

Risk of Bleeding and Ischemia in Elderly East Asian Patients with Diabetes Mellitus Treated with either Clopidogrel or Ticagrelor: From the Korean Acute Myocardial Infarction Registry-V

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Prescribing a P2Y12 inhibitor for patients with diabetes mellitus (DM) and acute myocardial infarction (AMI) who have undergone percutaneous coronary intervention (PCI) is challenging because of the risk of bleeding and ischemia. We compared the risk of ischemia and bleeding between clopidogrel and ticagrelor in elderly East Asian patients with diabetes using the Korea Acute Myocardial Infarction Registry (KAMIR)-V data. This study included 838 patients enrolled in the KAMIR-V who were > 75 years, had DM, AMI, and had undergone PCI. The patients were divided into two groups based on the treatment drug. After propensity score matching, 466 patients (ticagrelor: clopidogrel=233:233) were included in the Cox regression analyses to determine the risk of bleeding and ischemia. The baseline characteristics were not different. The type of antiplatelet therapy did not affect the incidence of Bleeding Academic Research Consortium type ≥ 2 bleeding. There was no significant difference between ticagrelor and clopidogrel treatment outcomes with respect to ischemia risk. This prospective study of a Korean patient cohort (elderly Korean patients with DM) showed no differences in bleeding and ischemia risks based on the use of either ticagrelor or clopidogrel. Large scale randomized controlled trials are warranted to determine the optimal antiplatelet agents for these patients.

Key Words: Myocardial Infarction; Percutaneous Coronary Intervention; Myocardial Ischemia; Hemorrhage; Platelet Aggregation Inhibitors

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INTRODUCTION

Cardiovascular disease is a major cause of death in the Republic of Korea and worldwide.^{1,2} Therefore, efforts have been made to improve outcomes in patients with acute myocardial infarction (AMI). Percutaneous coronary intervention (PCI) and dual antiplatelet therapy (DAPT) are the mainstay of AMI therapy, although there is concern regarding the risk of bleeding and ischemia associated with PCI and DAPT.³⁻⁵ Older age is a major factor contributing to ischemic and bleeding events.⁵⁻⁷ Diabetes is also a known

risk factor for ischemic events; however, its contribution to bleeding events remains controversial.⁸⁻¹⁰ In particular, in elderly East Asian patients with diabetes mellitus (DM), this concern is more pronounced, leaving clinicians conflicted over the choice of antiplatelet agent (potent P2Y12 inhibitor or an alternative antiplatelet agent). Previous studies have attempted to determine the optimal choice of DAPT; however, gaps in the evidence remain, especially relating to elderly East Asian patients with DM.¹¹⁻¹⁵ To provide clarity to clinicians, we analyzed the optimal antiplatelet agent for this patient group. We compared the risk of ischemia and bleeding between clopidogrel and tica-

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grelor in elderly East Asian patients with diabetes using the Korea Acute Myocardial Infarction Registry (KAMIR)-V data.

MATERIALS AND METHODS

1. Study population

We used data from the KAMIR-V registry. Between January 2016 and June 2020, 15,629 patients were enrolled in this registry and followed-up for 1 year. This study was approved by the Ethics Review Committee of the Chonnam National University Hospital Biomedical Research Institute (IRB number: BTMP-2023-061), and informed consent was obtained from all participants. This study was conducted according to the principles expressed in the Declaration of Helsinki. We analyzed the data collected from 838 patients (treatment groups: ticagrelor:clopidogrel=233:605) who were older than 75 years of age, had been diagnosed with DM and AMI, and who had undergone PCI during the index hospitalization. Patients with atrial fibrillation were excluded. We performed a 1:1 propensity score matching (PSM). Ultimately, 466 patients (ticagrelor:clopidogrel=233:233) were analyzed (Fig. 1).

2. Definitions and clinical endpoint

AMI was defined as evidence of myocardial injury, with an elevation of cardiac troponin levels with at least one value above the 99th percentile of the upper reference limit and with evidence of necrosis consistent with myocardial ischemia identified in a clinical setting. Clinical findings

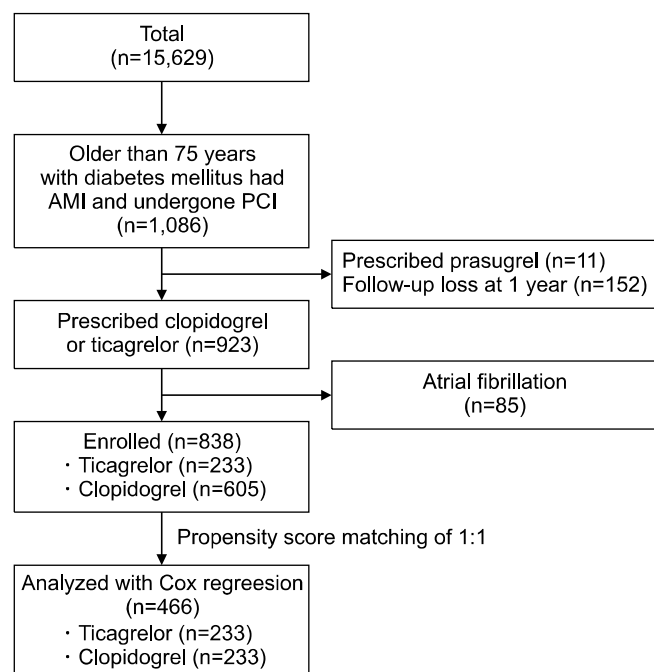


FIG. 1. Study population. The study population was derived from the nationwide prospective Korea Acute Myocardial Infarction Registry (KAMIR)-V. AMI: acute myocardial infarction, PCI: percutaneous coronary intervention.

consistent with myocardial ischemia included at least one of the following: 1) symptoms such as chest pain or discomfort; 2) electrocardiogram abnormalities (ST segment elevation at the J point in more than two continuous leads [over 0.2 mV elevation in V2-V3, 0.1 mV in other leads], ST segment changes except for elevation [downslope or horizontal ST segment depression over 0.05 mV, T wave inversion in more than two continuous leads], or newly detected left bundle branch block); and 3) imaging studies, such as echocardiography, suggestive of myocardial infarction (MI). Successful PCI was defined as a Thrombolysis in Myocardial Infarction (TIMI) flow \geq grade 2 after thrombolysis and residual stenosis $<$ 50%. Renal function was estimated using the Modification of Diet in Renal Disease study estimated glomerular filtration rate (MDRD eGFR).¹⁶ Major adverse cardiac and cerebrovascular events (MACCE) were defined as the composite of total death, MI, stroke, and revascularization, including PCI and coronary artery bypass graft. Bleeding events were counted according to the Bleeding Academic Research Consortium (BARC) type.¹⁷ The primary endpoint of the study was the first occurrence of MACCE or BARC type \geq 2 bleeding after admission. The dates of MACCE or BARC type \geq 2 bleeding were recorded until 1 year after the index hospitalization or until a change of the antiplatelet agent. It was difficult to determine which antiplatelet agent was responsible for the ischemic or bleeding event in cases where the antiplatelet agent was changed during follow-up. Thus, if the physician changed the antiplatelet agent for a patient within 1 year, we counted the occurrence of MACCE or BARC type at the date of antiplatelet agent change.

3. Statistical analysis

Continuous variables are presented as mean \pm standard deviation, and categorical variables are expressed as number of cases (percentages). Baseline characteristics and clinical findings were chosen based on previous studies.^{5-7,18-21} These included age, sex, systolic blood pressure, body mass index (BMI), Killip class, hypertension, dyslipidemia, previous MI, previous heart failure, previous cerebrovascular accident (CVA), smoking, ST-segment elevation myocardial infarction (STEMI), multivessel disease including left main coronary artery disease, transradial approach for PCI, TIMI flow, successful PCI, left ventricular ejection fraction (LVEF), MDRD eGFR, hemoglobin (Hb), hemoglobin A1c (HbA1c) and medications including a maintained dose of ticagrelor, prescription of angiotensin converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB), beta blockers, calcium channel blockers and statins. PSM and Cox regression analyses were performed to identify the bleeding and ischemic risks between the two groups. After PSM, 466 patients (ticagrelor:clopidogrel=233:233) were analyzed via Cox regression. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated, and statistical significance was defined as $p < 0.05$. All statistical analyses were performed using R version 4.2.0.

RESULTS

1. Baseline clinical characteristics after PSM

PSM was performed for 838 patients (ticagrelor:clopidogrel=233:605), after which 466 patients (ticagrelor:clopidogrel=233:233) were further analyzed (Table 1). Mean age was 79.6±3.7 years in the clopidogrel group and 79.2±3.8 years in the ticagrelor group. There were no statistical differences in age between the two groups (p=0.921). Other

factors including HbA1c (7.1±1.3% vs 7.2±1.4%, p=0.791) also did not show any statistical differences between the groups. Standardized mean differences of variables are presented in Supplementary Table 1.

2. Cox regression analysis for bleeding risk

Cox regression analysis was performed after PSM. Regarding bleeding risk, the type of antiplatelet agent did not affect the occurrence of BARC type ≥2 bleeding (HR, 1.50;

TABLE 1. Baseline clinical characteristics

	Before PSM			After PSM		
	Clopidogrel (n=605)	Ticagrelor (n=233)	p-value	Clopidogrel (n=233)	Ticagrelor (n=233)	p-value
Age	80.1±4.0	79.2±3.8	0.002	79.2±3.7	79.2±3.8	0.921
Sex						0.711
Female	285 (47.1%)	110 (47.2%)	1.000	115 (49.4%)	110 (47.2%)	
Male	320 (52.9%)	123 (52.8%)		118 (50.6%)	123 (52.8%)	
SBP (mmHg)	130.8±29.6	132.3±29.4	0.525	131.9±28.9	132.3±29.4	0.899
BMI (kg/m ²)	23.3±3.5	23.8±3.6	0.05	23.7±3.8	23.8±3.5	0.816
Killip class			0.225			0.580
I	419 (69.5%)	177 (76.0%)		171 (73.4%)	177 (76.0%)	
II	75 (12.4%)	20 (8.6%)		27 (11.6%)	20 (8.6%)	
III	71 (11.8%)	21 (9.0%)		24 (10.3%)	21 (9.0%)	
IV	38 (6.3%)	15 (6.4%)		11 (4.7%)	15 (6.4%)	
HTN	483 (79.8%)	193 (82.8%)	0.375	189 (81.1%)	193 (82.8%)	0.718
DL	104 (17.2%)	49 (21.0%)	0.234	42 (18.0%)	49 (21.0%)	0.483
Previous MI	78 (12.9%)	12 (5.2%)	0.002	14 (6.0%)	12 (5.2%)	0.840
Previous HF	19 (3.2%)	3 (1.3%)	0.208	4 (1.7%)	3 (1.3%)	1.000
Previous CVA	77 (12.8%)	25 (10.8%)	0.488	30 (12.9%)	25 (10.7%)	1.000
Current smoker	56 (9.7%)	31 (13.8%)	0.122	33 (14.2%)	34 (14.6%)	0.566
STEMI	195 (32.2%)	120 (51.5%)	<0.001	121 (51.9%)	120 (51.5%)	1.000
Multivessel disease (including LM ds.)	409 (67.7%)	148 (63.5%)	0.284	148 (63.5%)	148 (63.5%)	1.000
Transradial approach	288 (47.6%)	140 (60.1%)	0.002	133 (57.1%)	140 (60.1%)	0.573
Post TIMI flow			0.253			0.670
0	12 (2.0%)	4 (1.7%)		5 (2.1%)	4 (1.7%)	
1	3 (0.5%)	1 (0.4%)		1 (0.4%)	1 (0.4%)	
2	22 (3.6%)	16 (6.9%)		10 (4.3%)	16 (6.9%)	
3	567 (93.9%)	212 (91.0%)		217 (93.1%)	212 (91.0%)	
Successful PCI	595 (98.3%)	228 (98.3%)	1	231 (99.1%)	229 (98.3%)	0.681
LVEF (%)	49.4±12.5	50.4±11.6	0.3299	49.7±11.3	49.7±12.1	0.987
MDRD eGFR (mL/min/1.73 m ²)	61.2±30.3	63.3±27.2	0.349	63.0±31.0	63.0±27.1	0.990
Hemoglobin (g/dL)	11.8±2.0	12.4±2.0	<0.001	12.4±1.9	12.4±2.0	0.932
HbA1c (%)	7.1±1.3	7.2±1.4	0.260	7.1±1.3	7.2±1.4	0.791
Maintain dose of ticagrelor						
180 mg/day		210 (90.1%)			210 (90.1%)	
120 mg/day		8 (3.4%)			8 (3.4%)	
90 mg/day		15 (6.4%)			15 (6.4%)	
ACEi or ARB	433 (71.6%)	180 (77.3%)	0.115	186 (79.8%)	180 (77.3%)	0.573
Beta blockers	4,299 (70.9%)	181 (77.7%)	0.059	189 (81.1%)	181 (77.7%)	0.423
Calcium channel blockers	80 (13.2%)	28 (12.0%)	0.725	26 (11.2%)	28 (12.0%)	0.885
Statins	531 (87.8%)	209 (89.7%)	0.510	212 (91.0%)	209 (89.7%)	0.754

ACEi: angiotensin converting enzyme inhibitors, ARB: angiotensin II receptor blocker, BMI: body mass index, CVA: cerebrovascular accident, HbA1c : hemoglobin A1c, HF: heart failure, LM: left main coronary artery, LVEF: left ventricular ejection fraction, MDRD eGFR: modification of diet in renal disease estimated glomerular filtration rate, MI: myocardial infarction, PCI : percutaneous coronary intervention, PSM: propensity score matching, SBP: systolic blood pressure, STEMI: ST-elevation myocardial infarction, TIMI: thrombolysis in myocardial infarction.

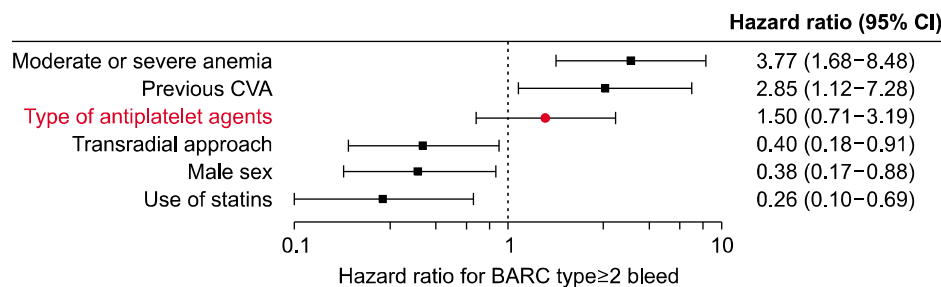


FIG. 2. Cox regression analysis for bleeding risk. BARC: Bleeding Academic Research Consortium, CI: confidence interval, CVA: cerebrovascular accident.

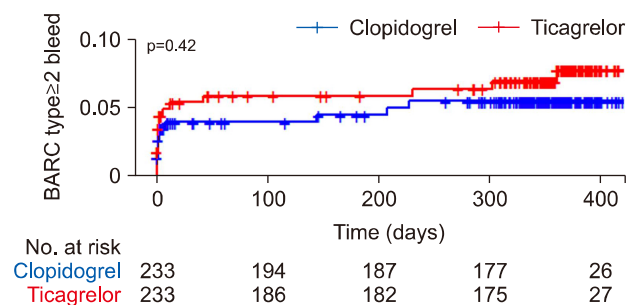


FIG. 3. Kaplan-Meier curve for bleeding risk. BARC: Bleeding Academic Research Consortium.

95% CI: 0.71-3.19, Fig. 2). This was shown as Kaplan-Meier curve in Fig. 3 ($p=0.42$). Use of the transradial approach for PCI (HR, 0.40; 95% CI: 0.18-0.91), male sex (HR, 0.38; 95% CI: 0.17-0.88), and use of statins (HR, 0.26; 95% CI: 0.10-0.69) lowered the risk of bleeding (Fig. 2). In contrast, moderate or severe anemia (grade ≥ 2 ; Hb < 10 g/dL) (HR, 3.77; 95% CI: 1.68-8.48) and previous CVA (HR, 2.85; 95% CI: 1.12-7.28) increased the risk of bleeding (Fig. 2). Detailed data for bleeding events (BARC type and origin) are presented in Table 2.

3. Cox regression analysis for ischemia risk

Cox regression analysis was also performed for the ischemia risk. There was no significant difference between ticagrelor and clopidogrel (HR, 1.16; 95% CI: 0.74-1.81, Fig. 4). This was shown as Kaplan-Meier curve in Fig. 5 ($p=0.73$). Low BMI (BMI < 18.5 kg/m²) (HR, 2.76; 95% CI: 1.41-5.42), high Killip class (Killip class ≥ 2) (HR, 2.40; 95% CI: 1.49-3.86) and LVEF $< 40\%$ (HR, 1.79; 95% CI: 1.07-2.99) increased the ischemia risk. Use of ACEi or ARB (HR, 0.57; 95% CI: 0.33-0.97), beta blockers (HR, 0.40; 95% CI: 0.24-0.68), and statins (HR, 0.14; 95% CI: 0.08-0.24) decreased the ischemia risk (Fig. 4). The detailed data for MACCE are presented in Table 3.

DISCUSSION

The choice of antiplatelet agent (either a potent P2Y12 inhibitor or an alternative antiplatelet agent) in elderly AMI patients is a difficult problem. This issue is more pronounced in the case of patients with diabetes, because its contribution to bleeding events remains controversial.⁸⁻¹⁰

TABLE 2. Type and origin of bleeding events

	Clopidogrel (n=233)	Ticagrelor (n=233)	p-value
BARC Type			
2	8 (3.4%)	8 (3.4%)	1.000
3a	4 (1.7%)	4 (1.7%)	1.000
3b	0 (0.0%)	2 (0.9%)	0.479
3c	1 (0.4%)	1 (0.4%)	1.000
5a	0 (0.0%)	1 (0.4%)	1.000
Origin			
Urogenital	1 (0.4%)	0 (0.0%)	1.000
Vascular access	3 (1.3%)	5 (2.1%)	0.721
Cerebral	1 (0.4%)	1 (0.4%)	1.000
GI bleeding and others	8 (3.4%)	10 (4.3%)	0.810

BARC: Bleeding Academic Research Consortium, GI bleeding: gastrointestinal bleeding.

In this prospective cohort study of elderly Korean patients with DM, the type of antiplatelet agents did not result in significant differences in risks for bleeding and ischemia (Figs. 2-5). Our Cox regression analyses showed that using the transradial approach for PCI, use of statins, and male sex lowered the occurrence of a bleeding event. In contrast, moderate or severe anemia and previous CVA increased the risk of bleeds. Low BMI, high Killip class and low LVEF increased the risk of ischemia. Conversely, use of ACEi or ARB, beta blockers and statins decreased the occurrence of an ischemic event.

Previous studies have attempted to identify the optimal antiplatelet agent for patients after AMI by comparing clopidogrel and other potent P2Y12 inhibitors.^{11-15,21} For example, according to the THEMIS trial, ticagrelor treatment was beneficial for ischemic events in patients with stable coronary artery disease and type 2 DM.²² The report of Park et al.¹⁵ showed that ticagrelor was associated with increased risk of bleeding complications during in-hospital period compared with clopidogrel. In our result, ticagrelor seemed to increase the risk of bleeding during the first week (Fig. 6). However, as time goes by, the difference between two groups was getting smaller and there was no difference at the end (Figs. 3 and 6). Selection of the optimal antiplatelet agent for elderly patients with DM is influenced by numerous factors, including angiographic findings, comorbidities, and patient history. We investigated this is-

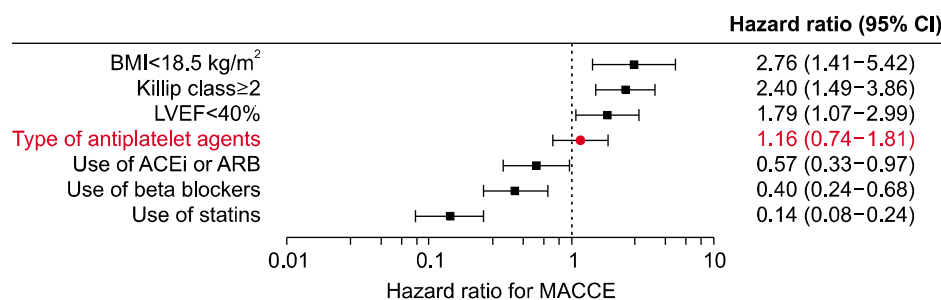


FIG. 4. Cox regression analysis for ischemia risk. ACEi: angiotensin converting enzyme inhibitors, ARB: angiotensin II receptor blockers, BMI: body mass index, CI: confidence interval, LVEF: left ventricular ejection fraction, MACCE: major adverse cardiac and cerebrovascular events.

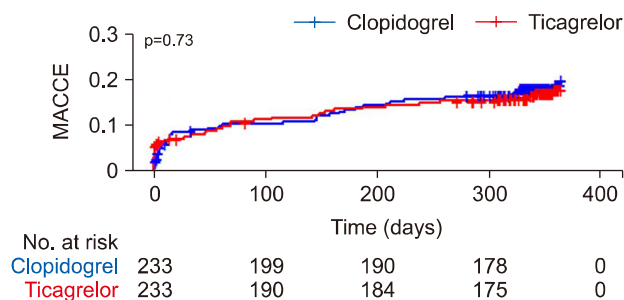


FIG. 5. Kaplan-Meier curve for ischemic risk. MACCE: major adverse cardiac and cerebrovascular events.

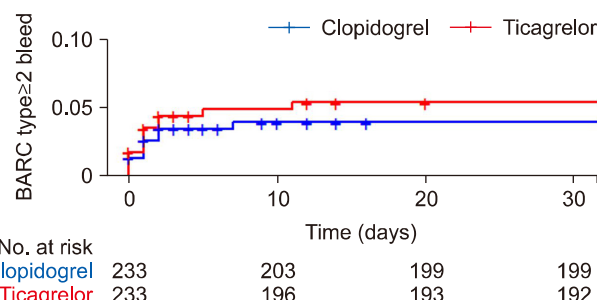


FIG. 6. Kaplan-Meier curve for bleeding risk up to 30 days. BARC: Bleeding Academic Research Consortium.

TABLE 3. Detailed data of ischemic events

	Clopidogrel (n=233)	Ticagrelor (n=233)	p-value
Total death	38 (16.3%)	31 (13.3%)	0.434
Cardiac death	23 (9.9%)	26 (11.2%)	0.763
Non cardiac death	15 (6.4%)	5 (2.1%)	0.040
STEMI	1 (0.4%)	1 (0.4%)	1.000
NSTEMI	2 (0.9%)	2 (0.9%)	1.000
TLR	2 (0.9%)	3 (1.3%)	1.000
TVR	1 (0.4%)	3 (1.3%)	0.616
de novo	3 (1.3%)	3 (1.3%)	1.000
CABG	0 (0.0%)	0 (0.0%)	1.000
CVA	3 (1.3%)	4 (1.7%)	1.000
Rehospitalization d/t HF	15 (6.4%)	9 (3.9%)	0.295
Stent thrombosis	1 (0.4%)	2 (0.8%)	
Acute	0 (0.0%)	1 (0.4%)	1.000
Subacute	1 (0.4%)	0 (0.0%)	1.000
Late	0 (0.0%)	1 (0.4%)	1.000

CABG: coronary artery bypass grafting, CVA: cerebrovascular accident, HF: heart failure, NSTEMI: non ST elevation myocardial infarction, STEMI: ST elevation myocardial infarction, TLR: target lesion revascularization, TVR: target vessel revascularization.

sue to identify the optimal DAPT strategy for this patient group, to inform decision making by physicians. To our knowledge, our study is the first to analyze the risks of bleeding and ischemia with reference to antiplatelet therapy for this specific population group.

According to our Cox regression results, moderate or severe anemia increased the risk of bleeding (Fig. 2). Anemia is very common in this older population, and its prevalence

and severity increase as the population ages.^{23,24} Based on our study and previous studies, physicians should identify the cause of the anemia and correct it to get better cardiovascular outcomes.^{6,25}

Previous CVA was not regarded as the major risk factor of bleeding in several scoring systems^{6,7}. However, several studies suggest that physicians should pay attention to the patient's previous CVA history. According to the British Cardiovascular Intervention Society database, patients with previous stroke had higher risk for hemorrhagic stroke after PCI and patients with prior hemorrhagic or ischemic stroke as compared with those with no-prior stroke had higher risk for intracranial hemorrhage, in Japanese data.^{26,27} Our Cox regression analysis found that previous CVA increased the risk of bleeding (HR, 2.85; 95% CI: 1.12-7.28). In our database, 12.2% (102/838) of the patients had previous CVA; the incidence rates of BARC type ≥ 2 bleeding were 6.1% (45/736) in those without prior CVA, and 9.8% (10/102) in the previous CVA group. A cerebral origin for the bleed was identified in 5% (3/55) in total. The incidence rate was almost 5-fold higher in previous CVA group (1%; 1/102 vs 0.2%; 2/736). These findings indicated that physicians should have caution about the occurrence of bleeding, especially cerebral origin and may consider using DAPT therapy for shorter duration in patients who have had a previous CVA.

Our study showed that males tend to experience fewer bleeding events than females (Fig. 2). Previous studies showed mixed results when considering sex as an independent predictor of post-PCI bleeding.^{28,29} Other authors have explained the reason for the sex difference in bleeding by the difference in baseline characteristics and

comorbidities, however, there is still uncertainty around this issue.²⁸ The transradial approach for PCI also decreased the occurrence of bleeding in our study population (Fig. 2). This finding is congruent with the recommendations in current guidelines.⁵⁻⁷

With respect to ischemia, low BMI, high Killip class, and low LVEF increased the risk. In contrast, the use of ACEi or ARB, beta blockers, and statins decreased the risk of ischemia (Fig. 3). Our Cox regression analyses showed that low BMI increased the risk of ischemia. According to recent studies, the low BMI group showed worse outcomes, especially all-cause mortality.^{20,21} The report of Faggioni et al.²¹, which analyzed 11,557 female patients treated by PCI with drug-eluting stents, found that during the 3-year follow-up period, the risk of cardiac events did not differ across BMI groups, however, the risk of all-cause mortality was significantly higher in underweight and lower in overweight patients than in patients with normal weight, with a trend toward increased risk in those with severe obesity. Because the primary end point of our study was the first occurrence of MACCE including total death, Cox regression analysis showed that low BMI increased the risk of ischemia. Considering our result and previous studies, physicians should exercise caution when treating patients with a low BMI in this study population and need to make an effort to overcome the malnutrition status of their patients to get better outcomes.

High Killip class and low LVEF are well-known risk factors for ischemia, and use of ACEi or ARB and BB is the guideline-recommended therapy, especially in patients with low LVEF.^{5-7,19,25} Our present findings were consistent with those of previous studies and guidelines. Figs. 2 and 3 depict the decrease in both bleeding and ischemia risk with the use of statins. Use of statins to improve the outcome of ischemic events in patients after AMI has been reported in previous studies and recommended by current guidelines.^{3,4} Several reports have analyzed the effect of statins on bleeding in other diseases; however, the results are inconsistent and unclear.^{30,31}

Based on our findings, when physicians treat this patient group, they should review the patient's comorbidities (presence of anemia, previous CVA, sex, malnutrition) and status (Killip class, LVEF) more carefully and focus on how to improve these factors with the optimal medical treatment including use of ACEi or ARB, beta blockers and statins as guidelines recommend, rather than focus on the choice of antiplatelet agents. Also, our findings indicate benefit from the use of the transradial approach for PCI, and shorter duration dual antiplatelet therapy for patients who have risk factors of bleeding, female with previous CVA and moderate or severe anemia.

This study had some limitations. Our study was not a randomized controlled trial; we used data from the KAMIR-V registry. Thus, clinicians' bias for patient inclusion might have occurred. To minimize this limitation, we performed PSM. As shown in Table 1, some patients in ticagrelor group were prescribed reduced maintenance dose of tica-

grelor like 120 mg/day or 90 mg/day. Physicians might have thought these patients had high risk of bleeding rather than ischemia and so decided to prescribe reduced maintenance dose of ticagrelor to them. Based on our data, only 1 BARC type ≥ 2 bleeding was occurred in patient who was prescribed 120 mg/day of ticagrelor. As the result, the percentage of BARC type ≥ 2 bleeding in these patients (1/23, 4.3%) was lower than the others (15/210, 7.1%) in ticagrelor groups (Tables 1 and 2) and this point may have influenced our final results. Considering these points, large scale, long term, randomized controlled trials should be performed to determine the DAPT strategy in this patient group more clearly.

The available data was missing some patient details, such as the total number and length of stents.³² Regarding bleeding risk, the impact of previous bleeding events, such as gastrointestinal bleeding history, the presence of a peptic ulcer, or prescription of proton pump inhibitors (PPI), could not be analyzed owing to the lack of data. The association of peptic ulcer, gastrointestinal bleeding, and antiplatelet agents has been well established in previous studies.^{33,34} Therefore, physicians should decide treatments by weighing the risks of bleeding and ischemia, especially with stent thrombosis. The interruption of antiplatelet agent treatment and bleeding events in the early period after stent implantation deserve careful thought and continue to challenge clinicians.³⁵ To minimize bleeding risk, the use of PPI is recommended according to guidelines. However, owing to the reported interactions between PPI agents and clopidogrel, clinicians must carefully decide whether to opt for a PPI and what type of PPI to prescribe for older patients.⁵

In this Korean prospective cohort of elderly patients with DM, no differences were observed in bleeding and ischemia risks based on the use of either ticagrelor or clopidogrel. Large scale randomized controlled trials are warranted to determine the optimal antiplatelet agents for these patients.

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CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, et al. Heart disease and stroke statistics-2021 up-

- date: a report from the american heart association. *Circulation* 2021;143:e254-743.
2. Kim JH, Chae SC, Oh DJ, Kim HS, Kim YJ, Ahn Y, et al. Multi-center cohort study of acute myocardial infarction in Korea - interim analysis of the Korea acute myocardial infarction registry-National Institutes of Health registry. *Circ J* 2016;80:1427-36.
 3. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, et al. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2021;42:1289-367.
 4. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018; 39:119-77.
 5. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the task force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2018;39:213-60.
 6. Costa F, van Klaveren D, James S, Heg D, Räber L, Feres F, et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *Lancet* 2017;389:1025-34.
 7. Yeh RW, Secemsky EA, Kereiakes DJ, Normand SL, Gershlick AH, Cohen DJ, et al. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. *JAMA* 2016;315: 1735-49.
 8. Lee SH, Jeong MH, Ahn JH, Hyun DY, Cho KH, Kim MC, et al. Predictors of recurrent acute myocardial infarction despite successful percutaneous coronary intervention. *Korean J Intern Med* 2022;37:777-85.
 9. Grodzinsky A, Arnold SV, Wang TY, Sharma P, Gosch K, Jones PG, et al. Bleeding risk following percutaneous coronary intervention in patients with diabetes prescribed dual anti-platelet therapy. *Am Heart J* 2016;182:111-8.
 10. Gargiulo G, Windecker S, da Costa BR, Feres F, Hong MK, Gilard M, et al. Short term versus long term dual antiplatelet therapy after implantation of drug eluting stent in patients with or without diabetes: systematic review and meta-analysis of individual participant data from randomised trials. *BMJ* 2016;355:i5483.
 11. Ahn KT, Seong SW, Choi UL, Jin SA, Kim JH, Lee JH, et al. Comparison of 1-year clinical outcomes between prasugrel and ticagrelor versus clopidogrel in type 2 diabetes patients with acute myocardial infarction underwent successful percutaneous coronary intervention. *Medicine (Baltimore)* 2019;98:e14833.
 12. Lee SH, Kim HK, Jeong MH, Yasuda S, Honda S, Jeong YH, et al. Practical guidance for P2Y12 inhibitors in acute myocardial infarction undergoing percutaneous coronary intervention. *Eur Heart J Cardiovasc Pharmacother* 2021;7:112-24.
 13. Park KH, Jeong MH, Kim HK, Ahn TH, Seung KB, Oh DJ, et al. Comparison of prasugrel versus clopidogrel in Korean patients with acute myocardial infarction undergoing successful revascularization. *J Cardiol* 2018;71:36-43.
 14. Kim MC, Jeong MH, Sim DS, Hong YJ, Kim JH, Ahn Y, et al. Comparison of clinical outcomes between ticagrelor and prasugrel in patients with ST-segment elevation myocardial infarction - results from the Korea Acute Myocardial Infarction registry-National Institutes of Health. *Circ J* 2018;82:1866-73.
 15. Park KH, Jeong MH, Ahn Y, Ahn TH, Seung KB, Oh DJ, et al. Comparison of short-term clinical outcomes between ticagrelor versus clopidogrel in patients with acute myocardial infarction undergoing successful revascularization; from Korea Acute Myocardial Infarction registry-National Institute of Health. *Int J Cardiol* 2016;215:193-200.
 16. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of diet in renal disease study group. *Ann Intern Med* 1999;130:461-70.
 17. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation* 2011;123:2736-47.
 18. Anand SS, Islam S, Rosengren A, Franzosi MG, Steyn K, Yusufali AH, et al. Risk factors for myocardial infarction in women and men: insights from the INTERHEART study. *Eur Heart J* 2008; 29:932-40.
 19. Park HW, Yoon CH, Kang SH, Choi DJ, Kim HS, Cho MC, et al. Early- and late-term clinical outcome and their predictors in patients with ST-segment elevation myocardial infarction and non-ST-segment elevation myocardial infarction. *Int J Cardiol* 2013;169:254-61.
 20. Won KB, Shin ES, Kang J, Yang HM, Park KW, Han KR, et al. Body mass index and major adverse events during chronic antiplatelet monotherapy after percutaneous coronary intervention with drug-eluting stents - results from the HOST-EXAM trial. *Circ J* 2023;87:268-76.
 21. Faggioni M, Baber U, Afshar AE, Giustino G, Sartori S, Sorrentino S, et al. Effects of body mass index on clinical outcomes in female patients undergoing percutaneous coronary intervention with drug-eluting stents: results from a patient-level pooled analysis of randomized controlled trials. *JACC Cardiovasc Interv* 2018; 11:68-76.
 22. Bhatt DL, Steg PG, Mehta SR, Leiter LA, Simon T, Fox K, et al. Ticagrelor in patients with diabetes and stable coronary artery disease with a history of previous percutaneous coronary intervention (THEMIS-PCI): a phase 3, placebo-controlled, randomised trial. *Lancet* 2019;394:1169-80.
 23. Stauder R, Valent P, Theurl I. Anemia at older age: etiologies, clinical implications, and management. *Blood* 2018;131:505-14.
 24. Le CH. The prevalence of anemia and moderate-severe anemia in the US population (NHANES 2003-2012). *PLoS One* 2016;11: e0166635.
 25. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A,

- Böhm M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021;42:3599-726.
26. Natsuaki M, Morimoto T, Watanabe H, Nakagawa Y, Furukawa Y, Kadota K, et al. Ischemic and bleeding risk after percutaneous coronary intervention in patients with prior ischemic and hemorrhagic stroke. *J Am Heart Assoc* 2019;8:e013356.
27. Myint PK, Kwok CS, Roffe C, Kontopantelis E, Zaman A, Berry C, et al. Determinants and outcomes of stroke following percutaneous coronary intervention by indication. *Stroke* 2016;47:1500-7.
28. Grodecki K, Huczek Z, Scisło P, Kowara M, Raposeiras-Roubín S, D'Ascenzo F, et al. Gender-related differences in post-discharge bleeding among patients with acute coronary syndrome on dual antiplatelet therapy: a BleeMACS sub-study. *Thromb Res* 2018;168:156-63.
29. Hess CN, McCoy LA, Duggirala HJ, Tavris DR, O'Callaghan K, Douglas PS, et al. Sex-based differences in outcomes after percutaneous coronary intervention for acute myocardial infarction: a report from TRANSLATE-ACS. *J Am Heart Assoc* 2014;3:e000523.
30. Ribe AR, Vestergaard CH, Vestergaard M, Pedersen HS, Prior A, Lietzen LW, et al. Statins and risk of intracerebral hemorrhage in individuals with a history of stroke. *Stroke* 2020;51:1111-9.
31. Shin D, Yoon D, Lim SG, Hong JM, Park RW, Lee JS. Comparison of the risk of gastrointestinal bleeding among different statin exposures with concomitant administration of warfarin: electronic health record-based retrospective cohort study. *PLoS One* 2016;11:e0158130.
32. Jukema JW, Verschuren JJ, Ahmed TA, Quax PH. Restenosis after PCI. Part 1: pathophysiology and risk factors. *Nat Rev Cardiol* 2011;9:53-62.
33. Sørensen HT, Mellekjaer L, Blot WJ, Nielsen GL, Steffensen FH, McLaughlin JK, et al. Risk of upper gastrointestinal bleeding associated with use of low-dose aspirin. *Am J Gastroenterol* 2000;95:2218-24.
34. Ng FH, Wong SY, Chang CM, Chen WH, Kng C, Lanas AI, et al. High incidence of clopidogrel-associated gastrointestinal bleeding in patients with previous peptic ulcer disease. *Aliment Pharmacol Ther* 2003;18:443-9.
35. Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* 2005;293:2126-30.