical School. The Center for Clinical Investigation in Jichi Medical School will monitor (1) progress of enrollment, (2) delay of input on EDC, (3) deviation from the protocol, and (4) serious adverse events every 1 year. Monitoring will be applicable to all participants with formal registration and randomization.

The ROTASOLO study will be audited by the Center for Clinical Investigation in Jichi Medical School. The Center for Clinical Investigation in Jichi Medical School will audit (1) the accuracy of documents of written informed consent and (2) the eligibility for the study participants twice during the enrollment period. Auditing will be applicable to selected participants (maximum 30 cases).

Discussion

The results of the ROTASOLO trial will determine whether a short single session strategy can reduce the incidence of slow flow following RA. Because the number of RA cases per operator is inversely associated with adverse events [26, 27], refinement of RA procedures would be important to reduce complications related to RA. However, RA procedures vary widely among RA experts. Although a total of 3 expert consensus documents

on RA have been published from Europe, North America, and Japan [19, 28, 29], recommendations to prevent slow flow are not sufficiently supported by robust evidence. The ROTASOLO trial will shed light on refinement of RA procedures to prevent slow flow after RA.

Slow flow includes both permanent severe slow flow and transient mild slow flow. Transient mild slow flow would be recovered immediately if operators stop RA procedures and inject intracoronary vasodilators. However, if operators ignore transient slow flow during RA, it can progress to permanent severe slow flow, which would be associated with PMI and subsequent death. The prevention and early management of slow flow is an important step to reduce unique complications in RA [19].

The ROTASOLO study has several limitations. First, quantitative coronary angiography and the evaluation of slow flow will not be performed by independent core laboratories. Second, the present definition of slow flow using TIMI-frame count has not been validated by other groups. Third, although the ROTASOLO study was designed as a multicenter study, only 3 institutions were included in this study. Fourth, the inability to blind operators might impact the trial results. Finally, our definition of PMI, which uses CK-MB as biomarker, is not sensitive enough to detect minor PMI.

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VIA MEDICA

IMAGE IN CARDIOVASCULAR MEDICINE

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Left-anterior descending chronic total occlusion percutaneous coronary intervention complicated by great cardiac vein fistula: An unusual route for intravascular ultrasound guided successful recanalization

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A 52-year-old gentleman, previously revascularized with double arterial conduit to left anterior descending (LAD) artery and to intermediate ramus branch, was admitted for worsening angina; echocardiography showed preserved left ventricular function with inferior wall akinesia. Coronary angiography revealed chronic total occlusion (CTO) of the native mid LAD (Fig. 1A) and of the right coronary artery, together with the occlusion of the arterial grafts. Multidisciplinary discussion prioritized the CTO-percutaneous coronary intervention of the native LAD. Consequently, antegrade wire escalation technique was performed.

The occlusion was supposed to be crossed by Gaia 3rd guidewire (Asahi) and a gentle dilatation with 2.0 semicompliant balloon was performed. However, angiography revealed a LAD to great cardiac vein (GCV) fistula with complete opacification of coronary sinus (Fig. 1B). The patient had no hemodynamic compromise and echocardiography ruled out pericardial effusion. After 1 week a second attempt with intravascular ultrasound (IVUS) guidance was performed. The entry-point of the CTO proximal cap could be accurately identified in an IVUS pullback from the GCV (Fig. 1C), that was thus successfully penetrated with a Conquest Pro 12 (Asahi) stiff guidewire supported by Corsair pro XS 135 cm microcatheter (Asahi), after a failed attempt with a soft polymer jacketed guidewire (Fileder XTA, Asahi). After multiple pre-dilatations, two drug-eluting stents were deployed from distal LAD to left main. Angiography revealed persistence of the fistula that was finally sealed with the implantation of two expanded Polytetrafluoroethylene covered stents (BeGraft, Bentley). Final angiography revealed complete occlusion of LAD to GCV fistula and recanalization of LAD with final TIMI 3-flow (Fig. 1D). The patient was discharged 2 days later in good clinical condition.

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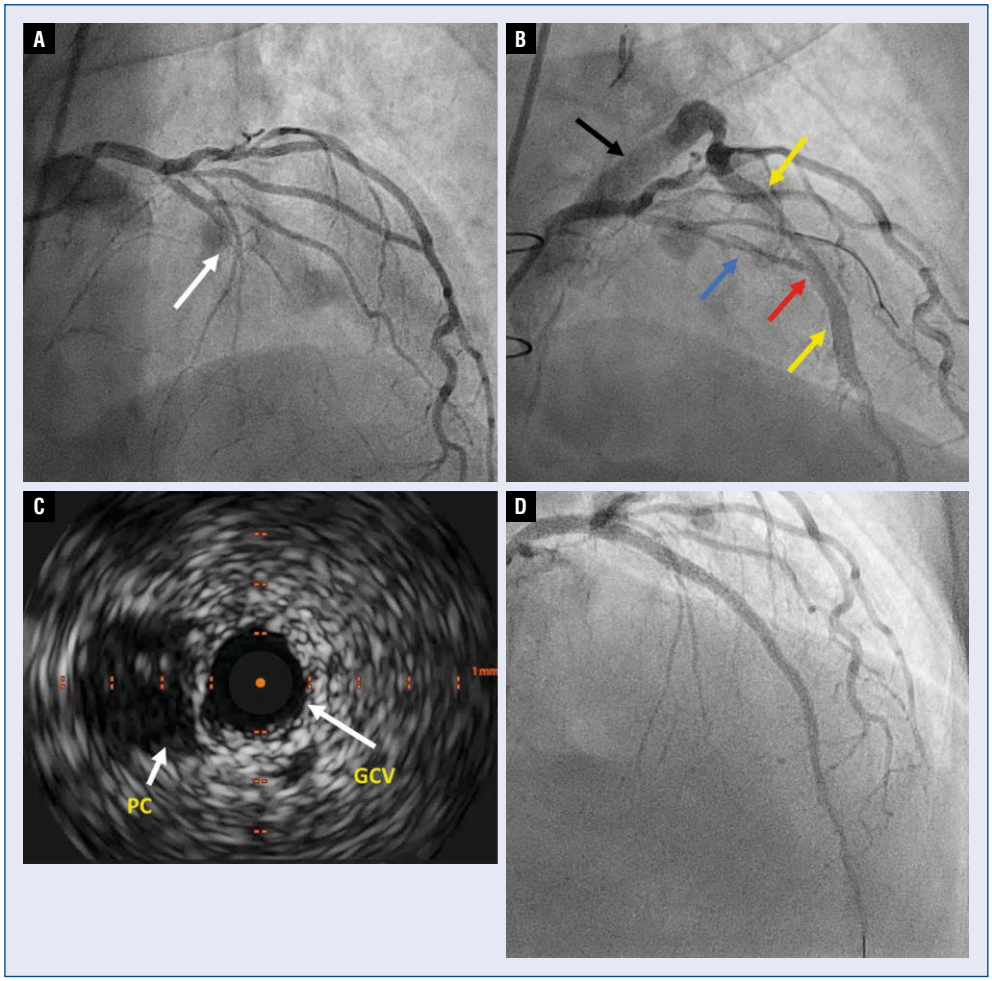

Figure 1. A. Left anterior descending (LAD) occlusion (white arrow); **B.** LAD to great cardiac vein (GCV) fistula; blue arrow — native LAD; red arrow — fistula; yellow arrows — GCV; black arrow — coronary sinus; **C.** Intravascular ultrasound identification of LAD proximal cap of occlusion with probe located in the GCV; PC — proximal cap; **D.** Final result of LAD percutaneous coronary intervention with complete sealing of the fistula.

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Percutaneous aspiration of a right atrial thrombus with the AngioVac system

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The AngioVac (AngioDynamics, USA) is a percutaneous aspiration system designed for removal of pathologic intracardiac structures with the use of large-bore catheter connected to extracorporeal circuit (ECC) filtering and returning blood.

A 46-year-old male was hospitalized due to myocardial infarction with ST segment elevation. This was complicated by mitral and aortic valve insufficiencies and refractory cardiogenic shock requiring urgent replacement of both valves in two separate surgical interventions and prolonged use of veno-arterial-extracorporeal-membrane--oxygenation. Follow-up echocardiography revealed a mobile structure in the right atrium (RA) of 4.5 × 1.5 cm resistant to anticoagulation (Fig. 1). A multi-specialty team agreed to utilize a percutaneous approach as surgical removal was deemed as too high-risk. The procedure was performed under fluoro- and transesophageal echocardiography (TEE) guidance and general anesthesia. The 22 French (Fr) AngioVac 180° angled cannula was introduced to the RA through a 26 Fr left femoral vein (FV) sheath, and connected to ECC to aspirate the clot and to return the blood through an 18 Fr reinfusion sheath to the right FV. FVs were chosen as jugular veins were occupied and the thrombus location near fossa ovalis made femoral access more suitable. Initiation of the ECC resulted in a rapid thrombus removal seen in TEE and safe procedure completion. The patient was extubated on the same day and started rehabilitation.

It was shown herein, that removal of an intracardiac structure with the use of AngioVac system was feasible and safe. This minimally invasive procedure may be an option for patients who are not candidates for an open heart surgery.

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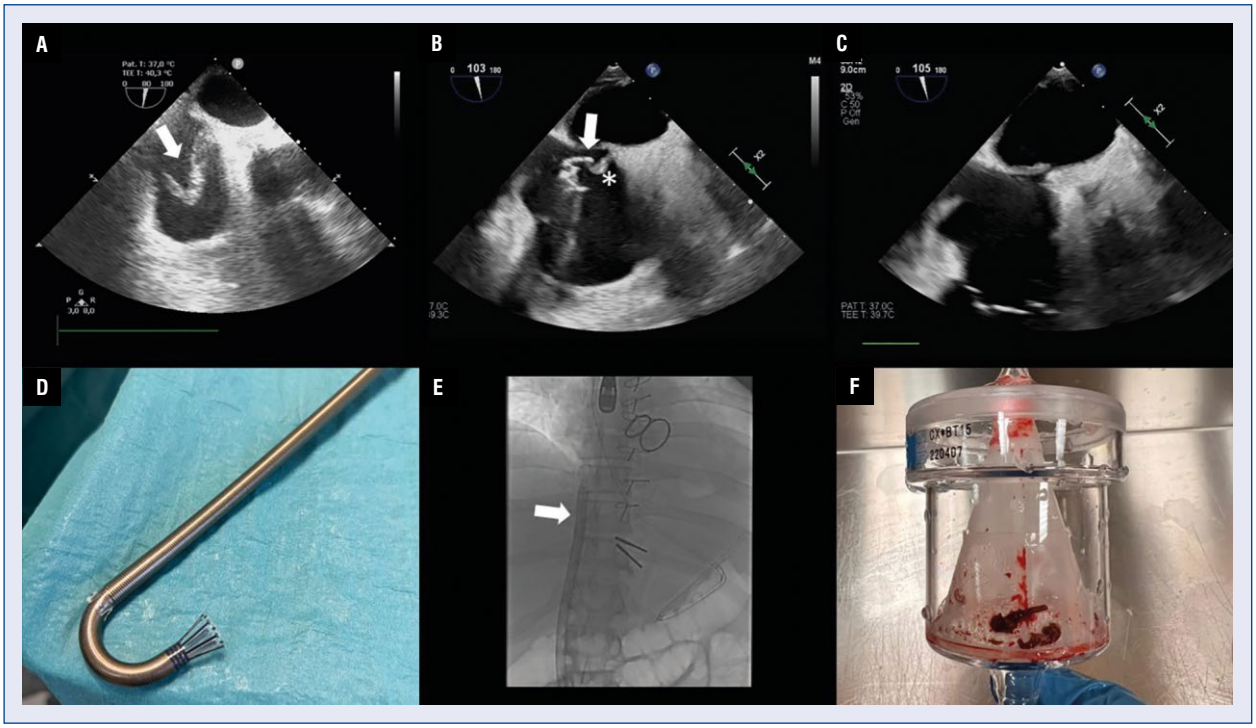

Figure 1. A. A transesophageal echocardiography (TEE) showing a mobile structure (arrow) in the right atrium (RA) of 4.5 × 1.5 cm in size posing a risk for pulmonary artery embolization; **B.** An expandable funnel-shaped distal tip of the AngioVac Cannula (arrow) aspirating the RA structure (*) with the suction forces generated by the extracorporeal circulation; **C.** The TEE showing the free from mobile structure RA; **D.** The 22 French (Fr) AngioVac 180° angled Cannula with an expandable funnel-shaped distal tip; **E.** Fluoroscopy showing the introduction of the AngioVac Cannula (arrow) to the RA structure through a 26 Fr left femoral vein sheath and a stiff wire; **F.** An extracorporeal circulation filter showing removed thrombus.

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Impella-assisted intracoronary lithotripsy of heavily calcified left main lesion in a patient with severely impaired ejection fraction and the last remaining patent vessel

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A 56-year-old man with the last remaining patent vessel, heavily calcified significant left main (LM) stenosis (Fig. 1A) and chronic total occlusion of both right coronary artery and circumflex branch was referred to our institution for revascularization of the LM lesion. Patient was turned down from surgery due to severely impaired left ventricular ejection fraction (LVEF) of 12% and multiple comorbidities. Due to high surgical risk (EuroScore II of 23.05%), the decision to proceed with Impella-assisted revascularization was made. Calcified LM lesion was predilated with multiple non-compliant balloons (NCBs) (up to 4.0 mm) (Fig. 1B), however the full balloon expansion was not achieved with 50% residual stenosis. The intravascular lithotripsy (IVL) with a 4.0 × 12 mm Shockwave balloon (80 pulses) was done (Fig. 1C, D), followed by dilatation with 4.5 NCB (Fig. 1E). After obtaining full balloon expansion a 4.0 × 15 mm drug eluting stent was implanted into LM/ /left anterior descending (LAD) with subsequent proximal optimization technique (POT) using 4.5 mm NCB and final kissing balloon of the LAD and intermediate artery bifurcation with 4.0 mm and 2.5 mm NCBs, respectively. During IVL pulses administration and balloon inflations, a flattening of the aortic pressure waveform was observed. Intravascular ultrasound (IVUS) imaging revealed only 60% stent expansion (Fig. 1F). Therefore, re-POT using 5.0 × 12 mm NCB was performed (Fig. 1G) with favorable final angiographic result (Fig. 1H). Repeated IVUS showed acceptable stent expansion (> 80%) with minimal stent area of 12.5 mm^2 (Fig. 1I). The Impella device was removed directly after the procedure and the patient was discharged after 48 hours without any complications.

Severely calcified lesions are challenging especially in the setting of complex coronary atherosclerosis and severely impaired LVEF. Use of percutaneous mechanical circulatory support with Impella CP provides a better safety margin for complex percutaneous coronary intervention, especially with the prospect of an uncontrolled interruption of flow due to challenging stent delivery. It diminishes the ischemic stress during the procedure while providing coronary perfusion which was especially important in the case of this patient with the last remaining patent vessel.

Conflict of interest: None declared

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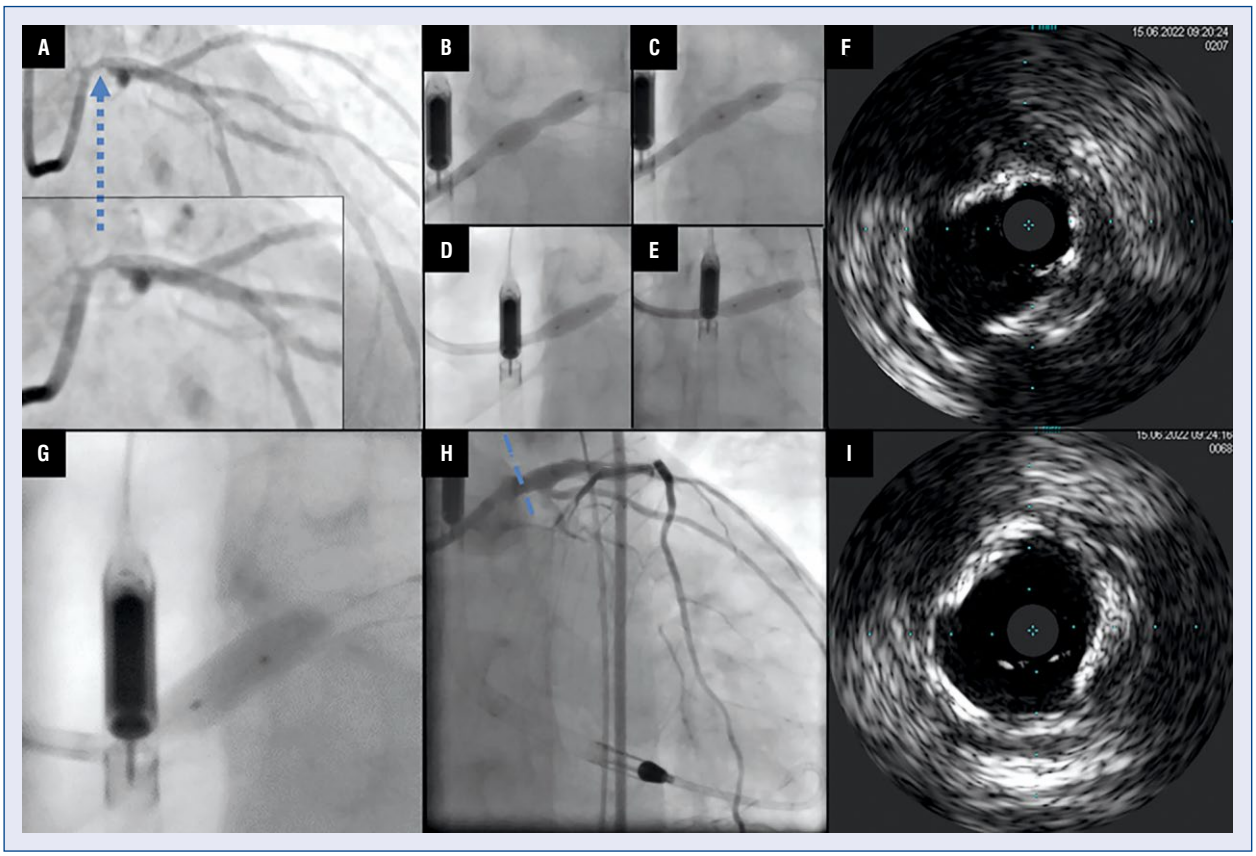

Figure 1. A. Baseline angiography revealed significant calcified stenosis in the left main (dotted line); **B.** Dog-bone shape of non-compliant-balloon (NCB) on the resistant calcified lesion; **C.** Intravascular lithotripsy (IVL) balloon during initial pulses application; **D.** Effect of IVL after 80 pulses; **E.** Repeated predilatation with NCB; **F.** Intravascular ultrasound (IVUS) following stent implantation revealed suboptimal 60% expansion; **G.** Optimal expansion was achieved with final proximal optimization technique using 5.0 mm NCB; **H.** Final angiographic effect — the dotted line indicates minimal stent area (MSA) on IVUS; **I.** Final intravascular ultrasound at the MSA level.

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LETTER TO THE EDITOR

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Risk of cardiovascular events and death according to COVID-19 reinfection

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The coronavirus disease 2019 (COVID-19) pandemic has significantly changed the health care system and turned medical services dysfunctional [1, 2]. During the pandemic, many reports were heard about the impact of COVID-19 infection on the cardiovascular system [3–5]. We now have access to much larger studies that reveal this phenomenon not only in the context of one infection but also reinfection. Data from the United States Department of Veterans Affairs' national healthcare database shows that each severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reinfection raises the probability of death, being hospitalized, and developing long-term effects on different organs and systems. Compared to the no-reinfection group (n = 5,334,729), reinfection group (second time or more) (n = 40.947) increased the risk of death (hazard ratio [HR] = 2.17), hospitalization (HR = 3.32) and consequences — pulmonary (HR = 3.54), cardiovascular (HR = 3.02) and renal (HR = 3.55). This risk persisted for up to 6 months (follow-up) and was independent of vaccination status. Compared to uninfected controls (n = 5,334,729), the burden of reinfection resulted in a cumulative risk depending on the number of infections; those who had only one infection had an increased risk of at least one of the sequelae at HR = 1.37, the risk was higher in those who had two infections (HR = 2.07), and the highest risk was in those with three or more infections (HR = 2.35) [6]. These studies indicate a significant problem that will be faced in the health care system and significant increases in the population of patients treated by cardiology specialists. Therefore, one of the most important tasks that should still be in force is reducing the number of infections through vaccination and personal protective equipment. Despite the fact that the public is not enthusiastic about it, they should also be informed and educated on what it entails. As we know, vaccination significantly reduces the risk of a severe course, but the latest vaccinations and booster doses aimed at new variants will significantly help us reduce the number of infections and, consequently, the side effects of diseases even in groups of patients who do not have a severe course of the disease [7–9]. In the context of epidemiology, widespread testing of infected people should also be restored, as is currently the case in many countries, such as China, which has recorded numbers of infections since the beginning of the pandemic. Widespread testing as well as self-testing and self-isolation would significantly reduce the number of infected people, especially with highly infectious variants such as Omnicron, which, despite the overall lower risk of a severe course, may contribute to the complications mentioned above [10].

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The head-up cardiopulmonary resuscitation method: Improving neurological outcomes

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The coronavirus disease 2019 (COVID-19) pandemic has significantly impacted the burden on the health service and its efficiency [1]. The pandemic contributed both to the increase in the rate of cardiovascular events as complications of the COVID-19 disease and to the issue of resuscitation and securing the respiratory tract due to the risk of infections [2–4]. For decades, the main form of management of patients experiencing cardiac arrest has been flat or supine cardiopulmonary resuscitation (CPR). No other technique has had a more significant impact on survival than conventional CPR, with the exception of fast defibrillation in appropriate situations. The novel head-up position method of CPR that incorporates controlled elevation of the head and thorax along with active compression decompression and an impedance threshold device has been shown to reduce intracranial pressure and enhance cerebral blood flow, cerebral perfusion pressure, and neurologically favorable survival. When tested on humans, the prefrontal region's median increase in cerebral blood flow in the head-up position was 14.6% higher than in the supine position and this was observed in 83.3% of the patients who were part of the analysis [5]. The main mechanism of benefit for head-up CPR is the use of gravity to improve venous drainage from the paravertebral venous plexus as well as the brain and cerebral venous sinuses, lowering intracranial pressure and opening the possibility for forward blood flow. Heads-up CPR also offers rebalancing blood flow through the lungs similar in manner to patients with heart failure sitting up straight. Another benefit is that compression during head-up CPR compared to conventional CPR is that it lowers the pressure that is conveyed to the brain via the venous and arterial vasculature, thus preventing concussive damage [6, 7]. Numerous research studies have already proved this in-depth on animal models, but now some demonstrate its efficacy in people [8]. In human models when compared to conventional CPR, the survival rates for the vast majority of out-of-hospital cardiac arrest patients with non-shockable presentations were significantly improved with the head-up position method CPR. Additionally, shorter reaction times to the start of head-up position CPR increased survival odds within highly attainable response times [9]. A significant advantage of this method is the use of automatic chest compression devices, which also relieves the staff by allowing a limited number of people conducting CPR, especially in intensive care units with a large number of COVID-19 patients requiring emergency interventions [10]. Currently, there remains a lack of data on the new resuscitation technique and more extensive research on its use is needed, but the initial results seem convincing and will continue. Its use may be limited by the costs associated with the purchase of new devices — both for automatic chest compression, which are still lacking in many facilities around the world, and for head-up/torso-up positioning devices themselves, however, they can significantly minimize fatigue for emergency medical services personnel in the case of out-of-hospital cardiac arrest and increase the capacity of the hospital systems while significantly improving neurological outcomes. The aforementioned changes could benefit the entire healthcare system.

Conflict of interest: None declared

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