

ORIGINAL RESEARCH

Clopidogrel Versus Aspirin as Chronic Maintenance Antiplatelet Monotherapy in Patients After Percutaneous Coronary Intervention With Chronic Kidney Disease: A Post Hoc Analysis of the HOST-EXAM Trial

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BACKGROUND: Clopidogrel monotherapy improved clinical outcomes compared with aspirin monotherapy during a chronic maintenance period in patients who underwent coronary stenting in the HOST-EXAM (Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis–Extended Antiplatelet Monotherapy) trial. However, it is uncertain whether the beneficial effect of clopidogrel over aspirin is different according to the renal function.

METHODS AND RESULTS: We conducted a post hoc analysis of the HOST-EXAM trial. Chronic kidney disease (CKD) was defined as baseline estimated glomerular filtration rate <60 mL/min per 1.73 m². The primary end point was a composite of all-cause death, nonfatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and Bleeding Academic Research Consortium bleeding type ≥ 3 , during the 2-year follow up. Among the 5438 patients enrolled in the HOST-EXAM trial, 4844 patients (mean age, 63.3 ± 10.6 years; 74.9% men) with a baseline creatinine value were analyzed in this study. A total of 508 (10.5%) patients had CKD, who were at higher risk of the primary end point compared with those without CKD (hazard ratio [HR], 2.01 [95% CI, 1.51–2.67]). Clopidogrel monotherapy was associated with a lower rate of the primary end point in both patients with CKD (HR, 0.74 [95% CI, 0.44–1.25]) and patients without CKD (HR, 0.71 [95% CI, 0.56–0.91]). No significant interaction was observed between the treatment effect and CKD status (P for interaction=0.889).

CONCLUSIONS: During the chronic maintenance period after coronary stenting, the risk of thrombotic and bleeding events was significantly higher in patients with CKD compared with those without CKD. There was no statistical difference in the treatment effect of clopidogrel monotherapy in those with versus without CKD.

Key Words: aspirin ■ chronic kidney disease ■ clopidogrel ■ percutaneous coronary intervention

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CLINICAL PERSPECTIVE

What Is New?

- In this post hoc analysis of the HOST-EXAM (Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis–Extended Antiplatelet Monotherapy) trial, the risk of thrombotic and bleeding events was significantly higher in patients with chronic kidney disease compared with those without chronic kidney disease.
- The clinical benefits of clopidogrel monotherapy were not statistically different according to renal function.

What Are the Clinical Implications?

- Clopidogrel may be preferred over aspirin for long term secondary prevention regardless of baseline renal function.

Nonstandard Abbreviations and Acronyms

CAPRIE	Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events
COMPASS	Cardiovascular Outcomes for People Using Anticoagulation Strategies
CREDO	Clopidogrel for the Reduction of Events During Observation
EVENT	Evaluation of Drug-Eluting Stents and Ischemic Events
HOST-EXAM	Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis–Extended Antiplatelet Monotherapy
PROMETHEUS	Prasugrel or Clopidogrel in Patients With Acute Coronary Syndromes at High Thrombotic Risk

Chronic kidney disease (CKD) is a well-known risk factor for cardiovascular morbidity and death due to its association with increased thrombotic and bleeding adverse events.^{1–3} The increased risk of hemostatic complications with opposite characteristics can be explained by dysfunction of platelets and the enzymatic coagulation cascade in patients with CKD.⁴ Therefore, the optimal lifelong antiplatelet therapy of choice is of paramount importance in patients with CKD who receive percutaneous coronary intervention (PCI).

Recently, the HOST-EXAM (Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis–Extended Antiplatelet Monotherapy) trial reported the

superiority of clopidogrel over aspirin as long-term monotherapy for secondary prevention after PCI with drug-eluting stents.⁵ Clopidogrel monotherapy reduced both thrombotic and bleeding risk compared with aspirin monotherapy.⁵ However, it is unknown whether these beneficial effects are maintained in patients with decreased renal function and whether any interaction exists between treatment effect and glomerular filtration rate. In this post hoc subgroup analysis of the HOST-EXAM cohort, we assessed the treatment effects of clopidogrel versus aspirin monotherapy according to the renal function.

METHODS

The HOST-EXAM trial is planning to continue follow-up until 2025. No individual participant data will be available before this. Any relevant inquiries should be sent to the corresponding author.

Trial Design and Population

This study was a post hoc analysis of the HOST-EXAM trial (NCT02044250), which was an investigator-initiated, randomized, multicenter, prospective, open-label trial conducted at 37 study sites in South Korea. The trial design has been reported previously.⁶ Patients aged ≥ 20 years who maintained aspirin plus any P2Y₁₂ inhibitor without any clinical events for 6 to 18 months after undergoing successful PCI with drug-eluting stents were eligible for this study. Key exclusion criteria were patients with known hypersensitivity or contraindications for clopidogrel or those who could not change their current antiplatelet agents. Patients who met all the inclusion criteria and none of the exclusion criteria were randomized 1:1 to a clopidogrel (75 mg once daily) or aspirin (100 mg once daily) arm as a single maintenance antiplatelet therapy. Other antiplatelet agents were not permitted to be used. Patients were followed up at 12 and 24 months after randomization. The trial protocol was approved by the institutional review board at each participating site, and all patients were required to provide written informed consent at the time of enrollment and randomization.

Clinical Outcomes

The primary end point was defined as a composite of all-cause death, nonfatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and major bleeding complications, defined as Bleeding Academic Research Consortium type 3 or 5 bleeding, during the 24-month follow-up period. The secondary end points included the thrombotic composite end point, which was defined as a composite of cardiac death, nonfatal myocardial infarction, ischemic stroke, readmission due to acute coronary syndrome,

and definite or probable stent thrombosis; and any bleeding, which was defined as Bleeding Academic Research Consortium type ≥ 2 bleeding. The individual components of the primary and thrombotic composite end point, revascularization, and minor gastrointestinal complication were also analyzed as secondary end points at 24 months. The cause of death was evaluated using the medical record classified by the *International Classification of Disease, Tenth Revision (ICD-10)*. To minimize potential bias by open-labeled study design, all clinical events were primarily assessed by the investigator and additionally adjudicated by the independent, blinded, and centralized clinical event committee.

Renal Function Assessment

Laboratory results collected from the screening date until randomization were used in this analysis. The estimated glomerular filtration rate (eGFR) was calculated by using the Chronic Kidney Disease Epidemiology Collaboration equation, and patients without creatinine values were excluded from this analysis. CKD was defined having an eGFR <60 mL/min per 1.73 m², and patients were classified into 3 groups according to the severity of renal dysfunction (normal renal function group, eGFR ≥ 90 mL/min per 1.73 m²; mild renal dysfunction group, eGFR 60 – 90 mL/min per 1.73 m²; moderate to severe renal dysfunction group, eGFR <60 mL/min per 1.73 m²).

Statistical Analysis

All clinical events were assessed in the intention-to-treat population. Baseline characteristics were evaluated according to the CKD status and treatment arm. They were expressed as mean $\pm$ SD for continuous variables and absolute count (percentage) for categorical variables. Independent *t* tests were used to compare the continuous variables, and categorical variables were compared by the χ^2 or Fisher exact test, as appropriate. Cumulative incidence rates of primary and secondary end points were estimated using the Kaplan–Meier method, and differences between groups were examined by log-rank test. A univariable Cox proportional hazards model was used to assess the effect of treatment arm on clinical outcomes according to the presence of CKD. An interaction test was performed to evaluate the differences in treatment effect of antiplatelet agents according to the renal function via introduction of interaction terms between randomized arm assignment and CKD status. A multivariable Cox proportional hazards model was used to assess the effect of renal function on clinical outcomes with adjustment for clinical and procedural characteristics (antiplatelet agent, age, sex, diabetes, hypertension, dyslipidemia, current smoker, history of myocardial infarction, extent of coronary artery

disease, presence of left main disease, and the presence of bifurcation). Per-protocol analyses were conducted as a sensitivity analysis. Using the conventional frequentist analysis, we examined whether the treatment effect of clopidogrel differed according to renal function. To calculate the probability that clopidogrel was superior to aspirin in each renal function group, Bayesian analysis was conducted using JAGS through the rjags package (version 4–15) in R version 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria)⁷ as another sensitivity analysis. Superiority was defined as a relative risk of clopidogrel over aspirin under the posterior distribution being <1.0 . Due to the lack of a previous direct comparison study between aspirin and clopidogrel as chronic maintenance monotherapy after PCI, we made no prior assumptions that one antiplatelet regime was likely to have better outcomes than the other. The 95% highest posterior density interval was selected as a 95% credible interval. All *P* values were 2-sided, and statistical significance was defined as $P<0.05$. The statistical analysis was performed using R version 4.3.0.

RESULTS

Patient Characteristics

Among 5438 patients enrolled in the HOST-EXAM trial from March 26, 2014, to May 29, 2018, full data to calculate the eGFR were available in 4844 patients (Figures S1). The mean eGFR in the entire population was 89.4 ± 19.5 mL/min per 1.73 m², and 508 (10.5%) patients had CKD (defined as eGFR <60 mL/min per 1.73 m²). The mean eGFR was 44.4 ± 14.6 mL/min per 1.73 m² and 89.9 ± 13.6 mL/min per 1.73 m² in the CKD and non-CKD groups respectively. Baseline characteristics according to the presence of CKD are presented in Table S1. Patients with CKD were older and more likely to be women, to be a current smoker, and to have a higher prevalence of various comorbidities including diabetes, insulin-dependent diabetes, and hypertension. Patients with CKD were likely to have a history of cardiovascular accident, left main disease, and multivessel disease. The baseline characteristics according to the randomized antiplatelet treatment within the CKD and non-CKD groups are presented in Table 1. The baseline characteristics were well balanced between the clopidogrel and aspirin groups with no significant differences.

Clinical Outcomes According to Renal Function

During the study period of 24 months, the cumulative incidence of the primary end point was significantly higher in the CKD group compared with the non-CKD group (11.7% versus 6.0%; hazard ratio [HR],

Table 1. Baseline Patient Characteristics

	CKD		<i>P</i> value	Non-CKD		<i>P</i> value
	Aspirin (n=244)	Clopidogrel (n=264)		Aspirin (n=2174)	Clopidogrel (n=2162)	
Age, y	71.9±9.3	71.9±9.3	0.994	62.3±10.3	62.4±10.3	0.690
Male sex, n (%)	139 (57.0)	149 (56.4)	0.905	1670 (76.8)	1668 (77.2)	0.794
Diabetes, n (%)	142 (58.2)	137 (51.9)	0.154	700 (32.2)	706 (32.7)	0.748
Insulin-dependent diabetes, n (%)	27 (11.1)	21 (8.0)	0.231	33 (1.5)	30 (1.4)	0.720
Hypertension, n (%)	199 (81.6)	205 (77.7)	0.276	1289 (59.3)	1285 (59.4)	0.923
Dyslipidemia, n (%)	175 (71.7)	198 (75.0)	0.403	1517 (69.8)	1518 (70.2)	0.755
Current smoker, n (%)	26 (10.7)	33 (12.5)	0.517	503 (23.1)	453 (21.0)	0.083
Previous myocardial infarction, n (%)	39 (16.0)	46 (17.4)	0.664	365 (16.8)	365 (16.9)	0.935
Previous cardiovascular accident, n (%)	23 (9.4)	21 (8.0)	0.556	101 (4.6)	84 (3.9)	0.215
Clinical indication of PCI, n (%)			0.781			0.686
Silent ischemia	8 (3.3)	5 (1.9)		59 (2.7)	45 (2.1)	
Stable angina	69 (28.3)	70 (26.5)		540 (24.8)	549 (25.4)	
Unstable angina	84 (34.4)	102 (38.6)		756 (34.8)	757 (35.0)	
NSTEMI	48 (19.7)	50 (18.9)		422 (19.4)	429 (19.8)	
STEMI	35 (14.3)	37 (14.0)		397 (18.3)	382 (17.7)	
Laboratory results						
Creatinine, mg/dL	1.9±1.9	2.0±1.9	0.763	0.9±0.2	0.9±0.2	0.383
eGFR, mL/min per 1.73m ²	44.8±14.2	44.0±14.9	0.517	89.7±13.6	90.0±13.6	0.370
Days from PCI to randomization	389.3±71.2	386.5±66.9	0.652	389.3±65.0	390.5±67.4	0.569
DAPT at the randomization, n (%)			0.120			0.398
Aspirin plus clopidogrel	214 (87.7)	224 (84.8)		1721 (79.2)	1733 (80.2)	
Aspirin plus ticagrelor	24 (9.8)	22 (8.3)		223 (10.3)	233 (10.8)	
Aspirin plus prasugrel	4 (1.6)	14 (5.3)		220 (10.1)	187 (8.6)	
Aspirin plus clopidogrel plus cilostazol	2 (0.8)	4 (1.5)		10 (0.5)	9 (0.4)	
Angiographic data per patient						
Extent of CAD			0.644			0.816
1-vessel disease, n (%)	85 (35.0)	100 (37.9)		1123 (51.7)	1112 (51.4)	
2-vessel disease, n (%)	81 (33.3)	90 (34.1)		666 (30.6)	679 (31.4)	
3-vessel disease, n (%)	77 (31.7)	74 (28.0)		385 (17.7)	371 (17.2)	
Left main disease, n (%)	16 (6.6)	21 (8.0)	0.545	96 (4.4)	110 (5.1)	0.298
Multivessel disease, n (%)	158 (65.0)	164 (62.1)	0.498	1051 (48.3)	1050 (48.6)	0.884
Bifurcation, n (%)	26 (10.7)	32 (12.1)	0.604	235 (10.8)	226 (10.5)	0.704
Number of treated lesions	1.4±0.7	1.4±0.6	0.475	1.3±0.6	1.3±0.6	0.538
Mean diameter of implanted stents, mm	3.0±0.4	3.0±0.4	0.867	3.1±0.4	3.1±0.4	0.894
Minimum diameter of implanted stents, mm	2.9±0.4	2.9±0.4	0.676	3.0±0.5	3.0±0.5	0.747
Total length of implanted stents, mm	40.5±26.8	39.8±28.0	0.793	34.9±22.8	35.5±23.7	0.394
Total number of implanted stents	1.6±1.0	1.6±1.0	0.816	1.4±0.8	1.5±0.8	0.324
Generation of DES, n (%)			0.878			0.639
First-generation DES	2 (0.8)	2 (0.8)		42 (1.9)	47 (2.2)	
Second-generation DES	239 (98.0)	260 (98.5)		2111 (97.1)	2089 (96.6)	
Unknown generation	3 (1.2)	2 (0.8)		21 (1.0)	26 (1.2)	

CAD indicates coronary artery disease; CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; eGFR, estimated glomerular filtration rate; NSTEMI, non-ST-segment-elevation myocardial infarction; PCI, percutaneous coronary intervention; and STEMI, ST-segment-elevation myocardial infarction.

2.01 [95% CI, 1.51–2.67; $P<0.001$; log-rank]; $P<0.001$; [Figure 1A](#)). CKD was also associated with a higher risk of the thrombotic composite end point (HR, 1.74 [95% CI, 1.21–2.50]; $P=0.003$; log-rank $P=0.002$; [Figure 1B](#)), any bleeding (HR, 2.82 [95% CI, 1.88–4.22]; $P<0.001$; log-rank $P<0.001$; [Figure 1C](#)), all-cause death (HR, 3.99 [95% CI, 2.44–6.53]; $P<0.001$), and cardiac death (HR, 7.47 [95% CI, 3.35–16.68]; $P<0.001$). After adjustment for differences in clinical characteristics, results were similar and consistent with that of the univariable analysis ([Table S2](#)).

When patients were divided into 3 groups according to renal function, 2353 (48.6%) were in the normal renal function group (eGFR ≥ 90 mL/min per 1.73 m^2), 1983 (40.9%) were in the mild renal dysfunction group (eGFR 60–90 mL/min per 1.73 m^2), and 508 (10.5%) were in the moderate to severe renal dysfunction group (eGFR <60 mL/min per 1.73 m^2). There was an increase in clinical events as the renal function deteriorated (primary end point: 5.3% versus 6.9% versus 11.7%, P for trend <0.001 ; thrombotic end point: 3.9% versus 4.5% versus 7.1%, P for trend $=0.008$; any bleeding: 2.1% versus 2.6% versus 6.4%, P for trend <0.001 ; [Figure S2](#)).

The association between continuous eGFR values and the risk of clinical events is shown in [Figure S3](#). The risk of clinical events significantly increased as eGFR decreased (adjusted HR for the primary end point per 10 mL/min per 1.73 m^2 decrease in eGFR: 1.09 [95% CI, 1.03–1.16]; adjusted HR for the thrombotic end point per 10 mL/min per 1.73 m^2 decrease in eGFR: 1.08 [95% CI, 1.01–1.17]; adjusted HR for any bleeding per 10 mL/min per 1.73 m^2 decrease in eGFR: 1.12 [95% CI, 1.03–1.23]).

Clinical Outcomes According to the Antiplatelet Strategy in the CKD and Non-CKD Groups

Within the CKD group, the primary end point occurred in 13.4% (32 patients) in the aspirin arm and 10.1% (26 patients) in the clopidogrel arm (HR, 0.74 [95% CI, 0.44–1.25]; $P=0.264$). In the non-CKD group, the incidence of the primary end point was 7.0% and 5.1% in the aspirin and clopidogrel arms, respectively (HR, 0.71 [95% CI, 0.56–0.91]; $P=0.007$). The number needed to treat for clopidogrel over aspirin to prevent 1 primary end point was 33 for the CKD group and 50 for the non-CKD group. There was no significant interaction between the treatment effect and the presence of CKD (P for interaction $=0.889$; [Figure 2A](#)). The results were similar for the thrombotic end point (CKD group: HR, 0.69 [95% CI, 0.35–1.34]; $P=0.269$; non-CKD group: HR, 0.67 [95% CI, 0.50–0.91]; $P=0.010$, P for interaction $=0.963$; [Figure 2B](#)) and any bleeding (CKD group: HR, 0.77 [95% CI, 0.38–1.56]; $P=0.466$; non-CKD group: HR, 0.60 [95% CI, 0.40–0.90]; $P=0.014$; P for

interaction $=0.548$; [Figure 2C](#)). No significant interactions were found between CKD status and treatment effects of any of the other outcomes (all P for interaction >0.10 ; [Table 2](#)). The per-protocol analyses yielded similar results to the intention-to-treat analyses for the primary end point and the secondary end points ([Table S3](#)).

Treatment Effect and Outcomes According to the Severity of Renal Dysfunction

The treatment effects of clopidogrel versus aspirin was analyzed according to the degree of renal dysfunction (normal renal function, mild renal dysfunction, and moderate to severe renal dysfunction). There was no significant interaction between the degree of renal dysfunction and the treatment strategy with regard to the primary end point (P for interaction $=0.570$), the thrombotic end point (P for interaction $=0.978$) and any bleeding (P for interaction $=0.161$; [Figure 3](#)).

Per Bayesian analysis, the probability that clopidogrel is superior to aspirin for the primary end point was 99% in the normal renal function group (relative risk, 0.67 [95% highest posterior density interval, 0.45–0.91]), 93% in the mild renal dysfunction group (relative risk, 0.79 [95% highest posterior density interval, 0.54–1.05]), and 88% in moderate to severe renal dysfunction group (relative risk, 0.78 [95% highest posterior density interval, 0.42–1.16]). The probability that clopidogrel is superior for the thrombotic end point was 96%, 97%, and 87% in the normal renal function, mild renal dysfunction, and moderate to severe renal dysfunction groups, respectively. That for any bleeding was 100%, 80%, and 78% in the 3 respective groups ([Table S4](#)).

DISCUSSION

In this post hoc analysis of the HOST-EXAM trial, we studied whether the beneficial effects of clopidogrel over aspirin during the chronic maintenance monotherapy following PCI is consistent in patients with CKD. Our principal findings are as follows: (1) Patients with CKD have a higher incidence of both thrombotic and bleeding events than those patients without CKD; and (2) there was no difference in the treatment effect of clopidogrel monotherapy according to CKD status and degree of renal function.

Clinical Implication of CKD in Patients Who Underwent PCI

The proportion of patients with CKD undergoing PCI is increasing due to the high prevalence of coronary artery disease in these patients, an aging society, and

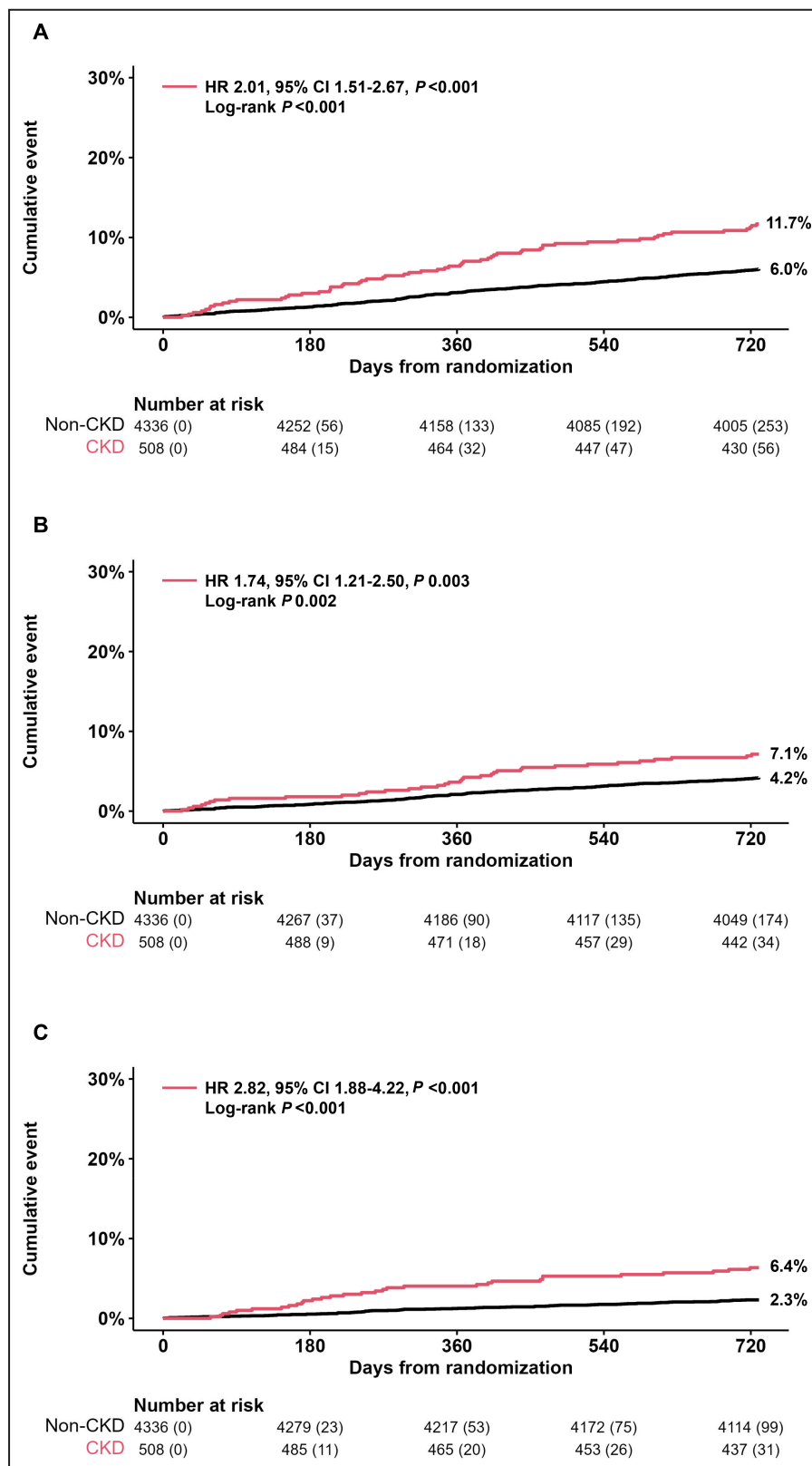


Figure 1. Effects of chronic kidney disease on clinical outcomes.

The cumulative incidences of primary composite end point (A), thrombotic composite end point (B), and any bleeding (C) were compared according to the chronic kidney disease. CKD indicates chronic kidney disease; and HR, hazard ratio.

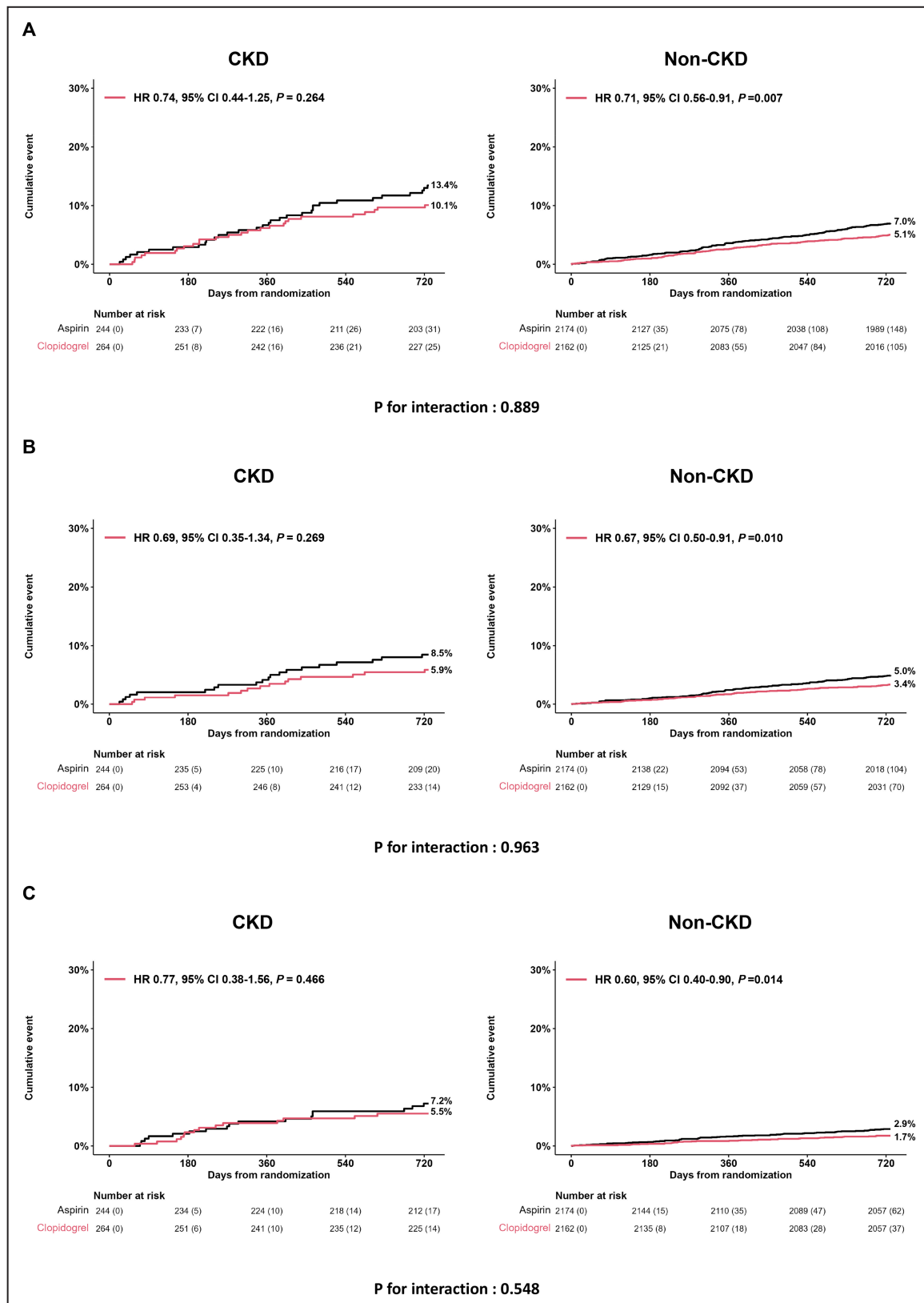


Figure 2. Effects of antiplatelet regimen on clinical outcomes according to CKD status.

The cumulative incidences of primary composite end point (A), thrombotic composite end point (B), and any bleeding (C) were compared according to antiplatelet regimen in patients with CKD and without CKD. CKD indicates chronic kidney disease; and HR, hazard ratio.

Table 2. Clinical Outcomes in Relation to CKD Status and the Randomized Antiplatelet Agents

	CKD (N=508)				Non-CKD (N=4336)				P for interaction
	Aspirin, n (%) (n=244)	Clopidogrel, n (%) (n=264)	HR (95% CI)	P value	Aspirin, n (%) (n=2174)	Clopidogrel, n (%) (n=2162)	HR (95% CI)	P value	
Primary composite end point	32 (13.4)	26 (10.1)	0.74 (0.44–1.25)	0.264	151 (7.0)	108 (5.1)	0.71 (0.56–0.91)	0.007	0.889
Thrombotic composite end point	20 (8.5)	15 (5.9)	0.69 (0.35–1.34)	0.269	107 (5.0)	72 (3.4)	0.67 (0.50–0.91)	0.010	0.963
Any bleeding (BARC type ≥ 2)	17 (7.2)	14 (5.5)	0.77 (0.38–1.56)	0.466	62 (2.9)	37 (1.7)	0.60 (0.40–0.90)	0.014	0.548
All-cause death	10 (4.2)	13 (5.1)	1.21 (0.53–2.77)	0.644	22 (1.0)	29 (1.4)	1.33 (0.76–2.32)	0.313	0.862
Cardiac death	4 (1.7)	7 (2.8)	1.63 (0.48–5.57)	0.435	7 (0.3)	6 (0.3)	0.87 (0.29–2.57)	0.794	0.447
Noncardiac death	6 (2.6)	6 (2.3)	0.94 (0.30–2.90)	0.909	15 (0.7)	23 (1.1)	1.55 (0.81–2.97)	0.188	0.452
Nonfatal myocardial infarction	2 (0.8)	1 (0.4)	0.46 (0.04–5.11)	0.530	24 (1.1)	15 (0.7)	0.63 (0.33–1.2)	0.159	0.812
Stroke	7 (3)	2 (0.8)	0.26 (0.05–1.27)	0.097	28 (1.3)	12 (0.6)	0.43 (0.22–0.85)	0.015	0.576
Ischemic stroke	4 (1.7)	2 (0.8)	0.46 (0.08–2.53)	0.374	17 (0.8)	9 (0.4)	0.53 (0.24–1.20)	0.127	0.885
Hemorrhagic stroke	3 (1.3)	0 (0)	NA	NA	11 (0.5)	3 (0.1)	0.27 (0.08–0.99)	0.047	0.997
Readmission due to ACS	13 (5.5)	6 (2.4)	0.43 (0.16–1.12)	0.083	84 (3.9)	57 (2.7)	0.68 (0.49–0.95)	0.025	0.368
Major bleeding (BARC type ≥ 3)	9 (3.8)	8 (3.2)	0.83 (0.32–2.16)	0.709	39 (1.8)	20 (0.9)	0.52 (0.30–0.88)	0.016	0.388
Any revascularization	4 (1.7)	6 (2.4)	1.40 (0.39–4.95)	0.604	57 (2.7)	44 (2.1)	0.78 (0.52–1.15)	0.208	0.380
Target-lesion revascularization	1 (0.4)	2 (0.8)	1.86 (0.17–20.48)	0.613	29 (1.4)	19 (0.9)	0.66 (0.37–1.18)	0.158	0.406
Target-vessel revascularization	3 (1.3)	4 (1.6)	1.25 (0.28–5.56)	0.774	38 (1.8)	29 (1.4)	0.77 (0.47–1.24)	0.284	0.543
Definite or probable stent thrombosis	1 (0.4)	0 (0)	NA	NA	12 (0.6)	9 (0.4)	0.76 (0.32–1.80)	0.528	0.997
Any minor gastrointestinal complications	30 (12.7)	36 (14.1)	1.14 (0.70–1.85)	0.605	264 (12.3)	212 (10.0)	0.80 (0.67–0.96)	0.015	0.182

ACS indicates acute coronary syndrome; BARC, Bleeding Academic Research Consortium; CKD, chronic kidney disease; and HR, hazard ratio.

increasing incidence of comorbidities including diabetes, hypertension, and obesity.^{4,8–10} There are few clinical trials comparing post-PCI pharmacotherapy in patients with CKD, but several registry studies have shown that CKD is associated with adverse clinical events in such patients.^{11–16}

In the PROMETHEUS (Prasugrel or Clopidogrel in Patients With Acute Coronary Syndromes at High Thrombotic Risk) study, CKD was significantly associated with a higher risk for both major adverse cardiac events and bleeding events at 1 year.¹⁵ Our study showed similar results where CKD was an independent risk factor for not only the primary end point, a composite of both ischemic and bleeding outcomes but also each thrombotic end point and any bleeding events. It is interesting that CKD is a co-risk factor for

both ischemic and bleeding events, which are considered to have opposite characteristics. Among various thrombotic events, CKD was associated with a higher risk of cardiac death and all cause death, which are the most fatal outcomes. In particular, CKD showed a strong association with cardiac death, even after other covariates were adjusted. Also, cardiac death accounted for nearly half of all-cause deaths (11/23) in patients with CKD, while cardiac death accounted for only about a quarter of all-cause deaths (13/51) in patients without CKD. These findings are consistent with previous studies. A subgroup analysis of the EVENT (Evaluation of Drug-Eluting Stents and Ischemic Events) registry assessed 1-year outcomes following PCI with drug-eluting stents according to renal function.¹⁶ In this study, there was an increase in fatal outcomes

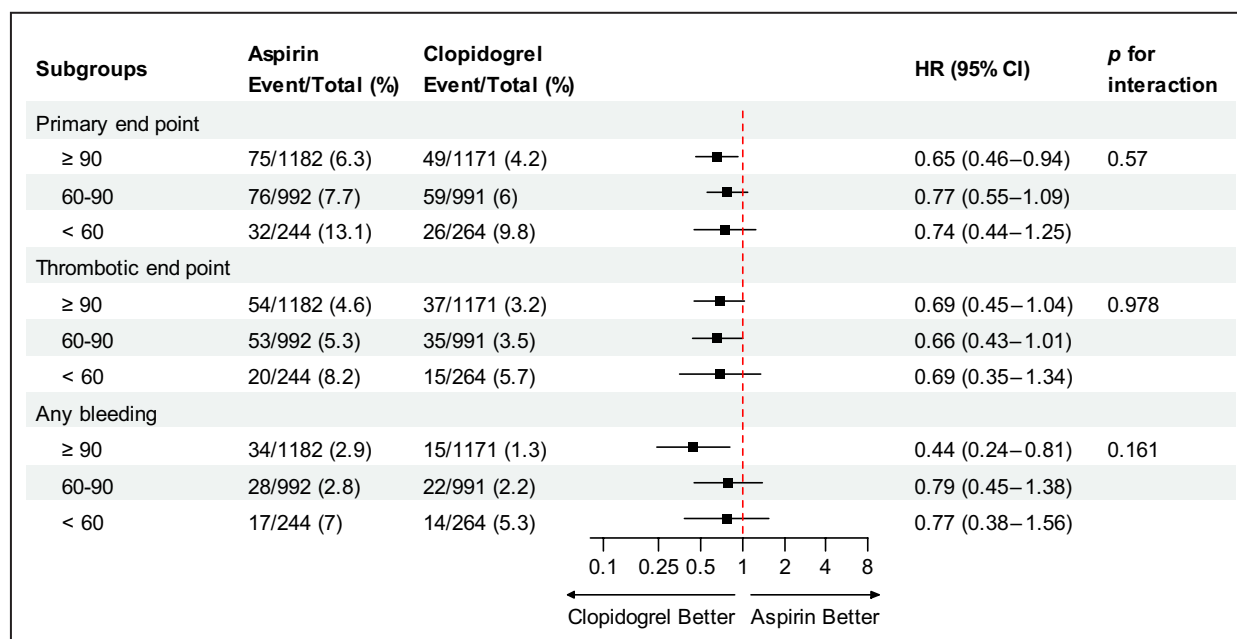


Figure 3. Clinical outcomes according to antiplatelet regimen in the normal renal function, mild renal dysfunction, and moderate to severe renal dysfunction groups.

The HR for primary composite end point, thrombotic composite end point, and any bleeding were shown according to antiplatelet regimen in the normal renal function, mild renal dysfunction, and moderate to severe renal dysfunction groups. HR indicates hazard ratio.

including cardiac death and myocardial infarction with decreasing creatinine clearance. In another study, the risk of death and myocardial infarction increased with worsening renal function, but the risk of target-vessel revascularization did not show a significant association with renal function.¹⁴ In addition, deteriorating renal function was associated with higher risk of adverse clinical events not only when patients were divided into CKD and non-CKD groups but also when analyzed in 3 groups according to the degree of renal dysfunction (normal, mild, and moderate to severe renal dysfunction) and when analyzed on the basis of continuous eGFR value. Taken together, our results along with data from previous reports suggest that optimal post-PCI pharmacotherapy may be especially important for patients with impaired renal function.

Long-Term Antiplatelet Strategy in Patients With CKD Who Underwent PCI

Antiplatelet agents are one of the most important medications to prevent adverse events in patients with coronary artery disease. Since patients who undergo PCI are indicated for lifelong antiplatelet therapy, finding the optimal agent is especially important.¹⁷ Among various antiplatelet agents, aspirin and clopidogrel have been used for a long time in patients with cardiovascular disease risk. However, there was no study comparing the traditionally used aspirin and clopidogrel as proper

monotherapy during chronic maintenance period in patients who underwent coronary stenting before HOST-EXAM trial.⁵ Although the CAPRIE (Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events) trial showed that clopidogrel was more effective than aspirin in reducing major adverse cardiovascular events in patients with atherosclerotic vascular disease, it did not focus on the patients who underwent PCI and was performed before the era of “high-dose, high-intensity” statins.¹⁸ In the HOST-EXAM trial, the most contemporary trial comparing long-term maintenance antiplatelet monotherapy in a dedicated PCI population, clopidogrel was superior to aspirin in reducing the risk of both thrombotic and bleeding events. The effect of antiplatelet drugs could be influenced by change in renal function because platelet function and the enzymatic coagulation cascade can be affected by renal function.^{1,3,4} Combined with thrombogenic and bleeding characteristics in patients with CKD, it is difficult to predict the final effect of antiplatelet agents adjusted by the impaired renal function. For example, the CKD substudy of the CREDO (Clopidogrel for the Reduction of Events During Observation) trial showed that clopidogrel reduced the risk of thrombotic events in patients with normal renal function but not in those with mild to moderate CKD.¹⁹ Therefore, it is important to study whether the benefits seen in the main trial are consistent and sustained in patients with CKD or those with renal dysfunction.

In our substudy, the clopidogrel arm had numerically lower rates of adverse outcomes including the primary composite end point, thrombotic composite end point, and any bleeding compared with the aspirin arm in both the CKD and non-CKD groups. Although the difference did not reach statistical significance, there was no significant interaction between the treatment effect and CKD status for any of the outcomes. These results were similar in the per-protocol analysis. Furthermore, when patients were divided into 3 groups according to degree of renal dysfunction ($\text{eGFR} \geq 90$, $60\text{--}90$, and $<60\text{ mL/min per } 1.73\text{ m}^2$), there was no significant difference in the treatment effects of clopidogrel over aspirin across the 3 groups.

While our conventional frequentist analysis showed no statistical difference in treatment effects of clopidogrel over aspirin according to renal function, it may be worthwhile to understand to what extent clopidogrel is beneficial in each renal function group. Due to the innate limitations of subgroups analyses, it may be challenging to precisely determine this. However, using a Bayesian analysis, we observed a much greater probability of a lower incidence of clinical events in the clopidogrel arm, even in the subgroup with $\text{eGFR} < 60\text{ mL/min per } 1.73\text{ m}^2$.

Recently, the COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial has demonstrated that dual pathway inhibition with low-dose rivaroxaban (2.5 mg twice daily) and aspirin compared with aspirin alone showed better cardiovascular outcomes (a composite of cardiovascular death, stroke, or myocardial infarction) in patients with stable cardiovascular disease at the cost of an increased risk in major bleeding.²⁰ Our findings of lower bleeding when using clopidogrel over aspirin could open the possibility of dual pathway inhibition using clopidogrel instead of aspirin. Of course, it is unknown how rivaroxaban will interact with clopidogrel, and further studies will be necessary to test whether this could be a feasible option for secondary prevention in patients with high ischemic risk.

Limitations

This study has several limitations. First, the randomization in HOST-EXAM trial was not stratified by CKD status, and it may cause some imbalance between the randomized groups among patients with CKD. Second, due to the limitation of subgroup analysis, the CKD group was underpowered to draw any definitive conclusions on the superior effect of clopidogrel over aspirin on clinical outcomes. Therefore, our results should be interpreted carefully and considered hypothesis generating at best. Third, we used the baseline renal function to define CKD, and thus any changes in renal function over the study period were

not incorporated in the analysis. Fourth, the prognostic value of continuous eGFR in each clopidogrel and aspirin group could not be investigated due to the limited number of patients with CKD. We will require further studies in a dedicated CKD population to determine the optimal chronic maintenance antiplatelet strategy in CKD patients undergoing PCI.

CONCLUSIONS

In patients indicated for chronic maintenance antiplatelet monotherapy after due duration of dual antiplatelet therapy following PCI, the risk of thrombotic and bleeding events was significantly higher in those with CKD compared with those without CKD. There were no significant differences in the treatment effect of clopidogrel over aspirin according to baseline renal function.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S4
Figures S1–S3

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