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Coronary Vasospasm and Cardiovascular Outcomes in Patients with Isolated Myocardial Bridging: A Retrospective Study

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Original Article

**Coronary vasospasm and cardiovascular outcomes in patients
with isolated myocardial bridging: A retrospective study**

Running title: CVS and cardiovascular outcomes in MB

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ABSTRACT

Background: Mounting evidence suggests an associated between myocardial bridging (MB) and coronary vasospasm (CVS); however, no consensus has been established on whether CVS worsens clinical outcomes in patients with MB. Therefore, this retrospective study aimed to compare the long-term clinical outcomes in patients with MB based on CVS presence.

Methods: This retrospective study enrolled 254 consecutive patients with MB undergoing provocative testing for coronary reactivity between January 1, 2009 and December 30, 2015, and stratified them into 2 groups: (a) group A (with CVS, n = 168); and (b) group B (without CVS, n = 86). The primary endpoints were major adverse cardiovascular events (MACEs), a composite of cardiac death, cardiac arrest, non-fatal myocardial infarction, ischemia-driven revascularization, ischemia-driven coronary angiography, and ischemia-related hospitalization. Diverse Cox models were used to determine whether CVS independently influenced MACE.

Results: The mean age of study participants was 50.8 years, and 60.2% of them were male. The median follow-up period was 8.15 years. The rate of MACE was 35.1% and 26.7% in groups A and B, respectively. Group A had a significantly higher risk of MACE than group B (the reference group) in model 3 (hazard ratio [HR]:1.92; 95% confidence interval [CI]:1.12–3.29) and model 4 (adjusted HR: 1.94; 95% CI: 1.04–3.59).

Conclusions: The presence of CVS adversely affects clinical outcomes in patients with MB. Further prospective clinical studies are required to confirm this association.

Keywords: comparative study; coronary vasospasm; myocardial bridging; outcome assessment

INTRODUCTION

Myocardial bridging (MB) is a common congenital anomaly when the coronary artery is encased by myocardial fibers [1], causing dynamic compression during systole [2]. Although MB prevalence is not clearly defined and depends on the evaluation modalities, a meta-analysis reported an overall prevalence of 19% [3, 4]. Most clinicians believe that MB is clinically harmless [5]. However, it may be fatal, contributing to the development of myocardial infarction, fatal arrhythmia, or cardiac arrest [6]. MB is considered substantially related to coronary vasospasm (CVS) [7]. MB causes a persistent compression-relaxation movement of the coronary segment beneath it, leading to endothelial dysfunction with impaired endothelium-dependent vasodilation and resultant vascular smooth muscle cell hyperactivity [8, 9], increasing CVS risk. Despite several studies on the impact of the coexistence of MB and CVS on clinical outcomes [2, 9], no consensus has been established on whether CVS augments adverse cardiovascular events in this population. Therefore, this study aimed to compare the long-term clinical outcomes in patients with MB based on CVS presence.

METHODS

Study design and data source

In this retrospective study, we searched for all patients with MB confirmed by coronary angiography (CAG) between January 1, 2009 and December 30, 2015 using the electronic medical record database of the Chonnam National University Hospital, a tertiary cardiovascular hospital in Gwangju, Korea. This study was designed to reflect ‘real-world’ practice. Among the 1523 consecutive patients with MB, 1148 patients with isolated MB were initially selected after

excluding patients with prior percutaneous coronary intervention (PCI) or current obstructive coronary artery disease (CAD). After excluding those who did not survive during the index hospitalization or those lost to follow-up, 1074 patients were enrolled in the study. Of these, 254 patients received ergometrine provocative testing (EPT) for coronary reactivity, while 820 did not. Patients undergoing EPT were categorized into 2 groups based on CVS presence: (1) group A, with CVS; and (2) group B, without CVS.

The protocol of this study was designed in accordance with the doctrines of the Helsinki Declaration 2023 and approved by the Institutional Review Board of Chonnam National University Hospital. The need for informed consent was waived due to the retrospective nature of the study.

Definition of myocardial bridging and coronary vasospasm

MB was defined as systolic compression or a milking effect of a coronary segment. Based on several clinical studies [9, 10], CVS was defined as the provocation of > 70% transient luminal narrowing of the coronary artery during EPT, irrespective of the presence of either changes in the 12-lead electrocardiogram or provoked chest pain. At least 2 board-certified interventional cardiologists confirmed all angiographic findings.

Provocative testing for coronary reactivity

Before testing, a diagnostic CAG was performed to confirm the absence of obstructive CAD. All vasoactive (vasodilatory or vasoconstricting) medications were discontinued at least 72 hours before CAG. Coronary reactivity testing was performed by intracoronary ergometrine administration immediately after the diagnostic CAG via the transradial or transfemoral approach. Ergometrine doses of 10, 20, and 40 µg were sequentially administered into the right

coronary artery. After checking a negative or an intermediate result, or depending on the discretion of the operator, 20, 40, and 80 µg ergometrine were sequentially administered into the left coronary artery. The drug administration time was approximately 60 seconds with approximately 5-minute intervals. Continuous monitoring of arterial blood pressure and 12-lead electrocardiogram were maintained during EPT. After completion of coronary reactivity testing, nitroglycerin (0.2 mg) was administered intracoronarily, followed by repeated CAG.

Clinical data assessment and baseline covariates

Body mass index was calculated using the height and weight of the participants. Experienced clinicians and nurses participated in the history-taking process to collect clinically relevant demographic data and detailed information on medical and social history, including medical history and smoking status. Medical histories of interest included hypertension, diabetes mellitus, dyslipidemia, and cerebrovascular accident. Myocardial necrosis was defined as any increase in cardiac troponin-I or troponin-T levels during the index admission. The left ventricular ejection fraction was calculated using a two-dimensional transthoracic echocardiogram and the biplane Simpson's method. Prescribed discharge medications included antiplatelet agents, renin-angiotensin system inhibitors (RASI), statins, calcium channel blockers (CCB), beta-blockers, and long-acting nitrates. Platelet agents included aspirin, clopidogrel, and potent P2Y inhibitors (ticagrelor or prasugrel). RASI included angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers.

Study endpoints

Major adverse cardiovascular events (MACEs) were the primary endpoints. They were defined as the composite of cardiac death, cardiac arrest, non-fatal myocardial infarction

(NFMI), ischemia-driven revascularization, ischemia-driven CAG, and ischemia-related hospitalization. The secondary endpoints included all individual components of the MACEs. Ischemia-driven revascularization was defined as any event of a revascularization procedure, including PCI or coronary artery bypass graft surgery, with at least one of the following conditions: (1) recurrent chest pain, (2) positive noninvasive testing, and (3) positive invasive physiological assessment. Ischemia-driven CAG was defined as any CAG event caused by recurrent chest pain. Ischemia-related hospitalization was defined as any hospital admission or emergency department visit for angina or angina-equivalent symptoms, with or without objective evidence of myocardial ischemia.

Statistical analysis

Categorical data are expressed as frequencies and percentages, and continuous data are expressed as means with standard deviations. We used Pearson's chi-square test, Fisher's exact test for univariate analyses, or the Mantel-Haenszel linear-by-linear association for categorical items. We used a multivariate Cox proportional hazard regression model, a commonly used model for survival data analysis, to assess the relationship between CVS presence and each outcome event after adjusting for baseline covariates.

We applied different Cox models to demonstrate the consistency and robustness of our analyses. Model 1, the crude model, provided crude hazard ratios (HRs), while model 2 was adjusted for age and sex. Model 3 was adjusted for the variables in model 2, as well as smoking history, body mass index, and medical history. Model 4, the fully adjusted model, included adjustments for model 2 and 3 variables, and the presence of myocardial necrosis, left ventricular ejection fraction, and prescribed medications. Univariate predictors of the primary endpoint with $P < 0.20$ were entered into a Cox proportional hazards regression analysis with backward

elimination. In each Cox model, group B was used as the reference group; thus, each HR was determined as the event rate ratio at any given time in group A relative to group B.

We also used propensity score matching (PSM) for balancing group-by-group differences of baseline covariates and reducing the selection bias effect while estimating clinical outcomes in the observational database. The method is detailed in **Supplemental Method 1**.

The cumulative incidence of the primary and secondary endpoints is presented as time-to-event survival curves using the Kaplan–Meier method and compared among the 3 groups using the log-rank test. Data manipulation and analyses were performed using STATA version 15.0 (StataCorp, College Station, TX, United States) and SPSS version 25.0 (SPSS Inc., Armonk, NY, United States). Statistical significance was set at p-value of < 0.05.

RESULTS

Characteristics in baseline covariates

Among 1074 study participants with isolated MB, 254 (23.6%) underwent EPT (153 men, mean age 50.8 years). As illustrated in Figure 1, 168 patients were diagnosed with CVS, and 86 had no CVS. All baseline covariates of each group are listed in Table 1. Group A had a higher proportion of patients with hypertension; higher prescriptions of statins, CCB, and long-acting nitrates; and lower prescription of beta-blockers than group B. After PSM, baseline covariate differences between groups A and B were statistically balanced.

Study endpoints

Table 2 summarizes the results of the Cox regression analyses of the incidence of primary and secondary endpoints. During a median follow-up interval of 8.15 years, the rate of MACE was 35.1% and 26.7% in groups A and B, respectively. The risk of MACE was

significantly higher in group A than that in group B in model 3 and model 4 (the fully adjusted model). In these models, the risks of MACE (model 3: HR, 1.92; 95% confidence interval [CI], 1.12–3.29) (model 4: HR, 1.94; 95% CI, 1.04–3.59), ischemia-driven CAG (model 3: HR, 2.50; 95% CI, 1.05–5.94) (model 4: HR, 3.01; 95% CI, 1.15–7.86), and ischemia-related hospitalization (model 3: HR, 2.17; 95% CI, 1.24–3.82) (model 4: HR 2.10; 95% CI, 1.10–3.98) were significantly higher in group A than that in group B.

In the time-to-event Kaplan–Meier curves (Figure 2), the cumulative incidence of MACE was comparable between groups A and B ($P = 0.184$). In the PSM-matched analysis between groups A and B, the cumulative incidence of MACE was slightly higher in group A than that in group B ($P = 0.082$).

DISCUSSION

The main finding of this study was that CVS presence was associated with an increased incidence of MACE, ischemia-driven CAG, and ischemia-related hospitalization. Our analysis demonstrated that the HRs associated with these outcomes were higher in patients with CVS in the fully adjusted Cox model.

MB can induce significant but dynamic systolic compression of the coronary artery tunneled segment [11, 12]. Because MB is clinically silent and harmless in most cases [12], many cardiologists tend to endorse simple observations of this clinical finding. However, MB is also a well-established etiology of myocardial ischemia [2] and appears to be a potential threat to several cardiovascular system abnormalities, including MI, certain types of fatal arrhythmia, and cardiac arrest [4, 6].

Based on autopsy and intravascular ultrasound, the main pathological features of MB include the absence of atherosclerotic plaques from the mid to distal MB segments but their

presence proximal to MB [13–16]. This can be explained by hemodynamic forces related to the MB; thus, the MB systolic compression leads to turbulent coronary blood flow, thereby promoting plaque formation at the proximal segment of the MB site. Low wall shear stress at the proximal segment of MB may induce the release of endothelial vasoactive agents, including endothelial nitric oxide synthase, endothelin-1, and angiotensin-converting enzymes, thereby contributing to atherosclerotic plaque formation. However, high wall shear stress in the middle segment of MB may have protective potential [16]. Moreover, systolic compression of the MB can increase local wall tension and stretch and induce endothelial injury or plaque rupture at the proximal segment of the MB, thereby leading to subsequent thrombus formation, which may contribute to the development of acute coronary syndrome [4, 16].

Meanwhile, CVS is widely accepted as an alternative mechanism by which MB leads to myocardial ischemia [5, 8, 17, 18]. Many studies have consistently demonstrated that patients with MB have positive EPT results more frequently than those without MB [2, 8, 18]. Moreover, CVS is strongly implicated in adverse cardiovascular events associated with MB [5, 18]. Alterations in endothelial function at the MB site have been proposed to play an important role in developing CVS [18, 19]. While a steady laminar flow inhibits endothelial cell apoptosis or tumor necrosis factor- α -induced endothelial cell activation, a turbulent flow activates these intracellular mechanisms [4], which may alter and enhance vasoreactivity [16], thereby leading to coronary vasomotor disorders [2, 20, 21].

Furthermore, some notable findings were observed in the baseline covariates listed in Table 1. Group A had a higher prevalence of hypertension than group B. Numerous studies have reported that hypertension is associated with alterations in endothelial function [22–24], and this alteration may result in coronary vasomotor disorders [6]. Although speculative, this finding was

sufficiently reasonable. Further analysis based on a multivariable logistic regression model revealed that the odds ratio associated with CVS presence was 2.408 in patients with hypertension (95% CI, 1.211–4.790) (**Suppl. Tab. 1**). However, because contradictory results have been reported in our analysis demonstrating a lower CVS risk in patients with hypertension [25, 26], further studies are needed to confirm these issues.

The prescription rates of discharge medications also varied among the groups. Patients in group A received more statins, CCBs, and long-acting nitrates but fewer beta-blockers than those in group B. Because CCBs are among the first-line therapeutic drugs, and beta-blockers are generally not prescribed in patients with CVS [27], our ‘real-world’ prescription patterns seem sufficiently reasonable. According to further analysis, as summarized in **Supplemental Table 2**, treatment with beta-blockers increased the risk of developing MACE in patients with MB and CVS.

Meanwhile, long-acting nitrates were prescribed more frequently to patients with CVS than to those without CVS. Although nitrates are widely used as an adjunctive CVS treatment along with CCB owing to their potential vasodilatory effects, previous studies have reported their ineffectiveness. In a clinical study based on a Japanese multicenter registry, chronic nitrate therapy did not improve the clinical outcomes in patients with CVS [28]. In a nationwide Korean prospective registry, nitrate treatment was associated with a greater risk of adverse cardiovascular events [29]. According to a clinical study on the prognostic impact of nitrates in patients with both MB and CVS, these agents did not improve clinical outcomes but were associated with a greater rate of recurrent angina [30]. Hence, our study proposes that more optimized medical treatment should be implemented to improve clinical outcomes in these selected patients.

In **Supplemental Table 2**, both tobacco smoking and obesity were negatively associated with MACEs in patients with both MB and CVS. As previous studies have extensively endorsed both “smoker’s paradox” and “obesity paradox” in patients with established cardiovascular disorders, these findings were interesting. However, as many studies have contradicted these hypotheses, further research is needed to elucidate these observations.

Several published studies align with our findings [2, 5, 9]. Kim et al. reported that, as compared with its absence, MB presence was associated with higher readmission and that CVS may predict rehospitalization among patients with MB [5]. Another study by Nam et al. revealed that patients with both MB and CVS had higher rates of recurrent angina than those with MB but no CVS in the setting of stable CAD (12.5% versus 5.5%), aligning with our results (34.5% [group A] versus 24.4% [group B]) [9]. Montone et al. also reported similar results, with higher rates of composite outcomes, angina-related hospitalization, and recurrent angina [2]. Although the study design and definition of the primary endpoint were quite different among studies, all 3 indicated that the rates of recurrent angina or angina-related hospitalization were significantly higher in patients with MB and CVS. Interestingly, these studies also reported that CVS did not increase the risk of cardiovascular death or NFMI. With a sufficiently long follow-up period, our results aligned with those reported in these studies.

This study has some limitations. First, MB presence was determined based only on conventional CAG. Although CAG is the gold standard for diagnosing MB [31], other diagnostic modalities have also been used to accurately assess the anatomic and physiological significance of MB [6, 12, 32]. Second, data on the angiographic characteristics were missing. No parameters on quantitative CAG including minimum narrowing diameter or reference diameter were assessed. Moreover, our analysis did not reveal the CVS anatomical site or location. Third,

previously published studies have defined CVS as > 70% luminal narrowing of the coronary artery to subtotal or total occlusion [7, 8, 33]. As stated previously, our analysis defined CVS as > 70% luminal narrowing of the coronary artery during EPT. Although our CVS definition appears less stringent than that in other studies, we should also note that patient safety is one of the most fundamental priorities of any healthcare service. As the provocation of extremely severe narrowing may cause harm, leading to hemodynamic compromise, we should consider reducing the risk of unnecessary harm. Fourth, we did not collect detailed information on the prescribed medications, including their subtypes, adherence, or transition rates, which may have been unmeasured confounders influencing the clinical outcomes. Finally, this was a retrospective study at a single institution, which might have caused a selection bias. Moreover, this was a non-randomized study, which might have produced a selection bias in the statistical analysis.

Although multivariate Cox models were used to adjust for potential selection bias, this issue might have persisted due to the inclusion or exclusion criteria, deletion of data with missing values, and many unmeasured or residual confounders. Therefore, our analysis might not have demonstrated a causal relationship. Because our results could not be generalized, our study was hypothesis-generating and not confirmatory. Therefore, our results should be interpreted with caution, and further multicenter, large-scale, and longer-term prospective clinical studies are warranted in the future.

CONCLUSIONS

In conclusion, CVS presence may adversely affect the clinical outcomes in patients with MB. Further multicenter, large-scale, and longer-term prospective clinical studies are needed to elucidate this association.

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Data statement: The datasets analyzed during the present study are available from the corresponding author on reasonable request.

Supplementary material:

Supplemental Method 1. Detailed information on the method of propensity score matching;

Supplemental Table 1. Independent factors for the presence of CVS (a multivariable logistic regression analysis of datasets from both groups A and B);

Supplemental Table 2. Multivariable analysis for predictors of MACE in patients with MB and concomitant CVS (group A).

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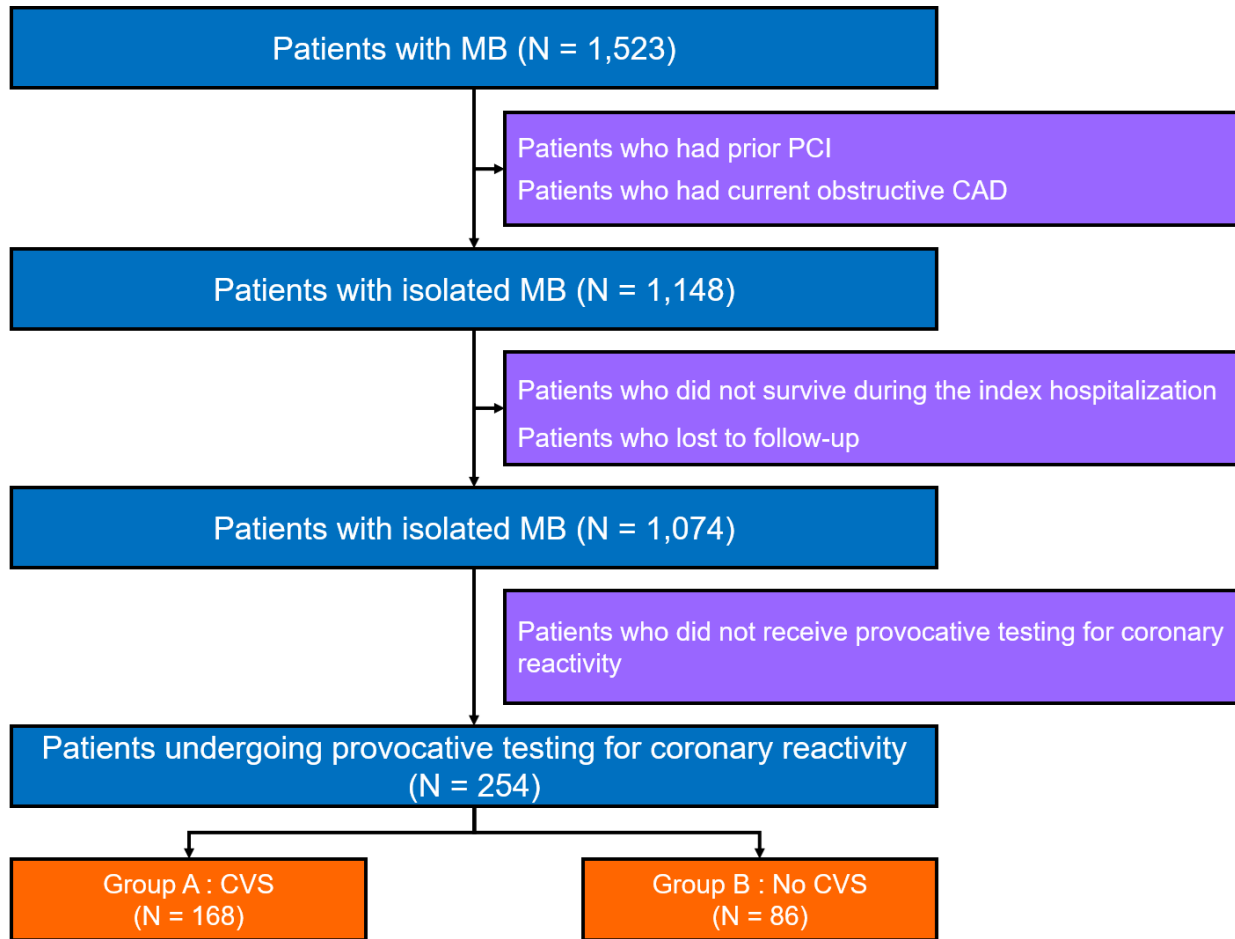
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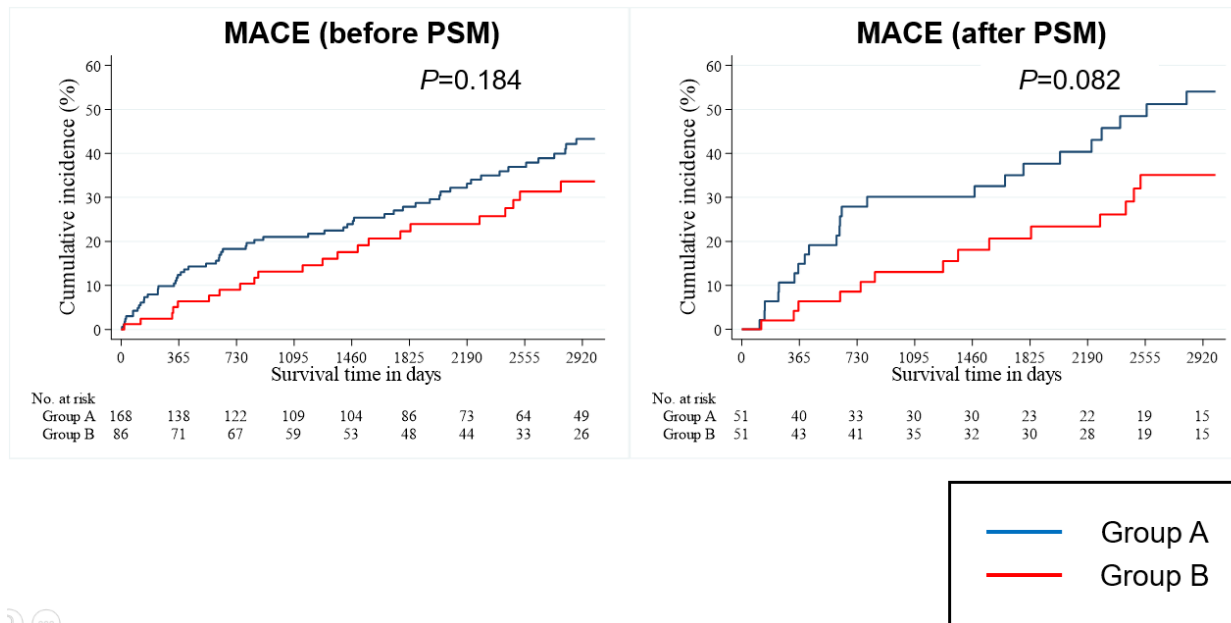
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Figure 1. Scheme flowchart for the inclusion of study participants



CAD — coronary artery disease; CVS — coronary vasospasm; MB — myocardial bridging; PCI — percutaneous coronary intervention

Figure 2. Kaplan–Meier cumulative incidence curves among patients with MB according to the presence or absence of CVS



CAG — coronary angiogram; CVS — coronary vasospasm; MACE — major adverse composite outcome; MB — myocardial bridging

Table 1. Characteristics in baseline covariates

	Before PSM				After PSM			
	Group A	Group B	P-value	SMD	Group A	Group B	P-value	SMD
	168	86			51	51		
Demographics								
Age ≥ 65 years	17 (10.1)	7 (8.1)	0.610	0.036	3 (5.9)	6 (11.8)	0.487	0.121
Male gender	108 (64.3)	45 (52.3)	0.065	0.284	25 (49.0)	25 (49.0)	1.000	0.044
Smoking history	63 (37.5)	25 (29.1)	0.181	0.22	17 (33.3)	14 (27.4)	0.518	0.073
BMI ≥ 25 kg/m ²	75 (46.6)	28 (36.8)	0.158	0.194	19 (37.2)	23 (45.1)	0.421	0.195
Past medical history								
Hypertension	54 (32.1)	16 (18.6)	0.022	0.338	10 (19.6)	12 (23.5)	0.630	0.194
Diabetes mellitus	15 (8.9)	8 (9.3)	0.922	0.058	8 (15.7)	6 (11.8)	0.565	0.0
Dyslipidemia	13 (7.7)	5 (5.8)	0.572	0.079	2 (3.9)	3 (5.9)	1.000	0.0
CVA	3 (1.8)	1 (1.2)	0.706	0.038	1 (2.0)	1 (2.0)	1.000	0.131
Presence of myocardial necrosis	23 (13.7)	9 (10.5)	0.464	0.037	3 (5.9)	7 (13.7)	0.318	0.014
LVEF < 40%	0 (0.0)	0 (0.0)	-	-	0 (0.0)	0 (0.0)	-	-
Prescribed medications at discharge								
Antiplatelet agents	71 (42.3)	33 (38.4)	0.551	0.028	24 (52.9)	22 (43.1)	0.691	0.131
RASI	26 (15.5)	13 (15.1)	0.94	0.066	9 (17.6)	9 (17.6)	1.000	0.271

Statins	123 (73.2)	40 (46.5)	<0.001	0.465	34 (66.7)	32 (62.8)	0.679	0.085
CCB	159 (94.6)	73 (84.9)	0.009	0.357	48 (94.1)	47 (92.2)	1.000	0.046
Beta-blockers	2 (1.2)	9 (10.5)	0.001	0.379	0 (0.0)	1 (2.0)	1.000	0.0
Long-acting nitrates	92 (54.8)	19 (22.1)	<0.001	0.796	13 (25.5)	14 (27.4)	0.822	0.026

Values are presented as percentages (numbers) for categorical values

BMI — body mass index; CCB — calcium channel blockers; CVA — cerebrovascular accident; LVEF — left ventricular ejection fraction; RASI — renin-angiotensin system inhibitors

Table 2. HRs and 95% CI showing associations between study groups and the incidence of each clinical outcome with respect to each Cox model

	Study group		Model 1	Model 2	Model 3	Model 4
	Group A	Group B	(Crude) HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
The primary endpoint						
MACE	59 (35.1)	23 (26.7)	1.38 (0.85–2.24)	1.46 (0.90–2.38)	1.92 (1.12–3.29)	1.94 (1.04–3.59)
The secondary endpoints						
Cardiac death	1 (0.6)	0 (0.0)	–	–	–	–

Cardiac arrest	2 (1.2)	1 (1.2)	0.99 (0.09–10.93)	0.93 (0.08–10.48)	–	–
NFMI	10 (5.9)	5 (5.8)	0.99 (0.34–2.89)	0.90 (0.30–2.65)	0.92 (0.30–2.86)	1.04 (0.25–4.27)
Ischemia-driven revascularization	1 (0.6)	1 (1.2)	0.48 (0.03–7.75)	0.51 (0.03–8.43)	–	–
Ischemia-driven CAG	29 (17.3)	7 (8.1)	2.14 (0.94–4.88)	2.25 (0.98–5.15)	2.50 (1.05–5.94)	3.01 (1.15–7.86)
Ischemia-related hospitalization	58 (34.5)	21 (24.4)	1.51 (0.92–2.49)	1.61 (0.97–2.67)	2.17 (1.24–3.82)	2.10 (1.10–3.98)

Model 1 — Crude model; Model 2 — Adjusting for age and sex; Model 3 — Adjusting for all components in model 2, plus smoking history, BMI, and past medical history; Model 4 (the fully-adjusted model) — Adjusting for all components in model 3 plus presence of myocardial necrosis, LVEF, and prescribed medications. BMI — body mass index; CAG — coronary angiogram; CI — confidence interval; HR — hazard ratio; LVEF — left ventricular ejection fraction; MACE — major adverse composite outcome; NFMI — non-fatal myocardial infarction