Supplemental Online Content

Rhee T-M, Bae J-W, Park KW, et al; the HOST-EXAM investigators. Aspirin vs clopidogrel for long-term maintenance after coronary stenting in patients with diabetes: a post hoc analysis of the HOST-EXAM trial. *JAMA Cardiol*. Published online April 12, 2023. doi:10.1001/jamacardio.2023.0592

This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods

Statistical analysis

Data were presented as numbers and frequencies for categorical variables, and as mean ± standard deviation for continuous variables. To compare between groups, the chi-square test was used for categorical variables, and an unpaired Student's *t*-test was used for continuous variables. Analyses were performed based on the intention-to-treat population. Cumulative incidences of the primary and secondary endpoints were compared between clopidogrel and aspirin monotherapy arms using Kaplan-Meier censoring estimates and the log-rank test. Hazard ratios (HRs) with 95% confidence intervals (CIs) of clopidogrel compared to aspirin monotherapy were calculated using Cox proportional hazard models with interaction testing according to the presence of DM. Assuming a non-informative prior, a Bayesian analysis for the thrombotic composite endpoint and any bleeding at 24-month according to the presence of DM was performed. The probabilities of absolute risk differences (ARD) in the 24-month thrombotic composite endpoint and any bleeding between clopidogrel and aspirin monotherapy arms being more than 0.0%, and at least 1.0%, or 2.5% were calculated for both DM and non-DM groups. Multivariable Cox proportional hazard models with stepwise selection method with a significance level of <0.15 for entry and exit were used to identify independent predictors of 24-month primary composite endpoint for DM and non-DM groups, including covariates as follows: randomization arm (aspirin versus clopidogrel monotherapy), age, sex, body mass index ≥25 kg/m^2, current smoker, hypertension, previous history of heart failure, previous history of MI, previous history of stroke, presented as acute MI at index PCI, type of P2Y12 inhibitor used during DAPT, hemoglobin concentration, HDL-cholesterol <40 mg/dL, serum glucose, serum creatinine, extent of CAD, left main CAD, complex PCI, and insulin-treated DM (for DM group only). Subgroup

analysis for primary composite endpoint was performed in DM and non-DM groups, respectively. In DM group, subgroup analyses according to the DM treatment and baseline HbA1c level were performed. *P*-values were two-sided, and a value of <0.05 was considered statistically significant. All analyses were conducted using Stata software, version 17.0 (StataCorp., College Station, TX, USA).

Inclusion and Exclusion Criteria

1) Inclusion Criteria:

- Male and female aged ≥20 years
- Maintenance of dual or triple antiplatelet therapy at least 12 ± 6 months after PCI with DES
- No history of further clinical event after PCI with DES
- Plan to change to antiplatelet monotherapy
- Agreement to give written informed consent

2) Exclusion Criteria:

- History of hypersensitivity to aspirin or clopidogrel
- History of contraindication to aspirin or clopidogrel

- Active pathologic bleeding, such as peptic ulcer, tumor bleeding or intracranial haemorrhage
- History of major bleeding, BARC type ≥3, resulting in stop of antiplatelet agents within 3 months
- Bleeding diathesis
- Known coagulopathy or refusal of blood transfusion
- Presence of non-cardiac comorbidity with life expectancy ≤2 years from randomization
- Plan to surgery or intervention which needs to stop antiplatelet agents ≥3 months
- Females with childbearing potential or breast-feeding
- Conditions that may result in protocol non-compliance by the committees
- Co-administration of contraindicated medications as follows: other P2Y12 inhibitors (prasugrel or ticagrelor); anticoagulants (warfarin, new oral anticoagulants, or chronic therapy of heparin); cytochrome P450 2C19 inhibitors (fluoxetine, moclobemid or voriconazole); probenecid; high dose of methotrexate (≥15 mg/week); lithium
- Refusal to give written informed consent

2.

3. Sample Size Calculation

Hypothesis: Clopidogrel is superior to aspirin in preventing clinical events, defined as a composite of all-cause death, nonfatal myocardial infarction, stroke, readmission due to acute coronary syndrome, or major bleeding at 24 months after randomization. Based on the event rates of a previous trials performed in various populations including Korean,[1,2] we predicted clinical event rate of clopidogrel and aspirin. Specifically, Lee et al[1] reported that the rates of patient-oriented composite events (all-cause death, non-fatal MI, and any revascularization) at 1- and 3-year follow-up were 7.5% and 13.3%, respectively. This would leave an event rate of approximately 6% from 1 year after PCI. Also, the CAPRIE trial[2] reported that bleeding events occurred in 1.5% and stroke occurred in 4.5% during the 2-year follow-up period.
The primary outcome of our study was a composite of all-cause death, non-fatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and major bleeding events, which would add up to 12%. Additionally, we assumed that clopidogrel would reduce the risk of clinical events and bleeding by 20%, based on analysis of the CAPRIE trial. Therefore, we predicted clinical event rates of clopidogrel and aspirin monotherapy to be 9.6% and 12%, respectively, at 24 months after single antiplatelet therapy.

- Primary endpoint: clinical events defined as a composite of all-cause death, nonfatal myocardial infarction, stroke, readmission due to acute coronary syndrome, or major bleeding at 24 months after randomization.
- Design: superiority
- Sampling ratio: Clopidogrel versus Aspirin = 1:1

Type I error (α): two-sided 5%

- Accrual time : 4 years
- Total time : 6 years (accrual year + follow-up 2 years)
- Assumption: Clinical event rate 9·6% in clopidogrel vs. 12·0% in aspirin group
- Statistical power (1- β): 80%
- Potential withdrawal rates : 5% in each groups

Based on the above assumption, the expected number of events in each test drug group is 567. We would need total 5530 patients (2765 patients in each group) with consideration of withdrawal rates.

Definition of Subgroups and Clinical Outcomes Death

All deaths are adjudicated and classified all-cause death, cardiovascular death, and non-cardiovascular death. Cardiovascular deaths are defined as all deaths excluding those for which underlying cause is solely documented as non-cardiovascular and all deaths for which cardiovascular contributing cause is suspected.

Myocardial infarction

The definition of myocardial infarction follows the third universal definition of myocardial infarction. Briefly, myocardial infarction is diagnosed by detection of an increased level of cardiac biomarkers, preferably cardiac troponins, with at least one value above the 99th percentile of the upper reference limit, accompanied with at least one of the followings: symptoms of myocardial ischemia, ECG changes (ST elevation, left bundle branch block, ST change without ST elevation), and imaging findings suggestive of myocardial infarction (loss of viable myocardium or new regional wall motion abnormality.

Stroke

Stroke is defined as any non-convulsive, focal or global neurological deficit of abrupt onset lasting for more than 24 hours or leading to death, which is caused by ischemia or hemorrhage within brain.

Ischemic Stroke

Ischemic stroke is defined as an acute episode of infarction of central nervous system tissue, causing any neurologic symptom. If the patients admitted for an acute neurologic symptom and thrombolysis or interventions resulting in complete recovery, these events are also classified at an ischemic stroke.

Hemorrhagic Stroke

Hemorrhagic stroke is defined as an acute neurologic episode that originated from a non-traumatic intraparenchymal, intraventricular, or subarachnoid hemorrhage.

Readmission due to acute coronary syndrome

Readmission due to at least one of following: 1) An episode of rest discomfort fulfilling criteria for Canadian Heart Association class III-IV angina, lasting at least 5 minutes; 2) Documentation of new ST segment shifts ≥0.05 mV on 12 lead ECG or lasting ≥20 minutes on ambulatory ECG monitoring; 3) An episode of acute pulmonary edema or hemodynamic instability presumed to be ischemic in origin; 4) A recurrent myocardial infarction.

Unstable angina

An episode of rest discomfort fulfilling criteria for Canadian Heart Association class III-IV angina, presumed to be ischemic in origin and lasting at least 5 minutes.

Urgent revascularization

Any coronary intervention or coronary artery bypass grafting that occurs as a rescue within 48 hours after admission for acute coronary syndrome.

BARC bleeding classification

Type 0: No bleeding

Type 1: Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a health care professional

Type 2: Any overt, actionable sign of hemorrhage (e.g. more bleeding than would be expected for a clinical circumstance; including bleeding found by imaging alone) that does not fit the criteria for Types 3, 4, or 5, but does meet at least one of the following criteria: (1) requiring non-surgical, medical intervention by a health care professional, (2) leading to hospitalization or increased level of care, (3) prompting evaluation

Type 3 Type 3a:
- Overt bleeding plus hemoglobin drop of 3 to ,5*g/dL (provided hemoglobin drop is related to bleed)

- Any transfusion with overt bleeding Type 3b:
- Overt bleeding plus hemoglobin drop ≥ 5 g/dL (provided hemoglobin drop is related to bleed)

- Cardiac tamponade

- Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoids)

- Bleeding requiring intravenous vasoactive drugs Type 3c:
- Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation; does include intraspinal)

- Subcategories; confirmed by autopsy or imaging or LP

- Intra-ocular bleed compromising vision Type 4: CABG-related bleeding
- Perioperative intracranial bleeding within 48 h

- Reoperation following closure of sternotomy for the purpose of controlling bleeding
- Transfusion of ≥ 5 units of whole blood or packed red blood cells within a 48 period**

- Chest tube output ≥ 2 L within a 24 h period

- If a CABG-related bleed is not adjudicated as at least a Type 3 severity event, it will be classified as 'not a bleeding event'

Type 5: fatal bleeding

Type 5a: Probable fatal bleeding: no autopsy or imaging confirmation, but clinically suspicious
Type 5b: Definite fatal bleeding: overt bleeding or autopsy or imaging confirmation

Repeat Revascularization

To reduce the change of so-called "oculostenotic reflex," whereby the rates of repeat revascularization are disproportionately high, the investigators in this study encouraged to perform a non-invasive stress test before the decision making. This study only counted on the clinically-driven revascularization. Clinically-driven revascularization was defined as repeat revascularization in the presence of % diameter stenosis ≥ 70%, or in % diameter stenosis ≥ 50% with at least one of the following: 1) Recurrence of anginal symptoms; 2) Positive non-invasive test; or 3) Positive invasive physiologic test.

Target lesion revascularization

Target lesion revascularization is defined as any repeat revascularization procedure (PCI or CABG) at the original lesion of the index procedure any time during the follow-up period **Target vessel revascularization**
Target vessel revascularization is defined as any repeat revascularization procedure (PCI or CABG) involving at least one of the target vessels that were treated in the index procedure

Stent thrombosis

Stent thrombosis is defined according to the Academic Research Consortium (ARC).[3] In brief, stent thrombosis is defined as abrupt onset of an acute coronary syndrome, which is confirmed with angiographic evidence of acute thrombotic occlusion in the stented segment of a coronary artery. Stent thrombosis is classified by the timing in to Acute thrombosis (occurs within 24 hours of initial placement), subacute thrombosis (occurs between 24 hours to one month of initial placement), late stent thrombosis (occurs between 1 and 12 months of initial placement), and very late stent thrombosis (occurs after 12 months of initial placement). Also, the classifications include definite, probable, and possible stent thrombosis.

Possible stent thrombosis

Consider with unexplained death 30 days or later after stent placement.

Probable stent thrombosis

Any unexplained death within 30 days of stent placement.

Consider if there is active ischemia on electrocardiogram or stress in the distribution of prior stent and absence of significant coronary lesion on angiography.

Definite stent thrombosis

The presence of a thrombus that originates in the stent/scaffold or in the segment 5 mm proximal or distal to the stent/scaffold or in a side branch originating from the stented/scaffolded segment and the presence of at least 1 of the following criteria: Acute onset of ischemic symptoms at rest OR New electrocardiographic changes suggestive of acute ischemia OR Typical rise and fall in cardiac biomarkers. Pathological confirmation of stent/scaffold thrombosis can be performed by evidence of recent thrombus determined at autopsy OR by examination of tissue retrieved following thrombectomy (visual/histology)

Minor gastrointestinal complications

Minor gastrointestinal complications are defined as patient-reported outcomes of newly developed GI symptoms including various symptoms such as epigastric soreness, dyspepsia, abdominal pain, nausea, vomiting, diarrhea, constipation, melena, or hematochezia. Also, newly added GI medications, or symptom-driven GI endoscopy were collected.

eTable 1. Baseline medications of study population

	DM group			Non-DM group		
	Clopidogrel (N=925)	**Aspirin (N=935)**	***P***	**Clopidogrel (N=1,785)**	**Aspirin (N=1,793)**	***P***
Baseline medications, % (n)						
Beta blockers	52.1% (482)	47.2% (441)	.033	49.4% (882)	50.7% (909)	.44
ACE inhibitors	15.4% (142)	12.6% (118)	.089	15.6% (278)	14.2% (255)	.26
ARBs	38.8% (359)	35.8% (335)	.18	32.5% (581)	32.9% (590)	.82
Calcium-channel blockers	27.9% (258)	28.3% (265)	.83	27.6% (492)	26.0% (466)	.29
Diuretics	12.5% (116)	14.3% (134)	.26	8.2% (146)	9.1% (163)	.33
Nitrates	9.9% (92)	8.4% (79)	.26	9.1% (163)	8.6% (155)	.61
Statins	82.8% (766)	80.3% (751)	.17	85.4% (1,524)	86.1% (1,543)	.56

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; DM, diabetes mellitus

eTable 2. Information on drug adherence and anticoagulation during follow-up

	DM group			Non-DM group		
	Clopidogrel (N=925)	**Aspirin (N=935)**	***P***	**Clopidogrel (N=1,785)**	**Aspirin (N=1,793)**	***P***
Drug adherence*	99.6% (921)	99.3% (928)	.37	99.5% (1,776)	99.2% (1,778)	.22
Concurrent anticoagulation	0.8% (7)	0.6% (6)	.77	0.6% (10)	0.5% (9)	.81

*Represents patients who maintained allocated medication per protocol during 24-month follow-up. Abbreviations: DM, diabetes mellitus

eTable 3. Predictors of primary composite endpoint according to presence of diabetes mellitus

Primary composite endpoint at 24-month*	**HR (95% CI)**	***P***
DM group (N=1,860)		
Aspirin monotherapy (Clopidogrel monotherapy as reference)	1.54 (1.04-2.30)	.033
Age (per 10 year increase)	1.58 (1.28-1.96)	<.001
HDL-cholesterol <40 mg/dL (≥40 mg/dL as reference)	1.60 (1.08-2.36)	.019
Insulin-treated DM	1.70 (0.93-3.11)	.085
Non-DM group (N=3,578)		
Aspirin monotherapy (Clopidogrel monotherapy as reference)	1.32 (1.01-1.73)	.042
Age (per 10 year increase)	1.41 (1.24-1.61)	<.001
Male sex	1.47 (1.05-2.05)	.024
Previous history of HF	1.59 (0.91-2.80)	.11

Independent predictors for 24-month primary composite endpoint were identified using multivariable Cox regression model with stepwise variable selection method. Primary composite endpoint is defined as a composite of all-cause death, nonfatal MI, stroke, readmission due to ACS, and major bleeding events (BARC type ≥3). Abbreviations: CI, confidence interval; DM, diabetes mellitus; HDL, high density lipoprotein; HF, heart failure; HR, hazard ratio.

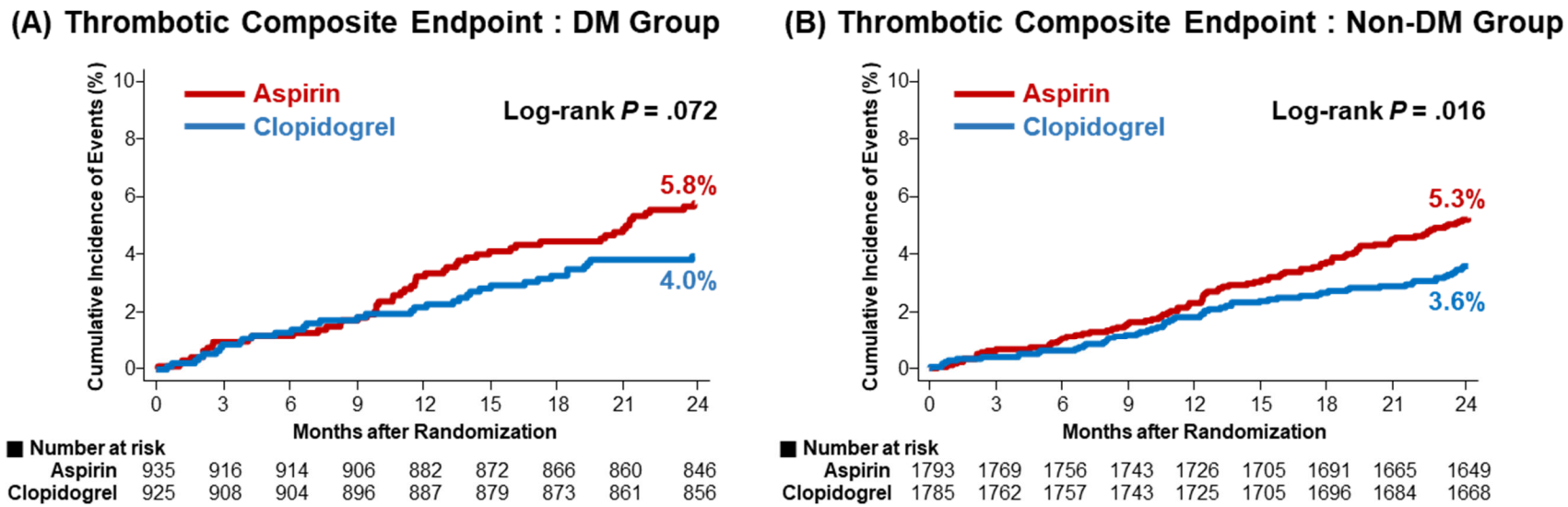
eTable 4. Risk of primary composite endpoint according to subsets related with diabetes mellitus

DM (N=1,860)				
Primary composite endpoint at 24-month*	**Clopidogrel (N=925)**	**Aspirin (N=935)**	**HR (95% CI)**	***P*** $_{interaction}$ ***P***
DM Treatment				.42
Newly diagnosed	2.4% (2/89)	5.3% (5/95)	0.43 (0.08-2.20)	.31
Non-pharmacological therapy only	2.0% (1/51)	3.8% (2/54)	0.51 (0.05-5.62)	.58
Oral hypoglycemic agent without insulin	6.3% (45/721)	9.8% (68/710)	0.64 (0.44-0.94)	.021
Insulin-treated	15.7% (10/64)	12.0% (9/76)	1.37 (0.56-3.38)	.49
Baseline HbA1c Level				.14
HbA1c <7.0%	4.4% (16/370)	8.9% (33/376)	0.49 (0.27-0.89)	.018
HbA1c 7.0~8.9%	5.6% (15/269)	6.1% (16/265)	0.93 (0.46-1.87)	.83
HbA1c ≥9.0%	14.3% (7/50)	9.3% (5/54)	1.56 (0.49-4.90)	.45

* Primary composite endpoint is defined as a composite of all-cause death, nonfatal MI, stroke, readmission due to ACS, and major bleeding events (BARC type ≥3)

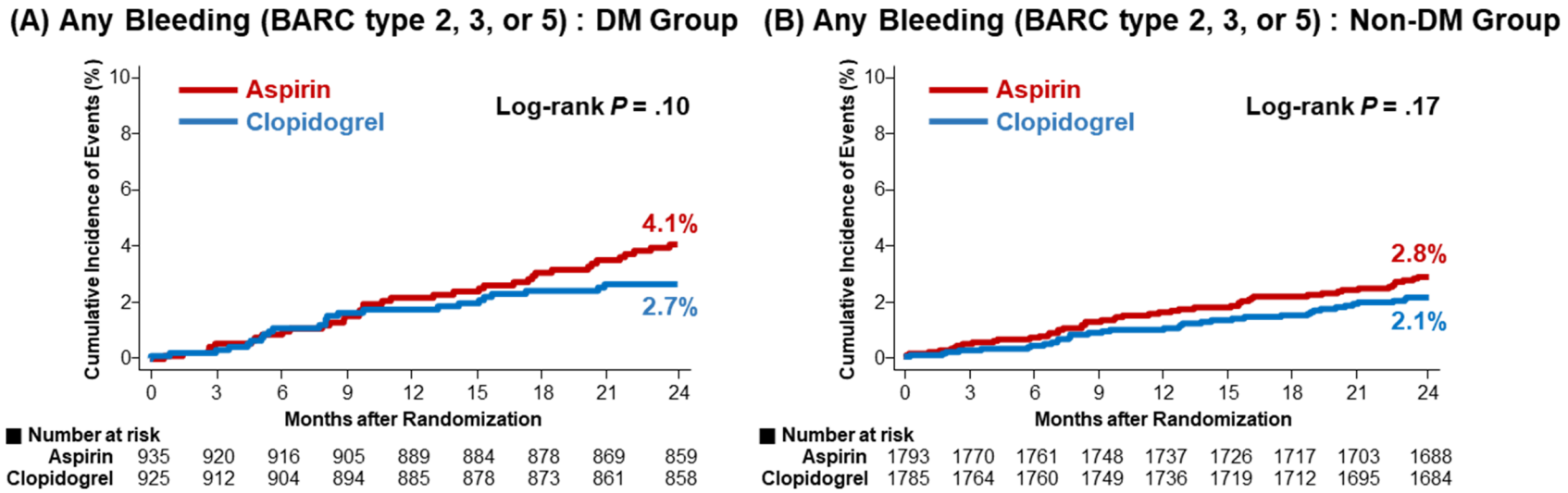
Abbreviations: CI, confidence interval; DM, diabetes mellitus; HbA1c, hemoglobin A1c; HR, hazard ratio.

eFigure 1. Cumulative Incidence of Thrombotic Composite Endpoint in Diabetic and Non-diabetic Subgroups



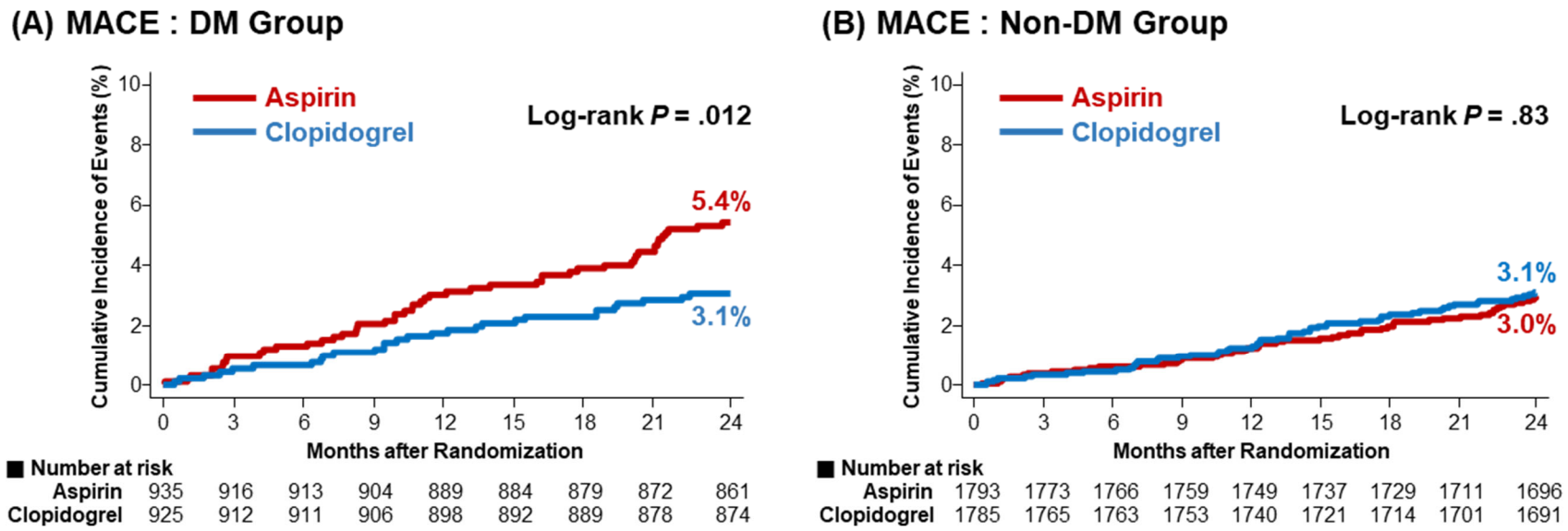
The cumulative incidence of thrombotic composite endpoint, consisting of cardiac death, nonfatal myocardial infarction, ischemic stroke, readmission due to acute coronary syndrome, and definite or probable stent thrombosis in (A) DM group and (B) Non-DM group are presented. Abbreviations: DM, diabetes mellitus; HR, hazard ratio.

eFigure 2. Cumulative Incidence of Any Bleeding in Diabetic and Non-diabetic Subgroups



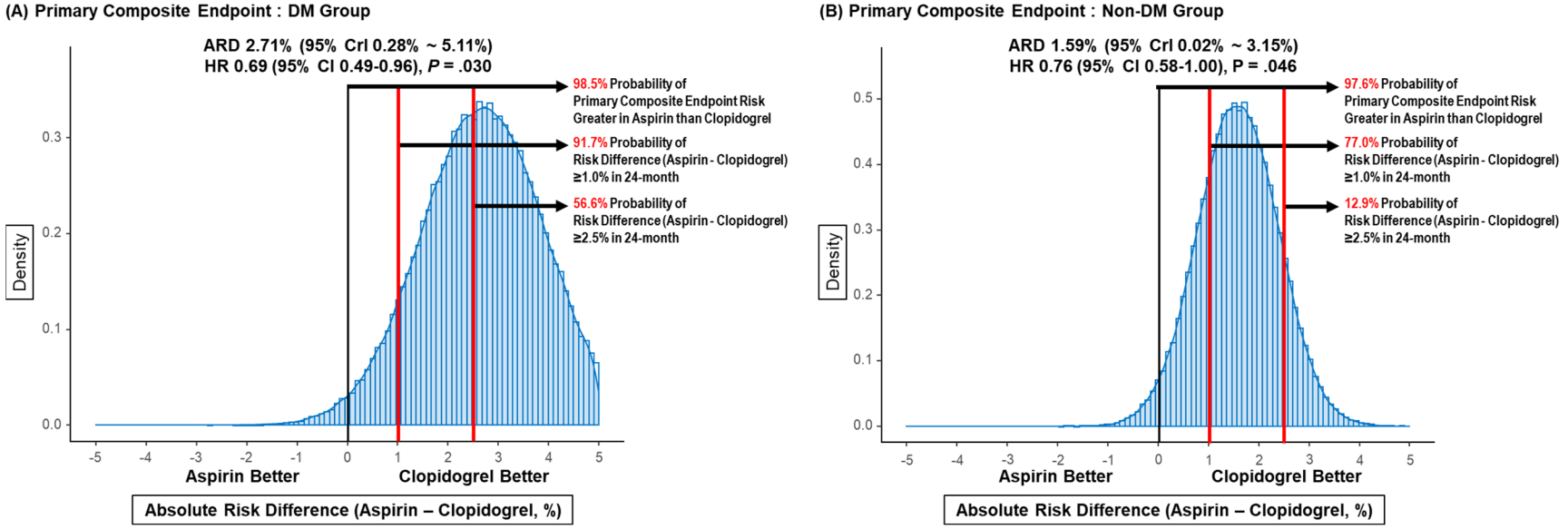
The cumulative incidence of any bleeding with BARC 2, 3, or 5 in (A) DM group and (B) Non-DM group are presented. Abbreviations: BARC, Bleeding Academic Research Consortium; DM, diabetes mellitus; HR, hazard ratio.

eFigure 3. Cumulative Incidence of MACE in Diabetic and Non-diabetic Subgroups



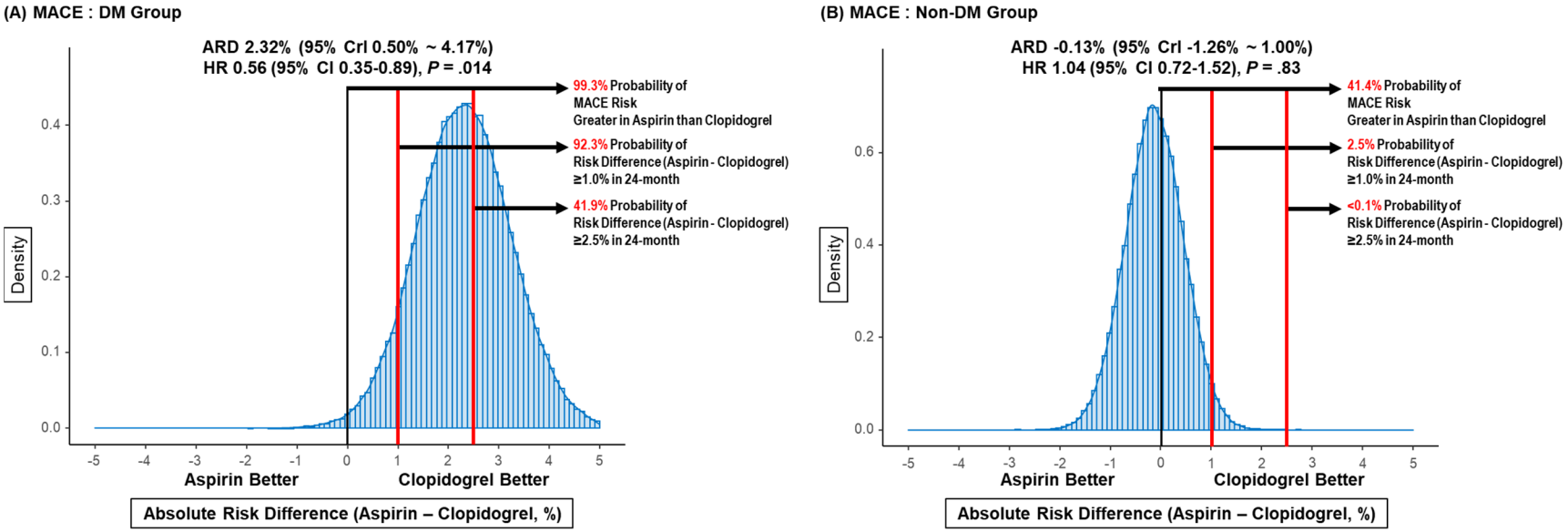
The cumulative incidence of MACE, consisting of all-cause death, MI, and stroke in (A) DM group and (B) Non-DM group are presented.
Abbreviations: DM, diabetes mellitus; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction.

eFigure 4. Bayesian Approach for Absolute Risk Difference of 24-Month Primary Composite Endpoint in Patients with Diabetes Mellitus



The density plots of the probability function for the absolute risk difference are presented for (A) Primary Composite Endpoint in DM group, and (B) Primary Composite Endpoint in Non-DM group. The primary composite endpoint is defined as a composite of all-cause death, nonfatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and major bleeding.
Abbreviations: ARD, absolute risk difference; CI, confidence interval; CrI, credible interval; DM, diabetes mellitus; HR, hazard ratio.

eFigure 5. Bayesian Approach for Absolute Risk Difference of 24-Month MACE in Patients with Diabetes Mellitus



The density plots of the probability function for the absolute risk difference are presented for (A) MACE in DM group, and (B) MACE in Non-DM group. MACE is defined as a composite of all-cause death, myocardial infarction, and stroke.
Abbreviations: ARD, absolute risk difference; CI, confidence interval; CrI, credible interval; DM, diabetes mellitus; HR, hazard ratio; MACE, major adverse cardiovascular event.

eReferences

1 Lee H, Koo BK, Park KW, Shin ES, et al. A randomized clinical trial comparing long-term clopidogrel vs aspirin monotherapy beyond dual antiplatelet therapy after drug-eluting coronary stent implantation: Design and rationale of the Harmonizing Optimal Strategy for Treatment of coronary artery stenosis-Extended Antiplatelet Monotherapy (HOST-EXAM) trial. *Am Heart J* 2017; 185: 17-25.

2 Lee JM, Park KW, Han JK, et al. Three-year patient-related andstent-related outcomes of second-generation everolimus-elutingXience V stents versus zotarolimus-eluting resolute stents in real-worldpractice (from the Multicenter Prospective EXCELLENT and RESOLUTE-Korea Registries). *Am J Cardiol* 2014; 114: 1329-38.

3 C.S. Committee, A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee, *Lancet* 1996; 348: 1329-39.