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ORIGINAL RESEARCH

Association of Clinical Outcomes With Sex in Patients Receiving Chronic Maintenance Antiplatelet Monotherapy After Percutaneous Coronary Intervention: A Post Hoc Gender Analysis of the HOST-EXAM Study

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BACKGROUND: Clopidogrel monotherapy was more effective in reducing the risk of adverse clinical events than aspirin monotherapy in patients who underwent percutaneous coronary intervention (PCI) with drug-eluting stent (DES), according to the HOST-EXAM (Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis–Extended Antiplatelet Monotherapy) trial. However, it remains unknown whether these effects differ based on sex.

METHODS AND RESULTS: This was a prespecified secondary analysis of HOST-EXAM in South Korea. Patients who maintained dual antiplatelet therapy without adverse clinical events for 6 to 18 months after PCI with DES were included. The primary end point was a composite of all-cause mortality, nonfatal myocardial infarction, stroke, acute coronary syndrome, or Bleeding Academic Research Consortium (BARC) bleeding type ≥3 at 24 months after randomization. The bleeding end point was BARC types 2 to 5. The primary end point was comparable between the sexes (adjusted hazard ratio [HR], 0.79 [95% CI, 0.62–1.02]; *P*=0.067), and the bleeding end point (adjusted HR, 0.79 [95% CI, 0.54–1.17]; *P*=0.240) was also similar. Compared with aspirin, clopidogrel was associated with lower risk of primary composite end point (adjusted HR, 0.70 [95% CI, 0.55–0.89]; *P*=0.004) and bleeding end point (adjusted HR, 0.65 [95% CI, 0.44–0.96]; *P*=0.031) in men but not in women.

CONCLUSIONS: The primary composite end point and bleeding events were comparable between the sexes during chronic maintenance antiplatelet monotherapy after PCI with DES. Clopidogrel monotherapy, compared with aspirin, significantly reduced the risk of the primary composite end point and bleeding events in men. However, the beneficial effect of clopidogrel on the primary end point and bleeding events was mitigated in women.

REGISTRATION INFORMATION: clinicaltrials.gov. Identifier: NCT02044250.

Key Words: aspirin ■ clopidogrel ■ drug-eluting stent ■ percutaneous coronary intervention ■ sex ■ women

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A complete list of the HOST-EXAM Investigators can be found in the Supplemental Material.

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CLINICAL PERSPECTIVE

What Is New?

- In this prespecified subgroup analysis of the HOST-EXAM (Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis–Extended Antiplatelet Monotherapy) randomized clinical trial including 5438 patients, the primary composite end point and bleeding events were comparable between the sexes during chronic maintenance antiplatelet monotherapy after percutaneous coronary intervention with drug-eluting stent.
- Clopidogrel monotherapy, compared with aspirin, significantly reduced the risk of the primary composite end point and bleeding events in men.
- However, such beneficial effect of clopidogrel over aspirin was mitigated in women by the higher all-cause mortality associated with clopidogrel.

What Are the Clinical Implications?

- These results support the importance of adjusting antiplatelet regimens according to sex during the chronic maintenance period following percutaneous coronary intervention with a drug-eluting stent.

Nonstandard Abbreviations and Acronyms

BARC	Bleeding Academic Research Consortium
DAPT	dual antiplatelet therapy
DES	drug-eluting stent
HPR	high platelet reactivity

Even in the contemporary era, aspirin has been the first choice of drug for antiplatelet monotherapy,[1] whereas clopidogrel has been used as an alternative for patients who cannot tolerate aspirin therapy during their chronic maintenance antiplatelet monotherapy after percutaneous coronary intervention (PCI) with drug-eluting stent (DES).[2] Recently, the HOST-EXAM (Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis–Extended Antiplatelet Monotherapy) trial showed that in the chronic maintenance period of patients who underwent PCI with DES, clopidogrel monotherapy compared with aspirin monotherapy significantly reduced the risk of all-cause mortality, nonfatal myocardial infarction (MI), stroke, readmission due to acute coronary syndrome (ACS), and Bleeding Academic Research Consortium (BARC) bleeding type ≥3.[3] Whether these effects vary in relation to sex remains unknown. Although women have an increased risk of ischemic and bleeding events after the early period of PCI compared with men,[4–7] whether they are also at an increased risk of these events during their chronic maintenance antiplatelet monotherapy after PCI with DES remains unclear. Therefore, we performed a prespecified secondary analysis to explore sex differences in the HOST-EXAM population and evaluate the possible association between sex and clinical outcome in patients receiving clopidogrel or aspirin monotherapy.

METHODS

The data, analytic methods, and study materials will not be made publicly available to other researchers for the purpose of reproducing the results or replicating the procedure.

Study Design

The HOST-EXAM trial was an investigator-initiated, prospective, randomized, open-label, multicenter trial conducted at 37 study sites in South Korea (Data S1). Details regarding the trial design have been described previously.[3,8] The Seoul National University Hospital Clinical Trial Center and Medical Research Collaborating Center were responsible for the scientific conduct of the trial and independent analysis of the data. The institutional review board at each participating site approved the trial protocol, and all patients were required to provide written informed consent at the time of enrollment and randomization. All events were adjudicated by an independent clinical event committee whose members were unaware of the trial group assignments. The HOST-EXAM trial was conducted between March 26, 2014, and May 29, 2018.

Study Population and Regimen

To be eligible for enrollment, patients must have undergone successful PCI with DES and maintained dual antiplatelet therapy (DAPT) without any clinical events for 6 to 18 months after PCI. Patients with ischemic and major bleeding complications (ie nonfatal MI, repeat revascularization, readmission due to a cardiovascular cause, or major bleeding) were excluded from randomization. Antiplatelet therapy before enrollment comprised aspirin plus a P2Y12 inhibitor. All patients received either clopidogrel (75 mg once daily) or aspirin (100 mg once daily) orally after randomization. Clinical follow-ups were scheduled at 12 and 24 months, and additional visits were at the attending physician's discretion. At each visit, active surveillance was performed for any adverse clinical events, along with the assessment of adherence to the use of study drug.

Outcomes

The primary end point was a composite of all-cause mortality, nonfatal MI, stroke, readmission due to ACS, and major bleeding complications during the 24-month follow-up period. Major bleeding was defined as BARC type ≥3; the bleeding end point was defined as BARC type ≥2.[9] Detailed definitions of each clinical event have been described previously.[3]

Statistical Analysis

Baseline clinical and procedural characteristics were summarized based on sex and randomized treatment assignment using means and SDs for continuous variables and numbers and frequencies for categorical variables. The Kaplan–Meier method was used to estimate the cumulative incidences of the primary end point. Patients without a primary end point between randomization and 2 years were censored at the time of death, last known contact, or 24 months, whichever came first. Cox proportional-hazards models were used to calculate hazard ratios (HRs) and 95% CIs; Cox regression was used to examine associations between sex and clinical outcomes. Models were adjusted for variables displaying baseline differences, including age, diabetes, hypertension, current smoking status, chronic kidney disease, previous MI, ACS, PCI of chronic total occlusion, and mean stent diameter. Treatment outcomes of clopidogrel monotherapy versus aspirin monotherapy were evaluated based on sex, and formal interaction testing using Cox regression was performed to assess for association modification. Primary end point and bleeding end point were analyzed as intention-to-treat. All patients randomly assigned were included in the primary intention-to treat analysis and a per-protocol analysis was also done. *P* values were 2-sided, and statistical significance was set at $P<0.05$. All statistical analyses were performed using R (version 3.6.3; R Foundation for Statistical Computing, Vienna, Austria). Data were analyzed from September to December 2021. This study is registered with ClinicalTrials.gov, NCT02044250.

RESULTS

Baseline Clinical and Procedural Characteristics

Of 5530 patients enrolled, 5438 underwent randomization (Figure S1). Of the randomized patients, 1384 (25.5%) were women, with a mean (SD) age of 63.5 (10.7) years. Table 1 shows the baseline clinical and procedural characteristics by sex. Compared with men, women were older (mean [SD] age in years, 68.9 [9.4] versus 61.6 [10.5]) and were more likely to have a higher prevalence of diabetes, hypertension, and chronic kidney disease (283 women [20.4%] versus 410 men [10.1%]). Conversely, women were less likely to be current smokers, have a history of MI, or have an ACS indication for PCI (Table 1). No significant differences were noted regarding the extent of coronary artery disease between the sexes, except for PCI rate for chronic total occlusion lesion (Table 1).

Table 1. Baseline Clinical and Procedural Characteristics by Sex

	No. (%)		
	Women (n=1384)	Men (n=4054)	*P* value
Age, y, mean (SD)	68.9 (9.4)	61.6 (10.5)	<0.001
Diabetes	521 (37.6)	1339 (33)	0.002
Hypertension	944 (68.2)	2394 (59.1)	<0.001
Dyslipidemia	959 (69.3)	2808 (69.3)	>0.999
Current smoker	60 (4.3)	1066 (26.3)	<0.001
Chronic kidney disease	283 (20.4)	410 (10.1)	<0.001
Previous myocardial infarction	194 (14.0)	678 (16.7)	0.020
Previous cerebrovascular accident	66 (4.8)	187 (4.6)	0.870
Clinical indication of PCI			
Stable coronary artery disease	423 (30.6)	1094 (27.0)	0.011
Acute coronary syndrome	961 (69.4)	2960 (73.0)	0.011
Day from PCI to randomization	384.3 (72.0)	387.8 (70.0)	0.115
Extent of coronary artery disease			
1-vessel disease	690 (49.9)	2053 (50.6)	0.652
2-vessel disease	417 (30.1)	1282 (31.6)	0.324
3-vessel disease	276 (20.0)	719 (17.7)	0.071
Left main disease	58 (4.2)	214 (5.3)	0.126
PCI for bifurcation lesion	137 (9.9)	443 (10.9)	0.308
PCI for chronic total occlusion lesion	102 (7.4)	409 (10.1)	0.003
Lesions treated, mean (SD), No.	1.3 (0.6)	1.3 (0.6)	0.927
Total stent number, mean (SD), No.	1.5 (0.8)	1.5 (0.8)	0.881
Mean stent diameter, mean (SD), mm	3.0 (0.4)	3.1 (0.4)	<0.001
Minimum stent diameter, mean (SD), mm	2.9 (0.4)	3.0 (0.5)	<0.001
Total stent length, mean (SD), mm	35.2 (23.4)	36.1 (24.0)	0.240

PCI indicates percutaneous coronary intervention.

Table 2 shows the baseline clinical and procedural characteristics according to sex and randomized treatment assignment. Among men, baseline clinical characteristics were well balanced between the treatment groups. However, among women, those receiving aspirin were more likely to have 3-vessel disease than those receiving clopidogrel (Table 2). The results from the per-protocol analyses are shown in the Tables S1 and S2 (Figures S2 and S3).

Table 2. Baseline Clinical and Procedural Characteristics by Sex and Randomized Treatment Assignment

	Women (n=1384)			Men (n=4054)		
	No. (%)			No. (%)		
	Clopidogrel (n=695)	Aspirin (n=689)	*P* value	Clopidogrel (n=2015)	Aspirin (n=2039)	*P* value
Age, y, mean (SD)	69.0 (9.4)	68.9 (9.4)	0.885	61.6 (10.4)	61.6 (10.5)	0.871
Diabetes	266 (38.3)	255 (37.0)	0.668	659 (32.7)	680 (33.3)	0.668
Hypertension	479 (68.9)	465 (67.5)	0.607	1185 (58.8)	1209 (59.3)	0.778
Dyslipidemia	476 (68.5)	483 (70.1)	0.554	1408 (69.9)	1400 (68.7)	0.421
Current smoker	30 (4.3)	30 (4.4)	1.000	515 (25.6)	551 (27.0)	0.306
Chronic kidney disease	147 (21.2)	136 (19.7)	0.559	209 (10.4)	201 (9.9)	0.623
Previous myocardial infarction	94 (13.5)	100 (14.5)	0.651	343 (17.0)	335 (16.4)	0.643
Previous cerebrovascular accident	30 (4.3)	36 (5.2)	0.505	90 (4.5)	97 (4.8)	0.714
Clinical indication of PCI						
Stable coronary artery disease	206 (29.6)	217 (31.5)	0.490	540 (26.8)	554 (27.2)	0.817
Acute coronary syndrome	489 (70.4)	472 (68.5)	0.490	1475 (73.2)	1485 (72.8)	0.817
Extent of coronary artery disease						
1-vessel disease	359 (51.7)	331 (48.1)	0.206	1008 (50.0)	1045 (51.3)	0.454
2-vessel disease	219 (31.5)	198 (28.8)	0.295	636 (31.6)	646 (31.7)	0.962
3-vessel disease	117 (16.9)	159 (23.1)	0.004	371 (18.5)	348 (17.1)	0.280
Left main disease	26 (3.7)	32 (4.6)	0.481	116 (5.8)	98 (4.8)	0.199
PCI for bifurcation lesion	66 (9.5)	71 (10.3)	0.679	219 (10.9)	224 (11.0)	0.945
PCI for chronic total occlusion lesion	59 (8.5)	43 (6.2)	0.134	198 (9.8)	211 (10.3)	0.617
Lesions treated, mean (SD), No.	1.3 (0.5)	1.3 (0.6)	0.637	1.3 (0.6)	1.3 (0.6)	0.417
Total stent number, mean (SD), No	1.5 (0.8)	1.5 (0.8)	0.515	1.5 (0.8)	1.5 (0.8)	0.195
Mean stent diameter, mean (SD), mm	3.0 (0.4)	3.0 (0.4)	0.771	3.1 (0.4)	3.1 (0.4)	0.746
Minimum stent diameter, mean (SD), mm	2.9 (0.4)	2.9 (0.4)	0.781	3.0 (0.5)	3.0 (0.5)	0.906
Total stent length, mean (SD), mm	35.2 (23.1)	35.3 (23.7)	0.978	36.4 (24.5)	35.9 (23.5)	0.513

PCI indicates percutaneous coronary intervention.

Outcomes Based on Sex

Figure 1A shows the incidences of primary composite end point at 2 years. No statistically significant differences were found between the sexes in the incidence of the composite of all-cause mortality, MI, ischemic stroke, readmission due to ACS, major bleeding, definite or probable stent thrombosis, or any revascularization. After multivariable adjustment, these results remained unchanged, thus demonstrating that the association between female sex and the risk was not significant (Figure 1A).

Figure 1B presents the rates of bleeding end points at 2 years. No significant differences between men and women were observed in the incidence of BARC type 2, 3, or 5 bleeding or hemorrhagic stroke. After multivariate adjustment, these results remained unchanged.

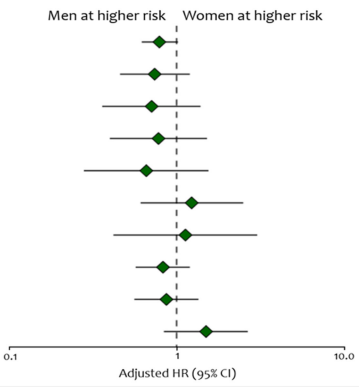
Outcomes Based on Sex and Randomized Treatment Assignment

Table 3 shows clinical outcomes based on sex and randomized treatment assignment at 2 years after randomization. Compared with aspirin, clopidogrel was associated with a lower risk of the primary composite end point in men (110 patients [5.5%] versus 155 patients [7.7%]; adjusted HR, 0.70 [95% CI, 0.55–0.89]; *P*=0.004) (Figure 2A) but not in women (42 patients [6.1%] versus 52 patients [7.7%]; adjusted HR, 0.79 [95% CI, 0.52–1.18]; *P*=0.252). No significant association was noted between randomized treatment assignment and sex (*P*=0.602) (Figure 2A).In terms of bleeding, compared with aspirin, clopidogrel was associated with lower rates of BARC type 2, 3, or 5 bleeding in men (43 patients [2.2%] versus 65 patients [3.3%]; adjusted HR, 0.65 [95% CI, 0.44–0.96]; *P*=0.031) but not in women (18 patients [2.7%] versus 22 patients [3.2%]; adjusted HR, 0.79 [95% CI, 0.42–1.47]; *P*=0.452). No significant association was noted between randomized treatment assignment and sex (*P*=0.595) (Figure 2B).

The effect of clopidogrel to reduce BARC type 3 or 5 bleeding or ischemic and hemorrhagic stroke was consistently observed in men but not in women. However, there were no significant associations between randomized treatment assignment and sex

A

Outcome	Women, No.(%)	Men, No.(%)	HR(95%CI)	*P* value	Adjusted HR (95% CI)	Adjusted *P* value
Primary composite end point	94 (6.9)	265 (6.6)	1.05 (0.83-1.33)	0.70	0.79 (0.62-1.02)	0.07
All-cause death	28 (2.1)	59 (1.5)	1.40 (0.89-2.20)	0.14	0.74 (0.46-1.20)	0.22
Cardiovascular death	14 (1.0)	29 (0.7)	1.42 (0.75-2.70)	0.28	0.71 (0.36-1.39)	0.32
Noncardiovascular death	14 (1.0)	30 (0.8)	1.38 (0.73-2.60)	0.32	0.78 (0.40-1.52)	0.47
Nonfatal myocardial infarction	7 (0.5)	39 (1.0)	0.53 (0.24-1.18)	0.12	0.66 (0.28-1.55)	0.34
Ischemic stroke	14 (1.0)	26 (0.7)	1.59 (0.83-3.05)	0.16	1.23 (0.61-2.50)	0.57
Stent thrombosis	6 (0.4)	20 (0.5)	0.89 (0.36-2.21)	0.80	1.13 (0.42-3.03)	0.81
Readmission due to ACS	41 (3.0)	134 (3.4)	0.90 (0.64-1.28)	0.57	0.83 (0.57-1.20)	0.32
Any revascularization	29 (2.1)	96 (2.4)	0.89 (0.59-1.35)	0.59	0.87 (0.56-1.35)	0.53
Target lesion revascularization	20 (1.5)	40 (1.0)	1.48 (0.87-2.54)	0.15	1.50 (0.84-2.66)	0.17



B

Outcome	Women, No.(%)	Men, No.(%)	HR(95%CI)	*P* value	Adjusted HR (95% CI)	Adjusted *P* value
BARC type 2, 3, or 5	40 (3.0)	108 (2.7)	1.09 (0.76-1.57)	0.63	0.79 (0.54-1.17)	0.24
BARC type 3 or 5	26 (1.9)	60 (1.5)	1.28 (0.81-2.03)	0.29	0.84 (0.51-1.36)	0.47
Hemorrhagic stroke	7 (0.5)	14 (0.4)	1.48 (0.60-3.66)	0.40	0.76 (0.29-1.97)	0.57

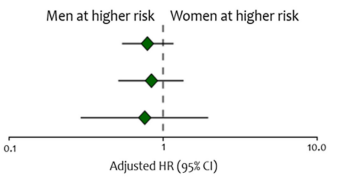


Figure 1. Primary composite end point and bleeding events at 24 months based on sex.
Women were used as the reference category. Adjusted hazard ratios were calculated for age, diabetes, hypertension, current smoking status, chronic kidney disease, previous myocardial infarction, acute coronary syndrome, percutaneous coronary intervention of chronic total occlusion, and mean stent diameter. Primary composite end points (**A**) and bleeding outcomes (**B**) were assessed in the intention-to-treat cohort. ACS indicates acute coronary syndrome; BARC, Bleeding Academic Research Consortium; and HR, hazard ratio.

(Table 3). All-cause death was higher in women treated with clopidogrel versus aspirin (21 patients [3.1%] versus 7 patients [1.0%]; adjusted HR, 2.75 [95% CI, 1.16–6.49]; *P*=0.021). However, such higher all-cause death in clopidogrel was not observed in men (30 patients [1.6%] versus 29 patients [1.5%]; adjusted HR, 1.07 [95% CI, 0.64–1.79]; *P*=0.792). Regarding all-cause mortality, a significant association was noted between randomized treatment assignment and sex (*P* for interaction=0.043). Readmission due to ACS was lower in women receiving clopidogrel than in those receiving aspirin (12 patients [1.8%] versus 29 patients [4.3%]; adjusted HR, 0.41 [95% CI, 0.21–0.81]; *P*=0.010); this finding was similar in men (54 patients [2.7%] versus 70 patients [4.0%]; adjusted HR, 0.66 [95% CI, 0.47–0.94]; *P*=0.020). No association was noted between randomized treatment assignment and sex (*P*=0.217). The per-protocol analyses yielded similar results to the intention-to-treat analyses for the primary end point (women: adjusted HR, 0.77 [95% CI, 0.51–1.15]; *P*=0.203; men: adjusted HR, 0.69 [95% CI, 0.54–0.88]; *P*=0.003; *P* for interaction=0.630) and the bleeding end point (Table S3).

DISCUSSION

In this prespecified subgroup analysis, substantial differences were observed in baseline characteristics between the sexes, including significantly older age and a higher prevalence of risk factors in women than in men. During chronic maintenance antiplatelet monotherapy after PCI with DES, the primary composite end point and bleeding event incidences were similar between the sexes. After adjustment for baseline and procedural characteristics, the results remained unchanged. Compared with aspirin monotherapy, clopidogrel monotherapy significantly reduced the risk of the primary composite and bleeding end points in men but not in women. These findings might have resulted from the low enrollment of women (25% of women in this trial), and no significant associations were observed between randomized treatment assignment and sex in terms of primary composite and bleeding end points. The only significant association observed was in the total mortality owing to significantly higher mortality associated with clopidogrel use in women but not in men.

Sex-based studies have consistently shown that women have higher crude or unadjusted incidences of ischemic and bleeding events after PCI.[4–7,10–13] This finding might have resulted from the differences in baseline comorbidities rather than biological factors, particularly older age in women and higher prevalences of diabetes, hypertension, and renal insufficiency and high platelet reactivity (HPR).[14] Previous studies have reported that HPR to clopidogrel has higher ischemic

Table 3. Clinical Outcomes by Sex and Randomized Treatment Assignment at 24 Months After Randomization

	Women (n=1384), No. (%)*				Men (n=4054), No. (%)*				
	Clopidogrel (n=695)	Aspirin (n=689)	Adjusted HR (95% CI)†	*P* value	Clopidogrel (n=2015)	Aspirin (n=2039)	Adjusted HR (95% CI)†	*P* value	*P* for interaction‡
Primary end point	42 (6.1)	52 (7.7)	0.79 (0.52–1.18)	0.252	110 (5.5)	155 (7.7)	0.70 (0.55–0.89)	0.004	0.602
Bleeding end point	18 (2.7)	22 (3.2)	0.79 (0.42–1.47)	0.452	43 (2.2)	65 (3.3)	0.65 (0.44–0.96)	0.031	0.595
Major bleeding, BARC 3 or 5	12 (1.8)	14 (2.1)	0.82 (0.38–1.78)	0.615	21 (1.1)	39 (2.0)	0.54 (0.32–0.91)	0.022	0.363
All-cause death	21 (3.1)	7 (1.0)	2.75 (1.16–6.49)	0.021	30 (1.6)	29 (1.5)	1.07 (0.64–1.79)	0.792	0.043
Cardiovascular death	10 (1.5)	4 (0.6)	2.12 (0.65–6.87)	0.211	15 (0.8)	14 (0.7)	1.11 (0.54–2.31)	0.771	0.261
Noncardiovascular death	11 (1.6)	3 (0.4)	3.60 (1.00–12.95)	0.049	15 (0.8)	15 (0.8)	1.03 (0.50–2.12)	0.930	0.087
Nonfatal myocardial infarction	2 (0.3)	5 (0.7)	0.39 (0.08–2.04)	0.267	16 (0.8)	23 (1.2)	0.67 (0.35–1.28)	0.220	0.574
Stent thrombosis	2 (0.3)	4 (0.6)	0.47 (0.09–2.59)	0.387	8 (0.4)	12 (0.6)	0.59 (0.23–1.51)	0.274	0.871
Stroke	7 (1.0)	14 (2.1)	0.45 (0.18–1.13)	0.091	11 (0.6)	29 (1.5)	0.37 (0.18–0.74)	0.005	0.635
Ischemic stroke	6 (0.9)	8 (1.2)	0.66 (0.22–1.92)	0.440	8 (0.4)	18 (0.9)	0.43 (0.19–1.00)	0.049	0.444
Hemorrhagic stroke	1 (0.1)	6 (0.9)	0.15 (0.02–1.24)	0.077	3 (0.2)	11 (0.6)	0.27 (0.08–0.98)	0.046	0.681
Readmission due to acute coronary syndrome	12 (1.8)	29 (4.3)	0.41 (0.21–0.81)	0.010	54 (2.7)	80 (4.0)	0.66 (0.47–0.94)	0.020	0.217
Any revascularization	9 (1.3)	20 (3.0)	0.46 (0.21–1.00)	0.051	47 (2.4)	49 (2.5)	0.95 (0.63–1.42)	0.790	0.107
Target lesion revascularization	6 (0.9)	14 (2.1)	0.45 (0.17–1.18)	0.106	18 (0.9)	22 (1.1)	0.77 (0.41–1.45)	0.414	0.351
Target vessel revascularization	8 (1.2)	15 (2.2)	0.55 (0.23–1.30)	0.173	29 (1.5)	33 (1.7)	0.84 (0.51–1.40)	0.512	0.401
Any minor gastrointestinal complications	89 (13.1)	97 (14.3)	0.90 (0.67–1.20)	0.479	183 (9.2)	223 (11.1)	0.82 (0.67–0.99)	0.042	0.586

Bleeding end point was defined as BARC type bleeding of 2 or more.

BARC indicates Bleeding Academic Research Consortium; and HR, hazard ratio.

*The percentages represent Kaplan–Meier rates at 24 months after randomization.

†Model adjusted for age, diabetes, hypertension, current smoking, chronic kidney disease, previous myocardial infarction, acute coronary syndrome, percutaneous coronary intervention of chronic total occlusion, and mean stent diameter.

‡Interaction test between randomized treatment assignment and sex after model adjustment. Primary end point is defined as a composite of all-cause death, nonfatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and major bleeding events (BARC type ≥3).

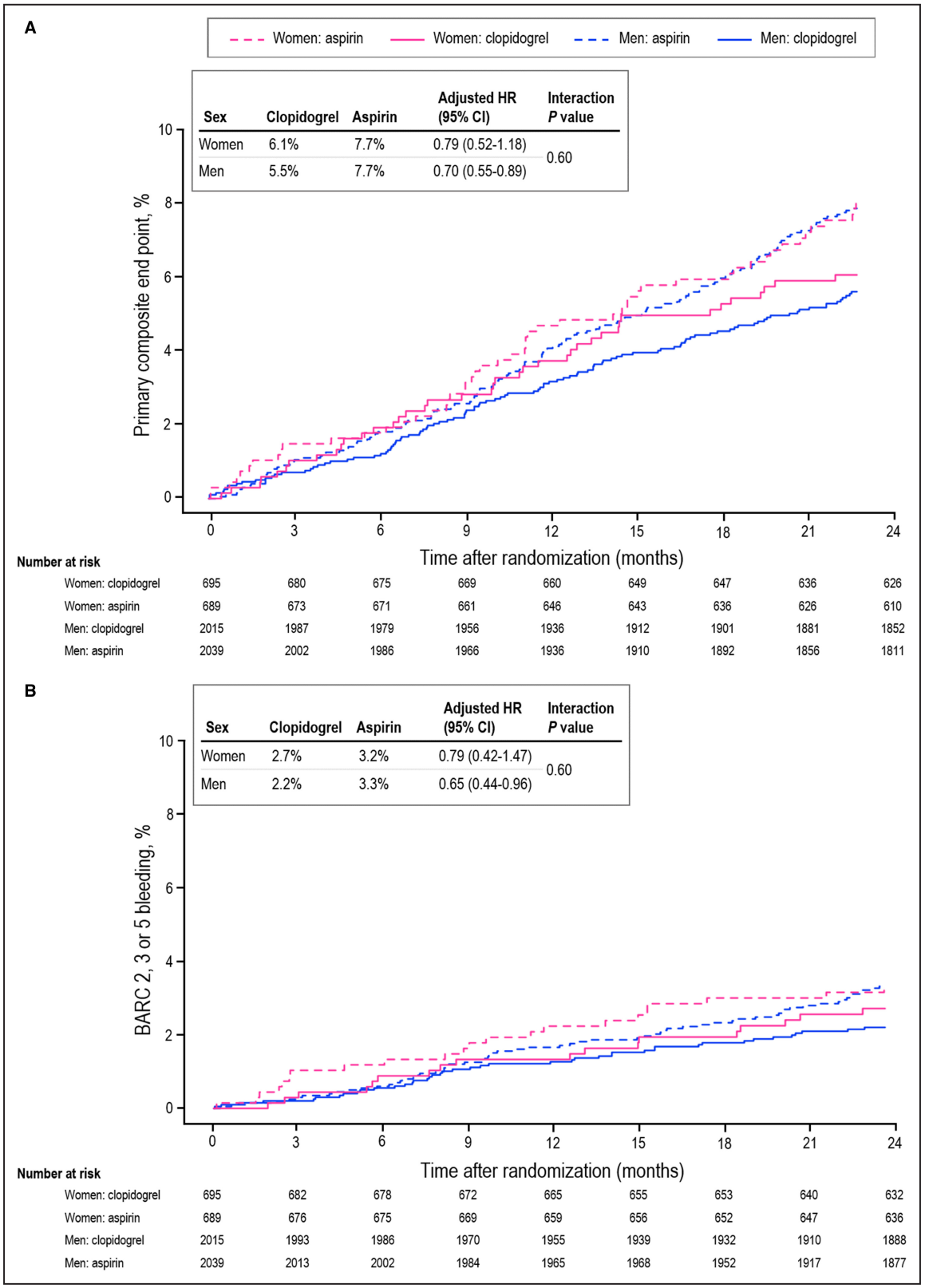


Figure 2. Primary composite end point and bleeding events based on sex and randomized treatment assignment. Kaplan–Meier estimates and adjusted hazard ratios for primary composite end point (**A**) and bleeding events (Bleeding Academic Research Consortium type 2, 3, or 5) (**B**) at 24 months after randomization. Data were adjusted for age, diabetes, hypertension, current smoking status, chronic kidney disease, previous myocardial infarction, acute coronary syndrome, percutaneous coronary intervention of chronic total occlusion, and mean stent diameter. BARC indicates Bleeding Academic Research Consortium; and HR, hazard ratio.

events in patients who have undergone PCI with DES, whereas low platelet reactivity is related to bleeding events.[15,16] The ADAPT-DES (Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents) study demonstrated an association between HPR on clopidogrel treatment and ischemic outcomes, albeit offset by a reduction in bleeding complications. In a post hoc analysis of the ADAPT-DES study, the associated risk of HPR for stent thrombosis was similar in men and women, whereas HPR was associated with significantly reduced bleeding events among women only during 1 year after DES implantation.[14] Although previous studies have suggested that women have higher ischemic and bleeding risks after PCI than men,[4–7] most of these results are within 1 year after PCI and whether they are also at an increased risk of these events during their chronic maintenance antiplatelet monotherapy after PCI with DES remains unknown.

To the best of our knowledge, the HOST-EXAM trial is the first large-scale randomized controlled trial to specifically enroll patients who received DES and had successfully received DAPT for 6 to 18 months without adverse events. This study demonstrates the long-term safety and efficacy of clopidogrel monotherapy during chronic maintenance antiplatelet monotherapy after PCI compared with aspirin monotherapy.[3,8] These results are important given that patients without events before chronic maintenance antiplatelet monotherapy constitute the main population for long-term clinical outcomes after PCI with DES. Compared with aspirin monotherapy, clopidogrel monotherapy was associated with a lower risk of the composite of all-cause mortality, nonfatal MI, stroke, readmission due to ACS, and major bleeding during the 2-year follow-up period. The benefit of clopidogrel monotherapy was observed in both thrombotic and bleeding end points; however, the results were not evaluated across sex subgroups, particularly in the chronic maintenance period for patients who underwent PCI with DES. Although increased bleeding risk in women compared with men after PCI has been documented previously,[5–7] the results of the present study demonstrated that the higher bleeding risk in women was no longer significant for patients receiving antiplatelet monotherapy in the chronic period after PCI with DES.

In this study, the effect of clopidogrel versus aspirin and differences between the sexes were analyzed. Clopidogrel significantly reduced primary composite and bleeding end points in men but not in women. Because there was a lower HR related to clopidogrel in both sexes but no association between randomized treatment effect and sex, the insignificant reduction of events by clopidogrel in women might be due to the small sample size that was one third of that of men in this trial. Thus, currently, we cannot deny the possibility that clopidogrel reduces ischemic and bleeding outcomes in women similarly to that in men. Interestingly, the incidences of primary composite and bleeding end points were very similar between the sexes receiving aspirin, whereas they were different between sexes receiving clopidogrel; the incidences were higher in women than in men receiving clopidogrel. Higher all-cause mortality was the main driver of higher primary composite end point in women receiving clopidogrel than in those receiving aspirin. The rate of clopidogrel metabolism to its active form has been shown to be similar between women and men.[17] However, women more commonly have a higher baseline platelet reactivity to adenosine diphosphate than men,[14,18] which is associated with a proinflammatory profile and higher levels of C-reactive protein and leukocytes.[19] Of note, the rates of all-cause mortality were very similar between men receiving clopidogrel and those receiving aspirin. The higher mortality in women receiving clopidogrel was mainly due to noncardiovascular death, and the adjusted HR was 3.6. Although not statistically significant, the risk of cardiovascular death was more than doubled in the clopidogrel group compared with aspirin. A previous meta-analysis of more than 23 000 women and 56 000 men shows that men receiving clopidogrel significantly reduced MI, stroke, and total death. However, in women, the total mortality was not reduced by clopidogrel compared with placebo.[20] The impact of sex on clopidogrel's efficacy and safety has been investigated in different clinical settings. Female sex was associated with an increase in bleeding from REPLACE-2 (Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events) and ISAR-REACT 3 (Un-fractionated Heparin Versus Bivalirudin During Percutaneous Coronary Interventions) clinical trials,[21,22] indicating that sex might play a role in clopidogrel clinical outcome, which may be associated with the one-size-fits-all dosing of clopidogrel in all patients and the relatively lower body weight of women compared with men. In this study, 59% of all noncardiovascular deaths occurred in the clopidogrel group, and 69% of them were due to malignancy. Women and men receiving clopidogrel had a 54% (n=6 patients) and 80% (n=12 patients) of noncardiovascular death due to malignancy, respectively. However, the number of events was too small to interpret. Further studies are needed to provide further insight into the true effect of chronic maintenance antiplatelet monotherapy on mortality according to sex. The HOST-EXAM trial reported the trend of higher mortality rates in patients receiving clopidogrel than in those receiving aspirin, which was mainly driven by a higher death rate related to clopidogrel use in women but not in men. In this prespecified secondary analysis of HOST-EXAM, we found that clopidogrel was associated with higher mortality than aspirin in only women but not men. As mentioned before, the sample size of women (nearly

25%) was one third of that of men (nearly 75%) in the HOST-EXAM trial, and the difference of mortality between women receiving clopidogrel and those receiving aspirin might have been because of the small sample size. Further analysis with long-term follow-up is warranted to explain the significantly lower incidence of all-cause mortality driven primarily by noncardiac death in women receiving aspirin than in those receiving clopidogrel. Therefore, we have launched the HOST-EXAM Extended study, in which we will be extending the median follow-up to 10 years and we expect this study to explain the findings.

Limitations

This study has some limitations. Although this subgroup analysis was prespecified, it should be considered hypothesis-generating research only and requires confirmation in future studies. Randomization was not stratified based on sex, and multiplicity was not accounted for, which increased the possibility of error in statistical decision-making. The female subgroup was modest in size, and there were substantial differences in baseline risk between the sexes and also some imbalances in patient characteristics between sex-specific treatment groups, including patients with diabetes, hypertension, or chronic kidney disease. Residual confounding factors could not be excluded despite multivariate adjustment for baseline differences. Neither of the sex-specific subgroups was individually powered to draw definitive conclusions regarding the effect of clopidogrel versus aspirin on the primary composite and bleeding end points. Another limitation of this study is that there were no HPR data, so the frequency of HPR in women and men could not be known. Therefore, it is not possible to know what effect HPR had on the outcome of men and women in this study. Furthermore, our findings are specific to the population during the chronic maintenance period after PCI with DES and may not be extrapolated to a broader population of patients undergoing PCI. In addition, our analyses considered only patients who had undergone successful PCI with DES and maintained DAPT without any adverse clinical events for 6 to 18 months after PCI. Thus, extrapolation of our results directly to those who use DAPT for a shorter time or those who had any adverse clinical events within 6 monthd is difficult.

CONCLUSIONS

In this prespecified subgroup analysis of the HOST-EXAM randomized clinical trial, the primary composite end point including ischemic events and bleeding events was similar between the sexes during chronic maintenance antiplatelet monotherapy after PCI with DES. Clopidogrel monotherapy, compared with aspirin monotherapy, significantly reduced the risk of the primary composite and bleeding end points in men but not in women because of the low enrollment of women. Further studies are needed to investigate this finding.

ARTICLE INFORMATION

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Supplemental Material

Data S1
Figures S1–S3
Tables S1–S3

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Table S1. Baseline Clinical and Procedural Characteristics by Sex.

	No. (%)		
	Women (n = 1345)	**Men (n = 3958)**	***P* value**
Age, mean (SD), year	68.9 (9.4)	61.6 (10.5)	<0.001
Diabetes mellitus	504 (37.5)	1308 (33.0)	0.003
Hypertension	918 (68.3)	2336 (59.0)	<0.001
Dyslipidemia	940 (69.9)	2751 (69.5)	0.818
Current smoker	59 (4.4)	1037 (26.2)	<0.001
Chronic kidney disease	272 (20.2)	394 (10.0)	<0.001
Previous myocardial infarction	190 (14.1)	664 (16.8)	0.025
Previous cerebrovascular accident	64 (4.8)	181 (4.6)	0.838
Clinical Indication of PCI			
Stable coronary artery disease	414 (30.8)	1074 (27.1)	0.011
Acute coronary syndrome	931 (69.2)	2884 (72.9)	0.011
Day from PCI to randomization	384.4 (71.4)	388.0 (69.6)	0.106
Extent of coronary artery disease			
1-vessel disease	668 (49.7)	2014 (50.9)	0.473
2-vessel disease	406 (30.2)	1249 (31.6)	0.375
3-vessel disease	270 (20.1)	695 (17.6)	0.042
Left main disease	56 (4.2)	208 (5.3)	0.129
PCI for bifurcation lesion	133 (9.9)	435 (11.0)	0.281
PCI for CTO lesion	101 (7.5)	399 (10.1)	0.006
Lesions treated, mean (SD), No.	1.3 (0.6)	1.3 (0.6)	0.954
Total stent number, mean (SD), No.	1.5 (0.8)	1.5 (0.8)	0.896
Mean stent diameter, mean (SD), mm	3.0 (0.4)	3.1 (0.4)	<0.001
Minimum stent diameter, mean (SD), mm	2.9 (0.4)	3.0 (0.5)	<0.001
Total stent length, mean (SD), mm	35.2 (23.4)	36.1 (24.0)	0.275

PCI, percutaneous coronary intervention; CTO, chronic total occlusion.

Table S2. Baseline Clinical and Procedural Characteristics by Sex and Randomized Treatment Assignment.

	Women (n = 1345)			Men (n = 3958)		
	No. (%)			No. (%)		
	Clopidogrel (n = 674)	Aspirin (n = 671)	*P* value	Clopidogrel (n = 1974)	Aspirin (n = 1984)	*P* value
Age, mean (SD), year	68.9 (9.4)	68.8 (9.3)	0.883	61.6 (10.5)	61.6 (10.5)	0.982
Diabetes mellitus	258 (38.3)	246 (36.7)	0.578	643 (32.6)	665 (33.5)	0.550
Hypertension	462 (68.5)	456 (68.0)	0.863	1160 (58.8)	1176 (59.3)	0.769
Dyslipidemia	463 (68.7)	477 (71.1)	0.370	1383 (70.1)	1368 (69.0)	0.469
Current smoker	29 (4.3)	30 (4.5)	0.986	504 (25.5)	533 (26.9)	0.359
Chronic kidney disease	140 (20.8)	132 (19.7)	0.664	199 (10.1)	195 (9.8)	0.832
Previous myocardial infarction	92 (13.6)	98 (14.6)	0.671	339 (17.2)	325 (16.4)	0.532
Previous cerebrovascular accident	28 (4.2)	36 (5.4)	0.360	87 (4.4)	94 (4.7)	0.673
Clinical Indication of PCI						
Stable coronary artery disease	202 (30.0)	212 (31.6)	0.558	533 (27.0)	541 (27.3)	0.878
Acute coronary syndrome	472 (70.0)	459 (68.4)	0.558	1441 (73.0)	1443 (72.7)	0.878
Extent of coronary artery disease						
1-vessel disease	347 (51.5)	321 (47.9)	0.209	993 (50.3)	1021 (51.5)	0.486
2-vessel disease	213 (31.6)	193 (28.8)	0.291	623 (31.6)	626 (31.6)	1.000
3-vessel disease	114 (16.9)	156 (23.3)	0.004	358 (18.1)	337 (17.0)	0.363
Left main disease	24 (3.6)	32 (4.8)	0.331	114 (5.8)	94 (4.7)	0.164
PCI for bifurcation lesion	63 (9.3)	70 (10.4)	0.565	218 (11.0)	217 (10.9)	0.955
PCI for CTO lesion	58 (8.6)	43 (6.4)	0.154	193 (9.8)	206 (10.4)	0.562
Lesions treated, mean (SD), No.	1.3 (0.6)	1.3 (0.6)	0.564	1.3 (0.6)	1.3 (0.6)	0.535
Total stent number, mean (SD), No	1.5 (0.8)	1.5 (0.9)	0.474	1.5 (0.9)	1.5 (0.8)	0.240
Mean stent diameter, mean (SD), mm	3.0 (0.4)	3.0 (0.4)	0.725	3.1 (0.4)	3.1 (0.4)	0.744
Minimum stent diameter, mean (SD), mm	2.9 (0.4)	2.9 (0.4)	0.694	3.0 (0.5)	3.0 (0.5)	0.900
Total stent length, mean (SD), mm	35.2 (22.9)	35.3 (23.9)	0.894	36.3 (24.6)	35.8 (23.4)	0.523

PCI, percutaneous coronary intervention; CTO, chronic total occlusion.

Table S3. Clinical Outcomes by Sex and Randomized Treatment Assignment at 24 Months After Randomization.

	Women (n = 1345), No. (%)*				Men (n = 3958), No. (%)*				
	Clopidogrel (n= 674)	Aspirin (n= 671)	Adjusted HR (95% CI)†	*P* value	Clopidogrel (n= 1974)	Aspirin (n= 1984)	Adjusted HR (95% CI)†	*P* value	*P* for interaction‡
Primary endpoint	41 (6.1)	52 (7.7)	0.77 (0.51-1.15)	0.203	108 (5.5)	154 (7.8)	0.69 (0.54-0.88)	0.003	0.630
Bleeding endpoint	18 (2.7)	21 (3.1)	0.83 (0.45-1.53)	0.545	41 (2.1)	64 (3.2)	0.63 (0.42-0.94)	0.022	0.450
Major bleeding (BARC 3 or 5)	12 (1.8)	14 (2.1)	0.82 (0.39-1.73)	0.602	21 (1.1)	39 (2.0)	0.54 (0.32-0.91)	0.021	0.360
All-cause death	21 (3.1)	7 (1.0)	2.73 (1.13-6.56)	0.025	30 (1.5)	29 (1.5)	1.07 (0.64-1.79)	0.790	0.043
Cardiovascular death	10 (1.5)	4 (0.6)	2.07 (0.61-7.05)	0.244	15 (0.8)	14 (0.7)	1.12 (0.54-2.31)	0.768	0.263
Non-cardiovascular death	11 (1.6)	3 (0.4)	3.61 (0.99-13.11)	0.051	15 (0.8)	15 (0.8)	1.03 (0.50-2.12)	0.932	0.087
Non-fatal myocardial infarction	2 (0.3)	5 (0.7)	0.40 (0.08-1.92)	0.252	15 (0.8)	22 (1.1)	0.65 (0.33-1.26)	0.201	0.597
Stent thrombosis	2 (0.3)	4 (0.6)	0.47 (0.08-2.68)	0.394	7 (0.4)	11 (0.6)	0.55 (0.21-1.45)	0.224	0.937
Stroke	6 (0.9)	14 (2.1)	0.39 (0.15-1.01)	0.051	11 (0.6)	29 (1.5)	0.37 (0.19-0.74)	0.005	0.839
Ischemic stroke	5 (0.8)	8 (1.2)	0.54 (0.17-1.72)	0.299	8 (0.4)	18 (0.9)	0.43 (0.19-0.99)	0.047	0.629
Hemorrhagic stroke	1 (0.1)	6 (0.9)	0.14 (0.02-1.36)	0.091	3 (0.2)	11 (0.6)	0.27 (0.08-0.96)	0.044	0.683
Readmission due to ACS	12 (1.8)	29 (4.3)	0.41 (0.21-0.80)	0.009	52 (2.7)	79 (4.0)	0.64 (0.45-0.91)	0.014	0.251
Any revascularization	9 (1.4)	20 (3.0)	0.46 (0.21-1.00)	0.050	44 (2.2)	47 (2.4)	0.92 (0.61-1.38)	0.678	0.126
Target lesion revascularization	6 (0.9)	14 (2.1)	0.45 (0.17-1.18)	0.106	17 (0.9)	20 (1.0)	0.78 (0.41-1.49)	0.455	0.338
Target vessel revascularization	8 (1.2)	15 (2.2)	0.55 (0.23-1.30)	0.171	27 (1.4)	31 (1.6)	0.83 (0.49-1.39)	0.475	0.429
Any minor GI complications	86 (12.9)	93 (13.9)	0.91 (0.68-1.22)	0.535	176 (9.0)	215 (10.9)	0.81 (0.67-0.99)	0.043	0.542

BARC, Bleeding Academic Research Consortium; HR, hazard ratio; ACS, acute coronary syndrome; GI, gastrointestinal.

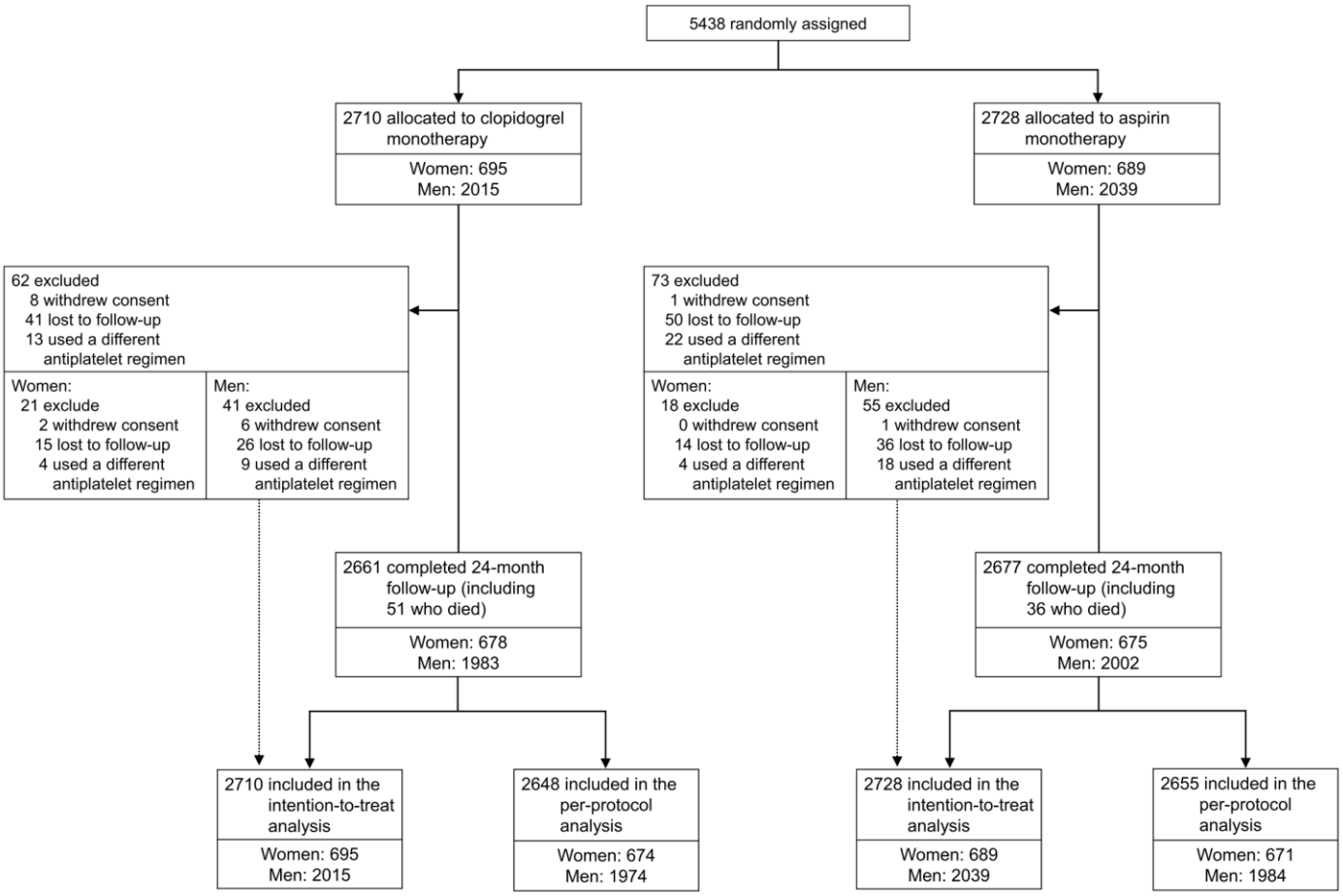
*The percentages represent Kaplan-Meier rates at 24 months after randomization.

†Model adjusted for age, diabetes mellitus, hypertension, current smoking, chronic kidney disease, previous myocardial infarction, acute coronary syndrome, percutaneous coronary intervention of chronic total occlusion and mean stent diameter.

‡Interaction test between randomized treatment assignment and sex after model adjustment.

Primary endpoint is defined as a composite of all-cause death, non-fatal myocardial infarction, stroke, readmission due to acute coronary syndrome and major bleeding events (BARC type ≥3). Bleeding endpoint was defined as BARC type bleeding of 2 or more.

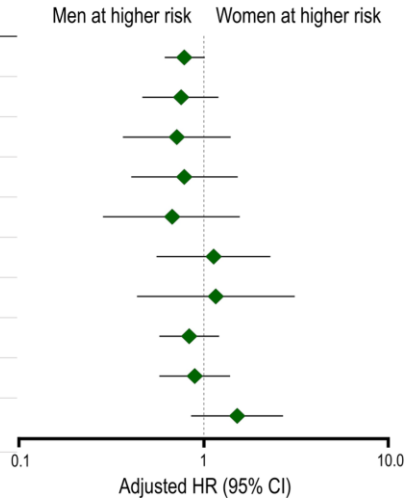
Figure S1. Flow Chart.



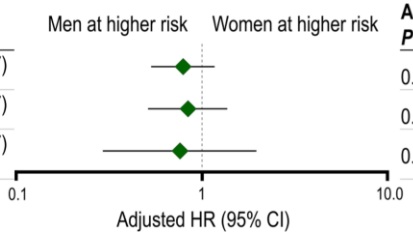
Patients who underwent percutaneous coronary intervention with a drug-eluting stent and maintained dual antiplatelet therapy without any clinical events within 6–18 months after the index procedure were eligible and underwent randomization. The number of women and men in each group is indicated.

Figure S2. Primary Composite Endpoint and Bleeding Events at 24 Months Based on Sex in the Per-Protocol Population.

Outcome	Women, No.(%)	Men, No.(%)	HR(95%CI)	*P* value	Adjusted HR (95% CI)	Adjusted *P* value
Primary composite endpoint	93 (6.9)	262 (6.6)	1.05 (0.83-1.33)	0.70	0.78 (0.61-1.01)	0.06
All-cause death	28 (2.1)	59 (1.5)	1.40 (0.89-2.20)	0.14	0.75 (0.46-1.20)	0.23
Cardiovascular death	14 (1.0)	29 (0.7)	1.42 (0.75-2.70)	0.28	0.71 (0.36-1.40)	0.33
Non-cardiovascular death	14 (1.0)	30 (0.8)	1.38 (0.73-2.60)	0.32	0.78 (0.40-1.53)	0.47
Non-fatal myocardial infarction	7 (0.5)	37 (0.9)	0.56 (0.25-1.25)	0.16	0.67 (0.28-1.57)	0.35
Ischemic stroke	13 (1.0)	26 (0.7)	1.48 (0.76-2.88)	0.25	1.13 (0.55-2.31)	0.75
Stent thrombosis	6 (0.4)	18 (0.5)	0.99 (0.39-2.48)	0.98	1.16 (0.43-3.14)	0.77
Readmission due to ACS	41 (3.1)	131 (3.3)	0.92 (0.65-1.31)	0.66	0.83 (0.57-1.21)	0.33
Any revascularization	29 (2.2)	91 (2.3)	0.94 (0.62-1.43)	0.78	0.89 (0.57-1.39)	0.61
Target lesion revascularization	20 (1.5)	37 (0.9)	1.60 (0.93-2.76)	0.09	1.52 (0.85-2.71)	0.16



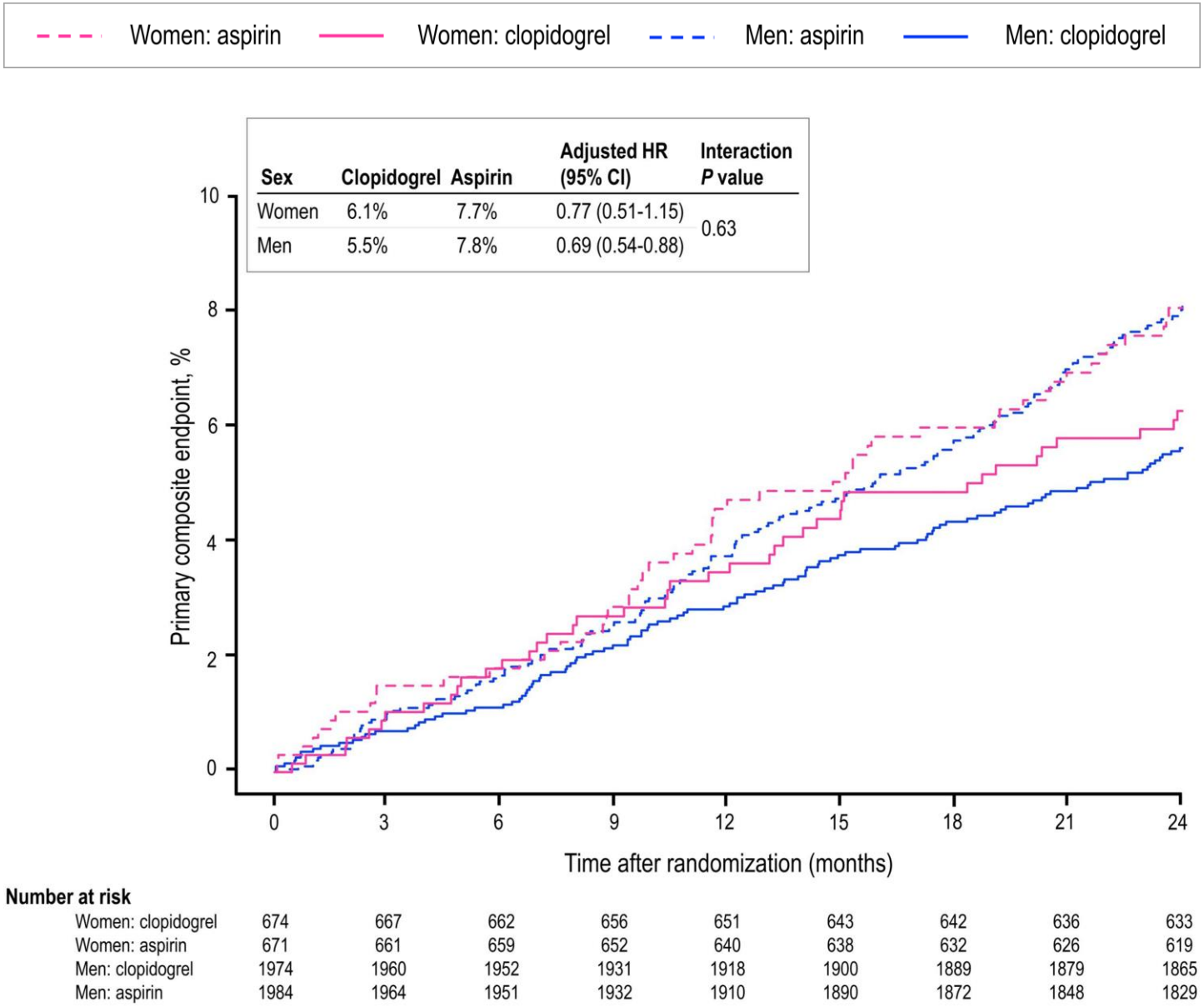
Outcome	Women. No.(%)	Men, No.(%)	HR(95%CI)	*P* value	Adjusted HR (95% CI)	Adjusted *P* value
BARC type 2, 3, or 5	39 (2.9)	105 (2.7)	1.10 (0.76-1.59)	0.62	0.79 (0.53-1.17)	0.24
BARC type 3 or 5	26 (1.9)	60 (1.5)	1.28 (0.81-2.03)	0.29	0.84 (0.51-1.37)	0.48
Hemorrhagic stroke	7 (0.5)	14 (0.4)	1.48 (0.60-3.66)	0.40	0.76 (0.29-1.97)	0.57

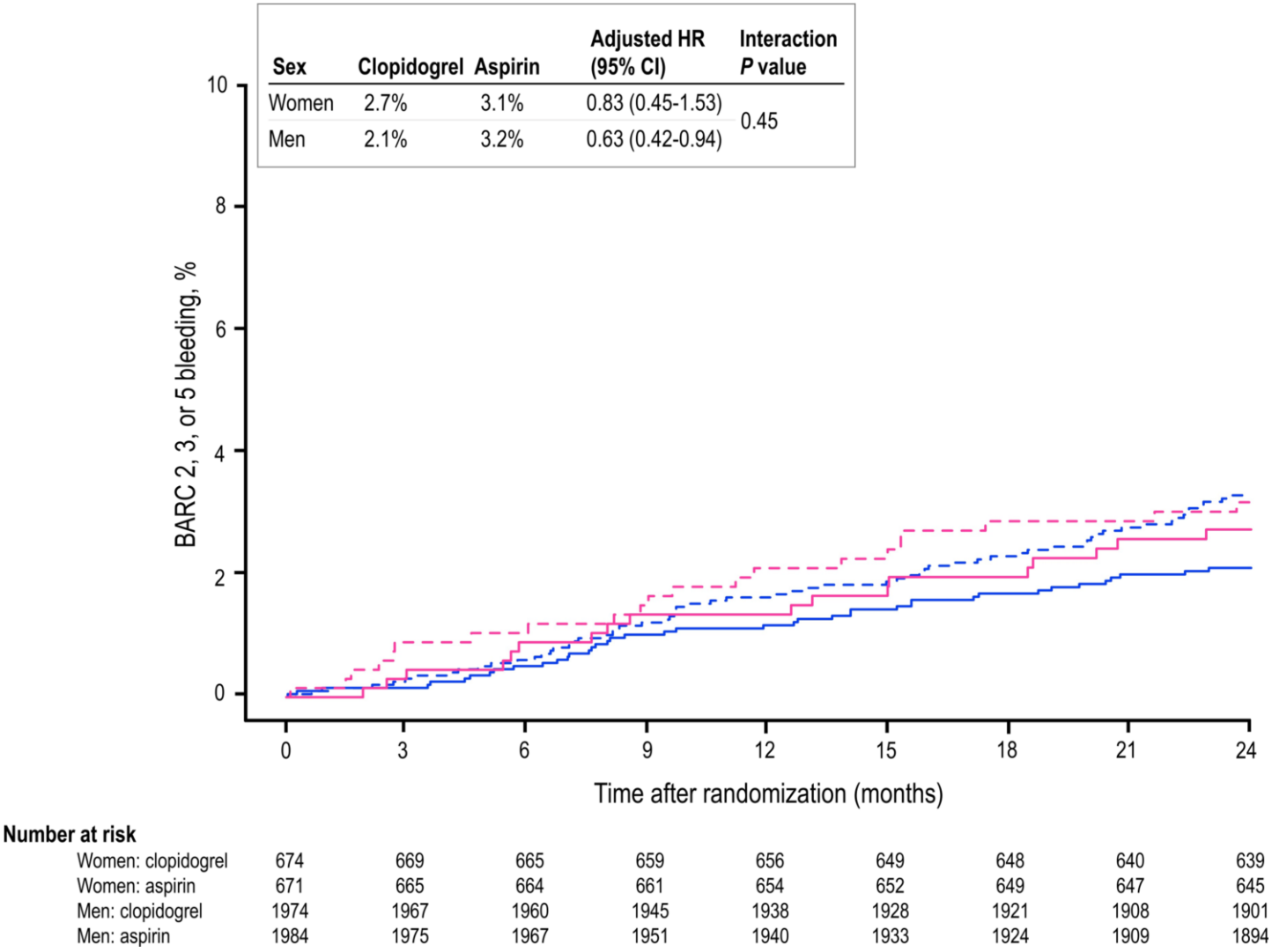


Women were used as the reference category. Adjusted hazard ratios (HRs) were calculated for age, diabetes mellitus, hypertension, current smoking status, chronic kidney disease, previous myocardial infarction, acute coronary syndrome, percutaneous coronary intervention of chronic total occlusion, and mean stent diameter. Primary composite endpoints (A) and bleeding outcomes (B) were assessed in the Per-Protocol cohort.

BARC indicates Bleeding Academic Research Consortium.

Figure S3. Primary Composite Endpoint and Bleeding Events Based on Sex and Randomized Treatment Assignment in the Per-Protocol Population.





Kaplan-Meier estimates and adjusted hazard ratios (HRs) for primary composite endpoint (A) and bleeding events (Bleeding Academic Research Consortium type 2, 3, or 5) (B) at 24 months after randomization. Data were adjusted for age, diabetes mellitus, hypertension, current smoking status, chronic kidney disease, previous myocardial infarction, acute coronary syndrome, percutaneous coronary intervention of chronic total occlusion, and mean stent diameter.