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Original Research

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Ticagrelor Monotherapy *vs.* Ticagrelor With Aspirin in Bleeding and Cardiovascular Events in Acute Coronary Syndrome Patients According to Renal Function: The Subanalysis From the TICO Trial

Ji Hyun Lee, MD[1], Hyeonju Jeong, MD[1], Eui-Seock Hwang, MD[1], Sung-Jin Hong, MD[2], Chul-Min Ahn, MD[2], Jung-Sun Kim, MD[2], Byeong-Keuk Kim, MD[2], Young-Guk Ko, MD[2], Donghoon Choi, MD[2], Myeong-Ki Hong, MD[2], Yangsoo Jang, MD[3], Yun-Hyeong Cho, MD, PhD[1], and Yongsung Suh, MD[1]

[1]Division of Cardiology, Department of Internal Medicine, Myongji Hospital, Hanyang University College of Medicine, Goyang, Korea
[2]Division of Cardiology, Severance Cardiovascular Hospital, Yonsei University College of Medicine, Seoul, Korea
[3]Division of Cardiology, CHA Bundang Medical Center, CHA University College of Medicine, Seongnam, Korea

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Correspondence to
Yongsung Suh, MD
Division of Cardiology, Myongji Hospital, Hanyang University College of Medicine, 55, Hwasu-ro 14beon-gil, Deokyang-gu, Goyang 10475, Korea.
Email: yongsung.seo@gmail.com

ORCID iDs
Ji Hyun Lee
https://orcid.org/0000-0003-1831-6735
Hyeonju Jeong
https://orcid.org/0000-0002-7916-3624
Eui-Seock Hwang
https://orcid.org/0000-0002-3025-8921
Sung-Jin Hong
https://orcid.org/0000-0003-4893-039X
Chul-Min Ahn
https://orcid.org/0000-0002-7071-4370
Jung-Sun Kim
https://orcid.org/0000-0003-2263-3274
Byeong-Keuk Kim
https://orcid.org/0000-0003-2493-066X
Young-Guk Ko
https://orcid.org/0000-0001-7748-5788

AUTHOR'S SUMMARY

This study demonstrated that for acute coronary syndrome patients treated with drug eluting stents, decreased renal function is related with poor clinical outcomes. Irrespective of renal function, ticagrelor monotherapy after 3 months of dual antiplatelet therapy (DAPT) resulted in a reduced risk of net adverse clinical events as well as major or minor bleeding, compared with ticagrelor-based 12-month DAPT. But, regardless of renal function, the risk of major bleeding and major adverse cardiovascular and cerebrovascular events was not significantly different between the two treatment groups.

ABSTRACT

Background and Objectives: Ticagrelor monotherapy after short-term dual-antiplatelet therapy (DAPT) has not been established in chronic kidney disease (CKD) patients. This study evaluated the effects of ticagrelor monotherapy after 3-month of DAPT on renal function in acute coronary syndrome patients.
Methods: From the TICO trial, the primary outcome was a composite of net adverse clinical events (NACEs), defined as a composite of major bleeding and major adverse cardiovascular and cerebrovascular events (MACCEs). The secondary outcomes were thrombolysis in myocardial infarction (TIMI) major or minor bleeding and MACCE.
Results: Among patients without CKD (n=2,436), ticagrelor monotherapy after 3 months of DAPT had a lower rate of NACE (hazard ratio [HR], 0.41; 95% confidence interval [CI], 0.21–0.78; p=0.007) and TIMI bleeding (HR, 0.86; 95% CI, 0.19–0.81; p=0.011) than those

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Donghoon Choi
https://orcid.org/0000-0002-2009-9760
Myeong-Ki Hong
https://orcid.org/0000-0002-2090-2031
Yangsoo Jang
https://orcid.org/0000-0002-2169-3112
Yun-Hyeong Cho
https://orcid.org/0000-0001-7581-9545
Yongsung Suh
https://orcid.org/0000-0002-1975-123X

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Conflict of Interest
The authors have no financial conflicts of interest.

Data Sharing Statement
The data generated in this study is available from the corresponding author upon reasonable request.

Author Contributions
Conceptualization: Lee JH, Jeong H, Hwang ES, Cho YH, Suh Y; Data curation: Lee JH, Jeong H, Hwang ES, Hong SJ, Ahn CM, Kim JS, Kim BK, Ko YG, Choi D, Hong MK, Jang Y, Cho YH, Suh Y; Formal analysis: Lee JH, Cho YH, Suh Y; Funding acquisition: Jang Y; Investigation: Lee JH, Jeong H, Hong SJ, Ahn CM, Kim JS, Kim BK, Ko YG, Choi D, Hong MK, Jang Y, Cho YH, Suh Y; Methodology: Lee JH, Hong SJ, Ahn CM, Kim JS, Kim BK, Ko YG, Choi D, Hong MK, Jang Y, Cho YH, Suh Y; Resources: Jang Y; Supervision: Cho YH, Suh Y; Writing - original draft: Lee JH; Writing - review & editing: Lee JH, Jeong H, Hwang ES, Hong SJ, Ahn CM, Kim JS, Kim BK, Ko YG, Choi D, Hong MK, Jang Y, Cho YH, Suh Y.

of ticagrelor-based 12-month DAPT. Among CKD patients receiving ticagrelor monotherapy, lower risk of NACE (HR, 0.45; 95% CI, 0.20–1.02; p=0.055) and bleeding (HR, 0.20; 95% CI, 0.06–0.68; p=0.009) were observed. Otherwise, ticagrelor monotherapy was not significantly associated with an increased MACCE risk in those without CKD (HR, 0.62; 95% CI, 0.30–1.27; p=0.192) or with CKD (HR, 0.55; 95% CI, 0.21–1.48; p=0.237), versus 12-month DAPT.
Conclusions: Regardless of renal function, ticagrelor monotherapy after 3 months of DAPT resulted in a reduced risk of not only NACE but also major or minor bleeding at 1 year compared with ticagrelor-based 12-month DAPT. Irrespective of renal function status, however, the MACCE risk was not significantly different between the two strategies.

Keywords: Acute coronary syndrome; Ticagrelor; Chronic kidney disease

INTRODUCTION

Acute coronary syndrome (ACS) patients remain at an increased risk of cardiovascular ischemic events, especially during the first year, even if successful revascularization has been accomplished.[1] In this regard, dual-antiplatelet therapy (DAPT) with aspirin and P2Y12 inhibitors has been established as an effective treatment to prevent recurrent ischemic events, including stent thrombosis, because these antiplatelet agents inactivate and inhibit independent signals of platelet activation.[2] Current guidelines recommend 12 months of DAPT with potent antiplatelet agents for ACS patients undergoing percutaneous coronary intervention (PCI).[3][4] However, the use of longer DAPT has raised concerns for an increased risk of bleeding[5] hence, an aspirin-free strategy after DAPT was recently introduced to lessen bleeding risk, and several randomized trials have evaluated this strategy to maintain potent P2Y12 inhibitors after short-term DAPT.[6][7] Of these, ticagrelor monotherapy after 3 months in patients treated with new-generation sirolimus-eluting stent for ACS (TICO) trial recently proved the superiority of ticagrelor monotherapy after 3 months of DAPT over ticagrelor-based 1-month DAPT in the occurrence of net adverse clinical events (NACEs) in ACS patients.[7]

Chronic kidney disease (CKD) is an emerging public health concern worldwide. The prevalence of CKD increases with age, reaching approximately 30% in the elderly.[8] CKD patients are at a higher risk for adverse cardiovascular events arising from a prothrombotic tendency related to CKD than are patients without CKD are.[9] The mechanism for the higher event rate remains unclear, but has been proposed, such as augmented atherosclerosis and high platelet reactivity.[10] Therefore, a potent P2Y12 inhibitor strategy may be effective in CKD patients with a high risk of thrombosis. Along with ischemic risk, however, CKD patients also have a higher tendency to bleed, and a higher major or minor bleeding risk has been reported in patients taking antiplatelet agents.[11][12] Decision-making for the optimal duration of DAPT is still challenging in CKD patients, and the best strategy remains to be elucidated. Therefore, we aimed to determine the effects and safety of ticagrelor monotherapy after 3 months of DAPT according to baseline renal function compared with the ticagrelor-based 12-month DAPT after drug-eluting stents (DESs) implantation in ACS patients.

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METHODS

Ethical statement

The trial was approved by the Institutional Review Board of Yonsei University College of Medicine (approval No. 1-2014-0066) and Myongji Hospital (MJH2015-01-059) and followed the ethical principles of the Declaration of Helsinki 2013. All participants provided written informed consent, and the Institutional Review Board of each study site approved the study protocol.

Study design and participants

The design of the TICO registry has been previously described.[13] Briefly, the TICO registry is a prospective, multicenter, open-label, randomized superiority study of 3,056 patients treated with DES for ACS (unstable angina, non-ST-elevation myocardial infarction (MI), or ST-elevation MI) to evaluate ticagrelor monotherapy followed by 3-month DAPT versus ticagrelor-based 12-month DAPT. Detailed information related to the study protocol, including the inclusion and exclusion criteria, study coordination, data management, and site management service, has been previously described.[7][13]

Renal function assessment

Standardized serum creatinine was used to appraise renal function and estimated glomerular filtration rate (eGFR) was calculated for each patient using the Levey Modification of Diet in Renal Disease (MDRD) formula: eGFR=175×Serum Creatinine–1.154×Age–0.203 [×0.742, if female].[14] The eGFR was expressed as mL/min/1.73 m^2. In the current analyses for the purpose of this study, all enrolled patients were stratified according to an eGFR cut-off of 60 mL/min/1.73 m^2 on the basis of the Kidney Disease Improving Global Outcomes 2012 Clinical Practice Guidelines for the Evaluation and Management of CKD.[15] Among paticipants with an eGFR <60 mL/min/1.73 m^2, 33 patients were on dialysis.

Study exposures and outcomes

All enrolled subjects were discharged with a single aspirin dose (100 mg) and two ticagrelor doses (90 mg) after successful PCI. Following 3 months of DAPT, aspirin was discontinued in the ticagrelor monotherapy group and continued in the ticagrelor-based 12-month DAPT group. The primary outcome was a NACE, defined as a composite of major bleeding and major adverse cardiac and cerebrovascular events (MACCEs), within 12 months following PCI. Major bleeding was defined according to the thrombolysis in myocardial infarction (TIMI) criteria, which included intracranial bleeding, hemorrhage with a hemoglobin decrease of at least 5 g/dL, or fatal bleeding that caused death within 7 days.[16] The composite of major and minor bleeding was assessed as a prespecified primary outcome. MACCE include all-cause mortality, MI, stent thrombosis, stroke, or target-vessel revascularization. The secondary outcomes were each component of TIMI, major or minor bleeding, or MACCE. Further outcomes included all-cause death, cardiac death, noncardiac death, acute MI, stent thrombosis, any stroke, ischemic or hemorrhagic stroke, stent thrombosis, and target-vessel revascularization. Detailed definitions of these events are described in a previous study.[7]

Statistical analysis

Baseline characteristics were compared across the presence and absence of CKD according to study exposure. Continuous variables were reported as mean ± standard deviation, and categorical variables were presented as counts with proportions. Differences between continuous variables were analyzed using the independent sample Student's t-test or the Whitney U-test. Between-group comparisons of categorical variables were computed using

Pearson's χ^2 test or Fisher's exact test, as appropriate. We constructed Cox proportional hazard models to calculate hazard ratios (HRs) and associated 95% confidence intervals (CIs) for the risk of the study outcomes. The heterogeneity of treatment effects for ticagrelor monotherapy versus ticagrelor-based DAPT for 12 months according to renal function was employed using the interaction term in an adjusted Cox proportional hazards model. Univariate and multivariate Cox regression analyses were performed to determine independent predictors of each adverse event. The prespecified 3 months landmark analyses were performed after excluding subjects who experienced adverse events within this period because the same treatment was administered in both groups during the first 3 months (**Figure 1**). For each adverse event, all variables (p<0.05) in the univariate analyses

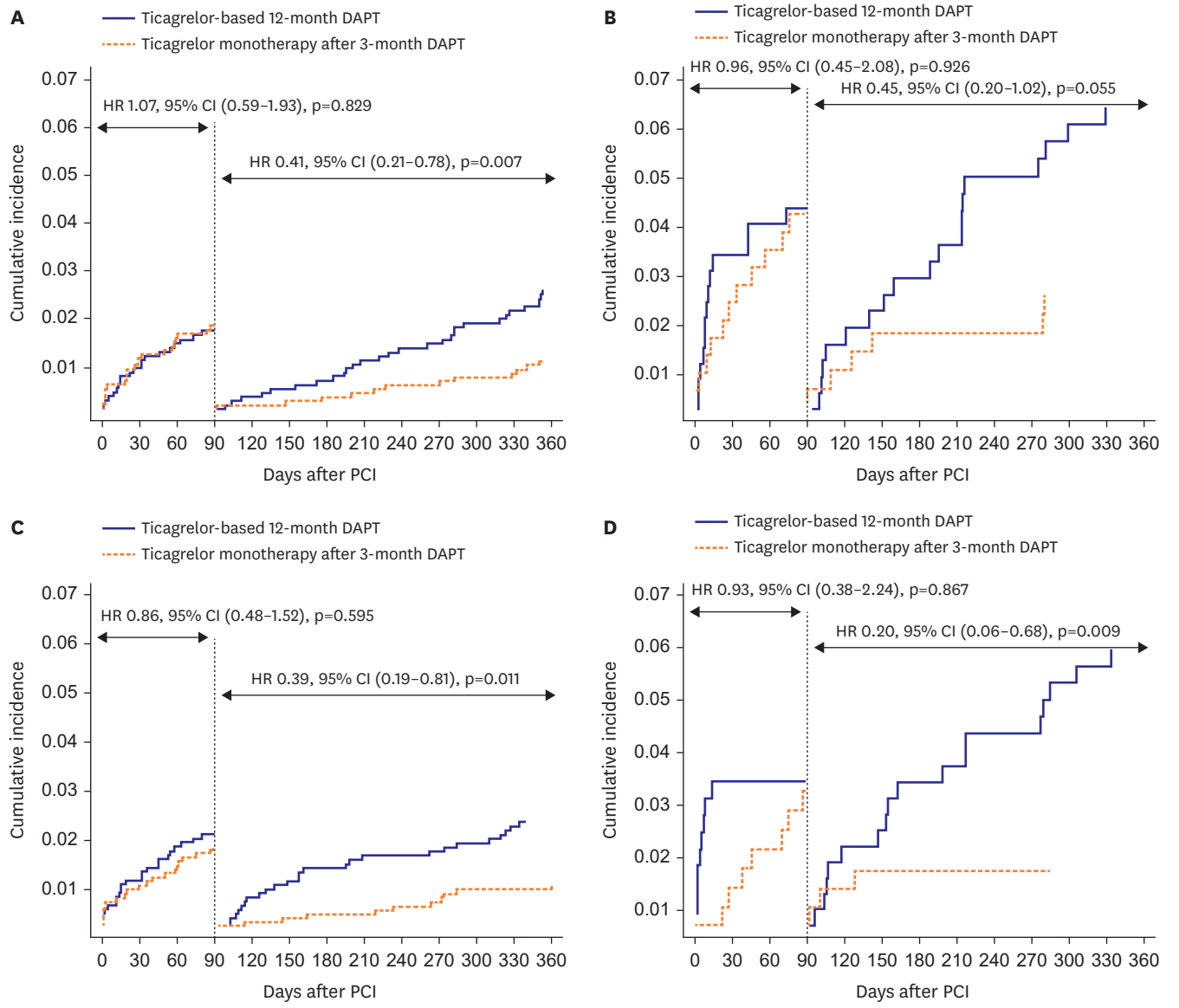

Figure 1. Landmark analyses: Time-to-event curves for the outcomes according to study exposures by the presence or absence of CKD. (A) NACE in no CKD, (B) NACE in CKD, (C) TIMI major or minor bleeding in no CKD, (D) TIMI major or minor bleeding in CKD, (E) MACCE in no CKD, (F) MACCE in CKD.
CI = confidence interval; CKD = chronic kidney disease; DAPT = dual-antiplatelet therapy; HR = hazard ratio; MACCE = major adverse cardiac and cerebrovascular event; NACE = net adverse clinical event; TIMI = thrombolysis in myocardial infarction; PCI = percutaneous coronary intervention.

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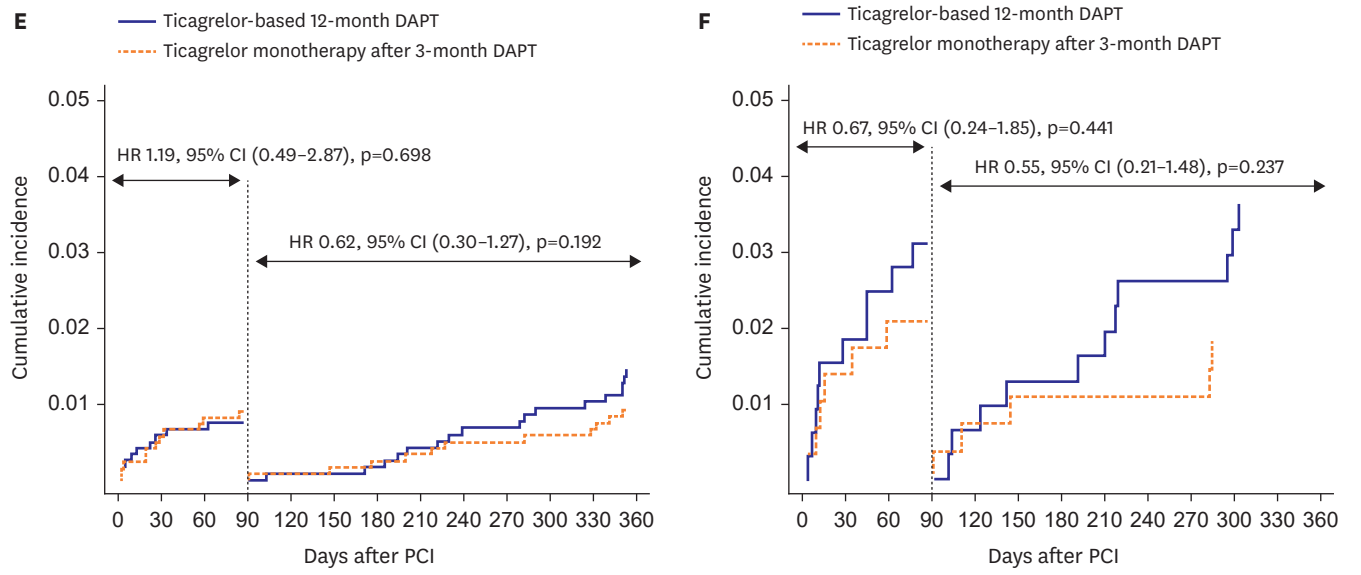

Figure 1. (Continued) Landmark analyses: Time-to-event curves for the outcomes according to study exposures by the presence or absence of CKD. (A) NACE in no CKD, (B) NACE in CKD, (C) TIMI major or minor bleeding in no CKD, (D) TIMI major or minor bleeding in CKD, (E) MACCE in no CKD, (F) MACCE in CKD.
CI = confidence interval; CKD = chronic kidney disease; DAPT = dual-antiplatelet therapy; HR = hazard ratio; MACCE = major adverse cardiac and cerebrovascular event; NACE = net adverse clinical event; TIMI = thrombolysis in myocardial infarction; PCI = percutaneous coronary intervention.

and ticagrelor monotherapy after 3 months of DAPT were entered into the multivariable analyses, as described in **Figure 2**. The Cubic spline curves of clinical outcomes according to renal function by study exposures were described based on a full adjusted confounders model (p for nonlinear <0.001, **Figure 3**), where the lines represent the HR and the colored arrears represent the 95% CI. All statistical analyses were performed using STATA version 13 (StataCorp LP, College Station, TX, USA), and a two-tailed p value less than 0.05 was considered statistically significant.

RESULTS

Baseline characteristics

Overall, the study population consisted of 3,056 participants; 79.5% were male, and the mean age of the cohort was 61±11 years between August 2015 and October 2018. We randomly assigned 1,527 patients (50%) to receive ticagrelor monotherapy after 3 months of DAPT, and 1,529 patients (50%) were randomized to receive ticagrelor-based 12-month DAPT. **Table 1** shows the baseline characteristics of the study exposures according to the presence or absence of CKD. In the ticagrelor monotherapy group, 1,235 (80.9%) had eGFR ≥60 mL/min/1.73 m^2 and 292 (19.1%) had eGFR <60 mL/min/1.73 m^2. Similarly, of the ticagrelor-based 12-month DAPT group, 1,201 (78.5%) had eGFR ≥60 mL/min/1.73 m^2 and 328 (21.5%) had eGFR <60 mL/min/1.73 m^2. In both groups, CKD patients were older, more often female, and had a higher likelihood of comorbid conditions such as dyslipidemia, hypertension, diabetes, and prior history of PCI, stroke, or MI. As for procedures, patients without CKD had a lower prevalence of multivessel coronary artery disease, multilesion or vessel intervention, treated lesions per patient, total number of stents per patient, and total stent length per patient than did CKD patients.

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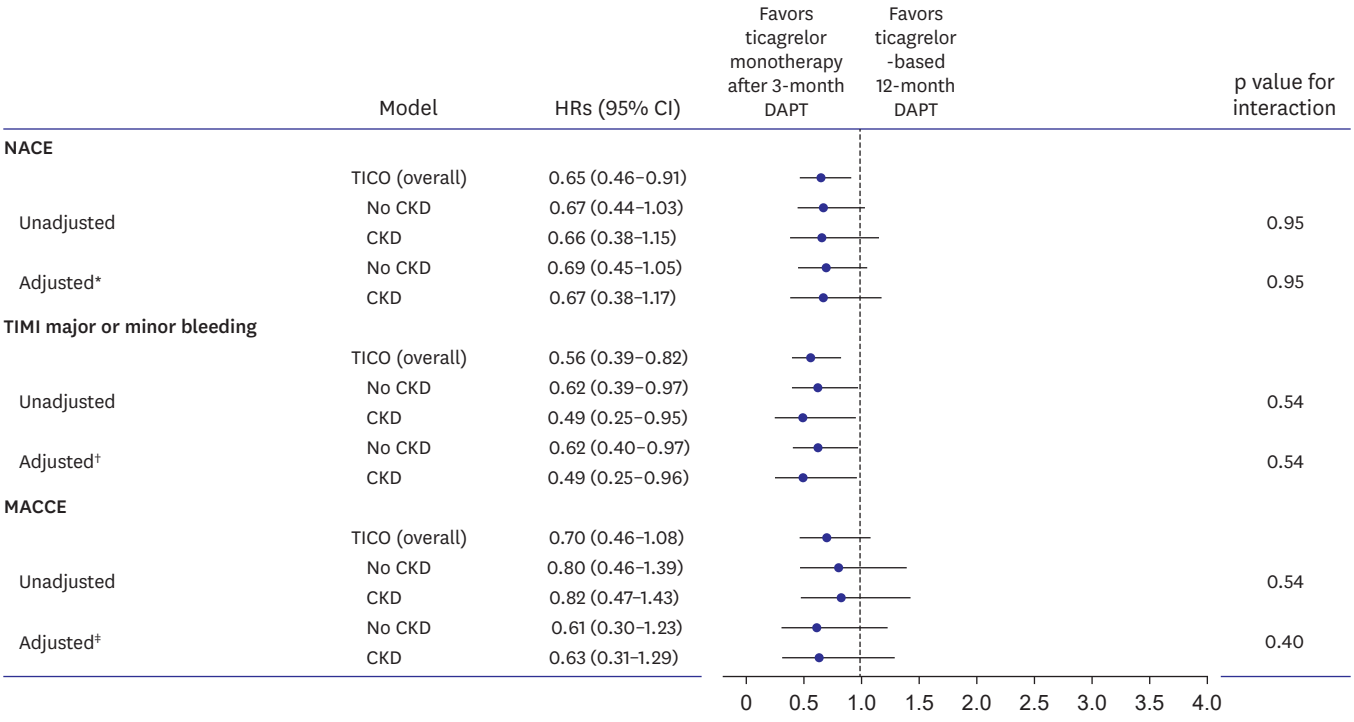

Figure 2. One-year clinical outcomes in relation to the absence of presence of CKD.
BMI = body mass index; CABG = coronary artery bypass grafting; CI = confidence interval; CKD = chronic kidney disease; DAPT = dual-antiplatelet therapy; HR = hazard ratio; MACCE = major adverse cardiac and cerebrovascular events; NACE = net adverse clinical event; TIMI = thrombolysis in myocardial infarction; TICO = ticagrelor monotherapy after 3 months in patients treated with new-generation sirolimus-eluting stents for acute coronary syndrome.
*Adjusted for age, BMI, sex, hypertension, diabetes, prior MI, prior CABG, femoral approach, and multivessel disease.
†Adjusted for age, BMI, sex, diabetes, and femoral approach.
‡Adjusted for age, BMI, sex, hypertension, diabetes, prior PCI, prior MI, prior CABG, and multivessel disease.

Primary composite outcome

During follow-up (median observation period, 365 days [interquartile range, 365–365)], the primary outcome of NACE occurred in 59 (3.9%) patients receiving ticagrelor monotherapy after 3 months of DAPT and in 89 patients (5.8%) receiving ticagrelor-based 12-month DAPT (**Table 2**). The incidence of NACE increased significantly in CKD patients in both study exposures. **Figure 1** displays the prespecified 3-month landmark analysis for NACE between 3 and 12 months. Among the patients without CKD, a NACE occurred in 13 patients (1.1%) received ticagrelor monotherapy after 3 months of DAPT and 31 patients (2.6%) received 12-month DAPT (HR, 0.41; 95% CI, 0.21–0.78; p=0.007) (**Figure 1A**). In CKD patients, NACE occurred in 8 patients (3.0%) receiving ticagrelor monotherapy after 3 months of DAPT and in 20 patients (6.5%) receiving ticagrelor-based 12-month DAPT (HR, 0.45; 95% CI, 0.20–1.02; p=0.055) (**Figure 1B**). No significant interaction was observed between antiplatelet therapy strategy and renal function status for the occurrence of the primary outcome (**Figure 2**).

Bleeding outcome

The secondary outcomes of TIMI major and minor bleeding occurred in 53 (3.5%) patients receiving ticagrelor monotherapy after 3 months of DAPT and in 83 patients (5.3%) receiving ticagrelor-based 12-month DAPT (**Table 2**). The prevalence of bleeding increased in subjects with CKD in both the groups. For the prespecified 3-month landmark analysis between 3 and 12 months among patients without CKD, major or minor bleeding occurred in 22 patients (1.8%) receiving ticagrelor monotherapy after 3 months of DAPT and in 39 (3.3%) receiving

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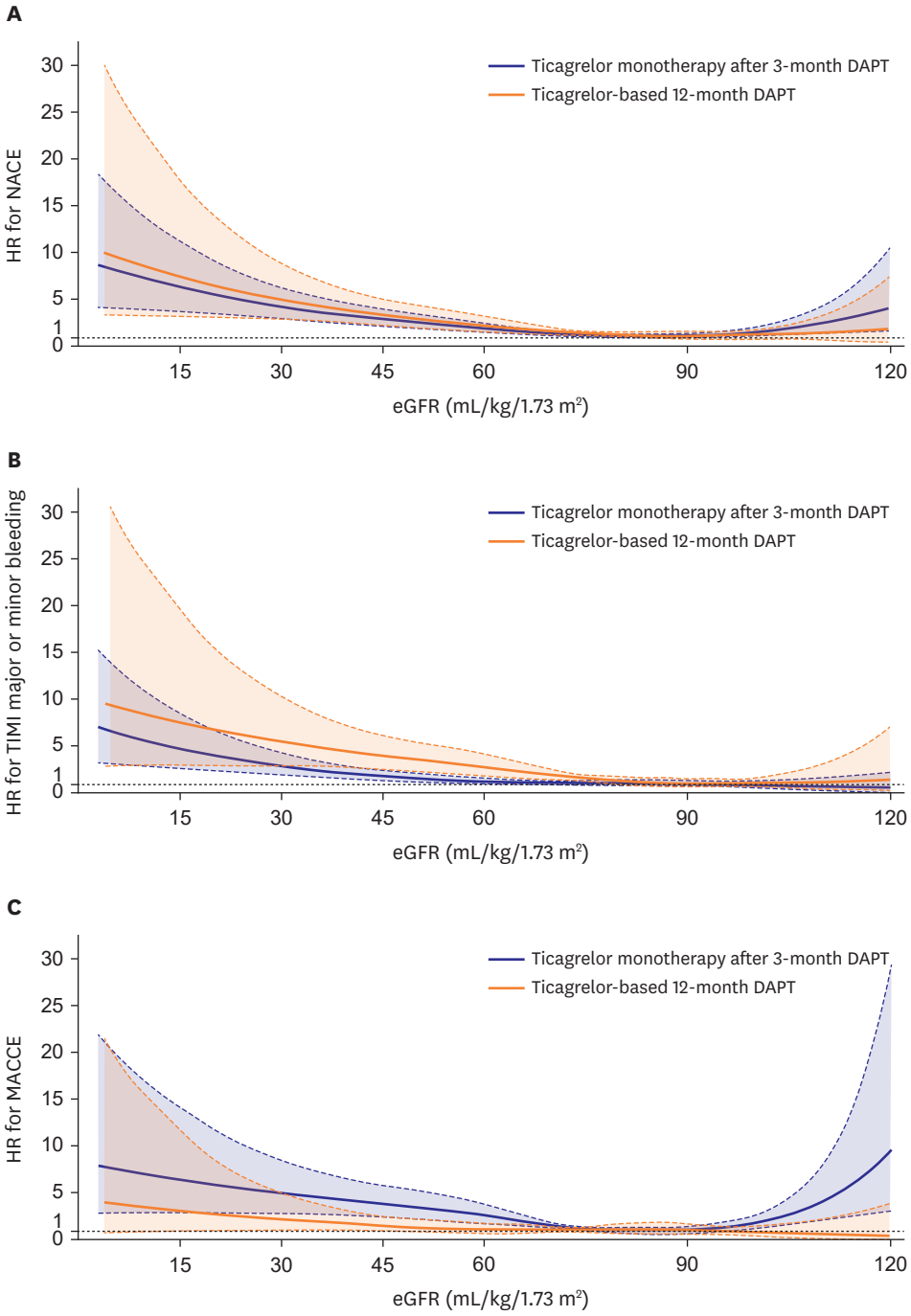

Figure 3. Cubic spline curves of clinical outcomes according to renal function by study exposures. (A) NACE, (B) TIMI major or minor bleeding, (C) MACCE.
eGFR = estimated glomerular filtration rate; HR = hazard ratio; MACCE = major adverse cardiac and cerebrovascular event; NACE = net adverse clinical event; TIMI = thrombolysis in myocardial infarction.

12-month DAPT (HR, 0.86; 95% CI, 0.19–0.81; p=0.011) (**Figure 1C**). Among CKD patients, major or minor bleeding occurred in 8 (3.0%) patients who received ticagrelor monotherapy after 3 months of DAPT and in 21 (6.8%) who received ticagrelor-based 12-month DAPT (HR, 0.20; 95% CI, 0.06–0.68; p=0.009) (**Figure 1D**). Between the antiplatelet therapy strategy

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Table 1. Demographic characteristics and presentation at admission by study exposures according to renal function

Variables	Overall (n=3,056)	Ticagrelor monotherapy after 3-months DAPT (n=1,527)		Ticagrelor-based 12-months DAPT (n=1,529)	
		No CKD ≥60 (n=1,235)	CKD <60 (n=292)	No CKD ≥60 (n=1,201)	CKD <60 (n=328)
Age (years)	61±11	60±11	66±10	60±10.5	66±10
Men	2,428 (79.5)	993 (80.4)	211 (72.3)	982 (81.8)	242 (73.8)
BMI (kg/m^2)	24.9±3.3	25.0±3.2	25.0±3.2	24.9±3.4	25.0±3.2
Creatinine (mg/dL)	1.0±0.8	0.8±0.2	1.6±1.5	0.9±0.2	1.8±1.8
eGFR (mL/min/1.73 m^2)	76.7±23.5	85.1±20.5	47.5±13.1	83.6±17.0	46.1±14.2
Comorbid conditions					
Dyslipidemia	1,846 (60.4)	736 (59.6)	188 (64.4)	717 (59.7)	205 (62.5)
Hypertension	1,541 (50.4)	572 (46.3)	188 (64.4)	574 (47.8)	207 (63.1)
Current smoker	1,142 (37.4)	486 (39.4)	59 (23.6)	482 (40.1)	105 (32.0)
Diabetes	835 (27.3)	294 (23.8)	124 (42.5)	280 (23.3)	137 (41.8)
Prior PCI	262 (8.6)	99 (8.0)	36 (12.3)	93 (7.7)	34 (10.4)
Prior stroke	126 (4.1)	35 (2.8)	25 (8.6)	46 (3.8)	20 (6.1)
Prior MI	113 (3.7)	48 (3.9)	16 (5.5)	31 (2.6)	18 (5.5)
Prior coronary bypass graft	18 (0.6)	7 (0.6)	1 (0.3)	5 (0.4)	5 (1.5)
Clinical presentation					
Unstable angina	926 (30.3)	366 (29.6)	76 (26.0)	396 (33.0)	88 (26.8)
Non-ST-elevation MI	1,027 (33.6)	443 (35.9)	96 (32.9)	378 (31.5)	110 (33.5)
ST-elevation MI	1,103 (36.1)	426 (34.5)	120 (41.1)	427 (35.6)	130 (39.6)
Antithrombotic drug before intervention					
Unfractionated heparin	1,898 (62.1)	749 (60.7)	198 (67.8)	729 (60.7)	222 (67.7)
Low-molecular-weight heparin	267 (8.7)	100 (8.1)	25 (8.6)	118 (9.8)	24 (7.3)
Glycoprotein IIb/IIIa inhibitors	197 (6.5)	77 (6.2)	23 (7.9)	69 (5.8)	28 (8.5)
Antiplatelet drug before intervention					
Aspirin	2,921 (95.6)	1,191 (96.4)	279 (95.6)	1,141 (95.0)	310 (94.5)
Clopidogrel	1,044 (34.2)	440 (35.6)	105 (36.0)	391 (32.6)	108 (32.9)
Ticagrelor	2,171 (71.0)	864 (70.0)	199 (68.2)	880 (73.3)	228 (69.5)
Prasugrel	7 (0.2)	2 (0.2)	1 (0.3)	3 (0.3)	1 (0.3)
Procedures					
Primary PCI	1,052 (34.4)	404 (32.7)	119 (40.8)	402 (33.5)	127 (38.7)
Transradial approach	1,698 (55.6)	689 (55.8)	148 (50.7)	705 (58.7)	156 (47.6)
Multivessel CAD	1,703 (55.7)	656 (53.1)	186 (63.7)	645 (53.7)	216 (65.9)
Multilesion intervention	618 (20.2)	239 (19.4)	67 (23.0)	241 (20.1)	71 (21.7)
Multivessel intervention	520 (17.0)	196 (15.9)	57 (19.5)	209 (17.4)	58 (17.7)
Treated lesions per patient	1.24±0.50	1.22±0.49	1.28±0.56	1.23±0.49	1.27±0.55
Total No. of stents per patient	1.37±0.67	1.35±0.65	1.44±0.74	1.35±0.65	1.42±0.70
Total stent length per patient	34.8±20.6	33.8±20.0	37.8±22.3	34.4±20.0	37.0±23.0

Values are presented as mean ± standard deviation or number (%).
BMI = body mass index; CAD = coronary artery disease; CKD = chronic kidney disease; DAPT = dual-antiplatelet therapy; eGFR = estimated glomerular filtration rate; MI = myocardial infarction; PCI = percutaneous coronary intervention.

and the stratification of renal function, there was no significant statistical interaction for the clinical presentation of bleeding events (**Figure 2**).

Ischemic outcome

Another secondary outcome of MACCE occurred in 35 (2.3%) patients receiving ticagrelor monotherapy after 3 months of DPAT and in 51 (3.3%) patients receiving ticagrelor-based 12-month DAPT (**Table 2**). There was also an increased incidence of MACCE in patients with decreased renal function, regardless of study exposure. The prespecified 3-month landmark analysis did not show statistical significance among those without CKD (HR, 0.62; 95% CI, 0.30–1.27; p=0.192) and the presence of CKD (HR, 0.55; 95% CI, 0.21–1.48; p=0.237) (**Figure 1E and F**). Of note, there was no significant interaction between the eGFR subsets and study exposures (**Figure 2**).

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Table 2. Clinical outcomes of subgroup at 1 year according to renal function

Variables	Overall (n=3,056)	Ticagrelor monotherapy after 3-months DAPT (n=1,527)			Ticagrelor-based 12-months DAPT (n=1,529)		
		No CKD ≥60 (n=1,235)	CKD <60 (n=292)	p value*	No CKD ≥60 (n=1,201)	CKD <60 (n=328)	p value*
Primary outcome							
NACE†	148 (4.8)	36 (2.9)	23 (7.9)	<0.001	54 (4.5)	35 (10.7)	<0.001
Secondary outcomes							
TIMI							
Major bleeding	70 (2.3)	13 (1.1)	12 (4.1)	<0.001	26 (2.2)	19 (5.8)	0.001
Major or minor bleeding	136 (4.5)	34 (2.8)	19 (6.5)	0.002	53 (4.4)	30 (9.2)	0.001
MACCE‡	86 (2.8)	23 (1.9)	12 (4.1)	0.021	29 (2.4)	22 (6.7)	<0.001
Cardiac death or acute MI	35 (1.2)	9 (0.7)	4 (1.4)	0.284	12 (1.0)	10 (3.1)	0.006
Cardiac death, acute MI, stent thrombosis, or target-vessel revascularization	48 (1.6)	13 (1.1)	5 (1.7)	0.348	1 (1.5)	12 (3.7)	0.012
Death	39 (1.3)	9 (0.7)	7 (2.4)	0.012	8 (0.7)	15 (4.6)	<0.001
Cardiac	19 (0.6)	4 (0.3)	3 (1.0)	0.109	5 (0.4)	7 (2.1)	0.002
Noncardiac	20 (0.7)	5 (0.4)	4 (1.4)	0.053	3 (0.3)	8 (2.4)	<0.001
Acute MI	17 (0.6)	5 (0.4)	1 (0.3)	0.878	7 (0.6)	4 (1.2)	0.227
Stent thrombosis	10 (0.3)	4 (0.3)	2 (0.7)	0.375	2 (0.2)	2 (0.6)	0.164
Stroke	19 (0.6)	5 (0.4)	3 (1.0)	0.185	8 (0.7)	3 (0.9)	0.637
Ischemic	14 (0.5)	4 (0.3)	1 (0.3)	0.960	7 (0.6)	2 (0.6)	0.955
Hemorrhagic	5 (0.2)	1 (0.1)	2 (0.7)	0.036	1 (0.1)	1 (0.3)	0.325
Target-vessel revascularization	18 (0.6)	6 (0.5)	2 (0.7)	0.672	7 (0.6)	3 (0.9)	0.509

Values are presented as number (%).
CKD = chronic kidney disease; MACCE = major adverse cardiac and cerebrovascular event; MI = myocardial infarction; NACE = net adverse clinical event; TIMI = thrombolysis in myocardial infarction.
*p values are derived from χ^2 test.
†NACE included the composite of major bleeding and major adverse cardiac and cerebrovascular events.
‡MACCE included the composite of death, MI, stent thrombosis, or target-vessel revascularization.

Event risk according to renal function status

Figure 3 shows the Cubic spline curves of the primary and secondary outcomes according to renal function and study exposure. There was a graded association between the risk of NACE and declined category of renal function compared to those with eGFR ≥90 mL/min/1.73 m^2 in both study exposures (**Figure 3A**). Likewise, the curves demonstrated that impaired renal function was related to a higher risk of major or minor bleeding in both study exposures (**Figure 3B**). This trend persisted with the risk of MACCE (**Figure 3C**).

DISCUSSION

Using data from the TICO registry, we sought to determine whether switching to ticagrelor monotherapy after 3 months of DAPT would reduce the composite outcome of major bleeding and adverse cardiac and cerebrovascular events in patients stratified by subsets of renal function. To our knowledge, this is the first report to evaluate the safety and feasibility of ticagrelor monotherapy after short-term DAPT in patients treated with DES only, in conjunction with renal function status, in patients presenting with ACS. Among patients undergoing PCI, the incidence of outcomes, including NACE, bleeding, and MACCE, increased along with the impairment of renal function in both study exposures. Our findings demonstrated that ticagrelor monotherapy after 3 months of DAPT was associated with a significant reduction in the occurrence of NACE between 3 and 12 months, irrespective of the renal function status. Regarding the occurrence of major or minor bleeding, ticagrelor monotherapy displayed a significantly lower rate of bleeding events than that associated with 12-month DAPT, regardless of the presence or absence of CKD. In contrast, ticagrelor monotherapy was not significantly associated with an incremental risk of MACCE between

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the two treatment groups. Notably, there was no interaction between DAPT duration and eGFR stratification for any of the study outcomes.

Up-to-date guidelines recommend 12-month of P2Y12 inhibitor therapy for all patients after acute MI and favor higher-potency P2Y12 inhibitor therapy, such as ticagrelor or prasugrel, in ACS patients treated with PCI.[17][18] Although CKD patients constitute around 20–40% of those who experience ACS, these populations have often been excluded from most of the published randomized controlled trials; therefore, specific recommendations for antiplatelet therapy in post-ACS patients undergoing PCI remain scarce. Meanwhile, bleeding tendency in CKD patients occasionally results in early discontinuation of P2Y12 inhibitors and an increased risk of consequent adverse ischemic events.[19] In this context, several studies have evaluated the efficacy and safety profile of potent P2Y12 inhibitors compared to clopidogrel in patients with renal dysfunction.[20][21] In a substudy of the PLATO trial, ticagrelor, when compared with clopidogrel, significantly reduced ischemic endpoints and mortality rate with no increase in major or fatal bleeding.[20] Likewise, the TRITON trial suggested the superiority of prasugrel over clopidogrel was consistent in ACS patients regardless of CKD status.[21] However, these trails were limited because of the small number of enrolled CKD patients with implantation of DES that was no longer commercially available; therefore, caution should be taken when extrapolating their outcomes to CKD populations in current real-world settings. In contrast, a meta-analysis of the effects of antiplatelet therapy in post-MI CKD patients proposed a potentially heightened bleeding risk with uncertain mortality benefit.[12] In the recent RENAMI and BleeMACS retrospective study, De Filippo et al.[22] revealed that ticagrelor and prasugrel were associated with a lower risk of death and recurrent MI with no increase in bleeding risk compared to clopidogrel among ACS CKD patients. The best strategy related to the efficacy and safety of antiplatelet agents among CKD patients with ACS remains debatable. However, the present study included more than one-fifth of ACS patients with CKD without strict inclusion or exclusion criteria, whom we prospectively randomized, further revealing the efficacy and safety of ticagrelor, a potent P2Y12 inhibitor, for patients with renal impairment and new-generation DES.

As a longer DAPT strategy is associated with an increased risk of bleeding, a few randomized trials have attempted not only to determine the optimal duration of DAPT, but also to assess the aspirin-free strategy after short-term DAPT utilizing P2Y12 inhibitors for the management of CKD patients, to achieve a balance between ischemic and bleeding risk. In the SWEDEHEAR study, the investigators appraised the efficacy and safety of the DAPT arm prolonged after 3 months, as compared to DAPT stopped at 3 months.[23] DAPT prolonged for more than 3 months was similarly associated with a lower risk of death or reinfarction regardless of CKD, without an interaction between the DAPT duration and subsets of CKD for any outcome; however, bleeding was more common with longer DAPT in each CKD subset. In a recent meta-analysis using five randomized trials, Mavrakanas et al. examined whether shorter DAPT in patient with CKD is associated with lower incidence of ischemic events as well as lower bleeding events.[24] They discovered that DAPT for less than 6 months was not inferior to DAPT for more than 6 months in CKD patients. More recently, the GLOBAL READERS randomized trial found no differential treatment effect on safety related to bleeding as well as efficacy regarding the primary endpoint of all-case death or new Q-wave MI with long-term ticagrelor monotherapy after 1 month of DAPT among patients with and without CKD. However, considering the rates of the patient-oriented composite endpoint in ACS patients with CKD, ticagrelor monotherapy was related to lower ischemic events and similar bleeding risk compared to standard DAPT.[25] Consistent with previous

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studies, our investigation provides positive results and expands the prevailing knowledge on the efficacy and safety of an aspirin-free strategy and the use of ticagrelor as a potent P2Y12 inhibitor in ACS patients with CKD. That is, regardless of the presence or absence of CKD, landmark analyses at 3 months showed that ticagrelor monotherapy resulted in a significant reduction in the composite outcome of NACE, as well as TIMI major or minor bleeding risk at 1 year. However, ticagrelor monotherapy after 3 months of DAPT did not show superior outcomes related to risk reduction of MACCE compared with 12 months of DAPT. These differences among previous trials and this study may be attributed to several reasons. This trial included only ACS patients and excluded those with a high bleeding risk.[7] Therefore, caution may be needed for the general extrapolation of ticagrelor monotherapy after short-term DAPT in ACS patients with CKD.

The long-term prognosis of CKD patients is generally poor and is usually attributed to a more severe atherosclerotic burden, more predominantly underlying cardiovascular disease, more likely to die of ACS, and underuse of guideline-recommended medical treatments.[26] Furthermore, the high thrombotic risk in patients with renal impairment is critical to their higher risk of recurrent ischemic events after ACS, and concomitantly, these patients tend to have an increased bleeding risk. Several plausible mechanisms are involved in CKD patients and may be attributed to altered platelet adhesion or aggregation, coagulation cascade, and endothelial injury,[27] which could underscore the optimal strategy of antiplatelet agents in ACS patients with renal impairment. In the present study, ticagrelor monotherapy after 3 months of DAPT reduced the rates of NACE risk among post-ACS patients with CKD with no increased risk of major or minor bleeding compared with ticagrelor-based 12-month DAPT. Of course, the patients with eGFR <60 mL/min/1.73 m^2 in the current study may not reflect all individuals with various ranges of renal impairment. Taken together, although ticagrelor monotherapy after 3 months of DAPT irrespective of the presence or absence of CKD, could be considered a reasonable antiplatelet treatment strategy that lessens the risk for bleeding as well as composite outcome, general extrapolation of a single-antiplatelet therapy following short-term DAPT in these patients seems to require scrupulous attention because of differences in the effects of randomly assigned treatment strategy across patient characteristics in the current study. In further investigations, therefore, more dedicated trials including appropriate inclusion criteria in relation to CKD patients need to be encouraged.

Interestingly, a U-shaped curve was displayed in our restricted spline curve for ticagrelor monotherapy. High eGFR levels may be related with an increased risk of CVD, however, the relationship between eGFR and CVD risk depends on the definition of high eGFR and other clinical factors. A very high eGFR could mean that the kidneys are over-filtering blood, probably due to conditions such as hyperfiltration or early stages of kidney disease, which may sometimes be linked to cardiovascular problems over time. While high eGFR itself may not be typically associated with direct cardiovascular risk, high eGFR can be associated with hypertension, prediabetes, and obesity, which may contribute to an increased CVD risk in the future.

This study entailed some limitations. First, despite a prespecified, randomly stratified subgroup analysis, this study was not individually powered to draw definite conclusions regarding the impact of ticagrelor monotherapy on the primary outcome. In particular, the MACCE assessment could have been underpowered, which requires further investigation to determine these findings with proper power. Second, this study was based on an open-label trial, was not placebo-controlled, and did not monitor drug compliance. However, members of an independent clinical event committee evaluated the clinical results, and

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independent statisticians performed the statistical analyses. Third, this study was conducted only in South Korea; thus, caution should be exercised when extrapolating our findings to other countries. Fourth, although randomization for treatment strategy was performed after the index PCI, not at 3 months after PCI, and the prespecified 3-month landmark analyses indicated consistent results for primary analyses, the primary and bleeding outcomes of the first 3 months after PCI might have affected the overall results; thus, caution should be taken regarding the general extrapolation of the current findings. Fifth, the majority of participants presented with a mildly decreased eGFR level; therefore, caution is needed when endeavoring to apply our results to others with various eGFR levels, including more advanced CKD, such as patients with end-stage renal disease on dialysis. An eGFR <60 mL/min/1.73 m^2 may include some patients on dialysis, so other causes of death related to dialysis-related complications might have played a role. In addition, we did not stratify CKD patients in more detail according to the recent guidelines. Indeed, in severely advanced CKD patients, evidence to support one P2Y12 inhibitor over the others remains scarce. In light of this, the TROUPER study recently compared the effectiveness of ticagrelor and clopidogrel in severe or terminal CKD with stage ≥3b presenting with ACS.[28] Finally, we used a single time-point estimation of eGFR and did not account for the chance of sampling errors. This may reflect the misclassification of subjects due to the characteristics of the MDRD equation, originally derived from CKD patients, and might have led to an underestimation of eGFR in those with a normal eGFR ≥90 mL/min/1.73 m^2.[29] In this context, a more recently established CKD-Epidemiology (CKD-EPI) Collaboration equation conferred less of an underestimation of eGFR in subjects with normal renal function and a more accurate stratification for the risk of mortality as well as end-stage renal disease according to the MDRD equation.[30]

Impaired renal function is associated with poor clinical outcomes in ACS patients treated with DES. Regardless of renal dysfunction, ticagrelor monotherapy after 3 months of DAPT resulted in a reduced risk of major or minor bleeding, as well as a composite outcome of NACE at 1 year, compared with those of ticagrelor-based 12-month DAPT. Irrespective of renal function status, however, the risk of MACCE was not significantly different between the two treatment groups, without a significant interaction with clinical presentation.

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