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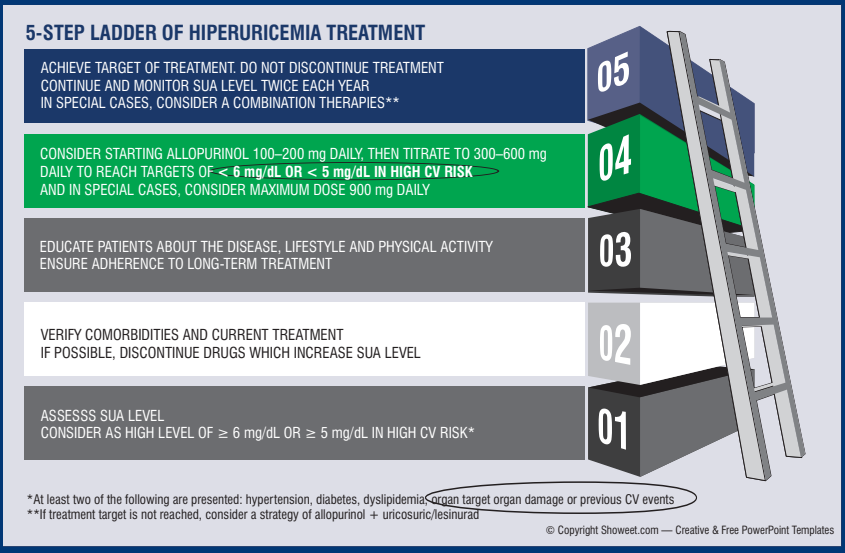

Claudio Borghi et al., see figure legend on page 9

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January 2024, Vol. 31, No. 1

Table of Contents

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Expert consensus for the diagnosis and treatment of patients with hyperuricemia and high cardiovascular risk: 2023 update

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This document updates previous documents [1, 2] and provides a condensed overview of the existing information. It aims to support healthcare professionals in developing optimal approaches to managing patients struggling with hyperuricemia (HU) and its related health conditions. The intention is to enhance the decision-making process for healthcare professionals in their daily clinical activities. However, it is important to note that the responsible healthcare provider should make the final decisions regarding patient care, considering what is most appropriate in the given context. Particular attention will be given to the latest advancements in this field. First, the focus herein,was on:

- pointing to the need to standardize the definition of HU;
- paying attention to HU in patients with chronic kidney disease (CKD);
- paying attention to HU values associated with the risk of various cardiovascular diseases (CVD);
- focusing on new medications supporting HU treatment with allopurinol in patients at increased cardiovascular risk.

Definition and epidemiology: The growing importance of hyperuricemia despite varying definitions and limited epidemiological data

Unfortunately, the definition of HU and the threshold for diseases of the cardiovascular system are still not clearly defined. This means that data on HU and the relationship between uric acid (UA) concentration and other diseases are often difficult to interpret and inconsistent in many publications. Undoubtedly, UA is the end product of purine metabolism. Its concentration in blood

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can increase in humans, great apes, and Dalmatian dogs as a consequence of a genetic mutation that occurred millions of years ago and contributed to human evolution from less evolved species [3]. Increased UA levels in the blood result from nearly three separate mechanisms, regulated by genetics and involving UA production, renal excretion, and intestinal absorption. Under normal circumstances, the body balances UA production and elimination. When this balance is disrupted, it results in HU [4]. Generally, UA levels exceeding 7 mg/dL (420 μmol/L) in males and 6 mg/dL (360 μmol/L) in females are classified as HU.

The latest scientific data [5, 6] suggest that the average serum UA (sUA) levels have consistently risen in various populations, in addition to concurrent illnesses. The frequency of HU escalates with advancing age. It is more pronounced in males compared to premenopausal females, attributable to the beneficial impact of estrogen on the elimination of UA by the kidneys [5]. Based on the information at hand, the occurrence of HU varies, spanning from 6% in individuals without health issues to 14% in those with hypertension and notably rising to 23% among patients affected by acute coronary syndrome (ACS) and chronic coronary syndrome (CCS) [7–9].

We are eagerly awaiting the publication of the results from the UAVID registry collecting UA concentration values in a group of over 30,000 Polish patients.

It is crucial to highlight significant variations in UA-related conditions based on the chosen threshold. When HU is defined using the traditional criterion (> 7.0 mg/dL in men and > 6.0 mg/dL in women), it was found in 6.3% of the entire population (7.3% in males, 2.8% in females). However, when considering the more recently established threshold (5.6 mg/dL for both sexes), the presence of HU was observed in a larger proportion, affecting 28.2% of the total population (37.3% in males, 4.7% in females) [9]. In a Chinese epidemiological study, the overall prevalence of HU was recorded at 15.1%. This prevalence was higher in specific subgroups such as males, current smokers, individuals with higher body mass index (BMI), those engaging in lower levels of physical activity, and those with noninfectious chronic diseases. Notably, a higher prevalence of HU was observed in subgroups following the non-vegetarian diets, having inadequate vegetable consumption and consuming excessive amounts of red meat and alcohol. Upon inclusion of all variables in the survey-logistic regression analysis, age and physical activity acted as protective factors against HU, while BMI emerged as a risk factor for its occurrence. Diseases such as hypertension and dyslipidemia were linked to an increased risk of HU, while diabetes mellitus demonstrated a negative association [10]. Subsequently, we should not forget about the findings from the United States National Health and Nutrition Examination Survey (NHANES) conducted from 2007 to 2016, which revealed that the prevalence of HU was 20.2% among men and 20.0% among women. To put it simply, 1 out of every 5 men and 1 out of every 5 women are affected by HU. Additionally, sUA levels exceeding 6.0 mg/dL were recorded at 32.3% in the general population, with figures of 49.5% among men and 16.4% among women. The collective average sUA level was measured at 5.39 mg/dL (95% confidence interval [CI] 5.34–5.45), while the specific average sUA levels were 6.04 mg/dL for men and 4.79 mg/dL for women. Moreover, the prevalence rates of HU remained consistent over the period between 2007 and 2016 (p for trend > 0.05) [6].

Hyperuricemia in patients with chronic kidney disease

Of note, the prevalence of HU increased significantly with worsening renal function, from 12.2% in patients with estimated glomerular filtration rate (eGFR) > 90 mL/min to 63.9% in patients with eGFR < 15 mL/min [11].

Tsai et al. [12] highlighted the prevalence of HU in the group of patients with CKD, and they revealed that an elevated UA level was strongly linked to a more pronounced deterioration in kidney function and an increased likelihood of advancing to kidney failure. A total of 739 patients were included in the analysis. In the comprehensive adjusted model, individuals with an initial UA level of ≥ 6 mg/dL experienced a more significant decrease in eGFR (with a β coefficient of –9.6 and a 95% CI of –16.1 to –3.1) when compared to those with a UA level below 6 mg/dL. Upon categorizing patients into four groups based on UA levels, all three groups with HU (UA levels of 6–8, 8–10, and ≥ 10 mg/dL) displayed a greater reduction in eGFR over the observation period. This effect exhibited a dose-response pattern, with higher UA levels correlating with more pronounced eGFR decline than the group with the lowest UA levels. The risk of advancing to renal failure escalated by 7% (with a hazard ratio [HR] of 1.07 and a 95% CI of 1.00 to 1.14) for each 1 mg/dL increase in baseline UA level [12].

Hyperuricemia values associated with the risk of various CVDs

In 2018 European Guidelines on Arterial Hypertension formally integrated the assessment of UA as one of the cardiovascular risk factors that should be considered for risk stratification in patients [13, 14]. Uric acid has been extensively studied and has been shown to predict not only overall and cardiovascular-related mortality independently but also incidents of myocardial infarction (MI), stroke, and heart failure (HF), among others. Despite numerous studies on this matter, a crucial unanswered question remains: determining the specific UA level at which it becomes a cardiovascular risk factor. The existing HU threshold (> 6 mg/dL in women and 7 mg/dL in men) is mainly based on the saturation point of UA. Still, previous evidence indicates that adverse cardiovascular effects might also occur at lower levels [1, 2, 15, 16]. Expert consensus on HU suggests a value of 5 mg/dL in patients with a strictly defined elevated cardiovascular risk.

Addressing this issue, the Working Group on UA and cardiovascular risk of the Italian Society of Hypertension introduced the Uric acid Right for heArt Health (URRAH) project. The central goal of this initiative is to establish the UA concentration above which the independent risk of CVD significantly rises. Details are presented in Table 1 [17–20].

Overall- and cardiovascular mortality

In multivariate Cox regression analyses, the URRAH study demonstrated an independent connection between sUA and overall mortality (HR 1.53; 95% CI 1.21–1.93) and cardiovascular mortality (HR 2.08; 95% CI 1.146–2.97; $p < 0.001$). Serum UA values that effectively distinguish between total- and cardiovascular mortality were determined to be 4.7 mg/dL and 5.6 mg/dL, respectively. Including sUA data resulted in a substantial improvement in net reclassification by 0.26 and 0.27 in relation to the Heart Score risk chart for overall mortality and cardiovascular mortality, respectively [16].

Moreover, URRAH supplementary analysis revealed that across the entire study population, sUA emerged as a predictor for both all-cause mortality (ACM) and cardiovascular mortality (CVM). This association held true when stratifying according to triglyceride (TG) levels: ACM predictions in individuals with normal TG levels and hypertriglyceridemia and CVM predictions in those with normal TG levels and hypertriglyceridemia. Therefore, the study reveals that sUA can anticipate ACM and CVM among individuals with cardiometabolic profiles without established CVD, independently of TG levels [21].

Heart failure

In Cox regression analyses, when considering sUA as a continuous measure, it emerged as a significant predictor for both overall- and fatal incident HF. Receiver operating characteristic curves were employed across the entire dataset to identify threshold values of sUA that could distinguish between the presence and absence of all HF and fatal HF. Specifically, a sUA level higher than 5.34 mg/dL (CI 4.37–5.6, sensitivity 52.32%, specificity 63.96%, $p < 0.0001$) was established as the univariate prognostic threshold for all HF, while a sUA level exceeding 4.89 mg/dL (CI 4.78–5.78, sensitivity 68.29%, specificity 49.11%, $p < 0.0001$) was identified as the univariate prognostic threshold for fatal HF [17].

Myocardial infarction

Receiver operating characteristic curves were utilized to pinpoint cut-off values of sUA that effectively distinguish MI status. These values were identified across the entire dataset (> 5.70 mg/dL), specifically for women (> 5.26 mg/dL) and separately for men (> 5.49 mg/dL). Through multivariate Cox regression analyses that were adjusted for various confounding factors (including age, arterial hypertension, diabetes, CKD, smoking habit, ethanol intake, BMI, hematocrit, low density lipoprotein cholesterol, and diuretic use), an independent relationship between sUA and fatal MI was determined. Moreover, in the overall dataset, there was an identified HR of 1.381 (with 95% CIs spanning from 1.096 to 1.758 and a p value of 0.006) for this association with fatal MI. Similarly, in the case of women, the HR was found to be 1.514 (with CIs of 1.105–2.075 and a p value below 0.01), signifying a notable independent link with fatal MI. However, this independent association was not evident among men [22].

Cerebrovascular events

Using a receiver operating characteristic curve, a predictive threshold value for sUA that effectively distinguishes combined cerebrovascular (CBV) events (> 4.79 mg/dL or > 284.91 μmol/L) was identified within the entire dataset. After accounting for confounding factors such as age, sex, arterial hypertension, diabetes, CKD, smoking habit, ethanol intake, BMI, low-density lipoprotein

Table 1. Key findings from Uric acid Right for heArt Health (URRAH) studies.

Title	Aim	Results	sUA level	References
Serum UA and LVMI independently predict CV mortality: The UA right for heart health	To examine the link between sUA and LVMI, as well as to determine if either sUA, LVMI or their combination can forecast the occurrence of CV mortality	A noteworthy correlation between sUA and LVMI was evident through multi-regression analysis for both men (beta 0.095, F 5.47, $p < 0.001$) and women (beta 0.069, F 4.36, $p < 0.001$). Over the follow-up period, 319 CV fatalities occurred. Kaplan-Meier plots demonstrated a considerably lower survival rate among individuals with elevated sUA levels (> 5.6 mg/dL in men and 5.1 mg/dL in women) and LVH (log-rank chi-square 298.105; $p < 0.0001$)	> 5.6 mg/dL in men, > 5.1 mg/dL in women	[18]
Serum UA levels threshold for mortality in diabetic individuals	To confirm the threshold levels of sUA that can predict overall mortality at 4.7 mg/dL and CV mortality at 5.6 mg/dL among individuals with diabetes	In the analysis involving multiple factors in the Cox regression model, accounting for various influencing variables, individuals with sUA levels of 5.6 mg/dL or higher demonstrated an elevated risk of both overall mortality (HR 1.23, 95% CI 1.04–1.47) and CV mortality (HR 1.31, 95% CI 1.03–1.66) when compared to those with sUA levels below 5.6 mg/dL. While an increased risk of mortality from any cause was observed in participants with sUA levels of 4.7 mg/dL or higher in comparison to those with levels below 4.7 mg/dL, this difference was not statistically significant after accounting for all the potential influencing factors		[19]
The association of UA with mortality modifies at old age	To explore the connection between sUA levels and the occurrence of both overall mortality and CV mortality in elderly individuals (aged over 65 years) enrolled in the extensive multicenter observational study known as URRAH	In individuals aged 65–74, a multivariate Cox regression analysis that accounted for CV risk factors and concurrent health conditions revealed an independent connection between sUA levels and both overall mortality (HR 1.169, 95% CI 1.107–1.235) and CV mortality (HR 1.146, 95% CI 1.064–1.235). The threshold value of 4.8 mg/dL accurately distinguished the mortality status. For participants aged 75 and older, a curving pattern in the relationship between sUA levels and both overall and CV mortality, where the risk increased at extremely high and low sUA levels	4.8 mg/dL	[20]
Serum UA predicts HF in a large Italian cohort: search for a cut-off value URRAH study	To determine the specific threshold levels of sUA that can predict the occurrence of severe and fatal HF	In the Cox analyses, when examining sUA as a continuous measure, it was found to be a significant predictor for both overall HF (with a HR of 1.29; 95% CI 1.23–1.359, and a p-value less than 0.0001) and fatal HF (with a HR of 1.268; 95% CI 1.121–1.35, and a p-value less than 0.0001) The identified threshold value for all HF was sUA levels above 5.34 mg/dL (with a CI of 4.37–5.6). This value exhibited a sensitivity of 52.32%, a specificity of 63.96%, and a p-value below 0.0001. Correspondingly, for fatal HF, the established cut-off value was sUA levels exceeding 4.89 mg/dL (with a CI of 4.78–5.78). This value demonstrated a sensitivity of 68.29%, a specificity of 49.11%, and a p-value below 0.0001	For all HF — sUA levels > 5.34 mg/dL; for fatal HF — 4.89 mg/dL	[17]

CI — confidence interval; CV — cardiovascular; HF — heart failure; HR — hazard ratio; UA — uric acid; LVH — left ventricular hypertrophy LVMI — left ventricular mass index; sUA — serum uric acid

cholesterol, and diuretic usage, multivariate Cox regression analysis unveiled an autonomous link between sUA and the occurrence of combined CBV events across the entire dataset. This independent association with combined CBV events was quantified as a HR of 1.249, with a 95% CI ranging from 1.041 to 1.497 and a significance level of p of 0.016. The findings of this study validate sUA as a distinct risk indicator for combined CBV events, even after adjusting for potential confounding variables, including arterial hypertension. Furthermore, the research confirms that the > 4.79 mg/dL threshold is a reliable predictive cut-off value for these events [23].

Risk models

Although many studies are helping us to understand the concepts of the relationship between HU and CVD, the independent association of sUA with CVD remains controversial as sUA is not currently included as one of the risk factors that increase the risk in both the Systematic COronary Risk Evaluation 2 (SCORE2) model and atherosclerotic cardiovascular disease risk (ASCVD-PCE), as per the most recent guidelines [24–26]. Hence, Moshkovits et al. [27] presented a study to assess how sUA affects the precision of modern 10-year ASCVD-PCE and SCORE2 risk classification models. They assessed 19,769 individuals aged 40–79 without CVD or diabetes who self-referred for screening in a preventive healthcare setting. The primary endpoint was the composite of death, ACS, or stroke, excluding those diagnosed with metastatic cancer during follow-up. The average age was 50 ± 8 years (69% men). Over a median follow-up of 6 years, 8% (1658 subjects) reached the endpoint. In a multivariable model, both ASCVD-PCE and SCORE2, along with high sUA, independently correlated with the study endpoint ($p < 0.001$ for all). When high sUA was added to either ASCVD-PCE or SCORE2, continuous net reclassification improvement analysis showed a 13% enhancement in classification accuracy ($p < 0.001$ for both). In conclusion, sUA notably boosts the accuracy of ASCVD-PCE and SCORE2 models, particularly among normal-weight and low-risk individuals [27].

Most recent observational data further support integrating sUA in the cardiovascular-risk assessment, especially in subpopulations where cardiovascular prognosis was either only partly explored or/and difficult to estimate precisely. In multivariate analysis, Obrycki et al. [28] showed that in the non-obese adolescent population with spurious hypertension, the main factor capable of predicting disadvantageous hemodynamic outcome (rise in central blood pressure after 1 year of non-pharmacological treatment) was sUA alterations. The clinical significance of their finding is that sUA alterations serve as a reasonable proxy and are much more accessible and easier to follow than central blood pressure monitoring.

Adults diagnosed with obstructive sleep apnea (OSA) constitute a group of high cardiovascular-risk patients where the treatment-resultant prognosis is difficult to predict, mainly due to low OSA-specific treatment adherence (nasal continuous positive airway pressure). Symptomatic therapy of OSA may reduce blood pressure, and it supports device-based strategies to address difficult-to-control hypertension in OSA. However, its role in cardiovascular outcomes remains obscure [14, 29]. Recent analyses of OSA cohorts, including patients after MI, strongly suggest that higher/lower sUA levels dichotomize patients concerning their clinical outcomes [30]. This phenomenon adds to our understanding of why long-term continuous positive airway pressure therapy produces inconsistent clinical effects, especially as OSA-OSA-symptomatic treatment appears to have minimal, if any, impact on sUA [31].

Recent studies connecting elevated uric acid levels with CKD and CVD

Hyperuricemia and chronic kidney disease

Elevated sUA levels often arise from impaired kidney function, even though some prior studies have disregarded the impact of renal health on sUA levels. Consequently, a new biomarker called renal function-normalized sUA, denoted as the ratio of sUA to serum creatinine (sUA/sCr), has emerged. This marker is considered a more accurate indicator of net sUA production. Multiple investigations have indicated significant links between sUA/sCr and a range of metabolic disorders, various cardiometabolic factors, as well as mortality. Wang et al. [32] confirmed that sUA/sCr and CVD are positively associated. In their study, they enrolled 96,378 participants from the Kailuan study who did not have a history of stroke or MI at the baseline in 2006. Over an average follow-up period of 11.01 years, 6,315 (6.55%) individuals experienced new-onset CVD. The study revealed that individuals in the highest quartile of sUA/sCr had the highest risk of developing CVD (HR 1.15; 95% CI 1.07–1.23), stroke (HR 1.16; 95% CI 1.07–1.26),

ischemic stroke (HR 1.12; 95% CI 1.02–1.22), and hemorrhagic stroke (HR 1.36; 95% CI 1.11–1.65). However, there was no significant association with MI (HR 1.07; 95% CI 0.92–1.25). Furthermore, they found that the link between elevated sUA/ /sCr and CVD was partially mediated by several factors, including TGs, BMI, total cholesterol, high-sensitivity C-reactive protein, diastolic blood pressure, and fasting glucose [32].

Hyperuricemia and ischemic heart disease

Unfortunately, the exact pathophysiological mechanisms leading to an increased risk of coronary artery disease in patients with elevated UA levels are still unknown. It has been postulated that HU leads to endothelial dysfunction, oxidative metabolic processes, and platelet adhesion and aggregation, ultimately resulting in coronary artery disease [33].

Several new studies have explored the potential connection between HU and the risk of developing ischemic heart disease. The outcomes were anticipated of the ALL-HEART study, a controlled and prospective trial conducted across multiple centers. This study utilized randomization and examined the impacts of allopurinol (up to 600 mg daily) compared to no treatment on cardiovascular outcomes (such as non-fatal heart attacks, non-fatal strokes, or cardiovascular-related deaths) in patients with coronary artery disease. The study also aimed to assess the cost-effectiveness of adding allopurinol to standard therapy, evaluate whether allopurinol enhances the patient's quality of life, and gauge the safety and tolerability of administering allopurinol to individuals with ischemic heart disease (excluding those with a history of gout). The primary criteria for inclusion were individuals aged 60 years and above with ischemic heart disease. In contrast, exclusion criteria involved a history of gout, eGFR below 30 mL/min, and moderate-to-severe HF, as well as significant hepatic disease [34].

The analysis, conducted on treatment-specific subgroups, was modified as per the intention-to--treat approach (ITT-analysis), encompassed 5721 randomized patients, out of whom 2853 were in the allopurinol arm, and 2868 were in the standard care arm (conventional treatment under general practitioner care). The mean observation time amounted to 4.8 years. There was no difference between the groups in the frequency of the primary endpoint, which occurred in 314 (11.0%) participants in the allopurinol arm (2.47 events per 100 patient-years) and 325 (11.3%) in the standard care arm (2.37 events per 100 patient-years (HR 1.04; 95% CI 0.89–1.21; p = 0.65).

Furthermore, no differences were observed between the groups in any of the secondary outcomes involving time to events, which included non-fatal MI, non-fatal stroke, cardiovascular--related death, all-cause mortality, hospitalization due to ACS, coronary revascularization, hospitalization due to HF, and all cardiovascular-related hospitalizations. A total of 288 (10.1%) patients in the allopurinol arm died, compared to 303 (10.6%) patients in the standard care arm, yielding an HR of 1.02 (95% CI 0.87–1.20; p = 0.77).

Moreover, some aspects of the study are worth paying attention to. Firstly, many patients discontinued treatment during the study, yet they were still considered in the final results according to the modified ITT analysis methodology. In the allopurinol group, a very high percentage of patients discontinued allopurinol treatment during the study. This is a substantial proportion: 57.4% (1637 individuals out of 2805 enrolled through randomization). These patients did not take the medication (we do not know precisely when they discontinued treatment), yet they were assessed in the allopurinol arm, which could have had an impact on the outcome. Secondly, the average age was 72 years, and the average observation period was 4.8 years. By the end of the observation, this was already a quite advanced-age group, from which outstanding effects are difficult to anticipate. It is important to note that in the United Kingdom, medications for this group are fully subsidized. The aim was not to exclude individuals who cannot afford medication for financial reasons. These patients also had well-controlled arterial hypertension and metabolic parameters; 90% of them were using statins, and 87% in both groups were on antiplatelet drugs.

The study did not present which statins and dosages were used in which groups or which antihypertensive drugs were used. As we know, both statins and angiotensin converting enzyme inhibitor, as well as angiotensin receptor blockers, influence oxidative stress, vascular inflammation, and, consequently, the development of atherosclerosis and cardiovascular complications. Based on this alone, it is difficult to determine whether both groups were truly homogeneous in terms of the "baseline level of oxidative stress" in the vessels.

Additionally, there was no information about the level of low density lipoprotein; finally, this patient group had a very low baseline UA level.

Namely, 5.7 mg/dL (standard deviation: 1.3) initially decreased to 3.02 at 6 weeks in the allopurinol arm. These are surprisingly low UA levels, considering the prevalence of HU in the population. This might stem from the fact that patients with gout were initially excluded (long history of HU, higher likelihood of gout); patients taking UA-lowering medications were excluded as well, so those likely diagnosed with HU were excluded. In any case, the conclusion is that the study was conducted in a group that does not have HU. Therefore, it is challenging to draw conclusions regarding the treatment of patients with HU and a high risk of sUA elevation [35].

In this extensive and widespread observational cohort study conducted by the CLIDAS Research Group, it was revealed that hyperuricemic individuals with CCS following percutaneous coronary intervention (PCI) experienced double the incidence of major adverse cardiovascular events (MACE) compared to those without HU over a median follow-up period of 910 days. Even after making multiple adjustments, HU was found to be independently linked to a heightened risk of MACE (Model 1: HR 1.52; Model 2: HR 1.31; Model 3: HR 1.33). Further analyses considering various adjustments indicated that HU was autonomously associated with an increased likelihood of hospitalization due to HF (Model 1: HR 2.19; Model 2: HR 1.76; Model 3: HR 1.71), while not significantly correlated with cardiovascular death and MI. These findings suggest that HU among patients with CCS following PCI might serve as a predictive factor for heightened risks of MACE, particularly concerning HF [36]. This aligns with a previous prospective observational study conducted across multiple centers. It was reported that an elevated sUA level served as an autonomous predictor of both cardiovascular events and mortality due to all causes among patients with coronary artery stenosis of at least 75% in one branch of the coronary arteries, as confirmed by coronary angiography. Over a follow-up period of 3 years, the highest quartile of sUA (sUA levels ≥ 6.8 mg/dL) exhibited a HR of 1.25 (with a 95% CI of 1.07 to 1.45) for all-encompassing events, encompassing both cardiovascular events and mortality from any cause. These findings remained consistent even after adjusting for other confounding factors. While the specific components of the combined endpoint in this study slightly differed from those in the present investigation, the overarching theme was that elevated sUA levels correlated with heightened rates of adverse events [37].

Hyperuricemia and hypertension

A significant body of evidence widely acknowledges that the association between an increased relative risk of hypertension and elevated levels of sUA remains unaltered by conventional risk factors [15, 38–45]. HU has long been acknowledged as having an association with an elevated cardiovascular risk, encompassing the susceptibility to develop hypertension. Epidemiological observations indicate this association is particularly pronounced among the younger demographic, specifically children and adolescents. UA is a potent extracellular antioxidant; however, its intracellular presence is linked to pro-inflammatory effects. Prolonged periods of HU are known to give rise to a chronic phase characterized by microvascular damage. This phenomenon is postulated to contribute to a condition known as afferent arteriolopathy, potentially leading to a persistent elevation of blood pressure that may eventually become unresponsive to therapies aimed at lowering UA levels. The establishment of a direct causal relationship between HU and hypertension has proven challenging in scientific investigations due to a multitude of confounding factors.

As it stands, the available evidence to endorse the effectiveness of UA-lowering treatments in attenuating the risk of hypertension remains limited. Nonetheless, it is important to recall a PAMELA (Pressioni Arteriose Monitorate e Loro Associazioni) study which validated that an increase in sUA by 1 mg/dL was linked to a notable elevation in the likelihood of developing new-onset home and ambulatory hypertension (odds ratio 1.34, 95% CI 1.06–1.7, p = 0.015; odds ratio 1.29, 95% CI 1.05–1.57, p = 0.014, respectively) [15].

Hyperuricemia treatment and cardiovascular outcomes: Allopurinol continues to be the preferred initial choice for uric acid-lowering therapy

In a comprehensive analysis of 24 guidance documents, most of them, specifically 19, outlined recommended target levels for long-term sUA control. The predominant target level suggested was 6.0 mg/dL (or 360 μmol/L), although it is worth noting that the South African guidelines deviated from this consensus by recommending a lower threshold of 5.0 mg/dL (300 μmol/L). However, it is important to highlight that the definition of HU varies significantly among different clinical trials, resulting in a wide range of interpretations. This variability makes it challenging to maintain consistency and comparability in epidemiological reports.

Xanthine-oxidase inhibitors (XOI), particularly allopurinol, are the preferred and recommended first-line uric acid-lowering therapy (ULT) approach. However, it is crucial to acknowledge that further research is required to fully understand the implications of using febuxostat, another XOI [46–48].

Febuxostat — Other significant studies are eagerly awaited

Febuxostat is an alternative to allopurinol for patients who do not respond well or cannot tolerate allopurinol, and it is suitable for CKD stages 1–3 without dose adjustments. It is a potent XOI with stronger UA-lowering effects than standard allopurinol doses. However, a 2017 Food and Drug Administration alert raised concerns about a potential cardiac risk associated with febuxostat, especially in high cardiovascular-risk patients, (this is based on the CARES studies). On the other hand, the Febuxostat versus Allopurinol Streamlined Trial (FAST), mandated by the European Medicines Agency and published in the Lancet, does not corroborate the increased cardiovascular risk associated with febuxostat. This conclusion comes despite the trial's use of higher dosages approved by European Medicines Agency, in contrast to those used in the CARES trial. In a study of 6128 patients with a history of CVD, the incidence of the primary endpoint showed that febuxostat (172 patients [1.72 events per 100 patient-years]) was not inferior to allopurinol (241 patients [2.05 events per 100 patient-years]; adjusted HR 0.85; 95% CI 0.70–1.03; $p < 0.0001$). Bardin and Richette [47] noted in their editorial comments that the CARES study participants had more advanced gout compared to those in the FAST study, and all CARES participants had a history of CVD, unlike only 2046 (33.4%) out of 6128 in the FAST study. No significant increase in death rates was noted in this subgroup in the FAST trial. However, they pointed out the possibility that the sample size might not be large enough to comprehensively evaluate the risk of febuxostat in patients with severe CVD. Bardin and Richette [47] analyzed 20 randomized controlled trials. The follow-up averaged 69.7 ± ± 81.5 weeks, with febuxostat doses ranging from 10 to 240 mg, most commonly at 80 mg. Quality concerns were noted in 65% of these studies. MACE were defined in 35% of the trials, showing varied reporting of cardiovascular outcomes. Overall, the cardiovascular safety data for febuxostat appeared reassuring. However, additional clinical trials are necessary to resolve this matter [47–51].

Management strategies: Revised recommendations comprising five-step suggestions for managing patients with elevated serum uric acid levels (Fig. 1)

STEP 1: Assess serum uric acid level and uric acid-to-GFR ratio

Experts from the European Society of Cardiology and the European Society of Hypertension recommend measuring sUA concentration as part of screening for patients with heart conditions or hypertension [46]. The advice remains consistent: the ideal objective for sUA levels should be 6 mg/dL (360 μmol/L). It's essential to regularly monitor sUA levels and ensure they are maintained below 6 mg/dL. However, even though there is a lack of randomized controlled trials, it is advisable to contemplate an sUA target of less than 5 mg/dL for patients with an increased cardiovascular risk, which includes having at least two of the following conditions: hypertension, diabetes, dyslipidemia, recent stroke, MI, or CKD. Considering the new knowledge, in patients with kidney disease, the assessment of the UA-to-GFR ratio can provide insights into how well the kidneys are handling UA excretion. It can help healthcare professionals monitor kidney health and make informed decisions about managing kidney disease progression.

STEP 2: Assess existing medical conditions and ongoing therapies, and discontinue using medications that impact serum uric acid levels

Suitable approaches need to be identified and executed for individuals with elevated UA, involving more proactive management of concurrent risk factors and the utilization of medications that indirectly impact UA levels. Effectively addressing concurrent conditions, depicted in Figure 2, that influence sUA levels should be the preferred course of action [52–56].

In clinical situations, practical modifications should be contemplated when the potential advantages outweigh the potential disadvantages, especially in the case of the drugs presented in the Table 2.

Forming interdisciplinary groups to achieve the best possible diagnostic and treatment approaches, along with accurately assessing the importance of elevated UA (HU), is imperative. Enhancing adherence to established clinical practice recommendations, increasing understanding of HU and its related coexisting conditions, and encouraging more rigorous and precise monitoring of these conditions are crucial.

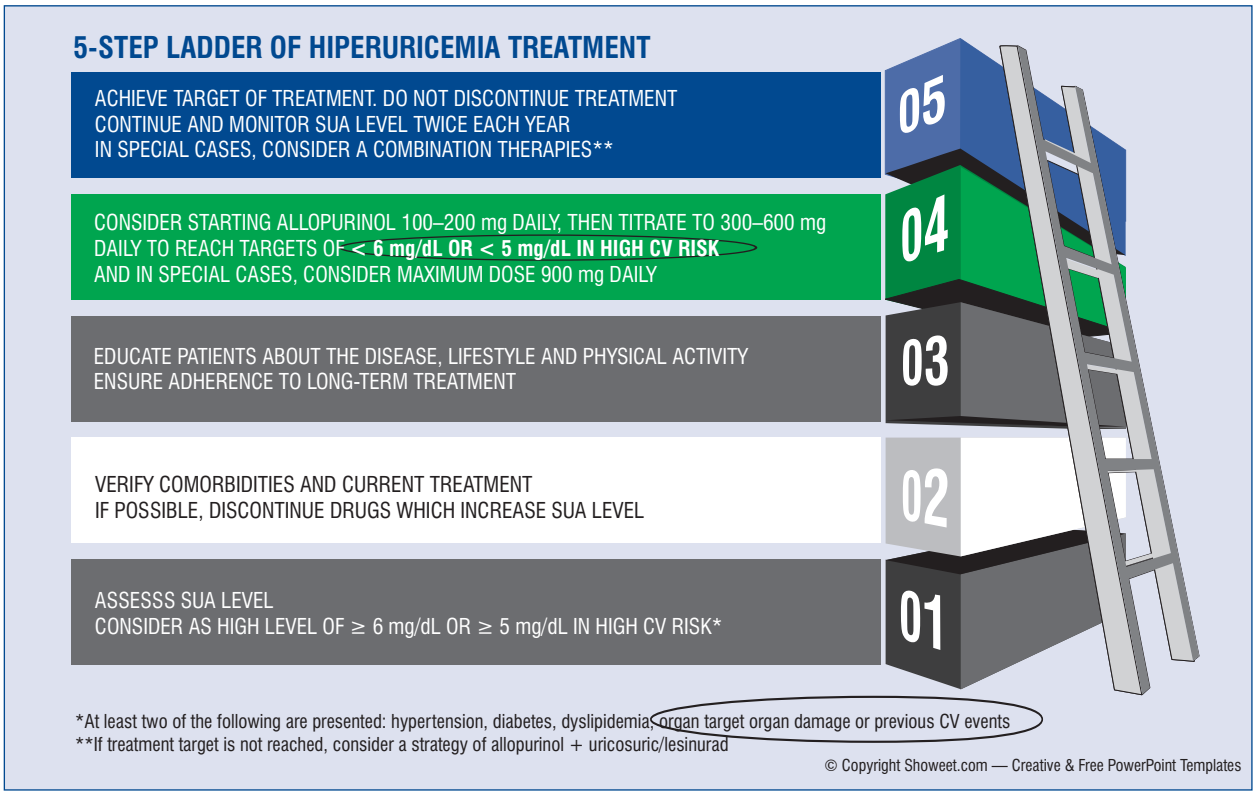

Figure 1. Five-step ladder of hyperuricemia treatment; CV — cardiovascular; SUA — serum uric acid.

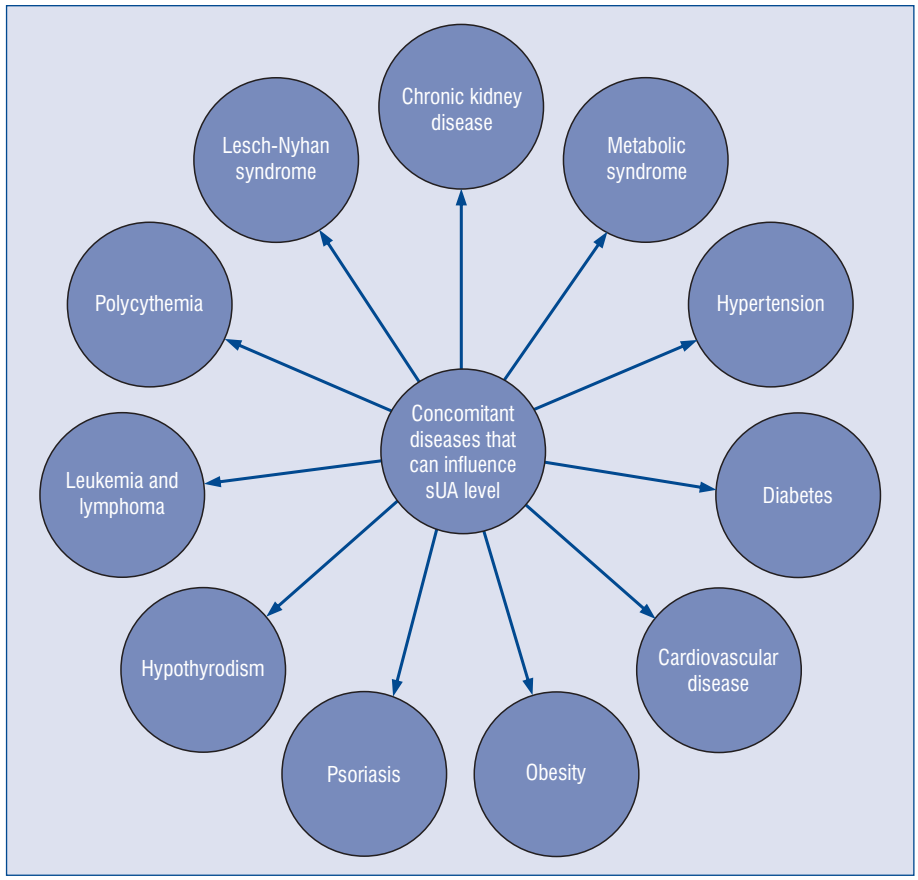

Figure 2. Concurrent conditions, that influence serum uric acid (sUA) levels.

Table 2. Medications requiring special attention during the treatment of hyperuricemia.

Medication	Drug class	Potential mechanism
Loop diuretics, thiazide diuretics and thiazide-like diuretics	Diuretics	Interaction with renal urate transporters
Low-dose ASA	NSAID	Acting as an exchange substrate to facilitate urate reabsorption
Niacin (nicotinic acid)	Vitamin B group	Decreases urinary excretion of UA
Cyclosporine	Immunosuppressant	Increase of proximal UA reabsorption, decrease in glomerular filtration rate secondary to afferent arteriolar vasoconstriction
Tacrolimus	Immunosuppressant	Not known
Levodopa	Antiparkinsonian	Not known
Ethambutol	Anti-tubercular drugs	Reduction in the fractional excretion of UA
Pyrazinamide	Anti-tubercular drugs	Causing the reabsorption of urate from the luminal side into tubular cells; interferes with OAT2 and OAT10
Cytotoxic chemotherapy	Chemotherapy	Massive disruption of tumor cells

ASA — acetylsalicylic acid; NSAID — nonsteroidal anti-inflammatory drug; UA — uric acid

STEP 3: Suggested modifications to patients's lifestyle

Among the most significant lifestyle changes are:

— following a nutritionally balanced dietary regimen with controlled intake of purine-rich foods;
— hydration emphasis — ensuring adequate water intake;
— limiting alcohol — reducing alcohol consumption, particularly beer and spirits;
— weight management — maintaining a healthy weight through proper diet and exercise;
— reduced sugar intake — minimizing high-fructose corn syrup and sugary foods;
— moderate protein — opting for lean protein sources and moderate consumption;
— adding coffee, dairy products, cherries and ascorbic acid [57–62].

STEP 4: Administer xanthine oxidase inhibitors as the initial treatment choice, adjusting the dosage to attain the desired serum uric acid target

Allopurinol, classified as a XOI, is advised as the primary choice for ULT. As outlined in the Summary of Product Characteristics (SmPC) for allopurinol, the suggested starting dosage ranges from 100 to 200 mg daily for mild cases, 300 to 600 mg daily for moderate cases, and 700 to 900 mg daily for severe conditions. The dosage should be incrementally adjusted to attain the target sUA level [63]. Hence, in cases of advanced CKD, it might be suitable to consider doses lower than 100 mg per day or to administer singular 100 mg doses at extended intervals exceeding 1 day. In specific circumstances and with the availability of suitable instrumentation, dosages should be fine-tuned to ensure that plasma oxypurinol concentrations remain below 100 μmol/L (15.2 mg/L). When allopurinol is employed for patients undergoing dialysis, a 300–400 mg dose is recommended immediately after dialysis, abstaining from additional doses on alternate days [63].

STEP 5: Reach the desired serum uric acid concentrations, avoid discontinuing the treatment, and maintain twice-a-year serum uric acid level assessments. In specific circumstances, contemplate the potential for combined therapy

Allopurinol

Only 40% of patients with HU successfully achieved the targeted sUA level with this therapy. If reaching the sUA goal proves difficult, the dosage should be gradually increased under supervision, reaching a maximum of 900 mg of allopurinol, or the patient's treatment could be switched to benzbromarone. Alternatively, a combined therapy approach involving benzbromarone and allopurinol (STEP 5) could be considered, excluding patients with an eGFR below 30 mL/min. However, these dose escalations should be undertaken cautiously to avoid adverse effects in patients who are intolerant to allopurinol. Another XOI, febuxostat, can be considered.

SGLT2

The exact mechanism of sUA reduction by sodium-glucose transport protein 2 (SGLT2) inhibitors remains uncertain, but most researchers suggest that it occurs through increased urinary excretion of UA. While clinical evidence is limited, animal and in vitro studies have shed some light on this effect. Notably, studies in healthy subjects receiving luseogliflozin demonstrated a reduction in sUA after a single dose, with a negative correlation between sUA and urinary excretion of UA. Urinary excretion of UA was also positively associated with urinary d-glucose excretion and SGLT2 inhibitors concentration. The most significant sUA reduction occurred on day 1 of a multiple-dose study, and urinary excretion of UA remained elevated for 7 days. In type 2 diabetes mellitus patients treated with tofogliflozin, sUA reached its lowest point after 4 weeks, plateauing thereafter. Empagliflozin and luseogliflozin seem to have the highest sUA lowering effects among flozins, and some experts connect it to their highest SGLT2/SGLT1 selectivity [64].

Lesinurad

Lesinurad is an oral selective inhibitor of the renal transporters URAT1 and OAT4. Impeding UA reabsorption enhances renal UA excretion, leading to decreased sUA levels. When patients fail to achieve treatment goals, a recommended dose of 200 mg daily of lesinurad can be combined with XOIs. This combination helps achieve therapeutic goals, amplifies the efficacy of XOIs (compared to monotherapy) and avoids the necessity for maximal XOI dosages. To emphasize, the usage of lesinurad alongside allopurinol presents a fresh approach for managing HU in adults afflicted with gout, especially when their desired sUA levels remain unattained solely with allopurinol treatment (STEP 5). After reaching the consistent sUA target, the dose of ULT should be perpetually upheld, accompanied by biannual sUA level assessments (STEP 5) [65–68].

Many unresolved questions still remain: Areas in need of further study

Primarily, it might be necessary to reconsider the desired treatment target for UA, particularly in light of recent findings from the URRAH study, which have illuminated novel cardiovascular thresholds and enhanced algorithms for the comprehensive evaluation of overall cardiovascular risk. This emerging data highlights the ongoing need to refine treatment approaches to ensure the best possible patient outcomes.

Furthermore, the presence of CKD and the potential elevation of sCr levels introduce additional complexities to the management of HU. Given the frequent coexistence of CKD and HU, a customized approach becomes indispensable. Deliberate attention must be devoted to selecting the appropriate ULT and determining suitable dosages to mitigate potential adverse effects on renal function. Vigilant monitoring of sCr levels and renal function becomes imperative in this context, as safeguarding kidney health takes precedence.

While the well-established effectiveness of ULT in relieving symptoms associated with asymptomatic HU is widely acknowledged, an expanding body of evidence is illuminating the favourable influence of these interventions on cardiovascular outcomes. Despite the absence of overt clinical symptoms, the potential advantages of ULT in mitigating the risk of cardiovascular events should not be understated.

In summary, the dynamic landscape of HU management mandates a comprehensive reevaluation of treatment objectives and methodologies. Incorporating the latest cardiovascular risk benchmarks, addressing the complexities associated with CKD, and acknowledging the potential cardiovascular merits of ULT collectively underscore the pivotal role of evidence-based decision-making within the clinical routine.

Most relevant recommendations: The take home message for clinical practitioners

Summarizing our viewpoints for clinical practitioners managing patients with HU and increased cardiovascular risk, we present the following key recommendations:

1. Prevalence and awareness:
   - hyperuricemia affects at least 20% of patients, and its prevalence continues to rise,
   - patients with HU should receive comprehensive education about the environmental and pharmacological factors influencing HU and associated comorbidities and cardiovascular risk factors,
   - immediate implementation of lifestyle adjustments, dietary modifications, and weight reduction when needed, along with consistent adherence to recommended treatments, is essential;
2. Uric acid management:
   - both patients and healthcare professionals across specialities, particularly primary

care physicians, cardiologists, and nephrologists, should work collaboratively to achieve and sustain sUA levels consistently below 6 mg/dL,
   — the target sUA level should be maintained at 5 mg/dL for patients at increased cardiovascular risk;
3. Choice of initial treatment:
   — as previously mentioned, allopurinol, classified as a XOI, is endorsed as the primary ULT option,
   — referring to the Summary of Product Characteristics (SmPC) for allopurinol, the recommended starting dose varies from 100 to 200 mg daily for mild cases, 300 to 600 mg daily for moderate patients, and 700 to 900 mg daily for severe conditions;
4. Caution with febuxostat:
   — due to concerns regarding cardiovascular risk, it is advisable to be cautious when considering febuxostat for patients with a high cardiovascular risk profile;
5. Individualized dosage and monitoring:
   — titration of XOI dosages is imperative to achieve the desired sUA target level,
   — post-achievement, twice-a-year monitoring of sUA levels ensures the maintenance of appropriate sUA levels;
6. Combining therapies:
   — in cases where XOI therapy is either poorly tolerated or the target sUA levels remain unachievable, combination therapy involving allopurinol with uricosuric agents, lesinurad, or febuxostat should be considered as a next step,
   — the role of SGLT2 in managing HU is growing, but it still requires further research.

In summary, effective management of HU necessitates a multidisciplinary approach, with an emphasis on patient education, personalized treatment strategies, and continuous monitoring to achieve.

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Comparison of successful versus failed percutaneous coronary intervention in patients with chronic total occlusion: A systematic review and meta-analysis

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Abstract

Background: *The optimal treatment strategy of chronic total occlusion (CTO) is currently debated. This meta-analysis aimed to evaluate the long-term clinical outcomes of successful percutaneous coronary intervention (PCI) of CTO.*

Methods: *Electronic databases were searched for studies comparing long-term outcomes between successful PCI in patients with CTO using drug-eluting stents and failed procedures. Meta-analysis was conducted with major adverse cardiac events (MACE) and all-cause mortality during the longest follow-up as endpoints. The combined hazard ratios (HRs) were applied to assess the correlation between successful CTO PCI and MACE/all-cause mortality.*

Results: *Eight studies consisting of 6,211 patients published between 2012 and 2020 met our inclusion criteria, and the CTO PCI success rate was 81.2%. Patients in the failed group were much older, and more likely to have morbidities (hypertension and prior myocardial infarction), reduced left ventricular ejection fraction, and severe lesion characteristics (multivessel disease and moderate/severe calcification). Pooled results indicated that successful CTO PCI was significantly associated with prognosis. Compared to failed recanalization, patients receiving successful procedures had an improved MACE (hazard ratio [HR]: 0.50, 95% confidence interval [CI]: 0.40–0.61, $p < 0.001$). Subgroup analyses further revealed the prognostic value of successful CTO PCI. However, no difference was observed regarding all-cause mortality (HR: 0.79, 95% CI: 0.61–1.02, $p = 0.074$).*

Conclusions: *The present study showed that CTO recanalization was associated with improved long-term outcomes. However, randomized trials are needed to confirm the results due to the mismatch of baseline characteristics.* (Cardiol J 2024; 31, 1: 15–23)

Key words: chronic total occlusion, percutaneous coronary intervention, major adverse cardiac events, meta-analysis

Introduction

According to the coronary Chronic Total Occlusion Academic Research Consortium (CTO-ARC) consensus recommendations, definite coronary chronic total occlusion (CTO) indicates CTO with typical appearance and definitive corroborating evidence of occlusion duration ≥ 3 months [1]. Typical

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appearance included Thrombolysis in Myocardial Infarction (TIMI) grade 0 flow through the lesion with no thrombus, no staining at the proximal cap, and presence of mature collaterals. CTOs are highly prevalent among patients undergoing diagnostic coronary angiography, ranging from one-quarter to one-third of patients, though the prevalence is related to the group studied [2–6]. Patients with a history of coronary artery bypass graft (CABG) surgery are found to have CTOs of their native vessels more frequently (54%) [3], while patients presenting with ST-segment elevation myocardial infarction (STEMI) are less likely to have a CTO (10%) [7].

Chronic total occlusion was once treated as the last frontier of interventional cardiology for low success rates and potential for increased complications. In the past two decades, the rate of successful percutaneous coronary intervention (PCI) has steadily increased due to the development of equipment, progression of technology, and accumulation of operation experience. The 2011 ACCF/AHA/SCAI PCI guidelines recommend PCI of CTO in patients with appropriate clinical indications and suitable anatomy when performed by operators with appropriate expertise (Class IIa, level of evidence [LOE] B) [8]. As recommended by the ESC/EACTS guidelines on myocardial revascularization, percutaneous revascularization of CTOs should be considered in patients with angina resistant to medical therapy or with a large area of documented ischemia in the territory of the occluded vessel (Class IIa, LOE B) [9].

Although success rates for recanalization of CTO continue to improve, the optimal treatment strategy remains debatable. This meta-analysis was performed to compare long-term clinical outcomes of successful PCI using drug eluting stent (DES) versus failed PCI in patients with CTO.

The following article is presented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting checklist.

Methods

Search strategy

A systematic search was conducted for eligible studies published in English in PubMed, MEDLINE, and Cochrane databases before July 2020. Search terms used include: "chronic total occlusion", "coronary occlusion", "percutaneous coronary intervention", and "recanalization". Additionally, the cited articles of the included studies and related reviews with the same topic were screened by the two authors of this study (M.Z. and M.D.Z.).

Inclusion criteria

Both prospective and retrospective studies were eligible for further evaluation. All of the CTO definitions were consistent with the CTO-ARC standard. For inclusion, studies needed to: focus on patients with single or multiple CTO with attempted PCI, have a patient population divided into successful and failed PCI groups, provide endpoint data of interest beyond 1 year, have adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the endpoints available, and use DES only. Studies that exclusively enrolled patients with acute myocardial infarction (MI) were excluded.

Additionally, unpublished data or conference abstracts were not considered for inclusion. All eligible studies for inclusion were reviewed to identify overlapping of the study population, and in these cases the most recent study with the largest sample size was used. Disagreements during article evaluation were resolved through discussion with another researcher (D.F.Z.).

Data extraction

The following information was collected from the included studies by two independent researchers (N.N. and Y.G.X.): the first author's name, year of publication, study design, patient characteristics, intervention variables, and endpoints. For articles in which interested endpoints were not provided, emails were sent to the primary author for detailed information. A consultation regarding differences in data extraction was held with another researcher (D.F.Z.). Quality of the included studies was assessed using the Newcastle-Ottawa Scale. A study could be awarded a maximum of 9 stars for quality, and studies with a score greater than 7 were considered to be of high quality. Each study was assessed independently by 2 investigators (J.F.T. and C.Z.C.).

Endpoints

Most of the studies defined success CTO PCI as technical success, which was defined as achievement of TIMI grade 2 or greater antegrade flow in all $\geq$ 2.5 mm distal branches with $<$ 30% residual stenosis of the target CTO lesion at the end of the procedure. Park et al. [10] defined as success of CTO revascularization procedure using DES implantation without serious procedure-related in-hospital deaths or major adverse events.

The following endpoints were collected from the eligible studies: the primary endpoint of major

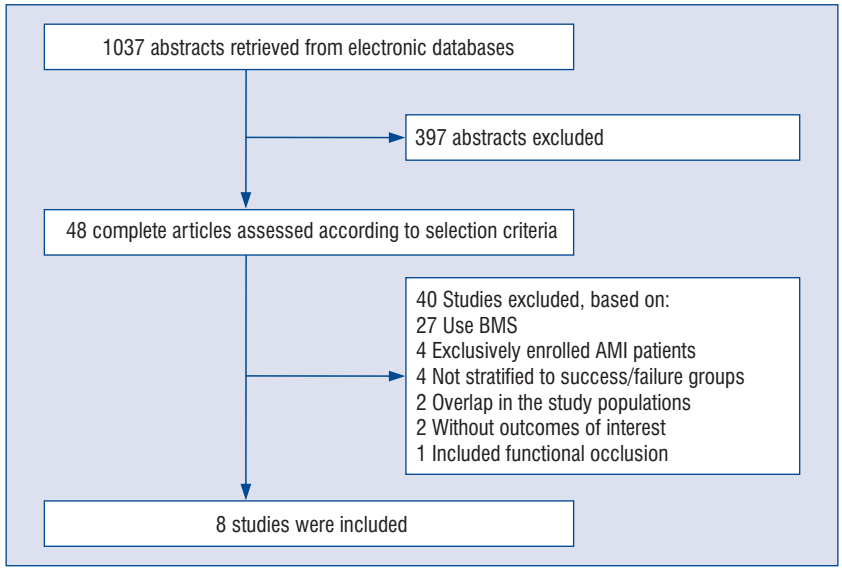

Figure 1. Flow diagram of study inclusion and exclusion criteria; AMI — acute myocardial infarction.

adverse cardiac events (MACE) and secondary endpoint of mortality from any cause during the longest follow-up. Follow-up periods were as reported in each study, which ranged from 1 year to 7 years. The definitions of MACE were also as those indicated in the individual studies. Most of the definitions, except the one carried by Park et al. [10] were the composite of death, MI, and target-vessel revascularization. Park et al. [10] defined MACE as all cause death or MI.

Statistical analysis

All statistical analyses were carried out using Stata 11.0 (Stata Corp, College Station, TX). The mean of continuous variables and percentage (%) of categorical variables were calculated. The associations between successful CTO PCI and endpoints were expressed as the HRs with their corresponding 95% CIs. Heterogeneity across studies were evaluated by Cochran's Q test and Higgins' I^2 statistic. The fixed effect model was adopted for nonsignificant heterogeneity ($I^2 < 50\%$, $p > 0.1$). Publication bias was assessed by the visible plot and Begg's test. Sensitivity analysis was performed for the measurement of the reliability of the combined results.

Results

Search results

A literature search identified 7 prospective trials and 1 retrospective trial published between 2012 and 2020 [10–17] which provided the HRs and 95% CIs in multivariate analysis for at least one of the endpoints, including 7 studies for MACE and 3 studies for all-cause mortality. If a study considered patients with failed CTO PCI as the reference, then the data was converted to HR estimations considering cases with successful CTO PCI as a reference group to reflect the impact of successful CTO PCI on CTO patients.

A total of 6,211 patients were included in these 8 studies. Figure 1 shows the inclusion and exclusion processes during the literature search process. Of these were 4 from Europe, 3 from Asia, and 1 from North America. Five were single-center experiences. The study characteristics and quality assessment results are shown in Table 1.

The final analysis comprised 5,044 patients who underwent successful recanalization of CTO lesions using DES and 1,167 patients with failed percutaneous interventions. The success rate of CTO PCI was 81.2%. **Supplementary Table 1** provides the demographic data, medical histories, and clinical characteristics of the included patients. In addition, summaries of variable means/percentages were calculated for the overall patient population. Compared with the successful recanalization patients, subjects in the failed group were much older (64.7 vs. 62.7 years, $p < 0.001$), more likely to suffer from hypertension (77.9% vs. 76.2%, $p = 0.004$), more likely to have a history of MI (37.5% vs. 29.9%, $p < 0.001$), have a left ventricular ejection fraction (LVEF) of ≤ 40% (15.8% vs. 11.9%, $p = 0.03$), have multivessel disease (MVD) (75.0% vs. 67.9%, $p < 0.001$), and have

Table 1. Main characteristics of included studies.

Primary author, year published	Period	Region	Setting	Lesions	CTO definition	Procedural subgroups, n		Maximum follow-up	Completed follow-up	NOS
						Success	Failure			
Borgia, 2012	2003.04–2009.07	UK	Single-center	≥ 1 CTO	> 3 months, TIMI 0	237	65	4 years	100%	9
Niccoli, 2012	2005.06–2009.03	Italy	2 centers	1 CTO	> 3 months, TIMI 0	196	121	3 years	100%	9
Toma, 2016	2005.01–2013.12	Germany	Single-center	≥ 1 CTO	> 3 months, TIMI 0	1662	340	2.6 years	N/A	8
Lee, 2016	2003.03–2014.05	Korea	Single-center	≥ 1 CTO	≥ 3 months, TIMI 0	1004	169	4.6 years	100%	9
Park, 2016	2003.02–2006.03	Korea	2 centers	≥ 1 CTO	≥ 3 months, TIMI 0	253	124	7 years	100%	9
Wu, 2019	2016.08–2017.03	China	Single-center	≥ 1 CTO	≥ 3 months, TIMI 0	127	18	1 year	94.5	8
Xenogiannis, 2020	2012.01–2019.11	USA	Multicenter	≥ 1 CTO	≥ 3 months, TIMI 0	1387	225	1 year	N/A	9
Stojkovic, 2018	2009.01–2010.12	Serbia	Single-center	N/A	≥ 3 months, TIMI 0	178	105	66 months	83.0%	9

CTO — chronic total occlusion; TIMI — Thrombolysis in Myocardial Infarction; N/A — not available; NOS — Newcastle-Ottawa Scale

moderate-to-severe calcification (61.7% vs. 46.2%, $p < 0.001$). No differences were observed between successful and failed recanalization for male sex (82.8% vs. 84.2%, $p = 0.13$), current smokers (24.6% vs. 24.6%, $p = 0.19$), diabetes (33.7% vs. 33.1%, $p = 0.60$) or hypercholesterolemia (62.4% vs. 62.0%, $p = 0.59$).

Newcastle-Ottawa Scale quality assessment for the included studies indicated that all studies were of high quality. No publication bias for the included trials was observed.

Main outcomes

In summary, 7 studies with a total of 4,209 definite CTO patients reported the HRs for the association between successful recanalization of CTO lesions and MACE. Heterogeneity was not observed with an I^2 statistic of 41.7%, and the fixed effects model was selected. The pooled analysis showed that compared with failed CTO PCI, successful CTO PCI had a significantly lower MACE (HR: 0.50, 95% CI: 0.40–0.61, $p < 0.001$), which indicates that the successful recanalization of CTO lesions may decrease the risk of MACE (Fig. 2).

The prognostic values of successful CTO PCI were further displayed in subgroup analyses. The setting (single-center vs. multicenter) and follow-up time (≤ 3 years vs. > 3 years) did not affect the significant association between successful CTO PCI and improved MACE (Fig. 3).

Three studies with 3,552 subjects assessed the association between successful CTO PCI and all-cause mortality. No heterogeneity was observed across studies according to the I^2 statistic (0%) thus, the fixed effects model was selected. No significant difference was found in the combined results of long-term death of any cause (HR: 0.79, 95% CI: 0.61–1.02, $p = 0.074$) (Fig. 4).

Sensitivity analysis

Sensitivity analyzes conducted by excluding one study at a time showed the results of the present analyzes were relatively stable in this meta-analysis (Fig. 5).

Discussion

The present meta-analysis showed that patients receiving successful PCI for CTO lesions using DES suffered less from MACE than those who underwent failed procedures. However, no advantage was observed with regard to all-cause mortality. However, the results should be interpreted with a view of certain bias. Patients with

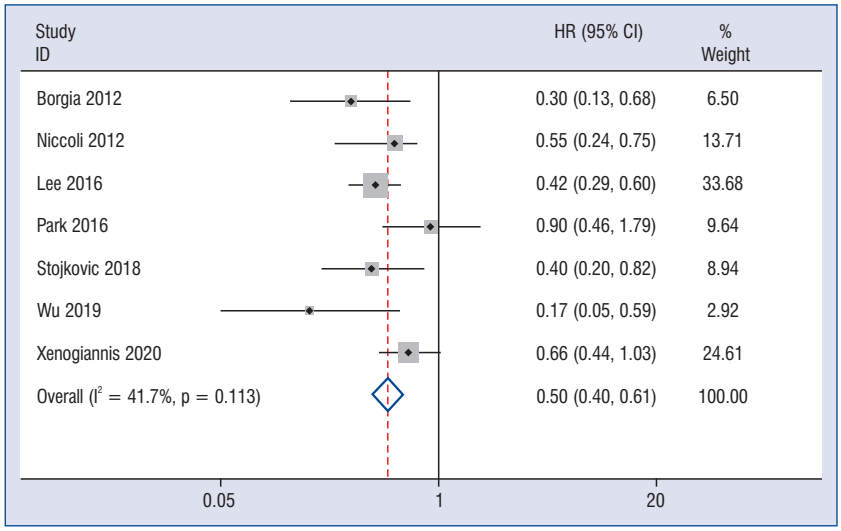

Figure 2. Forest plot for the correlation between successful chronic total occlusion percutaneous coronary intervention and major adverse cardiac events; HR — hazard ratio; CI — confidence interval.

failed intervention were much older, and more likely to have morbidities (hypertension and prior MI), reduced LVEF, and severe lesion characteristics (MVD and moderate/severe calcification), which have been shown to be poor prognostic factors in patients undergoing PCI. It is possible that the results represent the less favorable clinical profiles of patients with failed CTO PCI rather than the beneficial effects of successful CTO PCI. The worse outcome of the failed group might be partially due to a more severe coronary heart disease or to the resulted produced by the attempt of intervention.

Chronic total occlusion implies total occlusion of coronary arteries and is related to worse prognosis in select patient populations. Van der Schaff et al. [18] reported mortality in STEMI patients with single-vessel disease, MVD, and a CTO of 8%, 16%, and 35%, respectively. CTO is an independent predictor of mortality in patients receiving primary PCI. Bataille et al. [19] also proved that CTO was independently associated with the occurrence of mortality in STEMI patients presenting with cardiogenic shock. Although it is thought that retrograde collateralization provides adequate blood flow to reduce ischemia, prior studies have shown that normal coronary flow reserve could only be achieved in less than 10% of CTO patients despite well-developed collateral circulation [20]. Sachdeva et al. [21] further reported that all patients with occluded coronary arteries showed an ischemic fractional flow reserve, even with severe regional dysfunction or well-developed collaterals.

Nowadays, PCI is becoming the preferred revascularization method due to the rapid advancement in equipment and techniques as well as a growing expertise among dedicated operators [22–27]. The rate of successful CTO PCI has increased to 90% in experienced institutions [28]. Several original studies and meta-analyses proved that successful PCI of CTO was related to decreased rates of adverse clinical outcomes, such as mortality, MI, and revascularization. However, CTO recanalization was associated with a much higher risk of complications in comparison with non-CTO interventions, especially perforation. Across multiple contemporary registries, tamponade occurred in 0.4% to 1.3% of cases. However, most of the evidence comes from observational research, which inevitably has a lot of potential bias.

To address the potential bias caused by the observational nature of studies comparing successful with failed PCI of CTO, recently, 3 randomized controlled studies compared CTO PCI versus optimal medical therapy in CTO patients; Decision-CTO [29], Euro-CTO [30], and REVASC [31]. Decision-CTO and Euro-CTO showed no advantage of CTO recanalization regarding the composite endpoint MACE, which was inconsistent with the REVASC trial. It is widely established that CTO PCI carries advantages in terms of improving symptoms compared with drug therapy alone except Decision-CTO. These differences could be due to the limitations found in the Decision-CTO trial, such as the slow and early termination of enrollment, the high percentage of cross-over in

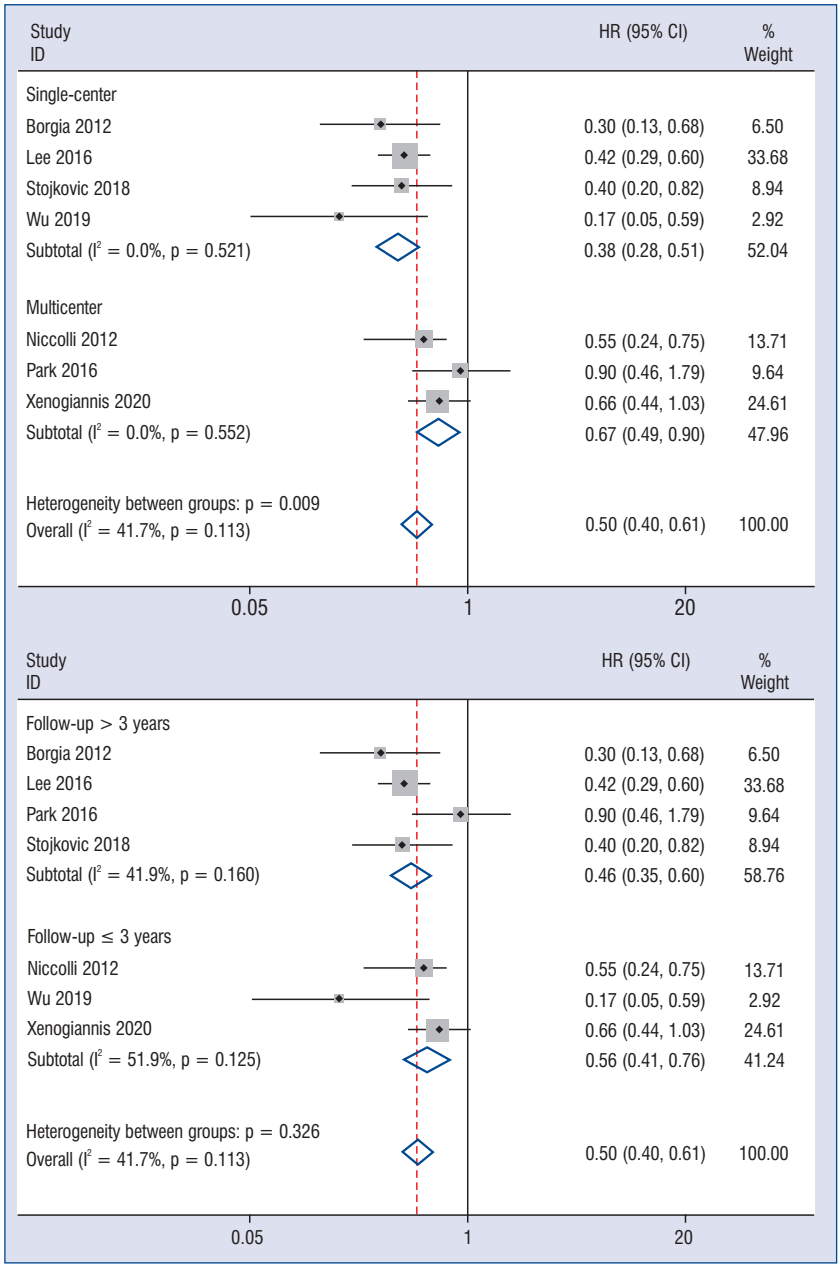

Figure 3. Forest plots for hazard ratios (HRs) of subgroup analyses for successful chronic total occlusion percutaneous coronary intervention; CI — confidence interval.

both arms, the high frequency of PCI for non-CTO lesions and the inclusion of patients with mild or absent symptoms. Meta-analysis including these randomized controlled trials (RCTs) and 5 observational studies revealed that CTO recanalization using DES was related to improved cardiac prognosis when compared with optimal medical therapy alone. However, no obvious difference was observed in the RCT subgroup consisting of 1,399 patients [32]. More RCTs are needed to explore the safety and efficacy of CTO PCI.

Current guidelines emphasize the critical role of evaluating viable myocardium in patients presenting with coronary CTO [8, 9]. The major considerations when selecting individuals who are clinically appropriate and will gain improved prognosis from recanalization of occluded lesions are the presence or absence as well as the extent of myocardial viability. However, myocardial viability assessments are not currently standard processes in real-world clinical diagnosis and treatment.

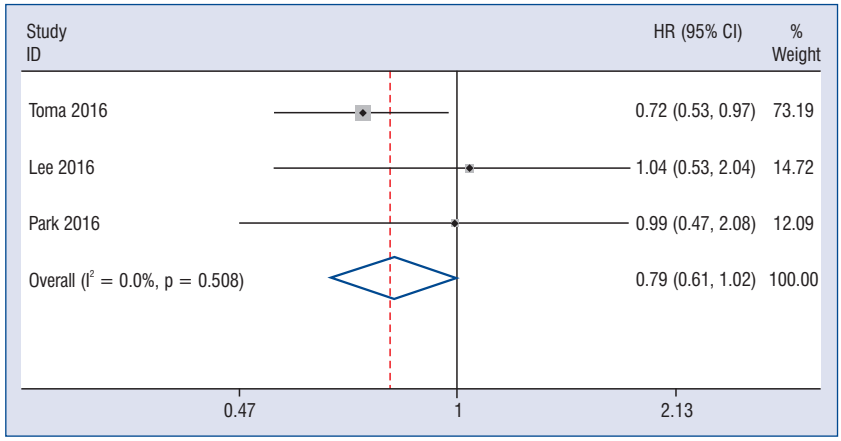

Figure 4. Forest plot for the correlation between successful chronic total occlusion percutaneous coronary intervention and all-cause mortality; HR — hazard ratio; CI — confidence interval.

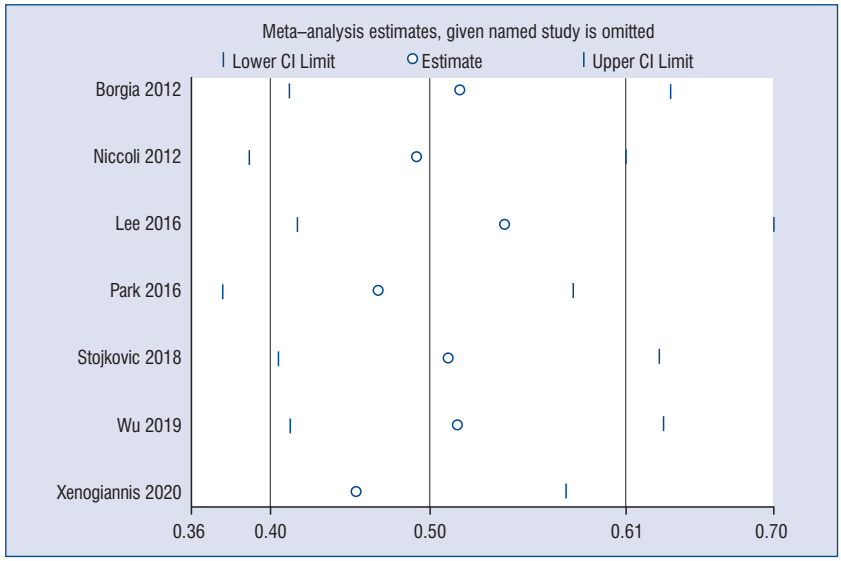

Figure 5. Sensitivity analysis for major adverse cardiac events; CI — confidence interval.

Apparently, prior studies have been suboptimally designed and performed. The absence of standardized end points and the discrepancy in definitions also prevent consistency and uniform interpretability of reported results in CTO intervention. CTO-ARC has provided uniform definitions for endpoints specific to CTO interventions and recommends a consensus framework for the design of clinical trials and registries.

Despite considerable retrospective and registry data suggesting a clinical benefit of PCI of a CTO, a clear demonstration of benefit from prospective randomized trials has not been forthcoming. Future trials using uniform definitions for endpoints may change the current landscape.

Limitations of the study

Since the study objective was to compare successful versus failed operations, the data of the current meta-analysis were obtained from observational trials without exception. The pooled results are affected by confounding factors, although the Newcastle-Ottawa Scale evaluation showed high quality. The baseline data and angiographic features of the two groups were obviously unbalanced, thus, the results could not be extended arbitrarily. In ad-

dition, post-discharge medication information was not collected in the original studies.

Conclusions

Despite certain limitations, this analysis showed that successful CTO PCI is associated with improved long-term outcomes. However, the presented data are a comparison between successful and failed PCI of CTO, and any extrapolation of these results to compare PCI and medical treatment should be undertaken with caution. RCTs are needed to further optimize treatment strategies for CTO.

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Conflict of interest: None declared

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Thrombus burden management during primary coronary bifurcation intervention: a new experimental bench model

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Abstract

Background: *Management of thrombus burden during primary percutaneous coronary intervention (pPCI) is a key-point, given the high risk of stent malapposition and/or thrombus embolization. These issues are especially important if pPCI involves a coronary bifurcation. Herein, a new experimental bifurcation bench model to analyze thrombus burden behavior was developed.*

Methods: *On a fractal left main bifurcation bench model, we generated standardized thrombus with human blood and tissue factor. Three provisional pPCI strategies were compared (n = 10/group): 1) balloon-expandable stent (BES), 2) BES completed by proximal optimizing technique (POT), and 3) nitinol self-apposing stent (SAS). The embolized distal thrombus after stent implantation was weighed. Stent apposition and thrombus trapped by the stent were quantified on two-dimensional-optical coherence tomography (OCT). To analyze final stent apposition, a new OCT acquisition was performed after pharmacological thrombolysis.*

Results: *Trapped thrombus was significantly greater with isolated BES than SAS or BES+POT (18.8 ± 5.8% vs. 10.3 ± 3.3% and 6.2 ± 2.1%, respectively; p < 0.05), and greater with SAS than BES+POT (p < 0.05). Isolated BES and SAS tended show less embolized thrombus than BES+POT (5.93 ± 4.32 mg and 5.05 ± 4.56 mg vs. 7.01 ± 4.32 mg, respectively; p = NS). Conversely, SAS and BES+POT ensured perfect final global apposition (0.4 ± 0.6% and 1.3 ± 1.3%, respectively, p = NS) compared to isolated BES (74.0 ± 7.6%, p < 0.05).*

Conclusions: *This first experimental bench model of pPCI in a bifurcation quantified thrombus trapping and embolization. BES provided the best thrombus trapping, while SAS and BES+POT achieved better final stent apposition. These factors should be taken into account in selecting revascularization strategy.* (Cardiol J 2024; 31, 1: 24–31)

Key words: primary percutaneous coronary intervention, trapped thrombus, embolized thrombus, nitinol self-apposing stent, provisional stenting

Introduction

Management of thrombus burden is one of the key-points in primary percutaneous coronary intervention (pPCI) during acute myocardial infarction. Distal thrombus embolization is directly correlated with cardiovascular prognosis, including final no-flow, stent thrombosis and death [1]. To limit this

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risk, direct stenting is strongly recommended [2]. At the same time, the pPCI is at risk of final stent malapposition, due to secondary resorption of thrombus "trapped" between stent and artery, and to acute ischemic vasoconstriction inducing stent undersizing [3]. Malapposition increases the risk of late stent thrombosis [4]. However, these concepts of thrombus embolization or "trapped" thrombus during the pPCI have never been clearly quantified.

Coronary bifurcation pPCI is even more complex [5]. The systematic difference in diameter between proximal and distal vessels, due to the fractal geometry [6], entails systematic proximal malapposition which usually needs to be corrected by post-dilatation. In the absence of thrombus burden, an initial proximal optimization technique (POT) is also recommended to correct these malappositions and to optimize the side-branch ostium [7]. But, in the specific context of pPCI, POT, like any post-dilatation, risks distal thrombus embolization in the branches. The mechanical properties of nitinol self-apposing stents (SAS) may, in bifurcation pPCI, enable spontaneous correction of proximal malapposition [8] without for need for POT [9], in contrast to balloon-expandable stent (BES) [10]. To date, all strategies to decrease thrombus burden before pPCI, whether mechanical thrombo-aspiration [11] or pharmacological resorption as minimalist immediate mechanical intervention (MIMI) strategy [12], failed to improve the clinical prognosis.

The present experimental bench study developed a new coronary bifurcation model to analyze thrombus behavior during pPCI according to procedural strategy and stent properties.

Methods

Experimental design

All experiments were performed in fractal left-main coronary bifurcation bench models [7] (Segula Technologies, Saint-Priest, France), with diameters 4.25 mm, 3.40 mm and 2.9 mm in the proximal main branch (MB), distal MB and side-branch (SB), respectively. Thrombus was generated in the MB, centered on the SB. Three provisional stenting strategies (Fig. 1) were compared (n = 10/group): 1) isolated BES (Synergy™, Boston Scientific, USA), 2) BES followed by POT, and 3) isolated SAS (Xposition S™, STENTYS, France). SASs were implanted after controlled opening of the protective sheath by balloon inflation at 12 atm, as recommended by the manufacturer. BES diameters and POT balloon inflation pressures were determined so as to obtain a proximal and distal stent-artery ratio between 1.0 and 1.1, as recommended (Fig. 1) [13].

After each stent implantation, saline serum was injected (200 mL) as coronary circulation. To quantify the "embolized" thrombus in the branches (distal MB and SB) during saline injection, all serum seeping from the branches was sieved, and trapped thrombus was weighed blind to the procedure. Experiments were concluded by pharmacological thrombolysis. During all experiments, the bench models were kept in a 37° bath under thermostat control.

Thrombus synthesis and thrombolysis

Blood samples were taken in an EDTA tube, from a single healthy subject without medication or medical history of bleeding or thrombosis (F.D.). Thrombus was generated by mixing 500 µL of blood with a pro-coagulant reagent associating 50 μL tissule factor (300 pM) (Innovin, Behring, Marburg, Germany) and 10 μL $CaCl_2$ (1 M). The mixture was directly injected into the bench model, always in the same position, according to marks, to obtain a homogeneous thrombus with 30 mm length (10 mm in the distal MB and 20 mm in the proximal MB). After 15 min, the thrombus was considered to be formed, and experimentation was performed (Fig. 2). At the end of all the experiments, thrombolysis solution (100 μL tPA; Actilyse, Boehringer, Ingelheim, France), diluted 50% in a Hepes-BSA tampon as previously described [14], was injected directly into the bench model for 24 h.

OCT analysis

Optical coherence tomography (OCT) acquisitions with the Lunawave™ OFDI system (Terumo Europe, Leuven, Belgium) were performed after the first saline wash and after complete thrombolysis at 24 h (Fig. 1). OCT analysis quantified lumen area, mean bench model diameter (D_{mean}) and stent diameter (D_{stent}). The stent-artery ratio was calculated as D_{stent}/D_{mean}. After millimetric cross-sectional stent analysis, global malapposition was calculated as percentage malapposed/total struts. Strut malapposition on OCT was defined by a 150 μm threshold (stent thickness + + OCT axial resolution). The trapped thrombus was estimated by blind computational planimetry on millimetric cross-sectional stent analysis as equal to $A_1/A_2 \times 100$ (with A_1 = thrombus area and A_2 = lumen area) (Figs. 3, 4).

Statistical analyses

Quantitative variables were expressed as mean ± standard deviation after confirmation

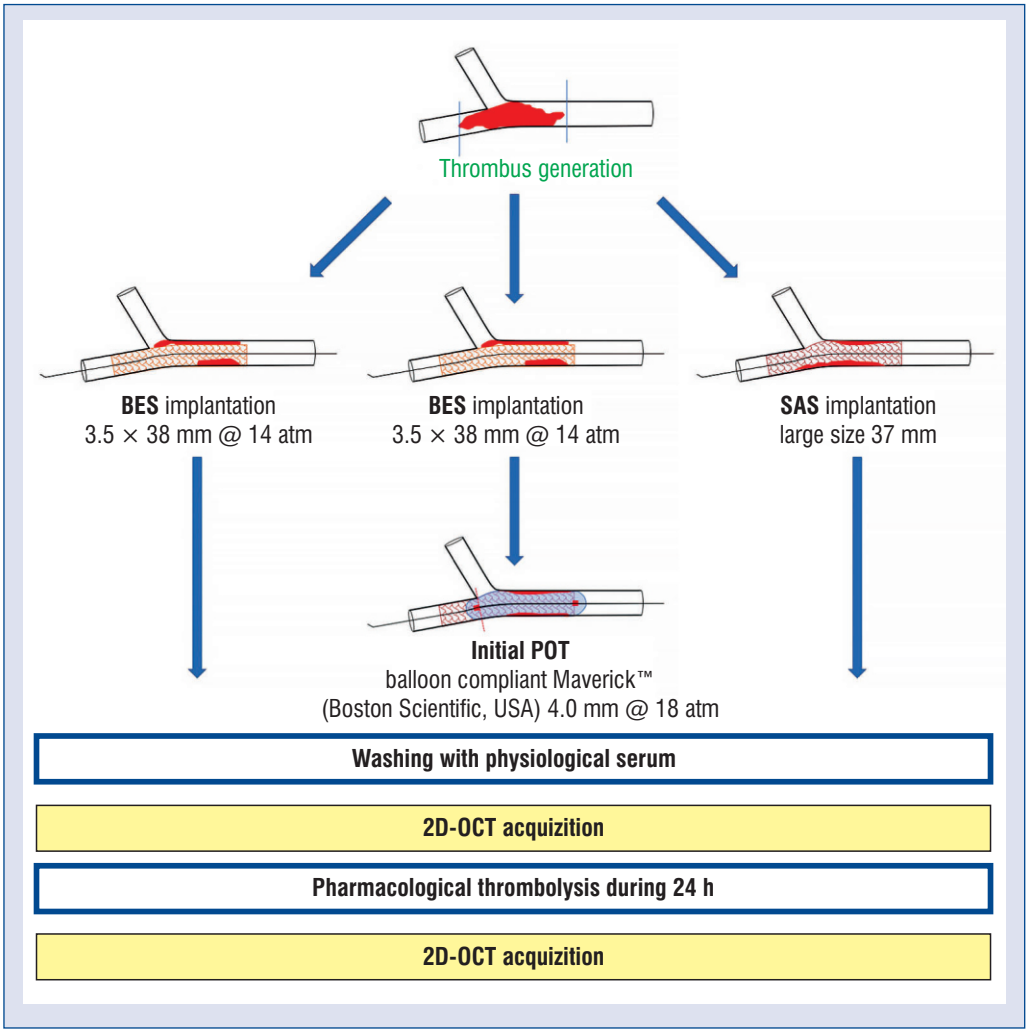

Figure 1. Study protocol; 2D — two-dimensional; BES — balloon-expandable stent; SAS — self-apposing stent; POT — proximal optimization technique; OCT — optical coherence tomography.

of normal distribution on the Shapiro-Wilk test. Quantitative effects were compared on ANOVA with Bonferroni correction and t-test, using SPSS® software, version 25 (IBM, NY, USA). The significance threshold was set at $p < 0.05$.

Results

All experiments (n = 30) were successfully completed. Table 1 and Figure 5 summarize the main results after isolated BES, BES+POT and SAS. Trapped thrombus was greater with isolated BES than with BES+POT or SAS (18.8 ± 5.8% vs. 10.3 ± 3.3% and 6.2 ± 2.1%, respectively; $p < 0.05$) and with BES+POT than with SAS ($p < 0.05$). This was in concordance with a trend for lower distal thrombus embolization in isolated BES and SAS (5.93 ± 4.32 mg and 5.05 ± 4.56 mg, respectively) than with BES+POT (7.01 ± 4.32 mg, p = NS) (Fig. 5).

At 24 h, after complete thrombolysis, final global stent apposition was optimal with both SAS and BES+POT, unlike with isolated BES (0.4 ± ± 0.6% and 1.3 ± 1.3% vs. 74.0 ± 7.6%, respectively, $p < 0.05$). Moreover, stent area in the mother vessel increased significantly after thrombolysis in the SAS group (+9.7%; $p < 0.05$) (Table 1), whereas with isolated BES and BES+POT, area and diameters were unchanged.

Discussion

According to available research, this bench study was the first experimental model specifically dedicated to analyzing thrombus behavior during pPCI, especially in coronary bifurcations. For the

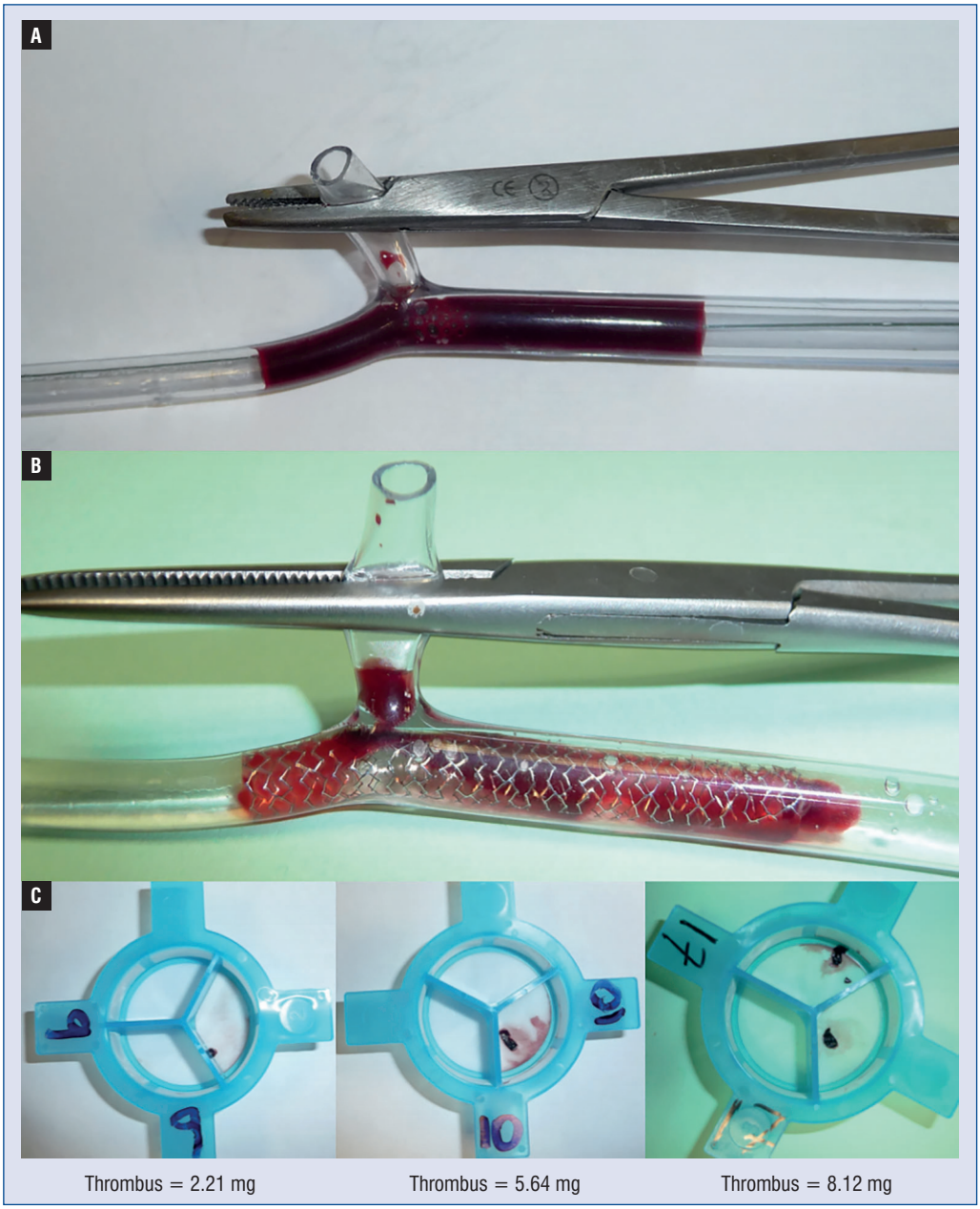

Figure 2. Bench experimentation; **A.** Thrombus before stent implantation; **B.** Residual thrombus after washing; **C.** Thrombus trapped in sieve.

first time, to the ability to confirm and quantify the concept of thrombus "trapping" and distal thrombus embolization following stent implantation was demonstrated. Thanks to this new model, comparing thrombus burden management according to different strategies and stents (BES or SAS) was shown. Thus, the trapped thrombus was greater in case of isolated BES than BES+POT or SAS, and in SAS than BES+POT. However, this greater trapping with isolated BES was at the cost of greater global malapposition, mainly proximal, as expected in light of the specific fractal geometry of coronary bifurcations. On the contrary, nitinol SAS and BES+POT both ensured perfect final apposition. Finally, thrombus embolization did not significantly differ between the three strategies, probably due to unexpected thrombus behavior during stent implantation and the relatively small sample sizes. However, there were trends for lower embolization in favor of isolated BES and SAS, in agreement with the greater thrombus trapping.

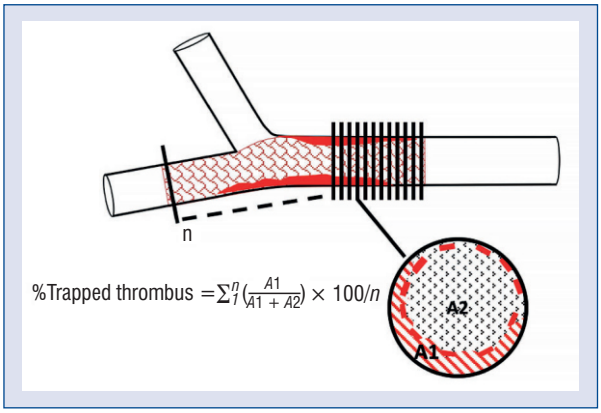

Figure 3. Quantification of trapped thrombus by computational planimetry by optical coherence tomography. Cross-sections were taken at each millimeter of the stent; A1 — thrombus area; A2 — complete lumen area.

Coronary bifurcation model

Specifically a fractal coronary bifurcation model was chosen in order to simulate the worst situation for thrombus management, given the differential of diameters between proximal and distal segments. In clinical practice, BES bifurcation revascularization requires systematic initial POT [7, 13] to correct the expected proximal malapposition [6]. Nitinol SAS experimentally demonstrated perfect spontaneous apposition in provisional stenting without need for specific bifurcation post-dilatation such as POT [9], and in contrast to balloon-expandable stents [7]. This may be useful in limiting the risk of embolization in the bench model. In this experimental model, exploring acute ischemic vasocontraction was not possible [3], which also increases the risk of global malapposition. However, according to the mechani-

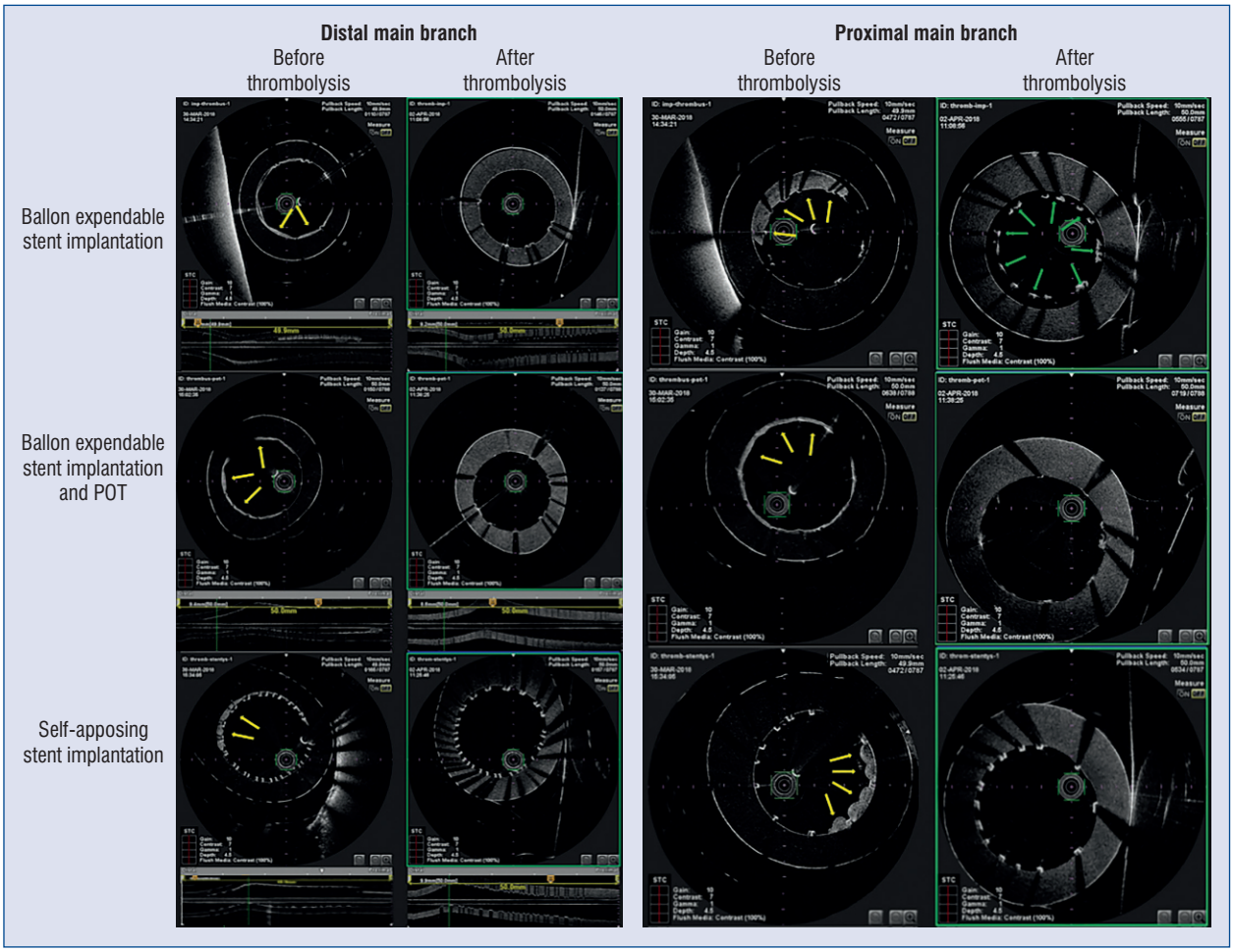

Figure 4. Optical coherence tomography acquisitions after provisional stenting in thrombus burden then after thrombolysis. Yellow arrows show thrombus, green arrows show malapposed struts; POT — proximal optimization technique.

Table 1. Balloon-expandable and self-apposing stent implantation in coronary bifurcation with thrombus burden (n = 10/group).

	Balloon-expandable Synergy™ alone	Balloon-expandable Synergy™ + POT	Self-apposing Xposition S™
After stent implantation in thrombus burden			
Mother vessel			
D_{mean} [mm]	4.07 ± 0.08	4.20 ± 0.04†	4.15 ± 0.10
D_{stent} [mm]	3.32 ± 0.09	4.17 ± 0.09†‡	4.06 ± 0.07†
Stent area [mm^2]	8.68 ± 0.47	13.66 ± 0.57†	12.95 ± 0.45†
Stent-artery ratio	0.82 ± 0.02	1.01 ± 0.03†	0.99 ± 0.03†
Main branch			
D_{mean} [mm]	3.37 ± 0.07	3.40 ± 0.09	3.34 ± 0.09
Stent area [mm^2]	8.90 ± 0.36	9.08 ± 0.49	8.80 ± 0.49
Stent-artery ratio	1.06 ± 0.03	1.08 ± 0.02	1.06 ± 0.02
Embolized thrombus mass [mg]	5.93 ± 4.32	7.01 ± 4.32	5.05 ± 4.56
Total thrombus trapping [%]	18.8 ± 5.8	6.2 ± 2.1†‡	10.3 ± 3.3†
Thrombus trapping MB	13.8 ± 4.4	6.8 ± 1.9†	8.9 ± 2.9†
Thrombus trapping MoV	19.6 ± 6.6	6.1 ± 2.2†‡	10.7 ± 4.6†
After complete thrombolysis			
Mother vessel			
D_{mean} [mm]	4.05 ± 0.09	4.20 ± 0.07†	4.25 ± 0.11†*
D_{stent} [mm]	3.36 ± 0.09	4.20 ± 0.09†	4.25 ± 0.11†*
Stent area [mm^2]	8.87 ± 0.47	13.85 ± 0.54†	14.20 ± 0.73†*
Stent-artery ratio	0.83 ± 0.03	1.02 ± 0.02†	1.03 ± 0.02†*
Main branch			
D_{mean} [mm]	3.34 ± 0.07	3.35 ± 0.08	3.42 ± 0.06†
Stent area [mm^2]	8.80 ± 0.48	8.84 ± 0.42	9.16 ± 0.23
Stent-artery ratio	1.06 ± 0.03	1.07 ± 0.03	1.07 ± 0.02
Global malapposition [%]	74.0 ± 7.6	1.3 ± 1.3†	0.4 ± 0.6†

Values are expressed as mean ± standard deviation; *p < 0.05 vs. before thrombolysis; †p < 0.05 vs. balloon-expandable stent alone; ‡p < 0.05 vs. self-apposing stent; D — diameter, MB — main branch; MoV — mother vessel

cal properties of nitinol, SAS seems to be able to optimize stent apposition secondarily by increasing the area and diameter, as seen after complete thrombolysis [8].

Embolized and trapped thrombus

According to available research, this is the time that this experimental model was able to quantify the trapped and embolized thrombus during stent implantation with large thrombus burden during pPCI. The best trapping and thus lowest embolization was obtained by BES implantation without post-dilatation, but at the cost of a greater final global malapposition after thrombolysis. On the other hand, final apposition was perfect with SAS or BES+POT, with better trapping for SAS (p > 0.05). This greater trapping was probably at least partly due to a greater metallic cover area with SAS Xposition S™ (20%) than DES Synergy™ (12%) (data provided by the manufacturers for a 3.5 mm stent at nominal pressure). Moreover, SAS implantation required only a single small-diameter inflation to open the sheath, compared to the larger stent balloons used for BES deployment and additional post-dilatation. Large balloon and successive inflations in thrombus burden exposes to distal embolization, by cutting the thrombus protruding in the lumen between struts. Even so, however, embolization did not significantly differ in these small samples. Importantly, the poorer crossing profile of SAS Xposition S™ compared with BES Synergy™ and the "brutal" sheath opening could also decrease the expected theoretic benefits for thrombus mobilization and/or embolization with SAS.

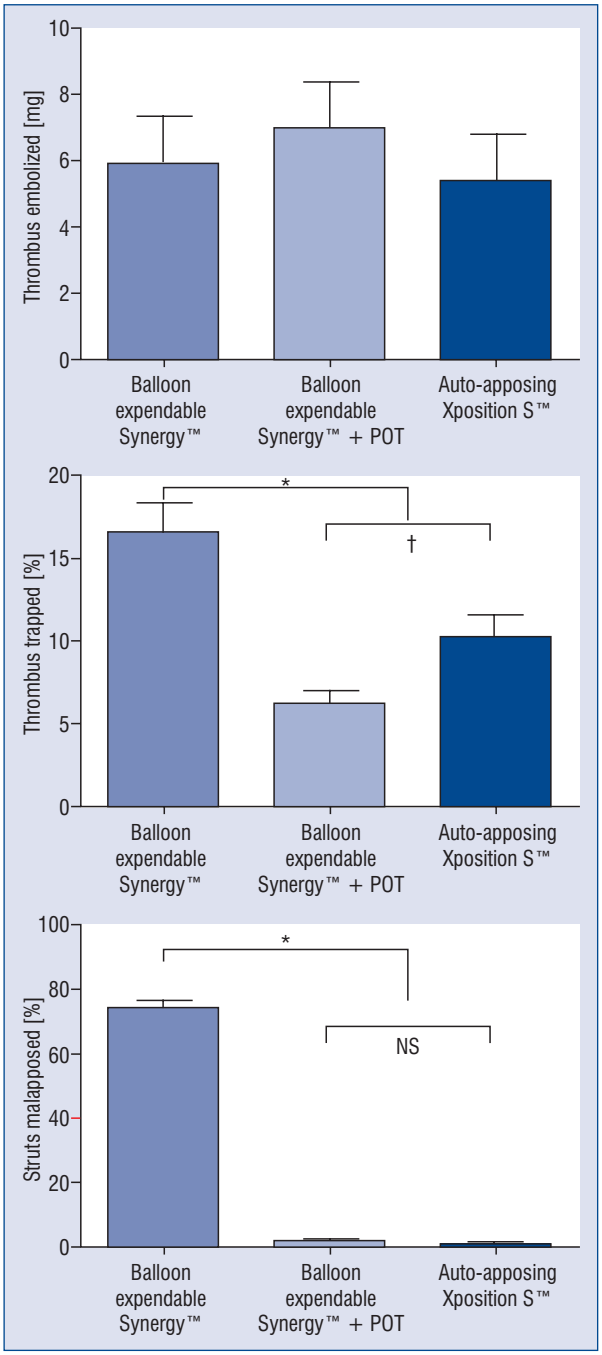

Figure 5. Main results after balloon-expandable and self-apposing stent provisional stenting in thrombus burden (n = 10/group); *p < 0.05 vs. balloon-expandable stent implantation alone; †p < 0.05 vs. balloon-expandable stent implantation plus proximal optimization technique (POT); NS — non significant.

Clinical implications

This first experimental demonstration of thrombus trapping and distal embolization must be taken into account in clinical practice, especially in case of large thrombus burden as found in large-diameter proximal arteries. Due to the higher risk of embolization, balloon inflation has to be cautious, and direct stenting should be preferred. Stent mobilization before implantation, because of the risk of positioning being destabilized by the thrombus, as observed in our experiments, has to be cautious and limited. SAS is no longer available, so when a BES is implanted in a bifurcation with high thrombus burden, especially in uncalcified lesions with large differences in diameter, final post-dilatation may be considered, to optimize apposition (as in POT) secondarily after the main pharmacological thrombus resorption, as in the MIMI strategy [12].

This first model is able to evaluate thrombus burden behavior (trapping, embolization) and could be useful for future evaluation of other new vascular devices or techniques specifically dedicated to acute artery reperfusion, in interventional cardiology or even neurology.

Limitations of the study

The main limitation of this study lay in the use of an experimental thrombus, unlike the usual formation after arterial wall plaque rupture. The potential effect of antithrombotic medication given in the acute phase of myocardial infarction was also not taken into account. All of this could influence thrombus structure and thus embolization and trapping mechanisms. However, in the present experiments, the thrombus behavior was close to that observed in clinical practice, and the OCT images were similar to those usually observed (Fig. 4).

Moreover, the model used herein is a non-pathological cylindrical bench model and thus did not reproduce the impact of atherosclerotic plaque on SAS deployment. Due to the low spontaneous expansion force of nitinol, global post-dilatation should be considered after SAS implantation, especially if the lesion was calcified or stiff, to avoid potential under-deployment due to a resistant lesion.

Conclusions

This first experimental coronary bifurcation model of pPCI in large thrombus burden confirmed and quantified the phenomena of thrombus trapping and embolization. Greater trapped thrombus was observed with the classic BES implantation without post-dilatation, at the cost of severe malapposition. Conversely, provisional stenting with the nitinol SAS achieved perfect apposition, as good as that of BES followed by POT, but with a high level of thrombus trapping.

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Conflict of interest: None declared

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Prolonged dual antiplatelet therapy in invasively treated acute coronary syndrome patients with different lipoprotein(a) concentrations

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Abstract

Background: *Lipoprotein(a) [Lp(a)] was positively associated with recurrent ischemic events in patients with acute coronary syndrome (ACS). This study was performed to investigate the effect of Lp(a) levels on outcomes of dual antiplatelet therapy (DAPT) > 1 year versus DAPT ≤ 1 year after percutaneous coronary intervention (PCI) in this population.*

Methods: *A total of 4,357 ACS patients who were event-free at 1 year after PCI were selected from the Fuwai PCI Registry, and patients were stratified into four groups according to DAPT duration (≤ 1 year vs. > 1 year) and Lp(a) levels (≤ 30 mg/dL vs. > 30 mg/dL). The primary endpoint was major adverse cardiovascular and cerebrovascular event (MACCE), defined as a composite of cardiac death, myocardial infarction or stroke.*

Results: *After 2.4-year follow-up, the incidence of MACCE (hazard ratio [HR]$_{adjusted}$ 0.284, 95% confidence interval [CI] 0.115–0.700; HR$_{IPTW}$ 0.351, 95% CI 0.164–0.751) were significantly reduced in DAPT > 1 year group than that in DAPT ≤ 1 year group in individuals with elevated Lp(a) levels. However, in individuals with normal Lp(a) levels, no statistically difference was found between these two groups in terms of MACCE, although the risks of all-cause death and definite/probable stent thrombosis were lower in DAPT > 1 year group. Notably, the risk of clinically relevant bleeding did not statistically differ between these two groups in individuals with different Lp(a) levels.*

Conclusions: *This study firstly demonstrated that extended DAPT (> 1 year) was statistically associated with lower risk of ischemic events in ACS patients with elevated Lp(a) levels after PCI, whereas this association was not found in individuals with normal Lp(a) levels.* (Cardiol J 2024; 31, 1: 32–44)

Keywords: lipoprotein(a), acute coronary syndrome, percutaneous coronary intervention, drug-eluting stent, dual antiplatelet therapy, prognosis

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Introduction

Lipoprotein(a) [Lp(a)] is an atherogenic low-density lipoprotein (LDL) subspecies, consisting of an LDL-like particle which apolipoprotein B100 is covalently linked to apolipoprotein(a) [apo(a)] [1, 2]. Over the last 10 years, genetic and epidemiologic evidence supported that high Lp(a) level was a risk factor for cardiovascular disease [3–6]. Moreover, previous studies, including the present authors, revealed that Lp(a) was positively associated with recurrent cardiovascular events in patients with acute coronary syndrome (ACS) who underwent percutaneous coronary intervention (PCI) [7–10]. However, there are no approved pharmacologic therapies that are specifically aimed at lowering Lp(a) levels. Actually, Lp(a) may result in a prothrombotic state due to the high degree of homology between apo(a) and plasminogen [2]. The ASPREE trial including 12,815 individuals showed that acetylsalicylic acid (ASA) may benefit older individuals with elevated Lp(a) genotypes in primary prevention [11]. In addition, similar results were obtained in the Women's Health Study [12]. Dual antiplatelet therapy (DAPT) with ASA plus a $P2Y_{12}$ inhibitor is prescribed for the prevention of thrombotic complications for patients with ACS after PCI. Current guidelines on DAPT from the United States and Europe recommend DAPT for ≥ 12 months after PCI in ACS patients who have tolerated DAPT without a bleeding complication and who are not at high-risk of bleeding [13]. Given the pathophysiological effect of apo(a), was speculated herein, that the extended duration of DAPT after PCI may reduce the risk of ischemic events for ACS patients who had elevated Lp(a) levels. Therefore, this study was performed to evaluate the impact of Lp(a) levels on clinical outcomes of extended DAPT (> 1 year) versus shortened DAPT (≤ 1 year) in ACS patients who underwent PCI with drug-eluting stent (DES).

Methods

Study design and population

This was a secondary analysis of a single-center, prospective registry and details on the study design have been published elsewhere [7, 14–16]. Briefly, 10,724 patients with coronary artery disease (CAD) who underwent PCI were consecutively enrolled between January 2013 and December 2013 from FuWai Hospital, National Center for Cardiovascular Diseases. The study was performed according to the principles of the Declaration of Helsinki and the study protocol had been approved by the ethical committee of Fuwai Hospital, National Center for Cardiovascular Diseases. All the participants provided written informed consent before enrollment. In addition, patient records were anonymized and de-identified before database merging and analysis.

In this paper, 3,607 patients with stable CAD, 28 patients who did not receive DAPT, 369 patients who did not use DES, and 848 patients who experienced major adverse events (death, myocardial infarction [MI], stent thrombosis [ST], stroke, repeat revascularization, or Bleeding Academic Research Consortium [BARC] type 2, 3 or 5 bleeding) within 1 year follow-up were excluded. In addition, 1,515 patients were excluded due to the reasons listed in Figure 1. For the final analysis, 4,357 ACS patients who were event-free at 1 year after PCI were evaluated.

Study procedures and biochemical analysis

After an overnight fasting before PCI, laboratory samples were obtained from each participant and all tests were performed through clinical chemistry department of the present center. Concentrations of Lp(a), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and total cholesterol were analyzed with the automated biochemical analyzer (Hitachi 7150, Tokyo, Japan), while hemoglobin A1c was measured with the Tosoh Automated Glycohemoglobin Analyser (HLC-723G8; Tosoh Corporation, Tokyo, Japan). Measurements were Lp(a) by the immunoturbidimetry method [LASAY Lp(a) auto; SHIMA Laboratories Co., Ltd, Tokyo, Japan] with a normal cutoff value of < 30 mg/dL. An Lp(a) protein validated standard was used to calibrate the examination, and the coefficient of variation for repetitive measurements was < 10% [17].

During hospitalization, all procedures and medical therapies were performed in compliance with contemporary guideline recommendations and the cardiologist's discretion. Demographics, cardiovascular risk factors, clinical parameters, laboratory results, angiographic and procedural details, and medications were prospectively recorded in our dedicated PCI registry by independent research personnel. Definitions of diabetes, hypertension, dyslipidemia and other variables were in compliance with previous studies [7, 15, 16].

Based on DAPT duration, patients were divided into DAPT > 1 year group and DAPT ≤ 1 year group. Notably, previous meta-analyses and current Chinese guidelines for the management

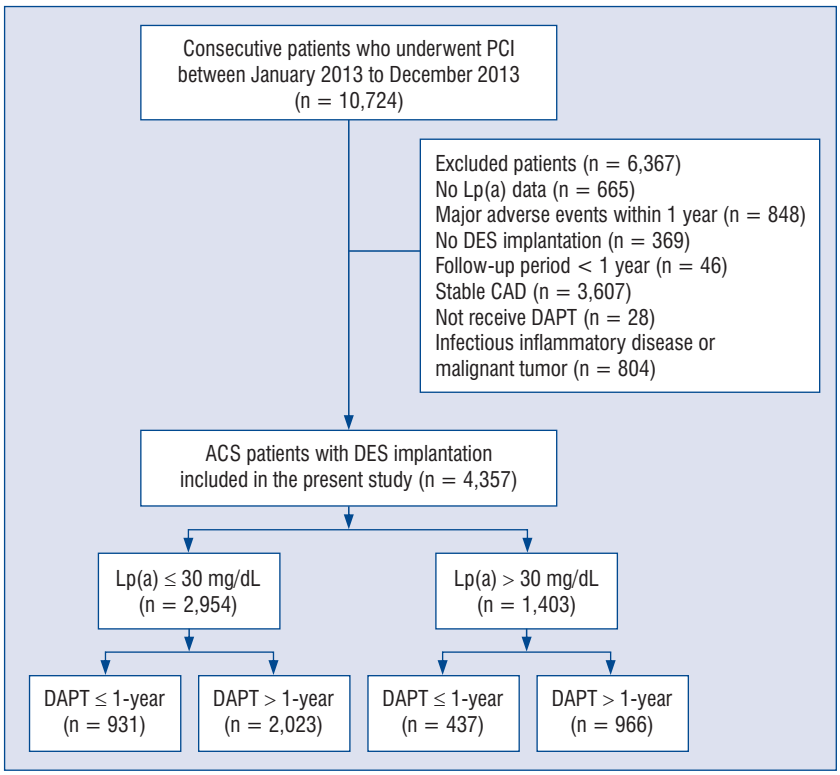

Figure 1. Flow chart of the study; ACS — acute coronary syndrome; CAD — coronary artery disease; DAPT — dual antiplatelet therapy; DES — drug-eluting stent; PCI — percutaneous coronary intervention.

of dyslipidemia in adults suggested that Lp(a) concentrations > 30 mg/dL were associated with a progressive increase in the incidence of cardiovascular events [1, 4, 18, 19]. In this paper, a threshold value of 30 mg/dL was used to assign abnormal Lp(a) levels. Then, patients were stratified into four groups according to the DAPT duration (≤ 1 year vs. > 1 year) and Lp(a) levels (≤ 30 mg/dL vs. > 30 mg/dL).

Follow-up and endpoints

After PCI, patients were followed up at 6-month intervals until January, 2016. Data for endpoints were collected from medical records, clinical visits, and/or telephone interviews by trained investigators who were blind to the clinical data. Of note, adherence to antiplatelet medication was routinely assessed at each time of follow-up, and the status of antiplatelet therapy was collected by dedicated questionnaires and the electronic prescribing system at the present center. The primary endpoint was major adverse cardiovascular and cerebrovascular event (MACCE), defined as a composite of cardiac death, nonfatal MI or stroke. The individual components of the primary endpoint, all-cause death, definite or probable ST, and BARC type 2, 3 or 5 bleeding were secondary endpoints. All deaths were considered to be cardiac-related unless a non-cardiac origin was documented. MI was defined based on the Third Universal Definition of MI [20]. Stroke was defined as new focal neurological deficit lasting > 24 hours and confirmed by imaging evidence. Definite or probable ST was adjudicated based on the Academic Research Consortium criteria [21]. In addition, bleeding events were categorized based on the BARC classifications [22]. All events must be validated by source documents.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation and differences in various characteristics were compared using the Student's t-test or Wilcoxon's rank sum test, when appropriate. Categorical variables were expressed as frequencies (percentages) and compared using Pearson's chi-square test or the Fisher exact test, when appropriate. Cumulative incidence of clinical outcomes was estimated using Kaplan-Meier curves, and differences were evaluated with the log-rank test. Univariable and multivariable Cox regression analyses were performed to calculate

hazard ratios (HRs) and 95% confidence intervals (CIs). In addition, an inverse probability of treatment weighting (IPTW) analysis was also conducted to adjust for differences in baseline characteristics between DAPT ≤ 1 year and DAPT > 1 year groups in overall population, individuals with normal Lp(a) levels, and individuals with elevated Lp(a) levels, respectively. A propensity score was developed using a non-parsimonious multivariable logistic regression model and considering DAPT time (DAPT > 1 year vs. DAPT ≤ 1 year) as the dependent variable. Covariates used for the propensity score model and multivariable Cox regression model were age, gender, body mass index, current smoking, diabetes, hypertension, dyslipidemia, previous MI, previous stroke, peripheral vascular disease, left ventricular ejection fraction < 50%, LDL-C, HDL-C, radial artery access, multivessel disease, severe calcification, total lesion length, minimum stent diameter, total stent length, and use of statin at discharge. All statistical analyses were conducted using SPSS version 23.0 (SPSS Inc., Chicago, IL, USA) and R version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria). A two-sided p value of < 0.05 was considered to indicate statistical significance.

Results

Of the eligible participants, 1,368 received DAPT ≤ 1 year and 2,989 received DAPT > 1 year, while 2,954 had normal Lp(a) levels and 1,403 had elevated Lp(a) levels (Fig. 1). Overall, patients who received DAPT > 1 year were more likely to have a history of dyslipidemia, multivessel disease, severe calcification, and smaller minimum stent diameter during PCI than those who received DAPT ≤ 1 year. Furthermore, at any time-point of follow-up, the use of ASA and $P2Y_{12}$ receptor inhibitor was significantly more frequent in DAPT > 1 year group than that in DAPT ≤ 1 year group (**Suppl. Table S1**). As shown in Table 1, baseline patient, angiographic and procedural characteristics were mostly similar between DAPT ≤ 1 year and DAPT > 1 year groups in both patients with normal Lp(a) levels and elevated Lp(a) levels. Similar to the overall ACS population, patients in DAPT > 1 year group were more likely to receive ASA and $P2Y_{12}$ receptor inhibitor than those in DAPT ≤ 1 year group in both patients with normal Lp(a) levels and elevated Lp(a) levels at any time-point of follow-up. The median follow-up period was 877 (807–942) days.

DAPT duration and clinical outcomes

Compared with patients who received DAPT ≤ 1 year, those who received DAPT > 1 year presented lower risks of MACCE, all-cause death, cardiac death, and definite/probable ST (Fig. 2; **Suppl. Table S2**). In Figure 3, all the candidate variables were well balanced between the DAPT ≤ 1 year group and DAPT > 1 year group after IPTW analysis. The risks of MACCE, all-cause death, cardiac death, and definite/probable ST were also significantly lower in extended DAPT group than that in shortened DAPT group. Notably, no significant difference was found between the two groups in terms of clinically relevant bleeding (**Suppl. Table S2**).

Extended DAPT vs. shortened DAPT in patients with different Lp(a) levels

In individuals with elevated Lp(a) levels, the incidence of 2.4-year MACCE was significantly lower in DAPT > 1 year group than that in DAPT ≤ 1 year group (1.2% vs. 2.7%; adjusted HR 0.284, 95% CI 0.115–0.700). In addition, patients in DAPT > 1 year group also presented lower risks of all--cause death, cardiac death, stroke, and definite/ /probable ST than those in DAPT ≤ 1 year group. Moreover, the risk of clinically relevant bleeding did not statistically differ between the extended DAPT and shortened DAPT groups (Fig. 4A, **Suppl. Fig. S1, Suppl. Table S2**).

In contrast, no statistically difference was found between DAPT > 1 year and DAPT ≤ 1 year groups in terms of the primary endpoint of MACCE at 2.4 years (1.3% vs. 2.0%; adjusted HR 0.736, 95% CI 0.374–1.449) in individuals with normal Lp(a) levels. Patients in DAPT > 1 year group had lower risks of all-cause mortality, and definite/ /probable ST compared with those in DAPT ≤ 1 year group. The risk of BARC type 2, 3 or 5 bleeding in extended DAPT group did not significantly differ from that in shortened DAPT group (Fig. 4B, **Suppl. Fig. S1, Suppl. Table S2**).

In IPTW analysis, all the candidate variables were well balanced between the DAPT ≤ 1 year and DAPT > 1 year groups in both the patients with normal and elevated Lp(a) levels (Fig. 3). Consistent with the results of multivariable Cox regression analysis, it suggested lower risks of MACCE and all-cause death in DAPT > 1 year group than that in DAPT ≤ 1 year group in individuals with elevated Lp(a) levels (Fig. 4A). In individuals with normal Lp(a) levels, the risk of MACCE did not statistically differ between DAPT > 1 year and DAPT ≤ 1 year groups, while extended DAPT was associated with lower risk of all-cause death and definite/probable ST in these patients (Fig. 4B).

Table 1. Baseline patient, angiographic and procedural characteristics according to lipoprotein(a) [Lp(a)] levels and dual antiplatelet therapy (DAPT) duration.

Variable	Lp(a) ≤ 30 mg/dL (n = 2954)			Lp(a) > 30 mg/dL (n = 1403)		
	DAPT ≤ 1-year (n = 931)	DAPT > 1-year (n = 2023)	P	DAPT ≤ 1-year (n = 437)	DAPT > 1-year (n = 966)	P
Age [years]	58 (50–65)	58 (50–65)	0.775	58 (50–65)	58 (50–64)	0.779
Male	755 (81.1%)	1674 (82.7%)	0.275	352 (80.5%)	750 (77.6%)	0.219
Body mass index [kg/m^2]	26.0 (23.9–27.8)	26.0 (24.0–28.0)	0.484	25.5 (23.5–27.7)	25.5 (23.7–27.7)	0.490
Current smoker	557 (59.8%)	1275 (63.0%)	0.096	275 (62.9%)	557 (57.7%)	0.063
Diabetes mellitus	376 (40.4%)	833 (41.2%)	0.685	177 (40.5%)	361 (37.4%)	0.264
Hypertension	583 (62.6%)	1240 (61.3%)	0.491	273 (62.5%)	622 (64.4%)	0.489
Dyslipidemia	605 (65.0%)	1334 (65.9%)	0.611	265 (60.6%)	664 (68.7%)	**0.003**
Previous myocardial infarction	116 (12.5%)	283 (14.0%)	0.259	59 (13.5%)	121 (12.5%)	0.613
Previous PCI	169 (18.2%)	395 (19.5%)	0.378	92 (21.1%)	204 (21.1%)	0.978
Previous CABG	31 (3.3%)	69 (3.4%)	0.910	20 (4.6%)	40 (4.1%)	0.709
Previous stroke	77 (8.3%)	197 (9.7%)	0.202	49 (11.2%)	94 (9.7%)	0.396
Peripheral vascular disease	14 (1.5%)	50 (2.5%)	0.093	7 (1.6%)	21 (2.2%)	0.478
Chronic kidney disease	85 (9.1%)	214 (10.6%)	0.226	35 (8.0%)	95 (9.8%)	0.275
COPD	23 (2.5%)	48 (2.4%)	0.872	15 (3.4%)	19 (2.0%)	0.098
LVEF [%]	64 (60–68)	64 (60–68)	0.551	64 (60–68)	64 (60–68)	0.652
LVEF < 50%	40 (4.4%)	79 (4.0%)	0.590	17 (4.0%)	34 (3.7%)	0.763
Systolic blood pressure [mmHg]	125 (120–140)	125 (120–138)	0.812	120 (115–137)	120 (115–140)	0.466
Laboratory data:						
WBC [10^3/μL]	6.51 (5.55–7.79)	6.55 (5.51–7.79)	0.968	6.46 (5.51–7.66)	6.64 (5.61–7.94)	0.167
Hemoglobin [g/L]	145 (135–155)	146 (136–155)	0.410	145 (135–156)	145 (135–154)	0.772
TC [mmol/L]	3.94 (3.38–4.71)	3.96 (3.36–4.69)	0.772	4.14 (3.55–4.89)	4.22 (3.60–4.97)	0.171
LDL-C [mmol/L]	2.26 (1.79–2.89)	2.27 (1.79–2.88)	0.842	2.47 (1.98–3.09)	2.53(2.00–3.20)	0.315
HDL-C [mmol/L]	0.99 (0.85–1.16)	0.96 (0.81–1.15)	**0.016**	1.02 (0.86–1.17)	1.01 (0.86–1.23)	0.729
HbA1c [%]	6.2 (5.8–6.8)	6.2 (5.8–6.9)	0.670	6.1 (5.7–6.8)	6.2 (5.8–6.9)	0.252
Lp(a) [mg/dL]	10.1 (4.9–17.9)	10.5 (5.2–17.7)	0.400	54.0 (39.1–81.5)	53.8 (39.5–81.2)	0.654
Radial artery access	883 (94.8%)	1871 (92.5%)	**0.018**	411 (94.1%)	893 (92.4%)	0.276
Multivessel disease	639 (68.6%)	1450 (71.7%)	0.092	315 (72.1%)	721 (74.6%)	0.313

→

Table 1 (cont.). Baseline patient, angiographic and procedural characteristics according to lipoprotein(a) [Lp(a)] levels and dual antiplatelet therapy (DAPT) duration.

Variable	Lp(a) ≤ 30 mg/dL (n = 2954)			Lp(a) > 30 mg/dL (n = 1403)		
	DAPT ≤ 1-year (n = 931)	DAPT > 1-year (n = 2023)	P	DAPT ≤ 1-year (n = 437)	DAPT > 1-year (n = 966)	P
SYNTAX score	9 (6–15)	9 (5–15)	0.643	10 (7–17)	10 (6–16)	0.203
SYNTAX score > 22	75 (8.2%)	168 (8.5%)	0.803	45 (10.7%)	90 (9.6%)	0.549
Total lesion length [mm]	28 (18–47)	30 (18–48)	0.282	30 (20–50)	32 (20–48)	0.962
Target lesion morphology:						
Bifurcation lesion	186 (20.0%)	371 (18.3%)	0.290	87 (19.9%)	187 (19.4%)	0.810
2-stent technique	39 (4.2%)	83 (4.1%)	0.913	18 (4.1%)	41 (4.2%)	0.914
Chronic total occlusion	134 (14.4%)	314 (15.5%)	0.427	73 (16.7%)	165 (17.1%)	0.862
In-stent restenosis	36 (3.9%)	90 (4.4%)	0.467	19 (4.3%)	42 (4.3%)	1.000
Severe calcification	16 (1.7%)	60 (3.0%)	**0.047**	7 (1.6%)	32 (3.3%)	0.071
Angulation > 45 degrees	104 (11.2%)	193 (9.5%)	0.171	47 (10.8%)	96 (9.9%)	0.639
Type B2 or C lesion	691 (74.2%)	1484 (73.4%)	0.620	341 (78.0%)	736 (76.2%)	0.449
No. vessels treated	1 (1–1)	1 (1–1)	0.161	1 (1–2)	1 (1–2)	0.780
No. lesions treated	1 (1–2)	1 (1–2)	0.421	1 (1–2)	1 (1–2)	0.944
No. lesions treated ≥ 3	58 (6.2%)	131 (6.5%)	0.800	27 (6.2%)	60 (6.2%)	0.981
Drug-eluting stent number	2 (1–2)	2 (1–2)	0.116	2 (1–2)	2 (1–2)	0.432
Drug-eluting stent number ≥ 3	184 (19.8%)	415 (20.5%)	0.637	92 (21.1%)	203 (21.0%)	0.987
Use of EES/ZES	513 (55.1%)	1153 (57.0%)	0.335	250 (57.2%)	534 (55.3%)	0.500
Minimum stent diameter [mm]	3.00 (2.50–3.50)	3.00 (2.50–3.50)	0.193	3.00 (2.50–3.50)	2.75 (2.50–3.00)	0.075
Total stent length [mm]	33 (23–51)	33 (21–52)	0.444	34 (23–54)	36 (23–52)	0.923
DAPT score	2 (1–3)	2 (1–3)	0.057	2 (1–3)	2 (1–3)	0.205
DAPT score ≥ 2	511 (54.9%)	1187 (58.7%)	0.053	262 (60.0%)	562 (58.2%)	0.531
Medications at discharge:						
ASA	931 (100%)	2023 (100%)	NA	437 (100%)	966 (100%)	NA
$P2Y_{12}$ receptor inhibitor	931 (100%)	2023 (100%)	NA	437 (100%)	966 (100%)	NA
Oral anticoagulant	4 (0.6%)	3 (0.2%)	0.241	0 (0%)	1 (0.2%)	1.000
Beta-blockers	811 (87.1%)	1780 (88.0%)	0.500	394 (90.2%)	864 (89.4%)	0.682
Statins	889 (95.5%)	1948 (96.3%)	0.298	423 (96.8%)	925 (95.8%)	0.352
Calcium channel blockers	459 (49.3%)	1029 (50.9%)	0.430	229 (52.4%)	510 (52.8%)	0.892

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Table 1 (cont.). Baseline patient, angiographic and procedural characteristics according to lipoprotein(a) [Lp(a)] levels and dual antiplatelet therapy (DAPT) duration.

Variable	Lp(a) ≤ 30 mg/dL (n = 2954)			Lp(a) > 30 mg/dL (n = 1403)		
	DAPT ≤ 1-year (n = 931)	DAPT > 1-year (n = 2023)	P	DAPT ≤ 1-year (n = 437)	DAPT > 1-year (n = 966)	P
Antiplatelet drugs at 6 months:	N = 931	N = 2023		N = 437	N = 966	
ASA	919 (98.7%)	2023 (100%)	< 0.001	432 (98.9%)	966 (100%)	**0.003**
$P2Y_{12}$ receptor inhibitor	915 (98.3%)	2023 (100%)	**< 0.001**	432 (98.9%)	966 (100%)	**0.003**
Antiplatelet drugs at 12 months:	N = 931	N = 2023		N = 437	N = 966	
ASA	887 (95.3%)	2023 (100%)	**< 0.001**	423 (96.8%)	966 (100%)	**< 0.001**
$P2Y_{12}$ receptor inhibitor	854 (91.7%)	2023 (100%)	**< 0.001**	398 (91.1%)	966 (100%)	**< 0.001**
Antiplatelet drugs at 18 months:	N = 931	N = 2023		N = 437	N = 965	
ASA	846 (90.9%)	2015 (99.6%)	**< 0.001**	408 (93.4%)	959 (99.4%)	**< 0.001**
$P2Y_{12}$ receptor inhibitor	23 (2.5%)	1829 (90.4%)	**< 0.001**	15 (3.4%)	861 (89.2%)	**< 0.001**
Antiplatelet drugs at 24 months:	N = 930	N = 2014		N = 437	N = 962	
ASA	841 (90.4%)	1973 (98.0%)	**< 0.001**	407 (93.1%)	943 (98.0%)	**< 0.001**
$P2Y_{12}$ receptor inhibitor	19 (2.0%)	840 (41.7%)	**< 0.001**	13 (3.0%)	408 (42.4%)	**< 0.001**
Antiplatelet drugs at 30 months:	N = 239	N = 779		N = 104	N = 367	
ASA	206 (86.2%)	763 (97.9%)	**0.003**	89 (85.6%)	361 (98.4%)	**< 0.001**
$P2Y_{12}$ receptor inhibitor	5 (2.1%)	230 (29.5%)	< 0.001	4 (3.8%)	104 (28.3%)	**< 0.001**
DAPT time [days]	349 ± 62	661 ± 164	**< 0.001**	348 ± 60	661 ± 163	**< 0.001**
	365 (365, 365)	548 (548, 802)		365 (365, 365)	548 (548, 790)	

ASA — acetylsalicylic acid; CABG — coronary artery bypass grafting; COPD — chronic obstructive pulmonary disease; DAPT — dual antiplatelet therapy; EES — everolimus-eluting stent; HDL-C — high-density lipoprotein cholesterol; LDL-C — low-density lipoprotein cholesterol; LVEF — left ventricular ejection fraction; PCI — percutaneous coronary intervention; TC — total cholesterol; WBC — white blood cell; ZES — zotarolimus-eluting stent

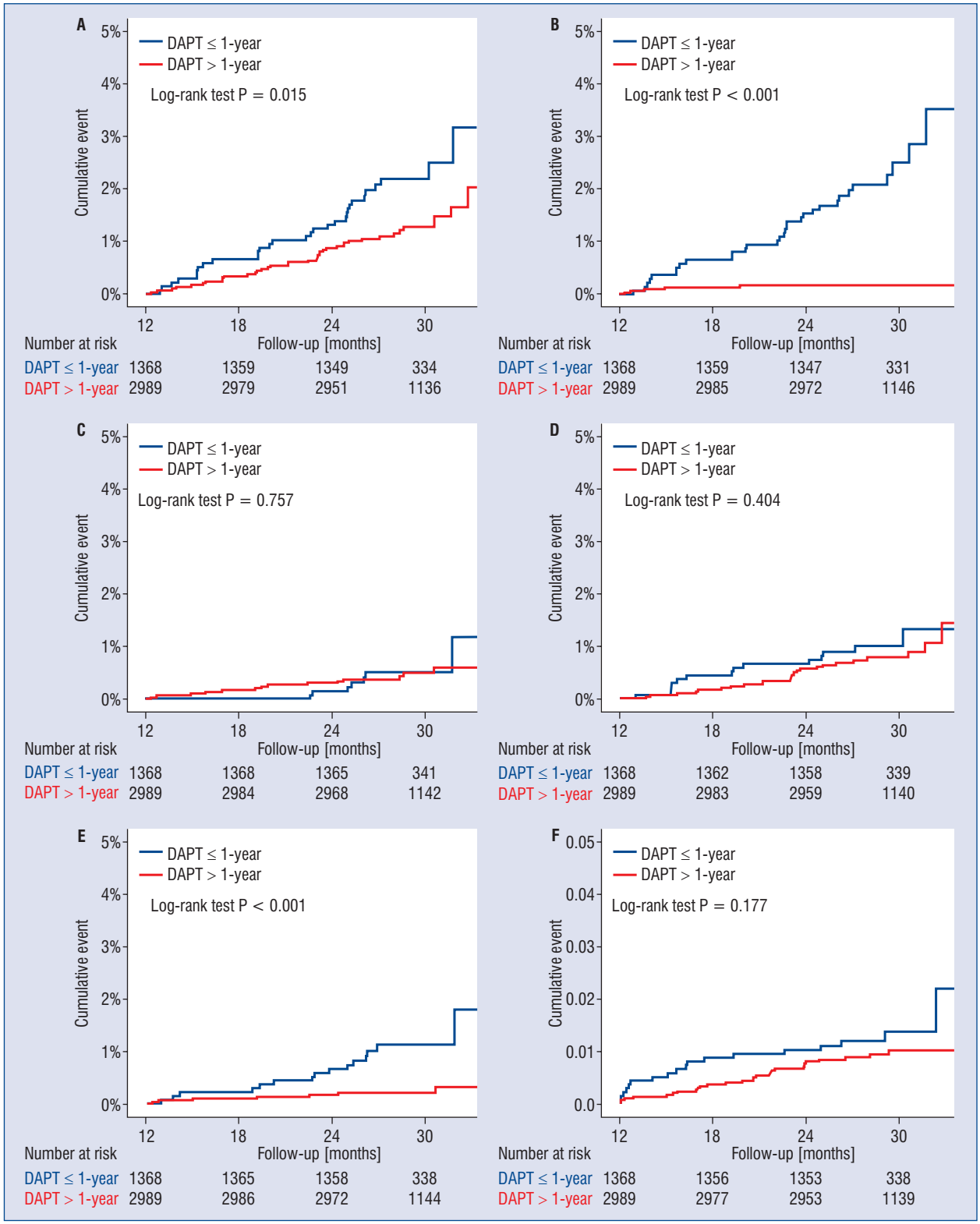

Figure 2. Kaplan–Meier curves for 2.4-year clinical outcomes according to dual antiplatelet therapy (DAPT) duration in overall population; **A.** Cardiac death/MI/stroke; **B.** All-cause death; **C.** MI; **D.** Stroke; **E.** Definite/probable ST; **F.** BARC type 2, 3 or 5 bleeding; BARC — Bleeding Academic Research Consortium; MI — myocardial infarction; ST — stent thrombosis.

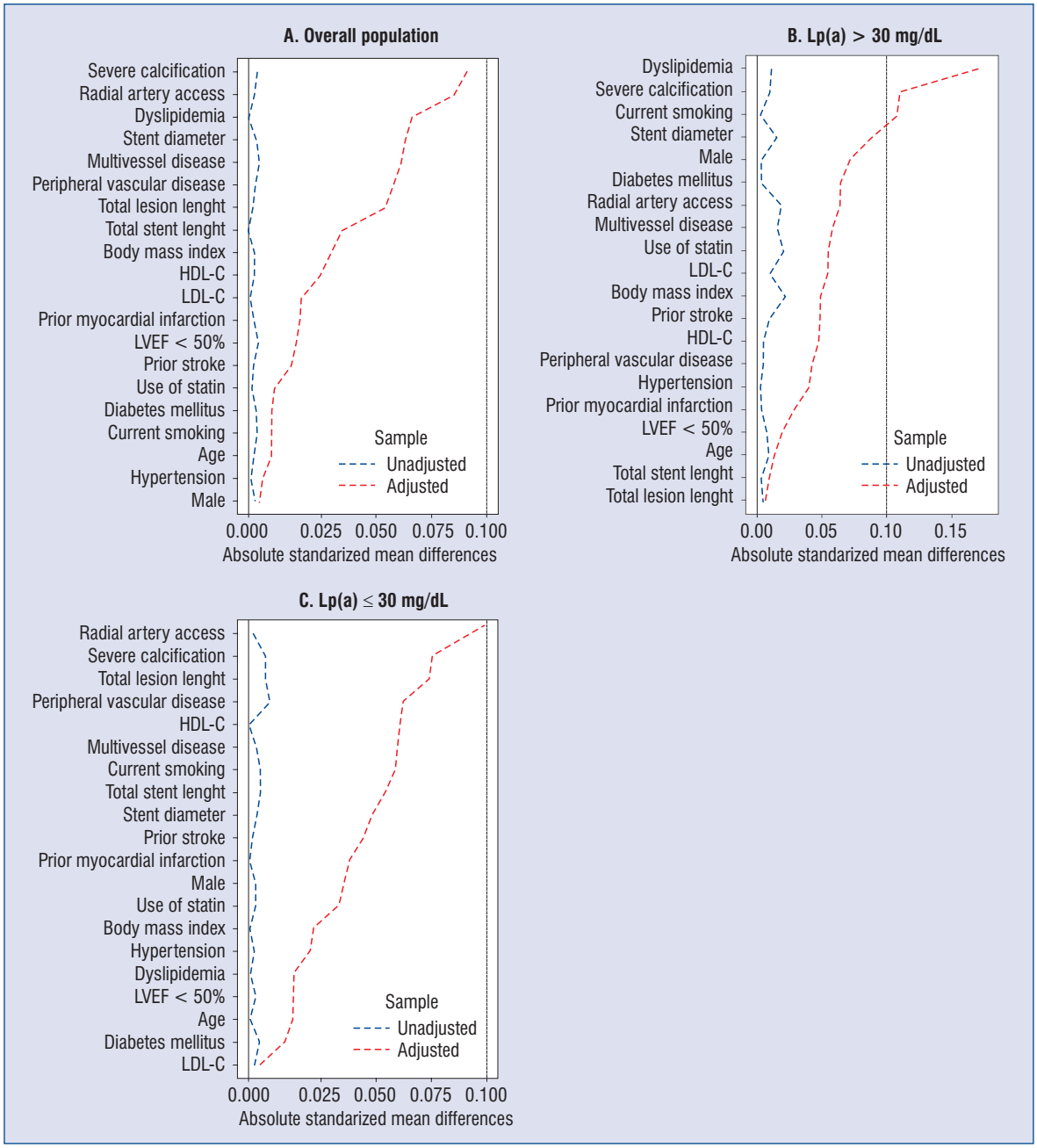

Figure 3. Absolute standard difference before and after inverse probability of treatment weighting analysis between the dual antiplatelet therapy (DAPT) > 1 year and DAPT ≤ 1 year groups in (**A**) overall population (**B**) patients with lipoprotein(a) [Lp(a)] levels > 30 mg/dL and (**C**) patients with Lp(a) levels ≤ 30 mg/dL, respectively; HDL-C — high--density lipoprotein cholesterol; LDL-C — low-density lipoprotein cholesterol; LVEF — left ventricular ejection fraction.

Discussion

The present study is the first to specifically evaluate the effect of Lp(a) concentrations on the clinical outcomes of extended DAPT among a cohort of consecutive ACS patients after PCI. The major findings are as follows: (1) Extended DAPT contributed to the reduction of cardiovascular events without statistically increasing clinically relevant bleeding events in patients with ACS after PCI with DES; (2) The clinical benefit of extended DAPT was more pronounced in individuals with Lp(a) > 30 mg/dL, whereas in individuals with Lp(a) ≤ 30 mg/dL, extended DAPT did not show significant evidence of benefit in reducing the composite endpoint of MACCE.

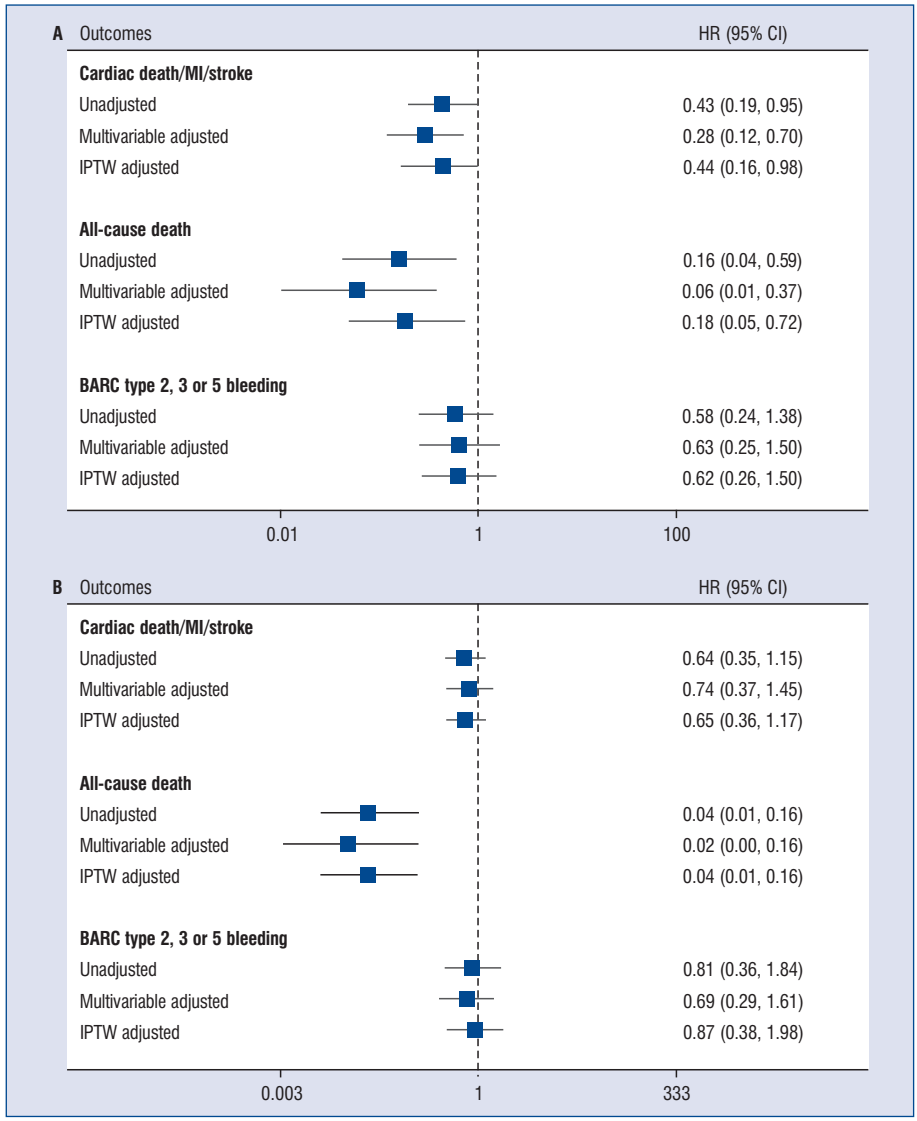

Figure 4. Unadjusted and adjusted association between dual antiplatelet therapy duration and main clinical outcomes in patients with (**A**) lipoprotein(a) [Lp(a)] levels > 30 mg/dL and (**B**) Lp(a) levels ≤ 30 mg/dL, respectively; BARC — Bleeding Academic Research Consortium; CI — confidence interval; IPTW — inverse probability of treatment weighting; HR — hazard ratio; MI — myocardial infarction.

Lipoprotein(a) is a lipoprotein particle formed by adding a carbohydrate-rich protein, i.e., apo(a), to apoB-100 on LDL particles via disulfide bonds. Although not fully understood, Lp(a) potentially contributes to cardiovascular disease through proatherogenic effects of its LDL-like moiety, prothrombotic effects through its plasminogen--like apo(a), and proinflammatory effects of its oxidized phospholipid content. Actually, there was overwhelming evidence from epidemiology and genetics that Lp(a) was an independent predictor of cardiovascular disease [1, 2]. For example, a large-scare meta-analysis including 126,634 patients confirmed a strong relationship between high Lp(a) levels and the incidence of CAD and stroke [4]. Furthermore, several studies demonstrated that high Lp(a) levels were associated with an increased risk of long-term recurrent cardiovascular events in patients undergoing PCI or with ACS. Based on data of 10,059 patients undergoing PCI (including 5923 ACS patients), it was found that Lp(a) > 30 mg/dL was positively related to higher risk of MACCE (death, MI, stroke or unplanned revascularization) at 2.4-year follow-up [7]. Konishi et al. [8] reported that elevated Lp(a) levels were significantly associated with higher incidence of

4.7-year cardiac death or ACS for diabetic patients who received PCI. Moreover, a study with 988 ACS patients who achieved target lipid levels suggested that Lp(a) was positively related to the composite endpoint of death, MI, or target vessel revascularization during 29-month follow-up [9].

One potential therapeutic approach to reduce the Lp(a)-associated poor prognosis is to reduce Lp(a) concentrations. Nevertheless, traditional lipid-lowering agents have little or moderate effect on reducing Lp(a) levels. Currently, there are no approved pharmacotherapies specifically targeting high Lp(a) concentrations. A post hoc analysis of the ODYSSEY OUTCOMES trial found a clinical benefit of PCSK9 inhibitors in ACS patients, however, the clinical benefit of PCSK9 inhibitors by reducing Lp(a) levels was very low [23]. Although a hepatocyte directed antisense oligonucleotides, APO(a)-L_{Rx}, could largely reduce the Lp(a) levels in patients with cardiovascular disease, whether it will provide clinical benefit remains to be seen [24]. Indeed, previous studies speculated that a reduction of 50–100 mg/dL in Lp(a) may be required to obtain significant clinical benefit [25–27]. However, many large-scale studies revealed that the incidences of cardiovascular events in participants with Lp(a) levels ranged from 30 mg/dL to 50 mg/dL are also very high, and these patients may not benefit from Lp(a)-lowering therapies [1, 4, 7, 18].

Due to the high degree of homology between apo(a) and plasminogen, Lp(a) potentiates thrombosis through inhibiting plasminogen activation and fibrin degradation, and promoting endothelial plasminogen activator inhibitor expression, tissue factor pathway inhibitor activity, and platelet reactivity [2]. The ASPREE trial enrolled 12,815 individuals without prior cardiovascular disease, and it reported that rs3798220-C carrier status or high LPA-GRS was associated with increased risk of cardiovascular events in the placebo group but not in the ASA group. Moreover, in the rs3798220-C and high LPA-GRS subgroups, the overall benefit of ASA may outweigh harm related to major bleeding, whereas the reduction of cardiovascular events and the increase of clinically significant bleeding was equal in overall participants [11]. Similarly, in the Women's Health Study with women ≥ 45 years old, although the overall trial was negative, women with elevated Lp(a) levels benefited from ASA use, which suggested the risk could be modified by antiplatelet therapy (age-adjusted HR 0.44, 95% CI 0.20–0.94) [12]. In this setting, it was hypothesized herein, that enhanced antithrombotic therapy or extended DAPT after PCI may be beneficial for ACS patients with high Lp(a) levels. Therefore, the relative efficacy was compared and safety of extended DAPT (> 1 year) versus shortened DAPT (≤ 1 year) in ACS patients with elevated Lp(a) levels and normal Lp(a) levels, respectively.

The present study revealed that extended DAPT (up to 30 months) could reduce the risks of MACCE and all-cause death without statistically increasing clinically relevant bleeding for ACS patients with elevated Lp(a) levels after PCI. However, extended DAPT was not significantly associated with reduced incidence of the composite cardiovascular events for patients with normal Lp(a) levels, although the risks of all-cause death and definite/ /probable ST were lower in extended DAPT group than that in shortened DAPT group. Similarly, the author's previous study with 3,201 stable CAD patients, the beneficial effect of extended DAPT was well established in patients with elevated Lp(a) levels, whereas extended DAPT tended to increase clinically relevant bleeding without reducing ischemic events in those with normal Lp(a) levels [16]. Notably, unlike the previous study, the present study did not find that extended DAPT increased the risk of clinically relevant bleeding in ACS patients with normal Lp(a) levels. This suggests that in this population, although the benefit of prolonged DAPT is not as great as that in ACS patients with elevated Lp(a) levels, it at least does not cause harm. Different from stable CAD patients who have not sustained a previous ischemic event, a heightened predisposition to thrombotic events may persist for years for patients with ACS [28, 29]. Therefore, ACS patients may be more likely to benefit from extended DAPT than those with stable CAD, and Lp(a) levels should be an important consideration in determining the DAPT duration after PCI for ACS patients.

Limitations of the study

There were several limitations in this study. First, this is a single-center, observational study, and the confounders might be complex. Although the confounding factors were adjusted through multivariable-adjusted analysis and IPTW analysis, it was not possible to control the unmeasured confounders and eliminate the selection bias. Second, the composite endpoint of MACCE did not reach statistical significance in ACS patients with normal Lp(a) levels, possibly due to the relatively small sample size and low incidence of ischemic events. It is well known that relatively low event rates can lead to an increased likelihood of overfitting. Third, although the clinical benefit of extended DAPT

was confirmed in ACS patients with elevated Lp(a) levels, the current findings were derived from subgroup analysis of the cohort study and the results should be interpreted as hypothesis generating. Fourth, clopidogrel, instead of ticagrelor or prasugrel was predominantly used as a $P2Y_{12}$ inhibitor for DAPT regimen (only 5 patients received ticagrelor), thus the clinical impact of extended DAPT with ASA plus a more potent $P2Y_{12}$ inhibitor in ACS patients with different Lp(a) concentrations is unclear. Given that current guidelines recommend ticagrelor or prasugrel in ACS, further well-designed, large-scale, randomized trials with new $P2Y_{12}$ inhibitors are needed. Last, the conclusions drawn from this study may not be generalized to those other than Asian ethnicities.

Conclusions

This study firstly demonstrated that extended DAPT (> 1 year) was statistically associated with lower risk of ischemic events in ACS patients with elevated Lp(a) levels after DES implantation, whereas this association was not found in individuals with normal Lp(a) levels. Further well-designed, large-scale, randomized trials are needed to confirm these findings.

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Conflict of interest: None declared

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Transcatheter edge-to-edge mitral valve repair in patients with acute decompensated heart failure due to severe mitral regurgitation

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Abstract

Background: *Transcatheter edge-to-edge mitral valve repair (TEER) has been established as a therapy for severe symptomatic mitral regurgitation (MR) in stable patients, and it has recently emerged as a reasonable option for acutely ill patients. The aim of this study was to evaluate the safety and efficacy of TEER in hospitalized patients with acute decompensated heart failure (HF) and severe MR that was deemed to play a major role in their deterioration.*

Methods: *We included 31 patients who underwent emergent TEER for MR ≥ 3+ from 2012 to 2022 at Sheba Medical Center. Outcomes included procedural safety, procedural success, all-cause mortality, HF readmission, and functional improvement. Outcomes were evaluated at 3 months and at 1 year. Data were obtained retrospectively by chart review.*

Results: *Implantation of a TEER device was achieved in 97% of patients, and reduction in MR severity of at least two grades and final MR ≤ 2+ at discharge was achieved in 74%. No intra-procedural mortality or life-threatening complications were noted. Mortality at 30 days was 23%. No excess mortality occurred beyond 6 months, with a total mortality of 41%. At 1 year all survivors had MR ≤ 2+, all were free of HF hospitalizations, and 88% were at New York Heart Association class ≤ II.*

Conclusions: *Mitral valve TEER for patients with acute decompensated HF and significant MR is safe, feasible, and achieves substantial reduction in MR severity. Despite high early mortality, procedural success is associated with good long-term clinical outcomes for patients surviving longer than 6 months.* (Cardiol J 2024; 31, 1: 45–52)

Key words: mitral valve, mitral regurgitation, acute decompensated heart failure, trans-catheter edge-to-edge repair, transcatheter edge-to-edge mitral valve repair

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Introduction

Heart failure (HF) is the leading diagnosis in hospitalized patients ≥ 65 years old, representing 1% to 2% of all hospital admissions [1, 2], and it is associated with increased mortality [3, 4]. Significant mitral regurgitation (MR) is prevalent among patients hospitalized for acute decompensated HF, and it is independently associated with excess 1-year mortality in those with left ventricular ejection fraction (LVEF) < 50% [5]. Owing to prohibitive surgical risk, therapeutic options are frequently limited for these critically ill hospitalized patients. Transcatheter edge-to-edge mitral valve repair (TEER) has been shown to be safe and effective in stable patients with severe MR who are at high surgical risk. Furthermore, data from large-scale clinical registries [6–9] and a large randomized clinical trial [10] suggest that TEER improves quality of life and reduces HF hospitalizations and mortality in patients with symptomatic MR. Nevertheless, data regarding the benefit of the procedure in critically ill patients are scarce, and the role of TEER as a salvage therapy in the acute setting has been described previously only by a limited number of case reports and case series [11–16]. The purpose of this study was to describe the outcomes and to evaluate the safety and efficacy of TEER in hospitalized patients with intractable HF and significant MR.

Methods

The study population included patients who underwent emergent TEER of the mitral valve from July 2012 to March 2022 at the Sheba Medical Center. All patients were hospitalized with acute decompensated HF (New York Heart Association [NYHA] class IV) resistant to intensive intravenous medical therapy and had MR ≥ 3+ that was deemed to play a major role in their deterioration. The decision to proceed with TEER was based on lack of improvement despite maximal medical therapy, high- or prohibitive-surgical risk, and anatomic suitability for TEER. All patients were evaluated by the Heart Team, which included a non-interventional cardiologist, an interventional cardiologist, and a cardiothoracic surgeon. All procedures were performed under general anesthesia and with transesophageal echocardiography (TEE) and fluoroscopy guidance. Leaflet approximation was performed using MitraClip (Abbott, Menlo Park, CA, USA) or PASCAL (Edwards Lifesciences, Irvine, CA, USA) devices. We retrospectively evaluated immediate, 3-month, and 1-year outcomes. All data were abstracted from patients' electronic medical records. Clinical, laboratory, echocardiographic, and electrocardiographic data were recorded at baseline and during follow-up. Acute procedural results were assessed by TEE at implantation and supplemented by transthoracic echocardiography before discharge. Safety was evaluated clinically, according to the occurrence of procedure-related adverse events. Mortality data were drawn from the national death registry. Descriptive statistics are used to report on the data. The study was approved by the local Ethics Committee and was conducted in accordance with the Declaration of Helsinki. Informed consent was provided by all subjects. Results are expressed as mean ± standard deviation for continuous variables or as numbers (percentages) for categorical variables.

Procedure description

Venous access was obtained via the femoral vein followed by puncture of the trans-atrial septum. A steerable guide catheter, through which the device delivery system was introduced, was advanced into the left atrium and positioned over the mitral valve. The device was steered towards the origin of the regurgitation jet, and its arms were then opened and oriented perpendicular to the line of coaptation. The opened device was advanced through the mitral valve into the left ventricle (LV) and subsequently pulled back to grasp the leaflets, which produced a double orifice. Device position and presence of residual MR were evaluated with color flow Doppler. If the results were adequate, the device was locked and released from the delivery system. In patients with suboptimal MR reduction after initial device implantation, additional devices were implanted according to the operator's discretion.

Results

We included in the current study 31 hospitalized patients who underwent emergent TEER for severe MR and intractable HF. All patients had MR grade 3+ (10%) or 4+ (90%) at baseline. The etiology of MR (Fig. 1) was secondary in 28 (90%) patients, of whom 22 (79%) were ischemic (of these, 13 [59%] patients presented after recent myocardial infarction (MI) [mean 29 ± 20 days from event], 2 patients presented with partial rupture of papillary head and acute flail, and 9 [41%] had long-standing ischemic cardiomyopathy). Non-ischemic secondary MR was found in 6 (19%)

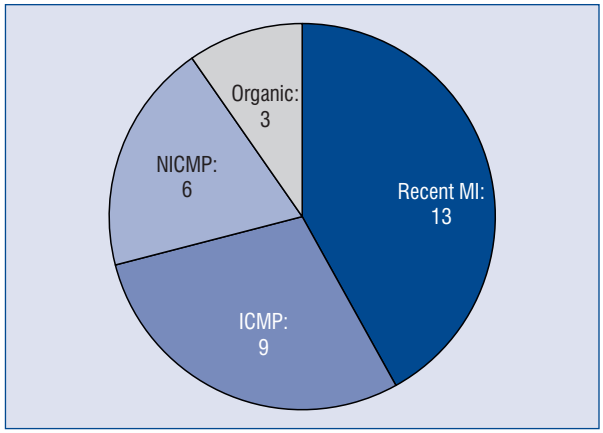

Figure 1. Etiology of mitral regurgitation; MI — myocardial infarction; ICMP — ischemic cardiomyopathy; NICMP — non-ischemic cardiomyopathy.

patients (5 with non-ischemic cardiomyopathy, 1 with annular dilatation secondary to long-standing atrial fibrillation). Primary MR with presence of prolapse and/or flail was found in 3 (10%) patients. Baseline characteristics are summarized in Table 1. The mean age was 73.5 ± 11 years and 32% were female. The indication for the procedure was intractable HF requiring intravenous (IV) therapy in patients with moderate to severe (3+) or severe (4+) MR that was considered to be etiologically significant in determining their clinical state. All patients were on high-dose (average 100 mg/ /day) IV furosemide, one-third were receiving IV vasodilators (nitroglycerin or nitroprusside), and two-thirds were receiving IV inotropes (dopamine, dobutamine, levosimendan, norepinephrine, or milrinone). In the days prior the procedure, 9 (29%) patients had been in cardiogenic shock (CS) and 20 (65%) were managed in the intensive care unit (ICU). During the 24 hours preceding TEER, 10 (32%) patients were receiving inotropic support, 4 (13%) were mechanically ventilated, and 1 (3%) had intra-aortic balloon pump.

Table 1. Baseline characteristics.

Age [years]	73.5 ± 10.9
Male gender	21 (67.7%)
Body mass index [kg/m^2]	27.3 ± 4.3
Ischemic heart disease	25 (80.6%)
Past stroke or TIA	3 (9.7%)
Diabetes	17 (54.8%)
Atrial fibrillation:	
Paroxysmal	14 (45.2%)
Chronic	3 (9.7%)
Hyperlipidemia	22 (71.0%)
Hypertension	25 (80.6%)
Chronic kidney disease	18 (58.1%)
Smoking:	
Past	8 (25.8%)
Current	3 (9.7%)
Permanent pacemaker:	
Pacemaker	8 (25.8%)
CRT	3 (9.7%)
Cardiomyopathy:	
Ischemic	23 (74.2%)
Non-ischemic	6 (19.4%)
Past MI	26 (83.9%)
MI within 60 days prior to procedure	13 (41.9%)
Past PCI	20 (64.5%)
PCI within 60 days prior to procedure	9 (29.0%)
Past coronary artery bypass graft	11 (35.5%)
HF hospitalization within previous 1 year	
1 to 3 admissions	26 (83.9%)
4 to 6 admissions	5 (16.1%)
Hemoglobin [g/dL]	11.2 ± 2.6
Creatinine [mg/dL]	1.9 ± 1.1
Albumin [g/L]	32.0 ± 6.0
GFR [mL/min/1.73 m^2]	47.5 ± 26.8

All data are presented as means ± standard deviation or numbers (percentages, %) unless stated otherwise. CRT — cardiac resynchronization therapy; GFR — glomerular filtration rate; HF — heart failure; MI — myocardial infarction; PCI — percutaneous coronary intervention; TIA — transient ischemic attack

Acute procedural outcomes and peri-procedural events

Implantation of a TEER device was achieved in 30/31 (97%) patients — 13 were implanted with a single device, 15 with two devices, and 2 patients with three devices. Acute procedural success, defined as a reduction in MR severity of at least two grades and final MR grade ≤ 2+ at discharge, was achieved in 23 (74%) patients. In 3 patients the MR grade was reduced by one grade to MR 3+. Patients in whom procedural success was not achieved had higher mean effective regurgitant orifice area (EROA; 0.55 ± 0.36 vs. 0.43 ± 0.35 cm^2), higher mean MR volume (65.4 ± 37.3 vs. 46.3 ± ± 23.2 mL), higher mean systolic pulmonary artery pressure (62.7 ± 22.5 vs. 57.9 ± 13.4 mmHg), and greater prevalence of severe LV dysfunction (62.5% vs. 26%) on baseline echocardiography. One patient developed mean transmitral gradient > 5 mmHg. An acute reduction in mean systolic

Table 2. Echocardiography before and after transcatheter edge-to-edge mitral valve repair (TEER).

	Baseline (n = 31)	Post-TEER (n = 31)	3 months (n = 14)	1 year (n = 9)
Mitral regurgitation severity:				
None	0 (0%)	2 (6.5%)	2 (14.3%)	1 (11.1%)
Mild	0 (0%)	10 (32.3%)	5 (35.7%)	3 (33.3%)
Moderate	0 (0%)	11 (35.5%)	5 (35.7%)	5 (55.6%)
Moderate-severe	3 (9.7%)	3 (9.7%)	1 (7.1%)	0 (0%)
Severe	28 (90.3%)	5 (16.1%)	1 (7.1%)	0 (0%)
Effective regurgitant orifice area [cm^2]	0.47 ± 0.35	0.27 ± 0.2	0.34 ± 0.43	0.26 ± 0.14
Mitral regurgitation volume [mL]	51.7 ± 28.6	31.4 ± 22.7	35.9 ± 37.5	31.3 ± 16.1
LV ejection fraction [%]	37.2 ± 13.4	37.0 ± 14.6	39.5 ± 13.1	43.9 ± 11.7
LV end-diastolic diameter [mm]	58.6 ± 9.9	57.8 ± 8.7	57.7 ± 8.8	54.4 ± 7.7
LV end-systolic diameter [mm]	46.7 ± 11.3	46.0 ± 11.6	45.5 ± 10.5	41.7 ± 7.2
Tricuspid regurgitation severity:				
Moderate	13/28 (46.4%)	5/29 (17.2%)	4 (28.6%)	2 (22.2%)
Moderate-severe	0/28 (0%)	2/29 (6.9%)	1 (7.1%)	0 (0%)
Severe	2/28 (7.1%)	3/29 (10.3%)	0 (0%)	0 (0%)
Systolic pulmonary arterial pressure [mmHg]	59.2 ± 16.1	48.6 ± 13.0	42.9 ± 13.1	41.4 ± 13.9
Tricuspid regurgitation systolic gradient [mmHg]	46.8 ± 15.3	37.6 ± 11.2	34.5 ± 12.0	32.6 ± 13.2
Left atrial volume index [mL/m^2]	63.4 ± 22.6	64.4 ± 19.1	57.4 ± 18.3	51.6 ± 20.6

All data are presented as means ± standard deviation or numbers (percentages, %) unless stated otherwise. LV — left ventricular

pulmonary artery pressure of 10.6 mmHg was noted after the procedure (Table 2), and a further decline was observed over the first year in patients for whom echocardiographic follow-up was available. No intra-procedural mortality was noted. Notable intra-procedural events occurred in 4 (13%) patients — hemodynamic instability in 2, access site bleeding requiring blood transfusion in 1, and suspected thrombus embolization in the left atrium without clinical sequelae in 1. Following the procedure, 8 (26%) patients remained mechanically ventilated (6 of them for more than 24 h) and 11 (36%) required inotropic support (8 of them for more than 24 h). During the early post-procedural period, 1 (3%) patient developed new CS, 3 (10%) developed septic shock, 4 (13%) patients had isolated acute kidney injury (AKI), and 6 (19%) patients required blood transfusion, 1 of them due to major upper gastrointestinal bleeding. A total of 19 (61%) patients required ICU care during their post-TEER hospitalization, with mean stay of 5.1 ± ± 4.0 days. Mean post-TEER hospitalization length was 10.6 ± 11.3 days.

Follow-up

Long-term mortality data were available for all patients. Estimates of the probability of survival are shown in Figure 2. Mortality at 30 days was 23% (7/31 patients), with higher rates observed among patients in whom TEER failed (37.5%) than in those it succeeded (17%). All patients who died within 30 days of intervention had ischemic cardiomyopathy with a past medical history significant for MI, which was recent (within 60 days) in 5 (71%) of them. They were more likely to present with CS (57% deceased vs. 21% alive at 30 days) or MI (57% vs. 25%) during the month preceding the procedure, and to have lower mean albumin levels (26 ± 4 vs. 34 ± 6 g/L) and lower mean glomerular filtration rate (38 ± 22 vs. 50 ± 28 mL/min/1.73 m^2) on pre-procedural evaluation. Furthermore, coronary artery disease with past percutaneous coronary intervention or coronary artery bypass graft, chronic kidney disease, diabetes mellitus, and smoking were more frequently observed in this patient group. Decreased 30-day survival was associated with higher rates of procedural failure (43% deceased vs. 21% alive) as well as major intra-procedural (43% deceased vs. 4% alive) and post-procedural (86% deceased vs. 12.5% alive) complications. Moreover, patients who died within 30 days were more likely to require ICU care, inotropic support, and mechanical ventilation within the 24 hours prior to or immediately following

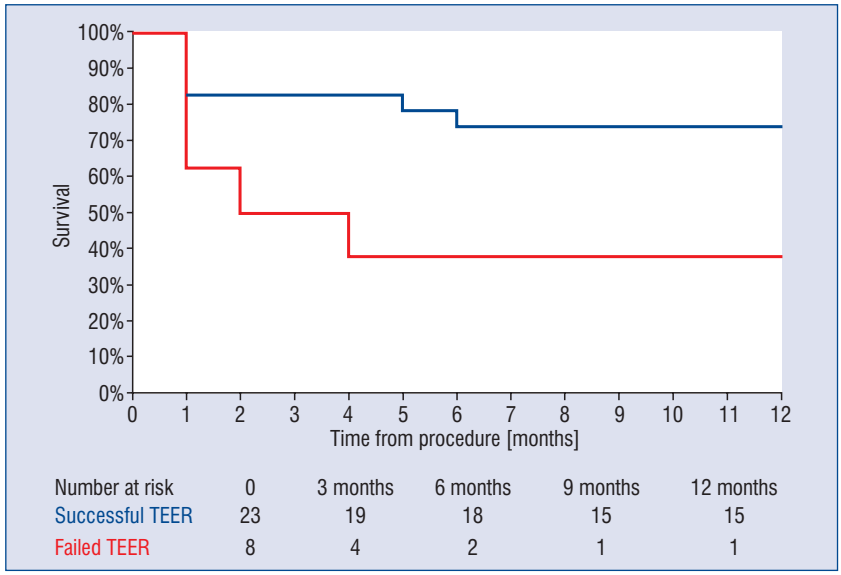

Figure 2. Kaplan–Meier estimates of 1-year survival stratified according to procedural outcome; TEER — transcatheter edge-to-edge repair.

the intervention. Pre-procedural CS and post--procedural AKI were associated with excess 30-day mortality (44% with vs. 14% without CS, 71% with vs. 8% without AKI). Survival at 3 months and 1 year was 74% (23/31 patients) and 59% (16/27 patients), respectively. Subgroups analysis according to procedural outcome demonstrated substantial differences between those who had successful compared to unsuccessful intervention (83% and 50% at 3 months, respectively, 71% and 17% at 1 year, respectively).

Echocardiography at 3 months (available for 14/23 patients) and 1 year (available for 9/16 patients) demonstrated durable reduction in regurgitation severity for all patients who underwent successful TEER. One patient had a mean trans-mitral gradient of 6 mmHg. While a notable improvement in EROA, regurgitant volume, systolic pulmonary artery pressure, and left atrial volume index was observed at 3 months and 1 year follow-up, there were only minor changes in LVEF, LV function, and LV dimensions. Echocardiographic parameters at baseline and follow-up are summarized in Table 2 and Figure 3.

NYHA class at baseline, 3-month, and 1-year follow-up is shown in Figure 4. At 3-month follow-up 82% of patients who underwent successful TEER were NYHA functional class I or II, 1 patient had been hospitalized for HF once, and 1 patient underwent implantation of a cardiac resynchronization therapy device. Two patients with residual severe MR underwent further treatment (1 patient underwent LV assist device implantation; 1 had attempted redo-TEER, but due to partial rupture of the papillary head this was also unsuccessful, and she subsequently underwent successful surgical mitral valve replacement). At 1-year follow-up 87.5% of patients in whom intervention succeeded were NYHA functional class I or II, and all were free of HF hospitalizations.

Discussion

In the present study we report the outcomes of emergent TEER as a salvage therapy for severe MR in hospitalized patients who failed to improve despite maximal medical therapy. Our data suggest that the procedure is feasible and safe, and, although associated with high early mortality, it can provide good long-term outcomes to a significant proportion of critically ill patients.

All patients in our study were severely ill, hospitalized for HF decompensation, and on maximal intravenous drug therapy. Over half were treated within an ICU setting, one-third had been treated for CS during the index hospitalization, and a similar proportion were on intravenous inotropes at the time of the procedure. None of the patients were eligible for discharge due to intractable HF symptoms, and all were deemed to be at very high surgical risk.

Transcatheter edge-to-edge mitral valve repair has been established as a therapy for severe symptomatic MR in stable patients and is associated with a very low risk for peri-procedural adverse

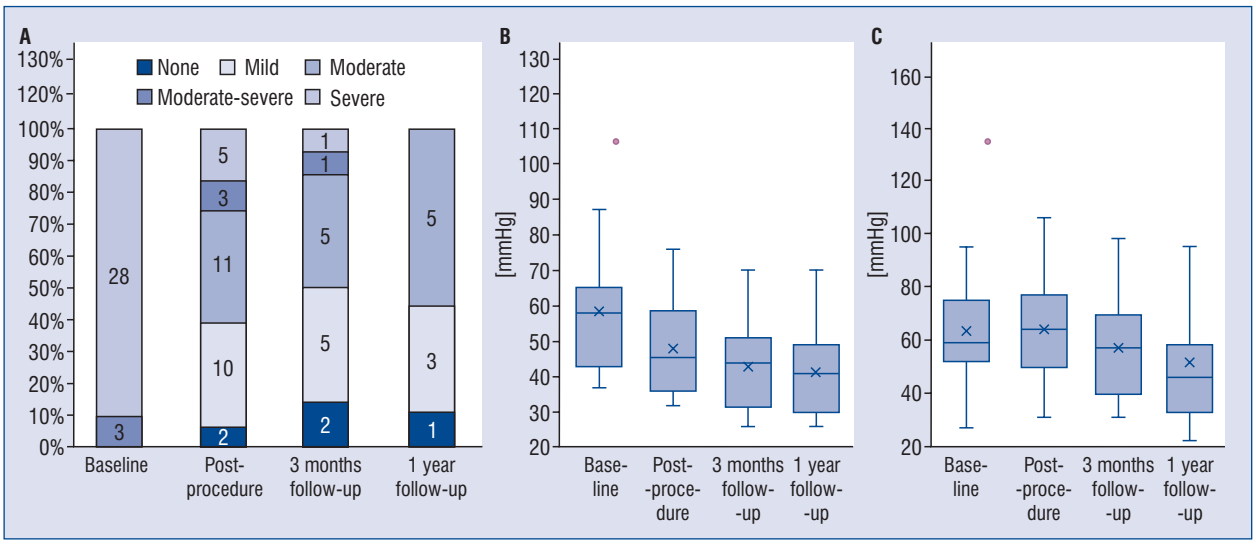

Figure 3. Echocardiographic data at baseline and follow-up; **A.** Mitral regurgitation grade; **B.** Systolic pulmonary arterial pressure; **C.** Left atrial volume index.

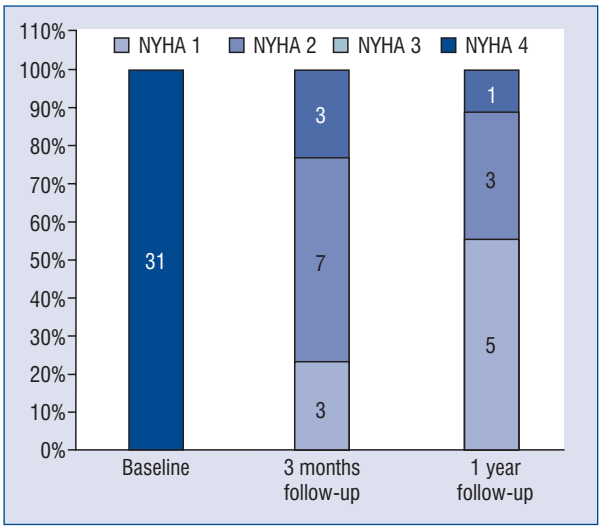

Figure 4. New York Heart Association (NYHA) classification at baseline and follow-up.

events. Indeed, the randomized EVEREST II trial demonstrated a superior safety profile compared with mitral valve surgery [17]. Two randomized trials and numerous large registries have corroborated these findings in higher-risk patients [7, 10, 18, 19]. Among the very sick patients undergoing TEER in our cohort, no patient died or suffered a life-threatening complication during or immediately following the procedure. Furthermore, none required urgent mitral valve surgery. However, the post-procedural course of these patients was much more complex and dramatic than observed in stable patients: within the first 3 post-procedural days CS was noted in 4 patients, septic shock in 3, isolated AKI in 4, and 6 patients required blood transfusion. Two-thirds of patients were managed post-procedurally in the ICU. Prolonged (longer than 24 h) inotropic support and mechanical ventilation were noted in 8 and 6 patients, respectively. While there are limited data on peri-procedural events in other series in a similar setting [11, 13, 15, 16], the occurrence of major peri-procedural complications seems to be similar to those we describe [12–16].

Procedural success, defined as a reduction in MR severity of at least two grades and final MR grade ≤ 2+ at discharge, was achieved in 74% of patients. Procedural failure was associated with higher pre-procedural mean EROA and mean MR volume. In fact, in our study mean EROA (0.47 ± ± 0.35 cm^2) and mean MR volume (51.7 ± 28.6 mL) were greater than those reported in a series of elective TEER [10, 18]. While procedural success in our cohort was similar to that reported in the historical EVEREST II trial [17], it was less than that reported in recent series of high-risk patients undergoing elective TEER, where success rates ranged from 91% to 97% [7, 9, 10, 18, 19]. Reported procedural success in series of acute TEER patients was higher than in our study. In a series similar to ours, in which the study population was fairly heterogenous with regards to their clinical presentation, the success rate was 85% [14]. In patients presenting post MI, success rates ranged

from 88% to 95% [12, 15, 16], and in patients with CS the rates were higher, between 90% and 100% [11, 13, 16]. This probably reflects the patient selection and possible selection bias in retrospective multicenter registries, which may not have included all consecutive patients. We report here on all consecutive cases performed in our center over a period of 10 years. As such, our data may better reflect success rates attainable in acutely ill, non-selected patients in whom TEER is performed as a salvage therapy. MR ≤ 2+ was observed in 86% of survivors at 3-month follow-up, which is consistent with other acute series reporting mid--term results. In these series, which focused on patients undergoing TEER after MI, 77% to 90.5% of patients had MR ≤ 2+ at 3 months follow-up [15, 16]. Long-term reporting on MR grade is lacking for most series. At 1-year follow-up all survivors in our cohort had MR grade ≤ 2+. In post-MI patients MR ≤ 2+ was reported in 71% to 89% of patients, depending on LV function and MR type [12, 15].

Early mortality within 1 month following the procedure was high at 23%, which was due to intractable HF or complications of protracted hospitalization such as septic shock in 2 patients. This early mortality was higher than reported in elective TEER [7, 9, 10, 17–19], but similar to emergent mitral valve surgery [20], and likely reflects the severe nature of patients chosen for the procedure as 4 of 7 patients died despite a significant improvement in MR grade. Data regarding early mortality following acute TEER varies, with most studies reporting somewhat lower mortality rates. In post-MI patients, 30-day mortality did not exceed 10% [12, 16], and in patients with CS mortality ranged between 10% and 17% [11, 16]. In a series comparable to ours, which included patients undergoing urgent or emergent TEER, 30-day mortality was almost identical to ours, at 21% [14]. Additional excess mortality was noted between 1 and 6 months, with a total mortality of 41% at 6 months. However, mortality curves plateaued thereafter. Mortality at 1 year (41% of the entire cohort, 29% of patients who had successful intervention) was higher than seen in high-risk patients undergoing elective TEER (17–24%) [7, 9, 10, 18, 19], but similar to another series reporting long-term outcomes following acute TEER (42%) [11]. Procedural success was associated with increased early (83% of successful vs. 62.5% of failed TEER), mid-term (83% vs. 50%), and long-term (71% vs. 17%) survival. Furthermore, all patients who experienced procedural failure and did not undergo further therapy died within 4 months of intervention. Although it is not possible to assume a causal relationship, there is a very positive association between procedural success and survival, which suggests that severe MR was probably a major contributor to the deteriorating clinical state of these patients, and that correction of MR may have played a part in the increased survival of those with procedural success.

In addition to lower mortality, patients with procedural success demonstrated significant clinical benefit, reflected by very low rates of HF hospitalizations and substantial improvement in functional status from baseline to 3-month and 1-year follow-up. Few data exist regarding the effect of acute TEER on quality of life. We report a readmission rate of 8% and NYHA class I or II in 77% of the cohort (82% of patients with successful procedure) at 3-month follow-up. Mid-term results following acute TEER were evaluated solely in a series assessing post-MI patients, reporting HF readmission rate of 13–23% and NYHA class I or II in 64–77% of patients [15, 16]. At 1-year follow-up all survivors in our cohort were free of HF hospitalizations and 88% were at NYHA class I or II.

Limitations of the study

The study has several limitations. This is a single-center, retrospective series, and as such suffers from all limitations inherent to such a design. Clinical and echocardiographic follow-up was not complete for all patients. However, mortality data were available for all patients. Moreover, our data do not enable us to assess optimal timing of TEER in these acutely ill patients. The major strength of our study is that it includes all consecutive patients who underwent TEER for intractable HF and severe MR and accurately reflects the outcome of these critically ill patients.

Conclusions

Mitral valve TEER for hospitalized patients with significant MR and intractable HF is safe and feasible, and it achieves a substantial reduction in MR severity. Despite high early mortality, procedural success is associated with good long-term clinical outcome for patients surviving longer than 6 months, thereby providing a therapeutic option for very high-risk sick patients with an otherwise poor prognosis. Further, larger-scale studies are needed to verify these results.

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Conflict of interest: None declared

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Predictive value of two different definitions of contrast-associated acute kidney injury for long-term major adverse kidney events in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention

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Abstract

Background: *It remains controversial whether contrast-associated acute kidney injury (CA-AKI) is associated with long-term major adverse kidney events (MAKE) in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI).*

Methods: *By the Acute Kidney Injury Network (AKIN) criteria, CA-AKI was defined as an increase in serum creatinine ≥ 0.3 mg/dL or 50% from baseline within 48 h after PCI; or an increase in serum creatinine ≥ 0.5 mg/dL or 25% within 72 h by the contrast-induced nephropathy (CIN) criteria. The primary endpoint was 1-year MAKE, defined as a composite of all-cause mortality and persistent renal dysfunction.*

Results: *A total of 402 patients were finally included in this study. The primary endpoint occurred in 29 (7.2%) patients. There was a significant association between CA-AKI and 1-year MAKE assessed by both the AKIN (hazard ratios [HR]: 11.58, 95% confidence interval [CI]: 4.29–31.24, p = 0.000) and CIN (HR: 6.45, 95% CI: 2.56–16.25, p = 0.000) definitions. However, the AKIN definition (HR: 4.95, 95% CI: 1.17–21.02, p = 0.030) was more reliable in the prediction of persistent renal dysfunction than CIN definition (HR: 4.08, 95% CI: 0.99–16.87, p = 0.052). Additionally, the area under receiver operating characteristic curve was larger for predicting 1-year MAKE with the AKIN definition than CIN definition (0.742 vs. 0.727).*

Conclusions: *In patients with STEMI undergoing primary PCI, CA-AKI was significantly associated with 1-year MAKE. Moreover, the AKIN definition might be more reliable in the prediction of long-term prognosis.* (Cardiol J 2024; 31, 1: 53–61)

Key words: contrast-associated acute kidney injury, definition, prediction, prognosis, major adverse kidney events

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**Lian Chen, Xiaolei Wang and Qianyun Wang contributed equally to this work.*

Introduction

Contrast-associated acute kidney injury (CA--AKI), previously described as contrast-induced acute kidney injury (CI-AKI), is characterized by a decline in renal function that occurs within days after the intravascular administration of iodinated contrast media [1]. It is a common adverse complication in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI), associated with a higher incidence of in-hospital and short- and long-term clinical outcomes [2–5]. Traditionally known as contrast-induced nephropathy (CIN), it is defined as an increase in serum creatinine ≥ 0.5 mg/dL or 25% from baseline within 48–72 h after contrast media exposure [6]. More recently, the Acute Kidney Injury Network (AKIN) recommends a novel standardized definition of CA-AKI, that is, an increase in serum creatinine ≥ 0.3 mg/ /dL or 50% from baseline within 48 h [7]. Irrespective of the definitions adopted, CA-AKI could be a useful predictor of long-term mortality in patients with STEMI treated by primary PCI [8, 9].

Recent observational studies reveal that CA--AKI also has a persistent impact on the impairment of renal function, such as progression to chronic kidney disease (CKD) or end-stage renal disease (ESRD) [10, 11]. However, depending on the definitions of CA-AKI used in other survival analyses, the results remain controversial [12]. Thus, this study aimed to assess the association between CA-AKI and long-term major adverse kidney events (MAKE) in patients with STEMI undergoing primary PCI, and compare the predictive value between the two different definitions of CA-AKI.

The following article is presented in accordance with the STARD reporting checklist.

Methods

Study population

A total of 441 consecutive patients diagnosed with STEMI undergoing primary PCI in Yuyao People's Hospital of Zhejiang Province between January 2015 and January 2020 were prospectively enrolled in this study. Inclusion criteria were (i) chest pain persisting for over 30 min with ST-segment elevation on the electrocardiogram of ≥ 0.1 mV in at least two contiguous leads or left bundle branch block; (ii) onset of chest pain within 12 h, or 24 h in the presence of ongoing symptoms suggestive of ischemia. Exclusion criteria included death within 24 h after admission, cardiogenic shock requiring intra-aortic balloon pump (IABP), ESRD on maintenance dialysis, recent exposure to contrast media (within 72 h before/after the procedure), concomitant use of nephrotoxic agents (e.g., non-steroidal anti-inflammatory drugs or aminoglycoside antibiotics, which are thought to be associated with increased risk of AKI [13, 14]), or inability to obtain informed consent.

Study protocol

For all patients, a 12-lead electrocardiogram was conducted in the emergency room. After cardiac intervention, blood samples for serum creatinine measurement were collected at baseline and daily. The estimated glomerular filtration rate (GFR) was calculated using the CKD-EPI equation [15], which had less bias than the Modification of Diet in Renal Disease (MDRD) equation especially at higher GFR. Primary PCI was performed based on the current guidelines [16, 17]. Before the procedure, acetylsalicylic acid (300 mg) and clopidogrel (300–600 mg) or ticagrelor (180 mg) were routinely administered. The anticoagulant agents and the glycoprotein IIb/IIIa inhibitor use were determined at the discretion of the physicians. Nonionic, low-osmolality contrast media and standard intravenous hydration were used in all patients. Within 24 h after admission, the left ventricular ejection fraction (LVEF) was measured by echocardiography using the biplane Simpson's method [18]. All patients were scheduled to return for follow-up by in- or outpatient clinic visits until 1 year after the procedure. The study protocol was approved by the Institutional Research Ethics Board. All patients provided informed consent prior to participation. All procedures were conducted in accordance with the principles outlined in the Declaration of Helsinki.

Definitions and endpoints

By the AKIN criteria, CA-AKI was defined as an increase in serum creatinine ≥ 0.3 mg/dL or 50% from baseline within 48 h [6], and by the CIN criteria, CA-AKI was defined as an increase in serum creatinine ≥ 0.5 mg/dL or 25% from baseline within 72 h after contrast media exposure [7]. The primary endpoint of this study was 1-year MAKE, which was defined as a composite of all-cause mortality and persistent renal dysfunction [19]. Persistent renal dysfunction was defined as a sustained elevation ≥ 1.5 times in serum creatinine at 1-year follow-up compared with baseline level or progression to ESRD requiring dialysis.

Statistical analysis

Continuous variables were expressed as means and standard deviation for normally distributed variables or as median and interquartile range for nonnormally distributed variables. The categorical variables were presented as numbers and percentages (%). The independent t-test for normally distributed values and the Mann–Whitney test for nonnormally distributed values were used to compare continuous variables across trial groups. The χ^2 was used to compare proportions, and if the expected frequency was < 5, the Fisher's exact test was conducted. The association between CA-AKI and 1-year MAKE was estimated by fitting a multivariable Cox regression model adjusted for risk factors based on univariate Cox regression. The results were shown as hazard ratios (HR) and 95% confidence intervals (CI). To compare the predictive accuracy between the AKIN and CIN definitions, the receiver operating characteristic (ROC) curve analysis and area under the curve (AUC) were assessed. $P < 0.05$ was considered significant. SPSS 23.0 software (SPSS Inc., Chicago, Illinois, USA) was used to perform all analyzes.

Results

Participant characteristics

During the study phase, 2 patients were excluded due to death within 24 h after admission. Another 11 patients were excluded for cardiogenic shock requiring IABP. We further excluded 2 patients with ESRD on maintenance dialysis, 7 patients with recent exposure to contrast media or concomitant use of nephrotoxic agents, and 17 patients who were unwilling to participate in the study. Therefore, a total of 402 participants were finally included in the study.

Table 1 shows the baseline characteristics of all patients. Briefly, the mean age was 60 ± 14.1 years. Among them, 72 (17.9%) patients were older than 75 years. The mean door-to-balloon time was 77.5 ± 16.9 min. Baseline renal dysfunction (eGFR < 60 mL/min/1.73 m^2) was detected in 35 (8.7%) patients. The mean volume of administered contrast medium was 92.7 ± 32.9 mL.

Incidence of CA-AKI by the AKIN and the CIN criteria

By the CIN criteria, CA-AKI was detected in 80 (19.9%) patients; while according to the AKIN criteria, only 41 (10.1%) patients were diagnosed as CA-AKI. Among 41 patients with CA-AKI by the AKIN criteria, 40 (97.6%) patients met the CIN criteria; on the contrary, only 50.0% (40/80) of them fulfilled the AKIN definition among patients with CA-AKI by the CIN definition.

Irrespective of the definition adopted, patients developing CA-AKI were older, more often female, had a higher proportion of Killip class 2 or 3, experienced prolonged door-to-balloon time, and had a reduced LVEF. The AKIN definition was more likely to distinguish patients with impaired baseline renal function, while patients with CA-AKI by the CIN definition tended to have an anterior STEMI.

Predictive value of the AKIN and the CIN criteria on long-term MAKE

During the 1-year follow-up period, the primary endpoint was documented in 29 (7.2%) patients, including all-cause mortality in 18 patients and persistent renal dysfunction in 11 patients (with 1 patient progressed to ESRD). Patients developing CA-AKI were more likely to suffer 1-year MAKE than those without CA-AKI, either by the AKIN (39.0% vs. 3.6%, p = 0.000) or by the CIN (22.5% vs. 3.4%, p = 0.000) definition (Fig. 1A). A similar trend was also found in the frequency of persistent renal dysfunction, which was higher in patients with CA-AKI by both the AKIN (9.8% vs. 1.9%, p = 0.018) and the CIN (6.3% vs. 1.9%, p = 0.047) criteria than that in those without CA-AKI (Fig. 1B).

By multivariable regression analysis, there was a significant association between CA-AKI and 1-year MAKE assessed by both the AKIN (HR: 11.58, 95% CI: 4.29–31.24, p = 0.000) and the CIN (HR: 6.45, 95% CI: 2.56–16.25, p = 0.000) definitions (Table 2). However, the AKIN definition (HR: 4.95, 95% CI: 1.17–21.02, p = 0.030) was more reliable in the prediction of persistent renal dysfunction than the CIN definition (HR: 4.08, 95% CI: 0.99–16.87, p = 0.052) (Table 3). Moreover, the ROC curve analysis showed a modest increase in the AUC for predicting 1-year MAKE with the AKIN definition (AUC: 0.742, 95% CI: 0.629–0.856, p = 0.000) than that with the CIN definition (AUC: 0.727, 95% CI: 0.620–0.834, p = 0.000, Fig. 2), though failing to reach statistically significance (p = 0.55).

Discussion

To the best of our knowledge, this was the first study to assess the association between CA-AKI and long-term MAKE in patients with STEMI undergoing primary PCI. Our data suggested that CA-AKI could be an independent predictor of

Table 1. Baseline characteristics of all patients.

Characteristics	All patients (n = 402)	CA-AKI according to AKIN definition		P	CA-AKI according to CIN definition		P
		Yes (n = 41)	No (n = 361)		Yes (n = 80)	No (n = 322)	
Age [years]	60 ± 14.1	69.4 ± 14.4	59.0 ± 13.7	0.000**	64.7 ± 14.3	59.0 ± 13.9	0.001**
Aged over 75 years	72 (17.9%)	17 (41.5%)	55 (15.2%)	0.000**	23 (28.8%)	49 (15.2%)	0.005**
Male gender	349 (86.8%)	31 (75.6%)	318 (87.6%)	0.025*	62 (77.5%)	287 (89.1%)	0.006**
Hypertension	195 (48.5%)	24 (58.5%)	171 (47.4%)	0.175	46 (57.5%)	149 (46.3%)	0.072
Diabetes mellitus	70 (17.4%)	9 (22.0%)	61 (16.9%)	0.419	16 (20.0%)	54 (16.8%)	0.495
Door-to-balloon time [min]	77.5 ± 16.9	85.3 ± 21.2	76.7 ± 16.1	0.015*	82.3 ± 19.5	76.3 ± 16.0	0.013*
Anterior MI	256 (63.7%)	30 (73.2%)	226 (62.6%)	0.182	60 (75.0%)	196 (60.9%)	0.019*
Killip class 2 or 3	47 (11.7%)	10 (24.4%)	37 (10.2%)	0.012*	15 (18.8%)	32 (9.9%)	0.028*
Multivessel coronary disease	158 (39.3%)	22 (53.7%)	136 (37.7%)	0.047*	41 (51.3%)	117 (36.3%)	0.015*
Post-procedural TIMI grade flow 3	360 (89.6%)	35 (85.4%)	325 (90.0%)	0.415	72 (90.0%)	288 (89.4%)	0.884
Contrast volume [mL]	92.7 ± 32.9	97.3 ± 39.6	92.2 ± 32.1	0.347	98.6 ± 41.2	90.7 ± 30.3	0.148
Creatinine [μmol/L]	78.4 ± 23.2	80.4 ± 23.6	78.2 ± 23.2	0.562	74.0 ± 19.9	80.6 ± 23.5	0.190
eGFR [mL/min/1.73 m^2]	89.7 ± 19.8	80.4 ± 22.0	90.8 ± 19.2	0.001**	92.0 ± 20.5	89.2 ± 19.6	0.254
eGFR < 60 mL/min/1.73 m^2	35 (8.7%)	7 (17.1%)	28 (7.8%)	0.045*	6 (7.5%)	29 (9.0%)	0.669
LVEF < 40%	22 (5.5%)	6 (14.6%)	16 (4.4%)	0.017*	9 (11.3%)	13 (4.0%)	0.017*
Statins	400 (99.5%)	40 (97.6%)	360 (99.7%)	0.194	79 (98.8%)	321 (99.7%)	0.359
ACEI/ARB	362 (90.0%)	36 (87.8%)	326 (90.3%)	0.784	71 (88.8%)	291 (90.4%)	0.664
MRA	19 (4.7%)	4 (9.8%)	15 (4.2%)	0.117	6 (7.5%)	13 (4.0%)	0.234

*p < 0.05; **p < 0.01; CA-AKI — contrast-associated acute kidney injury; AKIN — Acute Kidney Injury Network; CIN — contrast induced nephropathy; MI — myocardial infarction; TIMI — Thrombolysis In Myocardial Infarction; eGFR — estimated glomerular filtration rate; LVEF — left ventricular ejection fraction; ACEI — angiotensin converting enzyme inhibitor; ARB — angiotensin II receptor blocker; MRA — mineralocorticoid receptor antagonists

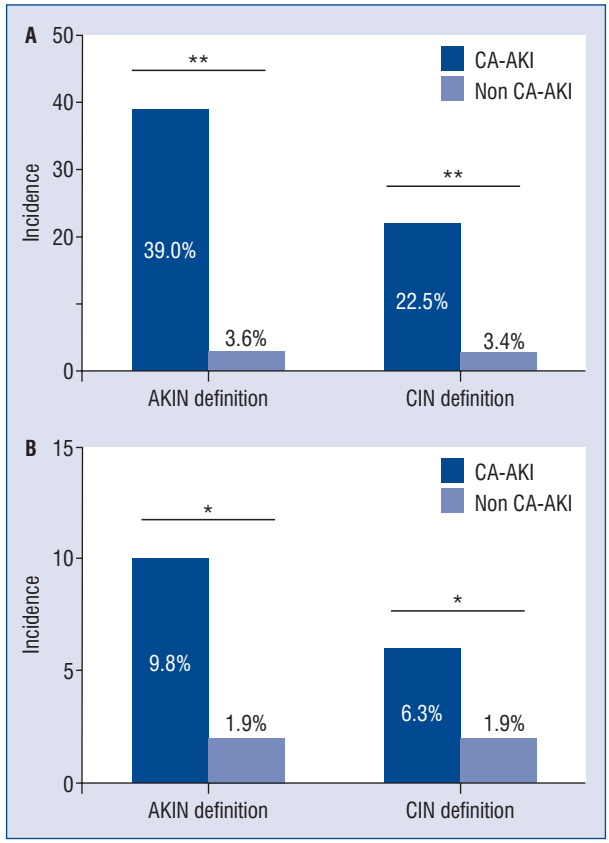

Figure 1. The incidence of 1-year major adverse kidney events (**A**) and persistent renal dysfunction (**B**) was significantly higher in patients with contrast-associated acute kidney injury (CA-AKI) by both the Acute Kidney Injury Network (AKIN) and the contrast-induced nephropathy (CIN) definitions; *p < 0.05; **p < 0.01.

1-year MAKE, regardless of the definition used; moreover, the AKIN definition might be more reliable in the prediction of long-term adverse prognosis than the CIN definition.

Multiple large studies have demonstrated that patients who survive an onset of AKI are at potential risk of progression to CKD or ESRD. A cohort study by Wald et al. [20] enrolling 17,367 patients with a median follow-up of 3 years showed that the absolute risk of ESRD was 0.4% among those with normal baseline renal function without AKI, while it rose up to 4.6% (more than 10-fold) when complicated by AKI. Another cohort study of 36,980 patients by Chawla et al. [21] showed that patients with AKI were 2-fold as likely to develop CKD or ESRD (HR: 2.07, 95% CI: 1.99–2.16) compared to those without AKI. Based on these findings, the endpoint of MAKE has been endorsed by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) clinical trial work-

Table 2. Regression model for long-term major adverse kidney events.

	Univariate analysis			Multivariate analysis					
				CA-AKI by the AKIN definition			CA-AKI by the CIN definition		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Aged over 75 years	6.04	2.83–12.91	0.000**	2.80	1.07–7.31	0.035*	3.33	1.33–8.34	0.010*
Male gender	0.63	0.25–1.61	0.336						
Hypertension	2.06	0.96–4.41	0.064						
Diabetes mellitus	0.49	0.15–1.66	0.251						
Anterior MI	1.73	0.75–3.97	0.197						
Killip class 2 or 3	6.10	2.74–13.60	0.000**	4.31	1.54–12.06	0.005**	4.45	1.61–12.30	0.004**
Multivessel coronary disease	2.00	0.96–4.18	0.066						
Post-procedural TIMI grade flow 3	0.21	0.09–0.48	0.000**	0.26	0.08–0.81	0.020*	0.28	0.09–0.85	0.024*
eGFR < 60 mL/min/1.73 m^2	3.60	1.42–9.07	0.007**	2.18	0.68–7.05	0.193	3.19	0.99–10.27	0.051
LVEF < 40%	14.36	5.55–36.95	0.000**	11.26	3.21–39.46	0.000**	9.76	2.90–32.87	0.000**
CA-AKI by the AKIN definition	14.85	6.59–33.48	0.000**	11.58	4.29–31.24	0.000**			
CA-AKI by the CIN definition	6.95	3.24–14.91	0.000**				6.45	2.56–16.25	0.000**

*p < 0.05; **p < 0.01; CA-AKI — contrast-associated acute kidney injury; AKIN — Acute Kidney Injury Network; CIN — contrast induced nephropathy; MI — myocardial infarction; TIMI — Thrombolysis In Myocardial Infarction; eGFR — estimated glomerular filtration rate; LVEF — left ventricular ejection fraction; HR — hazard ratio; CI — confidence interval

Table 3. Regression model for persistent renal dysfunction.

	Univariate analysis			Multivariate analysis					
				CA-AKI by the AKIN definition			CA-AKI by the CIN definition		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Aged over 75 years	9.75	2.77–34.35	0.000**	5.54	1.44–21.38	0.013*	6.00	1.57–22.92	0.009**
Male gender	0.40	0.10–1.57	0.190						
Hypertension	11.40	0.95–89.97	0.071						
Diabetes mellitus	0.47	0.06–3.72	0.474						
Anterior MI	1.03	0.75–3.97	0.197						
Killip class 2 or 3	5.31	1.49–19.00	0.010*	3.64	0.86–15.47	0.080	3.59	0.83–15.53	0.087
Multivessel coronary disease	0.93	0.27–3.23	0.909						
Post-procedural TIMI grade flow 3	1.04	0.13–8.39	0.968						
eGFR < 60 mL/min/1.73 m^2	6.94	1.92–25.08	0.003**	4.43	1.06–18.52	0.041*	6.03	1.36–26.74	0.018*
LVEF < 40%	9.15	2.20–38.00	0.002**	7.57	1.51–37.94	0.014*	6.31	1.23–32.29	0.027*
CA-AKI by the AKIN definition	6.94	1.92–25.08	0.003**	4.95	1.17–21.02	0.030*			
CA-AKI by the CIN definition	3.91	1.16–13.17	0.028*				4.08	0.99–16.87	0.052

*p < 0.05; **p < 0.01; CA-AKI — contrast-associated acute kidney injury; AKIN — Acute Kidney Injury Network; CIN — contrast induced nephropathy; MI — myocardial infarction; TIMI — Thrombolysis In Myocardial Infarction; eGFR — estimated glomerular filtration rate; LVEF — left ventricular ejection fraction; HR — hazard ratio; CI — confidence interval

Figure 2. The receiver operating characteristic (ROC) curve and area under the curve showed a better diagnostic accuracy of the Acute Kidney Injury Network (AKIN) definition for 1-year major adverse kidney events than that of the contrast-induced nephropathy (CIN) definition (0.742 vs. 0.727).

group to harmonize and encourage future clinical trials [22]. Hence, we systematically assessed pre-angiography renal function, prospectively tracked the development of CA-AKI and 1-year outcomes, seeking to evaluate the association between CA-AKI and long-term MAKE in patients with STEMI undergoing primary PCI. As shown in this study, a significant association was detected between CA-AKI and worse prognosis, irrespective of the definition used. The pathophysiologic mechanisms that CA-AKI would increase the risk of long-term MAKE remain unknown. Results from experimental animals suggest that AKI can induce tubulointerstitial fibrosis and a reduction in peritubular capillary density in the inner stripe of the outer medulla, thus resulting in persistent deterioration of renal function [23]. Although AKI has generally been considered reversible in nature, there may be subclinical damage that persists and mediates these adverse outcomes [24].

In this study, we further compared the difference between the AKIN and the CIN definitions. Over years, a debate has existed on a standardized definition of CA-AKI. The lack of consensus results in a significant variation in the incidence of CA-AKI in patients undergoing PCI, ranging from 3.3% to

10.5%, depending on the various definitions used [25]. In the setting of STEMI, the rate of CA-AKI was 16.1% according to the HORIZON-AMI trial, in which the CIN definition was adopted [26]. These results are quite similar to the findings in our study (19.8%). Meanwhile, the incidence of CA-AKI varied from 9.6% to 10.7% according to the previous observational study where the AKIN definition was applied [8, 27], which is also consistent with our data (10.1%). Besides, in this study, 97.6% (40/41) of the patients diagnosed with CA-AKI by AKIN definition fulfilled the CIN criteria; only 50.0% (40/80) of those with CA-AKI by CIN criteria met the AKIN definition. It seemed that the CIN definition was a more sensitive indicator, while the AKIN definition tended to be more rigorous and specific.

Most importantly, our data revealed that the AKIN definition was superior to the CIN definition in the prediction of long-term MAKE. It has been suggested that the AKIN definition is the most discriminant definition to identify patients at higher risk of mortality. A cohort study of 402 patients undergoing primary PCI for STEMI by Centola et al. [8] demonstrated that the AKIN definition (HR: 9.70, 95% CI: 5.12–18.37, p = 0.000) provided better accuracy in the prediction of 1-year mortality than the CIN criteria (HR: 4.84, 95% CI: 2.56–9.16, p = 0.000) [8]. In another cohort which enrolled 1114 patients with STEMI undergoing primary PCI, Silvain et al. [28] confirmed the value of the AKIN definition in predicting long-term mortality; in addition, the AKIN definition (odds ratio [OR]: 4.60, 95% CI: 1.88–11.27, p = 0.001) was superior to the CIN definition (OR: 3.54, 95% CI: 1.49–8.39, p = 0.004) in predicting a hemodialysis requirement at 1-year follow-up. However, the conclusions remain to be debated as patients with preexisting renal failure, hemodynamic instability and resuscitated cardiac arrest were unselectedly included, which might also contribute to the tendency of hemodialysis treatment. Moreover, merely the hemodialysis requirement, rather than assessment of serum creatine was adopted as the renal endpoint, which might be biased in the overall estimation of renal impairment. In the present study, kidney function was assessed by an in- or outpatient clinic visit, and innovatively evaluated the predictive value of the two definitions of CA-AKI with 1-year MAKE and persistent renal dysfunction, based on either progression to ESRD requiring dialysis or a sustained elevation ≥ 1.5 times in serum creatinine compared with the baseline level, in accordance with the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) definition [29].The adjusted HRs of CA-AKI for 1-year MAKE were 11.58 (95% CI: 4.29–31.24) and 6.45 (95% CI: 2.56–16.25) when the AKIN and the CIN definitions were, respectively, used. Nevertheless, the AKIN definition (HR: 4.95, 95% CI: 1.17–21.02, p = 0.030) seemed to be more reliable in the prediction of persistent renal dysfunction than the CIN definition (HR: 4.08, 95% CI: 0.99–16.87, p = 0.052). One plausible explanation for this phenomenon might be that the AKIN definition tended to distinguish patients with CKD in this study (17.1% vs. 7.8%, p = 0.045), who were more vulnerable to the deterioration of renal function than those without CKD [30]. Furthermore, the comparison of AUCs suggested that the AKIN definition was likely to provide better diagnostic accuracy for 1-year MAKE than the CIN definition (0.742 vs. 0.727). In a word, we complemented the previous results [8, 9, 28, 31], demonstrating that the AKIN definition might be a more reliable predictor of both long-term mortality and persistent renal dysfunction in patients with STEMI undergoing primary PCI, compared to the CIN definition.

Last but not least, the current study found that older age and reduced LVEF were also independent predictors of 1-year MAKE or persistent renal dysfunction after primary PCI for STEMI, apart from the episode of CA-AKI. The findings that elderly patients were prone to worse long-term prognosis were not surprising, since they generally had a high burden of medical comorbidity with physiologically reduced GFR [32]. On the other hand, our data also indicated that patients with cardiac insufficiency tended to develop long-term MAKE. The potential link between reduced LVEF and MAKE remains to be elucidated in the future study, while it is plausible that acute cardiorenal injury might induce a vicious cycle that persists long after the acute event [33].

Limitations of the study

There are several limitations to this study. First, this was a single-center study with a restricted sample size. A larger sample from multiple centers would make the results more reliable. Second, both the AKIN and CIN definitions refer to an increase in serum creatine, which could be affected in the setting of hemodynamic instability or decreased renovascular autoregulation [1, 34]. Therefore, patients with cardiogenic shock requiring IABP were excluded, which might have caused selection or surveillance bias. Third, we were unable to confirm whether CA-AKI was the

cause of, or definitively contributed to, or was just a mediator to the development of long-term MAKE in this study. Fourth, the incidence of MAKE was comparatively low, as the follow-up data in the present study were obtained merely 1 year after the procedure. Future studies will be encouraged for a longer period of follow-up in this subset of patients. Last but not least, though a modest increase was observed in the AUC for predicting 1-year MAKE with the AKIN definition compared to that with the CIN one, the discrepancy failed to reach statistical significance ($p = 0.55$). The superior diagnostic accuracy of the AKIN definition might be validated in a larger cohort by using ROC analysis.

Conclusions

Irrespective of the definition used, CA-AKI was significantly associated with MAKE at 1-year in patients with STEMI undergoing primary PCI. Moreover, the AKIN definition might be more reliable in the prediction of long-term adverse prognosis than the CIN definition.

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Long-term outcomes and quality of life following implementation of dedicated mitral valve Heart Team decisions for patients with severe mitral valve regurgitation in tertiary cardiovascular care center

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Abstract

Background: *This study was purposed to investigate which treatment strategy was associated with the most favourable prognosis for patients with severe mitral regurgitation (MR) following Heart Team (HT)-decisions implementation.*

Methods: *In this retrospective study, long-term outcomes of patients with severe MR qualified after HT discussion to: optimal medical treatment (OMT) alone, OMT and MitraClip (MC) procedure or OMT and mitral valve replacement (MVR) were evaluated. The primary endpoint was defined as cardiovascular (CV) death and the secondary endpoints included all-cause mortality, myocardial infarctions (MI), strokes, hospitalizations for heart failure exacerbation and CV events during a mean (standard deviation [SD]) follow-up of 29 (15) months.*

Results: *From 2016 to 2019, 176 HT meetings were held and a total of 157 participants (mean age [SD] = 71.0 [9.2], 63.7% male) with severe MR and completely implemented HT decisions (OMT, MC or MVR for 53, 58 and 46 patients, respectively) were included into final analysis. Comparing OMT, MC and MVR groups statistically significant differences between the implemented procedures and occurrence of primary and secondary endpoints with the most frequent in OMT-group were observed ($p < 0.05$). However, for interventional strategy MC was non-inferior to MVR for all endpoints ($p > 0.05$). General health status assessed at the end of follow-up were significantly the lowest for MVR, then for MC and the highest for OMT-group ($p < 0.01$).*

Conclusions: *In the present study it was demonstrated that after careful HT evaluation of patients with severe MR at high risk of surgery, percutaneous strategy (MC) can be considered as equivalent to surgical treatment (MVR) with non-inferior outcomes.* (Cardiol J 2024; 31, 1: 62–71)

Key words: Heart Team, mitral regurgitation, heart failure, mitral valve replacement, MitraClip

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Introduction

Mitral regurgitation (MR) — the most common valvular heart disease (VHD) in adults and the second most frequent indication for valve surgery in Europe — despite enormous development of medicine and pharmacotherapy, still remains a pressing problem of today's cardiology, associated with the development of heart failure (HF), poor prognosis and increased mortality [1–3]. Hence the concept of multi-specialist group — the Heart Team (HT) — responsible for management of patients who are at high surgical risk or qualified only for medical therapy is still evolving. With the development of new technologies and novel approaches many patients can be successfully treated, but advanced age and/or multiple co-morbidities often make it difficult or even impossible to obtain treatment goals of care in real clinical practice. Therefore, the necessity of HT creation was recognized and the role of HT in decisions-making for patients with VHD, including MR was emphasized both in the European and American guidelines [2, 3]. An approach of a multidisciplinary experienced team, taking into account clinical, angiographic and echocardiographic data, risk stratification, long-term prognosis and patients preferences seems to be a rational tool when deciding on the best treatment method for each patient, burdened with many co-morbidities. However, the idea of HT is generally considered in the medical society as an optimal therapeutic option for "difficult" patients, its concept is still not yet widely adopted and the supportive data in the literature is insufficient and poorly proved. According to available literature, only two research papers regarding the influence of HT decisions on prognosis of MR-patients were revealed [4, 5]. Notwithstanding, the results of these two are ambiguous and require further confirmation. More evidence investigating HT consistency and significance of decisions making and performance on hard clinical endpoints are required. We believe that the obtained results and conclusions formulated will be supportive for emphasizing the evidence-based role of HT in real-life clinical practice and its further development in the field of cardiovascular medicine.

Methods

This single-center cohort study was conducted in the 1st Department of Cardiology, Medical University of Warsaw, a large third-degree academic center. A total number of 254 patients consulted for symptomatic, both primary (PMR) and secondary (SMR) MR during 176 HT meetings in 2016–2019 were enrolled in this retrospective study. The inclusion criteria were: aged ≥ 18 years and complete clinical, echocardiographic and angiographic characteristics. The exclusion criteria included the following: pregnancy/lactation, disseminated neoplastic process, life expectancy < 1 year, lack of informed, written consent. All of patients were presented to an experienced HT–council consisting of at least four specialists: general (conservative) cardiologist, echocardiographer, interventional cardiologist and cardiac surgeon. Patients were qualified after HT discussion to one of three main strategies: optimal medical treatment (OMT) alone, OMT and MitraClip (MC) procedure or OMT and mitral valve replacement (MVR). OMT was defined as use of drugs in a manner that provides an optimal reduction of signs and symptoms associated with mitral valve (MV) defect or secondary to subsequent HF. The degree of MR was assessed using echocardiographic criteria on a scale from 1 to 4, where 1+ was determined as faint opacification of the left atrium with clearing of contrast during each beat, while 4+ meant immediate, dense opacification of the left atrium with filling of the pulmonary veins. The severe MR in the present study was defined as grade 3+ or 4+ and effective regurgitant orifice (ERO) ≥ 0.40 cm^2 for severe PMR and ERO ≥ 0.20 cm^2 for severe SMR assessed by echocardiography (in accordance to European guidelines) [2]. The severity of HF symptoms was assessed using New York Heart Association (NYHA) classification, chronic kidney disease (CKD) defined as glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2, anemia as hemoglobin level < 12 g/dL for women and < 14 g/dL for men, cancer — as active or up to 5 years prior and smoking — as active or in the past. Ultimately, after excluding non-eligible patients, the patients who died before decision implementation, did not consent with HT decision or loss of follow-up, 157 (61.8%) individuals with completely implemented HT decisions (OMT, MC, MVR — 53, 58, 46 patients, respectively) were included into the final analysis. As the primary endpoint the cardiovascular (CV) death was considered, while all-cause mortality, non-fatal myocardial infarctions (MI), non-fatal strokes, non-fatal hospitalizations for HF exacerbation and any CV events (including CV death, non-fatal MI, non-fatal stroke and non-fatal hospitalizations for HF exacerbation) per single patient were assessed as secondary endpoints. All participants were observed for occurrence of

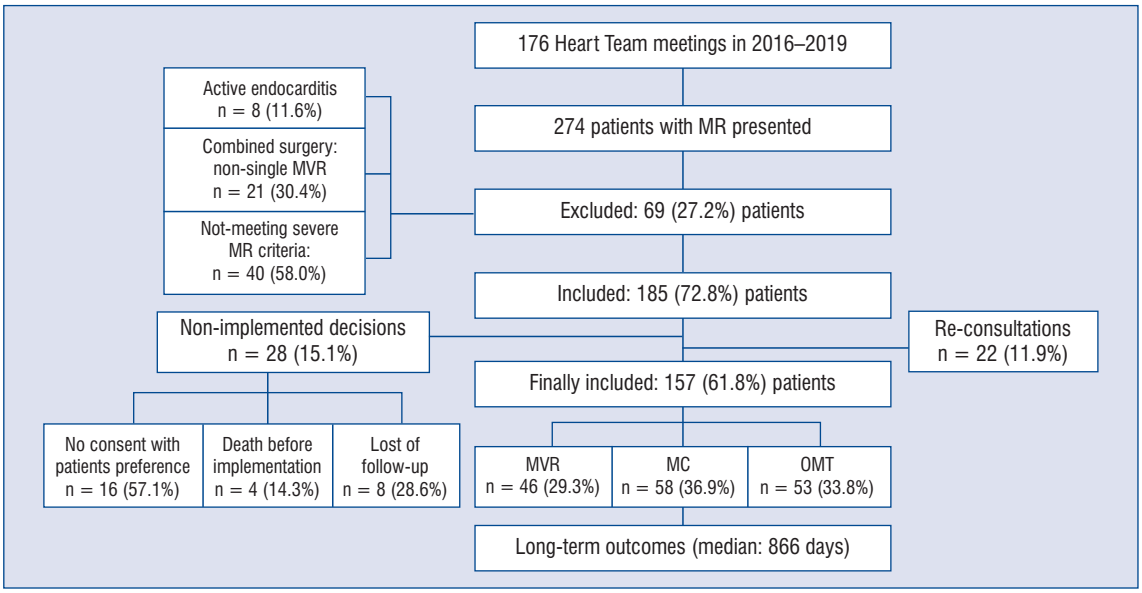

Figure 1. Study design; MR — mitral regurgitation; MVR — mitral valve replacement; MC — MitraClip; OMT — optimal medical therapy.

endpoints with mean ± standard deviation (SD) follow-up of 29 ± 15 months. The main outline of the study was presented in Figure 1. Additionally, general health status, using the short-form (SF)-36 questionnaire (totally and separately for physical component summary [PCS] and mental component summary [MCS]) before MVR, MC and HT discussion (for patients qualified for OMT) and at the end of follow-up for all living participants (31 December 2020) was assessed. Due to the observational nature of the study, an application to the ethical/institutional review board (IRB) for approval of the present study was unnecessary. All participants gave written informed consent for publication of study results.

Statistical analysis

The PQStat software (version 1.6.6, PQStat, Poznan, Poland) was used for statistical analysis. The normality of distribution for continuous variables was confirmed with the Shapiro–Wilk test. Categorical data were expressed as counts and percentages, while continuous data were presented as mean ± SD. The comparison between groups of patients qualified for individual treatment strategies was performed using χ^2 test and the statistical analysis was executed using one-way analysis of variance (ANOVA). To compare the outcomes for all strategies with each other, the hazard ratios (HRs) with 95% confidence intervals (95% CI) were calculated. Time to event analysis was performed using Kaplan–Meier curves. All p values (p) were given to at least two-sided and p value lower than 0.05 were considered statistically significant.

Results

Study population

From January 2016 to December 2019, 176 HT meetings were held and total of 157 patients with severe MR meeting inclusion and exclusion criteria with completely implemented HT decisions (100; 63.7%) male, age (years, mean ± SD) = 71.0 ± 9.2, body mass index (kg/m^2, mean ± SD) = 26.2 ± 4.8, 43 (27.4%) with primary MR, 154 (98.1%) with HF, NYHA (class, mean ± SD) = 3.50 ± 0.50, European System for Cardiac Operative Risk Evaluation II (EuroSCORE II, %, mean ± SD) = 7.71 ± 2.55 and given co-morbidities were followed up. The mean delay time from HT decision to implementation was: 59 ± 9 and 31 ± 6 days for MC and MVR, respectively (p = 0.001). As regards statistically significant differences between MVR, MC and OMT groups, patients qualified for OMT were older than those with implemented MVR or MC, primary MR was the most common in MVR-group, while participants with MC had the most severe symptoms (assessed by NYHA class). Diabetes, atrial fibrillation (AF) and chronic obstructive pulmonary disease (COPD) were the most common in OMT-group, while CKD and history of previous coronary artery bypass grafting were most often

Table 1. Baseline clinical characteristics (n = 157).

	Overall (157)	MVR (46)	MC (58)	OMT (53)	P
Age [years]	71.03 ± 9.18	67.8 ± 8.86	71.1 ± 9.72	73.7 ± 11.05	0.02
Gender — male	100 (63.7%)	31 (67.4%)	37 (63.8%)	32 (60.4%)	0.77
BMI [kg/m^2]	26.22 ± 4.76	26.76 ± 6.04	25.23 ± 13.8	26.82 ± 3.95	0.47
Etiology — primary MR	43 (27.4%)	26 (56.5%)	8 (11.9%)	9 (17.0%)	< 0.001
Heart failure	154 (98.1%)	44 (95.7%)	58 (100.0%)	52 (98.1%)	0.28
NYHA	3.50 ± 0.50	3.39 ± 0.49	3.64 ± 0.48	3.47 ± 0.50	0.03
Coronary artery disease	114 (72.6%)	29 (63.0%)	45 (77.6%)	40 (75.5%)	0.22
Diabetes	73 (46.5%)	8 (17.4%)	31 (53.4%)	34 (64.2%)	<0.001
Hypertension	148 (94.3%)	42 (91.3%)	55 (94.8%)	51 (96.2%)	0.57
Previous stroke/TIA	42 (26.8%)	14 (30.4%)	15 (25.9%)	13 (24.5%)	0.79
Atrial fibrillation	48 (30.6%)	8 (17.4%)	18 (31.0%)	22 (41.5%)	0.03
Previous MI	102 (65.0%)	24 (52.2%)	41 (70.7%)	37 (69.8%)	0.10
Previous PCI	111 (70.7%)	28 (60.9%)	43 (74.1%)	40 (75.5%)	0.22
Previous CABG	36 (22.9%)	4 (8.7%)	17 (29.3%)	15 (28.3%)	0.02
Chronic kidney failure	136 (86.6%)	33 (71.7%)	55 (94.8%)	48 (90.6%)	0.001
Anemia	122 (77.7%)	34 (73.9%)	47 (81.0%)	41 (77.4%)	0.69
Dyslipidemia	134 (85.4%)	39 (84.8%)	51 (87.9%)	44 (83.0%)	0.76
COPD	46 (29.3%)	6 (13.0%)	17 (29.3%)	23 (43.4%)	0.004
Cancer	36 (22.9%)	7 (15.2%)	13 (22.4%)	16 (30.2%)	0.21
Smoking	135 (86.0%)	40 (87.0%)	52 (89.7%)	43 (81.1%)	0.43
EuroSCORE II [%]	7.71 ± 2.55	6.65 ± 2.79	8.13 ± 2.90	8.05 ± 1.81	0.004
Medications at discharge:					
ACEI/ARB	143/152 (91.45%)	37/42 (88.10%)	51/57 (89.47%)	51/53 (96.23%)	0.16
ARNI	7/152 (4.61%)	2/42 (4.76%)	3/57 (5.26%)	2/53 (3.77%)	0.93
Beta–blockers	133/152 (87.50%)	34/42 (80.95%)	50/57 (87.72%)	49/53 (92.45%)	0.25
Loop diuretics agents	144/152 (94.74%)	38/42 (90.48%)	53/57 (92.98%)	53/53 (100.0%)	0.09
Aldosterone antagonists	75/152 (49.34%)	16/42 (38.10%)	28/57 (49.12%)	31/53 (58.49%)	0.14

MVR — mitral valve replacement; MC — MitraClip; OMT — optimal medical therapy; BMI — body mass index; MR — mitral regurgitation; NYHA — New York Heart Association; TIA — transient ischemic attack; MI — myocardial infarction; PCI — percutaneous coronary intervention; CABG — coronary artery bypass grafting; COPD — chronic obstructive pulmonary disease; EuroSCORE II — European System for Cardiac Operative Risk Evaluation II; ACEI — angiotensin-converting enzyme inhibitors; ARB — angiotensin receptor blockers; ARNI — angiotensin receptor-neprilysin inhibitors

found in MC-group ($p < 0.05$ for all). Participants qualified for MVR had the lowest perioperative risk of death as assessed using the EuroSCORE II scale ($p < 0.05$) — detailed in Table 1.

Echocardiographic parameters

All patients were assessed by echocardiography — from OMT-group at the time of HT discussion and from MVR- and MC-groups before and after intervention (at the time of discharge from the hospital). Statistically significant differences in echocardiographic parameters before HT decision implementation were observed in the following: ejection fraction of left ventricle (LVEF) with the highest in MVR-group, the diameter of left ventricle (LV) (assessed by left ventricular end-diastolic dimension [LVEDD]) and ERO with the lowest in MVR-group and mean mitral valve gradient (MVG) — the lowest in MC-group ($p < 0.05$ for all). The results of echocardiographic parameters assessed after MVR or MC implementation differ between these two groups for residual central MR degree ≥ 2 and paravalvular leak, ERO, MR volume, maximum and mean MVG and were significantly better in MVR-group ($p < 0.05$ for all) — as detailed in Table 2.

Endpoints

In-hospital mortality did not significantly differ between MVR and MC strategy (4 [8.7%] vs. 1 [1.7%]; $p = 0.10$). The occurrence of primary endpoint was statistically the most frequent in OMT-group (20 patients, 37.7%), while in MVR and

Table 2. Echocardiographic parameters before and after Heart Team decisions implementation.

	BEFORE Heart Team decisions implementation				P
	Overall (157)	MVR (46)	MC (58)	OMT (53)	
LVEF [%]	33.09 ± 9.54	42.43 ± 6.09	30.3 ± 11.1	30.3 ± 7.1	< 0.001
LVEDD [cm]	6.40 ± 0.66)	6.24 ± 0.65	6.36 ± 0.55	6.61 ± 0.66	0.03
MR [degree]	3.36 ± 0.48	3.35 ± 0.39	3.34 ± 0.53	3.38 ± 0.46	0.76
ERO [cm^2]	0.39 ± 0.09	0.37 ± 0.08	0.39 ± 0.11	0.42 ± 0.08	0.01
MR volume [mL/beat]	49.58 ± 12.71	48.50 ± 11.11	50.77 ± 17.33	49.46 ± 9.44	0.85
Max MVG [mmHg]	18.29 ± 8.27	17.17 ± 7.54	18.23 ± 6.24	19.24 ± 10.24	0.45
Mean MVG [mmHg]	5.80 ± 2.45	6.19 ± 2.29	4.12 ± 1.41	7.31 ± 2.36	< 0.001
	AFTER Heart Team decisions implementation				P
	MVR (42)		MC (57)		
Central MR degree ≥ 2	0 (0.0%)		8 (14.04%)		0.01
Paravalvular leak	3 (7.1%)		14 (24.56%)		0.02
ERO [cm^2]	0.12 ± 0.01		0.20 ± 0.08		< 0.001
MR volume [mL/beat]	15.40 ± 5.28		23.23 ± 7.93		< 0.001
Max MVG [mmHg]	6.64 ± 4.14		10.28 ± 5.90		< 0.001
Mean MVG [mmHg]	2.19 ± 0.94		3.02 ± 1.34		0.01

BEFORE — for MVR and MC — before procedure and for OMT — during Heart Team consultation; AFTER — after implemented procedure (MVR and MC); MVR — mitral valve replacement; MC — MitraClip; OMT — optimal medical therapy; LVEF — left ventricular ejection fraction; LVEDD — left ventricular end-diastolic dimension; MR — mitral regurgitation; ERO — effective regurgitant orifice; MVG — mitral valve gradient

Table 3. Primary and secondary endpoints.

	MVR (46 patients)	MC (58 patients)	OMT (53 patients)	P
Primary endpoint				
CV death	7 (15.2%)	10 (17.2%)	20 (37.7%)	0.01
Secondary endpoints				
All-cause mortality	10 (21.7%)	14 (24.1%)	29 (54.7%)	< 0.01
Non-fatal MI	2 (4.3%)	3 (5.2%)	9 (17.0%)	0.04
Non-fatal stroke	4 (8.7%)	3 (5.2%)	11 (20.8%)	0.03
Non-fatal hospitalizations for HF	11 (23.9%)	24 (41.4%)	44 (83.0%)	< 0.01
CV events/one patient	19 (41.3%)	34 (58.6%)	51 (96.2%)	< 0.01
In-hospital mortality	4 (8.7%)	1 (1.7%)	–	0.10

Hazard ratios (HR) with 95% confidence intervals (CI) comparing all strategies with each other (HR [95% CI]; P): **In-hospital mortality:** MC vs. MVR (0.2 [0.03–1.10]; 0.10); **CV death:** MC vs. MVR (1.13 [0.44–2.56]; 0.78), OMT vs. MC (2.19 [0.69–3.07]; 0.01), OMT vs MVR (2.48 [0.69–3.53]; 0.01); **all-cause mortality:** MC vs. MVR (1.11 [0.55–2.41]; 0.78), OMT vs. MC (2.27 [0.70–2.49]; < 0.01), OMT vs. MVR (2.52 [0.77–2.99]; < 0.01); **non-fatal MI:** MC vs. MVR (1.19 [0.27–5.03]; 0.85), OMT vs. MC (3.28 [0.55–6.40]; 0.05), OMT vs. MVR (3.91 [0.58–8.31]; 0.05); **non-fatal stroke:** MC vs. MVR (0.59 [0.16–2.24]; 0.48), OMT vs. MC (4.01 [0.69–6.13]; 0.01), OMT vs. MVR (2.39 [0.38–4.02]; 0.01); **non-fatal hospitalizations for HF:** MC vs. MVR (1.73 [0.88–2.78]; 0.06), OMT vs. MC (2.0 [0.99–2.75]; < 0.01), OMT vs. MVR (3.47 [1.47–4.52]; < 0.01); **CV events/one patient:** MC vs. MVR (1.42 [0.59–1.63]; 0.08), OMT vs. MC (1.64 [1.05–2.52]; < 0.01), OMT vs. MVR (2.33 [0.95–2.67]; < 0.01)
MVR — mitral valve replacement; MC — MitraClip; OMT — optimal medical therapy; CV — cardiovascular; MI — myocardial infarction; HF — heart failure

MC groups — 7 (15.2%) and 10 (17.2%) patients, respectively (p = 0.01). Additionally, MVR and MC were found to be significantly superior to OMT for all secondary endpoints (p < 0.05 for all endpoints) — detailed in Table 3. However, for interventional strategy — no statistically significant differences between MVR and MC outcomes were observed (p > 0.05 for all endpoints). The Kaplan-Meier curves for primary and secondary endpoints were presented in Figure 2.

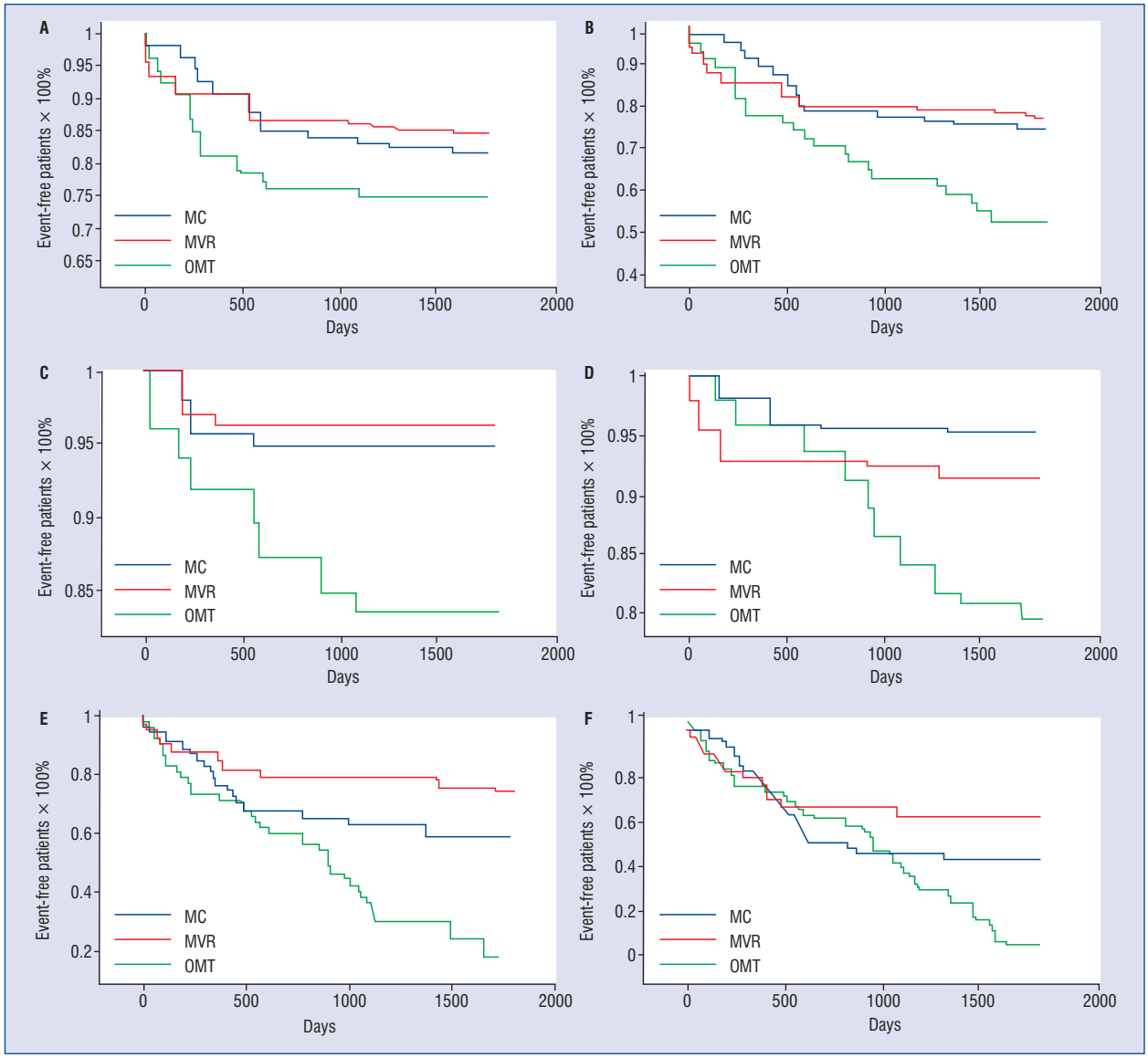

Figure 2. The Kaplan-Meier curves for endpoints; **A.** Cardiovascular deaths; **B.** Overall mortality; **C.** Non-fatal myocardial infarction; **D.** Non-fatal strokes; **E.** Non-fatal hospitalizations for heart failure exacerbation; **F.** Cardiovascular events; MC — MitraClip; MVR — mitral valve replacement; OMT — optimal medical therapy.

Quality of life

General health status before implementing HT decisions — PCS, MCS and total — did not statistically differ between treatment groups ($p > 0.05$ for all). At the end of follow-up the results of PCS, MCS and total for all living participants were significantly the lowest for MVR, then for MC and were the highest for OMT-group ($p < 0.01$) — detailed in Table 4. According to the Polish version of the questionnaire, with a maximum of 103 points for PCS and 68 points for MCS (171 points — total), the highest point value means the lowest quality of life assessment, while the lowest point value indicates the highest level of quality of life [6, 7].

Discussion

Mitral regurgitation caused by any structural or functional dysfunction of MV leaflets, MV apparatus or LV remodeling is a common problem of patients admitted to cardiology divisions all over the world [1–3, 8]. Regardless of the mechanism of this defect, MR results in the progression of HF symptoms, deterioration of the quality of life

Table 4. The quality of life before and after Heart Team (HT) decisions implementation.

	MVR (46 patients)	MC (58 patients)	OMT (53 patients)	P value
Physical component summary				
Before MVR, MC, HT discussion	76.15 ± 15.60%	77.84 ± 15.61	79.58 ± 11.89	0.50 (p for MVR vs. MC; MVR vs. OMT; MC vs. OMT: 0.58; 0.22; 0.51, respectively)
After MVR, MC, HT discussion — at the end of follow up	60.15 ± 14.49	68.34 ± 15.93	83.08 ± 9.44	< 0.01 (p for MVR vs. MC; MVR vs. OMT; MC vs. OMT: < 0.01 for all)
Mental component summary				
Before MVR, MC, HT discussion	51.07 ± 10.17	52.05 ± 8.43	53.81 ± 8.29	0.30 (p for MVR vs. MC; MVR vs. OMT; MC vs. OMT: 0.59; 0.14; 0.27, respectively)
After MVR, MC, HT discussion — at the end of follow up	43.07 ± 8.79	46.55 ± 8.82	57.31 ± 6.34	< 0.01 (p for MVR vs. MC; MVR vs. OMT; MC vs. OMT: 0.06; < 0.01; < 0.01, respectively)
Total				
Before MVR, MC, HT discussion	127.22 ± 20.85	129.90 ± 19.14	133.40 ± 12.11	0.22 (p for MVR vs. MC; MVR vs. OMT; MC vs. OMT: 0.50; 0.07; 0.26, respectively)
After MVR, MC, HT discussion — at the end of follow up	103.22 ± 17.42	114.90 ± 15.99	140.40 ± 8.84	< 0.01 (p for MVR vs. MC; MVR vs. OMT; MC vs. OMT: < 0.01 for all)

MVR — mitral valve replacement; MC — MitraClip; OMT — optimal medical therapy

and increased mortality, even despite the surgical and pharmacological treatment applied [1–3]. With an aging population, living with more chronic medical conditions, the frequency of this disease will continue to grow, as will be asking about new treatment options. Current evidence concerning survival outcomes of MR-patients qualified for different treatment modalities remains scarce, and although multiple reports have published survival data, only a few have compared outcomes post MC to surgical treatment. So far, only one randomized controlled trial (RCT), the Endovascular Edge-to-Edge Repair Study (EVEREST) II and some observational studies evaluating prognosis after conventional surgery versus MC were reported. In the EVEREST II trial [9] patients with grade 3/4+ MR were randomly assigned to MC or conventional MV surgery in a 2:1 ratio (178:80). At 5 years the rate of the composite endpoint of freedom from death, surgery for residual MR, or 3/4+ MR in the intention-to-treat population was 44.2% vs. 64.3% in the MC and surgical groups, respectively (p = 0.01). Five-year mortality rates were 20.8% and 26.8% (p = 0.4) for percutaneous repair and surgery, respectively, whereas in multivariable analysis, treatment strategy was not associated with survival.

In the recently updated meta-analysis of Oh et al. [10] (9 studies including the EVEREST II trial) demonstrating outcomes after MR-treatment, MC--patients (n = 533) as compared to surgical group — MVR (n = 644) had at baseline more comorbidities, further — residual moderate-to-severe MR was more frequent in MC-cohort both at discharge (OR = 2.81; p < 0.01) and at 5 years (OR = 2.46; p < 0.01) and the higher need for reoperation in MC-group at latest follow-up (OR = 5.28; p < 0.01) was observed. However, overall mortality was comparable between these two groups (p = 0.06) for a mean follow-up of 4.8 years.

Based on current European recommendations for MR-treatment the role of HT is poorly underlined with class IIb and level C, while in American guidelines with class IIa/b from nonrandomized trials [2, 3]. There is growing evidence confirming the multidisciplinary approach of HT for management of many CV diseases — coronary artery disease [11–15], aortic stenosis [16–20] and AF [21] which has demonstrated great merit. Only for the safety and efficacy of the HT concept in MR filling the gaps with evidence is still urgent, whereas only two papers on this issue are currently available in the literature [4, 5]. In the study of Heuts et al. [4] 158 patients with MR qualified by HT to different

treatment strategies 30-day mortality for surgery (isolated MVR and concomitant surgery — 67 patients), transcatheter intervention (MC or MVP — 20 patients) and conservative groups (71 patients) were 3 (4.4%), 0 (0.0%) and 3 (4.2%), respectively. Using the Kaplan-Meier curves at a median follow-up of 450 days for the various groups, a beneficial long-term survival for surgically treated patients was demonstrated [4]. In other research, Külling et al. [5] reported retrospective single-center cohort study of 400 patients treated for MR. As followed by HT decisions, 179 (44.8%) patients were treated using MC, 185 (46.2%) by MVP and 36 (9.0%) by MVR. Outcomes with a mean follow-up time of 32.2 ± 17.6 months revealed that patients treated with MVP had higher 4-year survival (HR 0.40; 95% CI 0.26–0.63; $p < 0.001$) and fewer combined endpoints [5]. The present research is one of the few studies involving the concept of HT for MR-patients and according to available literature, the first study in which the MR-patients quality of life following HT decisions and implementation was also assessed. Contrary to expectations created by guidelines for VHD [2, 3], where the surgical approach (MV-repair whenever possible) is a gold standard of treatment for MR-patients, in the current study the percentage of patients for whom surgical therapy following HT discussion was chosen and implemented was only 29.3%, while 36.9% received percutaneous therapy (MC) and 33.8% were disqualified from interventional strategy (OMT). What seems to be even more important, participants treated with MC compared with MVR-group were not statistically significant, but had lower in-hospital mortality, while MC strategy was non-inferior to MVR for primary and secondary endpoints. As expected, mainly participants with primary MR, acceptable valve anatomy and lower surgical risk were qualified for surgical treatment (MVR), while those with secondary MR and increased risk were treated with MC. Regardless the results obtained herein, and although all of treatment strategies were proven to be effective in reducing MR, it should be clearly emphasized that the efficacy of MVR, MC and OMT is highly dependent on patient selection. For individuals with primary MR (basically dysfunction of MV, commissural disease, perforations, clefts), mitral valve area < 3.0 cm^2, high mean MVG (> 5 mmHg), at early stage of LV remodeling, not at critically-high risk of cardiac surgery (i.e. LVEF > 30%, LVEDD < 7.0 cm, without severe pulmonary hypertension, end-stage renal disease or on dialysis), without bleeding/coagulation disorders (need for anticoagulation after MVR) and indications for concomitant surgery of other valve or coronary artery bypass grafting, the MVR is the preferred method of treatment. On the other side, there are severely burdened patients with a high risk of death associated with classical MVR. These of them with "disproportionate" MR (regurgitant volumes disproportionately higher than the degree of LV dilatation), with no calcification of MV, optimally mitral valve area > 3.0 cm^2 and mean MVG < 4 mmHg are likely to mainly benefit from a therapy targeted to MC. At this point, the incidence of iatrogenic atrial septal defect after MC procedure should be also stressed out. This kind of MC consequence, if persistent can lead to stroke, right-sided heart enlargement, worse tricuspid regurgitation, and a higher re-hospitalization rate for HF [22]. Finally, the present study had older patients with more advanced HF, NYHA class IV and severe tricuspid regurgitation who had a dismal prognosis and patients with "proportionate" MR (regurgitant volume totally commensurate to LV enlargement). These subgroups would likely benefit the most from strategies aimed at reducing LV size (i.e., OMT and cardiac resynchronization therapy) alone, not directed to MV apparatus. As the problem of patients with MR treatment becomes more challenging, new therapeutic strategies, such as percutaneous MVR (TMVR) will be a step towards more sufficient and safe treatment. Preliminary studies reported that TMVR by compassionate use of TMVR prostheses as valve-in-valve and valve-in ring was associated with lower-than-expected peri-interventional mortality and satisfactory outcomes in highly selected patients [23–25]. Undoubtedly, the results of the current study should be followed by further RCTs, however, it was demonstrated that after careful HT evaluation, percutaneous strategy (MC) can be considered as a comparably effective and safe to surgical treatment (MVR) for some subsets of patients with severe MR. This may have an impact on recommendations towards MC in subsequent VHD guidelines.

Limitations of the study

The main limitations of this study are its retrospective character, a small sample size, and single-center design. Above that, the decisions--making process must be assigned to our individual HT cooperation and cannot be considered as a general one. Additionally, the treatment results for used strategies were presented together for patients with primary and secondary MR, what it

does not make possible, is to clearly determine which therapeutic option is best for a given etiology. Moreover, patients with non-implemented decisions were not included into the final analysis, so data was not available on their follow-up.

Patients were not matched; hence comparison of groups should be considered with caution. Individuals qualified for interventional strategies differ significantly in some parameters, both clinical (especially the etiology of MR, diabetes, CKD and COPD) and echocardiographic (mostly LVEF and mean MVG), hence the obtained outcomes cannot be a contribution to formulating far-reaching and unquestionable conclusions.

Conclusions

The present study illustrates how the HT approach and decisions affect prognosis and the quality of life for patients with MR. It should be especially emphasized that for MR-patients choosing the best treatment method should never be individual and only HT seems to be a suitable tool to provide satisfactory outcomes and acceptable quality of life. Further research on this issue is required, but our initial results may state a cornerstone for the future.

Conflict of interest: None declared

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Impact of multivessel versus single-vessel disease on the association between low diastolic blood pressure and mortality after acute myocardial infarction with revascularization

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Abstract

Background: *Previous studies demonstrated a J-shaped relationship between low diastolic blood pressure (DBP) and adverse clinical outcomes in patients with acute myocardial infarction (AMI) that was sensitive to revascularization. Hypothesized herein, was that this relationship differs between patients with multivessel disease (MVD) and those with single-vessel disease due to differing degrees of myocardial ischemic burden.*

Methods: *Among 9,983 AMI patients from the Korea Acute Myocardial Infarction Registry database who underwent percutaneous coronary intervention and were followed up for a median duration of 3.2 years, average on-treatment DBP was calculated at admission, discharge, and every scheduled visit and divided into these parameters: < 70 mmHg, 70–74 mmHg, 75–79 mmHg, and ≥ 80 mmHg. The relationship between average on-treatment DBP and clinical outcomes including all-cause death, cardiovascular (CV) death, non-CV death, and hospitalization for heart failure was analyzed using the Cox regression models adjusted for clinical covariates.*

Results: *In patients with MVD, all-cause death (hazard ratio [HR]: 1.47; 95% confidence interval [CI]: 1.06–2.04, p = 0.012) and CV death (HR: 1.59; 95% CI: 1.02–2.46, p = 0.027) were significantly increased in patients with a DBP < 70 mmHg, showing a J-shaped relationship. However, these findings were not significant for single-vessel disease. On a sensitivity analysis excluding subjects with a baseline SBP < 120 mmHg, an increased risk of a low DBP < 70 mmHg remained in MVD.*

Conclusions: *The J-shaped relationship between low DBP and adverse clinical outcomes in AMI patients who underwent revascularization persisted in MVD, which has a high ischemic burden. These high-risk patients require cautious treatment.* (Cardiol J 2024; 31, 1: 72–83)

Key words: acute myocardial infarction, all-cause death, cardiovascular death, diastolic blood pressure, multivessel disease, revascularization

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Introduction

Although the beneficial effect of lowering blood pressure (BP) on cardiovascular (CV) morbidity and mortality is undeniable [1–3], aggressive lowering of diastolic BP (DBP) can lead to an increase in adverse events, especially in patients with CV risk; the so-called J-shaped relationship. The J-shape theory, which emerged over the past four decades, suggests a non-linear relationship between DBP and CV events based on many observational analyses [4–16]. This background can be explained by coronary blood flow perfusion occurring mainly during cardiac diastole. Therefore, intensive lowering of DBP may reduce cardiac perfusion by decreasing coronary perfusion and aggravate myocardial ischemia. In patients with acute coronary syndrome who have more complicated obstructive coronary artery disease (CAD), a J-shaped relationship between DBP and clinical outcomes was reported [17], but it was abolished with reperfusion therapy [18]. However, many patients with acute myocardial infarction (AMI) have multivessel disease (MVD), which adversely affects clinical outcomes and has a high ischemic burden [19–21]; thus, the existence of such an abolished J-shaped relationship depending on the number of stenotic vessels is unclear.

Therefore, the present study investigated the J-shaped relationship between average on--treatment DBP and clinical outcomes including all-cause death and CV death in AMI patients who underwent revascularization according to the number of stenotic vessels during long-term follow-up using data from a large multicenter AMI registry. Also under investigation was the same relationship using average on-treatment SBP. The aim was to explore the impact of the number of stenotic vessels on the association between DBP and clinical outcomes in patients with AMI who underwent percutaneous coronary intervention (PCI) with the fact that MVD has a higher ischemic burden than single-vessel disease (SVD) [21].

Methods

Data were collected from the Korea Acute Myocardial Infarction Registry-National Institutes of Health (KAMIR-NIH) database, a prospective open observational online registry of a nationwide multicenter cohort that evaluated the prognosis and surveillance index of post-AMI patients from 20 tertiary university hospitals capable of PCI. Patients were consecutively enrolled between November 2011 and October 2015. The detailed study protocol was published elsewhere [22]. Initially, AMI was defined as type 1 myocardial infarction (MI) based on the criteria of the Third Universal Definition of Myocardial Infarction [23]. Consequently, the current study confirmed that this definition of type 1 myocardial infarction (MI) is consistent with the criteria of the Fourth Universal Definition of Myocardial Infarction without patient dropout [24]. MVD was defined as ≥ 70% stenosis of two or more major coronary arteries with a diameter ≥ 2.5 mm or a fractional flow reserve ≤ 0.8 with visual stenosis of ≥ 50% in at least one major non-infarct-related artery (IRA) [25]. The KAMIR-NIH protocol was approved by the institutional review board and ethical committee of each participating center and written informed consent was provided by all participants upon enrollment.

Study population

Among the 13,104 patients enrolled in the KAMIR-NIH registry, those meeting the following criteria were excluded (n = 3,121): 1) in-hospital death, stent thrombosis, and cerebrovascular events (n = 670); 2) having undergone permanent pacemaker implantation (n = 14); 3) having undergone coronary artery bypass graft (n = 258) or not undergone PCI (n = 1,008); and 4) lack of available follow-up BP data since hospital discharge (n = = 1,171). Finally, 9,983 patients were included with AMI who underwent PCI and for whom follow-up BP data were available. Patients were divided into subgroups according to number of stenotic vessels: MVD (n = 4,545) and SVD (n = 5,438) (Fig. 1).

BP measurements

Hemodynamic measurements were obtained at each institution where the patient was hospitalized and attended an outpatient clinic. These institutions were certified as medical health examination centers by the Korean National Health Insurance Corporation. Brachial BP was measured by qualified medical personnel at each institution following at least 5 min of rest with the patient in the sitting position. An automatic, semiautomatic, or manual mercury sphygmomanometer was used for BP measurements. The preferred recommendations specified the use of manual mercury sphygmomanometers until 2015, when the sale of mercury sphygmomanometers was banned. BP was measured at admission, discharge, and on every outpatient clinic visit. The mean number of follow-up BP measurements for each patient was 3.9 ± 0.7. Average on-treatment DBP and SBP were cal-

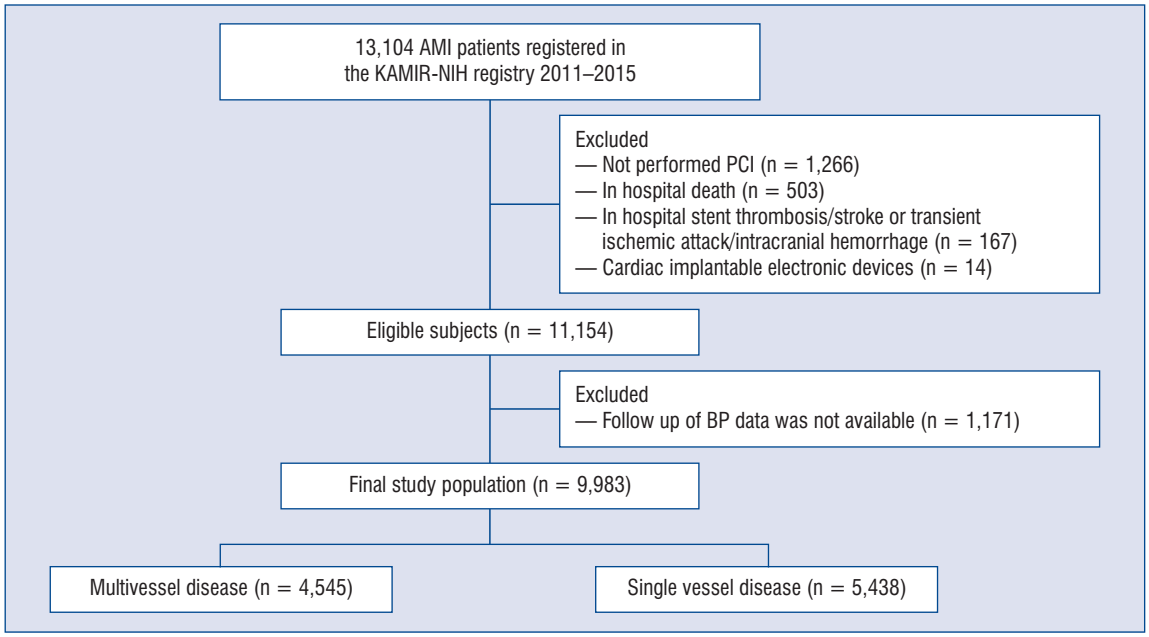


Figure 1. Flow diagram of the study population; AMI — acute myocardial infarction; KAMIR-NIH — Korea Acute Myocardial Infarction Registry-National Institutes of Health; BP — blood pressure; PCI — percutaneous coronary intervention

culated and divided into subgroups in 5-mmHg increments for DBP (< 70 mmHg, 70–74 mmHg, 75–79 mmHg, and ≥ 80 mmHg) and 10-mmHg increments for SBP (< 110 mmHg, 110–119 mmHg, 120–129 mmHg, and ≥ 130 mmHg).

Clinical outcomes and follow-up protocol

The relevant medical records of all clinical events were reviewed and adjudicated by an external clinical event adjudication committee using a web-based case report form on the Internet-based Clinical Research and Trial Management System (iCReaT), a data management system established by the Centers for Disease Control and Prevention, Ministry of Health and Welfare, Republic of Korea (iCReaT study no. C110016). The primary clinical outcome was all-cause mortality. The secondary clinical outcomes were CV death, non-CV death, and hospitalization for heart failure (HF). Clinical outcomes were monitored by the Standardized Data Collection for Cardiovascular Trials Initiative [26]. After discharge, regular follow-up was performed at an outpatient clinic at 6, 12, 24, and 36 months based on patient availability. Follow-up data were collected from the patients by the attending physicians. If patients did not visit the hospital, outcome data were assessed via telephone interviews.

Statistical analysis

The patients' baseline characteristics were compared using descriptive statistics and are presented as median (interquartile range) for continuous variables and number (percentage) for categorical variables. To compare the clinical outcomes, the Cox regression analysis we used based on average on-treatment DBP and SBP as categorical variables, which were also adjusted for age, sex, body mass index, history of smoking, hospital stay, symptom-to-door time, the Killip classification, previous history of HF, MI, ischemic stroke, intracerebral hemorrhage, hypertension, diabetes mellitus, dyslipidemia, MI type, left ventricular (LV) systolic impairment, the location of infarction (anterior vs. non-anterior), newly developed atrial fibrillation (AF), peak cardiac troponin level, and discharge medications including antiplatelet agents, beta-blockers, renin–angiotensin–aldosterone system blockers, statins, and calcium-channel blockers. The proportional hazards assumption was tested based on Schoenfeld residuals [27]. Restricted cubic spline functions presented with a hazard ratio (HR) curve and an area of 95% confidence interval (CI) based on average on-treatment DBP and SBP as continuous variables. In the sensitivity analyses, we additionally censored patients with a baseline SBP < 120 mmHg to avoid unmeasured

confounding factors affecting BP level. We also analyzed the same model using baseline BP levels. Two-sided p values < 0.05 were considered statistically significant. The statistical analyses were performed using R (version 4.0.0; R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

The baseline characteristics of the total population and by subgroups of average on-treatment DBP and SBP are reported in Table 1 and **Suppl. Table S1**, respectively. The median age was 63 (54–73) years, 75.8% were male, and the median hospital stay duration was 5 (4–7) days in the total population. All patients were prescribed antiplatelet agents, and 87.5%, 83.4%, and 95.5% were taking beta-blockers, renin–angiotensin–aldosterone system blockers, and statins, respectively, at hospital discharge. Among the study population, 25.3% (n = 2,531), 19.4% (n = 1,938), 21.1% (n = 2,111), and 34.2% (n = 3,403) had an average on-treatment DBP < 70, 70–74, 75–79, and ≥ 80 mmHg, respectively. Patients with a low DBP were older; more likely to be female, have a low body mass index, have elevated peak cardiac enzyme levels, be never smokers, have a high Killip classification, have a high GRACE risk score, have ST-segment elevated MI, have a previous history of MI, have a previous history of ischemic stroke, have diabetes, have chronic kidney disease, have newly developed AF, and have LV systolic impairment; and were less likely to have anterior wall infarction and a previous history of hypertension than those with a higher DBP. They also had lower prescription rates of beta-blockers, renin–angiotensin–aldosterone system blockers, and calcium-channel blockers than those with a higher DBP.

BP and clinical outcomes in MVD and SVD

Figure 2 depicts the spline curves based on average on-treatment DBP and SBP for patients with MVD and SVD, which showed a J-shaped relationship with the risk of all-cause death or hospitalization for HF. Patients with MVD and a low DBP showed a pronounced increased risk of all-cause death or hospitalization for HF compared to those with SVD and a low DBP. However, patients with a low SBP showed a similar increased risk for all-cause death or hospitalization for HF regardless of MVD or SVD.

Over a median follow-up duration of 3.2 years, 697 deaths were observed that were classified into 413 CV deaths and 284 non-CV deaths. The number of events and adjusted HR of clinical outcomes are shown in Figure 3. In MVD, after multivariable adjustment for clinical variables as described in the material and methods section, patients with a low DBP (< 70 mmHg) had a 53% increase in all-cause death (HR: 1.53; 95% CI: 1.10–2.14, p = 0.012) and a 65% increase in CV death (HR: 1.65; 95% CI: 1.06–2.56, p = 0.027) compared to patients with an average DBP (75–79 mmHg). Increased risks of all-cause death and CV death were also observed in patients with a DBP ≥ 80 mmHg (HR: 1.39; 95% CI: 0.99–1.96, p = 0.061; and HR: 1.36; 95% CI: 0.86–2.17, p = 0.191), but these differences were not statistically significant. The risk of non-CV death and hospitalization for HF did not increase in patients with a low DBP (< 70 mmHg) (HR: 1.41; 95% CI: 0.85–2.32, p = 0.184; and HR: 1.37; 95% CI: 0.82–2.28, p = 0.225) compared to patients with a DBP 75–79 mmHg. In patients with SVD, a low DBP (< 70 mmHg) was not associated with an increased risk of all-cause death (HR: 1.14; 95% CI: 0.81–1.61, p = 0.457), CV death (HR: 1.25; 95% CI: 0.81–1.96, p = 0.312), non-CV death (HR: 0.98; 95% CI: 0.59––1.63, p = 0.931), or hospitalization for HF (HR: 0.90; 95% CI: 0.59–1.35, p = 0.613), respectively.

Based on the average on-treatment SBP, although an increased risk of all-cause death and CV death was observed in patients with an SBP < 110 mmHg regardless of MVD or SVD, only the rate of CV death was significantly higher among those with MVD (HR: 1.81; 95% CI: 1.15–2.79, p = 0.007) versus patients with an SBP of 120–129 mmHg (**Suppl. Fig. 1**).

Sensitivity analysis

The data was analyzed after excluding patients with a baseline SBP < 120 mmHg. The risks of all-cause death and CV death (HR: 1.67; 95% CI: 1.15–2.44, p = 0.008; and HR: 1.78; 95% CI: 1.02–2.89, p = 0.041) was unchanged and significantly increased in patients with a low DBP (< 70 mmHg) compared to those of patients with a DBP of 75–79 mmHg and MVD. Patients with a low DBP (< 70 mmHg) and SVD were not at an increased risk of clinical outcomes as in the primary analysis (Fig. 4).

The spline curves based on baseline DBP and SBP at hospital admission were analyzed to address non-detected background morbidities affecting BP levels, and the results showed no J-shaped relationship with all-cause death or hospitalization for HF (**Suppl. Fig. 2**).

Table 1. Baseline characteristics of study population by average on-treatment diastolic blood pressure categories (n = 9,983).

	Overall (n = 9,983)	Average diastolic blood pressure during follow-up [mmHg]				P
		< 70 (n = 2,531)	70–74 (n = 1,938)	75–79 (n = 2,111)	≥ 80 (n = 3,403)	
Demographic						
Age [years]	63 (54, 73)	69 (58, 76)	65 (56, 74)	63 (54, 72)	59 (51, 69)	< 0.001
Male	7,569 (75.8%)	1,767 (69.8%)	1,450 (74.8%)	1,616 (76.6%)	2,736 (80.4%)	< 0.001
Body mass index [kg/m^2]	24.1 (22.1, 26.0)	23.4 (21.4, 25.2)	23.8 (21.9, 25.8)	24.1 (22.2, 25.9)	24.5 (22.9, 26.6)	< 0.001
Smoking:						< 0.001
Never	3,761 (38.6%)	1,042 (42.2%)	768 (40.5%)	791 (38.2%)	1,160 (35.0%)	
Former	1,904 (19.5%)	488 (19.8%)	399 (21.0%)	392 (18.9%)	625 (18.9%)	
Current	4,085 (41.9%)	939 (38.0%)	730 (38.5%)	888 (42.9%)	1,528 (46.1%)	
Clinical						
Hospital stays [days]	5 (4, 7)	6 (4, 8)	6 (4, 7)	5 (4, 7)	5 (4, 7)	< 0.001
Symptom to door time [h]	3.8 (1.5, 13.4)	3.8 (1.5, 13.3)	4.0 (1.6, 15.6)	3.7 (1.6, 12.9)	3.8 (1.5, 12.5)	0.142
Killip classification:						< 0.001
I	8,298 (83.1%)	1,949 (77.0%)	1,627 (84.0%)	1,805 (85.5%)	2,917 (85.7%)	
II	830 (8.4%)	209 (8.3%)	179 (9.2%)	172 (8.1%)	270 (7.9%)	
III	613 (6.1%)	195 (7.7%)	115 (5.9%)	116 (5.5%)	187 (5.5%)	
IV	242 (2.4%)	178 (7.0%)	17 (0.9%)	18 (0.9%)	29 (0.9%)	
GRACE risk score*:						< 0.001
Low	1,067 (10.7%)	49 (1.9%)	75 (3.9%)	159 (7.5%)	784 (23.0%)	
Intermediated	2,945 (29.5%)	392 (15.5%)	503 (26.0%)	746 (35.3%)	1,304 (38.3%)	
High	5,971 (59.8%)	2,090 (82.6%)	1,360 (70.2%)	1,206 (57.1%)	1,315 (38.6%)	
Previous heart failure	112 (1.1%)	37 (1.5%)	21 (1.1%)	17 (0.8%)	37 (1.1%)	0.203
Previous MI	699 (7.0%)	226 (8.9%)	154 (7.9%)	142 (6.7%)	177 (5.2%)	< 0.001
Previous ischemic stroke	543 (5.5%)	157 (6.2%)	121 (6.3%)	115 (5.5%)	150 (4.4%)	0.006
Previous ICH	50 (0.5%)	15 (0.6%)	10 (0.5%)	6 (0.3%)	19 (0.6%)	0.449
Hypertension	4,982 (49.9%)	1,165 (46.0%)	938 (48.4%)	1,039 (49.2%)	1,840 (54.1%)	< 0.001
Diabetes mellitus	2,708 (27.1%)	737 (29.1%)	546 (28.2%)	563 (26.7%)	862 (25.3%)	0.008
Dyslipidemia	1,164 (11.7%)	267 (10.5%)	219 (11.3%)	253 (12.0%)	425 (12.5%)	0.124
Chronic kidney disease	1,777 (17.8%)	613 (24.2%)	347 (17.9%)	315 (14.9%)	502 (14.8%)	< 0.001
Myocardial infarction:						< 0.001
NSTEMI	5,031 (50.4%)	1,120 (44.3%)	972 (50.2%)	1,105 (52.3%)	1,834 (53.9%)	
STEMI	4,952 (49.6%)	1,411 (55.7%)	966 (49.8%)	1,006 (47.7%)	1,569 (46.1%)	

→

Table 1. (cont.). Baseline characteristics of study population by average on-treatment diastolic blood pressure categories (n = 9,983).

	Overall (n = 9,983)	Average diastolic blood pressure during follow-up [mmHg]				P
		< 70 (n = 2,531)	70–74 (n = 1,938)	75–79 (n = 2,111)	≥ 80 (n = 3,403)	
Multivessel disease	4,545 (45.5%)	1,175 (46.4%)	902 (46.5%)	957 (45.3%)	1,511 (44.4%)	0.334
Anterior wall infarction	4,864 (48.7%)	1,031 (40.7%)	958 (49.4%)	1,083 (51.3%)	1,792 (52.7%)	< 0.001
LVEF < 40% in hospital	998 (10.0%)	328 (13.0%)	188 (9.7%)	183 (8.7%)	299 (8.8%)	< 0.001
Atrial fibrillation in hospital	189 (1.9%)	67 (2.6%)	40 (2.1%)	35 (1.7%)	47 (1.4%)	0.004
Hemodynamics at admission						
Systolic BP [mmHg]	130 (114, 150)	110 (100, 120)	120 (110, 135)	130 (120, 144)	150 (140, 169)	< 0.001
Diastolic BP [mmHg]	80 (70, 90)	60 (60, 70)	76 (70, 80)	80 (80, 88)	95 (90, 100)	< 0.001
Heart rate [bpm]	77 (66, 88)	72 (60, 84)	76 (66, 86)	78 (68, 88)	80 (70, 91)	< 0.001
Hemodynamics at discharge						
Systolic BP [mmHg]	110 (100, 120)	107 (100, 115)	110 (100, 120)	110 (100, 120)	120 (110, 130)	< 0.001
Diastolic BP [mmHg]	70 (60, 75)	60 (60, 70)	65 (60, 70)	70 (60, 74)	70 (66, 80)	< 0.001
Heart rate [bpm]	70 (64, 76)	70 (64, 76)	70 (64, 76)	70 (64, 77)	70 (64, 77)	0.363
Cardiac enzyme, peak level						
Troponin I [ng/mL]	19 (4, 50)	23 (6, 58)	19 (4, 47)	16 (3, 48)	16 (3, 49)	< 0.001
CK-MB [ng/mL]	52 (10, 169)	65 (14, 189)	49 (10, 164)	46 (9, 162)	47 (9, 162)	< 0.001
Medication*						
Antiplatelet agents	9,983 (100.0%)	2,531 (100.0%)	1,938 (100.0%)	2,111 (100.0%)	3,403 (100.0%)	1.000
Beta-blockers	8,734 (87.5%)	2,123 (83.9%)	1,669 (86.1%)	1,857 (88.0%)	3,085 (90.7%)	< 0.001
≥ 25% of optimal dose	1,353 (15.5%)	227 (10.7%)	210 (12.6%)	285 (15.3%)	631 (20.5%)	< 0.001
ACEI or ARBs	8,324 (83.4%)	2,024 (80.0%)	1,571 (81.1%)	1,756 (83.2%)	2,973 (87.4%)	< 0.001
Statins	9,534 (95.5%)	2,401 (94.9%)	1,845 (95.2%)	2,028 (96.1%)	3,260 (95.8%)	0.166
Moderate to high intensity	9,387 (98.4%)	2,355 (98.1%)	1,812 (98.2%)	1,996 (98.4%)	3,219 (98.7%)	0.223
Calcium channel blockers	610 (6.1%)	98 (3.9%)	93 (4.8%)	145 (6.9%)	274 (8.1%)	< 0.001

The data are presented as the number (%), and median (interquartile interval). Non-parametric continuous variables as assessed by the Kolmogorov-Smirnov method and were analyzed by Mann-Whitney U test. *GRACE risk score classification: 108 ≥: low, 109–140: intermediate, > 140: high; **Defined as a prescription at hospital discharge after acute coronary syndrome; ACEI — angiotensin converting enzyme inhibitor; ARB — angiotensin II receptor blocker; BP — blood pressure; ICH — intracranial hemorrhage; LVEF — left ventricular ejection fraction; MI — myocardial infarction; NSTEMI — non-ST--segment elevation myocardial infarction; STEMI — ST segment elevation myocardial infarction

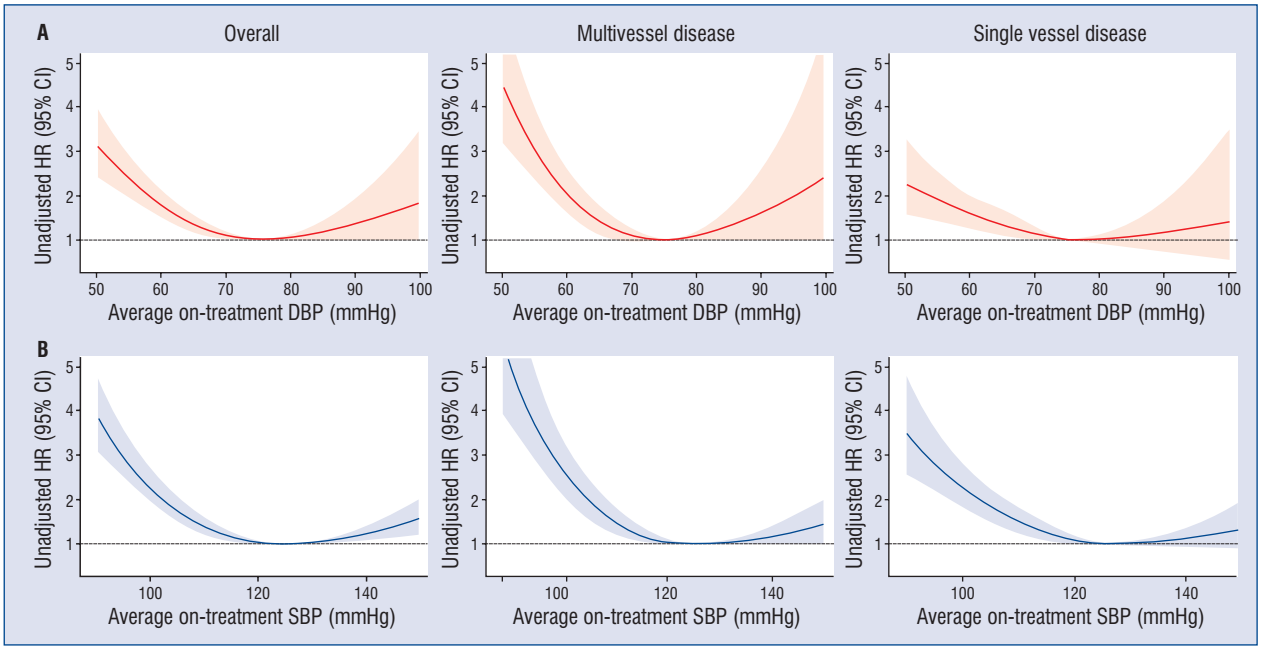


Figure 2. Restricted cubic spline model of all-cause death or hospitalization for heart failure (HF) in patients with multivessel disease (**A**) or single-vessel disease (**B**) during a 3-year follow-up according to on-treatment blood pressure. The dashed black horizontal lines indicate a hazard ratio (HR) of 1 and the painted areas indicate the 95% confidence interval (CI) (red line: diastolic BP [DBP]; blue line: systolic BP [SBP]).

Effect of multivessel revascularization strategies

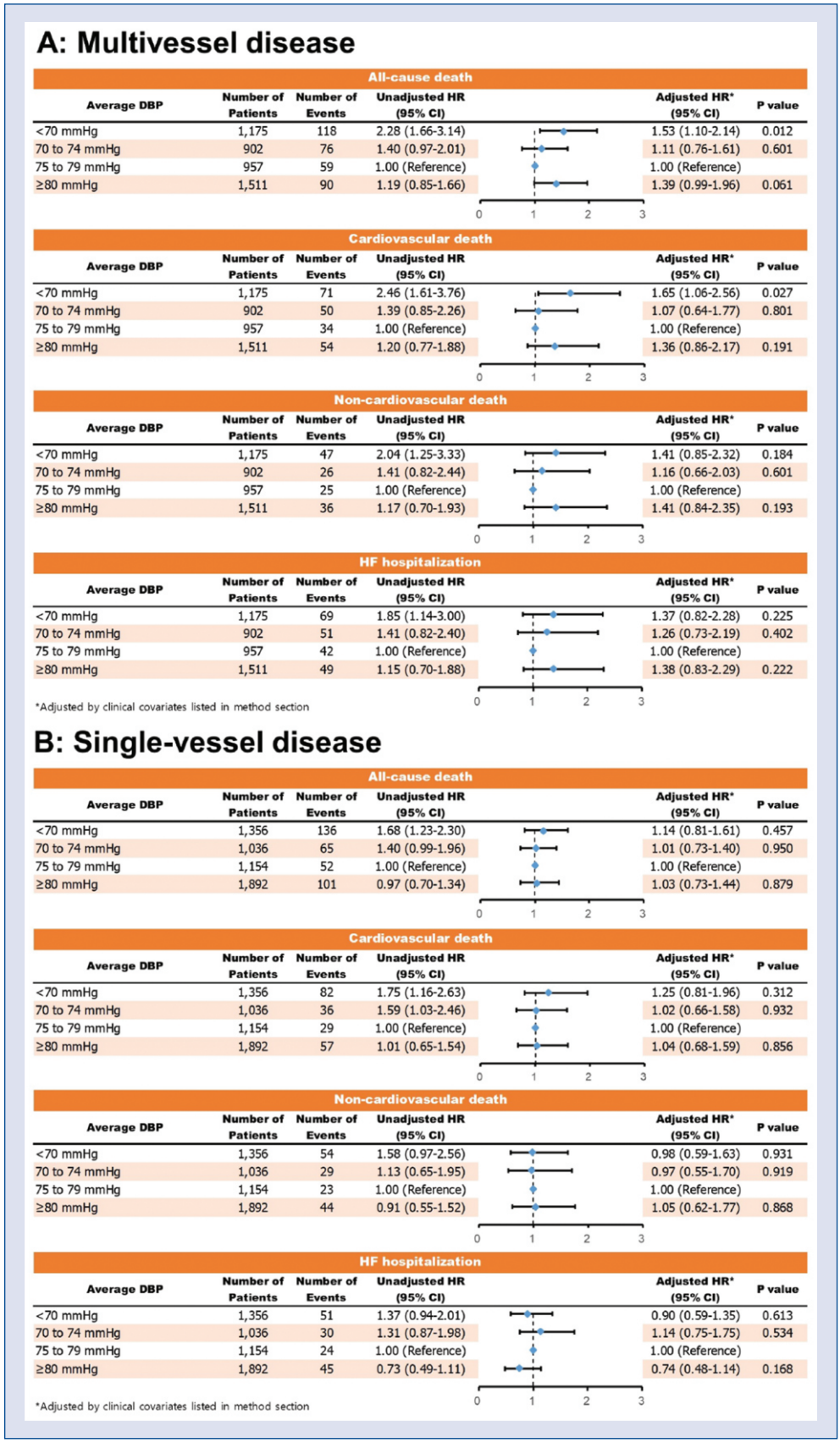
Procedural profiles were analyzed based on revascularization strategies in MVD (**Suppl. Table 2**). Of patients in MVD PCI, 1,235 (27.1%) patients underwent complete revascularization. Of these, 62% did non-IRA PCI immediately after culprit lesion PCI during the index procedure. According to revascularization strategies, the location of the culprit lesion, pre-PCI thrombolysis in myocardial infarction flow, and the number of diseased vessels were significantly different.

The effect of complete revascularization on clinical outcomes was also evaluated in patients with MVD. Whether or not complete revascularization was performed did not show a statistically significant effect on the risk of all-cause death, CV death, non-CV death, and hospitalization for HF (**Suppl. Fig. 3**).

Discussion

In this nationwide cohort study, it was demonstrated that a low average on-treatment DBP was associated with higher risks of all-cause death and CV death among patients with MVD compared to those with SVD, especially a DBP lower than 70 mmHg, among AMI patients who underwent PCI. An average on-treatment SBP of < 110 mmHg was associated with a higher risk of CV death in patients with MVD. Furthermore, these results are based on a J-shaped relationship, which was not observed based on baseline DBP and SBP. These findings suggest that the adverse effect of a low BP in patients with AMI who underwent revascularization through PCI is affected by the number of stenotic vessels with or without complete revascularization and associated with increased risks of all-cause death and CV death in patients with MVD, which has a high ischemic burden on the myocardium compared with SVD. These relationships were more emphasized by DBP, which is associated with coronary perfusion distal to the vessels.

Several studies have investigated the effects of low BP management on CV outcomes in CAD, and increasingly poor outcomes with a low BP have been reported with the presence of a J-shaped curve [4, 9, 14, 16–18]. Among the 54% of patients who underwent angioplasty among 10,001 patients with clinically evident CAD [16], a J-shaped relationship between BP management and CV events was demonstrated with an exponentially increased risk in patients with a low BP (< 110–120/ /< 60–70 mmHg). The same investigators [17] showed similar results in 4,162 ACS patients who underwent PCI. Among them, 26.7% showed a



A: Multivessel disease

All-cause death

Average DBP	Number of Patients	Number of Events	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	P value
<70 mmHg	1,175	118	2.28 (1.66-3.14)	1.53 (1.10-2.14)	0.012
70 to 74 mmHg	902	76	1.40 (0.97-2.01)	1.11 (0.76-1.61)	0.601
75 to 79 mmHg	957	59	1.00 (Reference)	1.00 (Reference)	
≥80 mmHg	1,511	90	1.19 (0.85-1.66)	1.39 (0.99-1.96)	0.061

Cardiovascular death

Average DBP	Number of Patients	Number of Events	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	P value
<70 mmHg	1,175	71	2.46 (1.61-3.76)	1.65 (1.06-2.56)	0.027
70 to 74 mmHg	902	50	1.39 (0.85-2.26)	1.07 (0.64-1.77)	0.801
75 to 79 mmHg	957	34	1.00 (Reference)	1.00 (Reference)	
≥80 mmHg	1,511	54	1.20 (0.77-1.88)	1.36 (0.86-2.17)	0.191

Non-cardiovascular death

Average DBP	Number of Patients	Number of Events	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	P value
<70 mmHg	1,175	47	2.04 (1.25-3.33)	1.41 (0.85-2.32)	0.184
70 to 74 mmHg	902	26	1.41 (0.82-2.44)	1.16 (0.66-2.03)	0.601
75 to 79 mmHg	957	25	1.00 (Reference)	1.00 (Reference)	
≥80 mmHg	1,511	36	1.17 (0.70-1.93)	1.41 (0.84-2.35)	0.193

HF hospitalization

Average DBP	Number of Patients	Number of Events	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	P value
<70 mmHg	1,175	69	1.85 (1.14-3.00)	1.37 (0.82-2.28)	0.225
70 to 74 mmHg	902	51	1.41 (0.82-2.40)	1.26 (0.73-2.19)	0.402
75 to 79 mmHg	957	42	1.00 (Reference)	1.00 (Reference)	
≥80 mmHg	1,511	49	1.15 (0.70-1.88)	1.38 (0.83-2.29)	0.222

*Adjusted by clinical covariates listed in method section

B: Single-vessel disease

All-cause death

Average DBP	Number of Patients	Number of Events	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	P value
<70 mmHg	1,356	136	1.68 (1.23-2.30)	1.14 (0.81-1.61)	0.457
70 to 74 mmHg	1,036	65	1.40 (0.99-1.96)	1.01 (0.73-1.40)	0.950
75 to 79 mmHg	1,154	52	1.00 (Reference)	1.00 (Reference)	
≥80 mmHg	1,892	101	0.97 (0.70-1.34)	1.03 (0.73-1.44)	0.879

Cardiovascular death

Average DBP	Number of Patients	Number of Events	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	P value
<70 mmHg	1,356	82	1.75 (1.16-2.63)	1.25 (0.81-1.96)	0.312
70 to 74 mmHg	1,036	36	1.59 (1.03-2.46)	1.02 (0.66-1.58)	0.932
75 to 79 mmHg	1,154	29	1.00 (Reference)	1.00 (Reference)	
≥80 mmHg	1,892	57	1.01 (0.65-1.54)	1.04 (0.68-1.59)	0.856

Non-cardiovascular death

Average DBP	Number of Patients	Number of Events	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	P value
<70 mmHg	1,356	54	1.58 (0.97-2.56)	0.98 (0.59-1.63)	0.931
70 to 74 mmHg	1,036	29	1.13 (0.65-1.95)	0.97 (0.55-1.70)	0.919
75 to 79 mmHg	1,154	23	1.00 (Reference)	1.00 (Reference)	
≥80 mmHg	1,892	44	0.91 (0.55-1.52)	1.05 (0.62-1.77)	0.868

HF hospitalization

Average DBP	Number of Patients	Number of Events	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	P value
<70 mmHg	1,356	51	1.37 (0.94-2.01)	0.90 (0.59-1.35)	0.613
70 to 74 mmHg	1,036	30	1.31 (0.87-1.98)	1.14 (0.75-1.75)	0.534
75 to 79 mmHg	1,154	24	1.00 (Reference)	1.00 (Reference)	
≥80 mmHg	1,892	45	0.73 (0.49-1.11)	0.74 (0.48-1.14)	0.168

*Adjusted by clinical covariates listed in method section

Figure 3. Forest plots of Cox regression analysis of clinical outcomes by multivessel disease (**A**) or single-vessel disease (**B**) of diastolic blood pressure (DBP) during a 3-year follow-up period; HR — hazard ratio; CI — confidence interval.

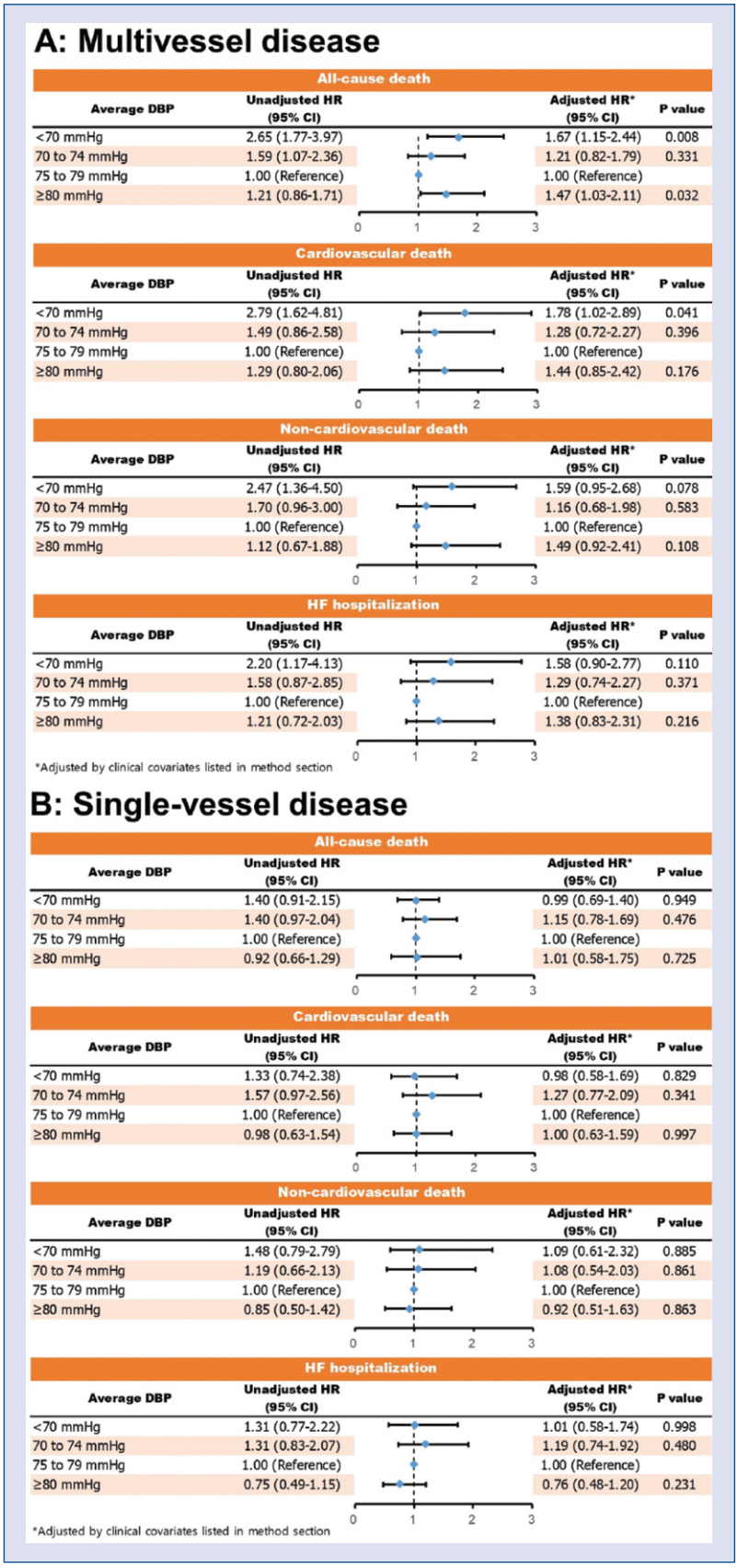


Figure 4. Sensitivity analysis: Forest plots of the Cox regression analysis for clinical outcomes by multivessel disease (**A**) and single-vessel disease (**B**) of diastolic blood pressure (DBP) during a 3-year follow-up period after excluding patients with baseline systolic blood pressure < 120 mmHg; HR — hazard ratio; CI — confidence interval.

plateau curve for BP at 110–130/70–90 mmHg. Böhm et al. [18] recently reported that the more frequent adverse outcomes associated with a low DBP (< 70 mmHg) were restricted to AMI patients with signs and symptoms of HF or to those with a low LV ejection fraction (< 40%) who did not undergo revascularization. In terms of SBP, there was an increase in the incidence of clinical outcomes at a low SBP (< 130 mmHg) irrespective of revascularization. Patients who underwent revascularization seemed to be at an increased risk of clinical outcomes at a low DBP, potentially due to improved coronary perfusion.

In the present study, an abolished J-shaped relationship between a low DBP and all-cause death and CV death in SVD was observed, concordant with a previous study and demonstrated that the association between low DBP and all-cause death and CV death appears pronounced in MVD with a J-shaped relationship despite revascularization. The effect of complete revascularization was also evaluated, which was expected to be superior to incomplete revascularization in preventing a major adverse cardiac event [25]. However, the present study showed no differences in clinical outcomes between revascularization strategies in MVD. The results herein, suggest that the association between a low DBP and clinical outcomes was not affected by reperfusion in patients with MVD due to the high ischemic burden compared to SVD. However, the association between a low SBP and poor outcomes was not affected by the number of stenotic vessels in the current study. These results are concordant with those of a prior study showing that reperfusion did not impact outcomes at a low SBP. Specific high-risk patients who required management with special attention to the low DBP during follow-up despite revascularization were found.

Myocardial blood flow depends on myocardial perfusion pressure during diastole [28]. Moreover, a low DBP is associated with increased arterial stiffness, which impairs the reservoir function of the aorta. This mechanism might be more pronounced in patients with complicated obstructive CAD, particularly those with MVD. This suggestion is reinforced by a previous study that showed a wide pulse pressure in patients with a low DBP, and more than 60% of patients with MVD had worse long-term mortality rates [29].

Although a low SBP appeared to increase adverse outcomes in both MVD and SVD, only an increased CV death rate was associated with MVD in the present study. A low SBP suggests more severe myocardial damage and could affect under-treatment. In an analysis of MI patients over 75 years of age, a low SBP within the first 48 hours of hospitalization was associated with increased incidence of all-cause death and CV death [30]. However, the fact that the current study population consisted of 53% of patients under 65 years of age should be considered, also the average on-treatment SBP were analyzed.

To address non-detectable background comorbidities affecting BP, patients with a baseline SBP < 120 mmHg were excluded from the sensitivity analysis. Also under evaluation, was the association between baseline BP level and clinical outcomes. Primary results were unchanged, indirectly suggesting that low DBP management might contribute to poor outcomes, especially in patients with MVD.

This study has several strengths, including its large AMI population derived from a nationwide multicenter registry. Long-term follow-up events were investigated using the average on-treatment BP. Due to the potential impact of reverse causality, results of the sensitivity analysis were compared. This study provides plausible explanations for the current results and is in line with previous studies. However, further studies are needed to determine whether more careful DBP management is necessary in AMI patients with MVD after revascularization

Limitations of the study

The present study has several limitations. This was a retrospective analysis of a preexisting registry and not a prospective trial. Therefore, the results cannot be extrapolated to other populations. Data regarding adverse events related to antihypertensive management are lacking, and adverse events might occur more frequently in subjects with a low BP. Due to insufficient data, no investigation was done into whether medication changes during follow-up could have affected the outcomes. Finally, BP was measured using different instruments across the hospital and clinical visits, which may have affected the relationship between BP and outcomes. However, the preferred recommendations specified the use of manual mercury sphygmomanometers during the study period. Finally, patients with in-hospital death and major adverse cardiac events were excluded from the analysis. Therefore, the results of the present study suggest that this association is possibly the result of selection confounders. Despite these limitations, this study was a large and comprehensive investigation that evaluated the impact of

MVD on the association between BP and clinical outcomes in patients with AMI who underwent revascularization through PCI. The study used data from a nationwide registry and reported some novel findings in addition to showing a trend similar to that observed in previous studies.

Conclusions

Among patients with AMI who underwent PCI, a low average on-treatment DBP was associated with increased risks of all-cause death and CV death, especially in patients with MVD. Thus, clinicians may need to exercise caution when treating specific individuals with a low DBP.

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Conflict of interest: None declared

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Procedural outcomes of chronic total occlusion percutaneous coronary interventions in patients with acute kidney injury

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Abstract

Background: *The prognostic impact of contrast-associated acute kidney injury (CA-AKI) in patients undergoing chronic total occlusion (CTO) percutaneous coronary intervention (PCI) remains underestimated.*

Methods: *We examined 2707 consecutive procedures performed in a referral CTO center between 2015 and 2019. CA-AKI was defined as an increase in serum creatinine ≥ 0.3 mg/dL or ≥ 50% within 48 h post-PCI. Primary endpoints were in-hospital major adverse cardiac and cerebrovascular events (MACCE, composite of all-cause death, myocardial infarction, target vessel revascularization, stroke) and at 1 year of follow-up.*

Results: *The overall incidence of CA-AKI was 11.5%. Technical success was comparable (87.2% vs. 90.5%, p = 0.056) whereas procedural success was lower in the CA-AKI group (84.3% vs. 89.7%, p = 0.004). Overall in-hospital MACCE was 1.3%, and it was similar in patients with and without CA-AKI (1.6% vs. 1.3%, p = 0.655); however, the rate of pericardial tamponade requiring pericardiocentesis was significantly higher in patients with CA-AKI (2.2% vs. 0.5%, p = 0.001). In multivariate analysis, CA-AKI was not independently associated with higher risk for in-hospital MACCE (adjusted odds ratio 1.34, 95% confidence intervals [CI] 0.45–3.19, p = 0.563). At a median follow-up time of 14 months (interquartile range [IQR], 11 to 35 months), 1-year MACCE was significantly higher in patients with vs. without CA-AKI (20.8% vs. 12.8%, p < 0.001), and CA-AKI increased the risk for 1-year MACCE (adjusted hazard ratio 1.46, 95% CI 1.07–1.95, p = 0.017) following CTO PCI.*

Conclusions: *Contrast-associated acute kidney injury in patients undergoing CTO PCI occurs in approximately one out of 10 patients. Our study highlights that patients developing CA-AKI are at increased risk for long-term MACCE.* (Cardiol J 2024; 31, 1: 84–94)

Key words: percutaneous coronary intervention, contrast-associated acute kidney injury, outcomes

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Introduction

Percutaneous coronary intervention (PCI) for chronic total occlusion (CTO) remains the most technically challenging lesion subset in contemporary interventional practice, which requires a larger amount of contrast media compared to PCI for non-occlusive coronary artery disease [1]. Furthermore, pre-existing chronic kidney disease in patients undergoing CTO PCI has been associated with an increased risk for major adverse cardiac and cerebrovascular events (MACCE) both in-hospital and in the long term, studied in various patient cohorts [2–9]. Novel strategies and techniques have been described that overcome the growing need for appropriate management to prevent renal function impairment, such as applying meticulous pre-procedural hydration protocols, device-based contrast reduction, or use of intracoronary imaging [10]. An expert consensus document [11] rephrased the definition of PCI-related renal function impairment by replacing the previously used contrast-induced nephropathy (CIN, defined as an increase of serum creatinine (seCr) ≥ 0.5 mg/dL and/or an increase of the baseline seCr ≥ 25% [12]) to contrast-associated acute kidney injury (CA-AKI, defined as an increase of baseline seCr ≥ 0.3 mg/dL or an increase of baseline seCr ≥ 50% [13]) with the ultimate goal of identifying patients in danger appropriately and to standardize further research efforts. Currently, however, the incidence of CA-AKI is rarely available in studies providing systematical renal function assessment following CTO PCI [14, 15]. Because of all the above, discrepancy between previously designed studies and current practices may exist, possibly leading to an underestimation of the impact of CA-AKI on the outcomes of CTO revascularization. Accordingly, we sought to examine a large single-center CTO PCI registry to examine the prognostic impact of CA-AKI on in-hospital outcomes and at 1 year following the index PCI.

Methods

Study population and patient selection

We analyzed retrospectively the clinical, angiographic, and procedural characteristics of overall consecutive 2707 procedures with 2801 target vessels, performed in a referral CTO PCI center at the Division of Cardiology and Angiology II, University Heart Center Freiburg, Bad Krozingen between 2015 and 2019. Patients undergoing CTO PCI for acute coronary syndrome or stable procedures without baseline renal function assessment were excluded. Informed consent for PCI was obtained from each patient, and the study was approved by the Ethics Committee of the Albert-Ludwigs – Universität Freiburg, Germany (ID: EK 21-1100) and is in accordance with the ethical guidelines of the Declaration of Helsinki as revised in 1983.

Endpoints and definitions

The primary endpoint was procedural success as a composite of technical success without in-hospital major adverse cardiac and cerebrovascular events (MACCE) and pericardial tamponade requiring either pericardiocentesis or surgery. Technical success was defined as successful revascularization of chronic occlusive coronary lesions with achievement of < 30% residual diameter stenosis within the treated segment and restoration or maintenance of thrombolysis in myocardial infarction (TIMI) grade 3 antegrade flow. In-hospital MACCE included any of the following adverse events prior to hospital discharge: mortality, myocardial infarction (MI), recurrent symptoms requiring urgent target vessel revascularization (TVR), target lesion revascularization (TLR) with PCI or surgery, and stroke. Myocardial infarction was defined using by the 4th Universal Definition (type 4a) described by Thygesen [16].

One-year MACCE is defined as the composite of adverse events after hospital discharge such as mortality, MI, urgent TVR or TLR with PCI or surgery, and stroke. Data collection on short- and long-term follow-up of patients who underwent PCI were obtained during office visits, via telephone contacts with the patient or family members, and careful assessment of medical records, as necessary.

Secondary endpoints were components of the primary endpoint, coronary perforation managed conservatively, and Bleeding Academic Research Consortium (BARC) class 3 to 5 during in-hospital stay.

All PCI procedures were performed in patients with stable angina. Chronic total occlusion was defined as a coronary lesion with TIMI grade 0 flow of at least 3 months duration as described by the 2019 Consensus Document of the EuroCTO Club [17]. The J-CTO score was calculated as described by Morino et al. [18]. A CTO procedure was defined as "retrograde" if an attempt was made to cross the lesion through a collateral vessel or bypass graft supplying the target vessel distal to the lesion; if not, the procedure was classified as "antegrade". Contrast injection was done exclusively via manual injection on both ipsilateral and contralateral

sides. Pre-procedural hydration was obtained in patients with pre-existing renal insufficiency and were discharged 48 hours after the procedure as the earliest. Aside from the pre-procedural hydration protocol, no other pharmacological regimens were used. Metformin intake was suspended 2 days prior to the index PCI in diabetic patients on oral antidiabetics. For all CTO PCIs non-ionic low osmolar contrast agent Iomeron 350 (Bracco Imaging, Milan, Italy) was used.

Renal function assessment

The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula and the serum creatinine measurement obtained prior to and temporally closest to the index procedure [19]. Chronic kidney disease (CKD) was defined as eGFR < 60 mL/min/1.73 m^2, and eGFR level was considered normal > 60 mL/min/1.73 m^2. Classification of CKD stages was based upon the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) [20] guidelines (normal or high [I] ≥ 90 mL/min/1.73 m^2; mildly decreased [II] 60–89 mL/min/1.73 m^2; mildly to moderately decreased [IIIa] 45–59 mL/min/1.73 m^2; moderately to severely decreased [IIIb] 30–44 mL/min/1.73 m^2; severely decreased [IV] 15–29 mL/min/1.73 m^2; kidney failure [V] < 15 mL/min/1.73 m^2).

Contrast-associated acute kidney injury (CA-AKI) was defined as proposed by Kidney Disease: Improving Global Outcomes (KDIGO) [11, 13], and was classified as an increase of baseline seCr ≥ 0.3 mg/dL or an increase of baseline seCr ≥ 50% (Stage I); an increase of baseline seCr by 100–200% (Stage II), and an increase of > 200% or a follow-up seCr of ≥ 4 mg/dL with an acute increase of ≥ 0.5 mg/dL (Stage III).

All patients had at least one creatinine measurement performed within 24 hours prior to the index procedure, and underwent post-procedural renal function assessment 8, 16, 24, and 48 hours post-PCI (data availability was 92.8%, 76.9%, 98.3%, and 72.3% of all patients, respectively).

Statistical analysis

Categorical variables were expressed as percentages and were compared using Pearson's χ^2 test or Fisher's exact test. Continuous variables were presented as mean ± standard deviation or median (interquartile range [IQR]) unless otherwise specified and were compared using the t-test and one-way analysis of variance (ANOVA) for normally distributed variables; the Wilcoxon rank-sum test and the Kruskal-Wallis test were applied for non-parametric continuous variables, as appropriate.

Multivariable logistic regression was used to identify the predictors for CA-AKI in CTO PCI after adjusting for confounding variables selected on the grounds of a) univariable association in the present study ($p < 0.05$) or b) previously established links with CA-AKI [14]; such variables included age, diabetes mellitus, reduced left ventricular ejection fraction (< 40%), CKD, baseline serum level of hemoglobin, periprocedural major perforation, and fluoroscopy time. Stepwise backward elimination was used forming the final model. We also used multivariable logistic regression to determine the association between CA-AKI, primary, and secondary endpoints. Crude and adjusted odd ratios (OR) were calculated after selection of the confounding variables based on an univariable association with the given endpoints at $p < 0.05$. MACCE-free survivals during 1 year of follow-up were calculated using the Kaplan–Meier method and compared between groups using the log-rank test. An adjusted Cox proportional hazard regression model was used to identify predictors of long-term MACCE and to calculate hazard ratios (HR). Confounding variables for the Cox proportional regression model were selected based on an univariable association with 1-year MACCE at $p < 0.05$. All statistical analyses were performed with JMP 13.0 (SAS Institute, Cary, North Carolina). A 2-sided p value of 0.05 was considered statistically significant.

Results

Clinical, angiographic, and technical characteristics

The overall incidence of CA-AKI was 11.5%. The baseline clinical features of the study cohort are shown in Table 1, categorized according to procedures with (n = 312) and without (n = 2395) CA-AKI. Patients developing kidney injury had significantly higher prevalence of diabetes mellitus, hypertension, congestive heart failure, and prior previous coronary artery bypass graft surgery (CABG) compared to those without CA-AKI. Baseline serum hemoglobin levels and eGFRs were significantly lower in patients with CA-AKI. Pre-existing CKD was more commonly observed in patients with post-PCI renal dysfunction (41.7% vs. 20.3%, $p < 0.001$).

The angiographic and technical parameters of the study interventions are given in Table 2. The most common CTO PCI target lesions were the

Table 1. Clinical characteristics of patients undergoing percutaneous coronary interventions for chronic total occlusion with and without contrast-associated acute kidney injury (CA-AKI).

Variable	Overall (n = 2707)	No CA-AKI (n = 2395)	CA-AKI (n = 312)	P
Age [years]*	65.6 ± 10.4	65.0 ± 10.3	70.1 ± 9.9	< 0.001
Men	83.6%	83.9%	81.7%	0.344
BMI [kg/m^2]*	28.5 ± 4.6	28.5 ± 4.6	28.4 ± 4.8	0.720
Diabetes mellitus	29.1%	28.0%	37.6%	< 0.001
Hypercholesterinemia	90.7%	90.8%	89.6%	0.492
Hypertension	86.2%	85.1%	94.1%	< 0.001
Smoking (current)	19.7%	20.2%	16.0%	0.079
LVEF‡:				< 0.001
Normal	65.4%	66.9%	54.0%	
Moderately reduced	20.0%	19.5%	23.5%	
Reduced	10.0%	9.6%	12.8%	
Low	4.6%	4.0%	9.7%	
Family history of CAD	44.6%	44.9%	41.8%	0.344
Heart failure	4.3%	3.8%	8.2%	0.001
NYHA classification:				< 0.001
I	18.6%	19.5%	12.6%	
II	50.2%	50.8%	45.4%	
III	29.0%	27.8%	37.8%	
IV	2.1%	1.9%	4.2%	
Prior MI	38.5%	37.9%	43.6%	0.066
Prior CABG	18.7%	17.7%	26.6%	< 0.001
Baseline hemoglobin [g/dL]*	14.2 ±1.5	14.2 ± 1.5	13.6 ± 1.7	< 0.001
Baseline creatinine [mg/dL]†	1.00 (0.89, 1.17)	1.00 (0.88, 1.14)	1.10 (0.93, 1.37)	< 0.001
Baseline eGFR [mL/min/1.73 m^2]*	74.5 ± 18.9	75.7 ± 18.1	65.5 ± 21.6	< 0.001
Chronic kidney disease	22.7%	20.3%	41.7%	< 0.001

*Mean ± standard deviation; †Median (interquartile range); ‡Left ventricular function groups are indicated as follows: normal (52–100%) moderately reduced (41–51%), reduced (30–40%), low (0–29) in males, and normal (54–100%), moderately reduced (41–53%), reduced (30–40%), low (0–29%) in females; BMI — body mass index; CABG — coronary artery bypass graft; CAD — coronary artery disease; eGFR — estimated glomerular filtration rate; LVEF — left ventricular ejection fraction; MI — myocardial infarction; NYHA — New York Heart Association

right coronary artery (49.1%) followed by the left anterior descending artery (24.9%) and circumflex artery (24.5%). Lesions were more complex in the CA-AKI group represented by higher J-CTO scores (2.9 ± 1.2 vs. 2.5 ± 1.2, p < 0.001) and the incidence of CA-AKI increased with lesion complexity (Fig. 1). Radial access was less frequently applied in patients post-PCI CA-AKI (23.2% vs. 28.9%, p = 0.034), whereas rotational atherectomy (11.3% vs. 5.3%, p < 0.001) and the retrograde approach (34.5% vs. 28.6%, p = 0.029) were more commonly used in these patients. The overall stent length was significantly longer in the CA-AKI cohort (64 [IQR 38–94 mm] vs. 56 [IQR 36–86 mm], p = 0.012).

In-hospital outcomes

The overall technical and procedural success rates were 90.2% and 89.1%, respectively. The procedural characteristics are presented in Table 3. Median contrast volume, dose area product, and procedure and fluoroscopy time were 270 (200–470) mL, 10028 (5723–17624) cGy × cm^2, and 86 (54–133) and 37.0 (22.0–65.0) minutes, respectively, and significantly differed across the groups (Table 3). The contrast-volume/eGFR ratio was significantly higher in patients with CA-AKI compared to patients with preserved post-PCI renal function (4.96 [IQR 3.03–7.83] vs. 3.63 [IQR 2.51–5.29], p < 0.001).

Table 2. Angiographic and technical characteristics of patients undergoing percutaneous coronary interventions (PCI) for chronic total occlusion with and without contrast-associated acute kidney injury (CA-AKI).

Variable	Overall (n = 2801)	No CA-AKI (n = 2482)	CA-AKI (n = 319)	P
J-CTO Score*	2.5 ± 1.2	2.5 ± 1.2	2.9 ± 1.2	< 0.001
Moderate/severe calcification	67.0%	65.8%	76.0%	< 0.001
Target vessel:				0.875
LM	1.0%	1.0%	0.9%	
LAD	25.2%	24.9%	27.3%	
CX	24.2%	24.5%	22.3%	
RCA	49.1%	49.1%	48.9%	
Graft	0.6%	0.6%	0.6%	
Radial access used	28.2%	28.9%	23.2%	0.034
Rotational atherectomy	6.0%	5.3%	11.3%	< 0.001
Crossing strategy used:				0.029
Antegrade-only	70.8%	71.4%	65.5%	
Retrograde	29.2%	28.6%	34.5%	
Number of DES used (n)†	2 (1, 3)	2 (1, 3)	2 (1, 3)	0.209
Overall stent length [mm]†	56 (36, 86)	56 (36, 86)	64 (38, 94)	0.012
Multivessel PCI	27.0%	26.4%	31.4%	0.0601
Technical success	90.2%	90.5%	87.2%	0.056

*Mean ± standard deviation; †Median (interquartile range); CTO — chronic total occlusion; CX — circumflex artery; DES — drug eluting stent; J-CTO — Japanese Chronic Total Occlusion; LAD — left anterior descending artery; LM — left main artery; RCA — right coronary artery

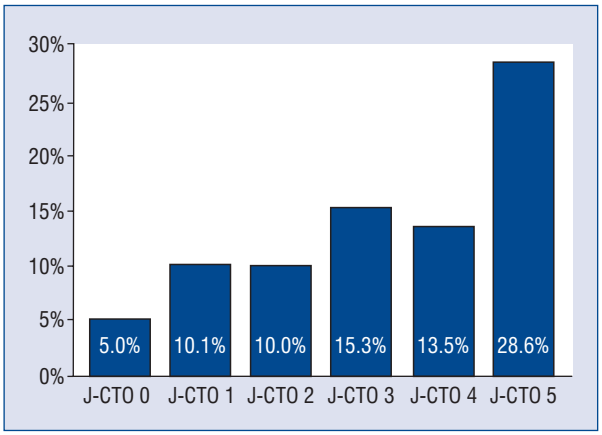

Figure 1. The incidence of contrast-associated acute kidney injury increased with lesion complexity classified by J-CTO score (p = 0.009); CTO — chronic total occlusion; J — Japanese.

On multivariable logistic regression the fluoroscopy time, level of serum hemoglobin at admission, age, left ventricular ejection fraction < 40%, hypertension, and pre-existing CKD were independent predictors for CA-AKI (Table 4).

The overall in-hospital MACCE was 1.3% (Table 3), and was comparable between patients with and without post-procedural kidney injury (1.6% vs. 1.3%, p = 0.655). Pericardial tamponade (2.2% vs. 0.5%, p = 0.001), vascular access complications (4.4% vs. 1.8%, p = 0.031), and bleeding (6.9% vs. 2.0%, p < 0.001), were more commonly observed in patients with CA-AKI vs. without CA-AKI.

As shown in Table 5, CA-AKI was independently associated with an increased risk for in-hospital BARC class 3–5 bleeding (OR 3.47 [95% confidence interval [CI] 1.88–6.18], p < 0.001), whereas technical success (OR 1.36 [95% CI 0.90–2.02], p = 0.144), coronary perforation (OR 1.40 [95% CI 0.64–3.46], p = 0.422), and in-hospital major complications (OR 1.18 [95% CI 0.45–2.73], p = 0.721) were not significantly linked with CA--AKI on a multivariate level.

Procedural outcomes at 1 year of follow-up

The median follow-up time was 14 months (IQR 11–35 months). The cumulative incidence of MACCE at 1 year was 13.7%, and it significantly differed in patients with vs. without post-procedural CA-AKI (20.8% vs. 12.8%, p < 0.001),

Table 3. Procedural outcomes of patients undergoing percutaneous coronary interventions for chronic total occlusion with and without contrast-associated acute kidney injury (CA-AKI).

Variable	Overall (n = 2707)	No CA-AKI (n = 2395)	CA-AKI (n = 312)	P
Procedural success	89.1%	89.7%	84.3%	0.004
Length of hospital stay [days]*	2 (2, 2)	2 (2, 2)	2 (2, 3)	< 0.001
Procedural time [min]*	86 (54, 133)	84 (53, 129)	100 (65, 170)	< 0.001
Fluoroscopy time [min]*	37.0 (22.0, 65.0)	36.0 (21.0, 63.0)	47.5 (28.3, 82.0)	< 0.001
Contrast volume [mL]*	270 (200, 400)	270 (200, 400)	300 (200, 418)	< 0.001
Dose area product [cGy × cm^2]*	10028 (5723, 17264)	9770 (5660, 16639)	12993 (6509, 22366)	< 0.001
CV/eGFR [min]*	3.72 (2.55, 5.48)	3.63 (2.51, 5.29)	4.96 (3.03, 7.83)	< 0.001
CV/eGFR ratio > 3.7	50.5%	48.7%	65.1%	< 0.001
Major complications‡	2.1%	1.8%	3.9%	0.019
In-hospital MACCE:	1.3%	1.3%	1.6%	0.655
Death	0.3%	0.3%	0.6%	0.233
MI	0.2%	0.3%	0.0%	—
Stroke	0.2%	0.1%	1.0%	0.013
TVR	1.0%	1.1%	0.6%	0.465
TLR	1.0%	1.0%	0.6%	0.761
Pericardial tamponade§	0.7%	0.5%	2.2%	0.001
Vascular access complication	2.1%	1.8%	4.4%	0.031
Bleeding#	2.5%	2.0%	6.9%	< 0.001
Perforation	2.4%	2.3%	3.2%	0.324

*Median (interquartile range); ‡Composite of in-hospital major adverse cardiac and cerebrovascular events (MACCE) and pericardial tamponade requiring either pericardiocentesis or surgical evacuation; §Pericardial tamponade requiring pericardiocentesis or surgical evacuation; #Bleeding Academic Research Consortium (BARC) class 3 to 5; CV — contrast volume; eGFR — estimated glomerular filtration rate; MI — myocardial infarction; TLR — target lesion revascularization; TVR — target vessel revascularization

Table 4. Multivariate logistic regression to predict confounders for contrast-associated acute kidney injury in patients undergoing percutaneous coronary interventions for chronic total occlusion.

Variable	Risk ratio	Lower 95% CI	Upper 95% CI	P
Fluoroscopy time [min]*	**1.03**	**1.01**	**1.05**	**< 0.0001**
Hemoglobin at admission [g/dL]†	**0.85**	**0.78**	**0.93**	**< 0.001**
Age [year]*	**1.18**	**1.11**	**1.26**	**< 0.001**
LVEF < 40%	**1.63**	**1.15**	**2.30**	**0.007**
Diabetes mellitus	1.28	0.97	1.69	0.087
Hypertension	**2.21**	**1.29**	**4.09**	**0.003**
Contrast volume [mL]‡	1.02	0.99	1.05	0.233
Rotational atherectomy	1.33	0.82	2.07	0.234
Chronic kidney disease	**1.39**	**1.01**	**1.89**	**0.041**
Pericardial tamponade	2.72	0.96	7.17	0.060

*Per 10-unit increment; †Per 1 unit increment; ‡Per 100-unit increment; CI — confidence interval; LVEF — left ventricular ejection fraction

mostly driven by TVR (19.6% vs. 10.9%, p < 0.001), all-cause mortality (4.5% vs. 1.7%, p = 0.001), and MI (1.9% vs. 0.9%, p = 0.038). The adjusted Cox regression model confirmed an independent association between CA-AKI and the risk of 1-year major adverse events (HR 1.46 [95% CI 1.07–1.95], p = 0.017).

Patients with CA-AKI showed worse MACCE-free (log-rank p < 0.001) survival on Kaplan–Meier analysis (Fig. 2), mostly driven by higher rate of

Table 5. Multivariate analysis between secondary endpoints (technical failure, major complications, perforation, bleeding, one-year MACCE) and contrast-associated acute kidney injury.

Variable	Non-adjusted			Adjusted		
	Odds ratio	95% CI	P	Odds ratio	95% CI	P
Technical failure	1.38	0.95–1.97	0.079	1.36	0.90–2.02	0.144
Perforation	1.41	0.67–2.67	0.326	1.40	0.64–3.46	0.422
In-hospital MACCE†	1.24	0.42–2.95	0.664	1.34	0.45–3.19	0.563
Major complications*	**2.14**	**1.07–3.96**	**0.033**	1.18	0.45–2.73	0.721
Bleeding	**3.64**	**2.08–6.16**	**< 0.001**	**3.47**	**1.88–6.18**	**< 0.001**
One-year MACCE†§	**1.65**	**1.26–2.14**	**< 0.001**	**1.46**	**1.07–1.95**	**0.017**

*Composite of in-hospital major adverse cardiac and cerebrovascular event (MACCE) and pericardial tamponade requiring either pericardiocentesis or surgical evacuation; †Composite of all-cause death, myocardial infarction, stroke, target vessel revascularization, and lesion revascularization; §Hazard ratio; CI — confidence interval

target vessel failure (log-rank $p < 0.001$), mortality (log-rank $p = 0.001$), and MI (log-rank $p = 0.042$). MACCE-free survivals significantly differed both in successful vs. failed CTO PCI, with less favorable outcomes in patients developing CA-AKI post-PCI (Fig. 3).

Discussion

To the best of our knowledge, our study is the largest to date evaluating the impact of CA-AKI following CTO PCI. The major findings of our analysis are the following: (a) CA-AKI occurs frequently in patients undergoing CTO PCI (11.5%); (b) the incidence of in-hospital MACCE is similar in patients with and without post-PCI AKI; (c) at 1 year of follow-up, patients with CA-AKI are more likely to have major adverse events, (d) due to higher risk of mortality, and TVR.

Contrast-associated acute kidney injury has been identified as a major predictor for in-hospital mortality, MI, and bleeding in the all-comer PCI population regardless the severity of CA-AKI [21]. Nevertheless, the risk of acquiring sustained renal dysfunction seems dependent on the severity of CA-AKI [22]. These latter associations have raised awareness that CA-AKI may have an impact on adverse events following invasive angiography and angioplasty [11], presumably as a marker rather than a mediator. Adequately designed randomized controls trials, however, have yet to prove that prevention of CA-AKI could positively impact long-term survival, especially in complex patient subgroups such as with CTO PCI requiring larger amounts of contrast media or exposing patients to higher risk of hemodynamic instability. Our study implies that symptomatic pericardial tamponade, bleeding, and vascular access site complications were more frequent in patients developing CA-AKI. The latter observational finding is a potential explanation of how renal hypoxia (direct [cardiogenic shock, low cardiac output syndrome] or indirect [bleeding]) triggers CA-AKI [23]; however, our study was not designed to assess the underlying pathophysiology of CA-AKI. Nevertheless, clinically significant BARC 3–5 bleeding showed the strongest impact on triggering CA-AKI, in combination with a significant association between CA-AKI and decreasing pre-procedural serum level of hemoglobin (Table 4).

The novel standardized definition of AKI provides a stable ground for comparative studies estimating the true impact of CTO-PCI-related renal dysfunction [11]. Werner et al. [14] examined 1924 consecutive CTO PCIs in a single-center study, designed prospectively to have at least 48 hours post-PCI renal function assessment for the majority of the patients. The incidence of CA-AKI was 5.6%, and predictors for CA-AKI were identified, such as baseline hemoglobin, ejection fraction < 40%, age, fluoroscopy time, major coronary perforations, diabetes, and CKD. Patients with post-PCI AKI had higher in-hospital mortality, major coronary perforations, and pericardiocentesis. Our study represents a 2-fold higher incidence of CA-AKI compared to the latter study, which can be explained with the higher pre-existing CKD rates (22.7% vs. 17.7%). Despite the higher incidence, predictors for CA-AKI in our study fully matched Werner's findings – extended fluoroscopy time, CKD, LVEF < 40%, and baseline hemoglobin level were similarly recognized in our cohort (Table 4). Additionally, our analysis shows that pericardial tamponade was significantly higher

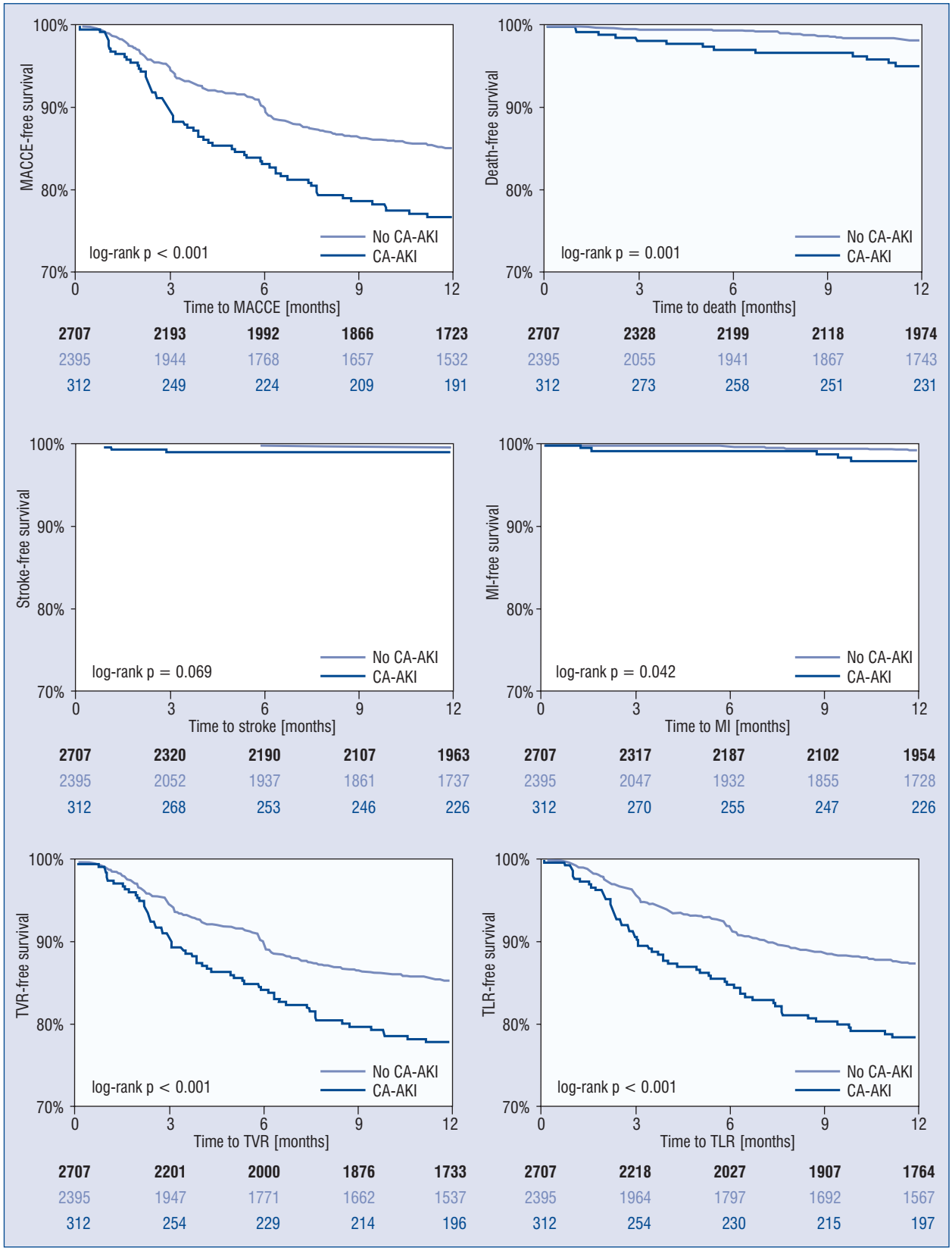

Figure 2. Kaplan–Meier curves of 1-year major adverse cardiac and cerebrovascular events (MACCE) in patients undergoing chronic total occlusion percutaneous coronary interventions (PCI) with and without contrast-associated acute kidney injury (CA-AKI); MI — myocardial infarction; TLR — target lesion revascularization; TVR — target vessel revascularization

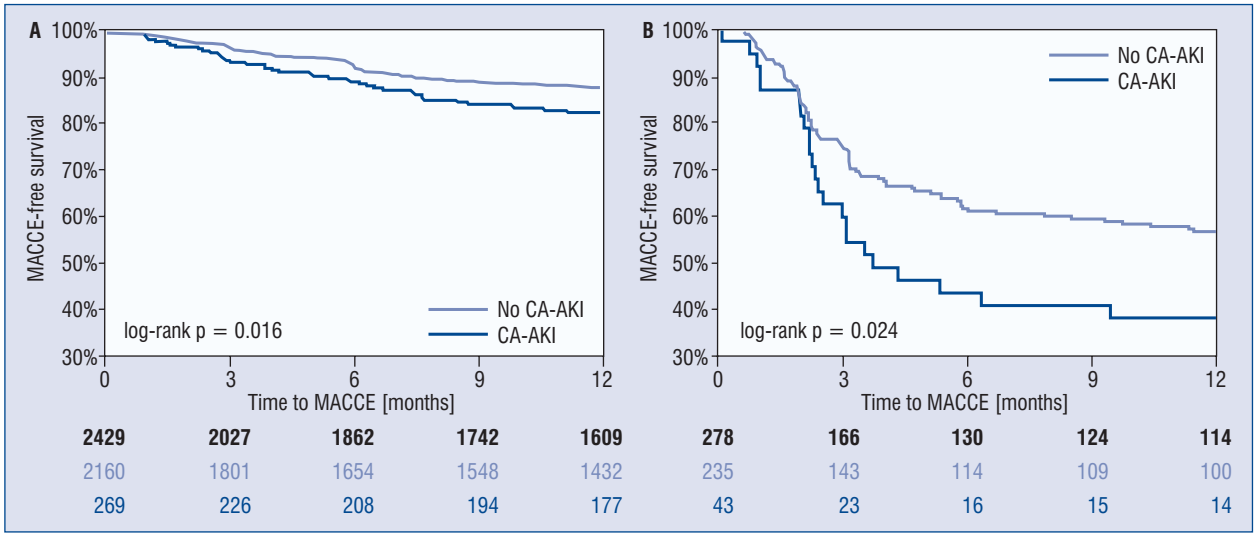

Figure 3. Kaplan-Meier curves of one-year major adverse cardiac and cerebrovascular events (MACCE) in patients undergoing successful (**A**) versus failed (**B**) percutaneous coronary interventions (PCI) for chronic total occlusion (CTO) with and without contrast-associated acute kidney injury (CA-AKI).

in the CA-AKI group (p = 0.001); however, on a multivariate level major coronary perforations requiring intervention were not significantly associated CA-AKI development (OR 2.78, p = 0.055). The potential role of significant pericardial effusion on post-PCI AKI, however, is inevitable because low cardiac output syndrome may cause prolonged medullar hypoxia, which leads to acute renal function impairment. In-hospital MACCE, major complications (composite of in-hospital MACCE and pericardial tamponade), and significant coronary perforations were not independently linked with newly developed AKI. The latter phenomenon is potentially explained by the immediate and appropriate treatment of coronary extravasation, which may decrease the probability of hemodynamic instability and the occurrence of any subsequent adverse event.

Azzalini et al. [15] reported 9.1% of CA-AKI from a more heterogenous but smaller cohort of 1092 patients undergoing CTO PCI cases, collected retrospectively from 5 dedicated international CTO centers. Although the primary endpoint of the study aimed to target the outcomes of CTO PCI in patients with baseline CKD (overall 19.6%), the impact of CA-AKI on long-term outcomes was also reported. There were significant differences reported at 1 year of follow-up (median follow-up time of 466 days [IQR 318–1124]) in terms of all-cause (9.3% vs. 3.7%, p = 0.001) and cardiac (8.1% vs. 1.7%, p < 0.001) mortality, but not with target-vessel MI and target lesion failure. Furthermore, on Kaplan–Meier curve analysis, only a higher trend was shown for CA-AKI related all-cause death at 1 year following the index PCI. Our study, however, showed slightly different outcomes because patients with CA-AKI suffered a higher rate of (a) all-cause death, (b) target vessel and lesion revascularization, and (c) MI on Kaplan–Meier analysis (Fig. 2) leading to inferiority in MACCE-free survival compared to patients with preserved renal function. These differences may be explained by the smaller patient cohort (n = 1092 vs. n = 2707), the patient heterogeneity (multi- vs. single-center design), lesion complexity (J-CTO score 1.7 ± 1.2 [Azzalini et al.] vs. 2.5 ± 1.2 [our cohort]), and other technical aspects of CTO PCI, such as the more frequent use of the retrograde approach (23% [Azzalini et al.] vs. 29% [our cohort]).

Novel advancements in CTO PCI, and the rapid evolution of wires, microcatheters, and other devices, have also reformed the preventive actions surrounding the PCI itself preserving the integrity of renal function post-PCI, with the ultimate goal of improving the long-term benefits of complex coronary interventions [10]. Strategies aiming to minimize the risk of CA-AKI are grouped as (a) pre-procedural preventive strategies (b) and procedural techniques. Preventive strategies have been thoroughly studied, but only appropriate hydration has been widely accepted, which can be adjusted to left ventricular end diastolic pressure [24], or central venous pressure [25]. In another

aspect, various techniques have been described to reduce contrast media during complex PCIs including zero- or very low-contrast (< 10 mL) procedures [26, 27], extensive use of intravascular imaging, coronary road-mapping (by software or side branch wiring/metallic roadmap), or using a dedicated contrast-sparing system such as the DyeVert Plus [28].

Limitations of the study

Our study has limitations. First, it has a retrospective, observational design without core laboratory assessment of the study angiograms or independent clinical event adjudication. Second, procedural complications, such as perforation, are self-reported; however, the occurrence of MACCE has undergone a quality check performed by a dedicated independent committee in our institution. Third, study procedures were performed in a dedicated, high-volume CTO referral center. Fourth, there are no available data on the post-PCI dialysis rate. Fifth, contrast dye exposure peaks 3 to 5 days post-PCI; hence, the incidence of CA-AKI might be underestimated. Sixth, the follow-up of CTO PCIs ranged between 11 and 35 months because the majority of patients already had 3 years of follow-up, but some proportion of the study cohort only completed 1 year of follow-up after the index procedure.

Conclusions

Contrast-associated acute kidney injury in patients undergoing CTO PCI for stable coronary artery disease occurs in approximately one out of 10 patients, albeit its significance may still be underestimated in current practice. Our study implicates that patients developing CA-AKI have increased risk for long-term major adverse events, highlighting the importance of preserving renal function post-PCI, which could further improve patient-oriented outcomes.

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Conflict of interest: None declared

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Left atrial appendage filling defect in exclusive early-phase scanning of dual-phase cardiac computed tomography: An indicator for elevated thromboembolic risk

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Abstract

Background: *Dual-phase cardiac computed tomography (CCT) has been applied to detect left atrial appendage (LAA) thrombosis, which is characterized as the presence of LAA filling defects (LAADF) in both early- and delayed-phase scanning. However, the clinical implication of LAAFD in exclusive early-phase scanning (LAAFD-EEpS) of CCT in patients with atrial fibrillation (AF) is unclear.*

Methods: *The baseline clinical data and dual-phase CCT findings in 1183 AF patients (62.1 ± 11.6 years, 59.9% male) was collected and analyzed. A further analysis of CCT and transesophageal echocardiography (TEE) data (within 5 days) in a subgroup of 687 patients was performed. LAAFD-EEpS was defined as LAAFD present in early-phase and absent in delayed-phase scanning of dual-phase CCT.*

Results: *A total of 133 (11.2%) patients were detected with LAAFD-EEpS. Patients with LAAFD--EEpS had a higher prevalence of ischemic stroke or transient ischemic attack (TIA) ($p < 0.001$) and a higher predefined thromboembolic risk ($p < 0.001$). In multivariate analysis, a history of ischemic stroke or TIA was independently associated with LAAFD-EEpS (odds ratio [OR] 11.412, 95% confidence interval [CI] 6.561–19.851, $p < 0.001$). When spontaneous echo contrast in TEE was used as the reference standard, the sensitivity, specificity, positive predictive value, and negative predictive value of LAAFD-EEpS was 77.0% (95% CI 66.5–87.6%), 89.0% (95% CI 86.5–91.4%), 40.5% (95% CI 31.6–49.5%), 97.5% (96.3–98.8%), respectively.*

Conclusions: *In AF patients, LAAFD-EEpS is not an uncommon finding in dual-phase CCT scanning, and is associated with elevated thromboembolic risk.* (Cardiol J 2024; 31, 1: 95–102)

Key words: atrial fibrillation, atrial appendage, thromboembolism, radiology

Introduction

Left atrial appendage (LAA) is the major source of thrombus in patients with non-valvular atrial fibrillation (AF) due to its anatomic feature and circulatory stasis nature [1–3], and transesophageal echocardiography (TEE) has long been regarded as the golden standard for detecting LAA thrombus [4]. However, the procedure is semi-invasive and operator-dependent [5]. Recently,

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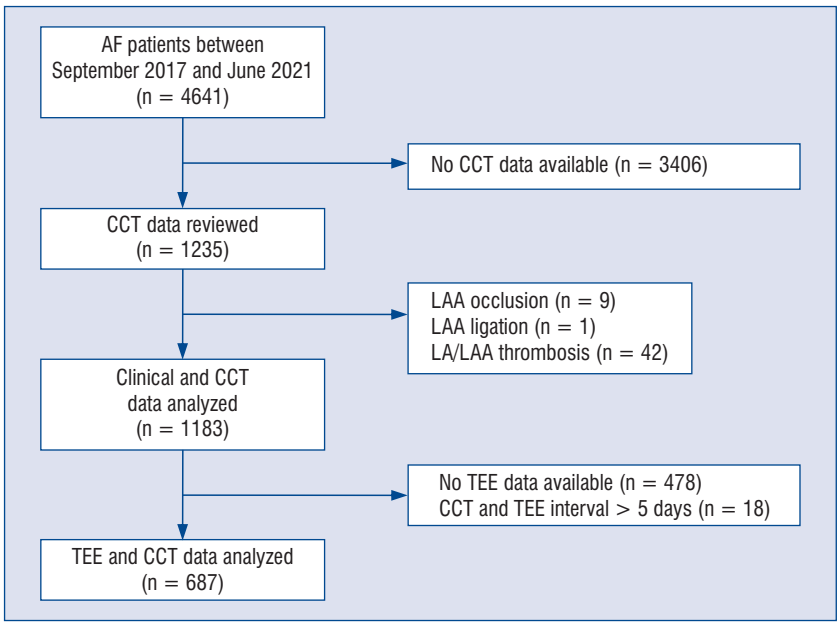

Figure 1. Flow chart of the study population; AF — atrial fibrillation; CCT — cardiac computed tomography; LA — left atrium; LAA — left atrial appendage; TEE — transesophageal echocardiography.

dual-phase cardiac computed tomography (CCT) has been demonstrated to be an alternative modality to detect LAA thrombus in AF patients, with high sensitivity and specificity [6–9]. In dual-phase CCT, the presence of LAA filling defects (LAAFD) in both early- and delayed-phase scanning is regarded as the manifestation of LAA thrombus [8], while the presence of LAAFD in exclusive early-phase scanning (LAAFD-EEpS) was assumed as the consequence of LAA circulatory stasis rather than thrombus [8, 10]. However, the clinical implication of LAAFD-EEpS remains unclear. Therefore, the present study was conducted to evaluate the prevalence of LAAFD-EEpS in dual-phase CCT and its association with thromboembolic risk in AF patients.

Methods

Study population

In the present retrospective single-center study, all in-hospital patients screened were diagnosed with AF in the present institution between September 2017 and June 2021, among whom, dual-phase CCT data were available in 1,235 patients. The exclusion criteria were: i) history of LAA occlusion or ligation; ii) left atrial (LA)/LAA thrombosis identified in CCT. After the screening process, 1,183 patients were included in the analysis. Under further review of the TEE data of all patients, a subgroup which included 687 patients, in whom both CCT and TEE data (the interval < 5 days) were available (Fig. 1). The study protocol was reviewed and approved by the institutional review board. The study complies with the Declaration of Helsinki.

Table 1. Predefined thromboembolic risk.

Thromboembolic risk	VHD	CHA_2SD_2-VASc score	
		Male	Female
Low	No	0	0–1
Moderate	No	1	2
High	Yes	NA	NA
	No	≥ 2	≥ 3

VHD — valvular heart disease; NA — not applicable

Demographic and medical data of all patients were collected. Valvular heart disease (VHD) was defined as moderate to severe mitral stenosis or mechanical prosthetic heart valve(s). Anti-platelet agent and anticoagulant intake within 7 days of administration was collected. The thromboembolic risk was predefined as low, moderate, and high according to the presence of VHD and the CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥ 75 years old (doubled), diabetes, stroke/transient ischemic attack [TIA]/thromboembolism [doubled], peripheral vascular disease/ /old myocardial infarction, age 65–74 years, female sex) (Table 1).

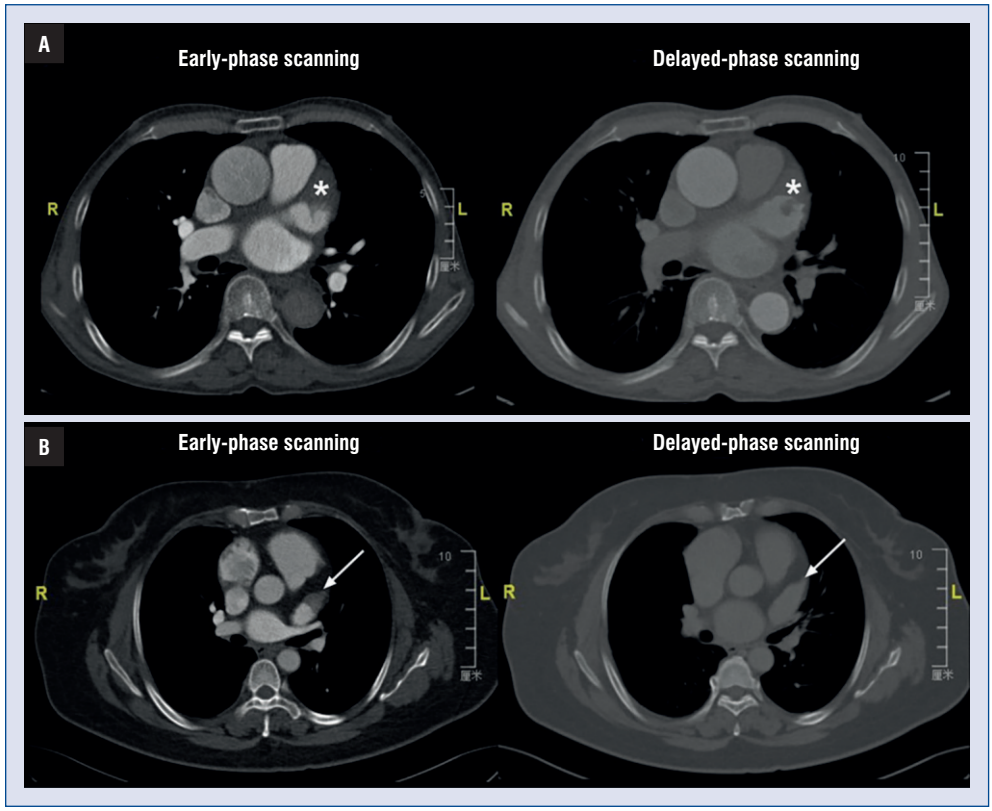

Figure 2. The definition of thrombus and left atrial appendage filling defects in exclusive early-phase scanning (LAAFD--EEpS) in dual-phase cardiac computed tomography; **A.** Left atrial appendage (LAA) thrombus was defined as LAAFD present in both early- and delayed-phase scanning (asterisk); **B.** LAAFD-EEpS was defined as LAAFD present in early-phase and absent in delayed-phase scanning (arrow).

Dual-phase CCT

Prospective electrocardiogram-gated dual--phase CCT was performed using 128-slice spiral scanners (SOMATOM Definition AS 128; SOMATOM Definition Flash, Siemens Medical Solutions). The imaging protocol complied with conventional clinical procedures. Collimation was 128 × 0.625 mm and the gantry rotation time was 330 ms. The tube voltage was 100–120 kV and the tube current 300–350 mA. A bolus of contrast media (50–60 mL) was injected via the antecubital vein with an infusion rate of 5 mL/s. Bolus tracking technique was used to properly time the onset of image acquisition: early-phase scanning started 6 s after the threshold of 100 HU reached in LAA; delayed-phase scanning began 60 s after the end of early-phase scanning. No beta-blocker was used for the regulation of heart rate, because CCT was performed to evaluate the intracardiac structures rather than the coronary arteries. After contrast injection, the imaging was acquired covering the region from the bottom of the aortic arch to the apex of the left ventricle so that the entire LA (including LAA) was scanned. The estimated radiation dose was 4–7 mSv.

TEE

Transesophageal echocardiography was performed after standard clinical preparation with a 5.0-mHZ, 128-element, multiplane probe (Phillips). Imaging acquisition of the LAA was performed by rotating the imaging sector from 0° to 180° to optimize the visualization of the entire LAA.

Image analysis

All of the imaging was independently reviewed by two experienced readers in a blind manner. In cases of disagreement, a consensus was achieved by a joint reading. In CCT, LAAFD was defined as a triangular, oval or irregular shape in LAA with homogeneous attenuation. A thrombus was defined as LAAFD present in both early- and delayed-phase scanning, while LAAFD-EEpS was defined as LAAFD present in early-phase and absent in delayed-phase scanning (Fig. 2). In TEE, a thrombus was defined as a uniformly consistent,

Table 2. Baseline characteristics of the study population.

Variables	LAAFD-EEpS		Total (n = 1,183)	P value
	Absent (n = 1,050)	Present (n = 133)		
Demographic characteristics				
Age [years]	61.5 ± 11.6	66.9 ± 10.1	62.1 ± 11.6	**< 0.001**
Male sex	629 (60.0%)	80 (60.2%)	709 (59.9%)	0.957
Body mass index [kg/m^2]	24.3 ± 3.4	24.2 ± 3.6	24.3 ± 3.4	0.696
Clinical characteristics				
Non-paroxysmal AF	389 (37.0%)	122 (91.7%)	511 (43.2%)	**< 0.001**
Hypertension	588 (56.0%)	86 (64.7%)	674 (57.0%)	0.057
Diabetes mellitus	159 (15.1%)	31 (23.3%)	190 (16.1%)	**0.016**
Chronic heart failure	55 (5.2%)	41 (30.8%)	96 (8.1%)	**< 0.001**
Coronary artery disease	160 (15.2%)	28 (21.1%)	188 (15.9%)	0.084
Ischemic stroke or TIA	100 (9.5%)	60 (45.1%)	160 (13.5%)	**< 0.001**
Valvular heart disease	35 (3.3%)	20 (15.0%)	55 (4.6%)	**< 0.001**
CHA_2DS_2-VASc score	2 (1, 3)	3 (2, 5)	2 (1, 3)	**< 0.001**
Antithrombotic therapy:				
Antiplatelet	109 (10.4%)	23 (17.3%)	132 (11.2%)	**0.017**
Anticoagulant	75 (7.1%)	13 (9.8%)	88 (7.4%)	0.276
Transthoracic echocardiography:				
LAD [mm]	38.0 ± 7.1	46.9 ± 9.1	39.0 ± 7.8	**< 0.001**
LVEDD [mm]	46.5 ± 5.5	48.8 ± 8.1	46.8 ± 5.9	**< 0.001**
LVEF [%]	62.9 ± 7.8	56.2 ± 11.1	62.2 ± 8.5	**< 0.001**

AF — atrial fibrillation; LAD — left atrial diameter; LAAFD-EEpS — left atrial appendage filling defects in exclusive early-phase scanning; LVEDD — left ventricular end-diastolic diameter; LVEF — left ventricular ejection fraction; TIA — transient ischemic attack

echo-reflective mass that distinguished itself from the surrounding LA or LAA wall. Spontaneous echo contrast (SEC) was characterized by dynamic clouds of echoes curling slowly in a circular or spiral shape within the LAA cavity.

Statistical analysis

Continuous variables were described as the mean ± standard deviation for normally distributed data and median (25% to 75% quartile) for non-normally distributed data. Comparisons between groups were performed with the Student t test (normally distributed data) or the Kruskal–Wallis test (non-normally distributed data). Categorical variables were described as counts (percentage) and compared by χ^2 analysis. Binominal logistic regression was used to calculate the odds ratio (OR) and 95% confidence interval (CI) for the presence of LAAFD-EEpS. Variables selected for testing in the multivariate analysis were those with $p < 0.05$ in the univariate model. With SEC in TEE as the reference standard, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated, including the 95% CI based on a binomial distribution. All tests were two-tailed, and a statistical significance was established at $p < 0.05$. All analyses were performed using SPSS software (version 22.0; SPSS, Inc.).

Results

Baseline characteristics of the study population

A total of 1,183 patients were included in the study. Mean age was 62.1 ± 11.6 years, and 709 (59.9%) were male. LAAFD-EEpS was detected in 133 (11.2%) patients with dual-phase CCT. The number of patients with low, moderate and high thromboembolic risk was 262 (22.1%), 307 (26.0%), 614 (51.1%), respectively. The baseline characteristics of the patients with or without LAAFD-EEpS were shown in Table 2. Patients with LAAFD-EEpS were older ($p < 0.001$), had a higher prevalence of non-paroxysmal AF ($p < 0.001$), chronic heart failure (CHF) ($p < 0.001$), diabetes mellitus ($p = 0.016$), ischemic stroke or TIA ($p < 0.001$),

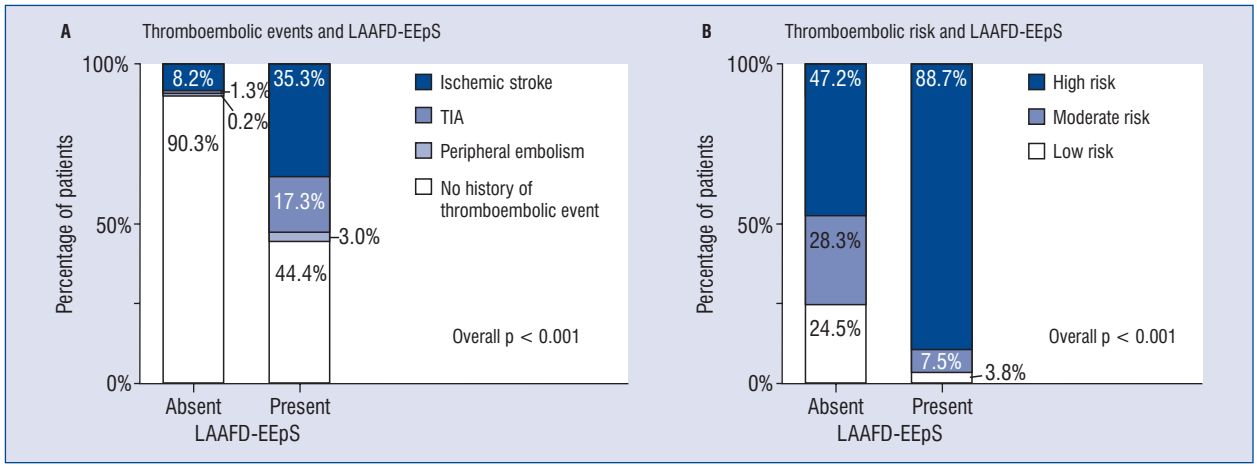

Figure 3. Association between left atrial appendage filling defects in exclusive early-phase scanning (LAAFD-EEpS) and thromboembolic risk; **A.** Percentage of patients who had a history of ischemic stroke, transient ischemic attack (TIA), peripheral embolism, and no history of thromboembolic events in patients with or without LAAFD-EEpS; **B.** Percentage of patients who were at high, moderate, and low risk of thromboembolic events in patients with or without LAAFD-EEpS.

VHD ($p < 0.001$), antiplatelet agent prescription ($p = 0.017$); and had higher CHA_2DS_2-VASc scores ($p < 0.001$). In transthoracic echocardiogram (TTE), patients with LAAFD-EEpS had significantly larger left atrial diameter (LAD) ($p < 0.001$), left ventricular end-diastolic diameter (LVEDD) ($p < 0.001$), and lower left ventricular ejection fraction (LVEF) ($p < 0.001$).

LAAFD-EEpS and thromboembolic risk

The association of LAAFD-EEpS and thromboembolic events is shown in Figure 3A. In patients with LAAFD-EEpS, 47 (35.3%), 23 (17.3%), 4 (3.0%) had a history of ischemic stroke, TIA, and peripheral embolism, respectively, while in patients without LAAFD-EEP, the number was 86 (8.2%), 14 (1.3%), and 2 (0.2%), respectively (overall $p < 0.001$). In addition, the percentage of patients who were at high, moderate, low risk of thromboembolic events in LAAFD-EEpS group was 93.6%, 5.6%, 0.8%, respectively, while that in patients without LAA LAAFD-EEpS was 47.0%, 28.3%, 24.7%, respectively (overall $p < 0.001$) (Fig. 3B).

Risk factors for LAAFD-EEpS

In multivariate analysis, older age (OR 1.048; 95% CI 1.020–1.076; $p = 0.001$), non-paroxysmal AF (OR 7.657; 95% CI 3.635–16.125; $p < 0.001$), a history of CHF (OR 2.140; 95% CI 1.123–4.081; $p < 0.021$), VHD (OR 3.435; 95% CI 1.446–8.160; $p = 0.005$), ischemic stroke or TIA (OR 11.412; 95% CI 6.561–19.851; $p < 0.001$), antiplatelet agent prescription (OR 2.416; 95% CI 1.232–4.737; $p = 0.010$), larger LAD (OR 1.099; 95% CI 1.059–1.141; $p < 0.001$) and lower LVEF (OR 0.949; 95% CI 0.921–0.978; $p = 0.001$) were independent predictors of the presence of LAAFD-EEpS (Table 3). After adjustment for confounding factors, a history of ischemic stroke or TIA increased more than tenfold risk for the presence of LAAFD-EEpS.

LAAFD-EEpS in CCT and SEC in TEE

A total of 687 patients with available CCT and TEE data (the interval < 5 days) were analyzed, in whom 319 (46.4%) were at high thromboembolic risk, while 368 (53.6%) were at low to moderate thromboembolic risk. The median interval of CCT and TEE were 1.7 (0.7–3.0) days. In TEE, none of the patients were detected with LAA thrombus, and 61 (8.9%) patients were detected with SEC. In CCT scanning, 116 (16.9%) patients were identified with LAAFD-EEpS. Figure 4 shows the image of CCT and TEE of a patient with both LAAFD-EEpS and SEC.

The concordance between LAAFD-EEpS and SEC were moderate, with the overall kappa value of 0.572. When SEC in TEE was used as the reference standard, the sensitivity, specificity, PPV, and NPV of LAAFD-EEpS was 90.2% (95% CI 82.7–97.6%), 90.3% (95% CI 87.9–92.6%), 47.4% (95% CI 38.3–56.5%), 98.9% (98.1–99.8%), respectively. In patients with high thromboembolic risk, the values were 87.9% (76.7–99.0%), 89.8% (86.4–93.4%), 50.0% (37.1–62.9%), 98.5% (97.0–

Table 3. Univariate and multivariate analysis of left atrial appendage filling defects in exclusive early-phase scanning (LAAFD-EEpS).

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.046 (1.028–1.064)	< 0.001	1.048 (1.020–1.076)	**0.001**
Male sex	0.990 (0.685–1.431)	0.957		
Body mass index	0.989 (0.937–1.044)	0.696		
Non-paroxysmal AF	18.846 (10.041–35.371)	< 0.001	7.657 (3.635–16.125)	**< 0.001**
Hypertension	1.438 (0.987–2.094)	0.058		
Diabetes mellitus	1.703 (1.101–2.634)	0.017	1.433 (0.788–2.605)	0.239
Chronic heart failure	8.062 (5.103–12.737)	< 0.001	2.140 (1.123–4.081)	**0.021**
Coronary artery disease	1.483 (0.946–2.325)	0.086		
Ischemic stroke or TIA	7.808 (5.240–11.635)	< 0.001	11.412 (6.561–19.851)	**< 0.001**
Valvular heart disease	5.133 (2.866–9.193)	< 0.001	3.435 (1.446–8.160)	**0.005**
Antiplatelet	1.805 (1.105–2.950)	0.018	2.416 (1.232–4.737)	**0.010**
Anticoagulant	1.408 (0.759–2.614)	0.278		
LAD	1.145 (1.114–1.178)	< 0.001	1.099 (1.059–1.141)	**< 0.001**
LVEDD	1.059 (1.030–1.089)	< 0.001	0.974 (0.932–1.018)	0.240
LVEF	0.931 (0.914–0.948)	< 0.001	0.949 (0.921–0.978)	0.001

AF — atrial fibrillation; CI — confidence interval; LAD — left atrial diameter; LVEDD — left ventricular end-diastolic diameter; LVEF — left ventricular ejection fraction; OR — odds ratio; TIA — transient ischemic attack

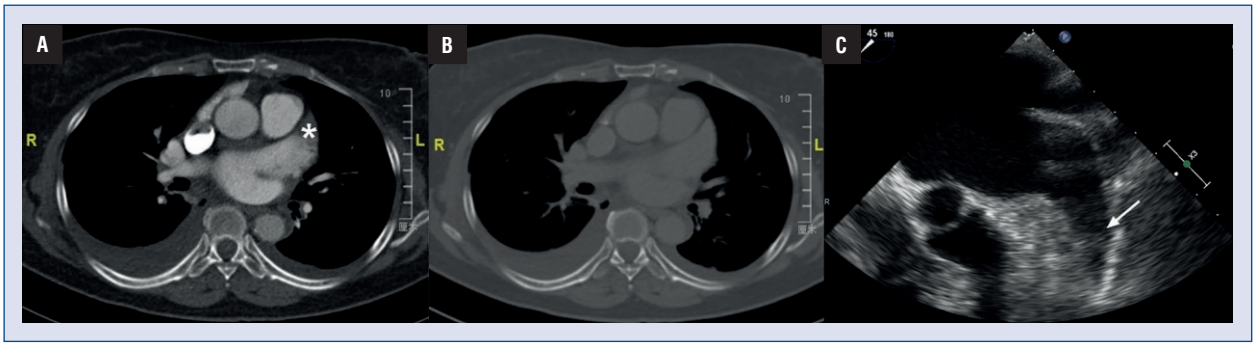

Figure 4. The image of cardiac computed tomography (CCT) and transesophageal echocardiography (TEE) of a patient; **A.** Early-phase scanning of CCT shows left atrial appendage filling defects (asterisk); **B.** Delayed-phase scanning of CCT shows normal filling in left atrial appendage (LAA); **C.** TEE shows spontaneous echo contrast in LAA (arrow).

–100.0%), respectively; while in patients with low to moderate thromboembolic risk, the values were 92.9% (83.3–100.0%), 90.6% (87.5–93.7%), 44.8% (32.0–57.6%), 99.4% (98.5–100.0%), respectively (Table 4).

Discussion

The major findings of the present study are: i) LAAFD-EEpS occurs in 11.2% of AF patients; ii) the predefined thromboembolic risk is remarkably elevated in patients with LAAFD-EEpS; iii) patients with a history of ischemic stroke or TIA are tenfold more likely to be detected with LAAFD--EEpS; iv) LAAFD-EEpS has a high sensitivity and specificity to predict SEC in TEE. According to available research, this study is the first report focusing on the clinical relevance of LAAFD-EEpS in dual-phase CCT.

The findings in the present study underline the clinical relevance of LAAFD-EEpS. Firstly, it was found that the presence of LAAFD-EEpS was significantly associated with the history of ischemic stroke/TIA as well as the predefined

Table 4. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of left atrial appendage filling defects in exclusive early-phase scanning.

Variables	High risk (n = 319)	Low/moderate risk (n = 368)	Total (n = 687)
Sensitivity (95% CI)	87.9% (99.0–76.7)	92.9% (83.3–100.0)	90.2% (82.7–97.6)
Specificity (95% CI)	89.9% (86.4–93.4)	90.6% (87.5–93.7)	90.3% (87.9–92.6)
PPV (95% CI)	50.0% (37.1–62.9)	44.8% (32.0–57.6)	47.4% (38.3–56.5)
NPV (95% CI)	98.5% (97.0–100.0)	99.4% (98.5–100.0)	98.9% (98.1–99.8)

CI — confidence interval

thromboembolic risk. Secondly, LAAFD-EEpS had a high sensitivity and specificity to predict the presence of SEC in TEE which was indicative of LAA circulatory stasis and even erythrocytes aggregation [11, 12]. Thirdly, in multivariate analysis, non-paroxysmal AF, CHF, VHD, LAD, LVEF were all independent predictors for LAAFD-EEpS other than ischemic stroke/TIA history were found. It was believed that all of these predictors predispose LA/LAA to a circulatory stasis status by their subsequent hemodynamic effect of elevated LA pressure. Therefore, LAAFD-EEpS may serve as a strong clue of LAA circulatory stasis and should be emphasized in clinical practice. Notably, in the present study, there were 3.8% of patients with low thromboembolic risk who were detected with LAAFD-EEpS. Although the evidence of LAA circulatory stasis is not an established indication for anticoagulation according to the current AF management guidelines [13], it deserves further investigation whether anticoagulation could benefit the patients with low CHA_2DS_2-VASc score but LAAFD-EEpS in CCT.

Cardiac computed tomography has been shown to be an alternative method to detect the presence of LAA thrombus in numerous studies [14–16], with various parameters proposed to improve the diagnostic accuracy [17–19]. Recent studies with dual-phase CCT demonstrated that LAAFD in early-phase scanning was of limited value for identification of LAA thrombus, whereas LAAFD in delayed-phase scanning could largely improve the diagnostic accuracy [6, 9]. According to a meta-analysis including 2,540 patients, the pooled sensitivity and specificity could be as high as 99.1% and 98.9%, respectively, when using delayed--phase scanning [6]. In previous studies, few data on the accurate prevalence of LAAFD-EEpS in AF patients was reported. In the present study, CCT imaging was screened in 1,183 in-hospital AF patients and it was found that LAAFD-EEpS could be identified in 11.2% of the patients, which was correlated with a higher thromboembolic risk. Therefore, it was believed herein, that the value of early-phase scanning has been underestimated over the past decade, and that dual-phase CCT could be an ideal modality not only for detecting LAA thrombus, but also for reflecting the presence of LAA circulatory stasis.

Spontaneous echo contrast in TEE has been demonstrated to be associated with increased thromboembolic risk in both AF and normal sinus rhythm patients [11, 12]. Previous studies assessed the relationship between LAAFD-EEpS in CCT and SEC in TEE. Kim et al. [10] prospectively performed CCT and TEE in 314 patients with suspected embolic stroke and found that if using LAAFD-EEpS to predict the presence of SEC, the sensitivity, specificity, PPV and NPV were 84.6%, 99.1%, 97.8%, 92.9%, respectively. The PPV in the present study is remarkably lower, which may be due to the different study population. Previous studies showed that the mechanism of SEC is a rouleau formation of erythrocytes [11, 12, 20]. Although this condition is closely correlated with circulatory stasis, it is a more advanced stage towards the final stage of clot formation. Theoretically, in patients with LAA circulatory stasis but no obvious erythrocyte aggregation, the LAAFD-EEpS can be observed but no SEC, which leads to false-positive cases. This could explain the lower specificity and PPV of LAAFD-EEpS to predict SEC.

Limitations of the study

The main limitation of the present study is that it is retrospective nature, thus some quantitative parameters such as grade of SEC, blood velocity in LAA, Hounsfield unit values of LAA are not available. However, the clinical data were prospectively recorded in the medical system. In addition, the percentage of anticoagulant use in the study is relatively low, which could possibly explain why anticoagulant use is not associated with LAAFD-EEpS. Finally, the present study employs

dual-phase CCT for detection of LAA circulatory stasis, which may potentially increase the radiation exposure to patients.

Conclusions

In conclusion, LAAFD-EEpS is not an uncommon finding in AF patients, which is associated with a history of thromboembolic events and elevated thromboembolic risk. Furthermore, LAAFD-EEpS has a high sensitivity and specificity to predict SEC in TEE. These observations underline the role of early-phase scanning in CCT. The prognostic value of LAAFD-EEpS is to be investigated in future research.

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Conflict of interest: None declared

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Characteristics of women with type 2 diabetes mellitus and heart failure in Spain. The DIABET-IC study

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Abstract

Background: *Heart failure (HF) is the second most common initial presentation of cardiovascular disease in people with type 2 diabetes mellitus (T2DM). T2DM carries an increased risk of HF in women. The aim of this study is to analyze the clinical characteristics and the treatment received by women with HF and T2DM in Spain.*

Methods: *The DIABET-IC study included 1517 patients with T2DM in 2018–2019 in Spain, in 30 centers, which included the first 20 patients with T2DM seen in cardiology and endocrinology clinics. They underwent clinical evaluation, echocardiography, and analysis, with a 3-year follow-up. Baseline data are presented in this study.*

Results: *One thousand five hundred and seventeen patients were included (501 women; aged 67.28 ± ± 10.06 years). Women were older (68.81 ± 9.90 vs. 66.53 ± 10.06 years; $p < 0.001$) and had a lower frequency of a history of coronary disease. There was a history of HF in 554 patients, which was more frequent in women (38.04% vs. 32.86%; $p < 0.001$), and preserved ejection fraction being more frequent in them (16.12% vs. 9.00%; $p < 0.001$). There were 240 patients with reduced ejection fraction. Women less frequently received treatment with angiotensin converting enzyme inhibitors (26.20% vs. 36.79%), neprilysin inhibitors (6.00% vs. 13.51%), mineralocorticoid receptor antagonists (17.40% vs. 23.08%), beta-blockers (52.40% vs. 61.44%), and ivabradine (3.60% vs. 7.10%) ($p < 0.001$ for all), and 58% received guideline-directed medical therapy.*

Conclusions: *A selected cohort with HF and T2DM attending cardiology and endocrinology clinics did not receive optimal treatment, and this finding was more pronounced in women.* (Cardiol J 2024; 31, 1: 103–110)

Key words: diabetes mellitus, heart failure, women, treatment

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Introduction

Heart failure (HF) is one of the leading causes of illness and death in both sexes, and it is estimated that the incidence of HF will increase in the United States by 46% by 2030, affecting more than 8 million people [1]. From 40 years of age, both sexes have the same risk of developing HF throughout their lives; this pathology affects 20% of the subjects [2]. In addition, as the years go by, the incidence of HF increases, more markedly in women. Patients with HF and preserved ejection fraction (HFpEF) are more frequently female and older than those with HF and reduced ejection fraction (HFrEF) [3]. Women with HFpEF have high blood pressure more often and coronary artery disease less often than men [4]. Despite these important differences between sexes, women have been less represented in HF studies.

Heart failure is the second most common initial presentation of cardiovascular disease in people with type 2 diabetes mellitus (T2DM), and HF patients with T2DM also have a higher mortality rate compared to HF patients without T2DM. T2DM, as occurs with other risk factors and cardiovascular complications, confers a higher risk of HF in women than in men [5, 6]. In diabetics, a greater risk of coronary artery disease in women than in men has been postulated among the possible explanations for the higher risk of HF in women with T2DM [7, 8], although the differences between sexes in the management of T2DM and other cardiovascular risk factors could also play a role [9].

Despite the importance of HF in women, this gender has been less studied in the large trials that have shown prognostic benefit of different drugs in this syndrome, especially in HFrEF [5, 10]. Similarly, whether women receive the treatments recommended by clinical practice guidelines with the same frequency as men has been little studied, although it has been shown that they also obtain a clear prognostic benefit [4]. Therefore, the objective of this preliminary study from DIABET-IC was to analyze the clinical characteristics and the treatment that women and men with HF and T2DM receive in our country.

Methods

The DIABET-IC study was designed to evaluate the prevalence and incidence of HF in patients with T2DM in our country and has a planned follow-up of 3 years. It is an observational study, without intervention, so the usual clinical practice was applied, without modifying the treatment or the examinations carried out on the patients in any case because they were included in the study. This manuscript is a preliminary work of the study and focuses on the baseline data of the patients included, emphasizing the comparison in the treatment between sexes, especially in patients who had HFrEF at baseline.

A total of 1517 patients with T2DM were included in 2018–2019 in Spain, in 30 centers distributed throughout all the autonomous communities. Patients were included in the Spanish provinces of A Coruña, Alicante, Asturias, Barcelona, Cáceres, Castellón, Córdoba, Ciudad Real, Granada, Guipuzcoa, Jaén, La Rioja, Las Palmas de Gran Canaria, Lugo, Lleida, Madrid, Málaga, Majorca, Murcia, Ourense, Pontevedera, Salamanca, Santa Cruz de Tenerife, Seville, Toledo, Valencia, Valladolid, Vizcaya, and Zaragoza. A cardiologist and an endocrinologist, both research collaborators, took part in the study in each center, including the first 20 patients with T2DM seen in their respective outpatient clinics. Participating centers could include more patients if desired. The patients were included in the autonomous communities of Andalusia (18.2%), Catalonia (13.5%), Madrid (13%), Castilla-La Mancha (10.9%), and Valencian Community (9.4%), with the rest of the autonomous communities having a representation of less than 5%. Tertiary care provided 68.4% of the patients, and the rest came from secondary care.

The patients provided signed informed consent to participate in the study. Subsequently, they underwent a clinical evaluation with a detailed medical history, a physical examination, an electrocardiogram, and 2-dimensional echocardiography, following standard techniques, as well as laboratory tests (blood and urine count, NT-proBNP, glycosylated hemoglobin [HbA1c]). After the inclusion, a 3-year follow-up was conducted, with an annual check-up by the doctor responsible. If HF was suspected, the Research Collaborator from Cardiology performed the diagnosis of congestive HF and monitored the patient throughout the study. All patients with HF present or suspected were monitored by the cardiologists without any intervention, so standard of care was applied without modifying the treatment or the examinations in any case because of inclusion in the study.

The participating centers' Ethics Committees approved the study.

Table 1. Baseline characteristics.

Diagnostics	Men (n = 1016)		Women (n = 501)		P
	Mean	SD	Mean	SD	
Age [year]	66.53	10.06	68.81	9.9	< 0.001
SBP [mmHg]	133.88	18.98	136.57	20.18	0.031
DBP [mmHg]	75.57	11.34	75.96	11.87	0.539
Heart rate [bpm]	72.67	13.06	76.59	12.75	< 0.001
Weight [kg]	86.38	16.4	76.82	14.58	< 0.001
Height [cm]	169.81	7.14	157.32	6.88	< 0.001
BMI [kg/m^2]	29.69	5.4	31.01	5.88	< 0.001
Waist circumference [cm]	105.42	13.72	103.81	14.81	0.159
LVEF [%]	53.54	14.04	57.8	11.59	< 0.001
BNP [pg/mL]	203.34	318.25	359.74	837.05	0.994
NT-proBNP [pg/mL]	975.72	2405.75	1115.91	2972.66	0.832
Hemoglobin [g/dL]	14.4	1.81	13.24	1.48	< 0.001
Creatinine [mg/100 mL]	1.1	0.39	0.9	0.39	< 0.001
eGFR	73.64	22.3	71.98	23.51	0.211
Cholesterol [mg/dL]	148.34	35.82	163.78	35.54	< 0.001
LDL-C [mg/dL]	77.56	30.16	85.86	29.59	< 0.001
Triglycerides [mg/dL]	153.94	96	149.72	76.27	0.772
HDL-C [mg/dL]	41.85	11.32	49.05	13.04	< 0.001
Glucose [mg/dL]	141.05	48.11	143.23	44.94	0.110
HbA1c [%]	7.27	1.3	7.38	1.31	0.088
Age at T2DM diagnosis [year]	53.13	12.65	53.48	14.13	0.512
Age of insulin therapy [year]	57.46	13.23	57.59	13.49	0.835
Insulin dose [U/day]	46.92	31.91	46.82	35.25	0.237

BNP — B-type natriuretic peptide; BMI — body mass index; DBP — diastolic blood pressure; HbA1c — glycosylated hemoglobin; HDL-C — high-density lipoprotein cholesterol; eGFR — estimated glomerular filtration rate; LDL-C — low-density lipoprotein cholesterol; NT-proBNP — N-terminal prohormone B-type natriuretic peptide; LVEF — left ventricular ejection fraction; SBP — systolic blood pressure; SD — standard deviation; T2DM — type 2 diabetes mellitus

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD). Categorical variables are presented as proportions. The comparison between two variables is carried out using Pearson's χ^2 tests or Student's t test, using analysis of variance for multiple comparisons. Values of $p < 0.05$ are considered significant.

Results

Baseline data are depicted in Table 1. A total of 1517 patients were included (501 women; 67.28 ± 10.06 years). At baseline, the women were older (68.81 ± 9.90 vs. 66.53 ± 10.06 years; $p < 0.001$) and had greater body mass index (BMI) (31.01 ± ± 5.88 vs. 29.69 ± 5.40 kg/m^2; $p < 0.001$). They also showed higher systolic blood pressure (136.57 ± ± 20.18 vs. 133.88 ± 18.98 mmHg; $p = 0.031$) and higher heart rates (76.59 ± 12.75 vs. 72.67 ± ± 13.06 bpm; $p < 0.001$) than men.

Regarding their cardiac history (Table 2), women less frequently had a history of heart disease, and especially of coronary heart disease. A total of 554 (37%) patients had a history of HF, which was more frequent in women (38.04% vs. 32.86%; $p < 0.001$), as was HFpEF (16.12% vs. 9.00%; $p < 0.001$), while a history of HFrEF (11.22% vs. 20.6%; $p < 0.001$) and mildly reduced ejection fraction (HFmrEF) (5.51% vs. 8.80%; $p < 0.001$) was more frequent in men. Women received implantable devices (cardioverter-defibrillators-cardiac resynchronization therapy [CRT]) (2.43% vs. 3.25%; $p < 0.001$) and implantable cardioverter-defibrillators (ICD) (1.01% vs. 5.42%; $p < 0.001$) less often than men, without differences in the rate of use of isolated resynchronization therapy (0.61% vs. 0.69%). There were no differences in the frequency

Table 2. Comorbidities and risk factors in the total population and by sex.

Diagnosis	Men		Women		P
	N	%	N	%	
Hypertension	832	81.89	411	82.04	0.945
Dyslipidemia	816	80.31	409	81.64	0.539
Tobacco	132	13.02	32	6.4	< 0.001
Alcohol	59	5.81	0	0	< 0.001
Heart disease	657	64.92	218	43.83	< 0.001
Ischemic heart disease	523	51.58	125	21.15	< 0.001
STE-ACS	187	19.72	44	8.06	< 0.001
NSTE-ACS	200	18.94	40	8.87	< 0.001
Coronary by-pass surgery	100	9.86	16	3.23	< 0.001
PCI	356	31.86	81	15.52	< 0.001
Stroke	93	9.26	39	7.78	0.626
PAD	143	14.12	21	4.21	< 0.001
Atrial fibrillation	223	22.01	104	20.88	0.616
CKD (stages 3–5)	229	22.56	122	24.35	0.437
COPD	133	13.9	33	6.59	< 0.001
Obstructive sleep apnea	175	17.22	57	11.38	0.003
Thyroid disease	71	7.10	112	22.15	< 0.001
Dementia	10	0.98	13	2.59	0.016
Type of heart failure:					< 0.001
LVEF reduced (< 40%)	188	18.65	52	10.63	
LVEF midrange-preserved (≥ 40%)	197	19.54	117	23.93	

CKD — chronic kidney disease; COPD — chronic obstructive pulmonary disease; LVEF — left ventricular ejection fraction; PAD — peripheral artery disease; PCI — percutaneous coronary intervention; NSTE-ACS — non-ST-segment elevation acute coronary syndrome; STE-ACS — ST-segment elevation acute coronary syndrome

of atrial fibrillation, valvular heart disease, and the use of pacemakers in our cohort. In patients with atrial fibrillation, the $CHAD_2DS_2$-VASc score was higher in women than in men (4.84 ± 1.37 vs. 3.93 ± ± 1.36 points; p < 0.001). Table 2 also shows the prevalence of HF in both sexes. HFrEF (< 40%) was more frequent in men (10.63% vs. 18.65%; p < 0.001), while HF with mild reduced or preserved ejection fraction (≥ 40%) was more prevalent in women (23.93% vs. 19.54%; p < 0.001).

Regarding the medical treatment received for HF, significant differences were observed in some of the pharmacological groups that have shown prognostic benefit in patients with HFrEF. In the group with HF, women less frequently received treatment with angiotensin-converting enzyme inhibitors (ACEI; 26.20% vs. 36.79%; p < 0.001), neprilysin inhibitors (ANRI; 6.00% vs. 13.51%; p < 0.001), mineralocorticoid receptor antagonists (MRA; 17.40% vs. 23.08%; p < 0.001), beta--blockers (BB; 52.40% vs. 61.44%; p < 0.001), and ivabradine (3.60% vs. 7.10%; p < 0.001); conversely, women received treatment with diuretics (54.80% vs. 48.82%; p < 0.02) and angiotensin receptor blockers (ARB; 40.00% vs. 32.94%; p < 0.001) more frequently than men. No differences were observed regarding the use of digoxin (5.60% vs. 4.05%; p = 0.173).

When analyzing only patients with HFrEF (n = 240; 21.45% women), in whom some treatments have been shown to improve prognosis (Table 3, Fig. 1), differences were observed in the use of some drugs such as ANRI, which was used less frequently in women (30.77% vs. 50.53%; p = 0.011), and ARB, which, on the contrary, was used more often in women (26.92% vs. 11.17%; p = 0.004). Women received treatment with ACEI or ARB more often (61.54% vs. 44.15%; p = 0.026) than men, with no differences in the use of other drugs analyzed individually. Women with HFrEF and T2DM were treated with sodium-glucose cotransporter-2 inhibitors (i-SGLT2) as often as men (40.38% vs. 39.36%; p = 0.894). As for the recommended treatment combinations, in

Table 3. Treatment in patients with heart failure with reduced ejection fraction.

Drugs	Total		Men		Women		P
	N	%	N	%	N	%	
Diuretics	200	75	142	75.53	38	73.07	0.819
ACEI	81	33.75	63	33.51	18	34.72	0.881
ARB	35	14.58	21	11.17	14	26.92	**0.004**
ACEI or ARB	115	47.92	83	44.15	32	61.54	**0.026**
ARNI	111	46.25	95	50.53	16	30.77	**0.011**
ACEI or ARB or ARNI	224	93.23	177	94.15	47	90.38	0.335
Beta-blockers	221	92.08	170	90.43	51	98.08	0.084
MRA	159	66.25	123	65.43	36	69.23	0.608
Ivabradine	43	17.92	35	18.62	8	15.38	0.591
Digoxin	21	8.79	15	8.02	6	11.54	0.414
iSGLT2	95	39.58	74	39.36	21	40.38	0.894
ACEI + MRA + BB	49	20.42	38	20.21	11	21.15	0.848
ARB + MRA + BB	17	7.08	8	4.26	9	17.31	**0.003**
ACEI or ARB or ARNI + MRA + BB	140	58.43	107	56.91	33	63.46	0.397

ACEI — angiotensin-converting enzyme inhibitor; ARNI — angiotensin receptor II blocker-neprilysin inhibitor; ARB — angiotensin receptor blocker; BB — beta-blockers; iSGLT2 — sodium-glucose cotransporter 2 inhibitor; MRA — mineralocorticoid receptor antagonist

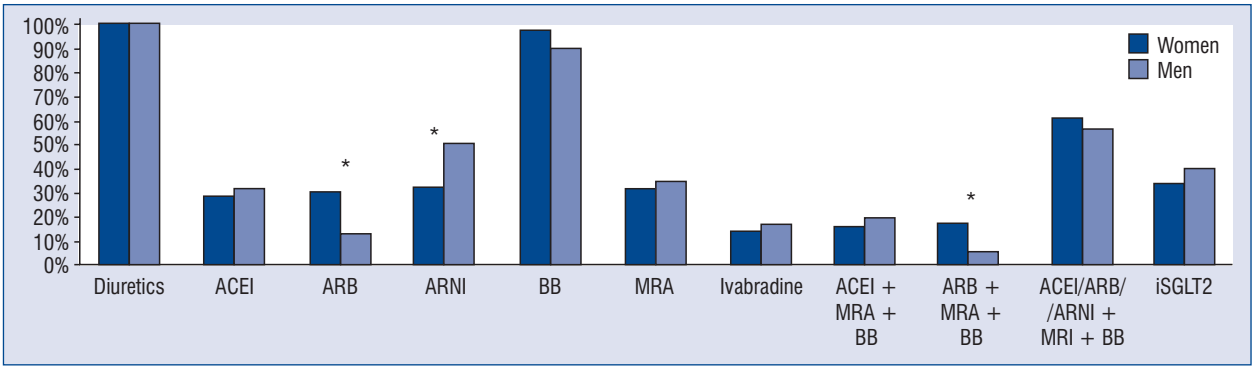

Figure 1. Medical treatment of heart failure with reduced ejection fraction in women and men; *p < 0.05; ACEI — angiotensin-converting enzyme inhibitor; ARNI — angiotensin receptor II blocker-neprilysin inhibitor; ARB — angiotensin receptor blocker; BB — beta-blockers; iSGLT2 — sodium-glucose cotransporter 2 inhibitor; MRA — mineralocorticoid receptor antagonist.

the subgroup of patients with HFrEF, women received the combination of ARB + MRA + BB more often (17.31% vs. 4.23%; p = 0.003), with no differences observed in the percentage of use of the rest of the drug combinations. Women with HFrEF also received ICDs (1.01% vs. 5.42%; p < 0.001) and CRT with or without associated cardioverter-defibrillator (3.04% vs. 3.94%; p < 0.001) less frequently than men.

Regarding T2DM (Table 1), no differences were observed in the age of T2DM diagnosis, the age of insulin therapy initiation, and HbA1c concentration at baseline. Hypothyroidism (19.56% vs. 4.43%; p < 0.001) and dementia (2.59% vs. 0.98%; p < 0.02) were more common in women. These differences, among others, made the Charlson Index higher in men than in women (0.48 ± 0.81 vs. 0.69 ± ± 0.91; p < 0.001). As for the treatment of T2DM, women received iSGLT2 less frequently (35.14% vs. 43.10%; p < 0.001), in contrast to insulin, which was used more often in this group (47.90% vs. 39.64%; p < 0.01). Finally, no differences were observed in lipid-lowering therapies with the use of statins, PCSK9 inhibitors, and fibrates, although

ezetimibe was used less frequently in women than in men (13.20 vs. 18.74%; $p < 0.01$).

Discussion

The preliminary results of the DIABET-IC study show significant differences between patients' treatment for HF and for T2DM according to their sex. Also, some baseline characteristics highlight relevant results: women were older and had higher BMI and blood pressure at baseline. Although women less frequently presented a history of heart disease, and especially ischemic heart disease, they did show a higher frequency of HF and, specifically, of HFpEF. Regarding the treatment received, it was observed that just over half (58%) of these high-risk patients with HF and T2DM receive optimal medical treatment, given that they were treated with all the drugs recommended by the clinical practice guidelines (ACEI/ /ARB/ARNI + MRA + BB). When comparing the treatment received by women with the treatment prescribed for men, it is observed that women, partly due to the different characteristics of their clinical picture, received treatment with ACEI, ARNI, MRA, BB, and ivabradine less frequently, but they were treated more frequently with ARBs. In addition, they also received less iSGLT2 for the treatment of hyperglycemia. When only patients with HFrEF are analyzed, a lower use of ARNI is still observed in women, with no differences in the use of the other groups of drugs between both sexes.

Greene et al. [11] recently analyzed the factors associated with non-use or sub-target dosing of drugs recommended by clinical practice guidelines in HF by analyzing studies on real-life patients targeting this problem. They found that the percentage of patients who reach the target doses recommended in the guidelines are 4–55% for ACEI/ /ARB, 11–87% for sacubitril/valsartan, 4–60% for BB, and 22–80% for MRA. The use of these drugs in our patients falls within these ranges of observed real-life use, being 47.9% for ACEI/ARBs, 46.2% for ARNI, 66.2% for MRAs, and 92.1% for BBs. It is evident that there is ample room for the improvement of these treatments recommended by clinical practice guidelines. Furthermore, Greene et al. [11] indicated that advanced age and worsening renal function are associated with the non-use of drugs recommended by clinical practice guidelines, which was also observed in patients with lower body weight, hyperkalemia, and hypotension. Female sex is also associated with the non-use of ACEI/ARB, as well as with the use of sub-target dosing of ACEI/ARB, which may help explain what was found in our female patients. This finding is especially important given that Owerkerk et al. [12] observed that patients treated with lower doses of ACEI/ARB and BB tend to have a higher mortality.

Although both HF and T2DM are individually associated with considerable morbidity and mortality, both pathologies occur frequently in the same patient [13, 14], which further worsens the health outcomes and quality of life of patients, as well as the cost for the health system [5]. Because both pathologies present a very different risk profile between both sexes [15], it is important to know in some detail the characteristics of these patients, especially in women, due to their lower representation in studies, emphasizing the aspects of improvement in their treatment, which can lead to a better prognosis. T2DM causes HF by different mechanisms, not all of which are well known [16]. In addition to the usual cardiovascular risk factors, women present some sex-specific risk conditions for HF related to their vulnerability during pregnancy, physical/emotional stress, such as the pathogenesis of Takotsubo syndrome or cardiovascular toxicity after chemotherapy, as well as some incremental pathophysiological features like the greater degree of endothelial inflammation and microvascular dysfunction and the vascular dysfunction with its impact on ventriculoarterial coupling) [5].

The profile of cardiovascular risk factors in our patients was similar to the one observed by López- -Vilella et al. [10] in a Spanish population admitted with decompensated HF, a series in which 40% of patients had T2DM. These authors also observed, as described elsewhere [17, 18], that women are older than men at the time of HF presentation. They suffer from arterial hypertension more frequently, in contrast to ischemic heart disease which occurs less often, probably because women develop HF at a more advanced age when other risk factors are also more prevalent. They also described a higher frequency of HFpEF in women, as has been pointed out by other authors [17].

Women obtain prognostic benefit from guideline-directed medical therapy, although some differences have been reported between the sexes with respect to the response to drugs used in HF [16]. In general, women obtain benefit from ACEI/ /ARB with lower doses than men, which probably makes it unnecessary to try to increase the dose of these drugs above 40–60% of the target dose [19], in the same way that it has been demonstrated

that women are more sensitive to the side effects of cardiovascular drugs [20]. In addition, in the PARAGON study [21], which includes patients with HEpEF, a significant interaction between female sex and ARNI has been observed, such that women obtain a benefit of these drugs, with a significant reduction of 27% ($p < 0.006$) in cardiovascular death and admission for HF, but with no significant difference observed in men. Despite these findings, in our series women received treatment less frequently with these drugs. We also observed low use of iSGLT2 in the treatment of T2DM, despite the drugs having demonstrated prognostic benefit in patients with HF, whether they have T2DM or not. It is noteworthy that around 60% of the patients, with no differences between the sexes, were receiving treatment with the four pharmacological groups that have shown prognostic benefit. Although the use of iSGLT2 was lower in women when considering the entire population, in contrast to what was found by other authors [7], in patients with HFrEF we did not observe differences in the percentage of use of iSGLT2 between the sexes; however, the percentage of use (35–40%) can clearly be improved in this high-risk population.

Women with HFrEF also less frequently received advanced HF therapy, such as ICDs, and CRT, with or without associated cardioverter-defibrillator. This lower use of advanced therapies for HF in women has been described by other authors, even after adjusting for confounding factors [22]. Although there are data that women, who have underlying ischemic heart disease less frequently, obtain less benefit from the use of the ICD and have a higher rate of complications [23], the truth is that, on the contrary, they benefit more from the use of cardiac resynchronization therapy [24], probably because they less frequently have areas of necrosis in the myocardium. For all the above, it can be concluded that there is a significant margin for improvement in the treatment received by all patients with HF and T2DM in our setting, both pharmacological and non-pharmacological. This deficiency in the treatment of HF, which is observed especially in women, can lead to a worse prognosis for these patients.

Limitations of the study

There are several limitations concerning our study. Of interest, the lack of randomization at baseline, and the overrepresentation of participant hospitals interested in their results and willing to provide the best care for the patients presenting the two conditions explored (T2DM and HF), might have led to a selection bias compromising the external validity of our results. Also, we highlight the low rate of devices used, although we cannot provide any information about the percentage of left bundle branch block/QRS data.

Conclusions

In conclusion, a selected cohort attending cardiology and endocrinology clinics because of HF and T2DM did not receive optimal treatment for their conditions, and this finding is more pronounced in women. Therefore, there is scope for improvement in the treatment of this high-risk population.

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Expression of miR-223 to predict outcomes after transcatheter aortic valve implantation

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Abstract

Background: *Transcatheter aortic valve implantation (TAVI) is an established treatment for aortic stenosis (AS) in patients at increased surgical risk. Up to 29% of patients annually experience major adverse cardiac and cerebrovascular events (MACCE) after TAVI. MicroRNAs (miRNA) are currently widely investigated as novel cardiovascular biomarkers. The aim of this study was to determine the influence of TAVI on the expressions of selected miRNAs associated with platelet function (miR-125a-5p, miR-125b and miR-223), and evaluate the predictive value of these miRNAs for MACCE in 65 patients undergoing TAVI.*

Methods: *Venous blood samples for miRNA expression analysis were collected 1 day before TAVI and at hospital discharge. The expression of miR-223, miR-125a-5p, miR-125b was evaluated in platelet-depleted plasma.*

Results: *The expression of miR-223 and miR-125b increased after TAVI, compared to the measurement before ($p = 0.020$, $p = 0.003$, respectively). Among 63 patients discharged from the hospital, 18 patients experienced MACCE (29%) during the median 15 months of observation. Baseline low miR-223 expression was a predictor of MACCE in univariate Cox regression analysis (hazard ratio [HR]: 2.71, 95% confidence interval [CI]: 1.04–7.01; $p = 0.041$). After inclusion of covariates, age, gender (male), New York Heart Association class and diabetes into the multivariate Cox regression model, miR-223 did not reach statistical significance (HR: 2.56, 95% CI: 0.79–8.33; $p = 0.118$).*

Conclusions: *To conclude, miR-223 might improve risk stratification after TAVI. Further studies are required to confirm the clinical applicability of this promising biomarker.* (Cardiol J 2024; 31, 1: 111–123)

Key words: aortic stenosis, transcatheter aortic valve implantation (TAVI), microRNA, prognosis

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Introduction

Aortic stenosis (AS) is the most prevalent primary valvular heart disease in Europe and North America, with increasing occurrence due to the ageing of the population. Transcatheter aortic valve implantation (TAVI) is an established treatment in patients at increased risk of surgery [1].

Although the outcomes after TAVI are improving, with the 5-year survival rate at 48% [2], 29% of patients annually experience major adverse cardiac and cerebrovascular events (MACCE) after TAVI [3]. Factors associated with MACCE include increased body mass index, reduced left ventricular ejection fraction (LVEF), carotid or peripheral artery disease, high aortic valve calcium score and SYNTAX score [4–6]. Nevertheless, none of these factors predict post-TAVI MACCE with clinically relevant sensitivity and specificity in an individual patient.

Turbulent blood flow in AS activates platelets and triggers a chronic pro-aggregatory state. It was demonstrated that activated platelets contribute to the progression of aortic valve calcification [7]. AS is known to activate platelets, TAVI might restore their function. On the other hand, the prosthetic valve and the intervention itself might aggravate the pro-aggregatory state, thus contributing to the development of MACCE after TAVI [8]. The effect of TAVI on platelet function has not been established.

MicroRNAs (miRNAs) have gained attention as potential novel biomarkers of platelet function. MicroRNAs are small, non-coding RNAs regulating posttranscriptional gene expression [9]. Platelets are a major source of circulating miRNAs [10, 11]. Since miR-125a-5p, miR-125b and miR-223 are associated with platelet function [11–14], acute myocardial infarction (AMI) [15] and stroke [16], these miRNAs may provide new biomarkers to predict MACCE after TAVI [10]. For example, miR-125a-5p regulates early stages of megakaryocyte development [17]. MiR-125b is involved in megakaryocytes maturation, proliferation and survival [18]. MiR-223, in turn, regulates gene expression in platelets and endothelium [19].

The effect of TAVI on miRNA expression was assessed in small groups of patients (n = 5–28), providing contradictory results [20–24]. The prognostic miRNA value, after TAVI has not been evaluated to date. Studies showed that several miRNAs including miR-223 and miR-125 are participating in the vascular system as they are highly expressed by endothelial cells [12, 25]. Moreover, studies also showed that their expressions can be altered by platelet activation due to antiplatelet therapies [10, 13, 26]. The present hypothesis was that TAVI modulates the expression of platelet-associated miRNAs, and that platelet-associated miRNAs may predict MACCE after TAVI. In a previous preliminary study, differences were found in the expression of miR-223 and miR-125 in patients with and without high on-treatment platelet reactivity [27]. The goal of this study was (i) to determine the effect of TAVI on the expression of miRNA associated with platelet function (miR-125a-5p, miR-125b and miR-223), and (ii) to evaluate the predictive value of these miRNAs for MACCE after TAVI.

Methods

Study design

This was a prospective study conducted at the 1st Chair and Department of Cardiology, Medical University of Warsaw, Poland in collaboration with the Vesicle Observation Center, Amsterdam University Medical Centers, the Netherlands. The study protocol, designed in compliance with the Declaration of Helsinki, was approved by the Ethics Committee of Medical University of Warsaw (approval number: KB/128/2018, KB/4/A2021).

Selection of participants

Patients diagnosed with severe AS and qualified for TAVI based on the Heart Team's decision were recruited. Severe AS was defined as aortic valve area (AVA) < 1.0 cm^2 or indexed AVA < 0.6 cm^2/m^2 as calculated by the continuity equation on transthoracic echocardiography (TTE). In patients with low-flow, low-gradient AS and reduced LVEF, dobutamine stress echocardiography was performed to differentiate between true severe AS and pseudo-severe AS, and in patients with low-flow, low-gradient AS and preserved LVEF, computed tomography was performed to assess aortic valve calcium score [1]. Exclusion criteria were transcatheter valve-in-valve implantation, chronic kidney disease (glomerular filtration rate < 30 mL/min), autoimmune diseases, active neoplastic disease, pregnancy, breast-feeding. All patients provided informed written consent.

Clinical data collection

The demographic and clinical data were collected during the index hospitalization.

A follow-up visit in the outpatient clinic was scheduled at 12 ± 3 months after TAVI, when control TTE was performed and data regarding

MACCE (all-cause death, cardiovascular death, myocardial infarction, stroke, transient ischemic attack [TIA], decompensation of heart failure, need for re-intervention) were recorded.

Treatment

Transcatheter aortic valve implantation was performed via femoral, subclavian, or carotid access by an interventional cardiologist (J.K., Z.H., B.R.) and a thoracic surgeon (R.W.) in a hybrid operating room. Pharmacotherapy after TAVI included dual antiplatelet therapy (acetylsalicylic acid [ASA] and clopidogrel) for 3–6 months, followed by lifelong ASA treatment in patients with no indication for oral anticoagulation (OAC), or OAC if required [1]. Other drugs were continued at the discretion of the treating physician, according to individual comorbidities.

Samples collection and handling

Blood samples were collected at two time points: 1 day before TAVI and 5–7 days following the procedure (at hospital discharge). Blood was collected in 7.5 mL ethylenediaminetetraacetic acid (EDTA) plastic tubes (S-Monovette, Sarstedt) via antecubital vein puncture using a 19-gauge needle, without tourniquet. The first 2 mL were discarded to avoid pre-activation of platelets. Within 15 minutes from blood collection, platelet-depleted plasma was prepared by double centrifugation (2500 g, 15 min, 20°C, acceleration speed 1, no brake). Supernatant was collected 10 mm above the buffy coat, re-centrifuged, mixed by pipetting, transferred to 1.5 mL low-protein binding Eppendorfs (Thermo Fisher Scientific, MA, USA), and stored in −80°C until analyzed.

RNA preparation and detection using quantitative PCR

The expression of miR-223, miR-125a-5p, miR-125b was evaluated in platelet-depleted plasma. Plasma RNA was extracted by miRVANA PARIS Kit. Total RNA was obtained as outlined above and diluted 1:10. Diluted RNA (5 μL) was reverse transcribed using the TaqMan miRNA Reverse Transcription kit (Applied Biosystems) according to the instructions of the manufacturer (Advanced miRNA assay, catalog number: A25576, Applied Biosystems). Subsequently, 3 μL of the product was used for detecting miRNA expression by quantitative polymerase chain reaction (PCR) using TaqMan miRNA Assay kits (Applied Biosystems) for the corresponding miRs on a The CFX384 Touch Real-Time PCR Detection System (BioRad Inc. Hercules, California, USA). Cel-miR-39 was spiked-in as an exogenous normalizer. Reactions were run in triplicate, and the mean value was used for all analyzes, to control variability associated with methodological reasons. MiRNA levels are expressed as 2-ΔCT [miRNA – cel-miR-39].

Endpoints

The primary end-point was the change in plasma expression of miR-223, miR-125a-5p and miR-125b before and after TAVI. The secondary endpoint was the predictive value of miR-223, miR-125a-5p and miR-125b for MACCE during the follow-up period.

Statistical analysis

Since there are no data regarding the differences in miR-223, miR-125a-5p and miR-125b before and after TAVI, power calculation for the primary end-point was based on the differences in miR-125a-5p and miR-125b expression in patients with calcified AS and healthy controls [28]. Patients with calcified AS had, on average, a 2-fold higher expression of miR-125a-5p and miR-125b, compared to controls. The required sample size was calculated by a 2-sided t-test at a significance level of 0.05 with the following assumptions: (i) mean difference between the groups = 1.0, (ii) standard deviation (SD) ± 2.0, and (iii) nominal test power = 0.8. It was estimated that a total of 64 patients should be enrolled in the study to observe a difference in miRNA expression before and after TAVI.

Statistical analysis was conducted using IBM SPSS Statistics, version 27.0 (IBM, New York, USA). MiRNA expressions data were log10-transformed for statistical analysis. Categorical variables were presented as number and percent and compared using χ^2 test. The Shapiro–Wilk test was used to assess normal distribution of continuous variables. Continuous variables were presented as mean and SD or median with interquartile range (IQR) and compared using an unpaired t-test or the Mann-Whitney U test. The predictive value of miRNAs for MACCE and the cut-offs were calculated using a receiver operating characteristic (ROC) curve. Logistic regression model incorporating miRNA expression and clinical characteristics were used to determine the best model for MACCE. A 2-sided p-value below 0.05 was considered significant.

Results

Figure 1 shows the study design and flow chart. Out of 135 patients who underwent TAVI be-

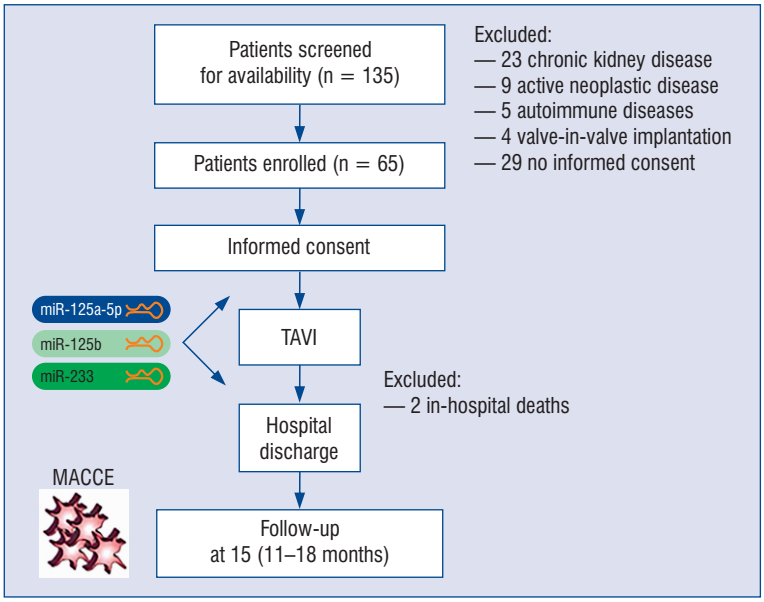

Figure 1. Study design and flow chart; MACCE — major adverse cardiac and cerebrovascular events; TAVI — transcatheter aortic valve implantation.

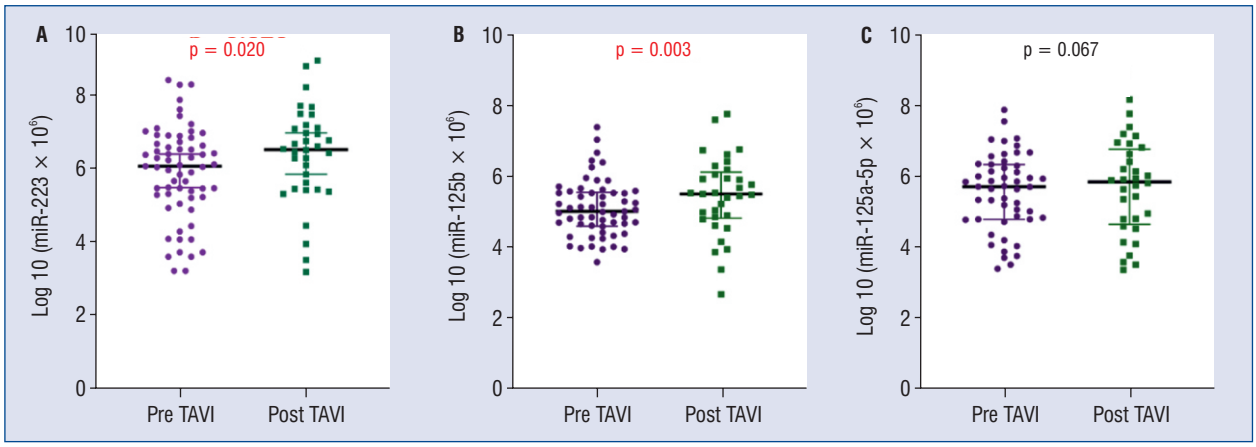

Figure 2. Comparison of plasma miRNAs expression before and after transcatheter aortic valve implantation (TAVI); **A.** miR-223; **B.** miR-125b; **C.** miR-125a-5p.

tween November 2018 and June 2020, 65 patients were enrolled in the study and 63 patients attended the follow-up. The median time to follow-up was 15 months (IQR 11–18 months).

Expression of miRNAs before and after TAVI

The expression of miR-223 and miR-125b increased after TAVI, compared to the measurement before ($p = 0.020$, $p = 0.003$, respectively; Fig. 2). There was a trend towards the increased expression of miR-125a-5p after TAVI ($p = 0.067$)

Expression of miRNAs after TAVI according to the antiplatelet and OAC treatment

Compared to the pre-TAVI measurement, expressions of miR-223 and miR-125a-5p increased after TAVI in patients taking P2Y12 inhibitors ($p = 0.045$, $p = 0.006$, respectively) (Fig. 3A, C). Concentration of all miRNAs decreased after TAVI in patients taking OACs ($p = 0.014$, $p = 0.047$,

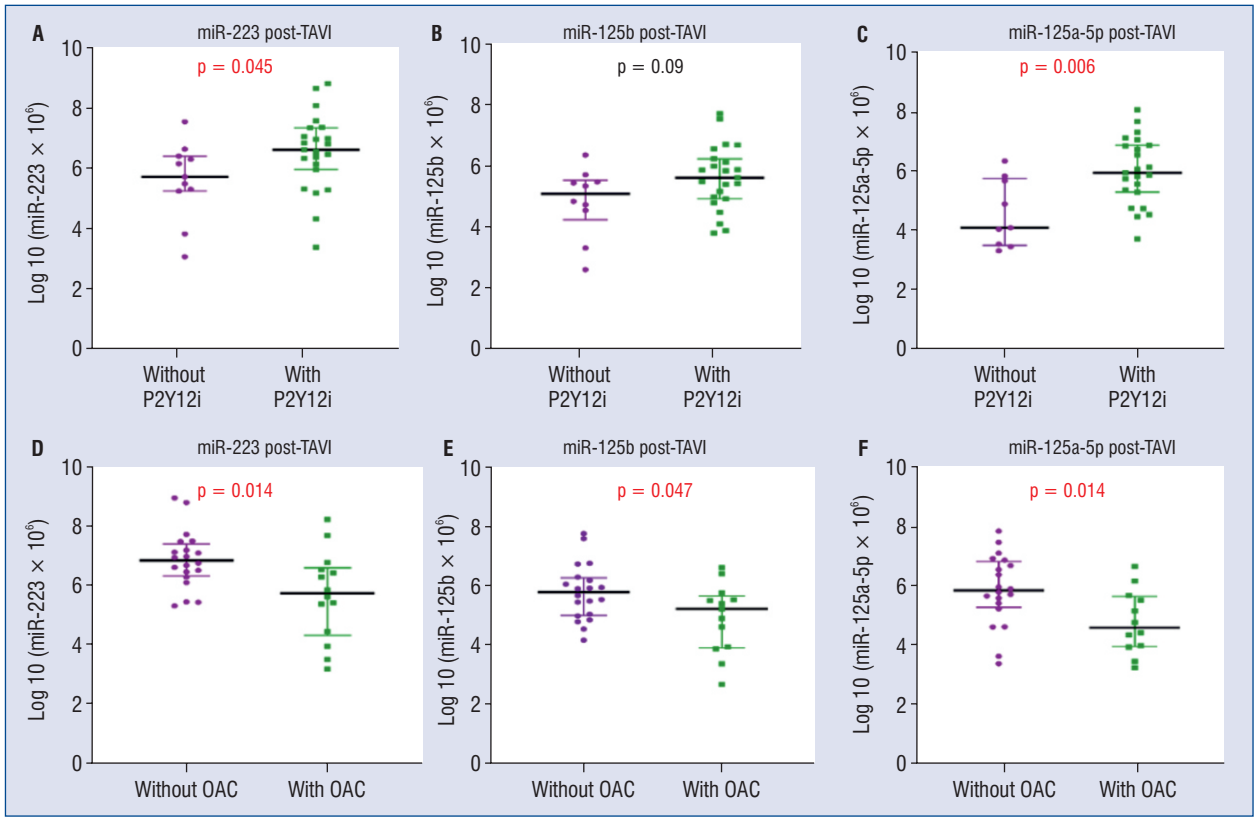

Figure 3. Post-transcatheter aortic valve implantation (TAVI) miRNAs expressions in regard to antiplatelet treatment and oral anticoagulant (OAC); **A.** miR-223 regarding P2Y12 inhibitors (P2Y12i); **B.** miR-125b regarding P2Y12i; **C.** miR--125a-5p regarding P2Y12i; **D.** miR-223 regarding OAC; **E.** miR-125b regarding OAC; **F.** miR-125a-5p regarding OAC.

p = 0.014, respectively; Fig. 3D–F). There was no significant difference between miRNA expression with or without ASA. Patients initially treated with antiplatelet drugs and OAC had comparable miRNAs expressions (data not shown).

Decreased baseline expression of miR-223 is associated with adverse outcomes

There were 2 in-hospital deaths. Among 63 discharged patients, 18 (29%) patients experienced MACCE: 2 (3.2%) all-cause deaths, 7 (11.1%) cardiovascular deaths, 2 (3.2%) TIA, 6 (9.5%) readmissions due to decompensated heart failure and 1 (1.6%) need for valve re-intervention. There were no AMI or strokes.

Patient characteristics are presented in Table 1. Patients who experienced MACCE were older (median age 84.0 vs. 81.0 years, p = 0.060) and were more frequently male (72.2% vs. 33.3%, p = 0.005). There were no other differences between the groups.

The procedural characteristics and device success rate were comparable in both groups (94.4% vs. 100.0%, p = 0.111). The incidence of procedural complications (life-threatening or disabling bleeding, major vascular complication, new permanent pacemaker implantation) were similar in both groups.

At follow-up, the mean LVEF and mean aortic valve gradient were comparable in both groups (60% vs. 50.5%, p = 0.075 and 8.5 mmHg vs. 8.7 mmHg, p = 0.804, respectively). No significant correlations between the studied miRNAs expressions and pressure gradient via the aortic valve were observed (data not shown).

The baseline miR-223 expression was lower in patients who experienced MACCE, compared to those who did not (p = 0.006; Fig. 4A) and discriminated between these two groups of patients (area under ROC curve [AUC] = 0.72, p = 0.006; Fig. 4B). MiR-125b and miR-125a-5p expression was comparable between patients with and without MACCE (p = 0.109, p = 0.118, respectively; Fig. 4C, 3F).

Table 2 shows the statistical estimates for the prediction of MACCE by baseline miR-223

Table 1. Comparison of baseline characteristics between patients who experienced MACCE and those who did not during a median follow-up of 15 months.

	Total populations (n = 63)	No MACCE (n = 45)	MACCE (n = 18)	P
Baseline characteristics				
Age [years]	81.0 (77.5–84.0)	81.0 (77.0–83.0)	84.0 (80.0–85.0)	0.060
Gender, male	28 (44.4%)	15 (33.3%)	13 (72.2%)	**0.005**
BMI [kg/m^2]	27.3 ± 3.8	27.5 ± 4.2	26.9 ± 3.1	0.661
Co-morbidities				
Hypertension	49 (81.7%)	34 (79.1%)	15 (88.2%)	0.408
Diabetes mellitus	22 (36.7%)	16 (37.2%)	6 (35.3%)	0.890
Atrial fibrillation	16 (26.7%)	10 (23.3%)	6 (35,3%)	0.342
Prior stroke/TIA	9 (15. 0%)	7 (16.3%)	2 (11.8%)	0.659
Prior myocardial infarction	13 (21.7%)	9 (20.9%)	4 (23.5%)	0.826
Prior PCI	27 (45.0%)	18 (41.9%)	9 (52.9%)	0.437
Prior CABG	3 (5.0%)	2 (4.7%)	1 (5.9%)	0.844
COPD	8 (13.3%)	5 (11.6%)	3 (17.7%)	0.537
Heart failure (NYHA III/IV)	15 (27.3%)	10 (25.6%)	5 (51.3%)	0.908
EuroSCORE II [%]	4.2 (3.3–5.4)	4.2 (3.2–5.3)	4.5 (3.7–5.8)	0.447
CKD > 3a	11 (18.3%)	6 (14.0%)	5 (29.4%)	0.163
Laboratory data				
Hemoglobin [g/d]	11.8 ± 2.0	11.9 ± 2.1	11.6 ± 1.4	0.512
Creatinine [mg/dL]	1.3 (1.0–1.6)	1.3 (1.0–1.6)	1.3 (1.0–1.5)	0.948
Estimated GFR [mL/min/1.73 m^2]	45.5 (36–57.7)	45 (35–57)	47 (43–61)	0.583
NT-proBNP	1811 (508–3901)	1777 (394.5–3804)	2670.5 (1584–9080)	0.199
Echocardiography before TAVI				
Ejection fraction [%]	57 (46–63)	57 (46–63)	55 (42–63)	0.868
V max [m/s]	4.1 (3.5–4.5)	4.1 (3.6–4.4)	4.1 (2.1–4.6)	0.589
Gradient max	68 (42.5–80.5)	70 (47–80)	44 (31–83)	0.486
Gradient mean	43 (31–51)	43 (31.5–51.5)	43 (15–51)	0.604
AVA (VTI)	0.7 (0.6–0.9)	0.7 (0.6–0.9)	0.9 (0.6–0.9)	0.309
AVAi	0.4 (0.3–0.5)	0.4 (0.3–0.5)	0.7 (0.4–1.0)	0.053
Low-flow, low-gradient AS	15 (23.8%)	12 (26.7%)	3 (16.7%)	0.400
Procedural characteristics				
Access site:				0.676
Transfemoral	55 (91.7%)	41 (95.4%)	14 (82.4%)	0.787
Subclavian	3 (5%)	2 (4.4%)	1 (6.7%)	0.732
Carotid	2 (3,3%)	2 (4.4%)	0 (0%)	0.378
Prosthesis size [mm]:				0.907
23	1 (1.7%)	1 (2.4%)	0 (0%)	0.521
25	13 (22%)	9 (21.4%)	4 (23.5%)	0.860
26	2 (3.4%)	2 (4.8%)	0 (0%)	0.360
27	14 (23.7%)	10 (23.8%)	4 (23.5%)	0.982
29	18 (30.5%)	13 (31%)	5 (29.4%)	0.806
31	0 (0%)	0 (0%)	0 (0%)	1.000
34	11 (18.6%)	7 (16.7%)	4 (23.5%)	0.610
Valve type:				0.672
EvolutR	22 (37.3%)	17 (40.5%)	5 (29.4%)	0.350
EvolutPRO	5 (8.5%)	3 (7.1%)	2 (11.8%)	0.610
Portico	32 (54.2%)	22 (52.4%)	10 (58.8%)	0.821

→

Table 1 (cont.). Comparison of baseline characteristics between patients who experienced MACCE and those who did not during a median follow-up of 15 months.

	Total populations (n = 63)	No MACCE (n = 45)	MACCE (n = 18)	P
Device success	62 (98.4%)	45 (100%)	17 (94.4%)	0.111
Procedure complications				
Life-threatening or disabling bleeding*	1 (1.6%)	1 (2.2%)	0 (0%)	0.524
Major vascular complication*	5 (7.9%)	4 (8.8%)	1 (5.5%)	0.658
Stroke	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.000
New pacemaker	7 (11.1%)	5 (11.1%)	2 (11.1%)	1.000
Echocardiography at follow-up				
Ejection fraction [%]	55 (46–65)	60 (46–65)	50.5 (40–55)	0.075
Peak AV gradient [mmHg]	17.2 ± 5.4	17 ± 5.2	17.5 ± 5.9	0.848
Mean AV gradient [mmHg]	8.5 ± 2.7	8.5 ± 2.8	8.7 ± 2.5	0.804
Paravalvular leak type 3 or 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.000
Post-TAVI procedure concomitant medications				
Beta-blockers	51 (81%)	37 (82%)	14 (78%)	0.950
ACE inhibitors	40 (64%)	27 (60%)	13 (72%)	0.177
MRA	17 (27%)	12 (27%)	5 (28%)	0.883
Diuretics	53 (84%)	27 (82%)	16 (89%)	0.115
Statins	49 (78%)	36 (80%)	13 (72%)	0.675
Proton pump inhibitors	68 (74%)	30 (67%)	13 (72%)	0.445
Antidiabetic drugs	22 (35%)	16 (37%)	6 (35%)	0.890
Acetylsalicylic acid	47 (75%)	37 (82%)	10 (56%)	0.046
P2Y12 inhibitor	44 (70%)	35 (78%)	9 (50%)	0.031
Anticoagulant	22 (35%)	14 (31%)	8 (44%)	0.242
miRNAs relative expressions:				
miR-223 pre-TAVI	1.14 (0.16–5.22)	1.64 (0.29–7.96)	0.20 (0.005–2.06)	0.006
miR-223 post-TAVI	3.92 (0.82–30.15)	4.26 (0.61–14.37)	1.27 (0.007–15.79)	0.196
miR-125b pre-TAVI	0.08 (0.29–0.15)	0.12 (0.05–0.46)	0.05 (0.02–0.19)	0.109
miR-125b post-TAVI	0.34 (0.07–2.40)	0.30 (0.07–0.99)	0.32 (0.01–4.71)	1.000
miR-125a-5p pre-TAVI	0.20 (0.06–0.73)	0.44 (0.06–2.98)	0.30 (0.01–0.68)	0.118
miR-125a-5p post-TAVI	0.59 (0.05–7.09)	0.30 (0.07–0.99)	0.32 (0.01–4.71)	0.654

*According to the Valve Academic Research Consortium (VARC). Bold p value indicates significantly different (< 0.05). Data are shown as number (percentage), median (interquartile range), mean ± standard deviation; ACE — angiotensin-converting enzyme; AS — aortic stenosis; AV — atrioventricular; AVA — aortic valve area; AVAi — aortic valve area index; BMI — body mass index; CABG — coronary artery bypass graft surgery; COPD — chronic obstructive pulmonary disease; CKD — chronic kidney disease; GFR — glomerular filtration rate; MACCE — major adverse cardiac and cerebrovascular events; MRA — mineralocorticoid receptor antagonists; NT-proBNP — N-terminal pro-B-type natriuretic peptide; NYHA — New York Heart Association; PCI — percutaneous coronary intervention; TAVI — transcatheter aortic valve implantation; TIA — transient ischemic attack; VTI — velocity time integral

expression below the cut-off value, determined based on the ROC curve. MiR-223 at admission predicted MACCE with 78% sensitivity and 61% specificity. MiR-223 expression levels after TAVI procedure were not predictive of MACCE (data not shown).

To check whether the baseline expression of miR-223 is an independent predictor of MACCE, the baseline expression of miR-223 was incorporated in the univariate Cox regression analysis. Low baseline expression of miR-223 was associated with MACCE in univariate analysis (HR: 2.71, 95% CI: 1.04–7.01; p = 0.041). However, after including the covariates (age, gender [male], New York Heart Association [NYHA] class and diabetes ([4–6]) into the multivariate Cox regression model, miR-223 did not reach statistical significance [HR: 2.56, 95% CI: 0.79–8.33; p = 0.118; Table 3).

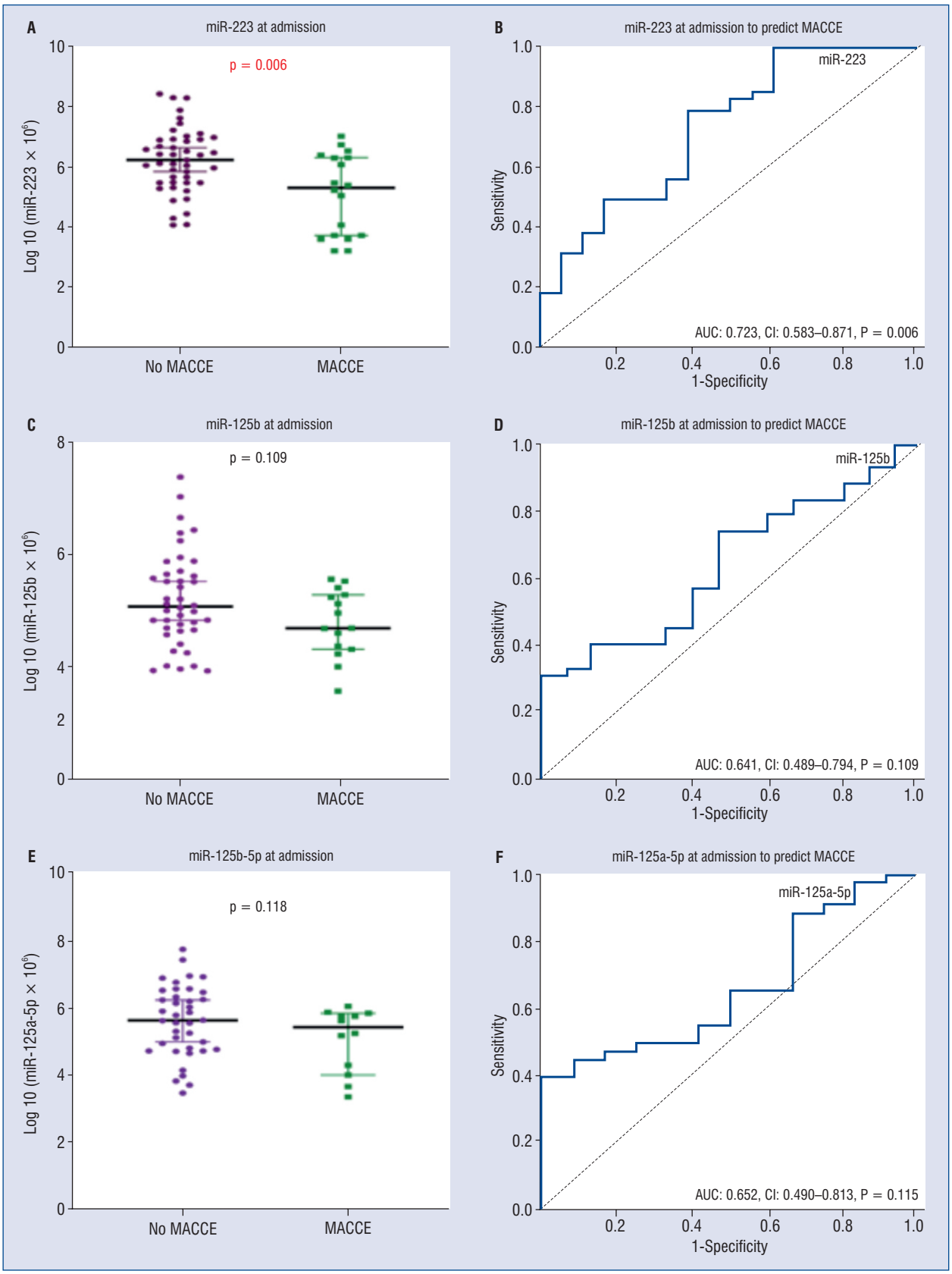

Figure 4. Expressions of baseline miRNAs (miR) in plasma of patients at admission before transcatheter aortic valve implantation in patients with and without major adverse cardiac and cerebrovascular events (MACCE) during a median follow-up of 15 months; **A, B.** (ROC-curve): MiR-223; **C, D.** (ROC-curve): MiR-125b; **E, F.** (ROC-curve): MiR-125a-5p; AUC — area under the curve; CI — confidence interval; ROC — receiver operating characteristic.

Table 2. Statistical estimates for prediction of major adverse cardiac and cerebrovascular events by baseline miR-223 expression.

miRNA	AUC (95% CI)	P	Cut-off	Sensitivity	Specificity	PPV	NPV	PLR
Baseline miR-223	0.72 (0.58–0.87)	0.006	0.285	78%	61%	83%	53%	2

AUC — area under the curve; CI — confidence interval; PPV — positive predictive value; NPV — negative predictive value; PLR — positive likelihood ratio

Table 3. Univariate and multivariate Cox regression analysis for prediction of major adverse cardiac and cerebrovascular events by low baseline miR-223 expression.

miRNA	Cox regression	Hazard ratio	95% confidence interval		P
			Lower	Upper	
Low baseline miR-223 expression	Univariate	2.713	1.043	7.054	0.041
	Multivariate*	2.560	0.787	8.329	0.118

*After adjustment for age, gender (male), NYHA class, and diabetes. Bold p value indicates significantly different (< 0.05).

Figure 5 shows the Kaplan-Meier analysis of event-free survival for MACCE in patients after TAVI stratified according to miR-223 baseline plasma expression, with low expression defined as expression below the established cut-off (7 out of 18 patients who experienced MACCE), based on the ROC curve analysis. Patients with low miR-223 expression at admission had a lower chance of event-free survival during follow-up, compared to patients with high miR-223 expression (p = 0.033 for the log-rank test).

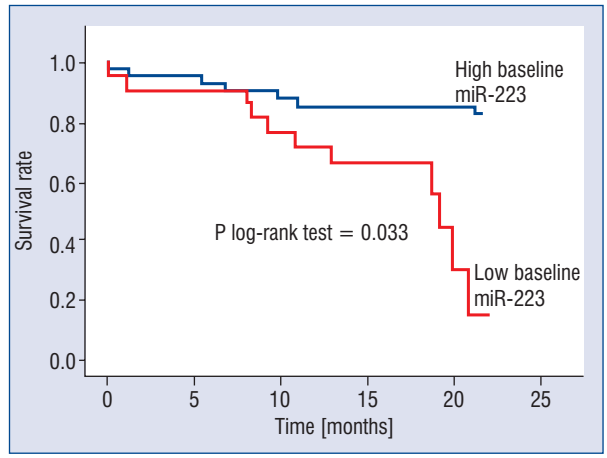

Figure 5. The Kaplan-Meier survival analysis for major adverse cardiac and cerebrovascular events (MACCE) after transcatheter aortic valve implantation in patients with high or low miR-223 at admission.

Discussion

The main findings of the present study are: (i) the expression of miR-223 and miR-125b increased after TAVI, compared to the baseline, and (ii) low baseline expression of miR-223 was a predictor of MACCE in univariate Cox regression analysis.

High shear stress in AS, is associated with endothelial dysfunction and increased platelet activation [29]. AS is associated with distinct miRNAs expression changes [30]. The resolution of high shear stress through TAVI was shown to have an anti-inflammatory effect, which was proposed to be a novel therapeutic benefit of TAVI [31].

The effect of TAVI on miRNA expression was evaluated by other authors providing contradictory results [1, 21–24]. The current study provides evidence that the expression of miR-223, miR-125b and potentially miR-125a-5p changes after TAVI, suggests their involvement in the adaptation to altered hemodynamic conditions after TAVI.

MiR-125a-5p plays a role in atherosclerosis [32] and stroke [33]. In the present study, there was only a trend towards increased expressions of miR-125a-5p after TAVI, and it did not predict MACCE. However, the lack of statistical significance might be due to the small sample size and no strokes during the observation period.

The influence of miR-125b on the cardiovascular system remains conflicting. Some authors showed deleterious effects miR-125b, including intravascular calcification [34], hypoxia-induced cardiomyocyte injury [35], among others [16,

36, 37]. Other authors reported beneficial effects of miR-125b, including protection against ischemia-reperfusion injury [37, 38] or alleviation of infarction-induced cardiomyocytes apoptosis [39]. Therefore, it is difficult to determine whether the increased expression of miR-125b after TAVI, found in the present study and by other authors [40], is a response to the procedure, or a part of the anti-inflammatory effect.

MiR-223 — one of the most abundant miRNAs in platelets — has been investigated in platelet function and thrombotic events [41]. In a murine model, elevated expression of miR-223 were observed in thrombin-activated platelets, suggesting that miR-223 might reflect platelet activation [42]. In cultured endothelial cells, miR-223 decreased tissue factor expression and procoagulant activity, implying its potential protective function following endothelial injury [43]. Decreased miR-223 was an independent predictor of MACCE in coronary artery disease patients receiving antiplatelet treatment [41]. However, the association between miR-223 and cardiovascular disease (CVD) remains complex. Downregulation of miR-223 in CVD patients was previously demonstrated, suggesting miR-223 might have a protective role in CVD [44]. Anti-inflammatory ability of miR-223 against various diseases has been published in literature. Wang et al. [45] showed exosomal miR-223 plays a role in cardio-protection through down-regulation of *Sema3A* and *Stat3* genes, which are direct targets of miR-223-5p and -3p. Moreover, during cerebral ischemia, cysteinyl leukotrienes are largely secreted and their receptors are also increased in activated microglia, previous studies showed that miR-223-3p may exert anti-inflammatory effect through inhibiting cysteinyl leukotrienes receptors [46, 47]. Besides the cerebrovascular protection properties, studies also aimed to analyze the molecular mechanism of miR-223 in myocardial infarction. MiR-223-3p mimics showed decreased myocarditis and apoptosis after myocardial infarction and improved cardiac function by targeted inhibition of *FBXW7* expression in in vitro analysis [48]. It was also suggested that miR-223 may serve as a potential target in AMI treatment in an animal study [49]. Furthermore, in a large cohort of coronary artery disease patients, upregulated miR-223 expression was a predictor of cardiovascular death [15]. On the other hand, a contradictory study reported an increase in miR-223 expression in patients with AMI and stroke [50]. Hence, the increase in miR-223 expression could either be a protective mechanism against an acute cardiovascular event in these patients, or contribute to cardiovascular injury. In the current study, low baseline expression of miR-223 was a predictor of MACCE in univariate analysis, supporting the protective effect of this miRNA on the cardiovascular system. However, the direct link between the decreased expression of miR-223 and adverse outcomes requires further investigation.

Lower miR-223, miR-125a and miR-125b expressions were also found in patients treated with OAC therapy after TAVI, and higher levels of miR-125a and miR-125b in patients taking P2Y12 inhibitors. Recent meta-analysis demonstrated that miR-223 is increased in patients with atrial fibrillation treated with OAC [51]. It was also shown that miR-223-3p is an independent predictor of thrombotic events and can be used for ischemic risk stratification after AMI [52]. Similarly, elevated miR-125a-5p, miR-125b-5p were early biomarkers in ischemic stroke [53]. The present observations may indicate that in some patients after TAVI, therapy with OAC might be more beneficial than single antiplatelet therapy (SAPT) or dual antiplatelet therapy (DAPT), which is in line with our recent meta-analysis showing that the use of OAC after TAVI is associated with a lower risk for subclinical leaflet thrombosis, compared with SAPT and DAPT [54].

Limitations of the study

The main limitation of this study is the small sample size, making the study underpowered to detect the predictive value of the investigated miRNAs for the individual components of the composite end-point. Second, since one miRNA can bind to various mRNAs and can be regulated by other miRNAs [55], the differences in miRNA expression before and after TAVI, and in patients with and without MACCE do not allow drawing conclusions regarding the causal association between the investigated miRNA and the development of adverse events. Moreover, the present study did not have blood collection and the miRNAs analysis right after, and a few months after the TAVI procedure in the population, which also limited monitoring of miRNAs expression levels. Third, given the hypothesis-generating study design, the analysis was limited to miRNA associated with platelet function, based on a preliminary analysis [27]. MiRNA sequencing might enable determining novel miRNAs with higher predictive value for post-TAVI MACCE. Fourth, since platelet reactivity in the study was not evaluated, we cannot exclude that the inverse relationship between

miR-223 expression and post-TAVI MACCE is related with poor response to DAPT in the patients [56]. Fifth, miR-223 is also related to systemic endothelial damage and platelet status-related biomarkers, not measured in this study [57]. Finally, all TAVI procedures were done by the same team, which eliminated the bias due to various expertise levels, but also limited the general results applicability. Altogether, results herein, should be confirmed in a larger, multi-center study before miRNAs can be used in risk stratification after TAVI in clinical practice.

Conclusions

Expression of miR-223 and miR-125b increased after TAVI, compared to the measurement before TAVI. Baseline low expressions of miR-223 is a promising marker of increased risk of MACCE after TAVI. Because the present study is limited by a small sample size, a composite end-point and lack of statistical significance in multivariate analysis, the results should be interpreted with caution.

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Long-term bio-functional performance of a novel, self-positioning balloon expandable transcatheter biological aortic valve system in the ovine aortic banding model

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Abstract

Background: *The aim of the study was to evaluate bio-functionality of a novel, proprietary balloon-expandable biological transcatheter aortic valve implantation (TAVI) system (InFlow, CardValve Consortium, Poland) in an ovine model of aortic banding.*

Methods: *Surgical ascending aorta banding was created in 21 sheep. Two weeks later, 18 biological valves were implanted within the model using 15–16 F InFlow TAVI systems and carotid cut-down approach. Follow-up transthoracic echocardiography was performed at 30, 90, and 180-day. At designated time, animals were euthanized and valves harvested for analysis.*

Results: *All sheep survived the banding procedure. There were 4 (22%) procedure related deaths within a 7-day period. During the observation an additional 2 sheep died. In one, the valve dislocated after the procedure — the animal was excluded. Two animals completed 30-day follow up, five 90-day follow-up and four terminal follow-up of 180 days. Valves examined via transesophageal echocardiography showed proper hemodynamic parameters without evidence of structural valve deterioration. The maximum and average flow gradients at 180 days were 31.4 (23.3–37.7) and 17.5 (13.1–20.2) mmHg, respectively. There was one case of moderate insufficiency and no case of perivalvular leaks. By histopathology, there were no inflammation, thrombosis, nor calcifications in any tested valves at long-term follow-up. Neointimal coverage of stent struts increased with time from basal part in "early" groups to nearly 3/4 of stent length in the 180-day group. The pannus tissue showed maturation that increased with time with no stenotic "collar" visible in orthotopically implanted valves.*

Conclusions: *The study showed good hemodynamic performance, durability and biocompatibility of the novel biological transcatheter heart valve.* (Cardiol J 2024; 31, 1: 124–132)

Key words: aortic stenosis, transcatheter aortic valve implantation (TAVI), artificial heart valve, biological heart valve, preclinical study

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Introduction

The aortic valve stenosis treatment evolved drastically with the introduction of transcatheter aortic valve implantation by Cribier et al. [1] in 2002. The method itself was refined through recent decades resulting in expanding indications for transcatheter aortic valve implantation (TAVI) procedures as stated in both European and American cardiology guidelines [2, 3]. Performed studies have proved superiority of the method to medical therapy and surgery in prohibitive risk patients' group, with non-inferiority/superiority achieved in intermediate and recently in low-risk cohorts [4–8]. The above-mentioned facts facilitated the rapid growth of TAVI procedures performed worldwide with transcatheter intervention volume exceeding for the first time that of all forms of surgical aortic valve replacements in 2019 in the United States [9]. Still, the quotes remain insufficient when considering the need. In the European Union, the average number of TAVI per million inhabitants is around 140 (range 50–270), with an estimated need of around 250–300 procedures per million citizens performed annually [10]. Researchers showed that approximately 180,000 patients can be considered potential candidates for TAVI in the European Union and in North America, with a potential to increase up to 270,000 cases annually if indications were to expand further [10]. Furthermore, although latest data show very good long-term durability, with low percentage of structural valve degeneration, as the indications expand and TAVI valves are being implanted in younger patients, this may raise issues in the future [11]. Additionally, the remaining limitations of transcatheter procedures, such as paravalvular leak, myocardial injury, need for pacemaker implantation and vascular complications prompt are yet to be addressed. Therefore, there is a need for new technologies to be researched and developed to upgrade the method itself, as well as, to increase and endorse socially equal accessibility, especially in low-income countries or patient cohorts.

Presented herein, are short- and long-term results of a novel, proprietary biological transcatheter aortic valve prosthesis which was tested in a preclinical model of the aortic banding in an ovine.

Methods

Study design

The study protocol has been accepted by the Local Ethics Committee for animal research, Decision No. 150/2016. The Experiment was conducted in a GLP certified Center for Cardiovascular Research and Development of American Heart of Poland, Kostkowice, Poland. Twenty-one blackface crossbred sheep, approximately 2 years old, weighing 40 to 80 kg were included. Animals received an acclimation period of at least 21 days. All animals received standard of care outlined in the study protocol and in accordance with the act of animal welfare and the "Guide for the Care and Use of Laboratory Animals" [12].

The banding methods have been described and previously validated [13]. Briefly, ascending aorta delicate stenosis (AS) and anchoring mechanism was created by fixing a surgical band around the aorta. After AS creation, animals were allowed a recovery period of at least 10 days. Subsequently, Inflow™ transcatheter heart valve was implanted via carotid cut-down utilizing. Follow up echocardiography and complete blood works was performed at 30-, 90- and 180-day follow-up.

Study device

Inflow™ biological transcatheter heart valve was comprised of a balloon-expandable, radiopaque, cobalt-chrome alloy frame with a proprietary stent design, and a tri-leaflet, ultrathin swine pericardium valve connected with a cuff (Fig. 1). Biomaterials were attached to the metal frame using the standard suturing technique. The prosthesis is a terminally sterilized (using an antibiotic solution), single use device, indicated for relief of AS in patients with symptomatic heart diseases due to severe native calcified AS in patients at high or greater risk for open surgical valve replacement. For the study purpose Inflow™ transcatheter heart valve was available in a diameter equaling 23 mm and was used with dedicated, proprietary delivery system including self-positioning balloon shape and left ventricle protection system. After proper crimping the device outer diameter is 15–16 F. Devices are stored in an aldehyde solution. This transcatheter heart valve and delivery is covered with 5 international patents issued (no. P.426429, P.426432, P.426433, P.426434, P.426463).

Aortic banding model

Sheep were anesthetized using a combination of ketamine 10 mg/kg IM/IV + xylazine 0.05–0.2 mg/kg IM + atropine 0.1–0.2 mg/kg IM. Propofol 2–4 mg/kg IV was administered to facilitate intubation. Following successful intubation, sheep were placed in right lateral recumbency. Anesthesia was maintained using isoflurane (1–3% concentration).

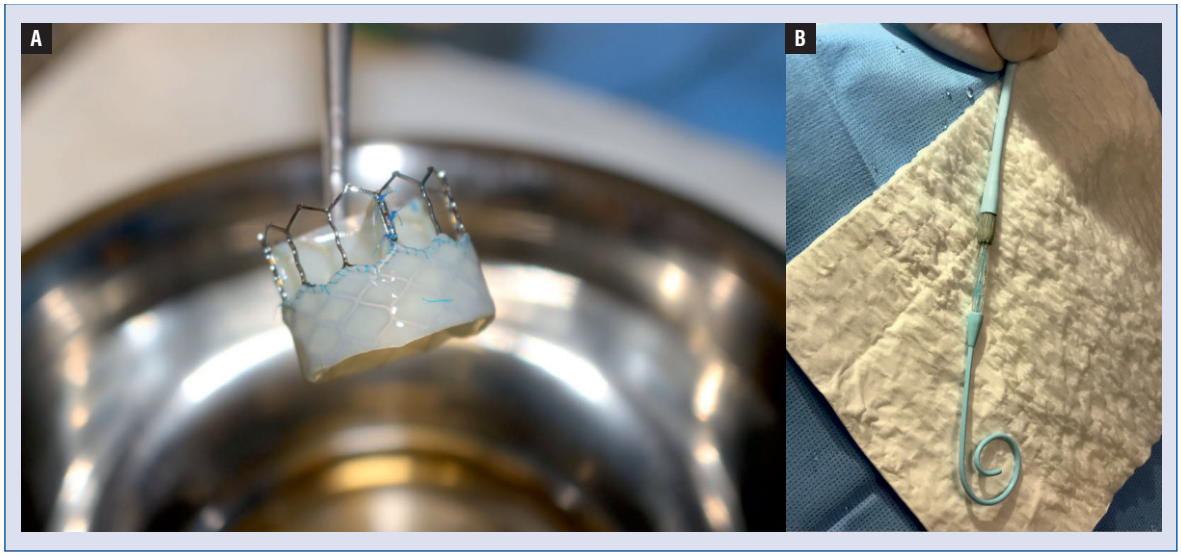

Figure 1. A. Biological Inflow heart valve prototype — lateral view; **B.** Inflow valve crimped on the balloon.

Additionally, continuous venous infusion of fentanyl was used to provide proper analgesia (0.003–0.006 mg/kg/h) during surgery. Aortic banding was achieved by means of a minimally invasive left side thoracotomy. An incision was made between the 4th and 5th intercostal space, and the ascending aorta was exposed. The target site for the banding implantation was mid-way from the native aortic valve and the common carotid trunk. With the help of sizer kits, the Dacron sleeve was measured, and the diameter of the aorta decreased between 2–4 mm. A surgical stainless-steel wire was sutured in the mid-line of the banding tissue to allow identification under fluoroscopy. After the procedure completion, the wound was closed, and the sheep moved to post-op recovery.

Transcatheter aortic valve implantation

Two weeks after the aortic banding, TAVI procedures were performed starting with anesthesia using the same procedures as outlined for the banding. Sheep were placed in dorsal recumbency with the legs stretched caudally. The left carotid artery was surgically exposed and prepared, as close to the thoracic inlet as possible. A 6 Fr arterial sheath was placed in the carotid artery. A J wire 0.035" was advanced through the arterial sheath in the left ventricle, and a 5 Fr pig-tail catheter with 10 mm markers was advanced over the J wire. A ventriculography and aortography along with invasive pressure evaluation were performed to assess the banding site and measure the target implantation site diameter. The pig-tail catheter markers were used to calibrate the distance. After all measurements were finished, the pig-tail catheter, and the J wire were removed. The valve was crimped on a balloon matching the valve size (a 23 mm balloon for a 23 mm valve), and the natural direction of blood flow from the heart (aortic position). The 6 Fr arterial sheath was removed and replaced with an arterial sheath bigger than the measured profile of the valve (usually 18–22 F). Once the large arterial sheath was inserted, heparin was administered at a dose of 300 IU/kg (3 mg/kg), IV, to achieve an activated clotting time over 300 s. A super stiff Amplatz wire was advanced through the arterial sheath into the left ventricle. The valve crimped on the balloon was advanced over the Amplatz wire and through the arterial sheath to the aortic banding. The valve was expanded with the help of a 50 mL syringe filed with 70:30 ratio of saline and contrast. Once the implantation was complete, the Amplatz wire, and the balloon were removed. Post implantation control ventriculography and aortography were performed as outlined above without changing the arterial sheath. The arterial sheath was removed, the carotid artery ligated, and the tissues and skin were sutured in three layers. The sheep was then transferred to post-op recovery. Post procedural anticoagulation regimen included daily administration of low molecular weight heparin (once daily, 1–2 mg/kg SC) for 30 days following intervention.

Echocardiography

Transthoracic echocardiography (TTE) was performed at 30, 90, and 180-day follow-up.

Transesophageal echocardiography (TEE) was performed at 180 days as a complement to TTE, while under anesthesia. All routine parameters were evaluated (left ventricle end-diastolic volume, aortic diameter, left ventricle end-systolic diameter, ejection fraction, cuspids separation, among others), and valve functionality, deployment, and any other visual findings were documented in the echo reports.

Pathological evaluation

The independent, pathology core lab (Silesian Center for Heart Diseases, Poland) received fixed, explanted hearts and ascending aorta for histopathology. Hearts were trimmed and the segment of tissue containing the explants was excised, grossly examined and radiographed. Aortic roots with valve implants were dehydrated in a graded series of ethanol, cleared in xylene, and infiltrated and embedded in SPURR plastic resin. After polymerization, the device with frame was sectioned radially twice to capture each cusp (left coronary cusp [LCC]; right coronary cusp [RCC]; non coronary cusp [NCC]) and stained with hematoxylin and eosin (H&E). In addition, the portion of the plastic block containing each of the three valve cusps (radial planes) was separated from the frame, cut serially twice (thin sections) and stained with Movat's pentachrome and Von Kossa. The block remnants were reassembled with appropriate spacers and cut crosswise (transverse plane) at two levels. All ground sections were ground and micro polished to optical finish using the Exakt cutting/grinding system. Resulting sections were stained with H&E. Trackable gross lesions submitted separately were processed, embedded in paraffin or SPURR resin as appropriate, sectioned and stained with H&E and/or Masson's trichrome (paraffin only). All resulting slides were evaluated via light microscopy by the study pathologist. In the event of identifying problems with valve function, the harvested tissues were then passed to the histopathology for analysis. If no correlation between reported death and valve function was revealed, further analysis was abandoned.

Statistical analysis

This is a prospective, observational and experimental study; therefore, no study hypothesis was made. Normally distributed data are presented as means and standard deviations, whereas non-parametric as proportions and percentage or medians and interquartile ranges. To test for temporal differences in echocardiographic parameters repeated measures ANOVA has been performed followed by the pairwise comparison with the Bonferoni modified paired T-test. A value of $p < 0.05$ was considered statistically significant. MedCalc Statistical Software version 14.12.0 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org) was used for analysis.

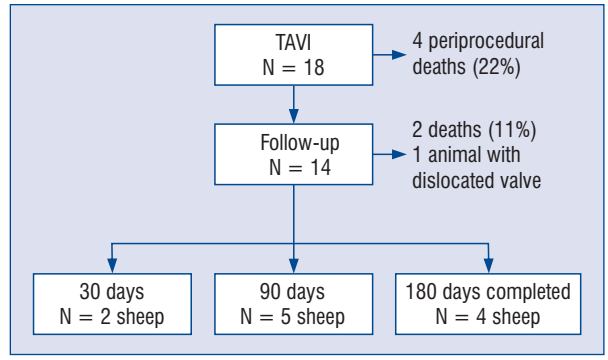

Figure 2. Study flowchart; TAVI — transcatheter aortic valve implantation.

Results

Surgical banding was performed in 21 sheep. All animals survived the banding-TAVI period. Out of these, 18 were assigned to the TAVI procedure. Three sheep were excluded due to the improper size of the banding location as reported in aortography. All valves were delivered successfully to the banding site and implanted. The aggregate periprocedural mortality (defined as up to 7 days after the procedure) amounted 4 (22%) animals. During the observation period an additional 2 sheep died. Complete observation was achieved in 11 animals, 2 for 30 days, 5 for 90 days and 4 for 180 days, respectively (Fig. 2). In 1 animal, that completed the 180 days observation, the implanted valve dislocated in the early days after the initial procedure and was later found anchored in the descending aorta, thus preventing the proper imaging and comparative histopathology evaluation — the animal was excluded from further analysis. The detailed mortality cause explanation is presented in Table 1.

Echocardiographic results

Echocardiographic analyses were conducted according to the protocol in respective time points of 30, 90 and 180 days. At the time of terminal control, TEE was utilized complementary to the standard transthoracic echo after previous induc-

Table 1. Mortality explained.

Cause of death	Number of animals
Sudden cardiac arrest — day 0, 9, procedural and anesthesia	2
Myocardial infarction — day 2, 7, low valve implantation	2
Stroke — day 7, high banding position, stenosis of common carotid trunk	1
Endocarditic and vegetations on prosthesis — day 63	1

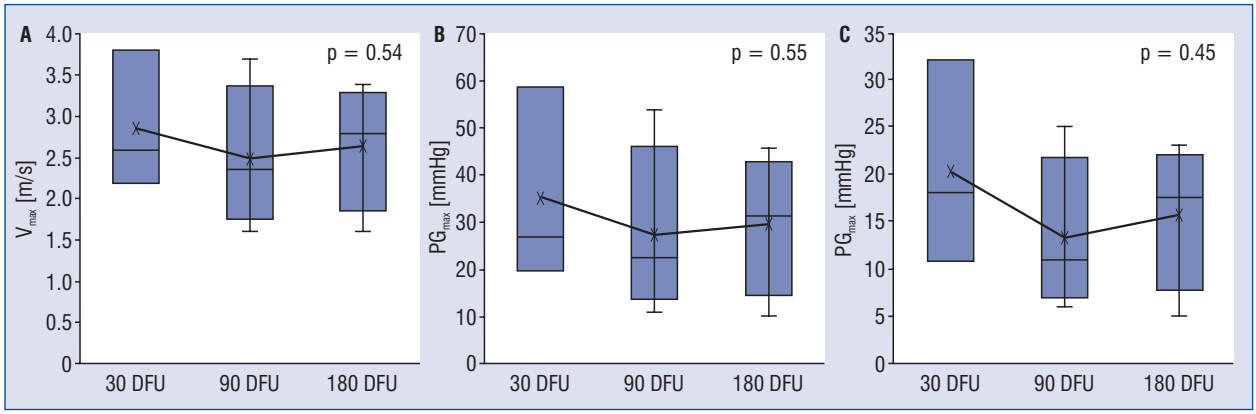

Figure 3. Maximal velocity (V_{max}) (**A**) and pressure gradients (PG_{max}, PG_{min}) (**B, C**) — serial measurements; DFU — days follow-up.

tion of anesthesia (at the time point of 30 and 90 days only TTE was performed). Imaging revealed consistent valve hemodynamics in respective time points, typical for percutaneously implanted prostheses (Fig. 3) There were no incidences of severe valvular insufficiency, with moderate grade regurgitation reported in 2 cases at 90 days and 1 at 180 days. No perivalvular leaks were observed. TEE revealed a probable vegetation present in 1 case at 30 days (confirmed in histopathology), and in 2 cases at 180 days (denied in histopathology). Detailed echocardiographic results are displayed in Table 2.

Histopathology

Necropsy evaluation encompassed 2 animals for 30 days, 5 animals for 90 days and 4 animals for 180 days. In the short-term observation group, the gross inspection showed in 1 case an intramyocardial abscess penetrating to the prosthetic element with subsequent bacterial vegetations. A second case evaluated showed elastic leaflets covered with endothelium, without any tears, fenestrations, or focal thickenings. Thin thrombi were visible as surface flat deposits. Radiogram showed punctiform linear calcifications inside leaflets. Histopathology revealed inflammatory infiltrations in periprosthetic and prosthetic tissues such as pannus and biological leaflet in both prostheses.

The mid-term group (90 days) pathology evaluation (5 cases) revealed thin elastic biological leaflets without any tears or fenestrations and with focal thickening of leaflets visible in 2 cases. In 1 case the leaflets were retracted with thickening of a free margin. Immature pannus was present only at the lower part of the stent. Neointima covered nearly 25% of leaflets and stent in 4 cases, with almost complete covering reported in 1 prosthesis. Small thrombi were reported in 2 valves. Detailed X-ray imaging displayed focal calcifications of free margin and commissures in 4 animals. No signs of inflammatory reaction were seen except for one animal, in which infiltration containing lymphocytes and histiocytes extended from pannus and covered the biological leaflet, and focally penetrated acellular leaflet tissue.

The 180-day group (4 cases) gross inspection showed thin elastic leaflets, without tears or fenestrations. Pannus was present only at stent. In 2 cases neointima covered only nearly 25% of leaflets and stent, nearly 50% in one and nearly

Table 2. Cumulative results of temporal transesophageal echocardiography and doppler evaluation.

Doppler measurements	30 DFU		90 DFU		180 DFU	
	Median	IQR	Median	IQR	Median	IQR
V_{max} [m/s]	2.6	2.5–3.2	2.3	1.94–2.73	2.8	2.4–3.1
PG_{max} [mmHg]	27.0	23.7–41.9	22.0	15–29.8	31.4	23.3–37.7
PG_{mean} [mmHg]	18.0	15.9–27.3	10.0	7.4–14.2	17.5	13.1–20.2
LVEDD	45.0	41–48	43.0	42–48	43	42.3–43
LVESD	27.5	25.8–30.5	29.0	29–31	28.5	27.5–30.5
ECHO findings	**N = 12**	**%**	**N = 9**	**%**	**N = 4**	**%**
Mild regurgitation	1	8.3	0	0	0	0
Moderate regurgitation	0	0	2	18.2	1	9.1
Possible calcification	0	0	0	0	1	9.1
Present calcification	1	8.3	1	9.1	1	9.1
Probable vegetation	1	8.3	0	0	2*	18.2
Mean PG > 30 mmHg	2	16.6	0	0	0	0

*Not confirmed in pathology; DFU — days follow-up; IQR — interquartile range; PG — pressure gradient; LVEDD — left ventricular end diastolic diameter; LVESD — left ventricular end systolic diameter

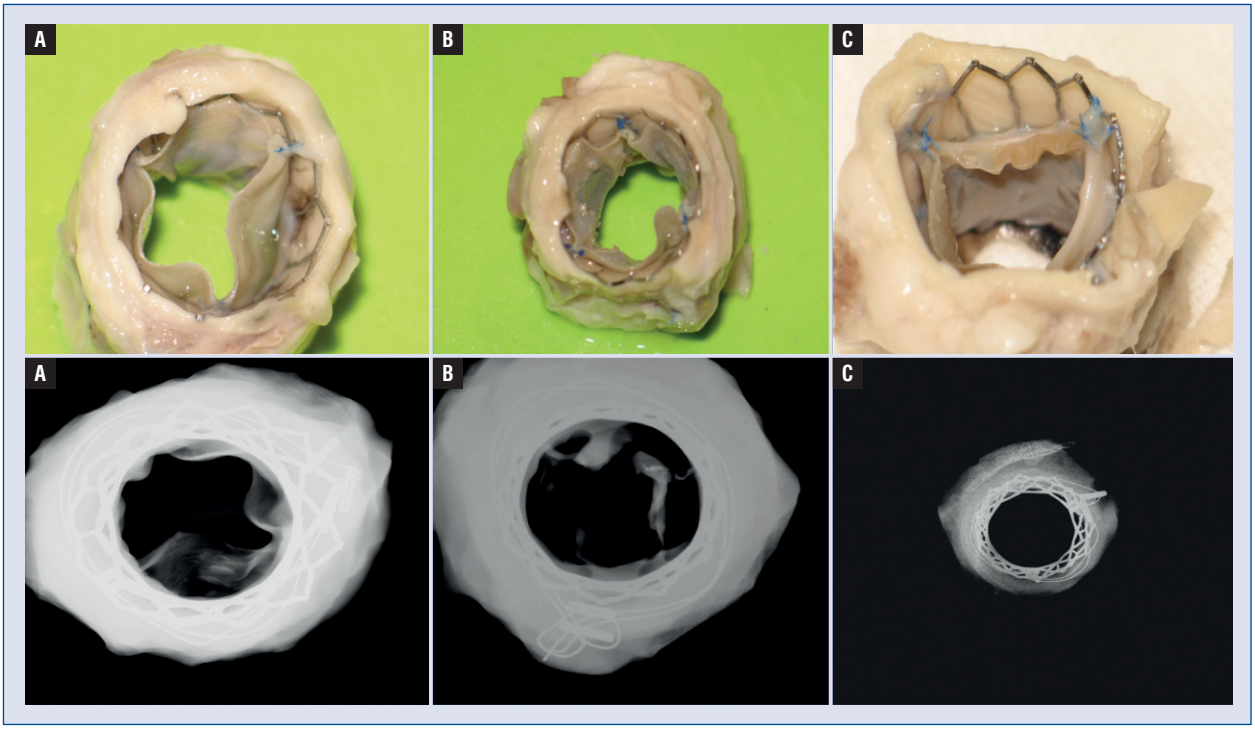

Figure 4. A–C. The representative images of explanted prostheses with radiograph and macroscopic inspection.

100% of both — leaflets in the remaining case. No thrombi were reported in any of the animals. Radiography did not find any symptoms of calcifications. Leaflets histopathology showed decellularized tissue covered by endothelial cells with no inflammatory infiltrations, whereas neointimal coverage contained dispersed mesenchymal cells and few lymphocytes (inflammation grade 0, endothelial grade 3/4). The representative images of explanted prostheses are displayed in Figures 4 and 5.

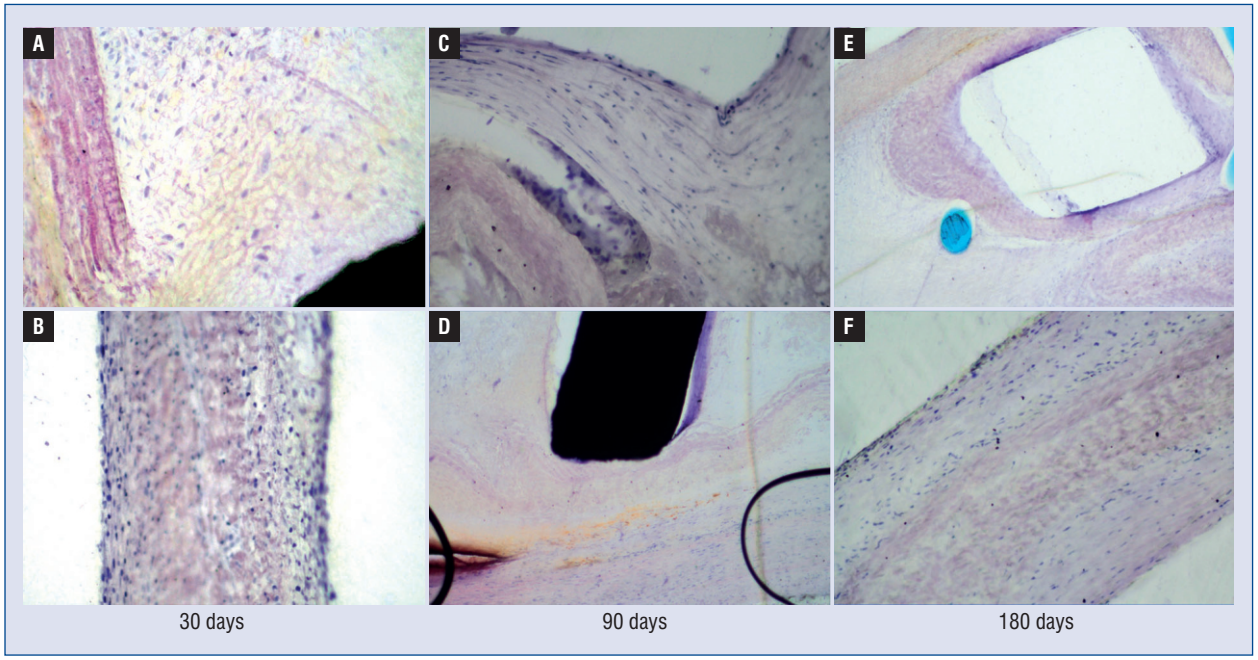

Figure 5. Representative images of microscopical biological response and healing; **A.** Stent (right bottom) hemmed with biological tissues. Visible matrix pattern, cellularity preserved, typical amount of extra-cellular substance; **B.** Biological valve leaflet — preserved cellularity numerous disrupted lymphocytes in the colic, leaflet covered with flattened cells on both sides; **C.** Endothelial cells cover the surface of the valve leaflet, connective tissue stroma, fibrous cell poor; **D.** Stent — no inflammatory reaction at the site of contact; **E.** The outline of the stent. Surrounding tissues are poorly cellular and homogeneous, without inflammatory, fibrotic and non-inflammatory infiltration. Cross section of the surgical suture visible; **F.** The valve leaflet. The correct histological structure of the flap is preserved. The oligocellular stroma. Segmental endothelial coverage.

Discussion

The present study reports the short- and long--term results of a new biological TAVI prosthesis tested in a preclinical setting. Thanks to the utilization of a novel aortic banding model, a repeatable process of valve implantation and anchoring was achieved that allows for a proper assessment of prosthesis functionality, durability and biological response [13]. At terminal follow-up, the tested prosthesis showed optimal functionality in echocardiography, with a decrease in pressure gradients over time and no significant structural valve deterioration. In pathology progressive, temporal stent healing was noted with mature neointima coverage beginning at day 30 and completion of healing being already reported at 90 days. There were no adverse inflammation or leaflet thickening, confirming optimal biocompatibility and functionality of the tested valve.

The cumulative mortality amounted to 33%, which is lower than those reported in a majority of other similar studies [14–16]. Four animals died within the periprocedural period, which was attributed to implantation in a highly placed banding resulting in the prosthesis partially occluding the brachiocephalic trunk or coronary ostia causing cardiac arrest, myocardial infarction or stroke. These incidences were especially prevalent in the first cases performed, where both banding suturing technique and optimal implantation in banding were not yet refined. A situation that changed along with learning curve. During the observation period we reported 2 deaths. First animal underwent a sudden cardiac arrest on day 9, without any abnormalities in necropsy, whereas second animal was found dead on day 63 after a rapid decline of the clinical state — histopathology confirmed endocarditis of the implanted prosthesis.

The performed echocardiography showed good hemodynamic outcomes and no structural valve deterioration of implanted devices at respective time points in all surviving animals. No heavy calcification or large thrombi were observed. The only mean gradients of > 30 mmHg were reported in 2 animals, that were diagnosed with having a significant endocarditis on the prostheses (one of them completed the 30-day follow-up, the other

died prematurely at day 63). The pressure gradients reported were comparable at all time points. The increased pressure gradient in 2 cases, can be related to the initial banding stenosis of around 20–30% of aorta diameter caused by the placing of banding for anchoring purposes. The sutured band has low longitudinal expansion capabilities which results in narrowing being only partially relieved through the TAVI procedure. What is more, as stated in histopathology report, the presence of neointimal pannus covering the stent surface and leaflets to varying degree, could have also influenced the gradient by inducing relative vessel stenosis and slightly impairing leaflet mobility. Lastly, the correlation of animal growth and gradient increase was previously described in other studies [14, 17]. Importantly all valves retained their functionality which was reflected in no severe aortic insufficiency reported across the study.

Histopathology analysis conducted in all 11 animals that completed the observation period revealed proper positioning and valve anchoring in the banding site. Gross inspection showed thin elastic leaflets, without any tears or fenestrations. Only in 1 animal, sacrificed after 30 days follow-up, showed an intramyocardial abscess penetrating to prosthetic elements with subsequent bacterial vegetations was described. Present in such an early phase, this might have been related to accidental procedural contamination. Biological valves displayed no significant calcifications at 180 days, and only minor/punctiform in 4/5 cases at 90 days and 2 in the 30-day group, respectively. Thrombosis was never seen as a pathologically significant process. Flat and scanty thrombi were reported in some prostheses occupying the place between lower basal part of the leaflet, stent strut and aortic wall, similarly to the ones visible in TAVI postmortem observations. All animals sacrificed according to the schedule showed healing and integration features in the cusps characterized by varying coverage of the cusps by endothelialized fibro-cellular neointima that frequently progressed to thicker pannus formation, due to stent apposition to the aortic wall. The inflammatory cell infiltration was reported in 1 animal at 90 days and both sheep at 30 days (one associated with endocarditis) with no foreign body reaction observed in remaining animals, proving an optimal biocompatibility profile of implanted prostheses.

The healing results of Inflow biological prostheses as evaluated in the preclinical setting, with no valve degeneration at 1, 3, and 6-month follow-up is similar to those reported with currently available balloon expandable valves, including the Edwards Sapien device [14, 15] and MyVal [13]. However, in the current study, a higher proportion of valves implanted at baseline reached the terminal follow-up, mostly because of model improvements.

Limitations of the study

The main limitation to be considered is the fact that although aortic banding model was created, the included animals were young and healthy, with no calcific native valve stenosis.

Secondly, as mentioned in the methodology section the prostheses were implanted in the ascending aorta region, pre-prepared with the banding procedure. Surgical intervention did not require the removal of the aortic apparatus, therefore a potential bias attributed to the proper function of a native valve influencing the overall hemodynamic could be perceived.

Conclusions

The study showed a proper hemodynamic performance and acceptable biocompatibility of the novel biological InFlow transcatheter heart valve, comparable to other biological counterparts, as evaluated in the long-term observation in the ovine banding model. The presented prosthesis may be a viable alternative to the currently used biological technologies and add up to the widespread utilization of TAVI procedures.

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Conflict of interest: None declared

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Cangrelor — Expanding therapeutic options in patients with acute coronary syndrome

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Abstract

Cangrelor is the only intravenous P2Y12 receptor antagonist. It is an adenosine triphosphate analog that selectively, directly, and reversibly binds to the platelet P2Y12 receptors exerting its antiaggregatory effect. Cangrelor is characterized by linear, dose-dependent pharmacokinetics and rapid onset of action providing potent platelet inhibition exceeding 90%. Cangrelor is rapidly metabolized by endothelial endonucleotidase; thus, its half-life is 2.9 to 5.5 min, and its antiplatelet effect subsides within 60 to 90 min. Data originating from three pivotal cangrelor trials (CHAMPION PLATFORM, CHAMPION PCI, and CHAMPION PHOENIX) indicate that cangrelor reduces the risk of periprocedural thrombotic complications during percutaneous coronary intervention at the expense of mild bleedings. Its unique pharmacological properties allow it to overcome the limitations of oral P2Y12 receptor inhibitors, mainly related to the delayed and decreased bioavailability and antiplatelet effect of these agents, which are often observed in the setting of acute coronary syndrome. Subgroups of patients who could theoretically benefit the most from cangrelor include those in whom pharmacokinetics and pharmacodynamics of oral P2Y12 receptor antagonists are most disturbed, namely patients with ST-segment elevation myocardial infarction, those treated with opioids, with mild therapeutic hypothermia, or in cardiogenic shock. Cangrelor could also be useful if bridging is required in patients undergoing surgery. According to the current guidelines cangrelor may be considered in P2Y12 receptor inhibitor-naïve patients undergoing percutaneous coronary intervention in both acute and stable settings. (Cardiol J 2024; 31, 1: 133–146)

Keywords: antiplatelet therapy, cangrelor, percutaneous coronary intervention, P2Y12 receptor inhibition

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Limitations of oral P2Y12 inhibitors

Oral platelet P2Y12 receptor inhibitors are one of the pillars of contemporary treatment of acute coronary syndrome (ACS) [1, 2]. One of the main mechanisms behind ACS is unrestrained platelet aggregation, which is most vivid during the early hours of an acute coronary event. P2Y12 receptor inhibition allows limitation of this excessive activation, thus preventing further thrombotic complications and hindering myocardial ischemia.

Although the benefits of oral P2Y12 receptor inhibitors in ACS are indisputable [3–5], several limitations restricting their efficacy have been identified. Bioavailability of orally administered antiplatelet agents is frequently decreased in patients with ACS, especially in those diagnosed with ST-segment elevation myocardial infarction (STEMI) [6], in critical condition [7], undergoing targeted temperature management [8, 9], or if morphine is used [10, 11]. The pharmacokinetics of oral P2Y12 receptor inhibitors are often altered not only due to reduced and delayed intestinal absorption, but also due to impaired drug metabolism, particularly when clopidogrel is used [12, 13]. This results in a significant inter-individual variability in onset and potency of antiplatelet response to oral P2Y12 receptor antagonists during the initial phase of ACS treatment, even when novel agents, prasugrel or ticagrelor, are administered [14–16]. As a result, regardless of the oral agent used, a significant proportion of ACS patients do not achieve a sufficient antiaggregatory effect by the time of percutaneous coronary intervention (PCI) or directly following the procedure [6, 11, 14, 15]. Patients with STEMI, receiving morphine, or undergoing mild therapeutic hypothermia are among those at greatest risk of insufficient platelet blockade in the first hours after the loading dose [6, 10, 11, 14, 16–20]. Sufficient platelet inhibition may also be uncertain in patients with nausea or vomiting, or in those who are unable to swallow or promptly absorb orally given P2Y12 receptor antagonists, i.e., patients who are sedated, intubated, or in shock [21–23]. On-treatment high platelet reactivity is a risk factor for stent thrombosis, myocardial infarction (MI), and death; therefore, timely antiaggregatory action is of great importance in all ACS patients, particularly if treated with PCI [24–27]. Additionally, the antiplatelet effect of clopidogrel, prasugrel, and ticagrelor endures for at least several days after the last dosing. Currently no antidote for oral P2Y12 receptor antagonists is commercially available, making attempts to restore platelet function in patients receiving these agents futile if an urgent surgery is necessary or if bleeding occurs [28]. The abovementioned restraints indicate a demand for a potent intravenous P2Y12 receptor inhibitor with rapid recovery of platelet activity after cessation of the infusion.

Comparison of P2Y12 inhibitors

Clopidogrel and prasugrel are prodrugs that require hepatic activation, and their active metabolites irreversibly inhibit the P2Y12 receptor. In contrast, ticagrelor and cangrelor are active drugs that directly and reversibly block this receptor. The characteristics of the key features of P2Y12 inhibitors are presented in Table 1. All P2Y12 inhibitors require a loading dose to achieve prompt onset of antiplatelet action, which is almost immediate for intravenous cangrelor, relatively fast for ticagrelor and prasugrel (30 min), and delayed for clopidogrel (2 h). The level of platelet inhibition is also the highest for intravenous cangrelor (> 90%), lower for prasugrel and ticagrelor (65–80%), and only 40–60% for clopidogrel. The longest time required to offset the antiplatelet effect of oral P2Y12 antagonists is for prasugrel, shorter for clopidogrel, and the shortest for ticagrelor; thus, recommended discontinuation of treatment before surgery is only 3–5 days for ticagrelor and 7 days for prasugrel. Recommended cessation of intravenous infusion of cangrelor is only 1 hour, due to its rapid metabolism. None of the P2Y12 inhibitors requires dose adjustment in renal failure; however, data for patients with creatinine clearance < 15 mL/min or dialyzed are limited.

Structure and mechanism of action

Cangrelor, N^6-[2-(methylthio)ethyl]-2-[(3,3,3-triflouropropyl)thiol]-5'-adenylic acid, is an adenosine triphosphate (ATP) analog. ATP is an agonist of the P2X1 receptor. Stimulation of the P2X1 receptor initiates the influx of Ca^{2+} to platelets translating into shape change and amplification of platelet activation induced by other agonists [29]. Although the P2X1 receptor mediates platelet activation, its stimulation cannot initiate platelet aggregation; therefore, it has not become the target of antiplatelet therapies. Cangrelor, unlike the parent compound, has high affinity for the adenosine diphosphate (ADP) P2Y12 receptor and longer half-life. It selectively, directly, and reversibly binds to the P2Y12 receptor.

Table 1. Comparison of P2Y12 inhibitors.

	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor
Chemical class	Thienopyridine	Thienopyridine	Cyclopentyl-triazolopyrimidine	Adenosine triphosphate analogue
Route	Oral	Oral	Oral	Intravenous
Prodrug	Yes (pro-drug, CYP dependent, 2 steps)	yes (pro-drug, CYP dependent, 1 step)	No	No
Bioavailability	15%	79%	36%	100%
Standard dosage	600 mg LD, then 75 mg once a day	60 mg LD, then 10 mg once a day	180 mg LD, then 90 mg twice a day	30 μg/kg bolus, then 4 μg/kg/min
Reversibility of binding	Irreversible	Irreversible	Reversible	Reversible
Onset of antiplatelet effect	2–6 h	0.5–4 h	0.5–2 h	2 min
Level of platelet inhibition at steady state	40–60%	65–80%	65–80%	90–98%
Offset of antiplatelet effect	3–10 days	5–10 days	3–4 days	30–60 min
Recommended stop of treatment before surgery	5 days	7 days	3–5 days	1 h
Excretion	50% renal, 46% biliary	68% renal, 27% feces	Biliary	Not dependent on hepatic or renal clearance mechanisms
Kidney failure	No dose adjustment	No dose adjustment	No dose adjustment	No dose adjustment
Dialysis or CrCl < 15 mL/min	Limited data	Limited data	Limited data	Limited data

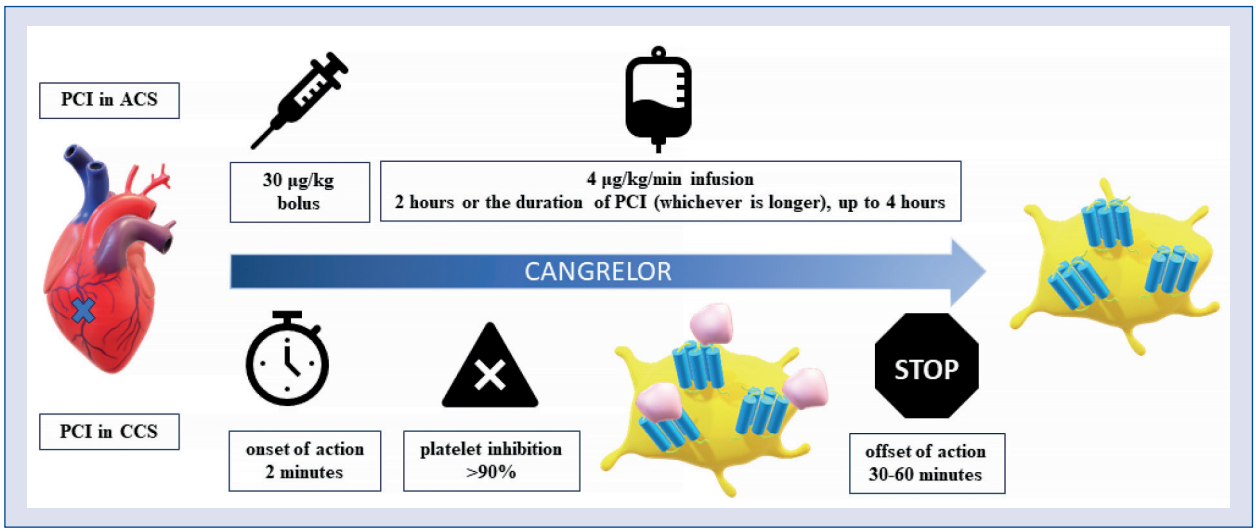
CrCl — creatinine clearance; LD — loading dose

A body of evidence suggests antithrombotic properties of cangrelor beyond P2Y12 receptor antagonism. Cangrelor can inhibit platelet function through an increase in cyclic adenosine monophosphate levels not related to P2Y12 receptor antagonism [30]. In a pharmacodynamic in vitro study in patients with coronary artery disease (CAD) cangrelor reduced platelet reactivity not only via potent P2Y12 blockade, but also through non-purinergic pathways with no influence on thrombin generation [31]. On the other hand, the antiplatelet effect of cangrelor was not observed in P2Y12 receptor-deficient mice [32]. In two experimental animal studies cangrelor exerted a cardioprotective effect in a mechanism resembling post-conditioning, reducing infarct size by up to 50% in rabbit and a primate model [33, 34]. The mechanism of the observed cardioprotective effect is likely to affect the signaling pathway seen in pre- and postconditioning [33].

Pharmacokinetics and pharmacodynamics

Cangrelor is the only intravenous P2Y12 receptor antagonist. The drug is characterized by a rapid onset of action, providing significant platelet inhibition within 2 minutes of bolus injection [31, 35]. Administration of initial bolus followed by an infusion provides inhibition of platelet aggregation exceeding 90% [36, 37]. Cangrelor follows linear, dose-dependent pharmacokinetics, achieving a steady-state plasma concentration within 30-minutes [37, 38]. Its volume of distribution is mainly limited to circulation [36]. Cangrelor plasma half-life ranges from 2.9 to 5.5 minutes, as it is rapidly dephosphorylated by endothelial endonucleotidase [39]. Platelet function returns to baseline within 60–90 minutes of cessation of the infusion [37, 38]. The main pharmacological features of cangrelor are presented in the Central illustration.

The metabolism of cangrelor is not liver or renal dependent, allowing administration in patients



Central illustration. Cangrelor — indications, main pharmacological features, and mechanism of action. Cangrelor may be considered in P2Y12-inhibitor-naïve patients undergoing percutaneous coronary intervention (PCI) for both acute coronary syndrome (ACS) and chronic coronary syndrome (CCS). It is an intravenous adenosine triphosphate analog that reversibly binds to platelet P2Y12 receptors and is characterized by rapid and potent platelet inhibition after an intravenous bolus followed by a continuous infusion, as well as quick offset of antiplatelet effect after discontinuation of infusion thanks to a rapid metabolism.

with abnormal liver or kidney function. The pharmacokinetics and pharmacodynamics of the drug are not affected by gender, age, ethnic background, diabetic status, administration of acetylsalicylic acid, heparin, nitroglycerin, bivalirudin, low-molecular-weight heparin, fondaparinux, glycoprotein IIb/IIIa inhibitors (GPI), or morphine [40–42].

The unique properties of rapid onset and offset of the antiplatelet effect make cangrelor an attractive therapeutic option complementary to available oral antiaggregatory drugs.

Scientific evidence for use of cangrelor

The results of three major, randomized, placebo-controlled clinical trials on the efficacy and safety of cangrelor in a broad range of PCI-treated patients with CAD are available: CHAMPION PLATFORM [43], CHAMPION PCI [44], and CHAMPION PHOENIX [45].

The CHAMPION PLATFORM trial consisted of 5362 patients requiring PCI due to non-ST-segment elevation myocardial infarction (NSTEMI) (59.4%) or unstable angina (35.4%) [43]. Patients with stable angina (5.2%) were also initially eligible before a protocol amendment. The occurrence of the primary efficacy endpoint, defined as a composite of death, MI, or ischemia-driven revascularization within 48 hours after PCI, was numerically lower in the cangrelor group than in the placebo group, but the difference was not significant. The rate of stent thrombosis was significantly lower in the cangrelor group at 48 hours and at 30 days. All-cause mortality rate was significantly lower in patients treated with cangrelor at 48 hours, but not at 30 days (Table 2). The rates of bleeding did not differ significantly between the two groups according to TIMI and GUSTO criteria. However, according to more sensitive ACUITY criteria, the bleeding rates were significantly higher in the cangrelor group. The difference in rates of bleeding defined as major according to the ACUITY criteria, was solely due to an excess of groin hematomas, with no contribution of more serious forms of bleeding [43].

The CHAMPION PCI trial included 8877 patients treated with PCI due to stable angina (15.0%), unstable angina (24.6%), NSTEMI (49.2%), or STEMI (11.2%; n = 996) [44]. The primary endpoint of death from any cause, MI, or ischemia-driven revascularization at 48 hours occurred in similar proportions in both study arms: the experimental arm (cangrelor plus clopidogrel) and the active control arm (placebo plus clopidogrel). No significant differences between the groups with regard to any single efficacy endpoint at 48 hours were found (Table 2). Minor, but not major, bleedings occurred more frequently in the cangrelor arm according to the ACUITY and GUSTO criteria. According to the TIMI criteria,

Table 2. Efficacy of cangrelor in the major clinical studies.

Acronym	N	Primary endpoint				All-cause mortality				Myocardial infarction				Stent thrombosis			
		Cangrelor, n (%)	Clopidogrel, n (%)	OR	P	Cangrelor, n (%)	Clopidogrel, n (%)	OR	P	Cangrelor, n (%)	Clopidogrel, n (%)	OR	P	Cangrelor, n (%)	Clopidogrel, n (%)	OR	P
CHAMPION PCI	8877	290 (7.5%)	276 (7.1%)	1.05	0.59	8 (0.2%)	5 (0.1%)	1.59	0,42	278 (7.1%)	256 (6.6%)	1.09	0.36	7 (0.2%)	11 (0.3%)	0.63	0.34
CHAMPION PLATFORM	5362	185 (7%)	210 (8%)	0.87	0.17	6 (0.2%)	18 (0.7%)	0.33	0.02	177 (6.7%)	191 (7.2%)	0.92	0.42	5 (0.2%)	16 (0.6%)	0.31	0.02
CHAMPION PHOENIX	11145	257 (4.7%)	322 (5.9%)	0.78	< 0.01	18 (0.3%)	18 (0,3%)	1	> 0.99	207 (3.8%)	255 (4.7%)	0.8	0.02	46 (0.8%)	74 (1.4%)	0.62	0.01
Pooled, redefined 1+2	14239	202 (3.1%)	244 (3.8%)	0.82	0.04	14 (0.2%)	23 (0.4%)	0.6	0.14	171 (2.6%)	194 (3.0%)	0.87	0.2	12 (0.2%)	27 (0.4%)	0.44	0.02

OR — odds ratio; n — number

no increase in bleeding was seen, irrespective of the type of bleeding [44].

Both CHAMPION trials were discontinued following a decision by the interim analysis review committee claiming that the studies would not show the persuasive clinical efficacy needed for approval, although 98% of the planned 9000 patients for CHAMPION PCI and 83% of the scheduled 6000 patients for CHAMPION PLATFORM had been enrolled [43, 44].

The definitions of all endpoints used in the CHAMPION PLATFORM and CHAMPION PCI trials were mutually consistent [43, 44]. The primary composite endpoint of these trials was negative; therefore, any single endpoint should be interpreted with caution. Interestingly, the primary endpoint in the CHAMPION trials was driven by the occurrence of MI. The universal definition of MI was developed after initiation of the CHAMPION PCI and CHAMPION PLATFORM trials.

Because both CHAMPION trials had the same composite primary endpoint and used similar inclusion and exclusion criteria, the studies were pooled together. The clinical events committee adjudicated all cases of MI, and the new universal definition was used. A total of 13,049 patients were included [46]. No effect of cangrelor with regard to the primary endpoint was revealed with the original definition of MI. However, after application of the universal definition of MI a significant reduction of the primary endpoint with the cangrelor–clopidogrel combination, compared with clopidogrel alone, was observed (Table 2). No increase in blood transfusions or major bleeding assessed with the TIMI or GUSTO bleeding scales were observed with cangrelor compared with clopidogrel. Only the more sensitive ACUITY scale showed an increase in clinically significant major bleedings with cangrelor, mainly because of an increased occurrence of groin hematomas [43, 44, 46].

The CHAMPION PHOENIX trial was designed to evaluate whether cangrelor reduces ischemic complications of PCI [45]. A total of 10,942 patients requiring PCI for stable angina (56.1%), non-ST-segment elevation ACS (NSTE-ACS) (25.7%), or STEMI (18.2%) received a bolus with a subsequent infusion of cangrelor or placebo. The rate of the primary composite efficacy endpoint of death from any cause, MI (according to the universal definition of MI), ischemia-driven revascularization, or stent thrombosis at 48 hours was significantly lower in the cangrelor group than in the clopidogrel group (Table 2). Apart from the reduction in stent thrombosis, the benefits of

cangrelor in the CHAMPION PHOENIX trial were mostly attributed to the decreased occurrence of MI. The observed 22% reduction in the likelihood of ischemic event in patients treated with cangrelor was not accompanied by a significant increase in severe bleeding or in the need for transfusions compared with patients on clopidogrel. More sensitive measures showed an increase in bleeding with cangrelor, as would be expected of a potent antiplatelet agent. The composite endpoint of the net rate of efficacy and safety adverse clinical events was 4.8% in the cangrelor group and 6.0% in the clopidogrel group (odds ratio [OR] 0.80; 95% confidence interval [CI] 0.68–0.94; p = 0.008) [45].

A prespecified, pooled analysis of data from the three pivotal CHAMPION trials [47] indicated that cangrelor reduces the risk of periprocedural thrombotic complications during PCI at the expense of mild bleedings. On the other hand, an exploratory analysis of pooled patient-level data from the CHAMPION trials revealed lower risk-adjusted bleeding risk in patients receiving cangrelor alone compared with GPI on the background of clopidogrel or placebo (TIMI-defined major or minor bleeding: 0.7% vs. 2.4%; OR 0.29; 95% CI 0.13–0.68) with no significant differences between the groups regarding the primary endpoint (the composite of all-cause mortality, MI, ischemia-driven revascularization, or stent thrombosis at 48 hours: 2.6% vs. 3.3%; OR 0.79; 95% CI 0.48–1.32) [48].

Specific indications for cangrelor

Cardiogenic shock

Cardiogenic shock (CS) is a life-threatening clinical syndrome caused by primary cardiac dysfunction, resulting in an inadequate cardiac output, comprising a state of tissue hypoperfusion, which can result in multi-organ failure and death. It may occur in up to 8–12% of patients with STEMI and up to 4% of patients with NSTE-ACS, with 30-day mortality of 40–55% [49, 50].

Acute myocardial ischemia is a predominant cause of CS in patients presenting with ACS. Mechanical complications of ACS, such as papillary muscle rupture with severe mitral valve regurgitation, ventricular septal defect, or free wall rupture, are additional causes of CS often requiring cardiac surgery [49]. Immediate coronary angiography and PCI of the culprit lesion is indicated for patients with ACS and CS, irrespective of initial clinical presentation (STEMI or NSTE-ACS) and time delay of symptom onset, if coronary anatomy is amenable to PCI [50].

In patients presenting with STEMI and CS it is usually difficult to exclude possible contraindications for aggressive antithrombotic treatment in the pre-hospital phase [51]. In patients with NSTE-ACS routine pretreatment with P2Y12 inhibitors is no longer recommended [52]. Thus, most patients with ACS and CS who arrive to the cath lab are P2Y12 receptor inhibitor naïve, and the decision to administer antiplatelet therapy is made after coronary angiography. The effect of oral P2Y12 receptor inhibitors is delayed in CS patients due to slower absorption in the gastrointestinal tract, which is exacerbated by morphine use and inefficient conversion of the prodrugs to their active forms in the liver, and challenges with adequate enteral access in intubated patients. In such cases, intravenous medications, such as GPI or cangrelor, are a reasonable option. Nonetheless, scientific evidence supporting their use in patients undergoing PCI in CS remains very limited.

Two meta-analyses and a "real-world" registry indicate that therapy with GPI as an adjunct to the standard treatment in CS is associated with better outcomes, including both short- and long-term survival, without increasing the risk of bleeding [52–54]. However, the limitations of the abovementioned studies limit the generalization of their results.

Excellent bioavailability, fast-acting properties, and safety in renal impairment make cangrelor an attractive option for P2Y12 receptor inhibitor-naïve patients with CS undergoing PCI. However, CS was an exclusion criterion in the abovementioned landmark clinical trials, and only few single-center experiences have evaluated the impact of intravenous P2Y12 receptor inhibition in high-risk patients with cardiopulmonary resuscitation or CS, especially compared with use of newer oral P2Y12 receptor inhibitors, prasugrel and ticagrelor. In a global, multicenter, matched pair analysis with oral P2Y12 inhibition from the IABP-SHOCK II trial, cangrelor treatment was associated with similar bleeding risk and significantly better TIMI flow improvement compared with oral P2Y12 receptor inhibitors in CS patients undergoing PCI. Thus, the use of cangrelor in CS offers a potentially safe and effective antiplatelet option and should be evaluated in randomized trials [55].

Out-of-hospital cardiac arrest

Out-of-hospital cardiac arrest (OHCA) frequently occurs in the early phase of acute MI. OHCA survivors presenting symptoms of acute MI require primary PCI with concomitant dual an-

tiplatelet therapy (DAPT), including acetylsalicylic acid and a P2Y12 receptor inhibitor [55–57]. Several studies showed insufficient efficacy of clopidogrel in patients undergoing targeted temperature management (TTM) at 32–34°C after OHCA, with an alarmingly high incidence of acute stent thrombosis [19, 58, 59]. This was mostly explained by accelerated platelet turnover, increased platelet activation, as well as by decreased bioavailability of clopidogrel due to its impaired absorption and diminished generation of active metabolite [19, 55, 60]. However, Joffre et al. [61] found TTM in patients after OHCA to be an independent risk factor for confirmed stent thrombosis (OR 12.9; 95% CI 1.3–124.6, p = 0.027), regardless of the type of oral P2Y12 antagonist, even when prasugrel or ticagrelor were used. The results of the ISAR-SHOCK registry demonstrated a weaker antiplatelet effect in shock patients receiving either clopidogrel or prasugrel without hypothermia [62]. This observation may suggest that the impaired effect of oral P2Y12 inhibitors in OHCA is related not only to hypothermia, but also to centralization of circulation in critically ill patients [7, 9, 12, 62–64]. Regardless of the exact mechanisms of ineffectiveness of these drugs, intravenous infusion of cangrelor is capable of inhibiting life-threatening platelet-mediated prothrombotic events in the setting of TTM. This innovative pharmacological strategy could significantly improve the safety of TTM; however, it still warrants evaluation in properly designed randomized trials in this setting [65–67].

Therapy with opioids

Opioids are the most commonly administered group of medications for pain management in the course of acute MI. Morphine and fentanyl have been found to negatively influence pharmacokinetic and pharmacodynamic profiles of P2Y12 receptor inhibitors, mainly by reducing the bioavailability of these agents. Of note, impairment of gastrointestinal motility, as well as pro-emetic effects of opioids, contribute to unfavorable outcomes of concomitant administration of P2Y12 receptor inhibitors. The IMPRESSION trial showed that patients diagnosed with MI who received morphine needed up to 4 hours to achieve adequate platelet inhibition after the ticagrelor loading dose [11]. A similar observation was made for prasugrel in STEMI patients [14]. Based on the CRUSADE registry, NSTE-ACS patients who received morphine were at higher risk of adverse effects including MI (OR 1.34, 95% CI 1.22–1.48), death (adjusted OR 1.48, 95% CI 1.33–1.64), or a composite of death and MI (adjusted OR 1.44, 95% CI 1.34–1.56) [68]. To date, several methods to overcome the so-called "morphine effect" have been proposed. Sublingual administration of ticagrelor, co-administration of metoclopramide or oral naloxone, as well as chewing or crushing tablets have aimed at improving the pharmacokinetics and pharmacodynamics of particular P2Y12 receptor inhibitors, but the outcomes were unsatisfactory [69–73]. Only crushing or chewing P2Y12 inhibitor tablets was associated with noticeably better results in ACS patients [69, 72–75].

The CANTIC trial showed that in STEMI patients the addition of cangrelor to crushed ticagrelor allows adequate platelet inhibition as little as 5 minutes after the initiation of a cangrelor infusion. A superior antiaggregatory effect of cangrelor with crushed ticagrelor vs. crushed ticagrelor alone was documented for the whole duration of cangrelor infusion. No differences in levels of platelet reactivity between the study arms were present after discontinuation of cangrelor, excluding a drug-drug interaction when cangrelor and ticagrelor were concomitantly administered [76].

Cangrelor provides rapid and effective platelet inhibition, and its antiplatelet activity is independent of gastrointestinal tract function. Based on the above, it appears that cangrelor could be considered as an optimal antiplatelet agent for ACS patients on concomitant therapy with morphine who are qualified for invasive treatment.

PCI in P2Y12-naïve patients

Despite the common availability of P2Y12 receptor inhibitors in ambulances, many ACS patients still arrive in the cath lab not pretreated. In STEMI, where time to primary PCI is critical, the delayed action of clopidogrel makes the platelets fully active at the time of reperfusion and stent deployment [77, 78]. Even in cases where potent and fast-acting oral agents are given (prasugrel, ticagrelor), their effect is often delayed due to selective shunting of blood to vital organs, vomiting, or malabsorption caused by opiate use [11]. New compounds with the potential to overcome these limitations and provide a timely and potent antiaggregatory effect in the acute setting are selatogrel and zalunfiban. These are new parenteral antiplatelet agents that are currently under investigation in phase 3 trials. The SOS-AMI trial (Selatogrel Outcome Study in Suspected Acute Myocardial Infarction; NCT04957719) and the CELEBRATE study (A Phase 3 Study of Zalunfiban in Subjects With ST-elevation MI; NCT04825743) will explore

the efficacy and safety of the respective agents in the prehospital phase of MI treatment. However, at this point it is unknown when they will be commonly available.

The problem of inappropriate platelet inhibition is not limited to ACS patients. In Poland, most elective PCI procedures are performed immediately after coronary angiography. Inadequate pretreatment with P2Y12 receptor inhibitors may contribute to a significantly increased risk of periprocedural thrombotic complications, mainly if complex PCI techniques are used.

An intravenous bolus of cangrelor fills this gap perfectly in all these situations, ensuring an extensive platelet blockade within minutes of administration. Later, cangrelor markedly inhibits platelet aggregation throughout infusion duration at all critical moments of PCI itself and immediately after [37]. As mentioned before, in the CHAMPION PHOENIX study, in P2Y12-naïve patients undergoing PCI with stable CAD and ACS, cangrelor significantly reduced the primary endpoint of death, MI, ischemia-driven revascularization, or stent thrombosis at 48 hours, and the key secondary endpoint of stent thrombosis alone (OR 0.62; 95% CI 0.43–0.90; p = 0.01), without a significant increase in the rate of major bleeding [79]. Importantly, cangrelor showed a more significant absolute effect with the increased complexity of the coronary procedure [80].

Due to the lack of head-to-head clinical comparative studies, it is still undetermined whether cangrelor is superior to intravenous GPI in P2Y12 receptor inhibitor-treated patients. In the FABOLUS FASTER study, cangrelor provided inferior platelet inhibitory effects than tirofiban, but it was more significant than that achieved with prasugrel [81]. Of note, it has been suggested that the inadequate antiaggregatory effect of cangrelor seen in this trial could have been due to a delay in platelet function testing related with the methodology of light transmittance aggregometry used in this study. Cangrelor has a very short half-life and binds reversibly to the P2Y12 receptors; thus, its antiplatelet effect could have been diminished at the time of pharmacodynamic assessment [82]. A retrospective, observational registry of 2072 patients (66% with ACS) who received adjunctive antiplatelet therapy during PCI (478 cangrelor, 1594 GPI) revealed that in-hospital ischemic events did not differ between the groups. In contrast, major bleeding events (1.7% vs. 5.1%, p = 0.001), or any vascular complication rates, were significantly lower in the cangrelor group [83].

Bridging to coronary artery bypass grafting

The recommended duration of DAPT depends on the clinical manifestation of CAD, the anatomy of coronary lesions, and the type of stent implanted. The risk of ischemic events in PCI-treated patients increases with comorbidities such as diabetes, chronic kidney disease, or heart failure. The necessity of DAPT after drug eluting stent implantation ranges from 3 to 12 months, like in ACS [1]. The shortening of DAPT duration has become possible thanks to rapid advances in stent technology [84, 85].

During DAPT, some patients require cardiac or non-cardiac surgery [86]. The surgery itself generates an inflammatory response, activates platelets, the sympathetic nervous system, vascular spasm, and release of cytokines that inhibit endogenous fibrinolysis and activate the endothelial coagulation cascade. These mechanisms result in an increased risk of thrombotic complications [87, 88].

The highest risk of thrombotic complications is within the first 3 months after drug eluting stent implantation and decreases over time [84]. On one side, interruption of DAPT is associated with the risk of stent thrombosis, and on the other, surgery during DAPT increases the risk of bleeding. Therefore, the use of bridging therapy with rapid and short-acting antiplatelet drugs is justified [87, 88].

Initially GPIs were used as a bridging therapy. Eptifibatide is a reversible GPI with a half-life of 2.5 hours. Platelet reactivity returns 4 hours after stopping the infusion. Bridging therapy with eptifibatide resulted in a reduction of ischemic complications; however, an increased rate of bleeding events was observed [89, 90]. Tirofiban, another short-acting and reversible GPI, showed similar results to eptifibatide in bridging therapy, reducing ischemic complications while major bleeding events and the need for transfusion were higher [90, 91].

Cangrelor with its rapid, predictable, and dose-dependent antiplatelet effect together with quick offset of action predispose it for use in bridging therapy as an alternative to GPI [88]. Cangrelor is the only drug used in bridging therapy with randomized trials evaluating its effectiveness and dosing schedule for these indications [92]. In the bridging therapy, a dose of 0.75 μg/kg/min was established, which shows a high degree of platelet inhibition with no increase in bleeding rate compared to placebo. The dose during PCI is 4 μg/kg/min. The use of a bridging dose of cangrelor is crucial to reduce the risk of perioperative bleeding [93]. Despite the limited number of studies on bridging

therapy, such a strategy should be considered in patients at high risk of ischemic complications requiring non-deferrable surgery.

New bridging strategies are being studied, including the use of a fast and short-acting subcutaneous P2Y12 receptor inhibitor (selatogrel), the use of a monoclonal antibody that inactivates ticagrelor, or strategies based on the rapid removal of ticagrelor during extracorporeal circulation [88].

Switching between P2Y12 inhibitors

Switching from intravenous to oral medication for PCI depends on the type of P2Y12 receptor inhibitor. The half-life and possible drug-drug interactions should be taken into account because of the risk of insufficient antiplatelet effect. Prasugrel and clopidogrel are prodrugs, and their active metabolites reveal an antiplatelet effect. These metabolites are formed sequentially in a one- (prasugrel) or two-step (clopidogrel) process. Cangrelor blocks their bindings to the platelet receptors; therefore, these drugs should not be started simultaneously [94, 95]. The active metabolite of clopidogrel is unstable and has a very short half-life, which means it is rapidly metabolized if not bound to the platelet receptor. The effect of cangrelor begins after 2 minutes and ends soon after stopping the infusion. Thus, clopidogrel in a loading dose of 600 mg should be administered immediately after discontinuation of the cangrelor infusion [39, 94, 95]. On the other hand, prasugrel metabolites have prolonged effects due to a longer half-life and higher plasma concentrations. After discontinuation of the cangrelor infusion platelet reactivity returns to normal within an hour, and, as a consequence, a gap in antiplatelet activity may appear [96, 97]. However, the administration of prasugrel in a dose of 60 mg at the end of the cangrelor infusion, or 30 minutes before the end, prevents complete platelet reactivation, which has not been observed with other P2Y12 inhibitors [96].

The third agent, ticagrelor, acts directly but has reversible binding. The administration of 180 mg ticagrelor can be initiated simultaneously with the start of the cangrelor infusion, because there is no interaction between these drugs and the half-life time of ticagrelor is longer than the infusion [94].

Prior to cardiac or non-cardiac surgery, switching from oral to intravenous therapy increases the percentage of platelet inhibition compared to placebo [92]. Prasugrel should be stopped 7 days before surgery, while clopidogrel should be withheld for 5 days and ticagrelor for 3–5 days prior to surgery [98]. Intravenous infusion of cangrelor at a dose of 0.75 μg/kg/min should be started within 48 hours of discontinuing oral P2Y12 receptor inhibitor and continued for at least 48 hours, but for a maximum of 7 days. The infusion should be stopped for 1–6 hours prior to the procedure, and then cangrelor should be restarted within 1–6 hours after the end of the procedure.

Official recommendations for cangrelor

Cangrelor is currently available in most European markets. It was approved by the European Medical Agency for a specific subgroup of CAD patients undergoing PCI, who did not receive another P2Y12 receptor inhibitor before the PCI, and in subjects for whom oral P2Y12 inhibitors therapy is not feasible or desirable. Cangrelor should be administered as a bolus of 30 mg/kg IV followed by 4 mg/kg/min infusion for at least 2 hours or the duration of the procedure (whichever is longer). Furthermore, it was specified that the infusion of cangrelor must not exceed 4 hours [40]. According to the European Society of Cardiology (ESC) guidelines on ACS, cangrelor has a class IIb recommendation with level of evidence A both in STEMI and NSTE-ACS settings, and it may be considered in P2Y12-inhibitor-naïve patients undergoing PCI [50]. Furthermore, the ESC guidelines on myocardial revascularization give the same recommendation for cangrelor use in peri-interventional treatment in stable patients [50]. It must be stressed that in patients receiving an infusion of cangrelor during intervention, the timing of administration of oral P2Y12 inhibitors should be drug specific, as mentioned above: ticagrelor 180 mg, at any time during infusion or immediately after discontinuation; prasugrel 60 mg, immediately after discontinuation of cangrelor; clopidogrel 600 mg, immediately after discontinuation of infusion. The United States Food and Drug Administration approved cangrelor as an adjunct to PCI to reduce the risk of stent thrombosis, periprocedural MI, and repeated revascularization in patients not pre-treated with an oral P2Y12 inhibitor and without indication to receive GPI [99]. This was reflected in the latest ACC/AHA/SCAI Guidelines for Coronary Artery Revascularization, in which cangrelor received class 2B recommendation with level of evidence B-R for patients undergoing PCI, who are naïve to oral P2Y12 receptor inhibitors, to reduce periprocedural ischemic events [100].

Conclusions

Cangrelor is the only available intravenous P2Y12 receptor antagonist, and it is characterized by a rapid onset of potent antiplatelet effect, which subsides quickly after discontinuation of the infusion. Its unique properties may prove very useful not only in ACS or CAD patients treated invasively, but also in specific subgroups of patients at risk of impaired antiaggregatory action after a loading dose of oral P2Y12 receptor inhibitor. According to the current guidelines, cangrelor may be considered in P2Y12 receptor inhibitor-naïve patients undergoing PCI in both acute and stable settings.

Article information

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Atrioventricular synchronous leadless pacing: Micra AV

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Abstract

Since the arrival of leadless pacemakers (LPs), they have become a cornerstone in remedial treatment of bradycardia and atrioventricular (AV) conduction disorders, as an alternative to transvenous pacemakers. Even though clinical trials and case reports show indisputable benefits of LP therapy, they also bring some doubts. Together with the positive results of the MARVEL trials, AV synchronization has become widely available in LPs, presenting a significant development in leadless technology. This review presents the Micra AV, describes major clinical trials, and introduces the basics of AV synchronicity obtained with the Micra AV and its unique programming options. (Cardiol J 2024; 31, 1: 147–155)

Key words: leadless pacing, Micra AV, transcatheter pacing system, atrioventricular synchrony, atrioventricular block

Introduction

The well-established consensus for high-degree atrioventricular (AV) block treatment is an implantable pacemaker therapy. Even though primary VVI mode is enough to reduce mortality, current guidelines underline the clinical significance of AV synchronization obtained via atrial sensing for improved quality of life and avoidance of pacemaker syndrome [1].

Leadless pacemakers (LPs) were first mentioned in cardiac pacing and cardiac resynchronization therapy guidelines in 2021 [1]. The first LP device — NANOSTIM — implanted in 2012, offered VVIR mode as the most sophisticated pacing option [2], but it was withdrawn from the market due to battery issues and docking button detachments during implantation or retrieval.

The first steps in the development of an AV synchrony algorithm were taken with the MASS and MASS2 trials. Participants had software downloaded into a Micra VR (MVR), allowing accelerometer signal telemetry. After a series of manoeuvre tests, the signal was collected from Micra's accelerometer vectors detailing four heart signals: A1, A2, A3, and A4 [3].

The subsequent trial exploring the field of AV synchrony in LPs was MARVEL, which proved the feasibility of ventricle pacing with AV synchronization in LPs [3]. The developed algorithm was downloaded into previously implanted Micra devices, which allowed for an average 87% AV synchrony, with 80% in high-degree AV block patients and 94.4% in patients with intrinsic AV conduction. After enhancing the algorithm, the MARVEL2 trial improved the median AV synchrony in high-degree AV block patients from 26.9% with VVI pacing to 94.3% in VDD mode, and the left ventricular outflow tract velocity–time integral (which stands for left ventricular stroke volume) by 8.8 ± 15.4% [4].

The rising importance of understanding indications for Micra AV (MAV) implantation, unique

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Figure 1. Build of the Micra AV; 1 — capsule; 2 — fixation tine; 3 — stimulation cathode; 4 — stimulation anode.

programming options, and precautions in specific clinical situations are necessary to achieve satisfactory results.

Build of the Micra AV-MC1AVR1

With a mass of 1.75 g, dimensions of 25.9 mm × 6.7 mm, and volume of 0.8 cc — around 1% of the hearts' right ventricle (RV) [5] volume — the MAV duplicates Medtronic's previous LP external construction: the MVR. The main body of the MAV is composed of a capsule (Fig. 1 — 1), a dexamethasone-coated stimulation cathode (Fig. 1 — 3), and an anode (Fig. 1 — 4). There are 4 fixation nitinol tines (Fig. 1 — 2) between the cathode and anode (Fig. 1 — 1) to attach the device to the heart tissue — myocardium. The MAV detects atrial contraction with a built-in accelerometer, providing AV synchronous pacing. The battery has (typical for pacemakers) 3 indicator states: recommended replacement time (RRT), which is shown 6 months before the end of service (EOS); elective replacement indicator, 3 months before EOS; and the state of EOS, which starts after 3 consecutive daily automatic measurements with ≤ 2.5 V.

Micra AVs longevity is estimated between 8 and 13 years and depends on the pacing mode, ventricle pacing percentage, impedance, and threshold.

Implantation technique

Because the MAV's external build is identical as the MVR, the implantation technique is the same. Vascular access is obtained by puncturing the femoral vein, preferably the right one, but it can also be achieved through the jugular vein [6]. With sheaths placed for vascular access, the introducer is inserted via a stiff guidewire to the right atrium. The delivery system is advanced into the introducer up to the mid-atrium. Subsequently, with the help of fluoroscopy guidance, the LP system is placed in the septal portion of the RV. Micra's position should be verified using different fluoroscopy views and contrast flow to achieve satisfactory adherence to the wall of the myocardium. The target location is the mid-high interventricular septum. Too high a position of the LP can interfere with the tricuspid valve or pulmonary valve and has less chance of being hooked in the trabeculae, which can happen especially in the right ventricular outflow tract. Avoiding the RV apex is also vital due to its thin wall approaching around 1 mm musculature.

Different projections and radiological signs help with appropriate LP navigation. The right anterior oblique (RAO) view allows recognition of the tricuspid valve passing and avoiding the true apex. Moreover, in this view, with a contrast-push and the presence of a space between the wedged sheath and myocardium border, one can achieve the confidence of Micra's septal contact, called the RAO space sign (Fig. 2) [7].

Left anterior oblique (LAO) and full lateral view give additional information and allows avoiding Micra implantation in the anterior wall, which is crucial to decrease the risk of free wall perforation. In the LAO view the catheter should be pointed towards the spine, and in the full lateral view the cup should point directly at the camera. During contrast injections, a flat flow pattern against the septum in LAO 30–40° indicates optimal contact, and the contrasted trabeculated surface only reassures a good position. If doubt persists, the use of intraprocedural transesophageal echocardiography can prevent the LP's implantation to the heart's free wall [8].

Recommended parameters for the device are R-wave ≥ 5 mV, impedance 400–1500 Ω, and threshold ≤ 1.00 V. A predictive model for the long-term electrical performance of an LP has been proposed by Kiani et al. [9]. Threshold less than or equal to 1 V after implantation seems to predict good future electrical properties of the positioned Micra. Higher values need to be re-checked after 3–5 min. With threshold of more than 2 V and impedance less than 800 Ω, repositioning of the Micra is strongly advised.

With stable parameters, one should assess the fixation of the tines with a pull-and-hold test and bending of the tines. Recognition of at least 2 out of 4 tines being straightened during a pull-and-hold test is necessary to confirm successful implantation (Fig. 3).

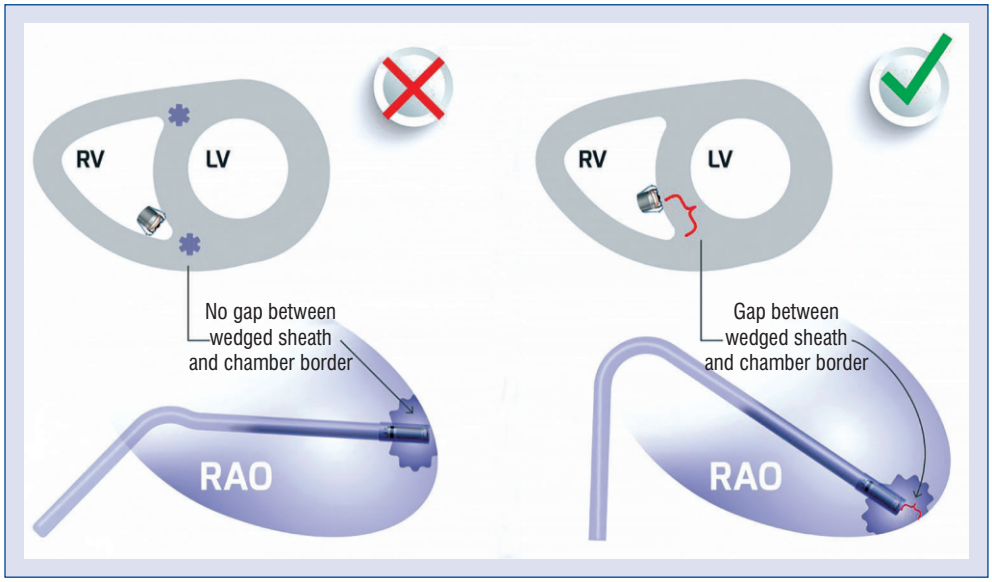


Figure 2. Right anterior oblique (RAO) space sign [7]; LV — left ventricle; RV — right ventricle.

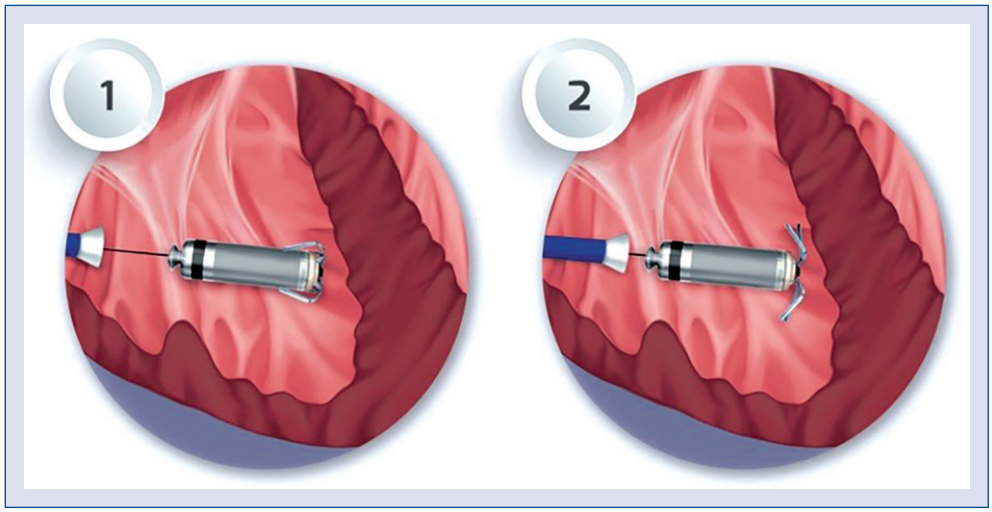


Figure 3. Pull-and-hold test; 1 — before the pull-and-hold test, no fixation tines bend; 2 — after pulling, 4 out of 4 fixation tines are bending, confirming the correct implantation of the Micra.

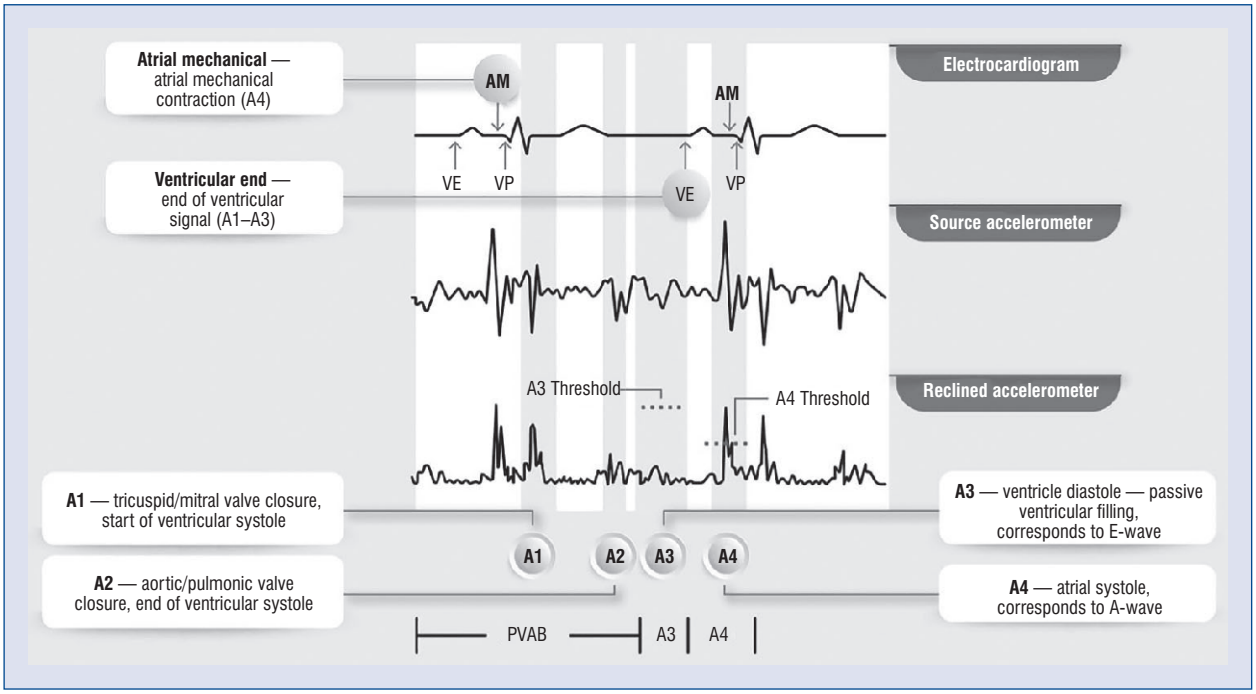
Clinical indications for the Micra-AV

Leadless pacemakers should be considered for patients with frailty syndrome, chronic kidney disease, especially those on dialysis, less than 10 years of life span, hindered access for the transvenous pacemakers (TV-PM), i.e., stenotic vena cava superior or its branches, or history of cardiac device-related infective endocarditis (CDRIE) [1].

Moreover, the decision for LP implantation during severe viral infection, i.e., SARS-CoV-2, seems safe [10].

Due to the stroke volume improvement with AV synchrony, MAV is preferred in patients considered for the LP with an AV block [4].

One should be aware that sick sinus syndrome, especially with maintained retrograde ventriculoatrial conduction or persistent supraventricular arrhythmia (including bradycardia), should not be regarded as an indication for MAV [11].



Central illustration. Accelerometer-based waves split in Micra AV [31]; AM — atrial mechanical; PVAB — post--ventricular atrial blanking; VE — ventricular end; VP — ventricular pacing.

Programming

With an introduction of AV synchronization in LPs due to a built-in accelerometer, programmable vectors were constituted, which characterize three space dimensions — X, Y, and Z, represented by numbers: 1, 2, and 3. They allow for a distinction between atrial and ventricle mechanical work with the possibility of being combined in different options for better signal quality to achieve optimal sensing results.

The heart work is split by an accelerometer into 4 waves (Central illustration). The A1 wave follows the QRS complex immediately. It consists of the mitral and tricuspid valve closure and represents the start of a ventricle contraction. Afterwards, the A2 wave occurs at the end of the ventricle contraction with an aortic and pulmonary valve closure. This signal is usually sharp and can be located near the end of the T-wave. The A1 and A2 signals should be located in a customizable post-ventricular atrial blanking (PVAB), nominally set to 550 ms. Moreover, there is also a post ventricular atrial refractory period (PVARP) extendable from 500 to 750 ms.

An A3 signal stands for the diastole of the ventricles. During that phase, the signal is usually rounder and corresponds to the passive filling of the ventricles. In Doppler ultrasonography, this part is known as an E wave. In Medtronic's programmer, the end of the A3 wave is annotated with the letters "VE", which is an abbreviation of "ventricular events". It corresponds to the A1–A3 waves. The last one, the A4 signal, represents the atrial contraction, which comes around 100 ms after the P-wave and stands for the Doppler's A wave. The A4 wave is aliased with the "AM" marker, as an abbreviation for "atrial mechanical".

The A7 wave can appear with an accelerometer overlap of the A3 and the A4 wave and corresponds to the gallop sound during heart auscultation. It occurs when the passive and active filling of the ventricles happens simultaneously, with higher heart rates or lack of AV synchronization.

The VDD pacing mode is initiated by obtaining AV synchronization and can be achieved in two ways. After implantation and turning on the VDD mode, the atrial sensing setup process is held automatically for 30 min, including a collection of atrial activity detection. After the auto setup test, based on the obtained data, the device offers automatic values for A3 and A4 thresholds and the ventricular window end (including minimum and maximum values).

However, the manual atrial mechanical test allows the manual setting of the parameters men-

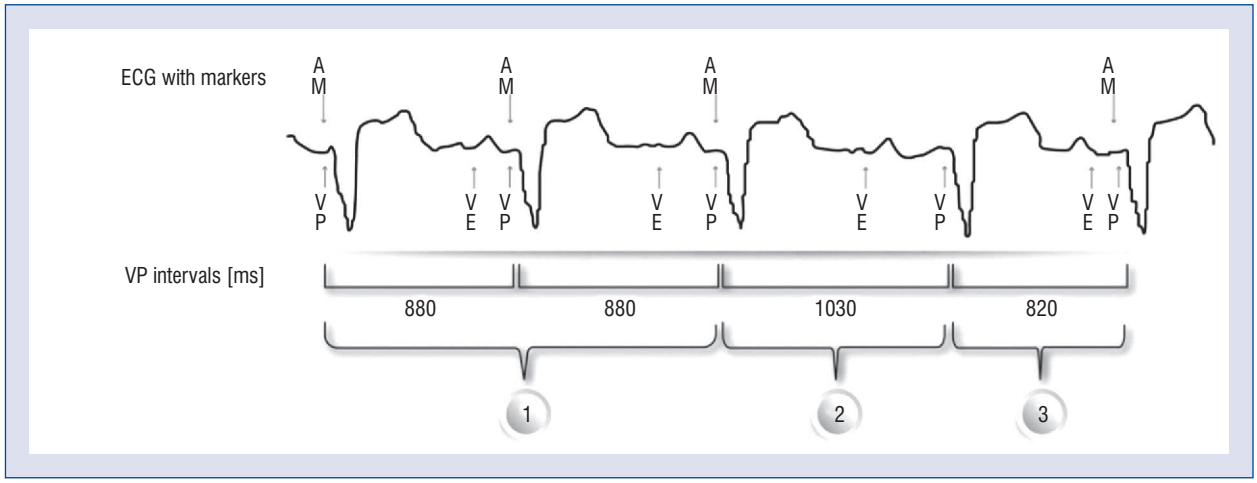


Figure 4. Rate smoothing algorithm: 1 — appropriate atrial mechanical (AM) sensing with synchronous ventricular pacing (VP); 2 — atrial undersense — VP occurs within the rate smoothing interval, instead of the lower rate; 3 — atrioventricular synchrony recovery [29]; ECG — electrocardiogram; VE — ventricular end.

tioned above: A3 and A4 threshold and the ventricular window end, along with the gathered data.

Unfortunately, the mechanical signals obtained from the accelerometer can be interfered with by various factors, i.e., accelerated heart rate or suboptimally programmed A3 and A4 signals. Thus, surface electrodes should be connected between the programmer and patient during the manual atrial mechanical test to recognize atrial detection correctly.

The window end for the A3 wave should be fixed below 700 ms to deactivate automatic adjustment, which can lead to excessive prolongation of the A3 window and worsening p-wave detection [12, 13]. A fixed threshold for the A3 wave should be set around 1 m/s^2 above the primary sensed A3 wave. It allows proper A7 signal sensing during higher sinus rates, the maintenance of AV synchrony and, at the same time, blanking of the A3 signal to avoid falsely recognizing the A4 waves [14].

In turn, the A4 threshold should be just below the A4 signal to recognize the AM, but it should not to be misled by signal noise.

Algorithms

Medtronic developed different algorithms that promote AV synchrony in VDD mode.

If intermittent A4 under sensing occurs, the rate smoothing algorithm (Fig. 4) maintains AV synchrony. With no sensed atrial contraction and when the rate smoothing interval times out, the device paces at the rate smoothing rate. Based on pacing history and an offset (which can be programmed via the smoothing delta), the MAV increases the probability of AV synchronous pacing and tracking the next atrial contraction.

Tracking check is another pacing feature that ensures the sensed atrial origin of the A3 and the A4 wave and prevents falsely induced paced tachycardia (Fig. 5). During a ventricular rate above the programmable tracking check rate, the algorithm extends the PVARP. Tracking check estimates the location of the subsequent AM signal with the stored and tracked patient sinus rate. The appropriate sinus tracking is confirmed if the next AM is within that window, and the device returns to the standard PVARP value for approximately 1.5 min.

Oversensing-induced tachycardia is confirmed if the next AM signal occurs outside the estimated range — tracking check maintains the extended PVARP for 40 s. The following falsely sensed AM signal should occur within the next refractory period, and ventricular pacing should be inhibited.

The tracking check algorithm can lead to an abrupt change in cycle length with arrhythmogenic short-long-short sequences. In rare situations, the algorithm can cause polymorphic ventricular tachycardia, especially in patients with long QT syndrome [15]. In this situation, tracking check should be turned off.

The MAV is also equipped with mode switching algorithms. The activity mode switch turns into a rate-responsive mode (VDIR) when the accelerometer detects high activity, and the ventricular

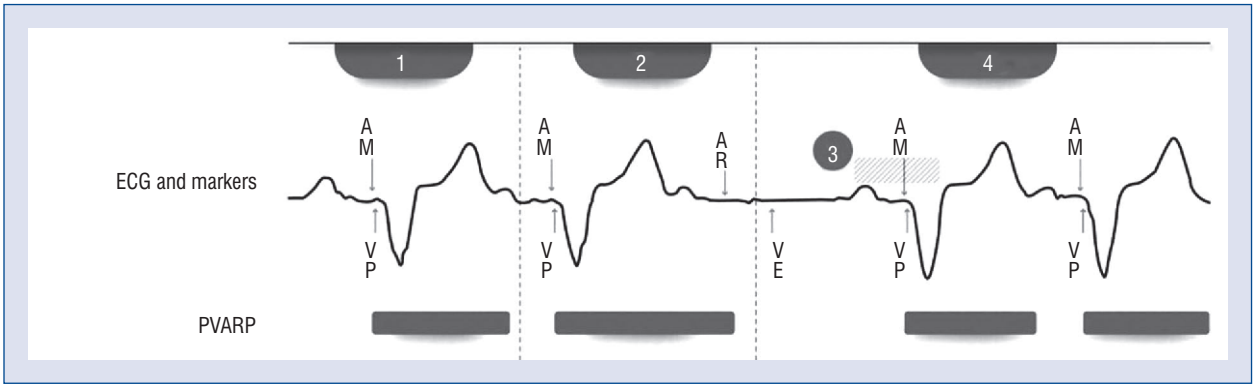


Figure 5. Tracking check algorithm; 1 — atrial mechanical ventricular pacing (AM-VP) rhythm at or above the tracking check rate; 2 — after the median ventricular rate reaches tracking check rate, the tracking check extends the post--ventricular atrial refractory period (PVARP) until the following AM occurs within; 3 — the tracking check estimates the location of the next AM; 4 — AM occurs in the expected range — appropriate tracking is confirmed, and the PVARP is returned to its basic value. Copyright Medtronic. Used with permission [30]; ECG — electrocardiogram; AR — atrial refractory sensing.

rate is low. Such a situation can happen due to loss of atrial tracking during VDD mode. After high activity stops, the MAV switches back to VDD mode.

Another mode switching option introduced with the MAV is AV conduction mode switch — the so-called "VVI+". It promotes intrinsic conduction and reduces battery usage and ventricular pacing by scanning for AV conduction by periodically switching to VVI mode with a lower rate of 40/min, regardless of the presence of an AV block. This option should be turned off in the case of complete AV block or clinically significant P-R interval prolongation with a heart rate above 40/min.

Clinical trials

While comparing LP safety to TV-PMs, the MVR and MAV should be considered as similar devices and combined into one group due to their similar external build.

One in 8 patients with TV-PM may experience peri- and post-procedural complications [16].

Thus, the vital clinical issue for Micra was safety assessment in the short- and long-term, which was proven in 2 studies: Micra VR Investigational Device Exemption (IDE) and Post-Approval Registry (PAR) — showing indisputable benefits. The IDE study showed 48% (hazard ratio [HR]: 0.52; 95% confidence interval [CI]: 0.35–0.77) fewer complications compared to TV-PMs, a high implant success rate (99.2%), and stable low pacing thresholds at 6 months in 98.3% of patients [17].

The PAR, which had 1817 participants with at least 12 months of follow-up for 465 of them, confirmed the general safety from the IDE study and proved a low rate of major complications throughout 12 months (2.7%; 95% CI: 2.0–3.6%) with no device--related infections [18]. The reduction in major complications was mainly driven by a 47% relative risk reduction in hospitalizations and 82% relative risk reduction in system revisions. Such outcomes can be associated with the lack of pocket and leads, which account for two-thirds of transvenous pacemaker complications [19].

Even though patients obtaining LP are usually burdened with more comorbidities, there is no difference in all-cause mortality at 2-year follow-up compared to the TV-PM comparator population. Moreover, after 2 years the benefits of LP in comparison to TV-PM were maintained — MVR was associated with a 38% lower rate of reinterventions and a 31% lower rate of chronic complications [20].

The feasibility of obtaining and maintaining high AV synchrony in patients with complete AV block and normal sinus function was proven with the AccelAv trial — a single-arm prospective study. After MAV implantation, at the first month, mean resting AV synchrony was 85.4% (95% CI: 81.1–88.9%; median 90.0%), and ambulatory AV synchrony, obtained via 24-hour Holter recording, was 74.5% (95% CI: 70.4–78.2%; median 75.0%). With A4 wave recognition optimization, the mean ambulatory AV synchrony increased to 82.6% (95% CI: 75.8–87.7%; median 85.3%). It was achieved mainly by fixing the A3 threshold approximately 1.0 m/s^2 greater than the obtained A3 signal to help track the sinus rate between 80 and 110 bpm. The authors also proved with the EuroQol

Five-Dimensions Three-Level questionnaire that quality of life improved after MAV implantation [13]. An even higher percentage of AV synchrony was achieved by optimizing atrial signal sensing by Briongos-Figuero et al. [12]. Deactivating the automatic A3 window end and manually shortening the A3 window end increased AV synchrony as determined by device counters significantly from 68.7 ± 14.7% to 87.3 ± 11.1% in the 6-month follow-up. More importantly, the 24-hour Holter monitoring in the follow-up demonstrated 87.3 ± 6.3% AV synchrony in patients undergoing daily activities. At the same time, most of the A4 thresholds were set automatically [12].

The rate of pericardial effusion following Micra implantation is similar to that observed with TV-PMs, i.e., 1.1%, with similar occurrence risk factors [21]. Increasing age, body mass index < 20, female sex, heart failure, prior myocardial infarction, chronic obstructive pulmonary disease, absence of prior cardiothoracic surgery, and hemodialysis raises the risk of post-procedure pericardial effusion. Several deployments of Micra are also associated with increased risk of pericardial effusion, especially in patients with elevated risk at baseline [15]. There has not been a reported case of CDRIE in LPs, even though LPs are often the first choice after the previous CDRIE. Its intracardiac fixation, small volume, and tendency for rapid encapsulation might be the reason for this [17].

Unfortunately, encapsulation may complicate extraction. Even though there is a report of successful retrieval of a 4-year-old MVR with commonly available tools [22], LPs lack a retrieval registry.

Between November 2020 and June 2021, 20 patients underwent transcatheter aortic valve implantation followed by MAV implantation. The safety and performance of the LP were proved with a 1-month follow-up. Atrial under sensing was listed as the main issue, which occurred in 2 patients, and the issue was resolved by reprogramming the MAVs [23].

Micra's implantation safety, performance, and post-procedural complications were also evaluated in a retrospective study comparing patients with pre-procedure AV-node ablation (AVNA). The study proved the procedural and performance safety of concomitant AVNA and LP implantation with the precaution of a higher risk of major complications in patients undergoing AVNA [24].

The AVNA patients were older, more frequently female, and tended to have more co-morbid conditions than non-AVNA patients. With high implantation success (99.5%) and a mean pacing threshold at implant of 0.58 ± 0.35 V, stable values during follow-up — major complications within 30 days occurred more frequently in AVNA patients than non-AVNA patients (7.3% vs. 2.0%, $p < 0.001$). Intermittent loss of capture occurred in 3 AVNA patients (1.6%) within 30 days of implant, requiring system revision.

Another exciting field for LPs is cardioinhibitory vasovagal syncope (VVS) treatment. Micra's battery performance has been evaluated in a retrospective study on patients suffering from frequent VVS episodes. Even though LPs provide a promising treatment option for patients with VVS with satisfactory battery performance (estimated during the study for 13.65 ± 2.97 years), the lack of a Micra retrieval registry and limited possibilities of LP reimplantation raises concerns in this strategy, especially in younger patients [25].

Currently, MAVs' PAR is ongoing, with the end of the study expected in 2025. It is a prospective, multicenter, single-arm registry with the aim of assessing the safety and performance of the MAV on more than 750 patients. The primary endpoint is a rate of pacemaker syndrome requiring revision at 3 years and a secondary endpoint is to assess acute and chronic complications after implantation.

Because the MAV is implanted in the heart's RV, atrial pacing is unavailable, unlike the TV-PM. However, Abbot's Aveir DR Leadless Pacemaker — a dual-chamber leadless pacemaker — is currently the subject of a pivotal Aveir DR i2i study.

Another ongoing study — MODULAR ATP — assess the safety, performance, and effectiveness of the mCRM™ Modular CRM System (EMBLEM™ S-ICD System and EMPOWER™ Modular Pacing System), which would deliver ATP as well as high-voltage therapy.

MC1AVR1 with EOS battery state

Usually, the Micra is recommended for patients with a shorter lifespan due to the absence of long-term data on LP performance and limited data on retrievability and end-of-life strategy [1]. However, the number of patients who encounter an EOS state of LP will rise. Even though the Micra occupies around 1% of the RV volume [5], the area of possible implantation is much more limited, and the Micra is considered an unremovable device. If further pacing is needed after RRT, the implantation of another LP in the RV is undertaken. With available data, there have been cases showing the feasibility of the procedure with 3 LPs implanted simultaneously [26].

Micra AV in Poland

Currently, there is no national registry for the MAV or LPs, although experts recommend the introduction of such a registry [27]. In 2021 there were 47 MC1AVR1 implanted, mainly in 2 high-volume centers. A medical center willing to implant the MAV must write a document to the NFZ for reimbursement. Till the 10th implantation, each procedure needs to be performed with the supervision of a Medtronic technical expert.

Specific clinical situations [28]

Electric cardioversion

Electric cardioversion can be safely performed with several precautions. Firstly — use the lowest clinically efficient energy level, because an increased energy level raises the probability of damage to the device. Secondly, defibrillator paddles should be placed more than 15 cm from the implanted device. One should note that the procedure can temporarily or constantly raise the threshold level.

Radiotherapy

The cumulative exposition dose should not exceed 500 cGy. Asynchronous therapy should be considered during radiotherapy to reduce intervention detection.

MRI

Magnetic resonance imaging (MRI) scans can be safely performed under certain conditions. Scanning is allowed only after turning on an MRI SureScan option. This function cannot be allowed while RRT is on, which needs to be underlined. In this situation, VOO should be considered. Other requirements are stimulation amplitude equal to or lower than 4.5 V, no phrenic stimulation observed during MRI while the SureScan is on, MRI of the strength 1.5 T or 3.0 T, and maximal volume gradient ≤ 25 T/m (2500 Gs/cm).

It is worth noting that it is not recommended to perform MRI during the stabilization period, i.e., the first 6 weeks after implantation.

Cremation

There is no need to explant Micra post-mortem; cremation is possible due to no significant emission expected.

Conclusions

Leadless pacing has indisputable advantages. Among them is the reduced number of major complications in the peri- and postprocedural period. Even though nowadays LP technology is limited compared to TV-PM, technological advancements have allowed them to be overcome, and AV synchrony is the next step in LP evolution. One should also remember about the small implantation area, restricted catheter flexibility, programming issues with the AV synchrony, and economic issues. Moreover, to date, there is no registry of long-term outcomes and retrieval. Atrial pacing, conduction-system pacing, simple retrieval protocol, and high-voltage therapy are crucial issues that must be resolved in the future.

Conflict of interest: Bruno Hrymniak and Dariusz Jagielski received speaker honoraria fees from Medtronic. Przemysław Skoczyński, Bartosz Biel, and Waldemar Banasiak declare no conflict of interest.

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Quality of life in heart failure: New data, new drugs and devices

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Abstract

Quality of life (QoL) is a therapeutic goal in heart failure. There are many evidence based medicine therapies for improving QoL. In this study, data is presented on new pharmacotherapies and devices that impact QoL in the heart failure population. (Cardiol J 2024; 31, 1: 156–167)

Keywords: quality of life, heart failure, pharmacotherapy, devices

Introduction

Heart failure (HF) is a progressive disease which has a detrimental effect on quality of life (QoL). The prevalence of HF appears to be 1–2% in adults and is increasing due to the ageing of populations around the world, sedentary lifespan and comorbidities. In the 2021 guidelines of the European Society of Cardiology (ESC) for the diagnosis and treatment of acute and chronic HF, QoL is still considered a part of management strategy [1]. Like the 2016 ESC Guidelines [2], the treatment goals in HF are: improvement of the clinical status, functional capacity and QoL, prevention of hospital admission and reduction of mortality [1]. The aim of the study was to describe new data on QoL in light of innovative therapies in HF.

Definitions of QoL and evaluation methods in clinical studies

The World Health Organization defines QoL as an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns [3]. QoL consists of objective and subjective indicators. It is a multidimensional, individual outcome, composed of five dimensions: physical wellbeing, material wellbeing, social wellbeing, emotional wellbeing, as well as development and activity [4]. Central illustration presents QoL dimensions.

There are many instruments to assess QoL, like the Health-Related Quality of Life Questionnaire, World Health Organization Quality of Life Instrument, Short Form 36 Health Survey Questionnaire (SF-36), Quality of Life Scale [5]. Some of them are dedicated to HF: the Chronic Heart Failure Assessment Tool, Cardiac Health Profile of congestive heart failure, Chronic Heart Failure Questionnaire (CHFQ), Kansas City Cardiomyopathy Questionnaire (KCCQ), Left Ventricular Disease Questionnaire, Minnesota Living with Heart Failure Questionnaire (MLHFQ), and Quality of Life in Severe Heart Failure Questionnaire. Table 1 shows selected QoL questionnaires.

The use of some questionnaires has clinical potential. Assessments of KCCQ is used to identify high-risk patients and design their individual treatment plans. Patients with lower or worsening KCCQ scores demonstrate an increased risk of cardiovascular events and mortality [6]. Iqbel at al. [7] showed that the baseline QoL predicts mortality and hospital admissions — patients with worse

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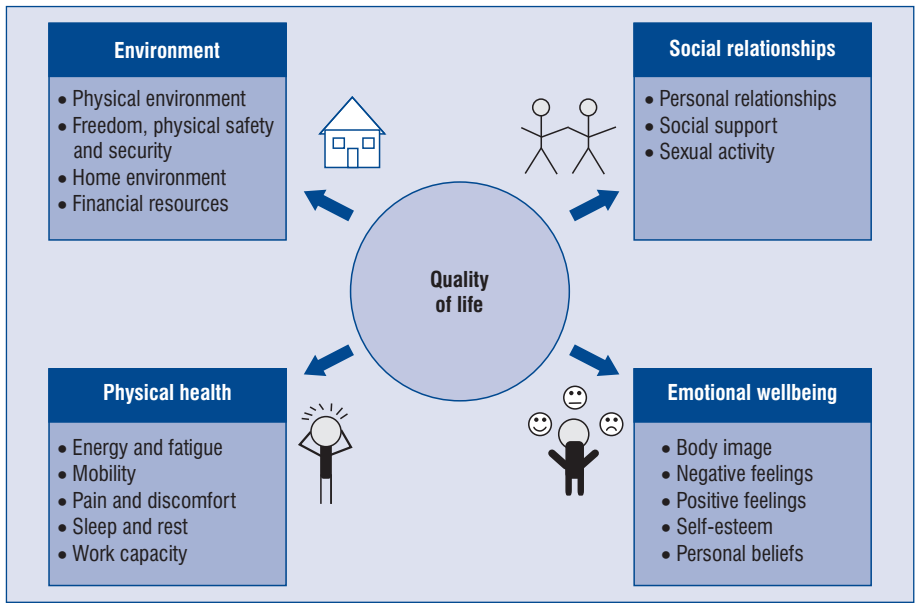

Central illustration: Dimensions of quality of life.

Table 1. Selected quality of life questionnaires.

	SF-36	KCCQ-23	WHOQOL-BREF	QOLS
Items	36	23	26	16
Domains	1. Physical functioning 2. Physical role limitations 3. Bodily pain 4. General health 5. Perceptions (energy/ /vitality) 6. Social functioning 7. Emotional role limitations 8. Mental health	1. Symptom frequency 2. Symptom burden and stability 3. Physical limitations 4. Social limitations 5. Quality of life; and self-efficacy	1. Physical health 2. Psychological 3. Social relationships 4. Environment	1. Material and physical well-being 2. Relationships with other people 3. Social, community and civic activities 4. Personal development and fulfillment 5. Recreation 6. Independence
Scale	0 to 100	0 to 100	0 to 100	16 to 112
Time to complete	10 minutes			5 minutes

SF-36 — The Short Form 36 Health Survey Questionnaire; KCCQ — Kansas City Cardiomyopathy Questionnaire; WHOQOL-BREF — The World Health Organization Questionnaire of QOL; QOLS — Quality of Life Scale

baseline QoL had a higher risk of mortality (hazard ratio [HR] 1.5, $p = 0.09$) and hospitalizations (HR 7.3, $p < 0.001$).

Impact of heart failure on QoL

Heart failure affects all fundamental spheres of human life at the same time. In the physical sphere, patients most often experience symptoms such as reduced general body efficiency, shortness of breath, fatigue, decreased energy levels, edema sleep problems. In the psychological sphere, HF patients are more likely to experience disorders at the emotional level, in particular strong anxiety and depression. In the social sphere, patients may experience deterioration of social contacts and

relationships with relatives, as well as difficulties in everyday work life.

Subjective assessment of QoL is also influenced by parameters such as gender and age. QoL is lower in women, which is consistent with the assessment of the QoL in the group of cardiac patients, as well as in younger patients. Among younger people, HF-related symptoms and treatment of the disease limit fulfillment of basic social roles, like starting a family or pursuing a professional career.

Quality of life in HF is significantly reduced not only by symptoms but also by numerous hospitalizations. Despite some improvement in reducing mortality in HF, the rehospitalization rate is still high, up to 30% in 60 to 90 days after discharge, regardless of ejection fraction (EF) [8, 9]. Thus, all therapies and procedures aimed at reducing the risk of HF hospitalization improve QoL.

Quality of life is also crucial in end-of-life care in HF. With every HF hospitalization the patient's condition and prognosis decline, which leads to advanced HF or death. In every patient with advanced stage of HF, palliative and end-of-life care should be considered. It can reduce the hospitalization rate and alleviate symptoms. End-of-life care should be focused on improving QoL of the patient and their family [10].

Impact of comorbidities on QoL

Many factors like comorbidities, the employment status, or social situation, influence both QoL and symptoms of HF. Comorbidities significantly reduce QoL in HF, mainly in older patients. However, the heart failure with preserved ejection fraction (HFpEF) phenogroup of young obese patients is considered to have the lowest QoL. Evangelista et al. [11] revealed that obese patients appeared to demonstrate higher values in MLHFQ (the higher score, the lower QoL), i.e., 48.5 ± 24.2 in mean ± standard deviation (SD) compared to normal weight patients (MLHFQ 39.4 ± 23.1) and the overweight group (MLHFQ 44.0 ± 24.70) with p value = 0.049 and worse depressive symptoms.

Many patients with HF suffer from diabetes. Concomitant diabetes worsens patient health status, increases the number of complications and reduces QoL. In CHMP-HF patients with heart failure with reduced ejection fraction (HFrEF) and diabetes mellitus exhibit worse results regarding health-related quality of life (HRQOL) compared to HFrEF patients without diabetes [12].

Benes et al. [13] study has shown that three common comorbidities (diabetes, chronic obstructive pulmonary disease, and chronic kidney disease) affect QoL in HFrEF patients. In this analysis, among patients with more comorbidities QoL was similar (evaluated with the MLHFQ). However, a multivariable regression analysis also showed that not the number of comorbidities in a stable advanced HFrEF patient but other factors like the New York Heart Association (NYHA) class, body mass index and furosemide daily dose affect their QoL [13].

Depression and anxiety disorders often occur in HF patients. Up to 20% of HF patients have depression. It may be responsible for aggravation of symptoms, increased hospitalization rates, reduced compliance, higher mortality and may also affect QoL. Nevertheless, depression often remains underestimated and untreated [14]. Psychological support and pharmacotherapies are considered. Selective serotonin reuptake inhibitors have proved to be safe in SADHART-CHF and MOOD-HF trials [15, 16]. Although they are recommended for patients with HF they did not significantly reduce hospitalization or all-cause mortality and show no significant improvement in depression when compared to placebo.

Impact of exercise on QoL

The 2021 ESC HF guidelines recommend exercise rehabilitation and multiprofessional disease management for all patients in order to reduce HF hospitalization and to improve their QoL [1]. It has been proved that physical exercise in the form of structured exercise training improves exercise tolerance and QoL and reduces the risk of hospitalization. There are many studies which show positive impact of cardiac rehabilitation on HF patients. Taylor et al. [17] in their meta-analysis of randomized trials showed a statistically significant benefit of exercise on health-related QoL (measured with MLHFQ) and exercise capacity (tested by a 6-minute walk test [6MWT]), compared to the placebo group, after 12 months of follow-up.

Also, Palmer et al. [18] showed in a meta-analysis that exercise improves QoL, which is manifested with the score of 8.5 points in MLHFQ. Moreover, the physical function was improved, measured by 6MWT [18]. The HF ACTION study revealed that after 3 months of exercise rehabilitation, patients exhibited higher KCCS-overall summary score (OSS) (the mean: 5.21, 95% confidence interval [CI] 4.42–6.00) compared with the standard care group not undergoing exercise rehabilitation (3.28, 95% CI 2.48–4.090) and this

result was statistically significant ($p < 0.001$) [19]. The positive effect in the exercise group was also observed in the follow-up period.

Impact of pharmacotherapy on QoL

Heart failure with reduced ejection fraction (HFrEF)

There are many pharmacological therapies in HFrEF that improve QoL. The following four groups of fundamental pharmacological treatment are effective and they include: angiotensin-converting enzyme inhibitors (ACEI)/angiotensin receptor-nephrilysin inhibitor (ARNI), sodium-glucose cotransporter-2 (SGLT2) inhibitors, beta-blockers and mineralocorticoid receptor antagonists (MRA).

ACEI and ARNI alleviate HF symptoms and increase exercise tolerance. The best effect for ACEI was visible in patients with the lowest left ventricular ejection fraction (LVEF) < 25% [20]. The drugs should be applied in maximum tolerated recommended doses. However, the PARADIGM-HF trial showed that sacubitril/valsartan contributed to a greater QoL improvement measured in the KCCQ clinical summary score (CSS) (+0.64 vs. –0.29; $p = 0.008$) and KCCQ-OSS (+1.13 vs. –0.14; $p < 0.001$) compared to enalapril [21]. In the PARASAIL study, in which 64.6% of patients were administered the maximum dose of sacubitril/valsartan 97/103 mg b.i.d. after 6 months, the improvement (slight, moderate, or marked) measured with the use of the patient global assessment at 4, 12 and 24 weeks of the study was 52.3%, 58.6% and 64.2%, respectively [22]. An improvement in QoL was also visible in decreasing MLHFQ total scores from the beginning of the study to 4, 12 and 24 weeks (with $p < 0.0001$ for all) [22].

Other studies suggest a positive effect of sacubitril/valsartan in patients equipped with an implantable cardioverter-defibrillator (ICD). This drug significantly prolongs survival without ventricular tachycardia and non-sustained ventricular tachycardia compared with ACEI/angiotensin receptor blocker (ARB) and increases in the number and percentage of biventricular stimulation (BiV) compared to patients treated with ACEI/ARB [23]. Moreover, results of the study revealed a lower number of adequate ICD discharges [23]. Another study suggests that sacubitril/valsartan reduces the risk of sudden cardiac death (SCD) and cardiac arrest compared to enalapril whether the patient had or had not been implanted with an ICD device [24]. The meta-analysis conducted by Fernandes et al. [25] also confirmed that ARNI therapy in HFrEF patients was associated with a reduced number of SCD events, ventricular arrhythmias and a reduced incidence of adequate ICD discharges. Patients treated with sacubitril/valsartan demonstrated increased BiV stimulation and reduced requirement for ICD [25]. These results are reflected in patients' QoL-reduced discharge rates and better control of arrhythmias are associated with an increase in a sense of caring and self-confidence, which leads to increased physical activity and improved KCCQ results.

Furthermore, in the CARVIVA HF trial, ivabradine added to carvedilol treatment demonstrated improvement in exercise capacity as measured in 6MWT and QoL ($p < 0.01$ vs. baseline for ivabradine and $p < 0.02$ for ivabradine with carvedilol) [26]. Docherty et al. [27], based on PARADIGM-HF and ATHMOSPHERE trials, have shown that lower HR values, contributed addition of ivabradine, reduced cardiovascular death and HF hospitalization as well as improvements in QoL, manifesting in higher KCCQ scores at 12 months ($p < 0.001$ in both) [27].

Iron deficiency often affects HF patients and can decrease QoL. In the AFFIRM study, QoL was measured with KCCQ-12 at the baseline and after randomization [28]. A 4-week observation with KCCQ-OSS (KCCQ-12 OSS) and KCCQ-CSS revealed a higher improvement in ferric carboxymaltose in comparison to the placebo group: 2.9 (0.5–5.3, $p = 0.018$) for OSS, and 2.8 (0.3–5.3, $p = 0.029$) for CSS; in the adjusted mean difference (95% CI). According to the AFFIRM study, intravenous ferric carboxymaltose can alleviate symptoms and increase the functional capacity and QoL in HF patients with LVEF < 45%, as well as reduce the hospitalization rate in HF patients with LVEF < 50% [28].

Results from SGLT2 inhibitors trials are described in a separate section.

Heart failure with preserved ejection fraction (HFpEF)

Heart failure with preserved ejection fraction constitutes about 50% of all cases of HF. Prognosis in HFpEF is equally unfavorable as in patients with HFrEF. In the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial) post-hoc analysis, 3 phenogroups were described [29]. Phenogroup 3 (patients with obesity, diabetes mellitus) had the lowest KCCQ overall score of 50 ± 22, compared to 55 ± 18 in phenogroup 1 and 58 ± 21 in phenogroup 2

Table 2. Outcomes of quality of life in EMPEROR-Reduced [34], EMPEROR-Preserved [35, 36], EMPULSE [38, 39] and DAPA-HF[43] trials.

EMPEROR-Reduced	Empagliflozin (n = 1863)	Placebo (n = 1867)	HR or absolute difference (95% CI)
Change in quality-of-life score on KCCQ at 52 weeks	5.8 ± 0.4	4.1 ± 0.4	1.7 (0.5–3.0)
No. of hospitalizations due to any cause	1364	1570	0.85 (0.75–0.95)
EMPEROR-Preserved	**Empagliflozin (n = 2997)**	**Placebo (n = 2991)**	**HR or absolute difference (95% CI)**
Total no. of hospitalizations for heart failure	407	541	0.73 (0.61–0.88)
Change in KCCQ clinical summary score at 52 weeks	4.51 ± 0.31	3.18 ± 0.31	1.32 (0.45–2.19)
Total no. of hospitalizations due to any cause	2566	2769	0.93 (0.85–1.01)
EMPULSE	**Empagliflozin (n = 265)**	**Placebo (n = 265)**	**HR or absolute difference (95% CI)**
≥ 5 point difference in the KCCQ-TSS change from baseline to day 90 (% wins)	35.91	27.48	
KCCQ-TSS improvement ≥ 10 points at day 90, n (%)	220.1 (83.1)	202.1 (76.3)	1.522 (0.927–2.501)
KCCQ-TSS change from baseline to day 90, adjusted mean (95% CI)	36.19 (33.28–39.09)	31.73 (28.80–34.67)	4.45 (0.32–8.59)
DAPA-HF	**Dapagliflozin (n = 2373)**	**Placebo (n = 2371)**	**HR or absolute difference (95% CI)**
Change in KCCQ-TSS at 8 months	6.1 ± 18.6	3.3 ± 19.2	1.18 (1.11–1.26)

CI — confidence interval; HR — hazard ratio; KCCQ — Kansas City Cardiomyopathy Questionnaire; TSS — total symptom score

($p < 0.001$) [29]. Phenogroup 3 also exhibited the highest rate of depression 197 (36%) compared to 64 (23%) in phenogroup 1 (the younger one) and 121 (19%) in phenogroup 2 (the older one) with $p < 0.001$ [29].

Until the introduction of SGLT2 inhibitors, there had not been a therapy improving prognosis in patients with HFpEF. Results of trials conducted earlier and meta-analysis of Zheng et al. [30], revealed that no single drug, including ACEI, MRAs and beta-blockers, administered to HFpEF patients, reduced HF hospitalization or cardiovascular mortality compared to placebo. Furthermore, neither exercise capacity nor QoL were improved in this population [30].

Sacubitril/valsartan administered in PARAGON-HF and PARALLAX-HF studies to population with HFpEF improved QoL measured in KCCQ and NYHA class at 8 months and 24 weeks, respectively, in comparison to valsartan in PARAGON-HF or individualized medical therapy (placebo, ACEI or ARB) in the PARALLAX-HF study [31, 32]. However, according to the 2021 ESC guidelines in HFpEF, before the SGLT2 inhibitors era, the optimal treatment of comorbidities and risk factors is recommended [1]. Results of EMPEROR-Preserved and DELIVER trials have completely changed our opinion on this issue and we believe that the goals of therapy in HFpEF patients should be defined in a similar way as those for HFrEF patients including QoL.

Lastly, diuretics are recommended in the I class in both HFrEF and HFpEF patients with volume overload to improve QoL and exercise capacity as well as alleviate symptoms by reducing congestion [1, 33].

SGLT2 inhibitors and QoL

Results of changes in QoL for SGLT2 inhibitors therapy are presented in Table 2.

In the EMPEROR-Reduced study [34], QoL was assessed with KCCQ at the beginning of the study and at 12, 32, and 52 weeks after randomization. Patients receiving empagliflozin demonstrated a significant improvement in KCCQ-CSS (by 1.94, 1.35, and 1.61 points), in the total symptom score (TSS) by 2.52, 1.64, 1.69 points and OSS by 1.77, 1.30, and 1.52 points at 12, 32 and 52 weeks compared to placebo. Moreover, patients treated with empagliflozin scored more than 5 points in

KCCQ-CSS (odds ratio [OR] 1.20 [1.05–1.37]), ≥ 10 points (OR 1.26 [1.10–1.44]), and more than |15 points (OR 0.75 [1.12–1.48]). Benefits of improved QoL was also visible at 3 months and continued for at least a year. Patients treated with empagliflozin were 20% to 40% more likely to exhibit an improvement in the NYHA class and 20% to 40% less likely to experience deterioration in the NYHA class. The clinical benefit was already seen on day 28 after randomization and continued in the follow-up [34].

The EMPEROR-Preserved study [35] revealed that empagliflozin is effective in patients with HF and EF > 40%. It decreased the risk of death from cardiovascular cause and hospitalization due to HF by 21%, reduced the risk of all hospitalizations by 27% and improved QoL. Table 2 shows selected EMPEROR-Preserved outcomes.

Quality of life was assessed with KCCQ at the beginning of the study and after 12, 32, and 52 weeks. Patients receiving empagliflozin demonstrated a significant improvement compared to those receiving placebo in KCCQ-CSS by +1.03, +1.24, and +1.50 points, TSS by 1.77, 1.53 and 2.07 points and in the OSS by 1.77, 1.53 and 2.07 points at 12, 32 and 52 weeks [36]. Already at 12 weeks, patients treated with empagliflozin scored more than 5 points in KCCQ-CSS (OR 1.23, 95% CI 1.10–1.37), ≥ 10 points (OR 1.15, 95% CI 1.03–1.27), and more than 15 points (OR 1.13, 95% CI 1.02–1.26) [36].

In the EMPEROR-Preserved study, the effect of empagliflozin was manifested in baseline KCCQ tertiles (Table 3). Improved QoL was also visible at 32 and 52 weeks, and was observed for at least a year [36]. Patients treated with empagliflozin were 20% to 50% more prone to demonstrate an improvement in the NYHA class. The effect was already seen at 12 weeks after randomization and continued for at least 2 years [37].

Empagliflozin also improves QoL in patients with acute HF, as it was revealed in the — EMPULSE study [38, 39]. Clinical benefits after taking empagliflozin were 36% higher in comparison to results obtained in the placebo group (stratified win ratio 1.36; 95% CI 1.09–1.68; p = 0.0054). Clinical benefits included: a decreased risk of cardiovascular death and decreased hospitalization due to HF as well as improved QoL. Such results were achieved irrespective of EF or concomitant diabetes [38].

In the EMPULSE trial, QoL was assessed using a difference in the change from baseline in the KCCQ-TSS at 90 days. The average change in KCCQ-TSS from baseline to 90 days was 36.2 (95% CI 33.3–39.1) in the empagliflozin group and 31.7 (95% CI 28.8–34.7) in the placebo group [39]. The clinical benefit was observed very early, already after 15 days and stayed to 90 days. At day 90, patients treated with empagliflozin exhibited better results in KCCQ-TSS, Physical Limitations (PLS), QoL, CSS and OSS in comparison to

Table 3. Effect of empagliflozin on outcomes by baseline KCCQ tertiles in EMPEROR-Preserved [36] and EMPULSE trial [39].

EMPEROR-preserved outcome	Hazard ratio (95% CI)
Cardiovascular death or HF hospitalization	
KCCQ-CSS	
Tertile 1 (< 62.5)	0.83 (0.69, 1.00)
Tertile 2 (62.5–83.3)	0.70 (0.55, 0.88)
Tertile 3 (≥ 83.3)	0.82 (0.62, 1.08)
KCCQ-TSS	
Tertile 1 (< 66.7)	0.85 (0.70, 1.04)
Tertile 2 (66.7–87.5)	0.76 (0.60, 0.96)
Tertile 3 (≥ 87.5)	0.71 (0.55, 0.93)
KCCQ-OSS	
Tertile 1 (< 61.2)	0.81 (0.67, 0.98)
Tertile 2 (61.2–82.3)	0.72 (0.57, 0.92)
Tertile 3 (≥ 82.3)	0.82 (0.62, 1.08)
Total number of HF hospitalizations	
KCCQ-CSS	
Tertile 1 (< 62.5)	0.82 (0.61, 1.08)
Tertile 2 (62.5–83.3)	0.62 (0.44, 0.88)
Tertile 3 (≥ 83.3)	0.70 (0.49, 1.00)
KCCQ-TSS	
Tertile 1 (< 66.7)	0.86 (0.64, 1.14)
Tertile 2 (66.7–87.5)	0.71 (0.51, 0.99)
Tertile 3 (≥ 87.5)	0.56 (0.39, 0.79)
KCCQ-OSS	
Tertile 1 (< 61.2)	0.82 (0.62, 1.08)
Tertile 2 (61.2–82.3)	0.64 (0.45, 0.90)
Tertile 3 (≥ 82.3)	0.65 (0.45, 0.93)
EMPULSE	
All-cause death or HF events, or 5-point or greater difference in KCCQ-TSS change	
KCCQ-TSS < 27.1	1.49 (1.01, 2.20)
KCCQ-TSS ≥ 27.1 and < 52.1	1.37 (0.94, 1.99)
KCCQ-TSS ≥ 52.1	1.48 (1.00, 2.20)

CI — confidence interval; CSS — clinical summary score; HF — heart failure; KCCQ — Kansas City Cardiomyopathy Questionnaire; OSS — overall summary score; TSS — total symptom score

placebo (95% CI); respectively, 4.45 (0.32, 8.59), p = 0.03; 4.80 (0.00, 9.61), p = 0.05; 4.66 (0.32, 9.01), p = 0.04; 4.85 (0.77, 8.92), p = 0.02; and 4.40 points (0.33, 8.48), p = 0.03 [39].

Data obtained in EMPEROR-Preserved, EMPEROR-Reduced and EMPULSE studies show that empagliflozin significantly improves QoL in a wide spectrum of HF patients, regardless of EF. Very few therapies have been previously shown to improve symptoms and the functional status in the early post-discharge period. Apart from empagliflozin, the only other pharmacotherapies include intravenous ferric carboxymaltose, ivabradine (OPTIMIZE Heart failure care program) and sacubitril/valsartan [28, 40, 41].

Another SGLT2 inhibitor, recommended in HFrEF, is dapagliflozin [42]. In the DAPA-HF study, in the group receiving dapagliflozin, the TSS in KCCQ was higher than that observed in the placebo group by 2.8, 2.5 and 2.3 points (p < 0.0001), from baseline to 8 months [43]. More often patients receiving dapagliflozin had increased in KCCQ results for at least 5 points in the total score than in the placebo group (58.3% vs. 50.9%; OR 1.15; 95% CI 1.08–1.23) and less frequently experienced important deterioration (25.3% vs. 32.9%; OR 0.84; 95% CI 0.78–0.90; p < 0.001 for both comparisons) [43].

Kosiborod [44] analyzed DEFINE-HF and PRESERVED-HF trials and concluded that dapagliflozin improved QoL in patients with HF irrespective of EF [44]. Patients receiving dapagliflozin at 12 weeks demonstrate a greater improvement in KCCQ-CSS (effect size: 5.0; 95% CI 2.6–7.5 points; p < 0.0001) compared to the placebo group [44]. There was also an improvement, manifested in scores of KCCQ-PLS (effect size: 5.0; 95% CI 1.8–8.2 points; p = 0.0023), KCCQ-TSS (5.0; 95% CI 2.3–7.7 points; p = 0.0003), and KCCQ-OSS (3.7; 95% CI 1.3–6.1; p = 0.003), despite LVEF [44].

The recently published DELIVER study confirmed a positive effect of dapagliflozin in HF patients with EF > 40%. Patients who were administered dapagliflozin had a greater chance of improvement in the NYHA class compared to placebo patients. The result was seen as early as at week 4 [45]. The beneficial impact of dapagliflozin on QoL was also seen in improvement of KCCQ--TSS compared to the placebo group in month 8 (win ratio 1.11; 95% CI 1.03–1.21; p = 0.009; mean placebo-corrected difference between baseline and month 8 in survivors, 2.4 points; 95% CI 1.5–3.4) [46]. A prospective analysis of the DELIVER trial showed that frailer patients demonstrated a higher improvement of QoL, while having worse KCCQ score at baseline [47]. On the basis of a pooled meta-analysis of DAPA-HF and DELIVER, dapagliflozin is the second most effective drug, after empagliflozin, which improves QoL in the whole spectrum of HF, regardless of EF [48].

Finally, the CHIEF-HF remote, patient-centered randomized, placebo-controlled trial determined superiority of canagliflozin administered at daily doses of 100 mg daily over placebo in improving the KCCQ-TSS at 12 weeks — the difference between the two groups was 4.3 points (p = 0.016) [49]. Results were similar irrespective of occurrence of EF and diabetes status.

Quality of life and implantable devices

Implantable devices, together with pharmacotherapy, have a considerable impact on QoL of patients. Although the primary goal of all implantable devices is to improve patient survival and prognosis, their implantation can have both a positive and a negative impact on patients' lives. Depending on the type of the implanted device, improvement can be observed immediately (as in the case of a pacemaker), gradually increasing over time (as in the case of left ventricular assist device) or only under special conditions (as in the case of an ICD). Some of them may take the form of bridging or continuous therapy, and some are only supposed to monitor patients' condition. Guidelines for their application must be adequately determined so that they can serve the proper purpose. Issues regarding adequate ICD discharges are described in this paper in the section on ARNI.

Cardiac resynchronization therapy (CRT) is a cardiac pacing method used in patients with left ventricular systolic dysfunction and non-synchronous ventricular activation, which provides simultaneous or near-simultaneous electrical activation of both ventricles. A special CRT pacemaker or a device which can be applied via a cardioverter-defibrillator is used. These devices are characterized by an additional lead whose purpose is to stimulate the left ventricle. This therapy can improve performance and reverse adverse ventricular remodeling, improve QoL, reduce the number of hospitalizations and improve survival rates. However, patients should be appropriately selected. In cases of preserved LVEF ≥ 50% EF, no significant improvement after administering CRT therapy has been found. The PACE trial after 1 and 2 years did not improve the quality of life compared to right ventricular pacing alone [50, 51].

When analyzing implantable devices, it is important to consider devices whose purpose is to improve the heart valve function. Surgical repair is the gold standard in treatment of severe degenerative mitral regurgitation. However, an impact of application of transcatheter repair with the Mitra-clip device should be also considered. Lim et al. [52] report that such intervention in patients with excessive surgical risk is safe and brings good clinical outcomes, including reduced hospitalizations, functional improvement and improved QoL [52]. Significant improvements were found in SF-36 QoL questionnaire scores for both physical and mental components for almost all SF-36 subscales at each time point, except for body pain and the role-emotion scale at day 30. Similarly, both surgery and transcatheter valve replacement are possible for severe aortic stenosis. The second option is an acceptable alternative for patients at high surgical risk. Current evidence demonstrates that transcatheter aortic valve implantation (TAVI) will provide a significantly better prognostic benefit in inoperable patients [53]. The SURTAVI trial evaluated both interventions in patients with a moderate surgical risk [54]. Regardless of the choice of the treatment modality, both surgery and TAVI implantation improved clinical condition, which was observed in the assessment of the NYHA scale. Besides, they also improved QoL, as measured by the KCCQ questionnaire. Moreover, a greater proportion of patients treated with TAVI showed improvement as early as 1 month after the procedure.

It should also be stressed that in recent years we have observed that the number of younger patients receiving TAVI who show a longer life expectancy is increasing. It can be assumed that patients will survive their bioprostheses and the number of repeated interventions after TAVI will increase. Transcatheter heart valve failure, treated with transcatheter aortic valve implantation (TAVI--in-TAVI), will become increasingly common. More research is needed to assess how this intervention will affect the QoL of these patients.

Quality of life and implantable devices — Left ventricular assist device

Left ventricular assist device (LVAD) systems are used as a bridge to transplantation, destination therapy, recovery or to candidacy. LVAD is a special pump that supports the left ventricle by transferring the blood through a mechanical device from the ventricle into aorta Recently, more than half of LVAD implantations has become a destination therapy. Maclever and Ross [55], having analyzed a review of LVAD clinical trials, showed that patients with LVAD demonstrated an early improvement in KCCQ 1 to 3 months after implantation, which stayed for the time of device support. Besides, HeartMate II–DT (destination therapy) arm of HeartMate II trial KCCQ score improved from baseline 27 to 63 in 3 months with $p < 0.001$ [56].

The negative impact on the patients' lives may relate to possible complications. Implantable devices are foreign bodies so they may induce a local and/or systemic infection. In some cases, apart from administering hospital antibiotic therapy, it may also be necessary to remove the device, which may have a negative impact not only on the health but also on the well-being of the patient. Bleeding from the gastrointestinal tract or into the central nervous system is another significant complication. This is due to the application of anticoagulants and changes in the circulatory system, possibly caused by less physiological continuous flow in most LVAD systems. On the other hand, implantable devices can also lead to blood clots that in turn lead to strokes. It should also be mentioned that potential mechanical complications, e.g., damage to the device, damage to the electrodes, the action of electromagnetic radiation, which may lead to malfunction of the device and other complications. To prevent the above potential side effects, patients are required to avoid certain activities, involving as submersing in water, such as swimming or having a bath in a bathtub. They are not allowed to practice contact sports, do jumps and undergo magnetic resonance imaging examinations. Every patient has to learn about their own device, keep additional batteries and supplies and put on new sterile dressings every day. All those factors may have an influence on their QoL.

Discussion

Quality of life in patients with HF depends on many physical and psychological factors, including disease stage, age, sex, comorbidities, social and economic status, therapeutic processes, mental state, etc. Many studies show that QoL of patients with HF is relatively poor in comparison to QoL of healthy patients or patients with other diseases, like thalassemia, diabetes, certain types of cancer. Lower QoL correlates with longer hospitalization and higher mortality rates and generates costs for healthcare systems, families and patients. Also, patients with more severe HF symptoms and no social support demonstrated worse QoL.

Due to the lack of understanding of HF and its effects in the general population, there is a lot of anxiety about the disease progression in both patients and their caregivers. It would be useful if psychosocial care and support of such patients were better defined, as it happens in other life-limiting diseases, such as cancers. In this area, patient associations and support groups can play a role in helping the patients understand their disease, treatment and expectations. Fortunately, for some time now, due to new treatment methods, the prognosis and survival rate in patients with HF has been significantly improving, hereby also improving their QoL [56–62].

It is very important for a patient to understand and accept HF and closely cooperate with the doctor during disease treatment. Symptoms of the disease appear in a different order in different HF patients, which makes the disease unique for each patient. Gaining a relevant knowledge about the disease is one of the first steps in treating HF and improving the quality of patients' lives. Diligent monitoring of symptoms is highly important. The patient should be aware of possible symptoms like dyspnea, weight loss or gain, which, if measured every day, can help to prevent deterioration of disease symptoms. Sedentary lifestyle can negatively affect the disease itself and QoL. Yet, patients often isolate themselves and limit their activities as they fear disease progression or sudden death. Therefore, due to the chronic nature of HF, it is extremely important to be supported by the family and friends as it may also improve QoL [63, 64].

It is important that patients with HF should not only receive optimal pharmacotherapy and treatment with implantable devices but also be provided with appropriate care, multidisciplinary care including, among others, rehabilitation, education, and psychosocial support. Recently, due to the pandemic of COVID-19 and its consequences, some chronically ill patients had poorer access to medical care. Hence, their therapy might not have been optimal, and their prognosis and QoL decreased.

The importance and potential perspectives of QoL were highlighted in the results of a cohort study conducted by Greene et al. [65] on 2,872 US outpatients with HFrEF. Changes in KCCQ-OSS from baseline to 12 months have a greater prognostic value than changes in the NYHA class. Greene et al. [65], on the basis of clinical practice-based population, revealed that an improvement by 5 or more points in KCCQ-OSS was independently associated with decreased mortality (HR 0.59; 95% CI 0.44–0.8; $p < 0.001$) and mortality or HF hospitalization (HR 0.73; 95% CI 0.59–0.89; $p = 0.002$), whereas such a correlation was observed in the improvement of the NYHA class.

Innovative treatment options are constantly being designed for HF patients [66–68]. They improve their prognosis and QoL. However, some patients, despite receiving made-to-measure pharmacological treatment and implantable devices, do not demonstrate expected benefits. It should be remembered about providing such patients with palliative care.

Lastly, the adopted treatment program in HF should focus equally well on improving the prognosis and providing care at physical, psychological and social levels. Patients should be partners for medical personnel and should themselves take optimal, integrated decisions regarding offered procedures that are supposed to protect their health and lives. Regular assessment of patients' QoL and health promotion are key measures to increase their prognosis and survival.

Conclusions

Quality of life in HF is an extremely important element of the course of the disease and treatment process. The higher level of QoL is associated with the better acceptance of the disease and better prognosis. A new therapeutic option, especially pharmacotherapy (ARNI, SGLT2 inhibitors or ferric carboxymaltose) and devices, enable to improve QoL in HF.

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TECHNOLOGY NOTE

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Electrocardiogram recording vest: A useful tool in explaining recurrent syncope

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Finding the underlying cause of recurrent unexplained syncope is often exhaustive work requiring many diagnostic measures. One of these is the prolonged electrocardiographic monitoring necessary to observe a correlation between the symptoms and electrocardiogram (ECG) abnormalities and therefore confirm arrhythmic syncope [1–3]. Current guidelines recommend considering Holter monitoring in patients who have frequent syncope or presyncope (≥ 1 per week) or external loop recorder (ELR), early after the index event, in patients who have an inter-symptom interval ≤ 4 weeks [4]. ELR devices can work as an event recorder activated by a patient shortly after an incident or as continuous recording.

One of the available ELR devices is the Comarch CardioVest ECG recording vest (Fig. 1) [5]. The vest itself is light, easy to wear, and created from biocompatible, non-allergenic materials. It comes in variable sizes fitting patients with chest circumference from 70 to 129 cm. The device allows recording ECG signals due to the usage of special textile electrodes. The technology enables continuous ECG monitoring up to 30 days, with two independent recorders carried interchangeably — each recording up to 24 h. While one of the recorders is in use, the other one set in dock transmission station automatically sends records to a telemedicine platform.

Implemented algorithms automatically detect crucial heart arrhythmias such as pauses,

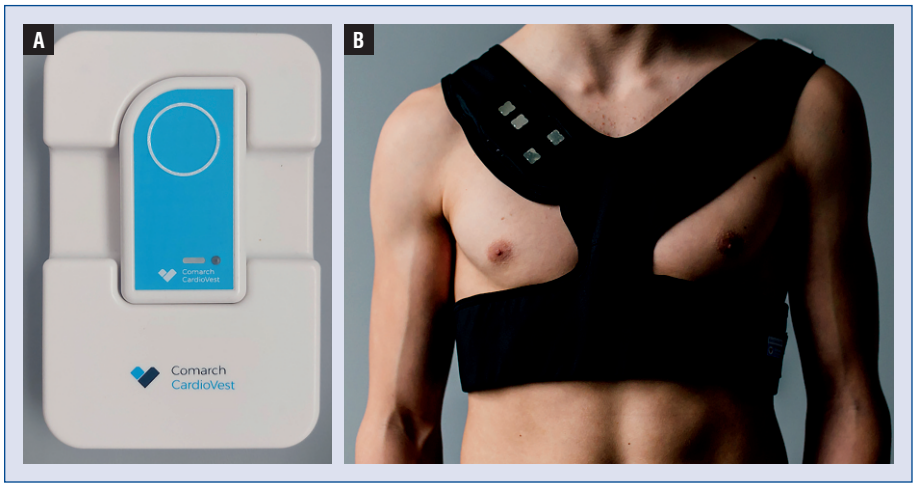

Figure 1. The Comarch CardioVest system; **A.** An electrocardiogram (ECG) recorder in dock transmission station; **B.** A vest that allows to properly attach and use the ECG recorder.

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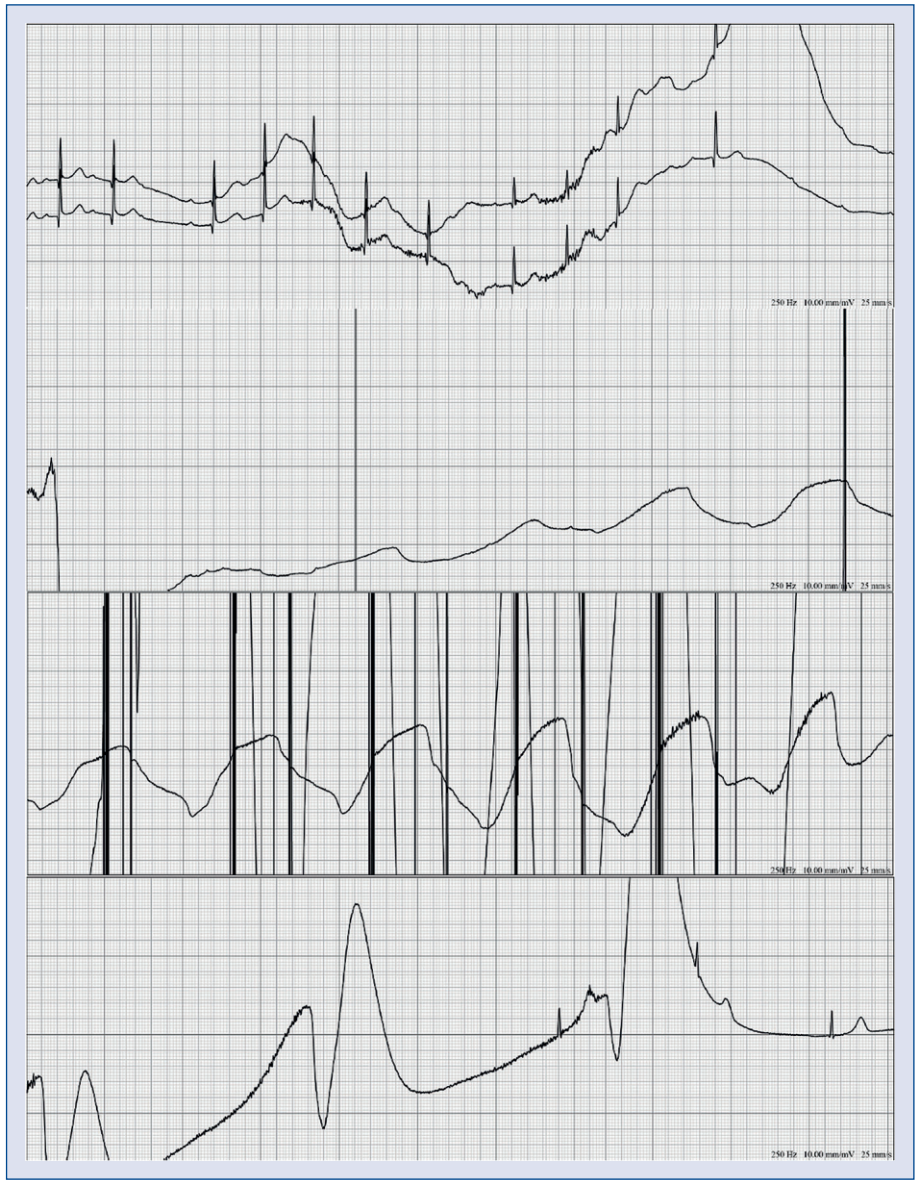

Figure 2. Elements of the 79 second pause recorded using CardioVest, Comarch.

ventricular tachycardia, atrial fibrillation (AF), or bradycardia, as well as minimal and maximal heart rate. Authorized medical personnel with access to the telemedicine platform can verify the automatic analysis, add significant ECG findings to daily reports or perform manual analysis in a case when the automatic one is not satisfactory. This solution significantly shortens monitoring of long-term ECG monitoring and allows day-by-day analysis in the case of symptoms.

Presented herein is the case of a 41-year-old woman with paroxysmal AF, with a history of cerebral ischemic stroke and percutaneous patent foramen ovale closure 3 years prior, who had been diagnosed for syncopal and presyncopal episodes since childhood. The CardioVest system has had an essential role in making a proper diagnosis in the presented case. The incidents of syncope and presyncope occurred once or twice a year, mainly after standing upright or a strong sensation of pain. They were not associated with episodes of AF or hypotonia, but were preceded by prodromal symptoms such as chest tightness, limb paresthesia, nausea and vertigo. Current pharmacotherapy (apixaban 5 mg b.i.d.) was well tolerated for many years and did not require escalation — no incidents of AF were recorded in the previous 5 years. Resting ECG showed no abnormalities.

Two head-up tilt tests were performed 4 years prior — the first one was negative, the second one was negative in the passive phase, but after nitroglycerin administration paroxysmal 3rd degree atrioventricular block (AVB) with following sinus arrest was recorded — the pause exceeded 3 s.

However, further ECG monitoring which included 7-day standard Holter ECG and event Holter ECG did not record any spontaneous arrythmias. The patient did not consent to the implantation of a loop recorder. Due to the rare frequency of symptoms, the analysis performed with ELR was necessary —use an ECG recording vest was decided upon (CardioVest, Comarch).

Prolonged electrocardiographic monitoring revealed sinus rhythm with an average rate of 60–70 bpm and episodes of 2nd degree AVB 2:1, advanced block 3:1 and 3rd degree block were recorded. Moreover, the patient reported episodes at the time of the monitoring — one presyncope, associated with the 2nd degree and advanced AVB and one syncope, associated with an episode of complete AVB with following sinus arrest with a total pause of 79 s (Fig. 2). Additionally, the recording shows artifacts which may correspond to a seizure. Both episodes occurred at daytime, between 8 AM and 10 AM and were preceded by similar prodromal symptoms. The device did not report the occurrence of AF.

The recording of the episode allowed for qualification of the patient to implantation of the dual-chamber pacemaker, which resulted in no further episodes of syncope in the following years.

Prolonged continuous ECG monitoring is essential in recognizing the arrhythmical cause of syncope. Using the ECG recording vest is non-invasive, easy to perform, and allows day-by--day online analysis to reveal the fast correlation between clinical symptoms and ECG findings. We believe the ECG recording vest may become one of the standard diagnostic tools of unexplained syncope of potential arrhythmic origin.

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Low-temperature electrocautery for high-risk cardiac implantable electronic device procedures

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With rising numbers of cardiac implantable electronic devices (CIEDs) implanted each year, the population of patients with those devices is growing extensively [1]. Large numbers of those patients will eventually require secondary procedures, including device replacements, or upgrades. As during passing years, the implanted systems become surrounded by adhesive tissue and fibers, the secondary procedures have been historically associated with a higher risk of short- and long-term complications, most often including lead damage. Moreover, due to comorbidities, a high percentage of patients with CIEDs are treated nowadays with anticoagulants, which increases the risk of bleeding and pocket hematoma. Thus, electrocautery is used to mitigate the risk of periprocedural bleeding. However, the use of conventional electrocautery can risk lead dysfunction due to its thermal injury.

The low-temperature electrocautery has been proven to improve local outcomes [2]. Few reports were published to date on its utilization in CIED-related procedures [3–5]. The aim of this analysis was to summarize its safety and efficacy in higher complication-risk procedures performed in a tertiary Polish center.

Between July 2021 and July 2022, a total of 150 CIED-related procedures considered as higher complication risk were performed with the use of PlasmaBlade™ low-temperature electrocautery (Medtronic, Inc., Minneapolis, MN). A higher complication risk was defined as any secondary procedure (e.g. generator replacement, device upgrade, transvenous lead extraction [TLE]), or subcutaneous implantable cardioverter-defibrillator (sICD) implantation. The choice of electrocautery was at the discretion of the operator. All similar procedures performed between January 2020, and June 2021, with the use of conventional electrocautery served as a control group.

All procedures including preprocedural antibiotics administration and management of anticoagulation were performed according to the established standards [6]. The periprocedural strategy, including capsulectomy and lead liberation were at the discretion of the operator. After completion of all procedures in the study period, each operator was asked to fill the survey on the perception and satisfaction with both types of electrocautery.

In all patients, the clinical and periprocedural characteristics were documented and summarized. As all patients after the procedures are routinely monitored in the device-focused outpatient clinic, the lead-related outcomes at follow-up could be analyzed based on the electronic records and were defined as any significant rise in lead impedance, or in pacing threshold, or the necessity for lead extraction or repeat procedure due to any causes. The routine scheme of visits places the post-procedural outpatient in-person visits at 2 weeks, 3 months, and after 6 or 12 months, depending on the type of device. The minimum follow-up was 6 months and the median 12 months. The research was performed as part of the Medical University of Silesia grant number PCN-1-083/N/0/K.

Of 150 patients, who underwent procedures with low-temperature electrocautery, the major-

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Table 1: Characteristics of patients and outcomes of procedures performed with the use of low--temperature electrocautery versus similar procedures performed in the years 2020–2021.

Demographics	N = 150	N = 436	P
Female gender	40 (26.7%)	152 (34.9%)	NS
Age [years]	71 (62–79)	74 (65–82)	NS
Procedural characteristics			
Secondary procedure (patient already with an implanted device), including TLE	136 (90.7%)	399 (91.5%)	NS
Time from baseline implantation to index procedure [years]	7 [4–8]	7 [4–9]	NS
Hematocrit at baseline [%]	41.0 [37.6–43.5]	40.5 (37.3–43.0)	NS
eGFR at baseline [mL/m^3]	60 [50–75]	60 [48–72]	NS
Lowest hematocrit during hospital stay [%]	37.6 [33.9–40.7]	37,5 (34.1–40.8)	NS
Maximal reduction in hematocrit during hospital stay [%]	2.5 [1.1–4.3]	2.6 [1.0–4.2]	NS
Hospitalization duration after the procedure [days]	1 [1–3]	2 [1–3]	NS
Procedural radiation dose [mGy]	0 [0–19]	1 [0–5]	NS
Procedural duration [min]	90 [65–130]	90 [50–100]	NS
AF on anticoagulation	62 (41.3%)	277 (63.5%)	< 0.001
Procedure types			
Generator replacement:	88 (58.7%)	316/436 (72.4%)	NS
PM replacement	45/88 (51.1%)	195/316 (61.7%)	
ICD replacement	19/88 (21.6%)	70/316 (22.1%)	
CRT replacement	24/88 (27.3%)	51/316 (16.1%)	
Device upgrade	7 (4.7%)	3 (0.7%)	NS
Lead repositioning	3 (2.0%)	8 (1.8%)	NS
Pocket revision	1 (0.7%)	4 (0.9%)	NS
sICD implantation	14 (9.3%)	36 (8.3%)	NS
TLE	37 (24.7%)	69 (15.8%)	NS
Immediate outcomes			
Pneumothorax	0/150 (0%)	0/436 (0%)	NS
Hemothorax	0/150 (0%)	0/436 (0%)	NS
Pericardial tamponade	0/150 (0%)	1/436 (0.2%)	NS
Bleeding, any	2/150 (1.3%)	10/436 (2.3%)	NS
Bleeding requiring transfusion	2/150 (1.3%)	8/436 (1.8%)	NS
Clinically significant pocket hematoma	0/150 (0%)	3/436 (0.7%)	NS
Lead dysfunction requiring acute implantation of the new lead	0/150 (0%)	4/436 (0.9%)	NS
Follow-up outcomes at 12 months			NS
Lead dysfunction	0/150 (0%)	7/436 (1.6%)	
Local or systemic CIED-related infection	0/150 (0%)	6/436 (1.3%)	
Need for pocket revision	0/150 (0%)	2/436 (0.5%)	

Data are shown as number (percentage) or median (minimum–maximum) or median [Quartile 1–Quartile 3]. Chi-square test and exact Fisher tests were used for the assessment of categorical variables, while non-paired Wilcoxon test was used to assess continuous variables after assessment of distribution normality in the Shapiro-Wilk test. AF — atrial fibrillation; CIED — cardiac implantable electronic devices; CRT — cardiac resynchronization therapy; eGFR — estimated glomerular filtration rate; ICD — implantable cardioverter-defibrillator; NS — non-significant; PM — permanent pacemaker; sICD — subcutaneous implantable cardioverter-defibrillator; TLE — transvenous lead extraction

ity (90.7%) underwent secondary procedures, including TLE, and the remaining were sICD implantations (Table 1). The median (Q1–Q3) number of years between implantation of the first device and the index procedure was 7 (4–8) years. Generator replacements constituted the majority (58.7%) of the procedures, among them, the most prevalent were pacemaker (51.1%) and cardiac resynchronization therapy (27.3%) replacements, and there were 37 TLE procedures. In general, the

procedures performed in the control group were comparable, with a slightly higher rate of generator replacements (72.4%), and a numerically lower rate of TLEs (15.8%).

The median duration, radiation doses and reductions in hematocrit during the hospitalization were comparable in both groups. However, the rates of bleeding were numerically lower in the studied group, with respectively 1.3% and 1.8% of patients in the control group requiring blood transfusion. No other major periprocedural complications were reported in the study group, with 0.9% rate of acute lead dysfunctions noted in the control group. Neither significant lead-related outcomes, nor local or systemic CIED-related infections were reported in the post-discharge follow-up of the studied group, and none of the patients required any following device-related procedures. In the control group, the rate of long-term complications was also low, with 1.6% rate of lead dysfunctions and 1.3% of device infections. The results of the query dispatched among the operators indicate that 4 of 5 would choose low-temperature electrocautery, what could be attributed to the subjectively higher lead safety and lower risk of tissue damage.

The most important benefits of low-temperature electrocautery during CIED-related surgical procedures are the reduction of the risk of lead damage during the liberation of the leads from surrounding tissues during the procedure and the reduction of the risk and intensity of periprocedural bleeding. Due to the different scheme of electrocautery pulse delivery, when compared with conventional electrocautery, it allows obtaining comparable tissue separation and cautery, while not exceeding the melting point of the majority of the materials constituting lead insulation [4]. In the sub-analysis of the WRAP-IT trial, its use was associated with a significant, 32% reduction in the incidence of any lead-related adverse events than the conventional electrocautery group [4]. In the other available literature sources evaluating low-temperature electrocautery, the risk of lead-related complications, ranged between 0.0% and 0.7%, which along with the present data, confirms that its utilization in generator replacement procedures yields high safety for leads [4, 5, 7].

The development of pocket hematoma has been identified as one of the most important risk factors of both pocket and systemic infection [8, 9]. Of 150 procedures performed in the current analysis with the use of low-temperature electrocautery, no clinically significant pocket hematoma developed, although almost 40% of patients were on anticoagulants. A recent study focused on the risk of bleeding in patients on anticoagulants after transcatheter aortic valve implantation demonstrated that the risk of pocket hematoma with low-temperature electrocautery was 1.2% [10]. As none of the patients from the studied group developed a clinically significant pocket hematoma, and the rates of hematomas from the prior studies with low-temperature electrocautery did not exceed 3.4%, it could be concluded that low-temperature electrocautery allows maintaining low risk of pocket hematoma and lead-related complications [4, 7].

Conflict of interest: None declared

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Percutaneous transaxillary approach for balloon aortic valvuloplasty and complex percutaneous coronary intervention with Impella support

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Managing complex coronary artery disease (CAD) in elderly patients with coexisting severe aortic stenosis and peripheral arterial disease can pose a significant challenge, particularly when complicated by acute coronary syndrome (ACS). Percutaneous coronary intervention (PCI) is often the preferred revascularization therapy in these situations, frequently accompanied by balloon aortic valvuloplasty (BAV) [1, 2]. However, for patients with left main stenosis (LMS), poor left ventricular function, and multiple comorbidities, PCI carries a high risk and may require mechanical circulatory support, such as the Impella pump [3]. The percutaneous transaxillary approach (PTAA) offers a promising alternative for large-bore interventions in patients without femoral access [4]. However, limited data are available on the effectiveness of PTAA in cases involving the aforementioned clinical issues.

We analyzed a series of 5 patients with complex LMS, severe aortic stenosis, and significant peripheral arterial disease, who were treated using PTAA. According to the Heart Team's recommendations, all patients were unsuitable for cardiac surgery but were eligible for PCI with Impella CP support. Given the complexity of the interventions and high risk of acute kidney injury, the Heart Team did not recommend ad-hoc transcatheter aortic valve implantation (TAVI), but instead advocated for BAV as a bridge to TAVI. Computed tomography scans revealed significant stenoses in iliac and femoral arteries, and concomitant aortic aneurysm with intraluminal thrombus in 2 cases. Because large-bore femoral access was not feasible in all patients, BAV and Impella implantation were performed using PTAA under local anesthesia, following a previously described method [5]. All patients provided their written informed consent for the procedure. The study was conducted in compliance with the principles of the Declaration of Helsinki. Due to its retrospective nature, it was not subject to the Medical Research Involving Human Subjects Act, as per the Institutional Review Board.

Percutaneous transaxillary approach began with the insertion of a long 0.035-inch guidewire through the radial access, which served as a safety wire to enable balloon delivery or stent placement in case of complications. Subsequently, retrograde angiography was performed by injecting contrast (diluted with saline in a 1:1 ratio) through the radial artery to visualize the arterial anatomy. The axillary artery was punctured near the clavicle (i.e., the first segment of axillary artery) under ultrasound guidance, and 2 Proglide sutures were deployed for later access closure. A peel-away 14F Impella sheath was inserted, and BAV was performed. For all cases, a semi-compliant Valver balloon (Balton) 20/40 mm was used, which was inflated to 5 atm, resulting in a balloon diameter of 22 mm, and finally, an Impella CP SmartAssist was implanted. Successful PCI of the left main coronary artery was carried out in all subjects, and in some cases, multivessel PCI was performed. Upon confirming the patient's stable condition, the Impella was removed immediately after the procedure. The axil-

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Table 1. Characteristics, procedure details, and outcomes of 5 patients undergoing balloon aortic valvuloplasty and complex percutaneous coronary intervention with Impella support *via* percutaneous transaxillary approach.

Patients' characteristics		Procedure and outcomes	
Age [years]	78 (73–84)	PCI of LM	5 (100)
Male/female	3 (60)/2 (40)	PCI of LAD/Cx/RCA	5 (100)/1 (20)/2 (40)
Body mass [kg]	76 (48–105)	IVUS/rotablation/IVL	5 (100)/3 (60)/1 (20)
BMI [kg/m^2]	26 (22–34)	Swan-Ganz	3 (60)
Hypertension	5 (100)	Final LVEF [%]	42 (30–60)
Prior stroke	1 (20)	Final mean AGr [mmHg]	35 (24–40)
Heart failure	5 (100)	Final SYNTAX I	12 (8–35)
NYHA class	3 (1–4)	Diameter of AxA [mm]	6 (5–7.5)
PAD	5 (100)	Left/right axillary access	4 (80)/1 (20)
Diabetes	3 (60)	AxA–subclavian angle [deg]	85 (79–108)
COPD	0 (0)	Radial access for PCI	3 (60)
Renal failure	4 (80)	Heparin [IU]	12500 (9500–15000)
Risk of AKI (Mehran) [%]	57.3 (57.3–57.3)	Contrast volume [mL]	290 (260–463)
GI disease/prior bleeding	4 (80) / 2 (40)	Intra-procedural fluid [mlL]	1000 (1000–2500)
Malignancy	2 (40)	Procedure time [min]	190 (150–254)
Prior MI	3 (60)	Radiation dose [mGy]	1490 (624–4912)
Prior PCI	3 (60)	Number of proglides	2 (2–3)
Prior CABG	1 (20)	Angioseal usage	3 (60)
Atrial fibrillation	2 (40)	Protamine usage	3 (60)
Pacemaker	1 (20)	Access site closure failure	0 (0)
Left main stenosis	5 (100)	Vascular surgery	0 (0)
Three-vessel disease	5 (100)	Hematoma	2 (40)
ACS	3 (60)	Hemoglobin drop [g%]	1.5 (1–5.3)
NSTEMI	2 (40)	Blood transfusion	2 (40)
UNA	1 (20)	Creatinine change [mg%]	0.06 (–0.17–0.19)
SYNTAX I	50 (33–64.5)	AKI	0 (0)
EuroSCORE II	18.51 (6.12–74.5)	Pacemaker implantation	0 (0)
STS Score	7.729 (4.152–15.69)	Peri-procedural MI	0 (0)
LVEF [%]	40 (15–56)	Peri-procedural stroke/TIA	0 (0)/0 (0)
Mean AGr [mmHg]	40 (15–56)	Brachial plexus injury	0 (0)
AVA [cm^2]	0.46 (0.3–0.5)	Hospital stay [days]	15 (6–26)
hsTNT [ng/L]	53.5 (31.6–1111)	Final NYHA class	1 (2–3)
ProBNP [ng/L]	5317 (1130–20823)	Hospital death	0 (0)

Values are number of cases (percentage) or median (lower–upper limit). ACS — acute coronary syndrome; AGr — aortic gradient; AKI — acute kidney injury; AVA — aortic valve area; AxA — axillary artery; BMI — body mass index; CABG — coronary artery bypass grafting; COPD — chronic obstructive pulmonary disease; Cx — circumflex artery; GI — gastrointestinal; hsTNT — high-sensitivity troponin T; IVL — intravascular lithotripsy; IVUS — intravascular ultrasound; LAD — left anterior descending artery; LM — left main; LVEF — left ventricular ejection fraction; MI — myocardial infarction; NSTEMI — non-ST-segment elevation myocardial infarction; NYHA — New York Heart Association; PAD — peripheral arterial disease; PCI — percutaneous coronary intervention; ProBNP — pro-B-type natriuretic peptide; RCA — right coronary artery; STS — Society of Thoracic Surgeons; TIA — transient ischemic attack; UNA — unstable angina

lary access was closed with Proglides, although AngioSeal was used in 3 cases to stop oozing. In 1 case, a peripheral 7.0 mm balloon was used to tamponade the axillary artery, and compression was applied using a Proglide's pusher and hemostatic sponge to address residual bleeding, following the method described elsewhere [6]. None of the patients required vascular surgery, stent grafts, or any other intervention. In each case, the integrity of the closure site was documented angiographically via retrograde contrast injection through the radial artery. Table 1 presents the patients' characteristics, procedural details, and outcomes.

All patients were elderly and had multiple comorbidities and complex coronary lesions, with the majority presenting with ACS. Consequently, the opinion of cardiac surgeons, the EuroSCORE, and the Society of Thoracic Surgeons score indicated that cardiac surgery would pose an unacceptable risk. Their primary issue was highly symptomatic CAD involving LMS, necessitating revascularization. As such, the Heart Team recommended PCI with BAV as the initial procedure, followed by staged TAVI. Two of our patients presented with chronic coronary syndrome and were in preparation for oncological treatment. In light of the ACTIVATION study, the benefit of PCI in stable CAD before TAVI remains a subject of debate [7]. However, given the patients' conditions, the Heart Team advocated for complete revascularization and BAV for both. Following PCI and BAV, all patients experienced significant improvement with release of angina and decrease in New York Heart Association class, along with an increase in the left ventricular ejection fraction, and they were all discharged home. One patient underwent successful staged TAVI via the same transaxillary access, while three others are under close monitoring in preparation for TAVI. Unfortunately, one patient died due to heart failure deterioration one month after the procedure.

The percutaneous transaxillary approach has proven to be a safe procedure for structural and complex coronary cardiac interventions. Both axillary arteries are suitable for this approach, but the left one is preferred due to the smoother arterial trace. It is noteworthy that even a quite sharp angle between the axillary and subclavian arteries (Table 1) does not preclude Impella insertion. Although challenging for elderly patients, none of them required general anesthesia, and they all cooperated well. However, the procedures were lengthy, lasting up to 4 hours, and were associated with high radiation doses and contrast volumes. Despite the very high risk of post-PCI acute kidney injury (57.3% in all subjects according to the Mehran risk score), no such event occurred, which may be attributed to the renal protective effects of the Impella pump and adequate hydration — the majority of patients were monitored with a Swan-Ganz catheter [8]. Two patients required red blood cell transfusion due to significant hematoma formation. Overall, two major and one minor vascular complications according to VARC-3 criteria, and one type 1 and two type 3b bleeding events as per BARC definition had to be recognized [9, 10]. There were no other adverse events such as myocardial infarction, stroke, or brachial plexus injury. Percutaneous access site closure was successfully achieved in each case, and no surgical intervention was needed. Based on this data, we conclude that PTAA is a viable alternative for large-bore complex cardiac interventions in elderly patients with high risk and lack of femoral access.

Conflict of interest: None declared

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RESEARCH LETTER

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Bicuspid aortic valve in transplanted hearts. Systematic study

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Bicuspid aortic valve (BAV) is the most frequent congenital cardiac anomaly, affecting 1–2% of the population [1]. The abnormality is followed by an increased risk of many potentially severe complications, such as BAV degeneration, dilatation of the ascending aorta (AAo) and others [2]. The recently published International Consensus Statement on nomenclature and classification of BAV distinguishes three types of BAV with specific phenotypes [3]. Although in many cases BAV may have a severe clinical outcome, in other patients it can go undetected. Orthotopic heart transplantation (OHT) remains the gold standard treatment of end-stage heart failure (HF). The presence of BAV in a donor-heart is not a contraindication for OHT, unless BAV is severely diseased. According to available research, only single reports of BAV in transplanted hearts have been reported to date.

Discharge summaries were retrospectively screened and the reports of transthoracic echocardiography (TTE) of 623 OHT-recipients in the electronic database from a tertiary high-volume heart center for the presence of BAV were included in the study. Key word: "bicuspid aortic valve" with its abbreviations and grammatical variations were used during screening. This database contains discharge summaries from January 2008 to October 2023. Nonetheless, some of these patients underwent OHT before 2008 (some of them are from another cardiovascular center, who were then followed-up at the present institution). All OHT-patients underwent typical of follow-up procedure and every patient underwent several echocardiographic assessments after OHT. All post-OHT TTE patients were screened for the presence of BAV. Only the last TTE was included in the results of the identified OHT-patients with BAV.

Six OHT-recipients (5 males) with BAV in transplanted hearts were identified. They ranged from 12 to 65 years of age. The follow-up was from 1.0 year to 21.0 years (Table 1). The prevalence of BAV among transplanted (donor) hearts was 0.96% (6/623).

Patient 1. He underwent OHT due to ischemic cardiomyopathy. Risk factors included male sex, diabetes mellitus and hypertension. Recent TTE (21 years after OHT) revealed degenerated and calcified BAV-fusion of the right coronary cusp (RCC) with the left coronary cusp (LCC), aortic peak pressure gradient of 17 mmHg, dilated AAo 39 mm (without any change in diameter over the last 7 years), moderate/significant tricuspid regurgitation and hypertrophied left ventricle (LV). Otherwise, systolic function of both ventricles was preserved.

Patient 2. He underwent OHT due to congenital heart defects. His recent TTE (3 years after OHT) showed BAV-fusion of the non-coronary cusp (NCC) with RCC, negligible aortic regurgitation (AR), discrete AAo dilatation 37 mm (without any change in diameter over the last 12 years), and impaired systolic function of the right ventricle (RV). Otherwise, LV systolic function was preserved.

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Table 1. Summary of patients with bicuspid aortic valve in transplantaed (donor) heart.

Patient	Sex	Age at OHT, years	Reason for OHT	Time of follow-up after OHT, years	Type of BAV (fusion)
1	M	49	Ischemic cardiomyopathy	21	RCC-LCC
2	M	29	CHD	3	NCC-RCC
3	M	48	Ischemic cardiomyopathy	15	RCC-LCC
4	F	12	Acute myocarditis	1.6	RCC-LCC
5	M	28	CHD	3.2	NCC-RCC
6	M	65	DCM	1.0	RCC-LCC

BAV — bicuspid aortic valve; CHD — congenital heart defect; DCM — dilated cardiomyopathy; F — female; LCC — left coronary cusp; M — male; NCC — non-coronary cusp; OHT — ortothopic heart transplantation; RCC — right coronary cusp

Patient 3. He underwent OHT due to ischemic cardiomyopathy. His recent TTE (15 years after OHT) revealed BAV-fusion of RCC-LCC, with mild to moderate AR, LV hypertrophy (14 mm). Sinus of Valsalva was mildly dilated (46 mm) and AAo was normal (without any change in diameter over the last 10 years). Systolic function of both ventricles was mildly impaired.

Patient 4. She underwent OHT due to acute myocarditis complicated by cardiogenic shock, requiring 4-months support by an LV assist device while on the OHT waiting list. During that period, she experienced two ischemic strokes. Post-OHT course was complicated by rupture of AAo, requiring two re-do operations with supra-aortic prosthesis of AAo. Her recent TTE (1.6 years after OHT) revealed BAV-fusion of RCC-LCC with negligible AR, impaired RV systolic function and supra-valvular aortic gradient at the prosthesis (41 mmHg). Otherwise, LV systolic function was preserved.

Patient 5. He underwent OHT due to congenital heart defects. His recent TTE (3.2 years after OHT) revealed BAV-fusion of NCC-RCC with dilated AAo (41 mm without any change in diameter over 3.2 years). Systolic function of RV was impaired, while LV systolic function was preserved.

Patient 6. He underwent OHT due to dilated cardiomyopathy. His recent TTE (1 year after OHT) revealed BAV-fusion of RCC-LCC, mild to moderate AR, dilated AAo (44 mm without any change over 1 year) and impaired RV systolic function. Otherwise, LV systolic function was preserved.

Very few papers have shed light on the natural history of BAV in transplanted hearts. Some points are worth emphasizing, namely:

— Type of BAV in transplanted heart. All presented patients showed two types of BAV: fusion of NCC-RCC and fusion of RCC-LCC;
— Degeneration of BAV in transplanted heart. Given the rarity of reported BAV in transplanted heart, its natural history and the impact of immunosuppressive drugs on BAV remains largely unknown. The first patient had already developed BAV degeneration (although insignificant) during 21-years of observation. When there is significant BAV degeneration, re-do intervention may be needed. Although successful surgical BAV replacements in OHT-recipients were previously reported [4, 5], nonetheless transcatheter aortic valve replacement (TAVI) seems to be a treatment of choice for degenerated BAV in transplanted heart [6]. Of note, mid-, and long-term results of TAVI in OHT recipients remain unknown;
— Dilatation of AAo in OHT-recipients of donor-heart with BAV. 4 patients (1, 2, 5, and 6) presented with modest AAo dilatation diagnosed before OHT, without any change during follow-up after OHT. To date nothing is known about AAo diameter over time in recipients of donor-heart with BAV;
— What is done when donor-heart presents with already degenerated BAV (before OHT)? Elde et al. [7] published an interesting report of an OHT-recipient. During peri-OHT work-up degenerated BAV was discovered and replaced by a bioprosthetic valve. Then the donor-heart with new bioprosthesis was implanted to the patient, who remained healthy for 12 months after OHT [7]. Similarly, Saito et al. [8] reported on a patient who received a donor-heart with a mechanical aortic valve (implanted after harvesting the organ). In these both cases the long-term follow-up is unknown.

The retrospective nature of the study has inherent limitations. This study did not specifically analyze every TTE, but instead specific keywords were searched for (BAV with its grammatical variations and abbreviations) in post-OHT TTE reports.

Conflict of interest: None declared

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Veno-arterial extracorporeal membrane oxygenation circuit as second vascular access for transcatheter aortic valve replacement

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A 65-year-old man, known for stage-IV chronic obstructive pulmonary disease and high gradient severe aortic stenosis presented with respiratory failure secondary to heart failure. Echocardiography showed a reduced left ventricular ejection fraction (25%) and a mean gradient at 23 mmHg. The patient developed multiple organ failure with acute renal failure, hepatic cytolysis and pulmonary edema requiring intubation.

A computed tomography scan showed an aortic root compatible with transcatheter aortic valve replacement (TAVR) (calcium score: 6161 HU) (Fig. 1A, C). The vascular access assessment showed significant stenosis of the right iliac artery and both subclavian arteries. It was decided to urgently perform transfemoral TAVR under veno-arterial-extracorporeal membrane oxygenation (ECMO) considering the patient's hemodynamic and respiratory instability.

Both femoral arteries were punctured under echo-guidance. Balloon dilation of the right iliac artery stenosis was performed before the 14F-eSheath insertion (Fig. 1D–G). The 15F-arterial ECMO cannula was inserted through the left femoral artery.

The second vascular access required during TAVR procedure (i.e.; for aortic root angiogram) was performed through the ECMO circuit tubing at the segment of the reinjection cannula using the Seldinger technique to insert a 6F-sheath (Fig. 1B). No bleeding was observed around the sheath.

After the Sapien-3 implantation, the ECMO circuit was briefly clamped and the portion of the ECMO cannula with the 6F-sheath was cut (Fig. 1B). Finally, the ECMO circuit was reconnected and unclamped.

The puncture of the ECMO circuit tubing at the segment of the reinjection cannula to obtain an arterial vascular access is feasible and safe.

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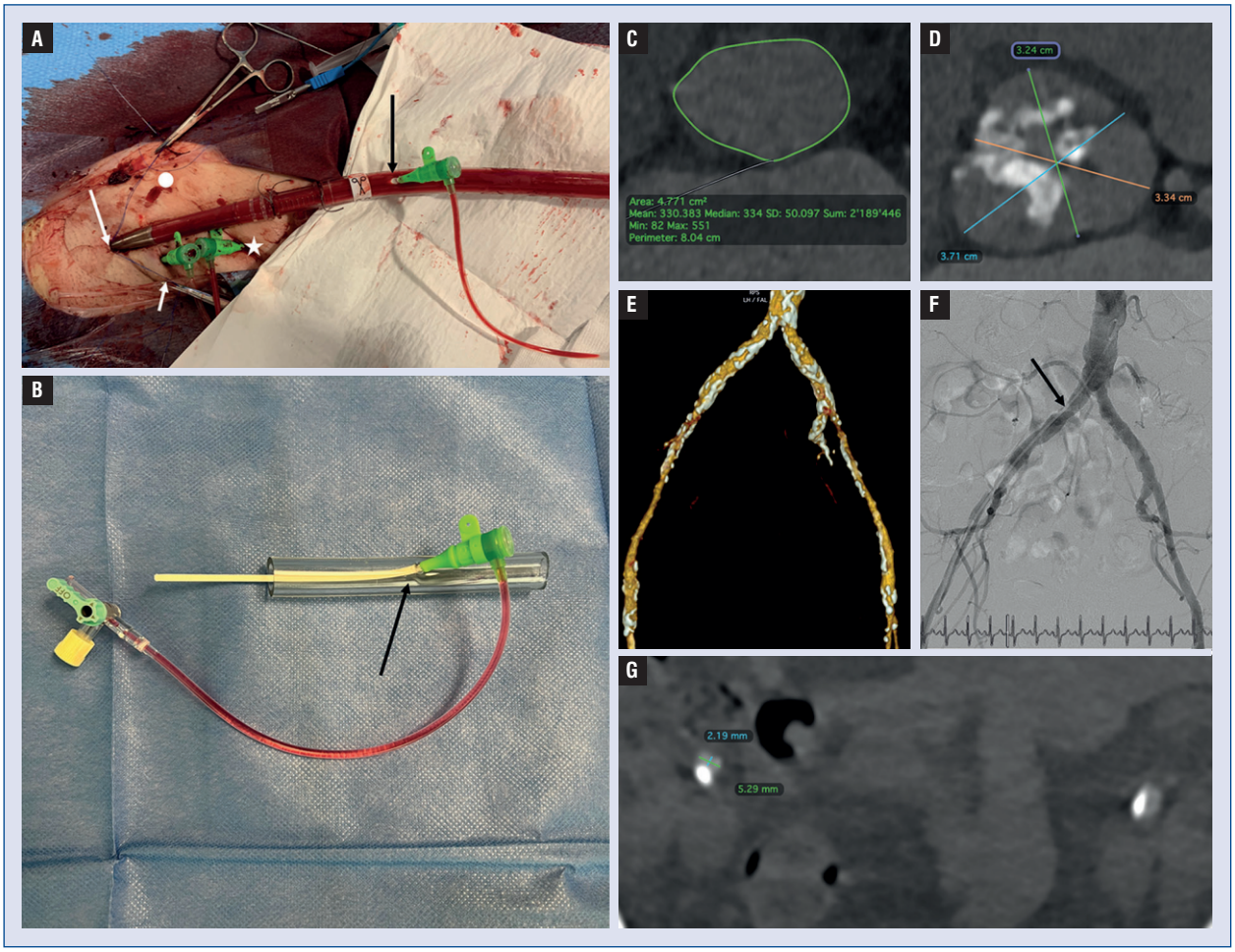

Figure 1. A. A 6F Terumo femoral introducer sheath (black arrow) was introduced in the circuit proximal to the connection to the arterial canula using a regular 18 G Seldinger Angiokard needle and a regular 0.35 wire. 6F-sheath inserted in the femoral vein (short white arrow). Reperfusion canula of the extracorporeal membrane oxygenation (ECMO) circuit inserted in the superficial femoral artery (white asterisk). 15F-ECMO reinjection canula access pre-closed using two ProStyle (white dot); **B.** Portion of the ECMO circuit with the 6F-sheath cut from the ECMO circuit (black arrow); **C.** Annulus sizing using the OsiriX software; **D.** Sinus of Valsalva measurements using the OsiriX software (green: left-, yellow: right- and blue: non-coronary cusps); **E.** Computed tomography scan three-dimensional reconstruction of the aorto-ilio-femoral vascular bed showing extensive calcification (white plaques); **F.** Aorto-ilio-femoral aortography showing severe calcified stenosis of the right common iliac artery; **G.** Measurement of the right common iliac artery.

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Myocarditis after mRNA COVID-19 vaccine administration in adult female

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This case study presents a 37-year-old female devoid of antecedent cardiovascular pathology. The subject was hospitalized following the manifestation of fatigue, dyspnea, and peripheral edema. It was observed that her symptoms began shortly (4 days) after receiving her second mRNA COVID-19 vaccination (BNT162b2 — 30 μg). Natriuretic peptides level was 1800 pg/mL while high sensitivity troponin T was normal. Electrocardiogram exhibited a normal electrical activity. The echocardiography demonstrated enlargement of the left ventricle (LV), 58 mm in diastole and 48 mm in systole, along with impaired function indicated by a LV ejection fraction (LVEF) of 30% and a global longitudinal strain (GLS) of –10% (Fig. 1A). Comprehensive infectious tests were conducted, and no communicable agents were detected. Heart failure pharmacology commenced, bisoprolol 5 mg, perindopril 2.5 mg, eplerenone 50 mg, empagliflozin 10 mg and ivabradine 5 mg bid. 44 days post-symptom onset, magnetic resonance imaging depicted intramural late gadolinium enhancement in the interventricular septum's basal and middle segments, alongside a dilated LV (volumes in diastole and systole: 252 mL, 159 mL) as well as an enhanced LVEF at 37% (Fig. 1C, D; **Suppl. Video 1**). Six months later, during follow-up, the LV systolic function improved, reaching an EF of 50% and GLS of –17.5% (Fig. 1B). Additionally, N-terminal-pro-B-type natriuretic peptide reduced by 218 pg/mL, and the symptoms decreased to first New York Heart Association class. This case underscores the likelihood of reversible dysfunction of the LV, likely tied to myocarditis following vaccination.

Conflict of interest: None declared

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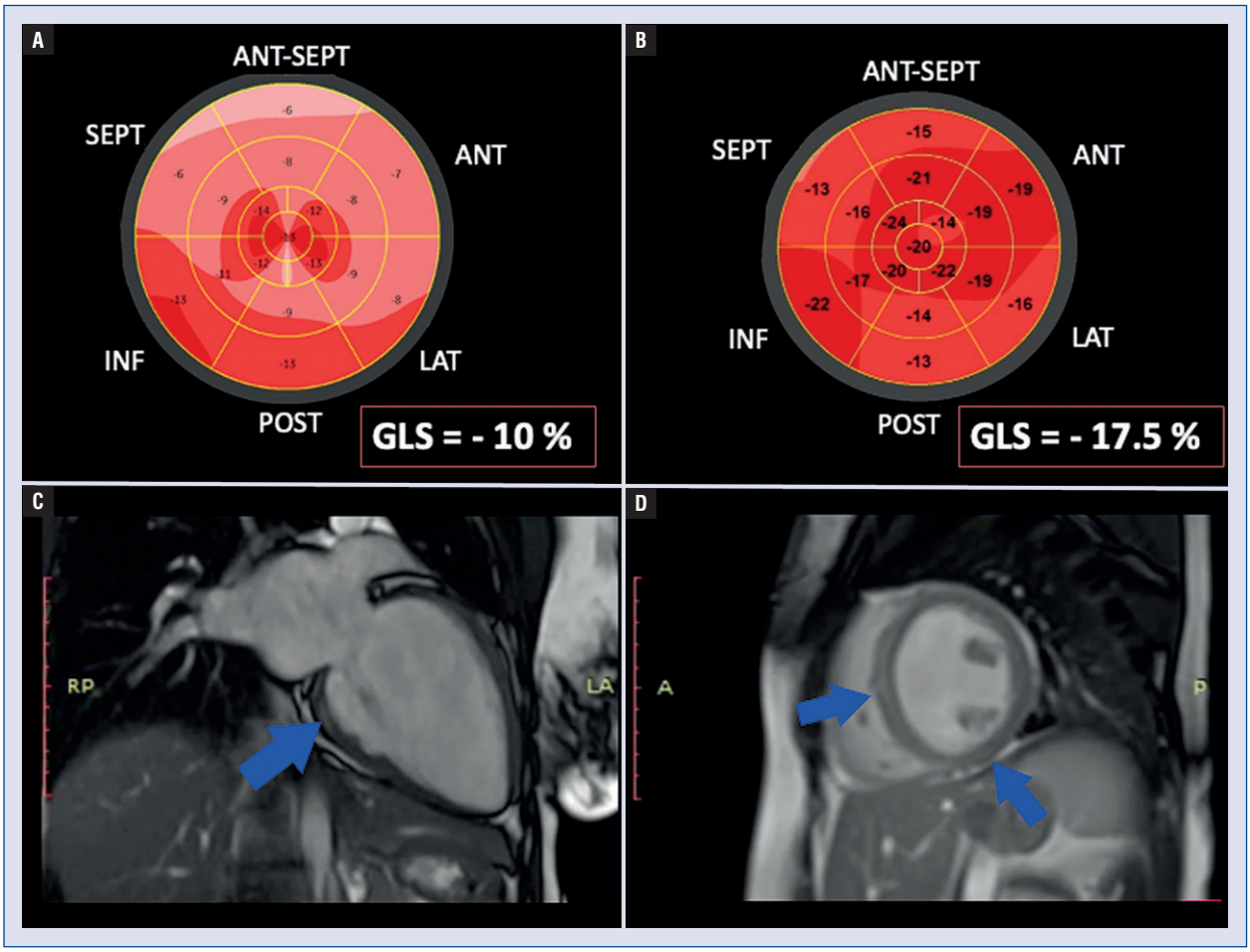

Figure 1. A. Left ventricular global longitudinal strain polar map, 4 days after vaccination; **B.** Left ventricular global longitudinal strain polar map after 6 months of follow-up; **C.** Late gadolinium enhancement (blue arrows) in magnetic resonance imaging — 2-chamber view, 44 days after vaccination; **D.** Late gadolinium enhancement (blue arrows) in magnetic resonance imaging — left ventricular short axis, 44 days after vaccination.

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A giant primary monophasic synovial sarcoma in the mediastinum

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A 32-year-old pregnant woman presented with bilateral lower extremity edema and was found to have an anterior and middle mediastinal mass on echocardiographic examination. Subsequently, the patient underwent caesarean section at 35 weeks of gestation and was referred to our hospital after delivery. Transthoracic echocardiography showed a large, cystic-solid space-occupying lesion situated anterosuperior to the heart and compressed the cardiac chambers and great vessels (Fig. 1A–D). An irregular mass with suture growth along the large vascular space in the middle and superior mediastinum and pleural effusion were noted on computed tomography (CT). Contrast-enhanced CT examination displayed the mass with heterogeneous enhancement of the solid components (Fig. 1E, F). For a better evaluation of the primary tumor and distant disease, positron emission tomography-CT (PET-CT) imaging was performed. PET-CT imaging revealed high 18F-FDG uptake of solid components in the mass, consistent with malignant tumor lesions without distant metastasis (Fig. 1G).

The cardiovascular surgeons opted for surgical resection of the mass. The postoperative pathological and immunohistochemical analysis indicated the extremely rare primary mediastinal monophasic spindle cell type synovial sarcoma (SS) with cystic degeneration (Fig. 1H). Fluorescence in situ hybridization demonstrated the presence of SS18 gene translocation in the SS (Fig. 1I). The patient was discharged half a month after surgery.

Synovial sarcoma is an extremely rare type of malignant mesenchymal tissue cell tumor and rarely appears in the mediastinum and pericardium. This case highlights the utility of multimodality imaging in the adjuvant definitive diagnosis and treatment planning of the mediastinal SS.

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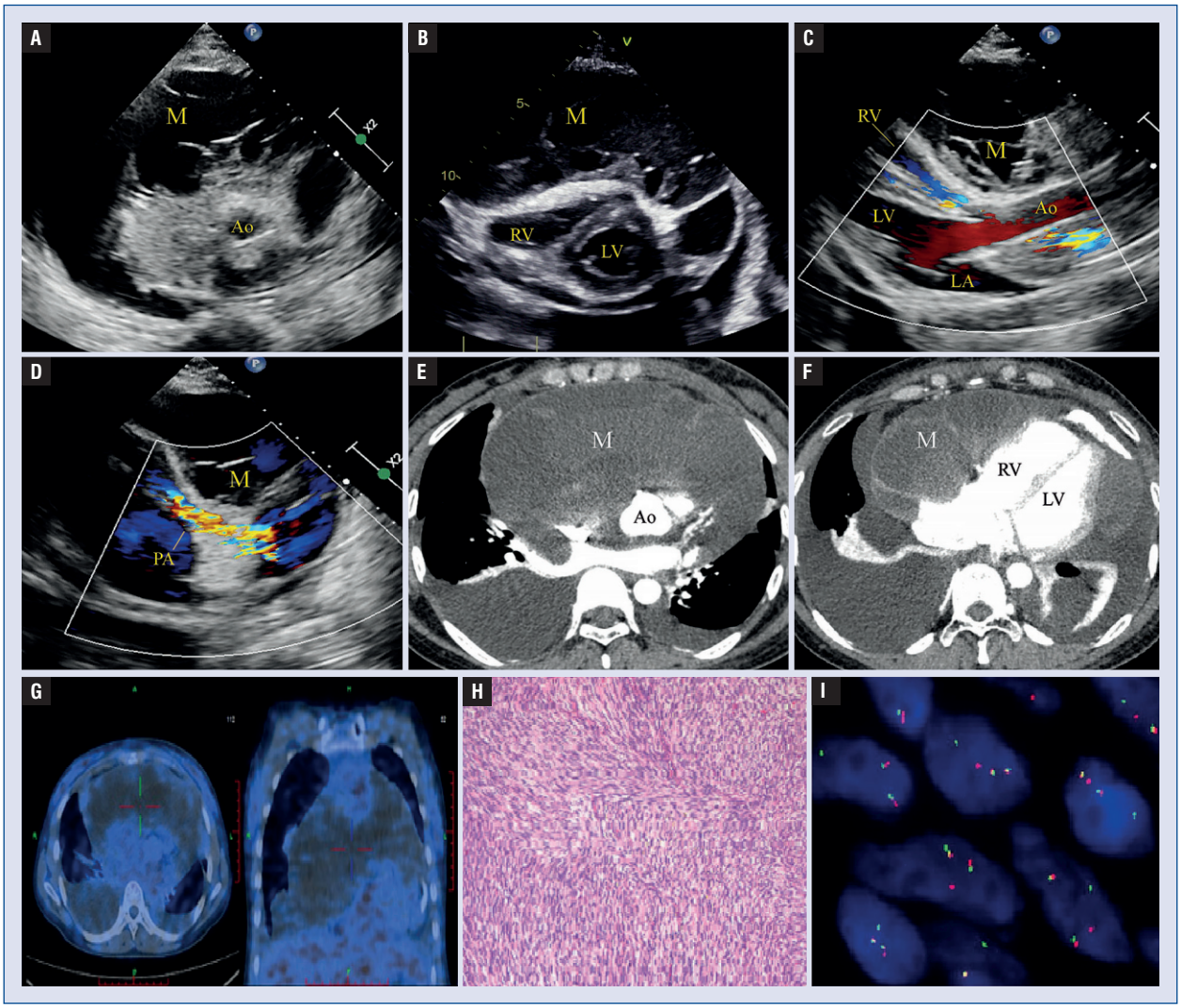

Figure 1. Multimodality imaging and histopathological findings; **A–D.** Transthoracic echocardiography indicating a large, cystic-solid space-occupying lesion situated anterosuperior to the heart and compressed the cardiac chambers and great vessels; **E, F.** Axial contrast-enhanced computed tomography (CT) examination showing the heterogeneous enhancing mass in the mediastinum; **G.** Positron emission tomography-CT revealing a hypermetabolic mass in the pericardium and superior mediastinum; **H.** Histology of the surgical specimen indicating the monophasic spindle tumor cells; **I.** Fluorescence in situ hybridization displaying the presence of SS18 gene translocation; Ao — aorta; LA — left atrium; LV — left ventricle; M — mass; PA — pulmonary artery; RV — right ventricle; SS — synovial sarcoma.