Risk of bleeding and ischemia in elderly East Asian patients with diabetes mellitus treated with either clopidogrel or ticagrelor: From Korea Acute Myocardial Infarction Registry-V

Sang Hoon Lee
Chonnam National University Hospital

Myung Ho Jeong (myungho@chollian.net)
Chonnam National University Hospital

Joon Ho Ahn
Chonnam National University Hospital

Dae Young Hyun
Chonnam National University Hospital

Kyung Hoon Cho
Chonnam National University Hospital

Min Chul Kim
Chonnam National University Hospital

Doo Sun Sim
Chonnam National University Hospital

Young Joon Hong
Chonnam National University Hospital

Ju Han Kim
Chonnam National University Hospital

Youngkeun Ahn
Chonnam National University Hospital

Jin Yong Hwang
Gyeongsang National University

Yong Hwan Park
Samsung Changwon Hospital, Sungkyunkwan University School of Medicine

Research Article

Keywords: Myocardial infarction, Percutaneous coronary intervention, Risk, Myocardial ischemia, Bleeding, Old age, Diabetes mellitus, Antiplatelet agents
Abstract

**Background:** The risk of bleeding and ischemia in patients with acute myocardial infarction (AMI) who have undergone percutaneous coronary intervention (PCI) is a common concern for physicians, with added conflict over prescribing a potent P2Y12 inhibitor. In particular, elderly East Asian patients with diabetes mellitus (DM) invoke a heightened concern.

**Methods:** We analyzed 839 patients who were enrolled in the Korea Acute Myocardial Infarction Registry-V, older than 75 years, with DM, had an AMI, and had undergone PCI. Propensity score matching (PSM) and cox regression analyses were performed to compare the bleeding and ischemic risks between the two groups. After PSM, 699 patients (ticagrelor: clopidogrel = 233:466) were analyzed. Patients with Bleeding Academic Research Consortium (BARC) type $\geq 2$ bleed and those at ischemic risk were analyzed based on major adverse cardiac and cerebrovascular events.

**Results:** Cox regression analyses showed the type of antiplatelet therapy did not affect the incidence of BARC type $\geq 2$ bleeds (HR, 1.67; 95% CI: 0.86–3.22). Use of the transradial approach for PCI, use of statins, and successful PCI lowered the risk of bleeding. In contrast, low body mass index (BMI) increased the risk of bleeds. In the aspect of ischemia, there was no difference based on the antiplatelet agents used (HR, 1.00; 95% CI: 0.68–1.46). Low BMI, hemoglobin <9 g/dL, high Killip class, left ventricular ejection fraction <40%, and multivessel disease increased ischemic risk. Post thrombolysis in myocardial infarction flow grade $\geq 3$, use of angiotensin converting enzyme inhibitors or angiotensin II receptor blockers, beta blockers and statins decreased the risk.

**Conclusions:** In this Korean prospective cohort study, there was no difference in the risks for bleeding and ischemia, based on the use of ticagrelor or clopidogrel, in elderly Korean patients with DM. To determine the optimal antiplatelet agents for these patients, large scale randomized controlled trials are warranted.

**Trial registration:** KCT0008355

**Background**

Cardiovascular disease is a major cause of death in the Republic of Korea and worldwide [1, 2]. Therefore, efforts have been made to improve the outcomes of patients with acute myocardial infarction (AMI). Percutaneous coronary intervention (PCI) and dual antiplatelet therapy (DAPT) are the mainstay of AMI treatments, although there is concern regarding the risk of bleeding and ischemia associated with PCI and DAPT [3–5]. Old age is a major factor contributing to ischemic and bleeding events [5–7]. Diabetes is also a known risk factor for ischemic events, but its contribution to bleeding events remains controversial [8–12]. In particular, in elderly East Asian patients with diabetes mellitus (DM), this concern is deepened, and leaves 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 [13–17]. 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 ticagrelor in elderly and diabetic East Asian patients using the Korea Acute Myocardial Infarction Registry (KAMIR)-V data.

**Methods**

1. **Aim Of Study**

We aimed to reveal which antiplatelet agent was more appropriate in elderly East Asian patients with DM by comparing the risk of bleeding and ischemia between ticagrelor and clopidogrel.

2. **Study Population**

We used the 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 839 patients (ticagrelor: clopidogrel = 233:606) who were older than 75 years of age, with DM, had AMI, and had undergone PCI during the index hospitalization. Patients with atrial fibrillation were excluded. We performed a propensity score matching (PSM) of 1:2. Ultimately, 699 patients (ticagrelor: clopidogrel = 233:466) were analyzed (Fig. 1).

2. **Definition 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 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 [dowlslope 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 Thrombolysis in Myocardial Infarction (TIMI) flow ≥ 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) [18]. 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 [19]. The primary endpoint of the study was the first occurrence of MACCE or BARC type ≥ 2 bleeding after admission. The dates of MACCE or BARC type ≥ 2 bleeding were recorded
until 1 year after the index hospitalization or until a change of the antiplatelet agent. 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. 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.

3. Statistical Analysis

Continuous variables were presented as mean ± standard deviation, and categorical variables were expressed as number of cases (percentages). Baseline characteristics and clinical findings were chosen based on previous studies [5–7, 20–27]; these included age, sex, systolic blood pressure, body mass index (BMI), Killip class, hypertension, dyslipidemia, previous MI, previous heart failure, previous cerebrovascular accident, 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, P2Y12 reaction units and medications included a maintained dose of ticagrelor, prescription of angiotensin converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB), beta blockers, and calcium channel blockers. PSM and cox regression analyses were performed to identify the bleeding and ischemic risks between the two groups. After PSM, 699 patients (ticagrelor: clopidogrel = 233:466) 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 843 patients (ticagrelor: clopidogrel = 235:608), after which 699 patients (ticagrelor: clopidogrel = 233:466) 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 (\( P = 0.162 \)). Other factors, except for the incidence of STEMI, also did not show any statistical differences between groups. The proportion of STEMI was larger in the ticagrelor group than in the clopidogrel group [120 (51.5%) vs. 183 (39.3%), \( P< 0.003 \)].

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 bleeds (HR, 1.61; 95% CI: 0.84–3.08). Use of the transradial approach for PCI (HR, 0.30; 95% CI: 0.15–0.60), use of statins (HR, 0.37; 95% CI: 0.16–0.86), and successful PCI (HR, 0.16; 95% CI: 0.04–0.68) lowered the risk of bleeding (Figure 2). In contrast, a low BMI (HR, 2.71; 95% CI: 1.18–6.21) increased the risk of bleeds (Figure 2). Detailed data for bleeding events (BARC type and origin) are presented in Table 2.
3. Cox regression analysis for ischemic risk

Further, cox regression analysis was performed for the ischemic risk. There was no significant difference between ticagrelor and clopidogrel (HR, 1.00; 95% CI: 0.68–1.46). Low BMI (HR, 3.01, 95% CI: 1.70–5.34), hemoglobin <9 g/dL (HR, 2.19, 95% CI: 1.27-3.80), high Killip class (HR, 1.99, 95% CI: 1.37–2.89), LVEF <40% (HR, 1.71; 95% CI: 1.16–2.54), and multivessel disease (HR, 1.58, 95% CI: 1.04–2.40) increased the ischemic risk. Post TIMI flow grade $\geq$3 (HR, 0.73; 95% CI: 0.54–0.99), use of ACEi or ARB (HR, 0.51; 95% CI: 0.34–0.76), beta blockers (HR, 0.49; 95% CI: 0.33–0.73), and statins (HR, 0.20; 95% CI: 0.13–0.30) decreased the ischemic risk (Figure 3). The detailed data for MACCE are presented in Table 3.

Discussion

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. According to our cox regression analyses, using the transradial approach for PCI, use of statins and successful PCI lowered the occurrence of a bleeding event. In contrast, low BMI increased the risk of bleeds. In the aspect of ischemia, low BMI, hemoglobin < 9 g/dL, high Killip class, low LVEF and multivessel disease increased the risk. On the other hand, post TIMI flow grade $\geq$ 3, use of ACEi or ARB, beta blockers and statins decreased the occurrence of an ischemic event.

Previous studies have attempted to reveal the optimal antiplatelet agent for AMI patients by comparing clopidogrel and the other potent P2Y12 inhibitors [13–17]. In patients with stable coronary artery disease and type 2 DM, ticagrelor was beneficial regarding ischemia according to THEMIS trial (the effect of ticagrelor on health outcomes in DM patients intervention study). [28, 29]. The difficulty of optimal antiplatelet agent selection for elderly patients with DM comprises of numerous factors, including angiographic findings, comorbidities, and patient history. We investigated this issue to reveal the optimal DAPT strategy for this patient group to make this treatment choice easier and less ambiguous for physicians. To our knowledge, our study is the first to analyze the risks of bleeding and ischemia according to antiplatelet agents in this specific group.

According to our cox regression results, low BMI increased the risk of both bleeding and ischemia. Referring to previous studies, physicians should take care when treating patients with a low BMI in this study population [26, 27]. Hemoglobin < 9 g/dL, high Killip class, low LVEF and multivessel disease also increased the risk of ischemia. On the other hand, transradial approach and successful PCI decreased the risk of bleeding, and post TIMI flow grade $\geq$ 3, use of ACEi or ARB, beta blockers and statins decreased the risk of ischemia. These findings were consistent with those of the previous studies [5–7, 23–25].

Figure 2 and 3 depicts the decrease in both bleeding and ischemia risks with the use of statins. Use of statins to improve the outcome of ischemic event in AMI patients has been reported in previous studies and recommended by current guidelines [3, 4]. There are several reports that analyze the effect of statin on bleeding in other diseases; however, the results are inconsistent and unclear [30–31].
Despite our efforts, there are some limitations to this study. Our study is not a randomized controlled trial; we used data from the KAMIR-V registry. This introduced clinician bias for patients who participated in this study. As previously mentioned, PSM was performed to minimize this limitation; however, the incidence of STEMI showed a statistically significant difference, with the proportion of STEMI being larger in the ticagrelor group than in the clopidogrel group. This points to the clinician bias toward reducing ischemic risk rather than bleeding risk in STEMI patients, reflected in our data. This highlights the necessity for large scale, long term randomized controlled trials to determine the DAPT strategy in this patient group.

The inadequacy of the data available resulted in a lack of patient details such as the total number and length of stents [32]. In other reports, clopidogrel resistance was commonly observed in East Asian people and this contributed to recurrent ischemic events [33–36]. Furthermore, according to a report focused on Koreans, approximately 47% of the study population carried at least one CYP2C19*2 allele, a critical gene associated with clopidogrel resistance [35]. However, according to TAILOR-PCI Randomized Clinical Trial, genotype-guided selection of an oral P2Y12 inhibitor, compared with conventional clopidogrel therapy without point-of-care genotyping, did not display statistically significant differences in a composite end point of cardiovascular death, MI, stroke, stent thrombosis, and severe recurrent ischemia at 12 months [36].

In KAMIR-V, P2Y12 reaction units were measured in only 9.8% (1,531 of 15,628) overall and 9.3% (78 of 839) in the study population. In the clopidogrel group, P2Y12 reaction units were measured in 51 patients before PSM (51 of 606, 8.4%) and 37 patients after PSM. In the ticagrelor group, it was measured in 27 patients before and after PSM (27 of 233, 11.5%). Significant differences were noted between the two groups ([219.2 ± 89.3 vs. 108.7 ± 83.0, P < 0.001 before PSM; 178.4 ± 97.4 vs. 81.5 ± 83.1, P < 0.001 after PSM], Table 1). However, it was measured only in small portion of study population. Therefore, it was unclear whether these values represent the whole study population. Comprehensively, we were unable to evaluate the extent to which these values affected our results.

Regarding bleeding risk, previous bleeding events, such as gastrointestinal bleeding history, peptic ulcer, or prescription of proton pump inhibitors (PPI), could not be analyzed due to lack of data. The association between peptic ulcer disease, gastrointestinal bleeding, and antiplatelet agents has been well established in previous studies [37, 38]. Therefore, the physician should make the decision by weighing the bleeding and ischemic risks, especially with stent thrombosis. The interruption of antiplatelet agent treatment and bleeding events in the early period after stent implantation deserves careful thought and continues to challenge clinicians [39]. To minimize bleeding risk, the use of PPI is recommended according to guidelines. However, due to reported interactions between PPI agents and clopidogrel, clinicians must decide carefully whether to use a PPI agent and what type of PPI agent to use [5].

Conclusions
In this Korean prospective cohort study, there were no significant differences in the risks for bleeding and ischemia, based on the use of ticagrelor or clopidogrel, in elderly Korean patients with DM. To determine the optimal antiplatelet agents for these patients, large scale, long term, randomized controlled trials are warranted.

**Abbreviations**

ACEi  
Angiotensin converting enzyme inhibitors

AMI  
Acute myocardial infarction

ARB  
Angiotensin ii receptor blockers

BARC  
Bleeding academic research consortium

BMI  
Body mass index

CABG  
Coronary artery bypass grafting

CI  
Confidence interval

CVA  
Cerebrovascular accident

DAPT  
Dual antiplatelet therapy

DM  
Diabetes mellitus

GFR  
Glomerular filtration rate

HF  
Heart failure

HR  
Hazard ratio

KAMIR  
Korea acute myocardial infarction registry

LM  
Left main coronary artery

LVEF  
Left ventricular ejection fraction

MACCE  
Major adverse cardiac and cerebrovascular events

MDRD eGFR  
Modification of Diet in Renal Disease Study estimated glomerular filtration rate

MI  
Myocardial infarction

NSTEMI  
Non ST elevation myocardial infarction
Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Review Committee of the Chonnam National University Hospital Biomedical Research Institute. Informed consent was obtained from all subjects. This study was conducted according to the principles expressed in the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing Interests

The authors declare that they have no competing interests.

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Authors' contributions

Conceptualization; Lee SH, Cho KH, Jeong MH


Formal analysis; Lee SH, Cho KH

Funding acquisition; Hyun DY, Cho KH, Sim DS, Jeong MH

Investigation; Lee SH, Cho KH

Methodology; Lee SH, Cho KH
Acknowledgements

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References


Tables

Table 1 is available in the Supplementary Files section.

Table 2. Type and origin of bleeding events
<table>
<thead>
<tr>
<th>BARC Type</th>
<th>Clopidogrel</th>
<th>Ticagrelor</th>
<th>p-value</th>
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<tr>
<td></td>
<td>n=466</td>
<td>n=233</td>
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<tr>
<td>2</td>
<td>12 (2.6%)</td>
<td>8 (3.4%)</td>
<td>0.688</td>
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<td>3a</td>
<td>6 (1.3%)</td>
<td>4 (1.7%)</td>
<td>0.910</td>
</tr>
<tr>
<td>3b</td>
<td>1 (0.2%)</td>
<td>2 (0.9%)</td>
<td>0.539</td>
</tr>
<tr>
<td>3c</td>
<td>2 (0.4%)</td>
<td>1 (0.4%)</td>
<td>1.000</td>
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<tr>
<td>5a</td>
<td>0 (0.0%)</td>
<td>1 (0.4%)</td>
<td>0.723</td>
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<tr>
<td>Origin</td>
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<tr>
<td>Urogenital</td>
<td>3 (0.6%)</td>
<td>0 (0.0%)</td>
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</tr>
<tr>
<td>Vascular access</td>
<td>2 (0.4%)</td>
<td>5 (2.1%)</td>
<td>0.081</td>
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<tr>
<td>Cerebral</td>
<td>1 (0.2%)</td>
<td>1 (0.4%)</td>
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<tr>
<td>GI bleeding and others</td>
<td>15 (3.2%)</td>
<td>10 (4.3%)</td>
<td>0.614</td>
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</table>

BARC: Bleeding Academic Research Consortium, GI bleeding: Gastrointestinal bleeding

Table 3. Detailed data of ischemic events
<table>
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<th></th>
<th>Clopidogrel</th>
<th>Ticagrelor</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=466</td>
<td>n=233</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total death</td>
<td>67 (14.4%)</td>
<td>31 (13.3%)</td>
<td>0.787</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>40 (8.6%)</td>
<td>26 (11.2%)</td>
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<tr>
<td>Non cardiac death</td>
<td>27 (5.8%)</td>
<td>5 (2.1%)</td>
<td>0.047</td>
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<td>STEMI</td>
<td>3 (0.6%)</td>
<td>1 (0.4%)</td>
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<tr>
<td>NSTEMI</td>
<td>6 (1.3%)</td>
<td>2 (0.9%)</td>
<td>0.900</td>
</tr>
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<td>TLR</td>
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<td>TVR</td>
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<td>de novo</td>
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<td>1 (0.4%)</td>
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<td>CABG</td>
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<td>CVA</td>
<td>9 (1.9%)</td>
<td>4 (1.7%)</td>
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<tr>
<td>Rehospitalization d/t HF</td>
<td>27 (5.8%)</td>
<td>10 (4.3%)</td>
<td>0.511</td>
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<tr>
<td>Stent thrombosis</td>
<td>7 (1.5%)</td>
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<tr>
<td>Acute</td>
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<td>Subacute</td>
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<tr>
<td>Late</td>
<td>3 (0.6%)</td>
<td>1 (0.4%)</td>
<td>1.000</td>
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</table>


**Figures**
Figure 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.
Figure 2

Cox regression analysis for bleeding risk

BARC: bleeding academic research consortium, BMI: body mass index, CI: confidence interval, PCI: percutaneous coronary intervention.

Figure 3
Cox regression analysis for ischemic risk

ACEi: angiotensin converting enzyme inhibitors, ARB: angiotensin II receptor blockers,

BARC: bleeding academic research consortium, BMI: body mass index, CI: confidence interval, LVEF: left ventricular ejection fraction, MACCE: major adverse cardiac and cerebrovascular events, STEMI: ST-segment elevation myocardial infarction, TIMI: thrombolysis in myocardial infarction.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.docx