



Renal Function-Stratified Comparison of Short- and Long-Term Dual Antiplatelet Therapy in Patients Undergoing Percutaneous Coronary Intervention With Third-Generation Drug-Eluting Stents

— Post Hoc Analysis From the HOST-IDEA Randomized Clinical Trial —

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Background: The optimal duration of dual antiplatelet therapy (DAPT) in patients with chronic kidney disease undergoing percutaneous coronary intervention (PCI), especially with third-generation drug-eluting stents (DES), remains unknown.

Methods and Results: We conducted a prespecified post hoc analysis of the HOST-IDEA trial, randomizing patients undergoing PCI with third-generation DES to 3- to 6-month or 12-month DAPT. In all, 1,997 patients were grouped by their estimated glomerular filtration rate (eGFR): high (>90 mL/min/1.73 m²), intermediate (60–90 mL/min/1.73 m²), and low (<60 mL/min/1.73 m²). The primary outcome was net adverse clinical events (NACE), a composite of cardiac death, target vessel myocardial infarction, clinically driven target lesion revascularization, stent thrombosis, or major bleeding (Bleeding Academic Research Consortium Type 3 or 5) at 12 months. Secondary outcomes were target lesion failure (TLF) and major bleeding. The low eGFR group had the highest rates of NACE, TLF, and major bleeding compared with the other 2 groups ($P<0.001$). Rates of NACE were similar in the 3- to 6-month and 12-month DAPT in the high (2.9% vs. 3.2%; $P=0.84$), intermediate (2.1% vs. 2.8%, $P=0.51$), and low (8.9% vs. 9.1%; hazard ratio 0.99; $P=0.97$; $P_{\text{interaction}}=0.88$) eGFR groups. TLF and major bleeding events showed similar trends.

Conclusions: In patients undergoing PCI with third-generation DES, 3- to 6-month DAPT was comparable to 12-month DAPT for clinical outcomes regardless of renal function.

Key Words: Chronic kidney disease; Dual anti-platelet therapy; Percutaneous coronary intervention; Renal function; Third-generation drug-eluting stent

Dual antiplatelet therapy (DAPT) is a pivotal treatment option for patients who have undergone percutaneous coronary intervention (PCI). However, DAPT is a double-edged sword, and careful selection of its duration is crucial for optimal outcomes. Current guidelines recommend 6 months of DAPT as the default for patients with stable ischemic heart disease (SIHD) following PCI, and 12 months for those presenting with acute

coronary syndrome (ACS), including ST-elevation myocardial infarction (MI), which can be reduced to 1–6 months depending on the patient's bleeding risk.^{1–4}

Chronic kidney disease (CKD) is widely acknowledged as a factor contributing to the emergence and progression of coronary artery disease.^{5,6} Moreover, patients with renal dysfunction are at a higher risk of both ischemic and bleeding complications.^{5,6} Therefore, careful assessment of

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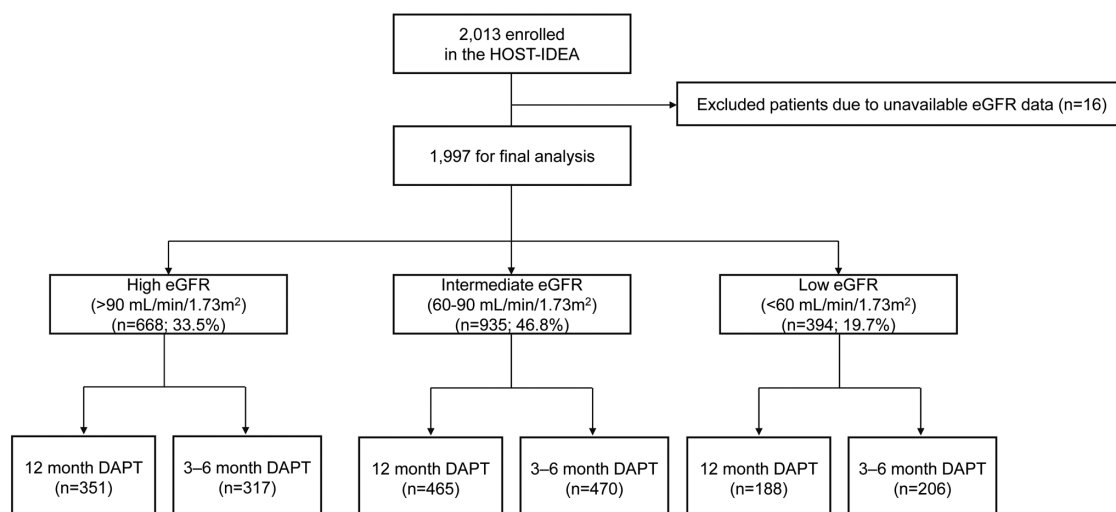


Figure 1. Flow diagram of patient selection. In all, 1,997 patients were included in this study. Patients were divided into 3 groups according to renal function: estimated glomerular filtration rate (eGFR) >90 mL/min/1.73 m² (high eGFR), eGFR 60–90 mL/min/1.73 m² (intermediate eGFR), and eGFR <60 mL/min/1.73 m² (low eGFR). DAPT, dual antiplatelet therapy; HOST-IDEA, Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis-Coronary Intervention With Next Generation Drug-Eluting Stent Platforms and Abbreviated Dual Antiplatelet Therapy.

potential risks is paramount when considering PCI for CKD patients. The challenge lies in striking a balance between the benefits and risks associated with extended DAPT. Unfortunately, most randomized trials regarding DAPT duration have excluded patients with CKD,⁷ and there are only limited data, mainly derived from retrospective studies or post hoc analyses, on this subject.⁸ Consequently, current guidelines do not indicate any specific recommendations on the duration of DAPT for this patient population.

Third-generation drug-eluting stents (DES) featuring ultrathin struts and advanced polymer technologies have recently been introduced. These stents may reduce the risk of stent-related complications and shorten the default duration of DAPT.⁹ However, the ideal duration of DAPT in patients with CKD undergoing PCI with third-generation DES remains unknown. We previously reported the results of the Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis-Coronary Intervention With Next Generation Drug-Eluting Stent Platforms and

Abbreviated Dual Antiplatelet Therapy (HOST-IDEA) trial (ClinicalTrials.gov ID: NCT02601157), demonstrating that a shortened 3- to 6-month DAPT was non-inferior to the conventional 12-month DAPT for net adverse clinical events (NACE) in patients receiving third-generation DES.¹⁰ Herein, we conducted a prespecified post hoc analysis of the HOST-IDEA trial to assess the impact of abbreviated DAPT on clinical outcomes according to renal function.

Methods

Study Overview

This study was a prespecified subgroup analysis of the HOST-IDEA trial. The HOST-IDEA study was an investigator-initiated multicenter open-label randomized controlled trial conducted at 37 sites in Korea with patients treated with third-generation DES with ultrathin struts and advanced polymer technology.¹⁰ The comprehensive

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trial design, inclusion and exclusion criteria, and initial results have been documented previously.^{10,11} All patients provided written informed consent before being randomly assigned to the study. This study adhered to the guidelines of the Declaration of Helsinki and was approved by the institutional ethics committee of each participating site.

Patients who underwent PCI for SIHD or non-ST-elevation ACS with either an Orsiro biodegradable polymer sirolimus-eluting stent (SES; $n=1,449$) or a Coroflex ISAR polymer-free SES ($n=559$) were randomly assigned to 1 of the 2 groups: the abbreviated DAPT group, with DAPT duration of 3–6 months (60–150 days) or the conventional 12-month DAPT group, with the duration of DAPT being ≥ 12 months (≥ 300 days). Patients were prescribed either 3–6 months of DAPT followed by single antiplatelet therapy (SAPT; $n=1,002$) or they received 12 months of DAPT ($n=1,011$). The antiplatelet regimen used during DAPT or SAPT was determined by the treating physician. Clinical follow-up was conducted up to 12 months after the initial PCI. Of the initial 2,013 patients who were randomly assigned to the original trial, 16 were excluded from the analysis because of the unavailability of estimated glomerular filtration rate (eGFR) data. The present study enrolled 1,997 patients. These patients were categorized into 3 groups based on eGFR values (**Figure 1**), as described below.

Renal Function Assessment and Definition of Clinical Outcomes

Glomerular function was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation for eGFR, which takes into account factors such as sex, age, ethnicity, and serum creatinine levels, and is currently the most commonly used method.¹² The eGFR variables were obtained during the screening process for study enrollment.

Participants were divided into 3 groups based on their eGFR levels: high, eGFR >90 mL/min/1.73 m²; intermediate, eGFR ranging from 60 to 90 mL/min/1.73 m²; and low, eGFR <60 mL/min/1.73 m². The prespecified eGFR cut-off values to define CKD and end-stage renal disease (ESRD) were <60 and <15 mL/min/1.73 m², respectively.

Endpoints

The primary endpoint of the study was NACE, the net effect of combined ischemic and bleeding complications 12 months after the initial procedure. NACE is a composite of cardiac death, target vessel MI (TVMI), clinically driven target lesion revascularization (CD-TLR), stent thrombosis, or major bleeding, defined as Bleeding Academic Research Consortium (BARC) Type 3 or 5,¹³ 12 months after the index procedure. The key secondary endpoints were target lesion failure (TLF), a composite of cardiac death, TVMI, or CD-TLR as an ischemic outcome, and major bleeding (BARC Type 3 or 5) as a bleeding outcome. All the clinical outcomes adhered to the definitions provided by the Academic Research Consortium.¹⁴

Statistical Analysis

The baseline characteristics are presented as the mean $\pm$ SD for continuous variables and as numbers and percentages for categorical variables. To compare groups, we used unpaired Student's *t*-test for continuous variables and either the Chi-squared test or Fisher's exact test for categorical variables. When comparing the 3 eGFR groups, 1-way analysis of variance was used for continuous vari-

ables. All analyses of clinical outcomes were performed in the intention-to-treat cohort. Kaplan-Meier analysis was used to assess the cumulative incidence of clinical outcomes, and differences between groups were evaluated using the log-rank test. Hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs) were calculated using the Cox proportional hazards regression analysis. The estimated risk of clinical outcomes was determined using multivariate Cox proportional hazards regression analysis, considering the influence of these covariates. An interaction analysis was used to identify the modifying effect of renal function on the association between DAPT duration and clinical outcomes. All statistical tests were 2-sided, with statistical significance set at $P<0.05$. All statistical analyses were conducted using R programming language version 4.2.1.

Results

Baseline Characteristics

The baseline characteristics of patients according to eGFR (high, intermediate, low), including demographics, medical history, laboratory data, and angiographic and procedural characteristics at admission, are presented in **Table 1** and **Supplementary Table 1**. In all, 1,997 patients were enrolled in the cohort, with 663 (33.4%), 935 (46.8%), and 394 (19.7%) categorized as having high, intermediate, and low eGFR, respectively. Among the entire cohort, 993 individuals were prescribed DAPT for a duration of 3–6 months, whereas the remaining 1,004 received DAPT for 12 months. Overall, the covariates were evenly distributed between the patients receiving DAPT for 3–6 and 12 months within each eGFR subgroup (**Table 1**). There were no significant differences in procedural characteristics between the randomized strategies (**Table 1**). The low eGFR group had a higher proportion of women, was older, and exhibited more clinical risk factors, including dyslipidemia, diabetes, hypertension, and higher angiographic complexities, than the other 2 eGFR groups (**Supplementary Table 1**). In the 3- to 6-month DAPT arm, after the completion of DAPT, 64.2% of patients received aspirin, 33.7% received clopidogrel, and 2.2% received potent P2Y₁₂ inhibitors (ticagrelor or prasugrel) as monotherapy (**Supplementary Figure 1**).

Effects of Renal Function on Clinical Outcomes

At 12 months after PCI, the low eGFR group exhibited the highest rates of NACE, compared with the high and intermediate eGFR groups (9.0% vs. 3.0% and 2.5%, respectively; $P<0.001$; **Figure 2**; **Supplementary Table 2**). This difference was mainly driven by a higher risk of cardiac death and major bleeding (BARC Type 3 or 5) in the low eGFR group. TLF was more frequent in the low eGFR group than in the high and intermediate eGFR groups (5.1% vs. 2.0% and 1.7%, respectively; $P<0.001$). In addition, the incidence of major bleeding increased with decreasing baseline renal function (1.1%, 0.9%, and 5.0% in the high, intermediate, and low eGFR groups, respectively; $P<0.001$). A decline in eGFR was significantly associated with NACE (HR 1.28 per 10-mL/min/1.73 m² decrease in eGFR; 95% CI 1.19–1.37; $P<0.001$), TLF (HR 1.23 per 10-mL/min/1.73 m² decrease in eGFR; 95% CI 1.12–1.35; $P<0.001$), and major bleeding (HR 1.38 per 10-mL/min/1.73 m² decrease in eGFR; 95% CI 1.25–1.53; $P<0.001$; **Supplementary Table 3**).

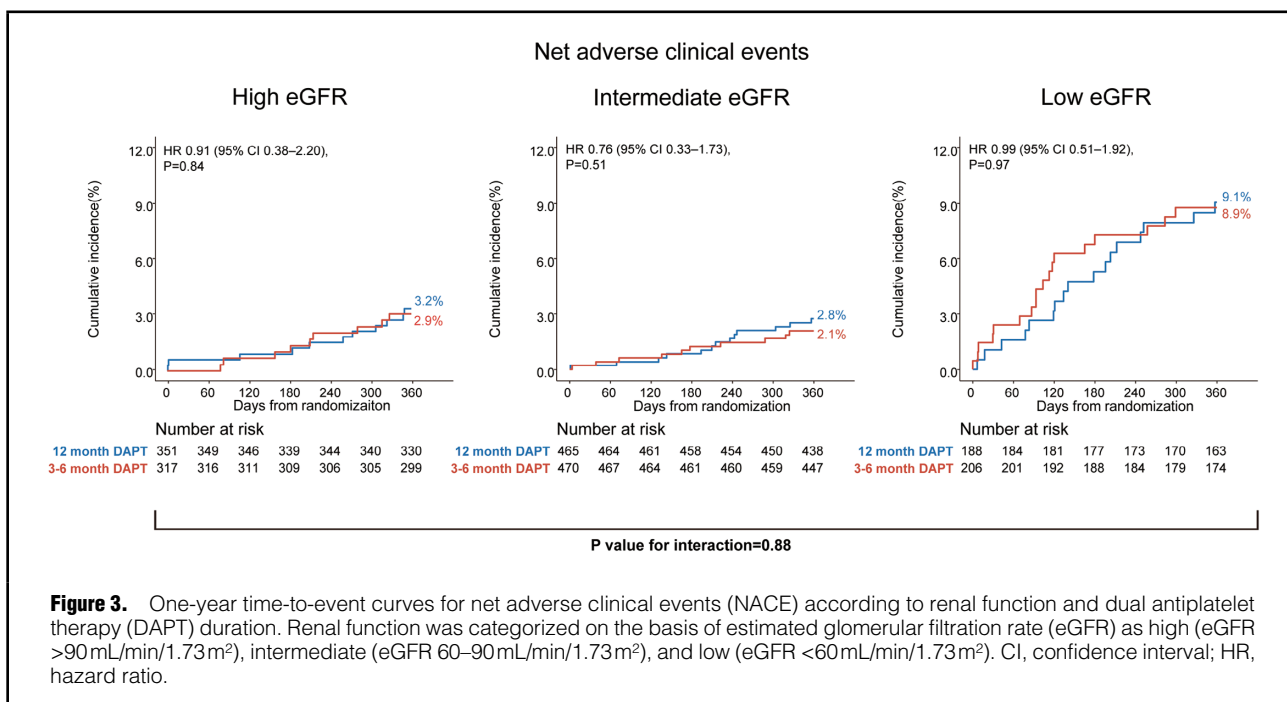
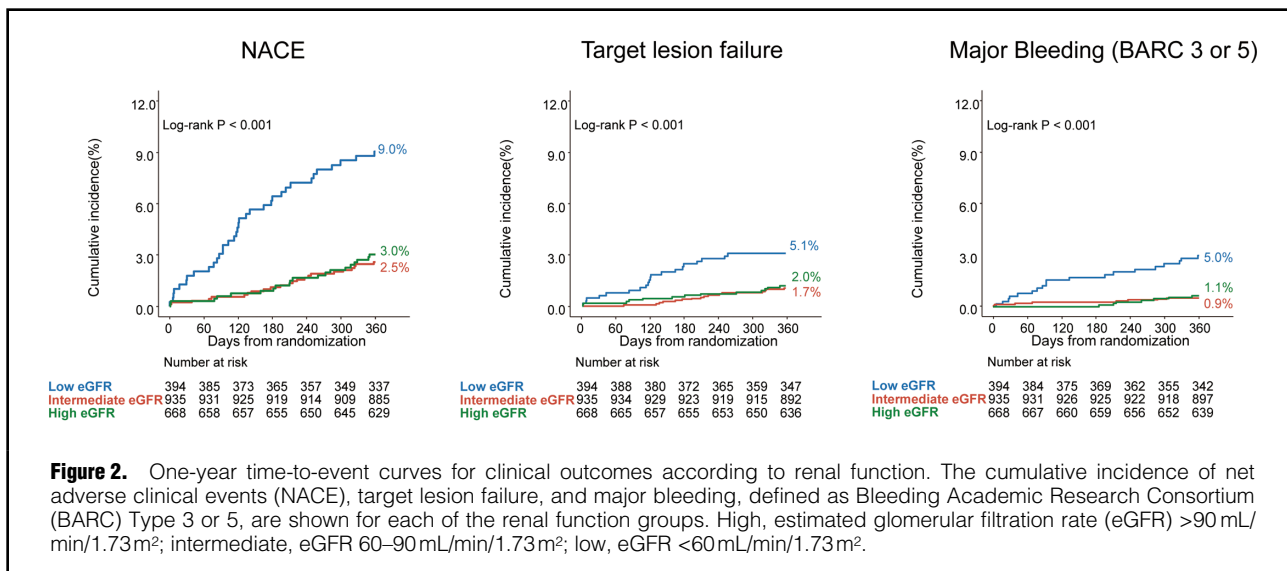
Table 1. Baseline Characteristics of Patients Receiving DAPT for 3–6 or 12 Months in Each of the Renal Function^A Groups

	High eGFR (n=668)			Intermediate eGFR (n=935)
	3–6 months DAPT (n=317)	12 months DAPT (n=351)	P value	3–6 months DAPT (n=470)
Clinical characteristics				
Age (years)	58.8±8.6	59.5±8.4	0.26	67.3±9.3
Male sex	257 (81.1)	292 (83.2)	0.54	341 (72.6)
Hemoglobin (g/dL)	14.3±1.6	14.2±1.4	0.37	13.6±1.6
eGFR (mL/min/1.73m²)	98.6±6.5	98.2±6.2	0.46	77.9±8.5
Hypertension	215 (67.8)	225 (64.1)	0.35	331 (70.4)
Diabetes	110 (34.7)	102 (29.1)	0.14	167 (35.5)
Treated with insulin	5 (5.2)	6 (5.8)	1.00	15 (9.6)
Dyslipidemia	254 (80.1)	264 (75.2)	0.15	377 (80.2)
Previous MI	13 (4.1)	13 (3.7)	0.95	21 (4.5)
Previous PCI	32 (10.1)	33 (9.4)	0.86	60 (12.8)
Previous CABG	2 (0.6)	2 (0.6)	1.00	5 (1.1)
Previous CVA	11 (3.5)	11 (3.1)	0.98	35 (7.4)
Peripheral vessel disease	1 (0.3)	0 (0)	0.96	7 (1.5)
Clinical diagnosis			0.89	
NSTEMI	57 (18.0)	62 (17.7)		101 (21.5)
SIHD	145 (45.7)	167 (47.6)		203 (43.2)
Unstable angina	115 (36.3)	122 (34.8)		166 (35.3)
LVEF (%)	60.3±8.7	59.3±9.1	0.19	58.7±9.5
Discharge medication				
DAPT regimen at discharge			0.70	
Aspirin+clopidogrel	276 (87.1)	311 (88.6)		421 (89.6)
Aspirin+prasugrel	9 (2.8)	11 (3.1)		12 (2.6)
Aspirin+ticagrelor	32 (10.1)	29 (8.3)		37 (7.9)
Medication at discharge				
β-blocker	113 (35.6)	118 (33.6)	0.64	199 (42.3)
ACEi/ARB	146 (46.1)	167 (47.6)	0.75	234 (49.8)
Calcium channel blocker	76 (24.0)	106 (30.2)	0.09	141 (30.0)
Statin	303 (95.6)	342 (97.4)	0.27	448 (95.3)
Angiographic findings				
Left main disease	15 (4.7)	19 (5.4)	0.82	31 (6.6)
Extent of CAD			0.74	
1-vessel disease	178 (56.2)	187 (53.3)		223 (47.4)
2-vessel disease	89 (28.1)	103 (29.3)		149 (31.7)
3-vessel disease	50 (15.8)	61 (17.4)		98 (20.9)
Chronic total occlusion	24 (7.7)	30 (8.7)	0.75	42 (9.0)
Bifurcation lesion	33 (10.6)	42 (12.1)	0.61	56 (12.0)
ACC/AHA Type B2/C lesion	221 (71.1)	243 (70.4)	0.93	358 (76.7)
Procedural characteristics				
Mean stent diameter (mm)	3.1±0.4	3.1±0.4	0.72	3.1±0.4
Stent length (mm)	27.9±15.8	28.1±15.2	0.86	28.8±15.2
No. stents per patient	1.5±0.9	1.5±0.9	0.60	1.6±0.9
Stent type			0.50	
Both	1 (0.3)	0 (0.0)		1 (0.2)
Coroflex ISAR	115 (36.3)	121 (34.5)		104 (22.1)
Orsiro	201 (63.4)	230 (65.5)		365 (77.7)
Procedural success	305 (97.8)	337 (97.4)	0.96	459 (98.1)

Unless indicated otherwise, data are presented as the mean±SD or n (%). ^ARenal function was categorized on the basis of eGFR as high (eGFR >90 mL/min/1.73 m²), intermediate (eGFR 60–90 mL/min/1.73 m²), and low (eGFR <60 mL/min/1.73 m²). ACC/AHA, American College of Cardiology/American Heart Association; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CAD, coronary artery disease; CVA, cerebrovascular accident; DAPT, dual antiplatelet therapy; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; SIHD, stable ischemic heart disease.

(Table 1 continued the next page.)

	Intermediate eGFR (n=935)		Low eGFR (n=394)		
	12 months DAPT (n=465)	P value	3–6 months DAPT (n=206)	12 months DAPT (n=188)	P value
Clinical characteristics					
Age (years)	68.4±9.3	0.06	72.6±9.9	71.5±10.7	0.33
Male sex	333 (71.6)	0.80	127 (61.7)	125 (66.5)	0.37
Hemoglobin (g/dL)	13.6±1.7	0.69	11.8±2.0	11.6±2.0	0.47
eGFR (mL/min/1.73 m ²)	77.2±8.4	0.21	37.4±18.9	36.1±19.3	0.50
Hypertension	351 (75.5)	0.10	183 (88.8)	162 (86.2)	0.52
Diabetes	164 (35.3)	0.99	82 (39.8)	78 (41.5)	0.81
Treated with insulin	11 (6.7)	0.47	32 (25.2)	29 (26.1)	0.99
Dyslipidemia	388 (83.4)	0.23	176 (85.4)	153 (81.4)	0.34
Previous MI	18 (3.9)	0.77	11 (5.3)	11 (5.9)	1.00
Previous PCI	66 (14.2)	0.59	38 (18.4)	42 (22.3)	0.40
Previous CABG	7 (1.5)	0.76	3 (1.5)	7 (3.7)	0.27
Previous CVA	35 (7.5)	1.00	22 (10.7)	17 (9.0)	0.71
Peripheral vessel disease	8 (1.7)	0.98	11 (5.3)	10 (5.3)	1.00
Clinical diagnosis		0.47			0.25
NSTEMI	85 (18.3)		50 (24.3)	45 (23.9)	
SIHD	208 (44.7)		81 (39.3)	88 (46.8)	
Unstable angina	172 (37.0)		75 (36.4)	55 (29.3)	
LVEF (%)	59.7±8.6	0.11	54.1±11.4	55.0±12.8	0.51
Discharge medication					
DAPT regimen at discharge		0.10			0.78
Aspirin+clopidogrel	416 (89.5)		183 (88.8)	171 (91.0)	
Aspirin+prasugrel	12 (2.6)		3 (1.5)	2 (1.1)	
Aspirin+ticagrelor	37 (8.0)		20 (9.7)	15 (8.0)	
Medication at discharge					
β-blocker	191 (41.1)	0.74	98 (47.6)	93 (49.5)	0.78
ACEi/ARB	227 (48.8)	0.82	115 (55.8)	116 (61.7)	0.28
Calcium channel blocker	149 (32.0)	0.55	81 (39.3)	71 (37.8)	0.83
Statin	442 (95.1)	0.97	181 (87.9)	166 (88.3)	1.00
Angiographic findings					
Left main disease	23 (4.9)	0.35	12 (5.8)	11 (5.9)	1.00
Extent of CAD		0.81			0.92
1-vessel disease	225 (48.4)		77 (37.4)	73 (38.8)	
2-vessel disease	151 (32.5)		64 (31.1)	59 (31.4)	
3-vessel disease	89 (19.1)		65 (31.6)	56 (29.8)	
Chronic total occlusion	31 (6.7)	0.25	21 (10.3)	11 (5.9)	0.16
Bifurcation lesion	45 (9.7)	0.32	20 (9.9)	17 (9.1)	0.92
ACC/AHA Type B2/C lesion	338 (73.5)	0.30	158 (78.2)	138 (73.8)	0.37
Procedural characteristics					
Mean stent diameter (mm)	3.1±0.4	0.74	3.0±0.4	3.0±0.4	0.34
Stent length (mm)	28.8±16.2	0.99	32.5±18.9	32.3±19.9	0.91
No. stents per patient	1.6±0.9	0.91	1.7±1.1	1.8±1.0	0.34
Stent type		0.24			0.16
Both	0 (0.0)		0 (0.0)	3 (1.6)	
Coroflex ISAR	121 (26.0)		48 (23.3)	48 (25.5)	
Orsiro	344 (74.0)		158 (76.7)	137 (72.9)	
Procedural success	456 (98.7)	0.62	198 (97.5)	183 (97.9)	1.00



Clinical Outcomes According to DAPT Duration and Renal Function

The clinical outcomes were assessed according to the duration of DAPT in the groups stratified according to renal function. No statistically significant interaction ($P_{\text{interaction}}=0.88$) was identified between DAPT duration and renal function in relation to NACE at 12 months after PCI (**Figure 3**; **Table 2**). The incidence of NACE was comparable between the 3–6- and 12-month DAPT groups across all renal function groups: for high eGFR: 2.9% vs. 3.2%, respectively (HR 0.91; 95% CI 0.38–2.20); for intermediate eGFR, 2.1% vs. 2.8%, respectively; (HR 0.76; 95% CI 0.33–1.73); and for low eGFR, 8.9% vs. 9.1%, respectively (HR 0.99; 95% CI, 0.51–1.92; **Figure 3**; **Table 2**).

Similar trends were seen for TLF as an ischemic outcome in comparisons of groups treated with DAPT for 3–6 or 12 months in the high (1.9% vs. 2.0%, respectively; HR 0.95; 95% CI 0.32–2.83), intermediate (1.5% vs. 2.0%, respectively; HR 0.77; 95% CI 0.29–2.06), and low (5.4% vs. 4.8%, respectively; HR 1.14; 95% CI 0.47–2.75) eGFR groups (**Figure 4**; **Table 2**), with no significant interaction between DAPT duration and renal function ($P_{\text{interaction}}=0.84$). In the low eGFR group, the incidence of TVMI (2.5% vs. 0.6%), MI (3.0% vs. 1.1%), and ischemic stroke (2.5% vs. 1.1%) was numerically higher in the group treated with DAPT for 3–6 months rather than 12 months, but the differences were not statistically significant. **Supplementary Figure 2** shows the cumulative incidence of these events over time

Table 2. Clinical Outcomes of Patients Receiving DAPT for 3–6 or 12 Months in Each of the Renal Function^A Groups

	High eGFR (n=668)			Intermediate eGFR (n=935)	
	3–6 month DAPT (n=317)	12 month DAPT (n=351)	P value	3–6 month DAPT (n=470)	12 month DAPT (n=465)
Net adverse clinical events					
TLF, ST, or major bleeding	9 (2.9)	11 (3.2)	0.84	10 (2.1)	13 (2.8)
Bleeding outcome					
BARC Type 2	13 (4.2)	16 (4.6)	0.79	13 (2.8)	19 (4.1)
BARC Type 2, 3, or 5	15 (4.8)	20 (5.8)	0.70	16 (3.4)	23 (5.0)
BARC Type 3 or 5	3 (1.0)	4 (1.2)	0.82	3 (0.6)	5 (1.1)
Ischemic outcome					
TLF	6 (1.9)	7 (2.0)	0.93	7 (1.5)	9 (2.0)
Cardiac death	1 (0.3)	1 (0.3)	0.94	0 (0.0)	2 (0.4)
Target vessel MI	2 (0.6)	2 (0.6)	0.92	3 (0.6)	4 (0.9)
Clinically driven TLR	4 (1.3)	6 (1.7)	0.64	5 (1.1)	7 (1.5)
Definite or probable ST	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)
Patient-oriented composite outcome ^B	13 (4.2)	18 (5.2)	0.54	19 (4.1)	31 (6.7)
All-cause death	2 (0.6)	1 (0.3)	0.50	0 (0.0)	5 (1.1)
MI	2 (0.6)	2 (0.6)	0.92	5 (1.1)	6 (1.3)
Any revascularization	11 (3.5)	15 (4.3)	0.60	16 (3.4)	21 (4.6)
Ischemic stroke	0 (0.0)	2 (0.6)	0.18	2 (0.4)	6 (1.3)

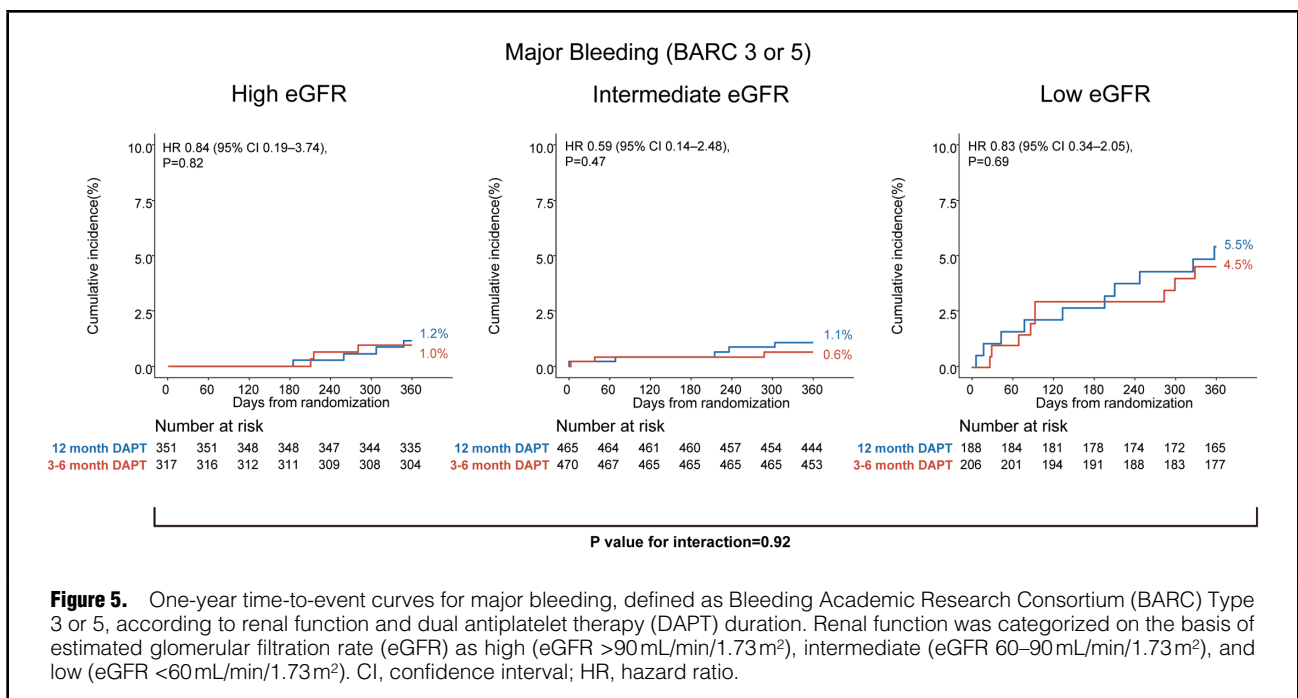
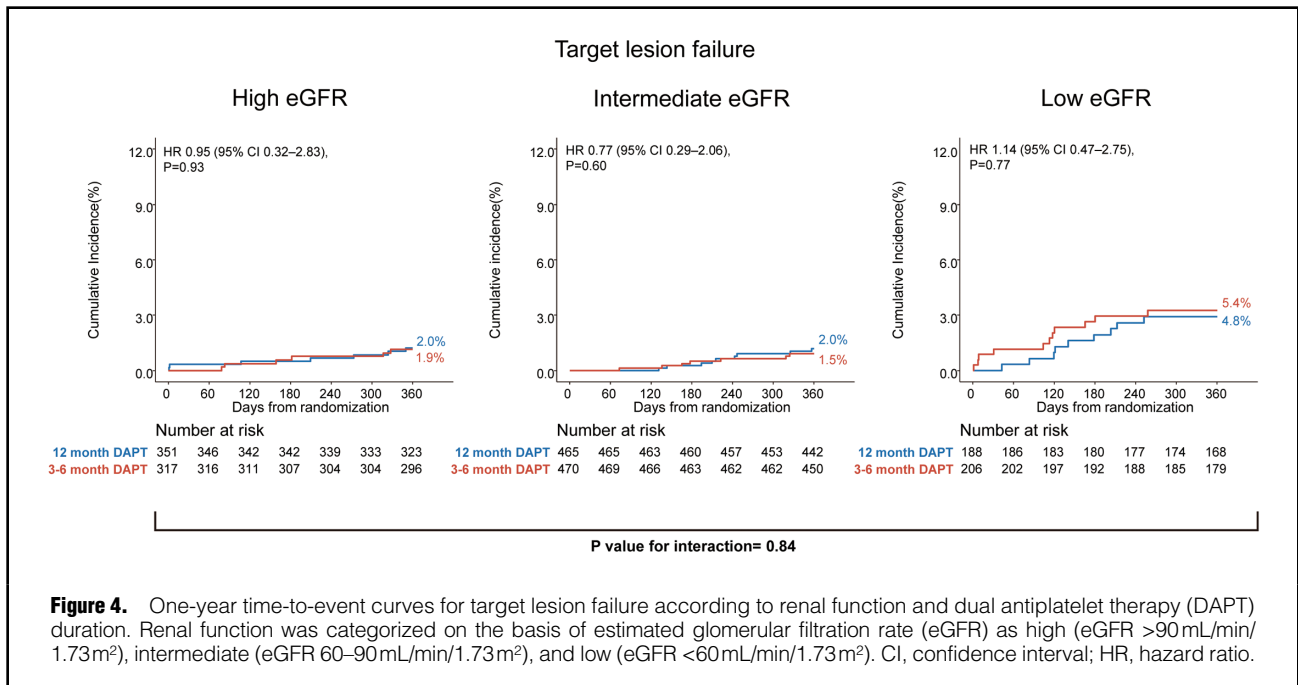
	Intermediate eGFR (n=935)	Low eGFR (n=394)			P _{interaction}
	P value	3–6 month DAPT (n=206)	12 month DAPT (n=188)	P value	
Net adverse clinical events					
TLF, ST, or major bleeding	0.51	18 (8.9)	17 (9.1)	0.97	0.88
Bleeding outcome					
BARC Type 2	0.26	11 (5.5)	14 (7.7)	0.41	0.84
BARC Type 2, 3, or 5	0.31	20 (10.1)	22 (12.0)	0.63	0.88
BARC Type 3 or 5	0.47	9 (4.5)	10 (5.5)	0.69	0.92
Ischemic outcome					
TLF	0.60	11 (5.4)	9 (4.8)	0.77	0.84
Cardiac death	0.15	6 (2.9)	7 (3.8)	0.67	0.32
Target vessel MI	0.69	5 (2.5)	1 (0.6)	0.12	0.32
Clinically driven TLR	0.55	5 (2.5)	4 (2.2)	0.82	0.83
Definite or probable ST	NA	1 (0.5)	0 (0.0)	0.34	1.00
Patient-oriented composite outcome ^B	0.08	28 (13.7)	20 (10.7)	0.36	0.16
All-cause death	0.03	15 (7.3)	14 (7.4)	0.98	0.03
MI	0.75	6 (3.0)	2 (1.1)	0.19	0.45
Any revascularization	0.37	9 (4.5)	7 (3.8)	0.95	0.72
Ischemic stroke	0.15	5 (2.5)	2 (1.1)	0.30	0.07

Data are presented as n (Kaplan-Meier estimates, %). ^ARenal function was categorized on the basis of eGFR as high (eGFR >90 mL/min/1.73 m²), intermediate (eGFR 60–90 mL/min/1.73 m²), and low (eGFR <60 mL/min/1.73 m²). ^BThe patient-oriented composite outcome was a composite of all-cause death, any MI, any revascularization, and stroke. BARC, Bleeding Academic Research Consortium; ST, stent thrombosis; TLF, target lesion failure; TLR, target lesion revascularization. Other abbreviations as in Table 1.

after randomization.

There was no significant difference in major bleeding between the 3–6- and 12-month DAPT groups regardless of renal function categories: for high eGFR groups, 1.0% vs. 1.2%, respectively (HR 0.84; 95% CI 0.19–3.74); for intermediate eGFR, 0.6% vs. 1.1%, respectively (HR 0.59; 95% CI 0.14–2.48); and for low eGFR, 4.5% vs. 5.5%, respectively (HR 0.83; 95% CI 0.34–2.05; P_{interaction}=0.92; **Figure 5; Table 2**). The predicted association between

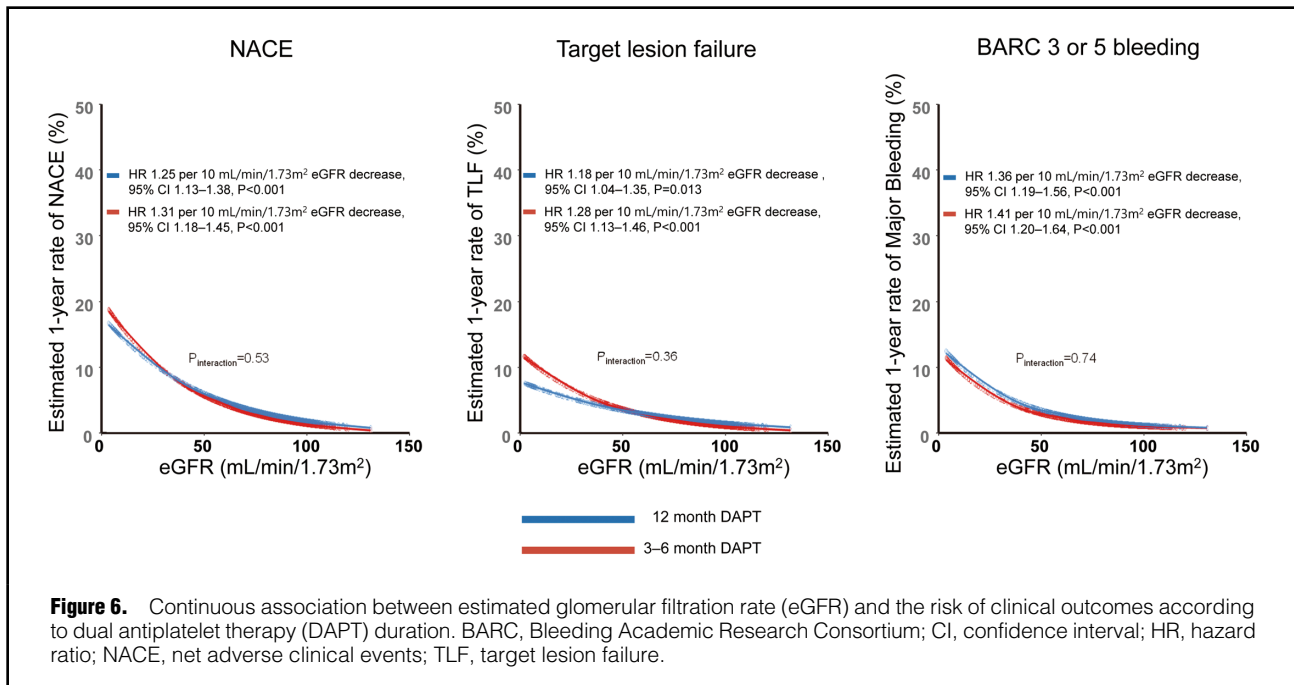
continuous eGFR values and the risk of clinical events is shown in **Figure 6**. The risk of NACE, TLF, and major bleeding increased as eGFR decreased, regardless of DAPT duration. Although a crossover was observed in NACE and TLF, there were no statistically significant differences between the 2 DAPT treatment groups. When further analyzed in end-stage renal disease patients with a severe reduction in eGFR (<15 mL/min/1.73 m²), the risk of clinical events did not differ between the 2 DAPT groups



(Supplementary Table 4; Supplementary Figure 3). When the impact of the monotherapy regimen (aspirin or clopidogrel) on clinical outcomes was analyzed in the 3- to 6-month DAPT group, no statistically significant differences were found between the 2 groups in any of the eGFR groups (Supplementary Figure 4). In addition, we demonstrated that there were no significant clinical differences based on renal function when comparing the groups according to stent type, as shown by the Forest plot in Supplementary Figure 5.

Discussion

This study assessed the efficacy and safety of shortened (3–6 months) DAPT according to patients' renal function, compared with conventional 12-month DAPT, in patients receiving third-generation DES. The main findings of our study are that: (1) impairments in renal function were associated with an increased risk of both bleeding and ischemic adverse events; (2) a shortened DAPT duration of 3–6 months did not decrease the risk of bleeding outcomes in



patients with CKD compared with the longer DAPT duration of 12 months; and (3) a longer DAPT duration did not reduce the risk of ischemic outcomes in patients with CKD compared with a shortened DAPT duration. To the best of our knowledge, this is the first study to assess the impact of DAPT duration on the outcomes of patients with CKD following PCI exclusively with third-generation DES with ultrathin struts.

CKD is a complex risk factor that increases both bleeding and ischemic risks after PCI. Patients with CKD often present with multiple comorbidities, such as old age, hypertension, diabetes, and heart failure.¹⁵ In addition, CKD itself induces chronic inflammation and endothelial dysfunction,⁸ and accelerates vascular calcifications and atherosclerotic processes, leading to more extensive coronary arterial disease and more complex lesion characteristics.¹⁶ Furthermore, patients with CKD demonstrate higher on-treatment platelet reactivity,¹⁷ enhanced blood coagulation profiles, and increased Factor VIII activity than patients without CKD.¹⁸ Collectively, these characteristics increase the risk of ischemic adverse events in patients with CKD undergoing PCI. However, platelet dysfunction and abnormal coagulation cascades in patients with CKD also expose them to a higher risk of bleeding events.¹⁹ Therefore, determining the ideal duration of DAPT in patients with CKD after PCI is challenging. Given that the prevalence of CKD in patients undergoing PCI could be $>40\%$,²⁰ addressing this issue is imperative. Unfortunately, there is currently no evidence available from randomized trials.

In our study, shortening DAPT duration to 3–6 months did not increase the risk of ischemic outcomes in patients with CKD compared with conventional 12-month DAPT. In contrast, a previous registry-based study reported a lower risk of death or MI in CKD patients on prolonged DAPT (>12 months) following PCI with first-generation DES compared with a DAPT duration of ≤ 12 months.²¹ We suggest that this discrepancy may arise from the safer

profile of the third-generation DES (Orsiro SES or Coroflex ISAR SES) used in our study. The third-generation DES are characterized by an ultrathin strut thickness (60–80 μm for Orsiro SES; 50–60 μm for Coroflex ISAR SES) and advanced polymer technology. Stents with thick struts have a slower re-endothelialization process, leading to an increased risk of thrombogenicity and restenosis.²² In contrast, DES with ultrathin struts (thickness $\leq 70 \mu\text{m}$) were associated with a lower risk of ischemic events, even compared with second-generation DES with thin struts.²³ The Orsiro SES uses hybrid polymer technology, featuring an outer layer of biodegradable polymer and an inner layer of inert matrix that insulates the metallic stent.²⁴ The Coroflex ISAR SES uses a polymer-free technology for drug release.²⁵ These advanced polymer technologies in third-generation DES further reduce the risk of thrombogenicity. Collectively, these features of third-generation DES may result in the efficacy of 3- to 6-month DAPT being comparable to that of 12-month DAPT in patients with CKD undergoing PCI.

In this study, we used TLF as the main ischemic outcome following the design of the original study.¹¹ Given the more extensive coronary artery disease and a higher prevalence of comorbidities that elevate the risk of cardiovascular events in CKD patients, long-term DAPT may be justified to prevent ischemic events in non-stented coronary segments in this patient group. Notably, when considering the patient-oriented composite outcome as the most comprehensive measure of ischemic events, 3- to 6-month DAPT demonstrated event rates comparable to those of 12-month DAPT across all eGFR groups. In our study, the rates of TVMI, MI, and ischemic stroke were numerically higher with DAPT for 3–6 months compared with 12 months in the low eGFR group, although these differences were not statistically significant (Table 2). Notably, these events occurred more than twice as frequently with short DAPT, but most of the events occurred during the period when the patients were taking DAPT,

suggesting that this finding may be due to chance (**Supplementary Figure 2**). Future randomized trials with larger sample sizes are required to ensure sufficient statistical power to address this concern. The rate of all-cause death, but not cardiac death, was significantly higher with 12-month DAPT in the intermediate-eGFR group. This observation may be attributed to the limited statistical power resulting from the nature of the subgroup analysis, which involves a small sample size, and analysis of a secondary outcome.

Our study also showed that conventional 12-month DAPT did not increase the risk of bleeding in patients with CKD compared with shorter (3–6 months) DAPT. Paradoxically, this could result from the hyporesponsiveness to P2Y₁₂ inhibitors in patients with CKD. A higher prevalence of high platelet reactivity was reported in patients on clopidogrel.¹⁷ In addition, a higher incidence of cytochrome P450 family 2 subfamily C member 19 (CYP2C19) poor metabolizers among East Asian populations²⁶ may also increase the risk of clopidogrel resistance in our study population. Potent P2Y₁₂ inhibitors, such as prasugrel and ticagrelor, demonstrate superior platelet inhibition efficacy compared with clopidogrel in CKD patients.²⁷ Although our study population included patients presenting with ACS (accounting for as much as 55%), most (89%) were prescribed clopidogrel as the P2Y₁₂ inhibitor in their DAPT regimen. This may have led to the lack of an increased bleeding risk in patients with CKD taking 12-month DAPT in our study. This study was pragmatically designed to allow any antiplatelet regimen during DAPT or SAPT at the physician's discretion. Thus, the low usage rate of potent P2Y₁₂ inhibitors reflects their limited penetration in South Korea, likely due to physicians' concerns over the high bleeding risk in the East Asian population.²⁸ In addition, the Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis–Extended Antiplatelet Monotherapy (HOST-EXAM) trial demonstrated an elevated risk of bleeding associated with aspirin compared with clopidogrel.²⁹ The majority of patients in 3- to 6-month DAPT group (64%) were on aspirin monotherapy after completing DAPT. Therefore, we speculate that aspirin monotherapy in the 3- to 6-month DAPT group further attenuated the potential differences in bleeding risk between this and the 12-month DAPT group. In contrast to the present study, a substudy of the Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention (TWILIGHT) trial using a potent P2Y₁₂ inhibitor that randomized patients to ticagrelor monotherapy following ticagrelor-based 3- or 12-month DAPT showed that the abbreviated DAPT regimen reduced the risk of bleeding, regardless of the presence of CKD.³⁰

Our study suggests that CKD alone should not be the main determinant of DAPT duration. We observed similar ischemic and bleeding outcomes between short- and conventional-duration DAPT regardless of renal function. However, determining the optimal DAPT duration for CKD patients remains complex due to the multifaceted nature of bleeding and ischemic risks. Therefore, it is important to consider other concomitant risk factors in addition to CKD when deciding on DAPT duration.

Study Limitations

Although our study was based on individual patient-level data from a well-designed randomized trial, several limita-

tions should be considered. First, the open-label design of the trial may have introduced a risk of bias in reporting outcomes. However, it is important to note that standardized definitions were applied to all study endpoints, which were verified by an independent event adjudication committee. Importantly, this committee operated in a blinded manner with respect to the randomization results, which served to mitigate potential bias. Second, although this was a prespecified subgroup analysis, randomization did not include stratification based on renal function, rendering the study underpowered to compare the outcomes between the 2 DAPT arms in patients stratified according to kidney function. In addition, the lower-than-expected event rates could have further contributed to the relatively limited statistical power of this analysis.¹ Third, although more than half the study population presented with ACS, only a small proportion of patients were prescribed potent P2Y₁₂ inhibitors, probably due to physicians' concerns over the high bleeding risk in the East Asian population.² Consequently, caution should be exercised when extrapolating our study's findings to other populations. Fourth, this study was conducted exclusively in the South Korean population. Considering the high bleeding risk² and variations in CYP2C19 among East Asian populations,³ further studies are required to generalize the findings of this study to other populations.

Conclusions

In this prespecified subgroup analysis of the HOST-IDEA randomized trial, we found that the risks of bleeding and ischemic outcomes were comparable across renal function categories between patients receiving DAPT for 3–6 months and those receiving DAPT for 12 months following PCI with a third-generation DES. Further randomized trials that specifically address this subject are warranted.

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IRB Information

This study was approved by the ethics committee of Seoul National University Hospital (Reference no. 1508-118-697).

Data Availability

The deidentified participant data will not be shared.

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Supplementary Files

Please find supplementary file(s);
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