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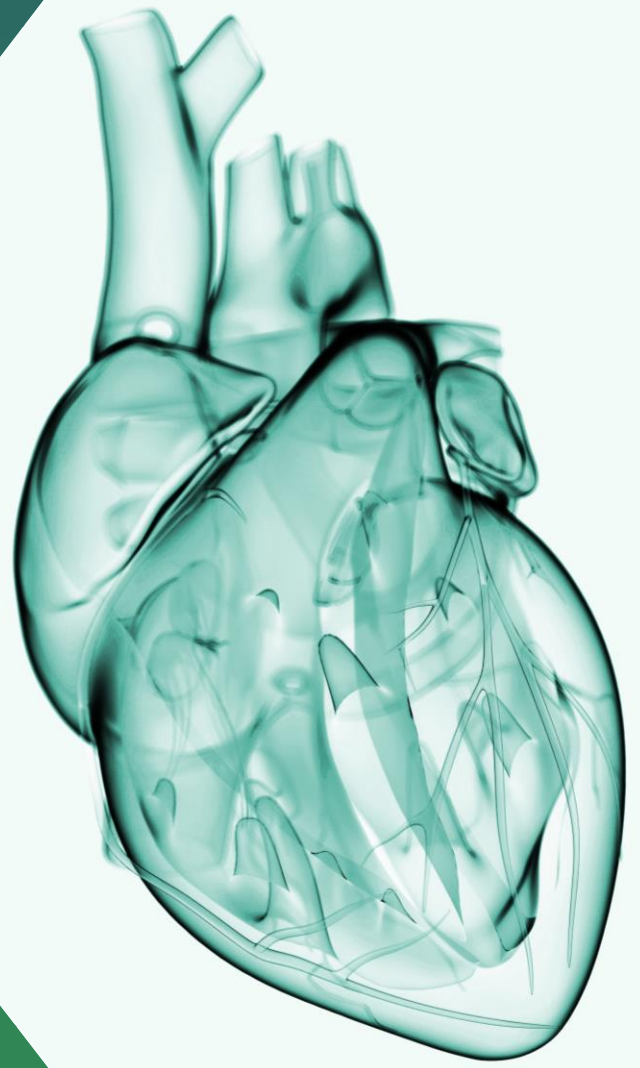
Beyond the Initial Event

: Long-Term Management with Antiplatelet Therapy



Choongki Kim

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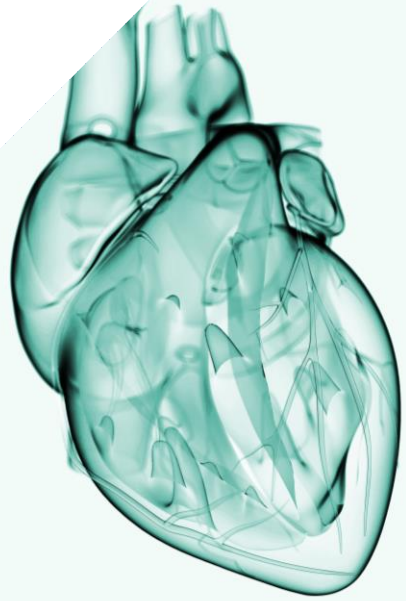


2023 ESC guideline for the management of ACS

: New recommendations

New recommendations

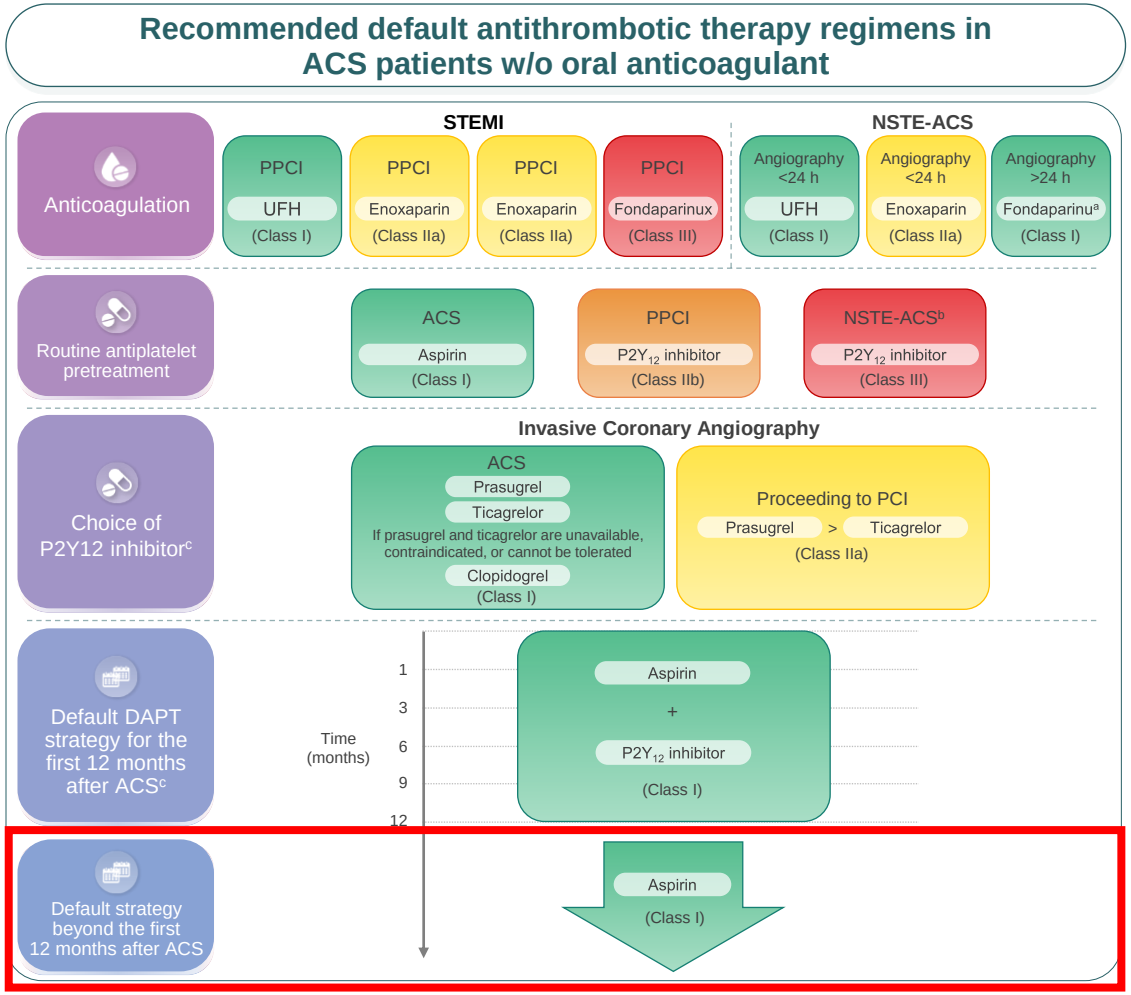
Recommendations	Class[a]	Level[b]
Recommendations for antiplatelet and anticoagulant therapy in acute coronary syndrome		
If patients presenting with ACS stop DAPT to undergo coronary artery bypass grafting, it is recommended they resume DAPT after surgeryfor at least 12 months.	I	C
In older ACS patients, especially if HBR, clopidogrel as the P2Y12 receptor inhibitor may be considered.	IIb	B
Recommendations for alternative antithrombotic therapy regimens		
In patients who are event-free after 3–6 months of DAPT and who are not high ischaemic risk, single antiplatelet therapy (preferably with a P2Y12 receptor inhibitor) should be considered.	IIa	A
P2Y12 inhibitor monotherapy may be considered as an alternative to aspirin monotherapy for long-term treatment.	IIb	A

ACS, acute coronary syndrome; **DAPT**, dual antiplatelet therapy; **HBR**, high bleeding risk.
[a]Class of recommendation [b]Level of evidence.

Reference 1. Byrne RA, et al. *Eur Heart J*. 2023 Aug 25;ehad191. doi: 10.1093/eurheartj/ehad191.

2023 ESC guideline for the management of ACS

: antiplatelet & anticoagulant therapy in ACS



Q) Is aspirin a better choice compared to clopidogrel for single antiplatelet agent as maintenance therapy?

ACS, acute coronary syndrome; **b.i.d.**, twice a day; **DAPT**, dual antiplatelet therapy; **HBR**, high bleeding risk; **LD**, loading dose; **MD**, maintenance dose; **NSTE-ACS**, non-ST-elevation acute coronary syndrome; **o.d.**, once daily; **PCI**, percutaneous coronary intervention; **PPCI**, primary percutaneous coronary intervention; **UFH**, unfractionated heparin.

[a]Class of recommendation [b]Level of evidence. [c]HBR should be assessed in a structured manner, e.g. presence of a single major or two minor characteristics as defined by ARC-HBR

※ 급성관상동맥증후군(불안정성 협심증 또는 비Q파 심근경색)이 있는 환자에는 이 약 투여개시 일에 이 약으로서 1일 1회 300 mg을 부하용량(loading dose)으로 시작하고 이후에 1일 1회 75 mg을 유지용량으로 경구투여한다.

Reference 1. Byrne RA, et al. *Eur Heart J*. 2023 Aug 25;ehad191. doi: 10.1093/eurheartj/ehad191.

AHA Scientific Statement 2020

Antithrombotics in stable patients with T2DM and CAD

Clopidogrel alone may be a reasonable option compared with aspirin in stable patients with T2DM and CAD (i,,e., no stent or acute coronary syndrome in the prior year).

Management of Stable CAD: Antithrombotics

Underlying issue: T2DM is a generalized prothrombotic state caused by both altered coagulation and altered platelet function.

Aspirin alone	Lowest risk of bleeding but high residual platelet reactivity increases cardiovascular risk
Clopidogrel alone	Decreased cardiovascular risk **without** meaningfully increased risk of bleeding vs aspirin alone
Aspirin+clopidogrel/ticagrelor	Decreased cardiovascular risk with increased risk of bleeding; targets patients with additional risk factor and low risk of bleeding (use risk scores)
Aspirin+low-dose rivaroxaban	Decreased cardiovascular risk with increased risk of bleeding; targets the aberrant coagulation with T2DM

CAD, coronary artery disease; **T2DM**, type 2 diabetes.

Reference 1. Arnold SV, *et al. Circulation*. 2020;141(19):e779-e806

2021 ESC Guidelines of CVD Prevention

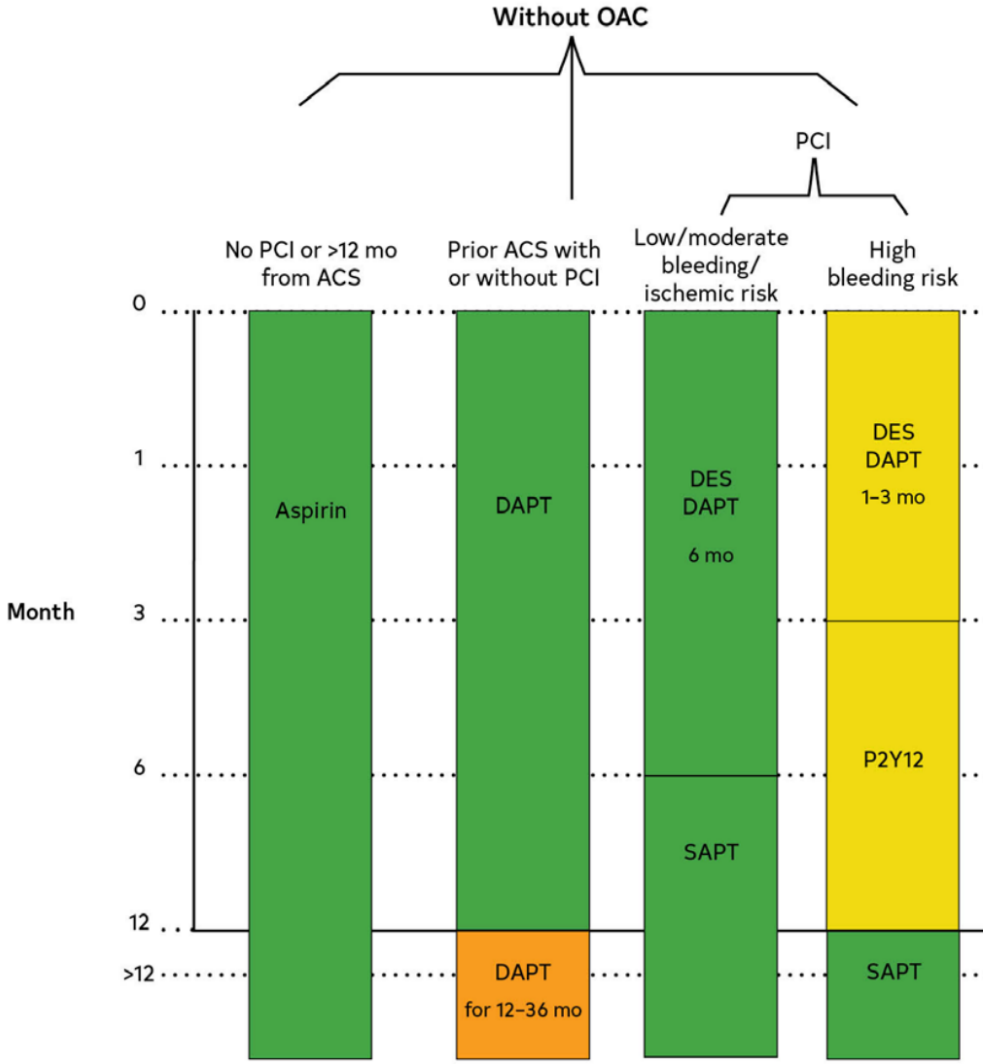
Recommendations for antithrombotic therapy

RECOMMENDATIONS	Class[a]	Level[b]
Aspirin 75-100 mg daily is recommended for secondary prevention of CVD.	I	A
Clopidogrel 75 mg daily is recommended as an alternative to aspirin in secondary prevention in case of aspirin intolerance.	I	B
Clopidogrel 75 mg daily may be considered in preference to aspirin in patients with established ASCVD.	IIb	A
Concomitant use of a proton pump inhibitor is recommended in patients receiving antiplatelet therapy who are at high risk of gastrointestinal Bleeding	I	A
In patients with DM at high or very high CVD risk, low-dose aspirin may be considered for primary prevention in the absence of clear contraindications	**IIb**	A

[a]Classes of recommendations: I, recommended/indicated; IIa, should be considered; IIb, may be considered
[b]Level of evidence; A, Data derived from multiple randomized clinical trials or meta-analyses; B, Data derived from a single randomized clinical trial or large non-randomized studies
[c]Contraindications for ticagrelor: previous intracranial haemorrhage or ongoing bleeds. Contraindications for prasugrel: previous intracranial haemorrhage, previous ischaemic stroke or transient ischaemic attack, or ongoing bleeds; prasugrel is not recommended for patients ≥75 years of age or with a body weight <60 kg.
ASCVD, atherosclerotic cardiovascular disease; **CV,** cardiovascular; **CVD**, cardiovascular disease; **DM,** diabetes mellitus

Reference 1. Visseren FLJ, *et al. Eur Heart J.* 2021;42(34):3227-3337

2023 AHA/ACC Guidelines for Chronic Coronary Disease



As an alternative to low-dose aspirin, clopidogrel may be used in individuals who cannot tolerate aspirin therapy, and many of the contemporary trials have used clopidogrel monotherapy after a short course of DAPT.[46,47]

further clinical trials would be useful to guide recommendations regarding the long-term use of clopidogrel versus aspirin as SAPT in CCD.[46,48,49]

Reference 1. Viran S et al. Circulation. 2023 29;148(9):e9-e119.

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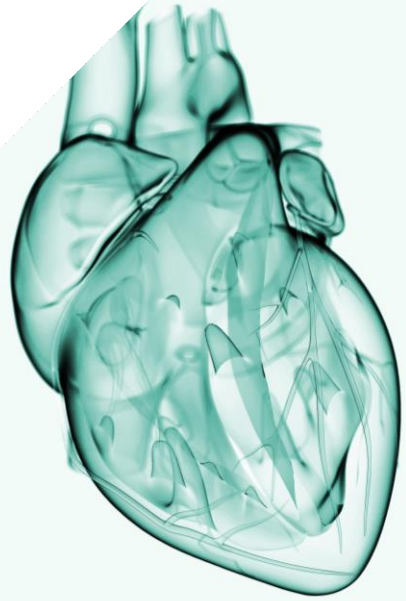
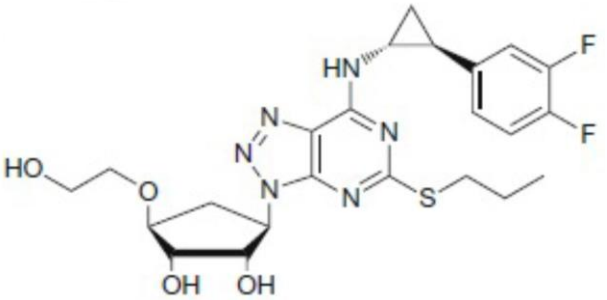


Consideration when choose aspirin

Uncertainties surrounding the use of acetylsalicylic acid for secondary prevention

Bleeding risk
Increased risk of intracranial and extracranial bleeding, especially in combination with other antithrombotic drugs

ASPIRIN
?



Risk reduction
Contemporary drugs favourably alter the baseline individual risk of cardiovascular events, translating the relative benefits of aspirin into smaller absolute effects

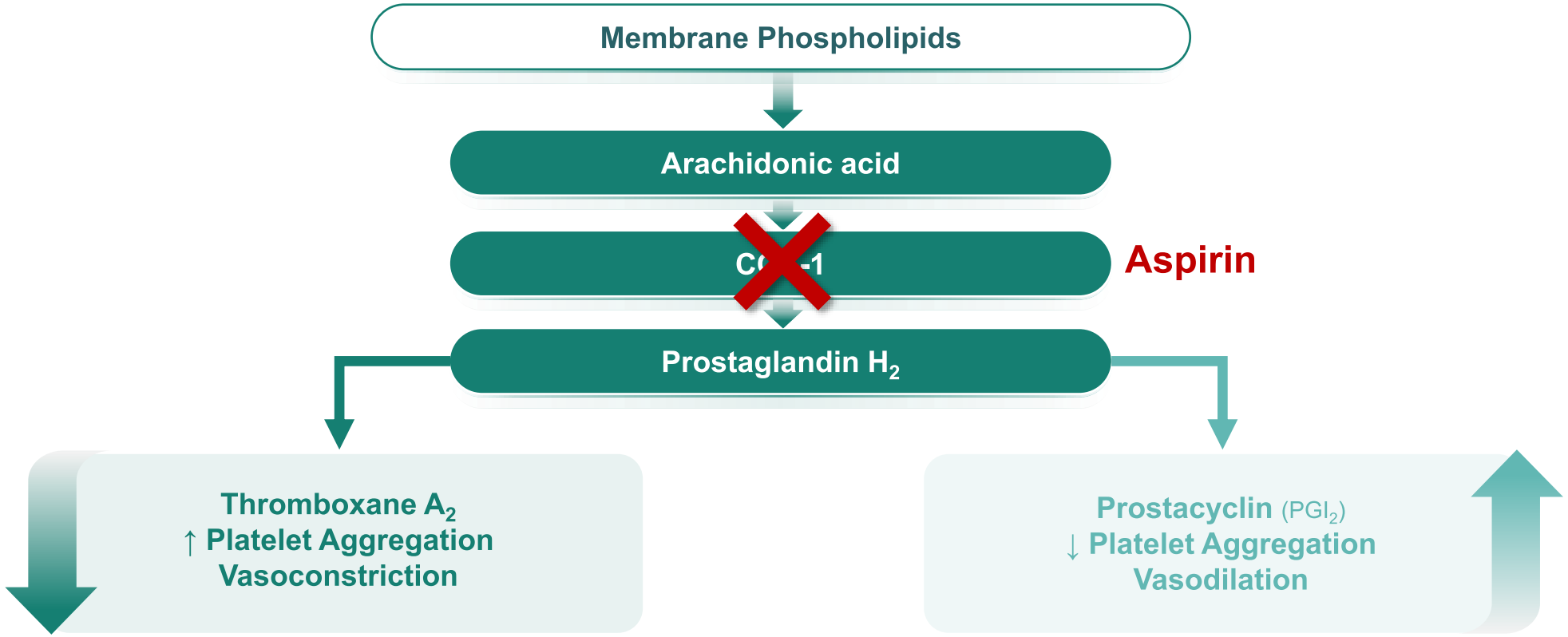
Novel antithrombotics
The availability of new compounds with potent antithrombotic efficacy could make the use of aspirin no longer necessary

Reference 1. Capodanno, et al., *Nat Rev Cardiol.* 2018;15(8):480-496.

Mechanism of Action:

Aspirin

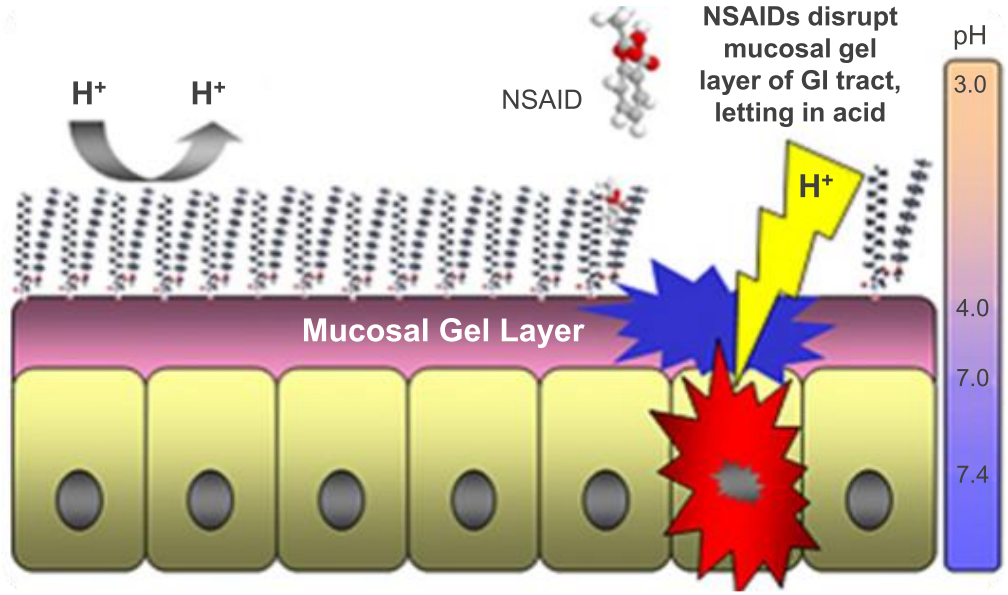
- **Irreversible inhibition of cyclooxygenase enzyme** (COX-1) **via acetylation**
- **Small dose of aspirin inhibits thromboxane** (TXA_2) **synthesis in platelets but not inhibit prostacyclin** (PGI_2) **synthesis in endothelium** (larger dose)



Reference 1. Capodanno D *et al. Circulation*. 2016;134: 1579-1594.

NSAIDs Disrupt the Normal Barrier to Acid by Interacting with Components of the GI Lining

- When NSAIDs are taken, they bind to the lipids in the GI lining and compromise the lining's acid-repelling properties



Alterations in Gastric Mucosal Barrier

- ↓ Prostaglandin synthesis
- ↓ Mucus and bicarbonate secretion
- ↓ Submucosal blood flow
- ↓ Mucosal ATP
- ↓ Cell turnover
- ↓ Platelet function (irreversible)

- Over time, the disruption of the GI lining can lead to clinically significant and sometimes life-threatening damage, such as ulceration, bleeding and perforation, as well as discontinuation of NSAID use

GI, gastrointestinal; **NSAIDs**, non-steroidal anti-inflammatory drugs.

References 1. Ivey KJ. *Am J Med.* 1988;84: 41-48. **2.** Lichtenberger LM. *Biochem Pharmacol.* 2001;61: 631-637.

Bleeding from Antiplatelet Drugs

The individual risks of upper gastrointestinal bleeding (UGIB): aspirin 4.0 (3.2-4.9), clopidogrel 2.3 (0.9-6.0).

UGIB Risk Associated with Various Antiplatelet Drugs

Medications in week before the index day, by dose

Drug and Daily Dose (mg)	Cases (%)	Controls (%)	OR (95% CI)
Aspirin	**467** (16.8)	**642** (9.1)	**4.0** (3.2-4.9)
≤100	126 (4.5)	206 (3.0)	3.8 (2.8-5.2)
101-150	102 (3.7)	138 (2.0)	3.3 (2.3-4.7)
151-200	154 (5.5)	168 (2.4)	6.0 (4.4-8.2)
>200	79 (2.8)	79 (1.1)	3.9 (2.5-5.9)
Clopidogrel	**12** (0.4)	**17** (0.2)	**2.3** (0.9-6.0)
Dipyridamole	12 (0.4)	31 (0.4)	0.9 (0.4-2.0)
≤100	4 (0.1)	12 (0.2)	0.7 (0.2-3.1)
>100	8 (0.3)	17 (0.2)	1.2 (0.4-3.2)
Indobufen	10 (0.4)	10 (0.1)	3.8 (1.2-12.2)
Ticlopidine	52 (1.9)	55 (0.8)	3.1 (1.8-5.1)
≤250	26 (0.9)	35 (0.5)	2.9 (1.4-5.8)
>250	23 (0.8)	12 (0.2)	4.9 (2.1-11.5)
Triflusal	28 (1.0)	66 (0.9)	1.6 (0.9-2.7)
≤300	11 (0.4)	28 (0.4)	1.4 (0.6-3.4)
>300	17 (0.6)	33 (0.5)	1.8 (0.9-3.5)

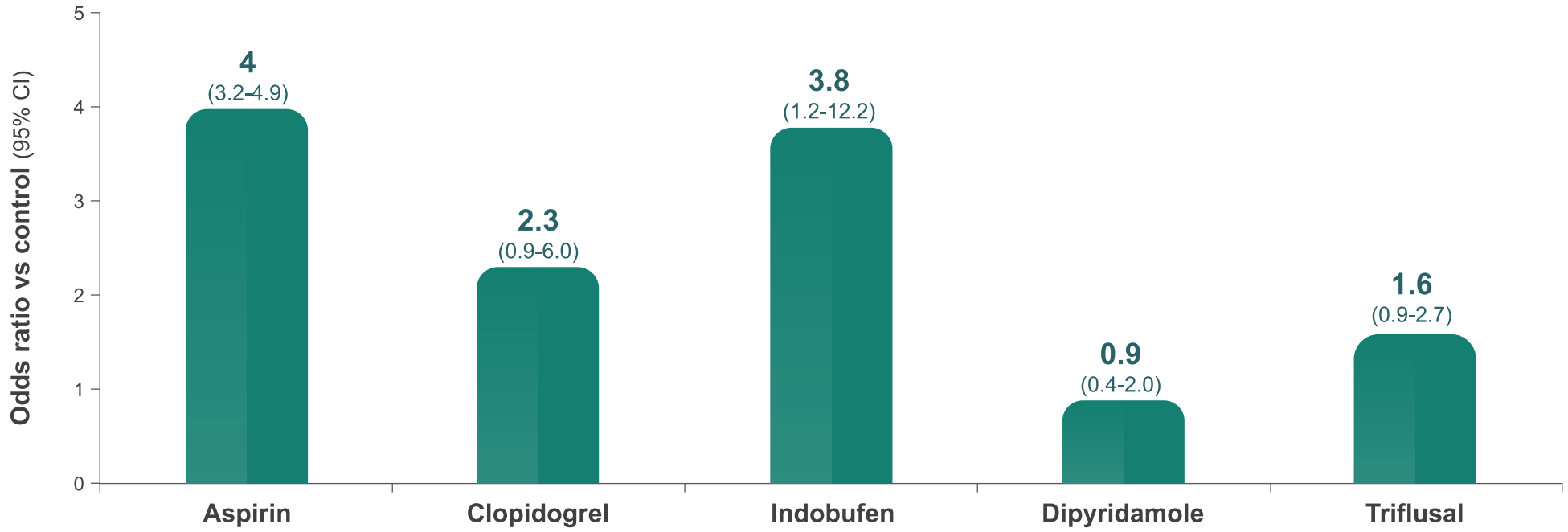
Study design In a case-control study, we compared all cases of upper gastrointestinal bleeding from a gastric or duodenal lesion in patients over 18 years of age (2,813 cases), with 7,193 matched controls. Odds ratios of upper gastrointestinal bleeding for individual antiplatelet drugs with adjustment for potential confounders were estimated.

Reference 1. Ibáñez L, *et al. Aliment Pharmacol Ther.* 2006;23: 235-242.

Bleeding from Antiplatelet Drugs

UGIB risk associated with various antiplatelet drugs suggested a weaker association for clopidogrel than aspirin.

UGIB risk associated with various antiplatelet drugs in week before the index day, by all dose



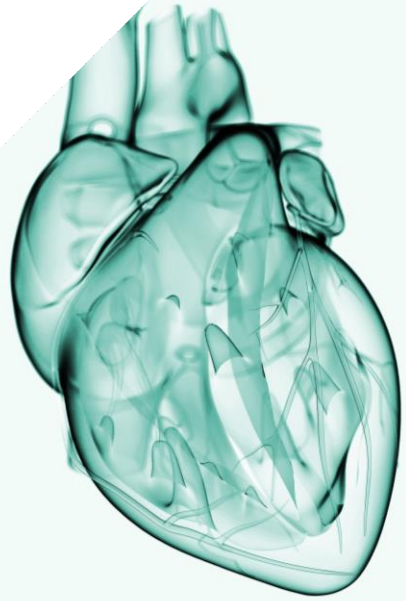
Study design In a case-control study, we compared all cases of upper gastrointestinal bleeding from a gastric or duodenal lesion in patients over 18 years of age (2,813 cases) to estimate the risk of upper gastrointestinal bleeding associated with the use of antiplatelet drugs and its prevention by gastroprotective agents, with 7,193 matched controls. Odds ratios of upper gastrointestinal bleeding for individual antiplatelet drugs with adjustment for potential confounders were estimated.

Index day, the day on which UGIB started

CI, confidence interval; **HR,** hazard ratio; **MI,** myocardial infarction; **TIMI,** Thrombolysis in myocardial infarction; **UGIB,** upper gastrointestinal bleeding

Reference 1. Ibáñez L, *et al. Aliment Pharmacol Ther.* 2006;23: 235-242

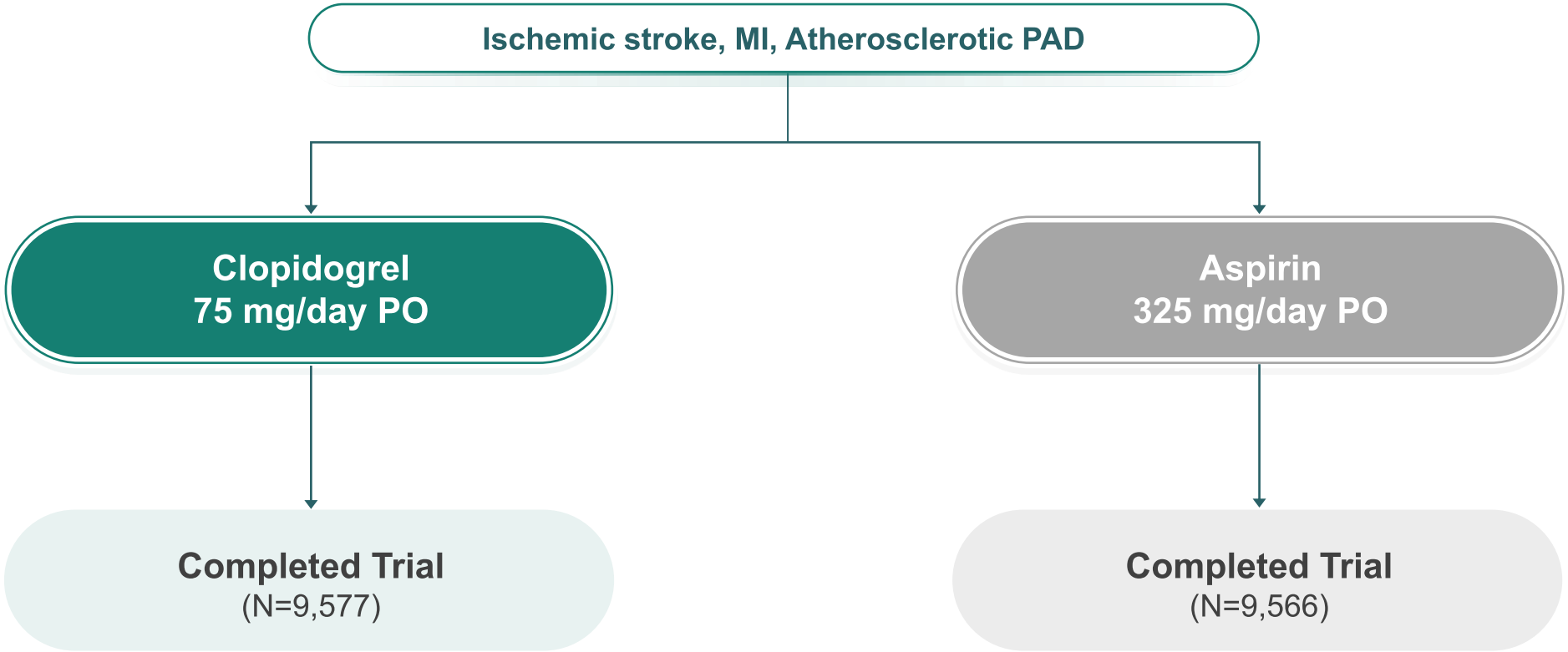
Contents



CAPRIE

Head to Head Design

- **Design:** Multicenter, multinational, randomized, double-blind, parallel group
- **Patients:** 19,185 patients with atherosclerotic vascular disease (either recent ischemic stroke, recent MI or symptomatic peripheral arterial disease)



MI, myocardial infarction; **PAD,** peripheral arterial disease; **PO**, oral.

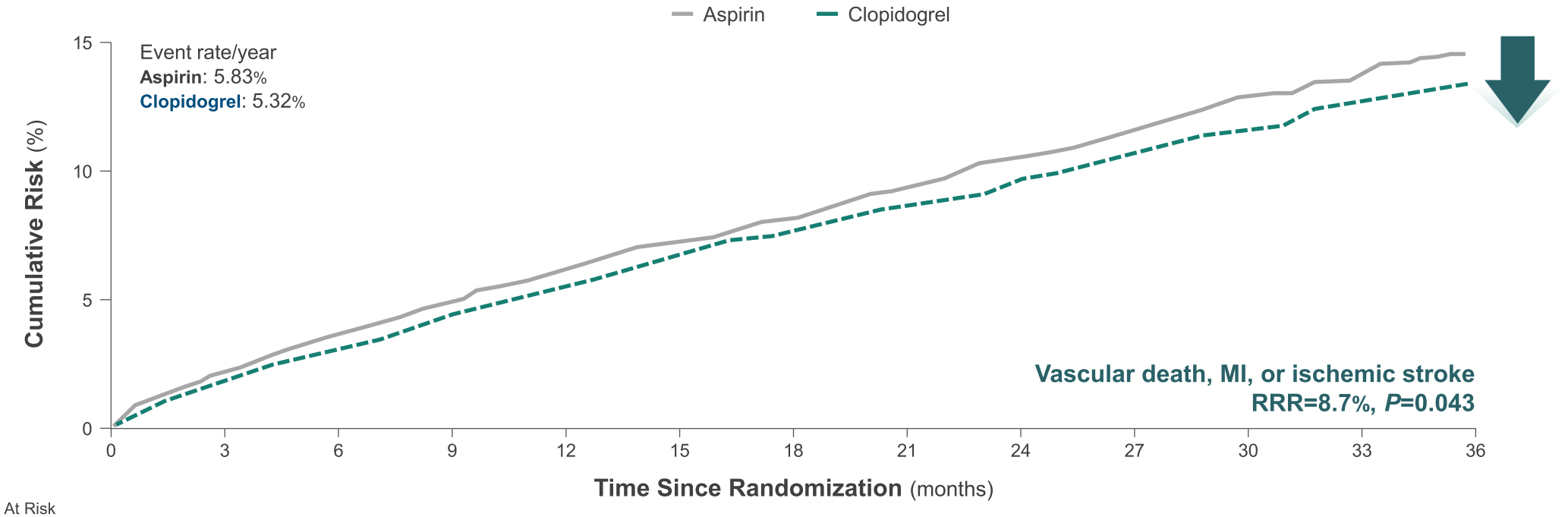
Reference 1. CAPRIE Steering Committee. *Lancet.* 1996;348: 1329-1339.

CAPRIE

Efficacy of Clopidogrel

Clopidogrel reduced the long-term risk of ischaemic events compared with ASA in a wide population of atherothrombotic patients (n=19,185)

Patients with Recent Ischemic Stroke, Recent MI, or Symptomatic PAD (N=19,185)



Patients At Risk

Aspirin	9,586	9,190	8,087	6,139	3,979	2,143	542
Clopidogrel	9,599	9,247	8,131	6,160	4,053	2,170	539

ASA, acetylsalicylic acid; **MI,** myocardial infarction; **PAD,** peripheral arterial disease; **RRR,** relative risk reduction.

Reference 1. CAPRIE Steering Committee. *Lancet.* 1996;348: 1329-1339.

CAPRIE

Comparative Benefits of Clopidogrel in High-Risk Patient Populations

High-risk groups in the CAPRIE studies would be expected to derive enhanced benefit from treatment with clopidogrel over that achieved by ASA.

Enhanced Risk Reduction with Clopidogrel Therapy in High-Risk Patients in the CAPRIE Study

High-risk Population	**Clopidogrel:** ER, %	**ASA:** ER, %	Clopidogrel		
			RRR, %	ARR, %	NNT
Total CAPRIE population	12.57	13.67	7.9	1.1	91
Patients with previous CABG	15.9	22.3	28.9	6.4	16
Patients with a history of ≥1 ischemic event	18.4	20.4	10.0	2.0	50
Patients with involvement of multiple vascular beds	17.39	19.84	12.4	2.45	41
Patients with diabetes	15.6	17.7	12.5	2.1	48
Patients with hypercholesterolemia	12.3	13.6	9.7	1.3	77

ARR, absolute risk reduction, **ASA**, acetylsalicylic acid; **ER,** event rate; **NNT,** number of patients needed to treat to prevent an event; **RRR,** relative risk reduction.

Reference 1. Hirsh J, Bhatt DL. *Arch Intern Med.* 2004;164:2106-10.

CAPRIE

Limitations

CAPRIE trial showed the superiority of clopidogrel over aspirin in the pre-DES era

- ☑ No PCI patients was enrolled.
- ☑ No de-escalation from DAPT to SAPT

CAPRIE trial compared clopidogrel 75 mg vs. Aspirin 325 mg.

- ☑ Aspirin 100 mg is prescribed generally these days

Caucasian population mostly included.

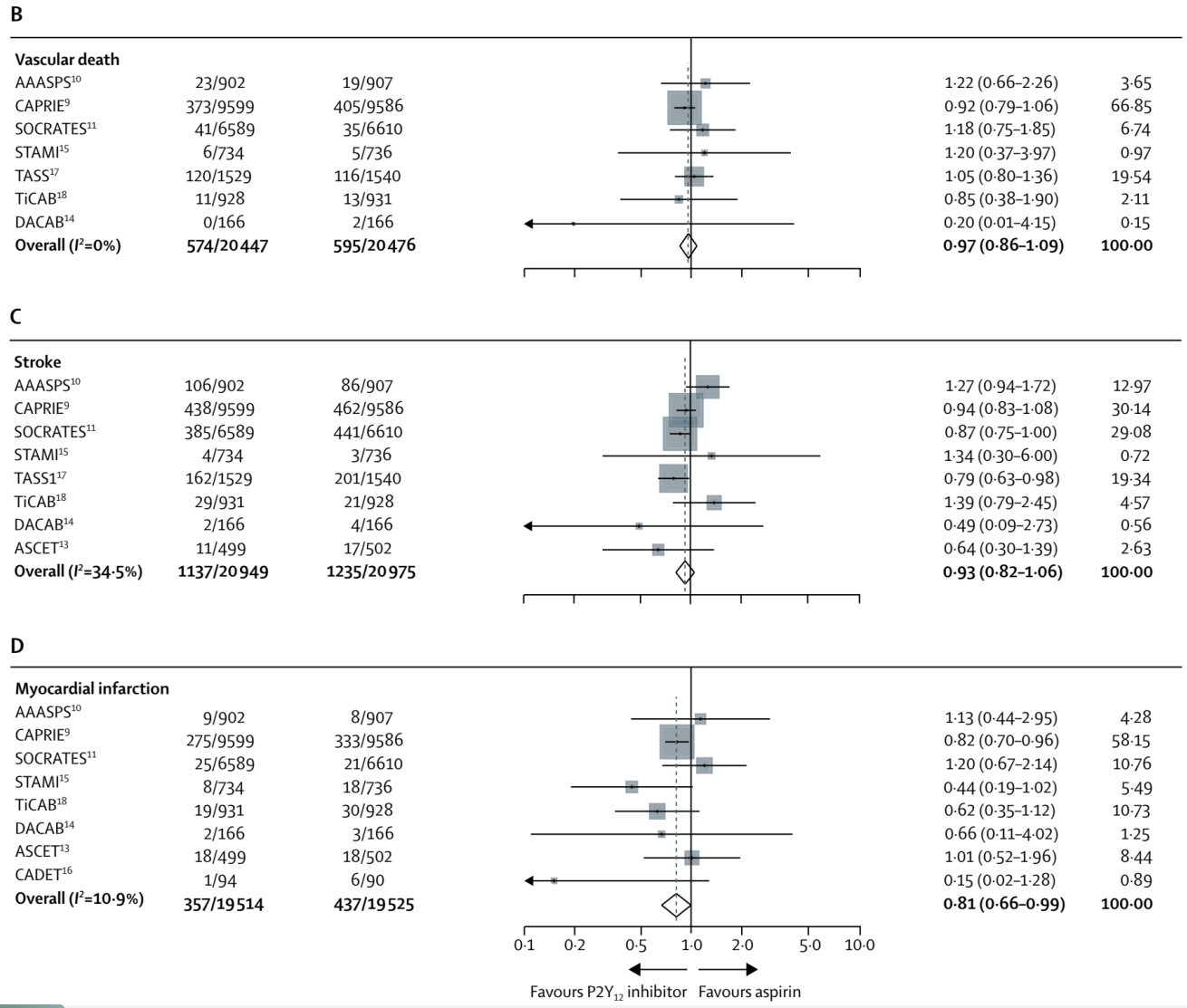
- ☑ Genetic phenotype might affect the clinical outcomes of clopidogrel.

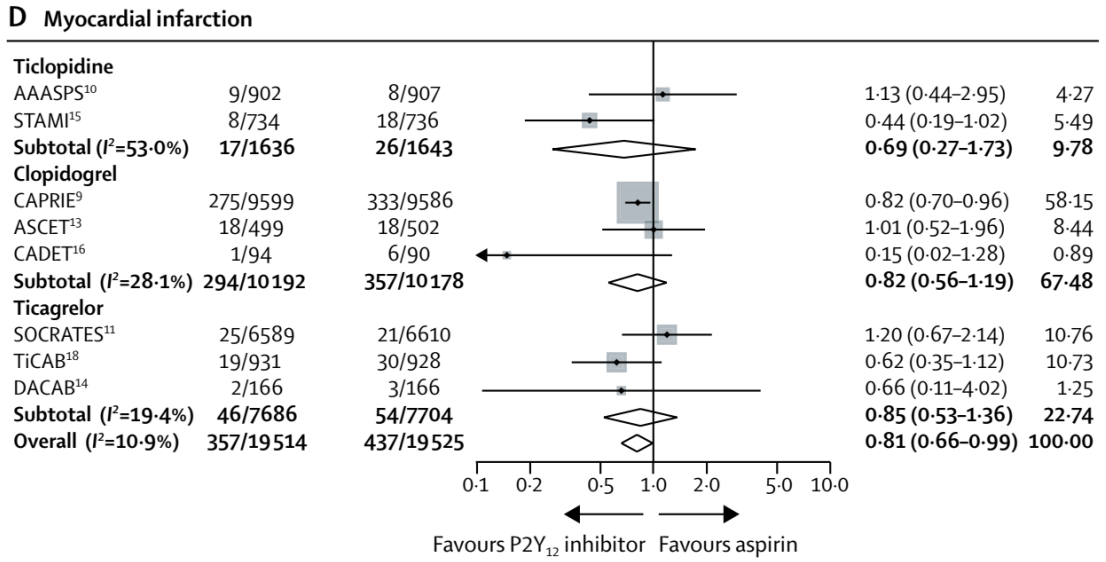
DAPT, dual antiplatelet therapy; **SAPT,** single antiplatelet therapy.

References 1. Levine GN, *et al. J Am Coll Cardiol.* 2016;68: 1082-1115. **2.** CAPRIE Steering Committee. *Lancet.* 1996;348: 1329-1339.

Meta-analysis: Monotherapy with P2Y12i vs. ASA

Patients with cerebrovascular, coronary, or peripheral artery disease





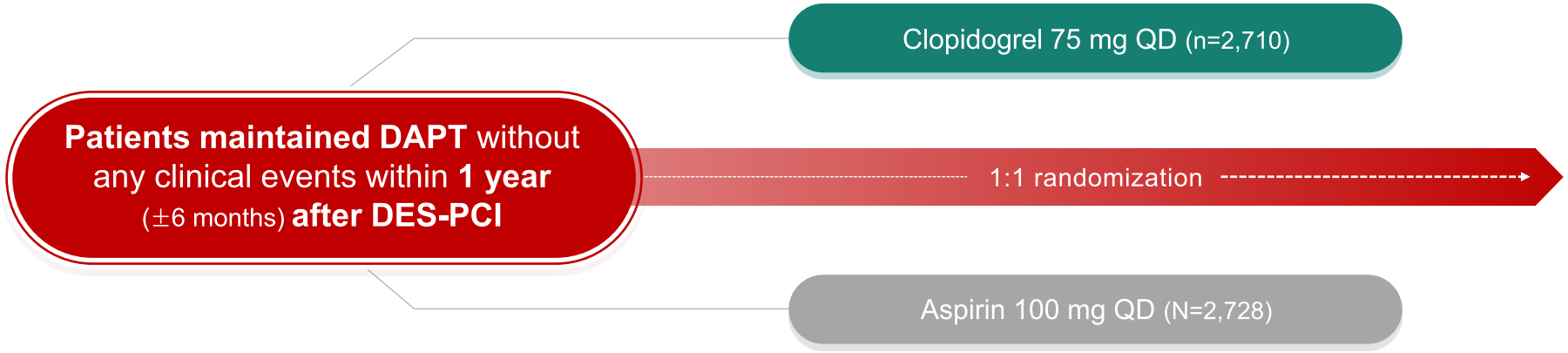
Reference 1. Chiarito M, et al. Lancet 2020; 395: 1487–95

HOST-EXAM

Aspirin versus clopidogrel for chronic maintenance monotherapy after PCI

Study design

- **Study design**: Investigator-initiated, prospective, randomized, open-label, multicenter trial
- **Objectives**:
  To compare the efficacy and safety **of clopidogrel monotherapy** with **aspirin monotherapy** in patients **who received dual antiplatelet therapy for 1 year** (±6 months) **after drug-eluting stent implantation** for coronary artery disease
- **Patient Enrollment**: 5,530 patients enrolled at 37 centers in Korea



DAPT, dual antiplatelet therapy; **DES,** drug-eluting stents; **HOST-EXAM,** Harmonizing Optimal Strategy for Treatment of coronary artery stenosis-Extended Antiplatelet Monotherapy; **PCI,** percutaneous coronary intervention; **QD,** once daily

References 1. Lee H, *et al*. *Am Heart J*. 2017;185:17-25 **2.** Koo BK *et al*. *Lancet* . 2021 May 14;S0140-6736 (21)01063-1

HOST-EXAM

Method

- **Patients aged 20 years or older who underwent PCI with DES and maintained DAPT without any clinical events within 6-18 months after PCI were eligible for this study.**
- **Patients with any ischemic and major bleeding complications** (i.e., non-fatal myocardial infarction, Any repeat revascularization, readmission due to a cardiovascular cause, and major bleeding) **were Excluded from randomization.**
- **Antiplatelet therapy before enrolment was composed of aspirin plus any P2Y12 inhibitor.**

Primary Endpoint

- A composite of all-cause death, non-fatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and major bleeding complications during the 24-month follow-up period. Major bleeding was defined as Bleeding Academic Research Consortium (BARC) type bleeding of ≥3.

Secondary Endpoint

- The individual components of the primary endpoint, revascularization, and minor gastrointestinal complications were analyzed at 24 months

Post-hoc secondary composite endpoints

- The thrombotic composite endpoint (defined as cardiac death, non-fatal myocardial infarction, ischaemic stroke, readmission due to acute coronary syndrome, and definite or probable stent thrombosis) and any bleeding (defined as BARC type ≥2 bleeding), were analysed.

DAPT, dual antiplatelet therapy; **DES,** drug-eluting stents; **HOST-EXAM,** Harmonizing Optimal Strategy for Treatment of coronary artery stenosis-Extended Antiplatelet Monotherapy; **PCI,** percutaneous coronary intervention

References 1. Lee H, *et al*. *Am Heart J*. 2017;185:17-25 **2.** Koo BK *et al*. *Lancet* . 2021 May 14;S0140-6736 (21)01063-1

HOST-EXAM

Baseline characteristics of the population

- **The two groups were well balanced for demographic, clinical, and procedural characteristics, and non-trial-related medications.**
- **The DAPT regimen before randomization was mainly aspirin plus clopidogrel** (4,430 [81.5%])**.**

Baseline characteristics of population by DAPT regimen and angiographic data per patient

		Clopidogrel (n=2,710)	**Aspirin** (n=2,728)
DAPT at the randomisation			
Aspirin plus clopidogrel		2,218 (81.8%)	2,212 (81.1%)
Aspirin plus ticagrelor		226 (9.8%)	268 (9.8%)
Aspirin plus prasugrel		212 (7.8%)	235 (8.6%)
Aspirin plus clopidogrel plus cilostazol		14 (0.5%)	13 (0.5%)
Angiographic data per patient			
Extent of CAD	One-vessel disease	1,367 (50.4%)	1,376 (50.4%)
	Two-vessel disease	855 (31.5%)	844 (30.9%)
	Three-vessel disease	488 (18.0%)	507 (18.6%)
Generation of DES	First generation DES	54 (2.0%)	52 (1.9%)
	Second generation DES	2,627 (96.9%)	2,651 (97.2%)
	Unknown generation	29 (1.1%)	25 (0.9%)

CAD, coronary artery disease; **DAPT,** dual antiplatelet therapy; **DES,** drug-eluting stents

Reference 1. Koo BK *et al. Lancet* . 2021 May 14;S0140-6736 (21)01063-1

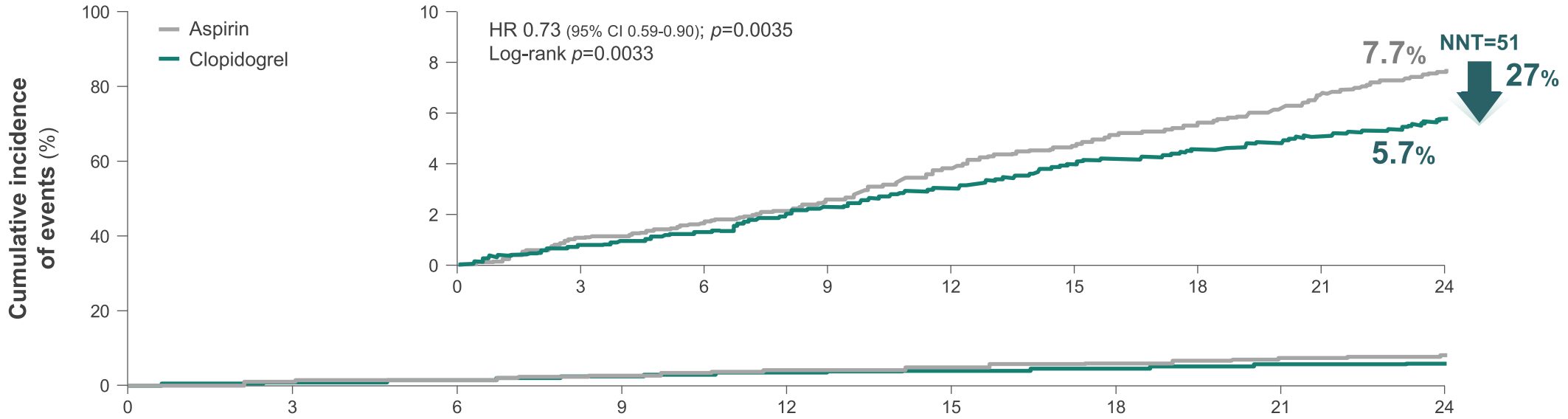
HOST-EXAM

Primary endpoint

During the 24-month follow-up, the primary endpoint occurred in 152 patients (5.7%) **who received clopidogrel monotherapy and in 207 patients** (7.7%) **who received aspirin monotherapy** (hazard ratio [HR] 0.73 [95% CI 0.59-0.90]; *p*=0.0035) **with an absolute risk reduction of 2.0%** (95% CI 0.6-3.3)**.**

The cumulative incidence of the primary endpoint

(All-cause death, non-fatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and major bleeding (BARC ≥3) complications)



No. At Risk (number censored)									
Aspirin	2,728 (0)	2,677 (22)	2,657 (22)	2,629 (24)	2,585 (40)	2,555 (48)	2,531 (49)	2,493 (64)	2,456 (66)
Clopidogrel	2,710 (0)	2,667 (23)	2,654 (26)	2,626 (24)	2,597 (33)	2,565 (41)	2,549 (43)	2,521(54)	2,500 (58)

BARC, Bleeding Academic Research Consortium; **CI,** confidence interval; **HR,** hazard ratio; **NNT,** number needed to treat

Reference 1. Koo BK *et al. Lancet* . 2021 May 14;S0140-6736(21)01063-1

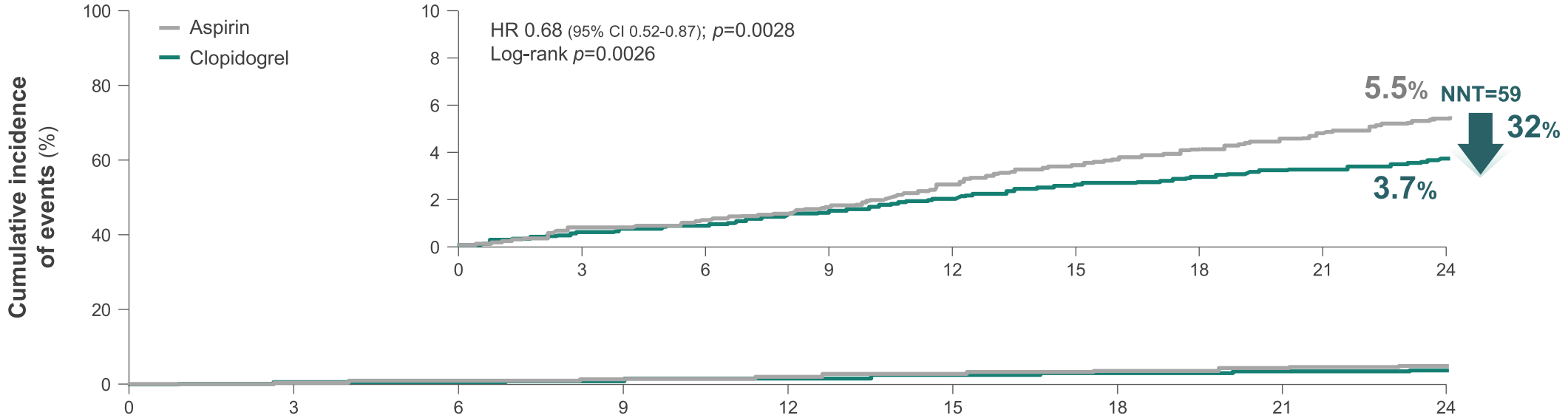
HOST-EXAM

Secondary composite thrombotic endpoint

The secondary composite thrombotic endpoint of cardiac death, non-fatal myocardial infarction, stroke, readmission due to acute coronary syndrome, or definite or probable stent thrombosis occurred in 99 (3.7%) **patients in the clopidogrel group and 146** (5.5%) **patients in the aspirin group** (HR 0.68 [95% CI 0.52-0.87]; *p*=0.0028)**, for a difference in risk of 1.7%** (95% CI 0.6-2.8)**.**

The cumulative incidence of the secondary composite thrombotic endpoint

(All-cause death, non-fatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and major bleeding (BARC ≥3) complications)



No. At Risk (number censored)									
Aspirin	2,728 (0)	2,685 (23)	2,670 (28)	2,649 (35)	2,608 (49)	2,577 (59)	2,557 (64)	2,525 (82)	2,495 (87)
Clopidogrel	2,710 (0)	2,670 (25)	2,661 (26)	2,639 (34)	2,612 (46)	2,584 (58)	2,569 (64)	2,545 (79)	2,524 (86)

CI, confidence interval; **HR,** hazard ratio; **NNT,** number needed to treat

Reference 1. Koo BK *et al*. *Lancet* . 2021 May 14;S0140-6736(21)01063-1

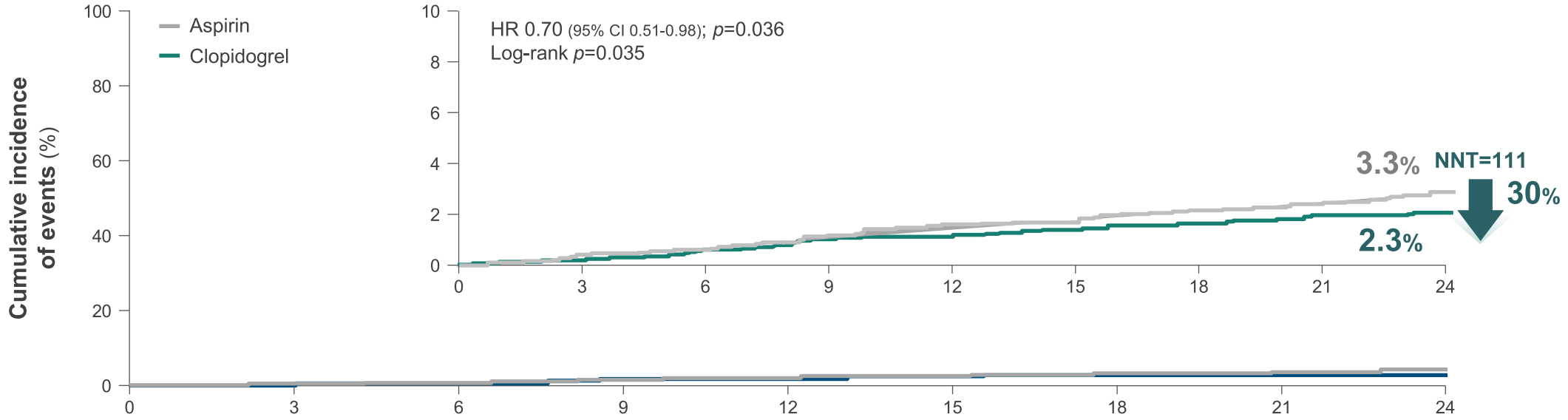
HOST-EXAM

Any bleeding events

Any bleeding (BARC type ≥2) **occurred in 61** (2.3%) **patients in the clopidogrel group and 87** (3.3%) **patients in the aspirin group** (HR 0.70 [0.51-0.98]; *p*=0.036)**, for a difference in risk of 0.9%** (0.0-1.8)**.**

The cumulative incidence of any bleeding events (BARC type ≥2)

(Cardiac death, non-fatal myocardial infarction, ischaemic stroke, readmission due to acute coronary syndrome, or definite or probable stent thrombosis)



No. At Risk (number censored)									
Aspirin	2,728 (0)	2,690 (26)	2,677 (31)	2,653 (39)	2,626 (54)	2,610 (65)	2,595 (67)	2,572 (85)	2,547 (93)
Clopidogrel	2,710 (0)	2,676 (28)	2,664 (29)	2,643 (37)	2,621 (56)	2,597 (72)	2,585 (77)	2,556 (98)	2,542 (105)

BARC, Bleeding Academic Research Consortium; **CI,** confidence interval; **HR,** hazard ratio; **NNT,** number needed to treat

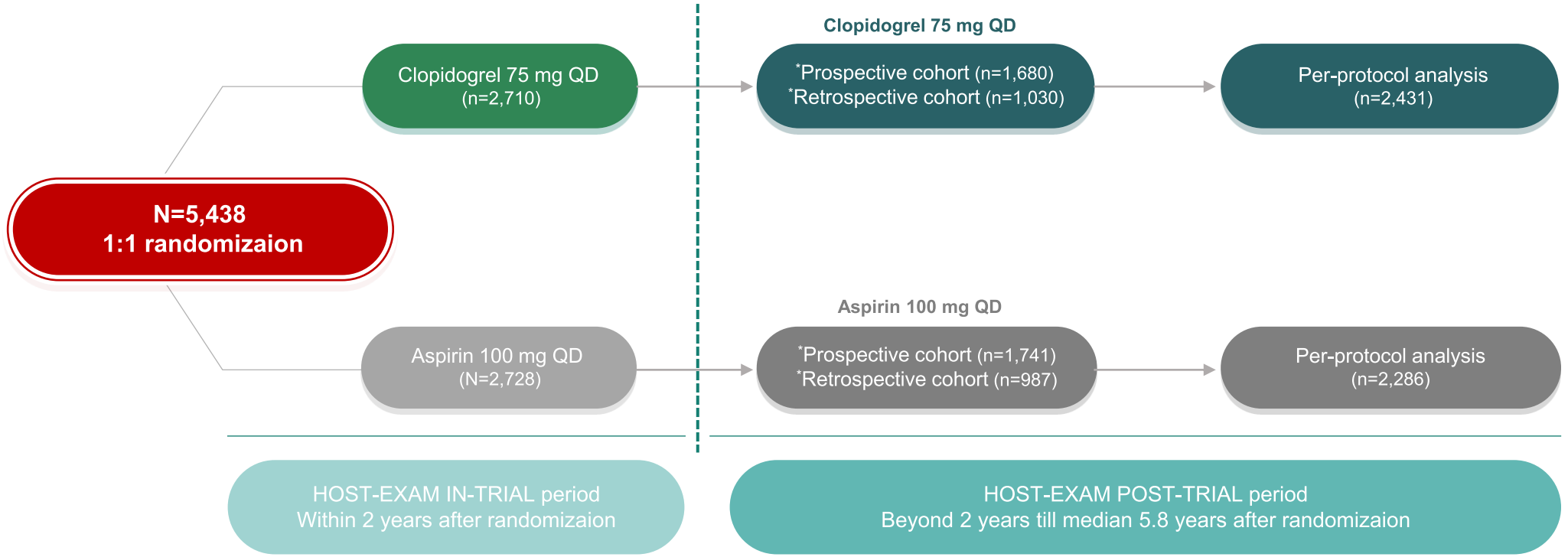
Reference 1. Koo BK *et al*. *Lancet*. 2021 May 14;S0140-6736(21)01063-1

HOST-EXAM Extended Study

Post-trial follow-up results of the HOST-EXAM trial

The HOST-EXAM Extended study was designed to perform a post-trial extended follow-up of the patients enrolled in the HOST-EXAM trial to compare the long term outcomes between clopidogrel and aspirin monotherapy.
: Median follow-up duration was 5.8 years (interquartile range, 4.8 and 6.2 years).

Study design: HOST-EXAM Extended Study



*The patients who performed clinical follow-up in the original center were enrolled in the prospective cohort after obtaining informed consent, while those who could not provide informed consent (already had events before study initiation or were being followed up at centers other than the original participating hospitals) were enrolled in the retrospective cohort

PCI, percutaneous coronary intervention; **QD,** once daily

Reference 1. Kang J, et al. *Circulation*. Circulation. 2023 Jan 10;147(2):108-117.

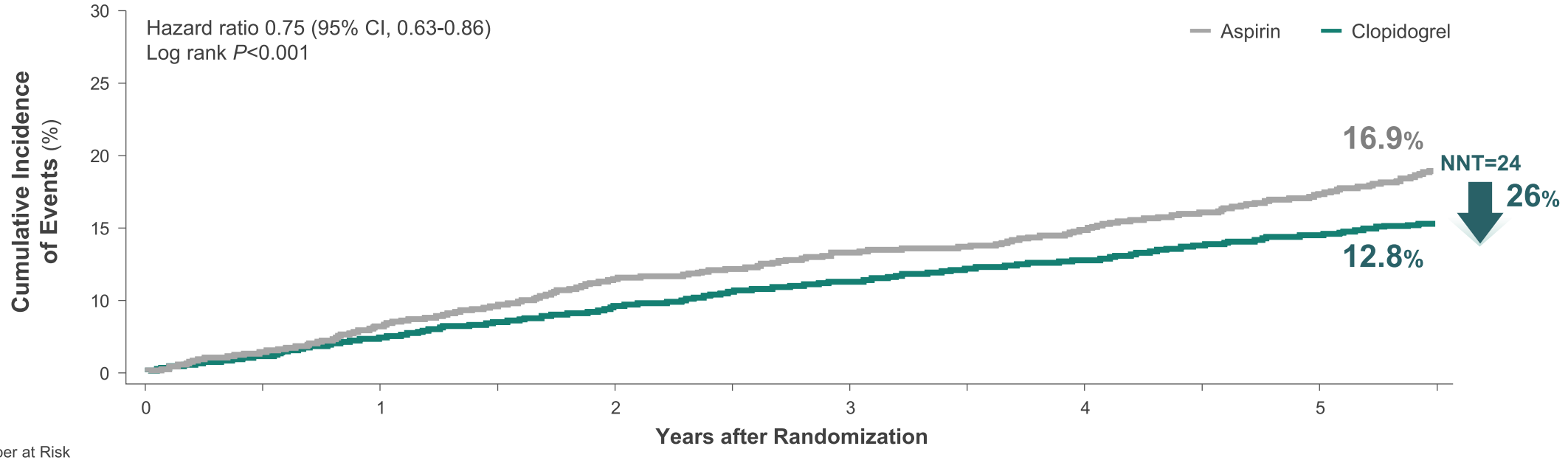
HOST-EXAM Extended Study

Primary endpoint

During the follow-up duration, the primary endpoint occurred in 311 patients (12.8%) **who received clopidogrel monotherapy, and in 387 patients** (16.9%) **who received aspirin monotherapy** (HR, 0.74; 95%CI, 0.63 to 0.86; p<0.001)**. The results were similar to HOST-EXAM trial** (HR 0.73, 95% CI 0.59–0.90)**, which clopidogrel monotherapy significantly reduced the risk of the composite primary endpoint.**

The cumulative incidence of the primary endpoint

(All-cause death, non-fatal MI, stroke, readmission due to ACS, and major bleeding (BARC ≥3) complications)



Number at Risk

Aspirin	2286	2189	2086	2014	1777	1287	1007
Clopidogrel	2431	2355	2280	2214	1964	1462	1181

ACS, acute coronary syndrome; **BARC,** Bleeding Academic Research Consortium; **CI,** confidence interval; **HR,** hazard ratio; **MI,** myocardial infarction; **NNT,** number needed to treat

Reference 1. Kang J, et al. *Circulation*. *Circulation*. 2023 Jan 10;147(2):108-117.

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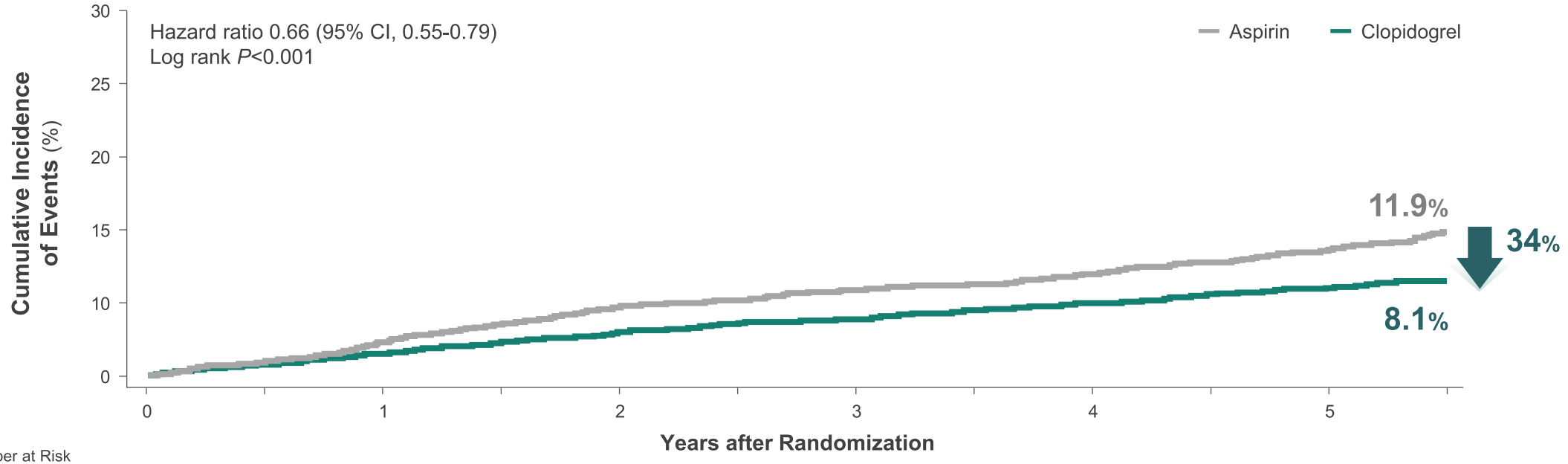
HOST-EXAM Extended Study

Secondary thrombotic endpoint

The secondary thrombotic endpoint of cardiac death, non-fatal MI, stroke, readmission due to ACS, or definite or probable stent thrombosis, occurred in 196 patients (8.1%) **in the clopidogrel group and 273 patients** (11.9%) **in the aspirin group** (HR 0.66, 95% CI 0.55 to 0.79, p<0.001).

The cumulative incidence of the secondary thrombotic endpoint

(Cardiac death, non-fatal MI, ischaemic stroke, readmission due to ACS, or definite or probable stent thrombosis)



Number at Risk

Aspirin	2286	2208	2120	2053	1819	1322	1040
Clopidogrel	2431	2371	2304	2245	1992	1489	1202

ACS, acute coronary syndrome; **CI,** confidence interval; **HR,** hazard ratio; **MI,** myocardial infarction

Reference 1. Kang J, et al. *Circulation. Circulation*. 2023 Jan 10;147(2):108-117.

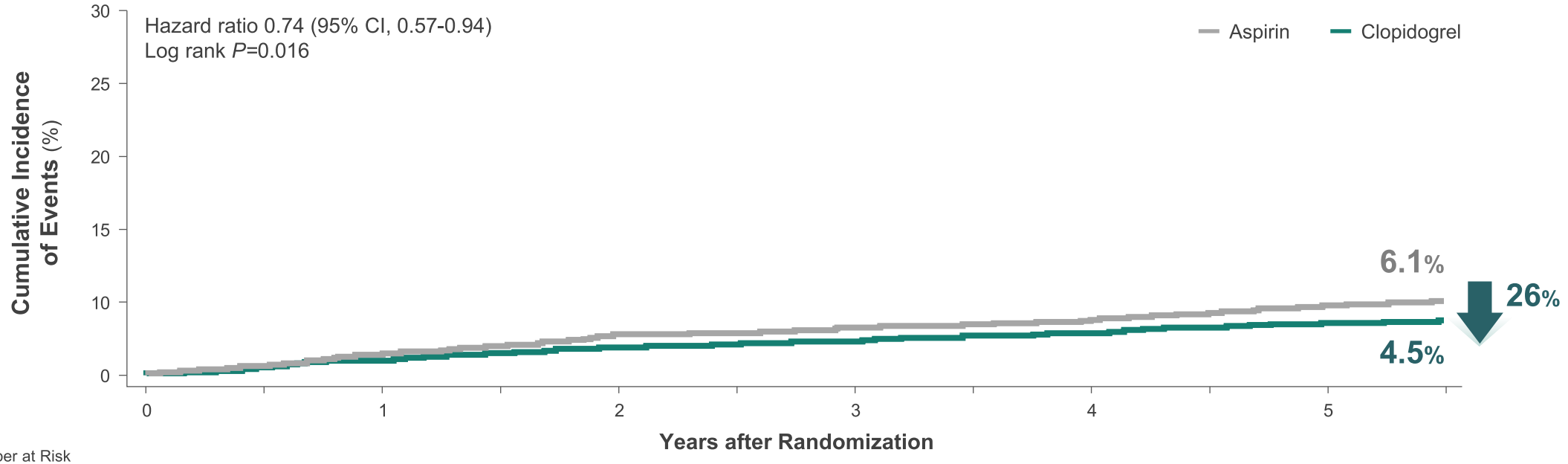
HOST-EXAM Extended Study

Any bleeding events

Any bleeding (BARC type ≥2) occurred in 110 patients (4.5%) **in the clopidogrel group and 140 patients** (6.1%) **in the aspirin group** (HR 0.74, 95% CI 0.57 to 0.94, p=0.016), **which was significantly low incidence of any bleeding events in clopidogrel group.**

The cumulative incidence of any bleeding events (BARC type ≥2)

(Cardiac death, non-fatal MI, ischaemic stroke, readmission due to ACS, or definite or probable stent thrombosis)



Number at Risk

Aspirin	2286	2229	2175	2123	1888	1395	1104
Clopidogrel	2431	2375	2323	2271	2028	1525	1238

ACS, acute coronary syndrome; **BARC,** Bleeding Academic Research Consortium; **CI,** confidence interval; **HR,** hazard ratio; **MI,** myocardial infarction

Reference 1. Kang J, et al. *Circulation*. *Circulation*. 2023 Jan 10;147(2):108-117.

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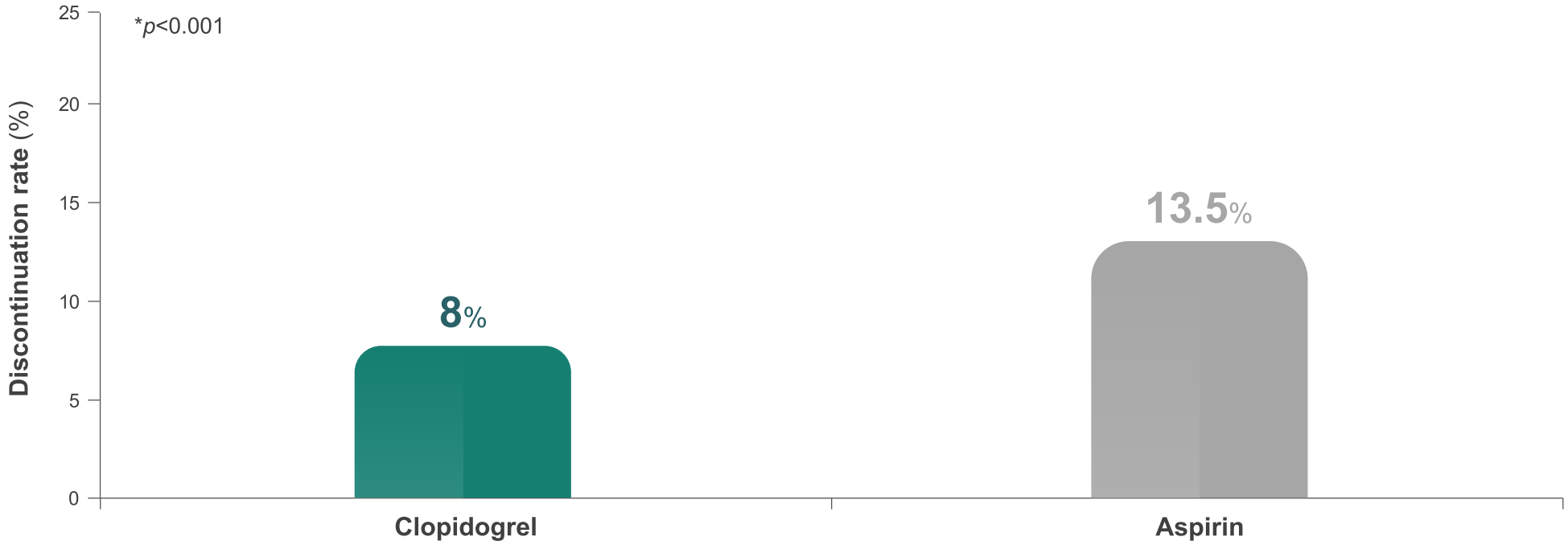
HOST-EXAM Extended Study

Discontinuation rate

- During the extended follow-up duration, the **discontinuation rate was significantly higher for aspirin monotherapy, implying a higher compliance of clopidogrel monotherapy**.

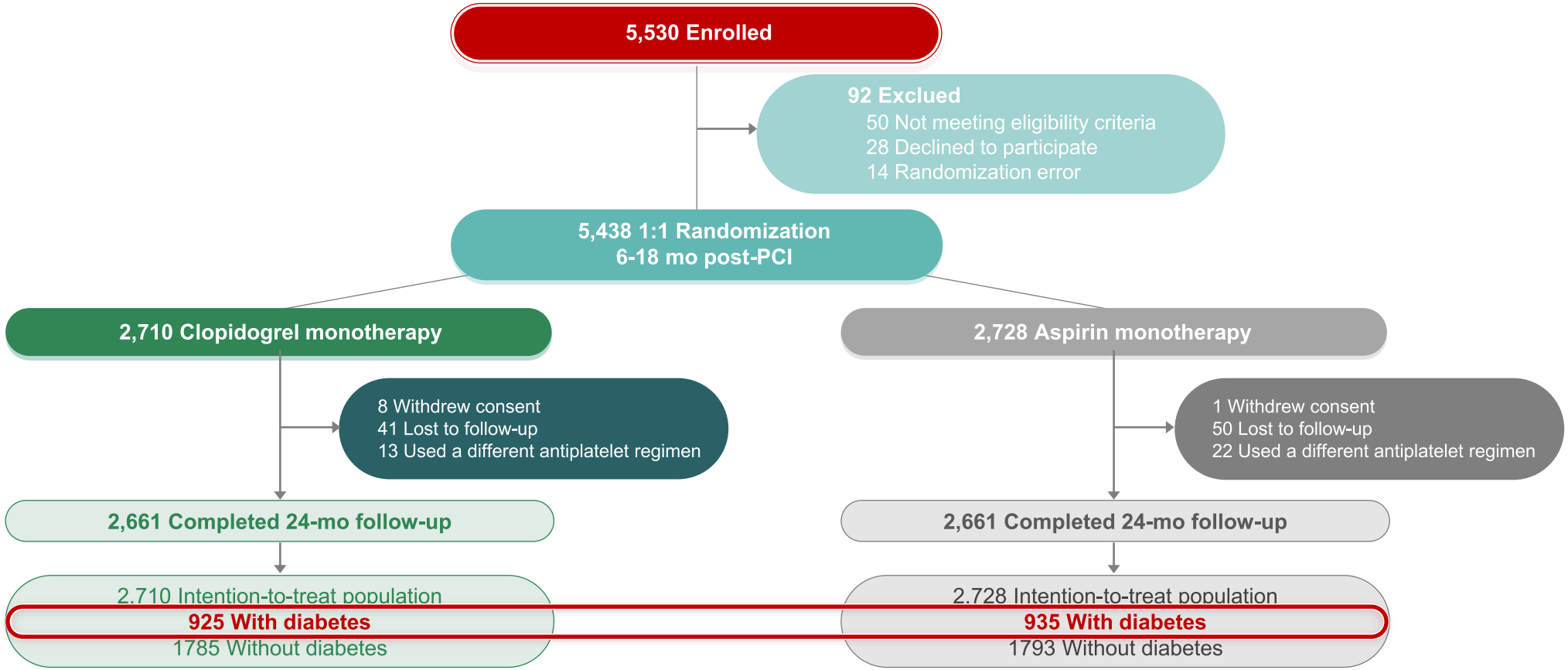
The Discontinuation rate



Reference 1. Kang J, et al. *Circulation*. Circulation. 2023 Jan 10;147(2):108-117.

HOST-EXAM post hoc analysis in DM

- Selecting the antiplatelet agents **in patients with diabetes after PCI** is especially important due to heightened ischemic risk in this population. A post hoc analysis of HOST-EXAM trial was conducted in subgroup of patients with diabetes.



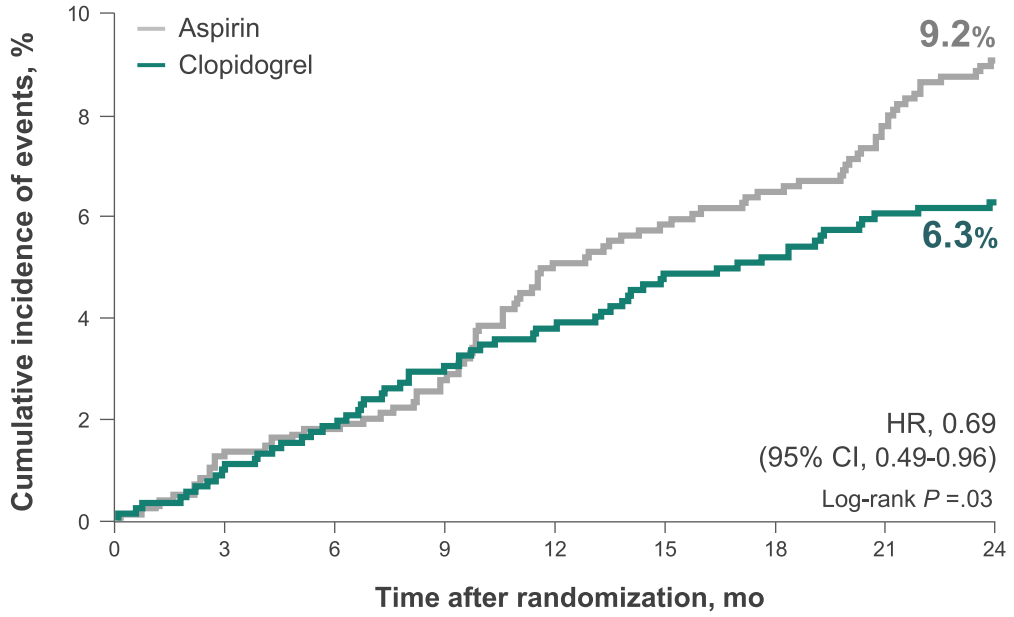
Reference 1. Rhee TM, et al. *JAMA Cardiol*. 2023;8(6):535-544.

HOST-EXAM post hoc analysis in DM

Primary composite outcome

Primary composite outcome
All-cause death, non-fatal MI, stroke, readmission due to ACS, or major bleeding (BARC ≥3)

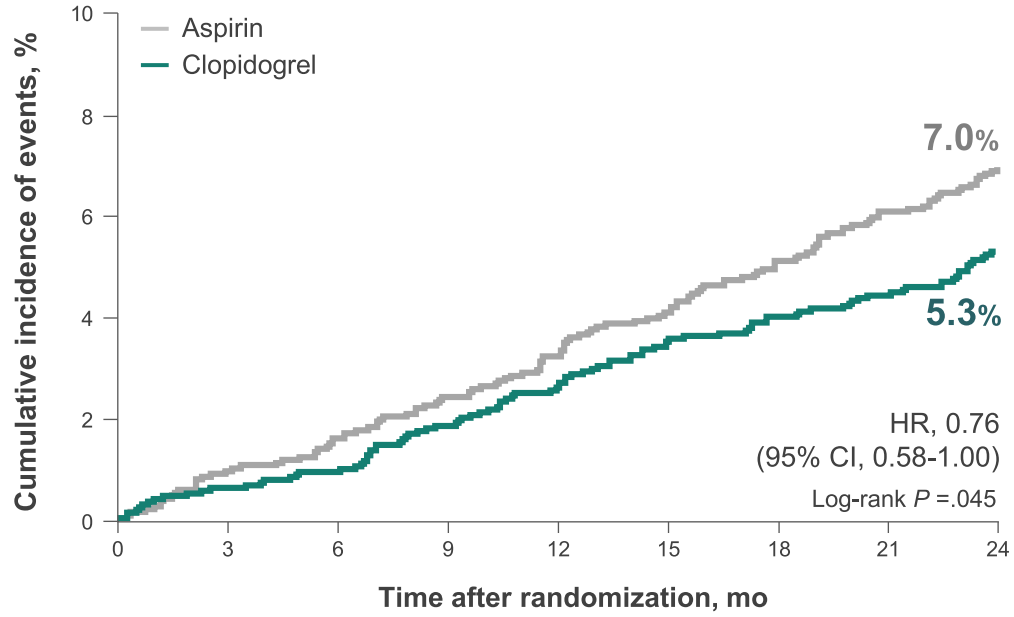
Primary composite end point :diabetes group



No. at Risk

Aspirin	935	913	908	897	871	862	855	845	827
Clopidogrel	925	907	900	889	879	869	863	849	845

Primary composite end point : no diabetes group



No. at Risk

Aspirin	1793	1764	1749	1732	1714	1693	1676	1648	1629
Clopidogrel	1785	1760	1754	1737	1718	1696	1686	1672	1655

P interaction=0.65

ACS, acute coronary syndrome, **BARC,** Bleeding Academic Research Consortium; **CI** confidence interval; **DM**, diabetes mellitus; **HR,** hazard ratio; **MI**, myocardial infarction.

Reference 1. Rhee TM, et al. *JAMA Cardiol*. 2023;8(6):535-544.

HOST-EXAM post hoc analysis in DM

Clinical outcomes

	Diabetes group				No diabetes group				*P* value for inter-action
	No.(%)				No.(%)				
	Clopidogrel (n = 925)	Aspirin (n = 925)	HR (95% CI)[a]	*P* value	Clopidogrel (n = 1785)	Aspirin (n = 1793)	HR (95% CI)[a]	*P* value	
Composite end point	58 (6.3)	84 (9.2)	0.69 (0.49-0.96)	0.03	94 (5.3)	123 (7.0)	0.76 (0.58-1.00)	.046	0.65
Primary[b]									
Thrombotic[c]	36 (4.0)	53 (5.8)	**0.68** (0.45-1.04)	**0.07**	63 (3.6)	93 (5.3)	0.68 (0.49-0.93)	0.02	0.99
Bleeding									
Any (BARC type 2, 3, or 5)	24 (2.7)	37 (4.1)	0.65 (0.39-1.09)	0.11	37 (2.1)	50 (2.8)	0.74 (0.48-1.13)	0.17	0.71
Major (BARC type 3 or 5)	14 (1.6)	25 (2.7)	**0.57** (0.29-1.09)	**0.09**	19 (1.1)	28 (1.6)	0.68 (0.38-1.22)	0.20	0.68
MACE[d]	28 (3.1)	50 (5.4)	0.56 (0.35-0.89)	0.01	55 (3.1)	58 (3.0)	1.04 (0.72-1.52)	0.83	0.04

[b]Primary composite outcome

All-cause death, non-fatal MI, stroke, readmission due to ACS, or major bleeding (BARC 3 or 5)

[c]Thrombotic composite outcome

Cardiac death, non-fatal MI, ischemic stroke, readmission due to ACS, or Stent thrombosis

[d]MACE

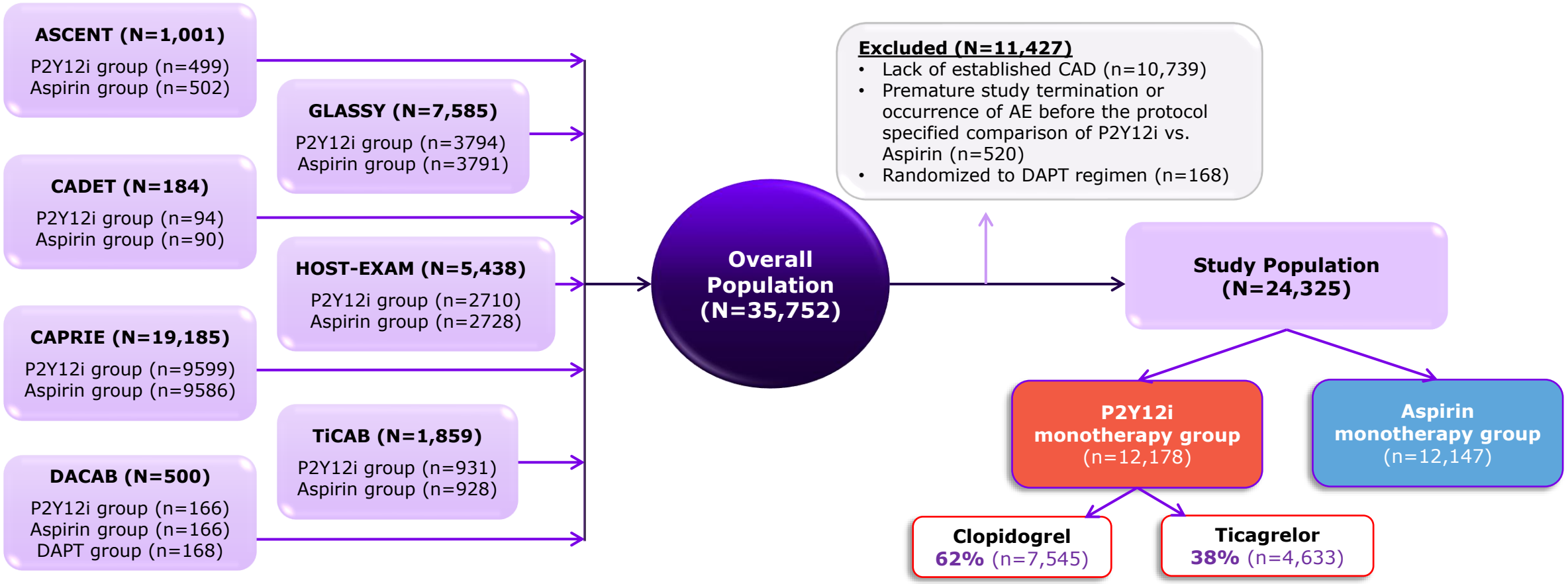
All-cause death, MI or stroke

ACS, acute coronary syndrome, **BARC,** Bleeding Academic Research Consortium; **CI** confidence interval; **DM**, diabetes mellitus; **HR,** hazard ratio; **MACE**, major adverse cardiovascular event; **MI**, myocardial infarction.

Reference 1. Rhee TM, et al. *JAMA Cardiol*. 2023;8(6):535-544.

PANTHER meta-analysis

A total of **2,748** unique citations were identified, of which 61 were judged potentially eligible by screening of titles and abstracts. After a full-text review, **7 randomized trials were identified as eligible for inclusion**



Reference 1. Gragnano F, et al. J Am Coll Cardiol. 2023;82(2):89-105.

PANTHER meta-analysis

Baseline characteristics were well balanced between the two groups (1)

Baseline characteristics, n (%)	N = 24,325	P2Y12 Inhibitor (n=12,178)	Aspirin (n=12,147)
Age (years), mean ± SD	15,879	64.3 ± 10.2	64.3 ± 10.3
Male, n (%)	24,325	9,538 (78.3)	9,499 (78.2)
Body mass index (kg/m^2), mean ± SD	15,330	26.9 ± 4.4	26.9 ± 4.3
Geographical region			
Asia		2,876 (23.6)	2,894 (23.8)
Europe		6,997 (57.5)	6,977 (57.4)
North America		2,305 (18.9)	2,276 (18.7)
Diabetes mellitus	24,132	3,036 (25.1)	3,004 (24.9)
Insulin-treated diabetes	15,325	404 (5.3)	428 (5.6)
Current cigarette smoker	24,314	3,161 (26.0)	3,250 (26.8)
Hypercholesterolemia	22,868	6,862 (59.9)	6,887 (60.3)
Hypertension	24,299	7,388 (60.7)	7,286 (60.0)
Liver disease	15,363	53 (0.7)	49 (0.6)
Peripheral artery disease	24,098	1,085 (9.0)	1,118 (9.3)
Previous myocardial infarction	24,285	6,839 (56.2)	6,798 (56.1)
Previous revascularization	24,135		
PCI		6,634 (54.9)	6,607 (54.8)
CABG		1,260 (10.4)	1,287 (10.7)
PCI and CABG		501 (4.1)	552 (4.6)
No revascularization		3,687 (30.5)	3,607 (29.9)

Reference 1. Gragnano F, et al. J Am Coll Cardiol. 2023;82(2):89-105.

PANTHER meta-analysis

Baseline characteristics were well balanced between the two groups (2)

Baseline characteristics, n (%)	N = 24,325	P2Y12 Inhibitor (n=12,178)	Aspirin (n=12,147)
Previous stroke	24,133	807 (6.7)	791 (6.6)
Previous bleeding	15,684	32 (0.4)	32 (0.4)
History of chronic kidney disease	15,678	870 (11.1)	849 (10.8)
Chronic lung disease	15,661	335 (4.3)	325 (4.1)
Clinical presentation	24,325		
Acute coronary syndrome		7,394 (60.7)	7,352 (60.5)
Chronic coronary syndrome		4,784 (39.3)	4,795 (39.5)
Type of P2Y12 inhibitor	24,325		
Clopidogrel		7,545 (62.0)	–
Ticagrelor		4,633 (38.0)	–
Aspirin dose*	24,325		
High dose		–	4,706 (38.7)
Low dose		–	7,441 (61.3)
Use of proton pump inhibitors, n(%)	24,141	2,866 (23.7)	2,895 (24.0)
Statins	15,850	7,057 (89.1)	7,061 (89.0)
Ejection fraction, mean ± SD	5,266	54.6 ± 10.9	55.1 ±10.8
PRECISE-DAPT score** mean ± SD	14,081	15.6 ± 9.9	15.5 ± 9.7
PRECISE-DAPT score ≥25	14,081	1,240 (17.6)	1,260 (17.9)

Reference 1. Gragnano F, et al. J Am Coll Cardiol. 2023;82(2):89-105.

PANTHER meta-analysis

Primary efficacy outcome

- Relative risk of the primary composite outcome (*composite of CV death, MI, and stroke*) was **reduced by 12%** in patients receiving a P2Y12 inhibitor monotherapy
- The median follow-up time was 493 days. NNT of 121 over 2 years follow-up

Figure. Kaplan-Meier curve for primary outcome (1-step meta-analysis)

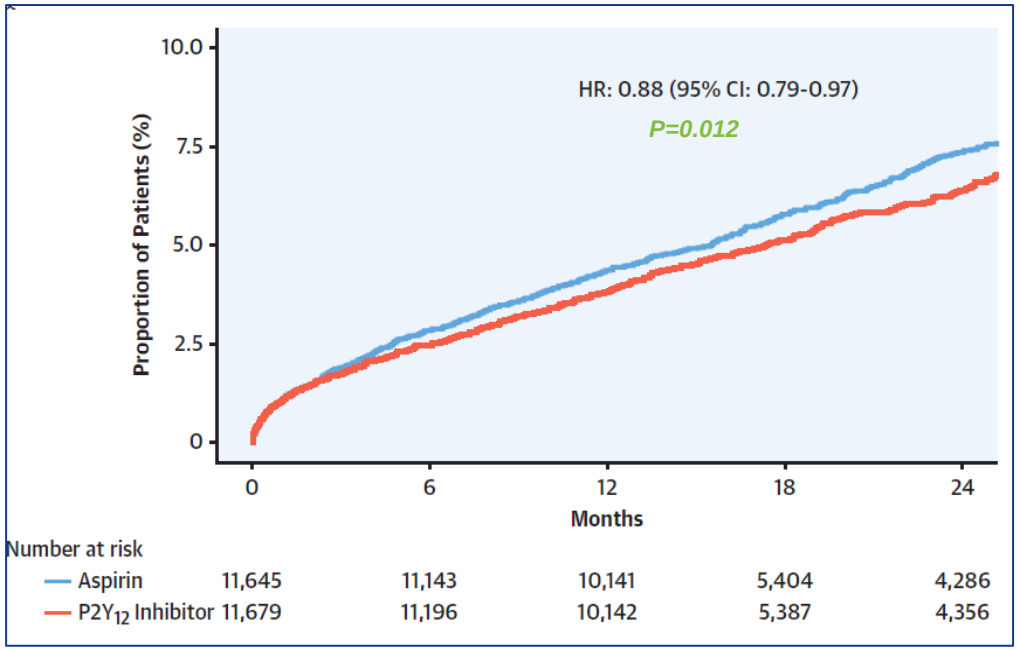
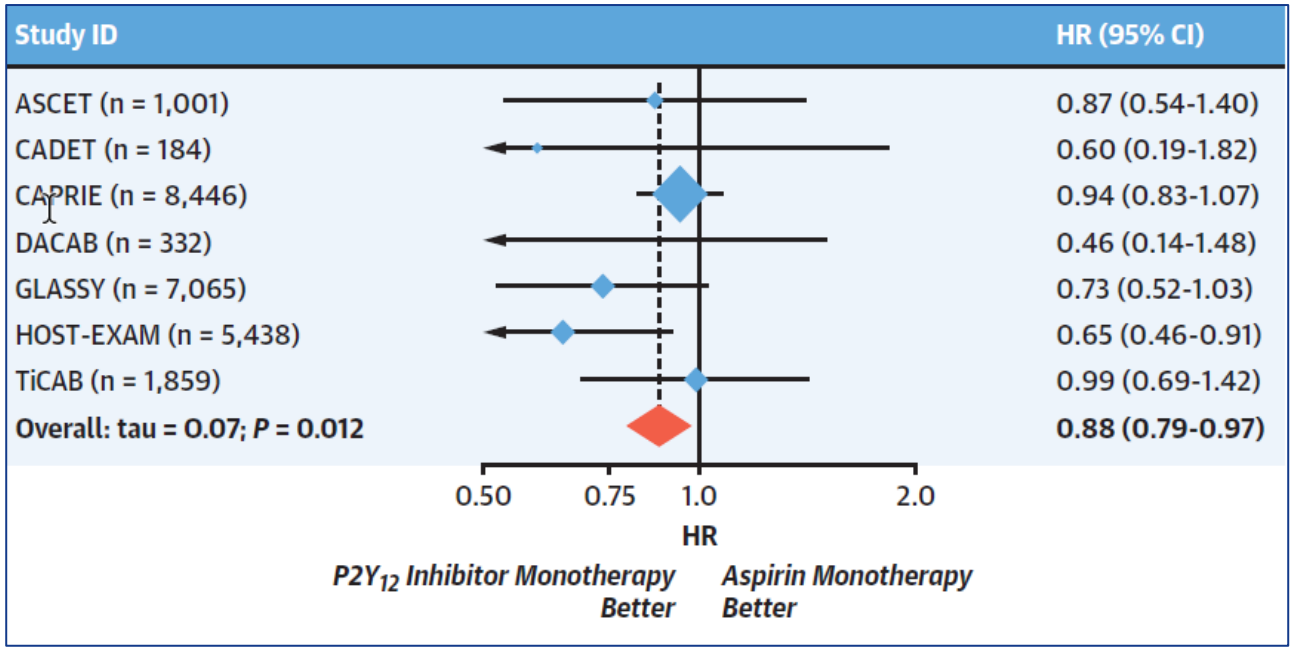


Figure. HRs for primary outcome (2-step meta-analysis)



*Composite of CV death, MI, and stroke.

ASCET, ASpirin non-responsiveness and Clopidogrel clinical Endpoint Trial; CADET, Clopidogrel and Aspirin: Determination of the Effects on Thrombogenicity; CAPRIE, Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events; CI, confidence interval; DACAB, Different Antiplatelet Therapy Strategy After Coronary Artery Bypass Graft Surgery; CV, cardiovascular; DAPT, dual antiplatelet therapy; GLASSY, GLOBAL LEADERS Adjudication Sub-Study; HOST-EXAM, Harmonizing Optimal Strategy for Treatment of coronary artery stenosis-Extended Antiplatelet Monotherapy; HR, Hazard ratio; MI, myocardial infarction; TiCAB, Ticagrelor in Coronary Artery Bypass.

Reference 1. Gragnano F, et al. J Am Coll Cardiol. 2023;82(2):89-105.

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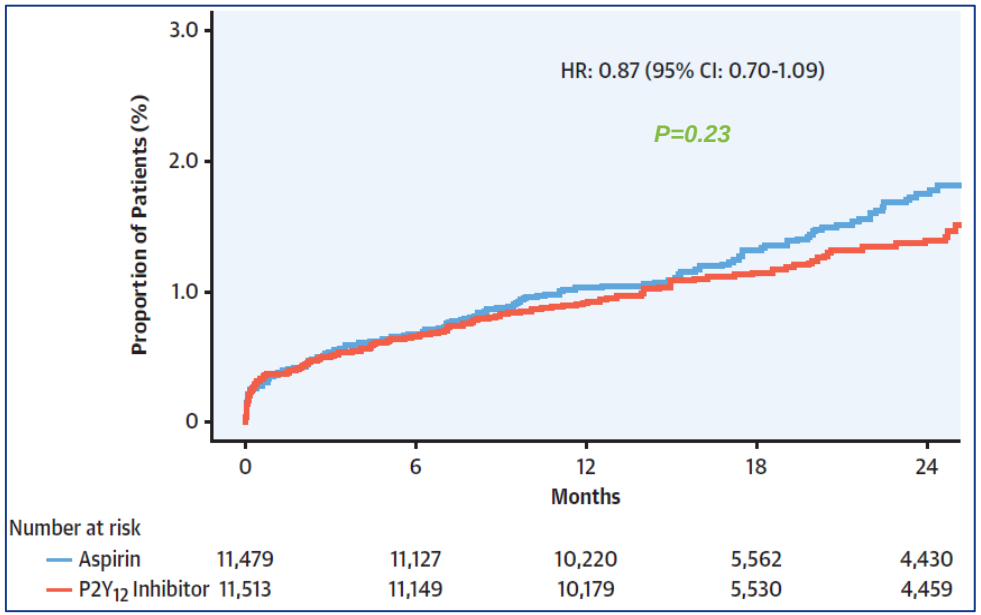
PANTHER meta-analysis

Major bleeding

Figure. Kaplan-Meier curve for major bleeding (1-step meta-analysis)



	$P2Y_{12}$ Inhibitor (n = 12,178)	Aspirin (n = 12,147)	HR (95% CI)	*P* Value
Major bleeding[b]	146 (0.76)	167 (0.87)	0.87 (0.70-1.09)	0.23
Major GI bleeding	31 (0.17)	46 (0.25)	0.67 (0.43-1.06)	0.089
Any GI bleeding	99 (0.52)	132 (0.69)	0.75 (0.57-0.97)	0.027
Any bleeding	646 (3.54)	587 (3.22)	1.10 (0.98-1.23)	0.10
Stroke				
Any	202 (1.06)	239 (1.25)	0.84 (0.70-1.02)	0.076
Ischemic	178 (0.98)	192 (1.06)	0.93 (0.75-1.13)	0.45
Hemorrhagic	13 (0.07)	30 (0.17)	0.43 (0.23-0.83)	0.012

Major bleeding was defined as Bleeding Academic Research Consortium type 3 or 5 where available, or Thrombolysis in myocardial infarction major or minor bleeding, or (if not available) using trial-specific definitions.
ASCET, ASpirin non-responsiveness and Clopidogrel clinical Endpoint Trial; CADET, Clopidogrel and Aspirin: Determination of the Effects on Thrombogenicity; CAPRIE, Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events; CI, confidence interval; DACAB, Different Antiplatelet Therapy Strategy After Coronary Artery Bypass Graft Surgery; DAPT, dual antiplatelet therapy; GLASSY, GLOBAL LEADERS Adjudication Sub-Study; HOST-EXAM, Harmonizing Optimal Strategy for Treatment of coronary artery stenosis-Extended Antiplatelet Monotherapy; HR, Hazard ratio; TiCAB, Ticagrelor in Coronary Artery Bypass.

Reference 1. Gragnano F, et al. J Am Coll Cardiol. 2023;82(2):89-105.

PANTHER meta-analysis

NACE

- NNT for NACE was 121 over 2 years follow-up

Figure. Kaplan-Meier curve for NACE* (1-step meta-analysis)

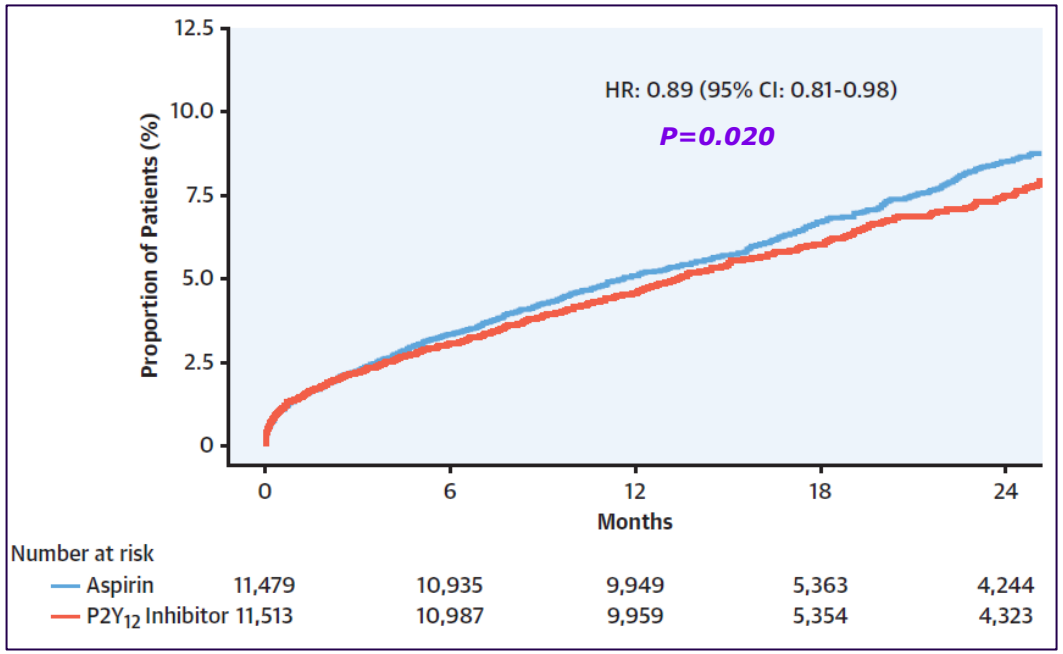
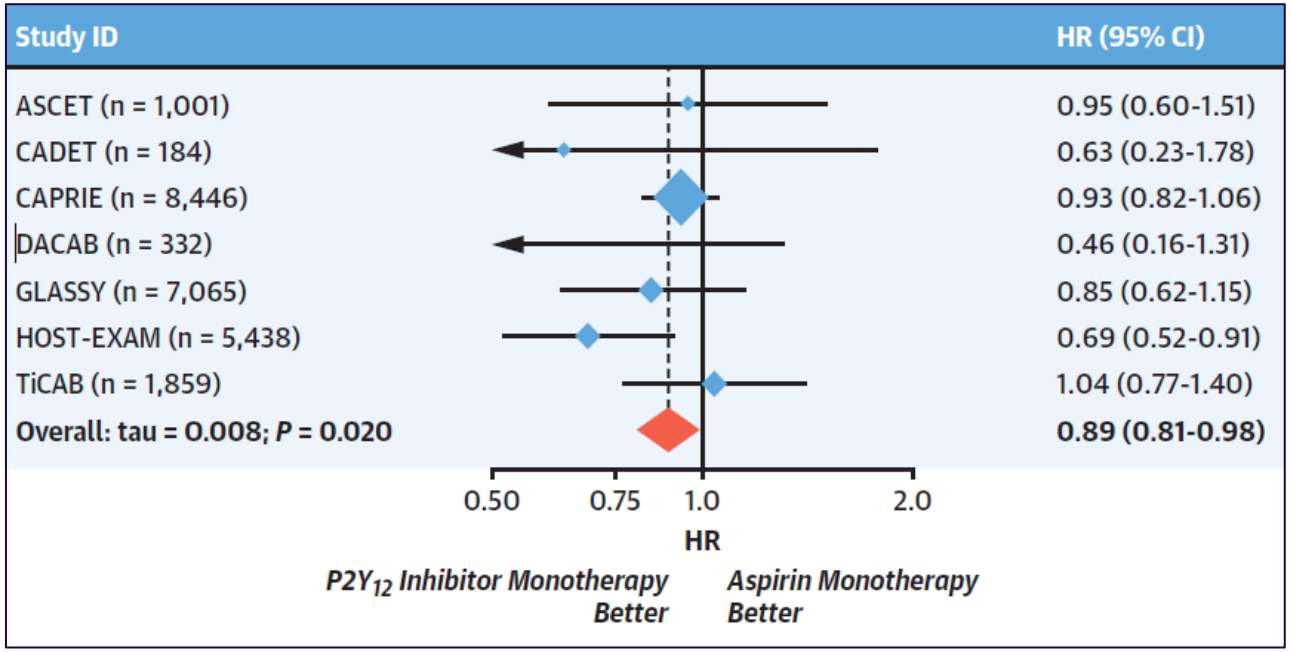


Figure. HRs for NACE* (2-step meta-analysis)



*NACE were defined as the composite of the primary endpoint and major bleeding.
ASCET, ASpirin non-responsiveness and Clopidogrel clinical Endpoint Trial; CADET, Clopidogrel and Aspirin: Determination of the Effects on Thrombogenicity; CAPRIE, Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events; CI, confidence interval; DACAB, Different Antiplatelet Therapy Strategy After Coronary Artery Bypass Graft Surgery; DAPT, dual antiplatelet therapy; GLASSY, GLOBAL LEADERS Adjudication Sub-Study; HOST-EXAM, Harmonizing Optimal Strategy for Treatment of coronary artery stenosis-Extended Antiplatelet Monotherapy; HR, Hazard ratio; NACE, net adverse clinical events; TiCAB, Ticagrelor in Coronary Artery Bypass.

Reference 1. Gragnano F, et al. J Am Coll Cardiol. 2023;82(2):89-105.

PANTHER meta-analysis

MI

- Significant **reduction of 23%** was observed in P2Y12 inhibitor monotherapy group relative to aspirin monotherapy
- NNT was 136 over 2 year follow-up

Figure. Kaplan-Meier curve for MI (1-step meta-analysis)

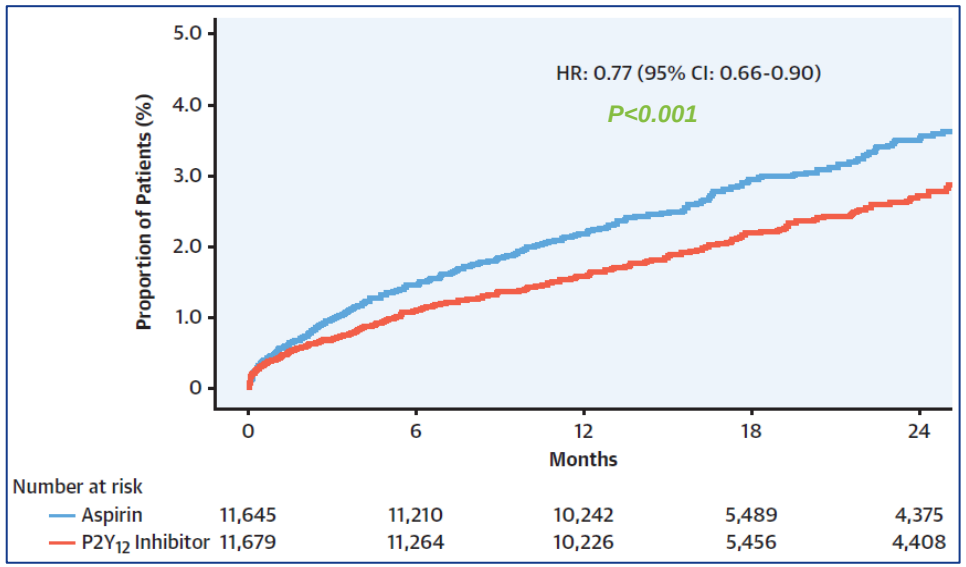
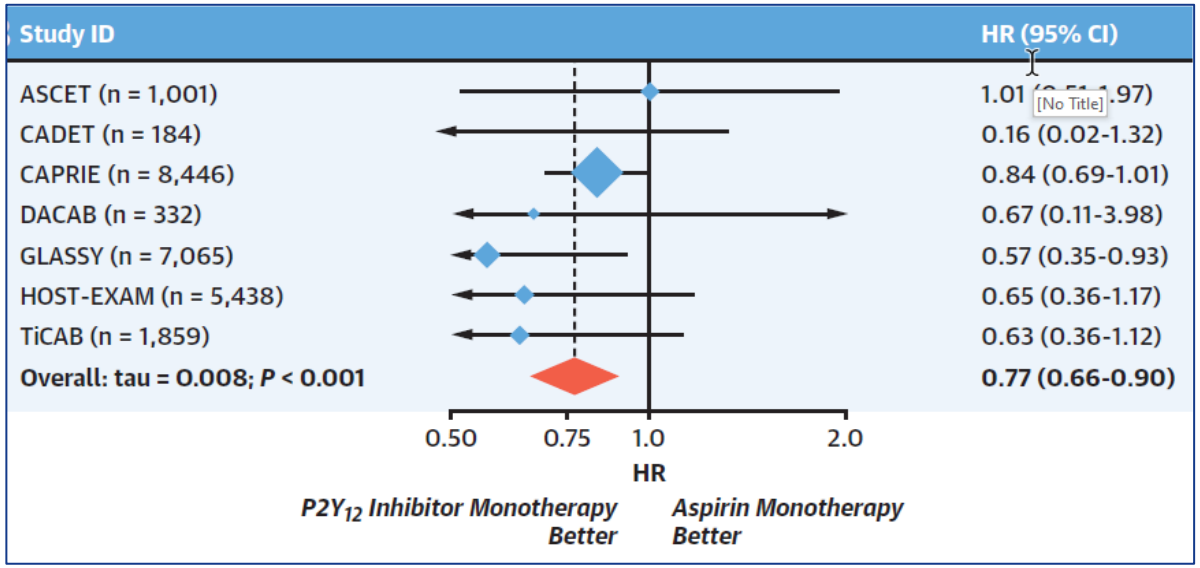


Figure. HRs for MI (2-step meta-analysis)



MI was defined according to the original definition used for event adjudication in each trial.
ASCET, ASpirin non-responsiveness and Clopidogrel clinical Endpoint Trial; CADET, Clopidogrel and Aspirin: Determination of the Effects on Thrombogenicity; CAPRIE, Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events; CI, confidence interval; DACAB, Different Antiplatelet Therapy Strategy After Coronary Artery Bypass Graft Surgery; DAPT, dual antiplatelet therapy; GLASSY, GLOBAL LEADERS Adjudication Sub-Study; HOST-EXAM, Harmonizing Optimal Strategy for Treatment of coronary artery stenosis-Extended Antiplatelet Monotherapy; HR, Hazard ratio; MI, myocardial infarction; TiCAB, Ticagrelor in Coronary Artery Bypass.

Reference 1. Gragnano F, et al. J Am Coll Cardiol. 2023;82(2):89-105.

PANTHER meta-analysis

Other secondary outcomes

- **Risk of stent thrombosis was significantly reduced by P2Y12 inhibitor monotherapy**
- **Stroke was not significantly reduced with P2Y12 inhibitor monotherapy,**
- **No difference was observed between the groups for risk of CV death and all-cause mortality**
- **Risk of GI bleeding was significantly lower with P2Y12 inhibitor compared to aspirin**

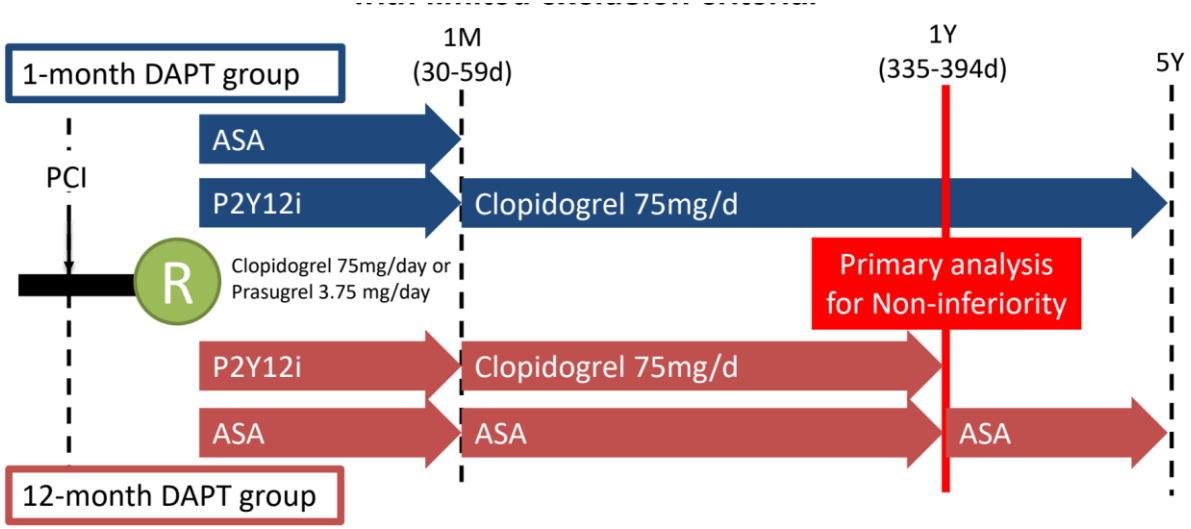
Other secondary endpoints 1-Stage Individual Participant Data Meta-Analysis

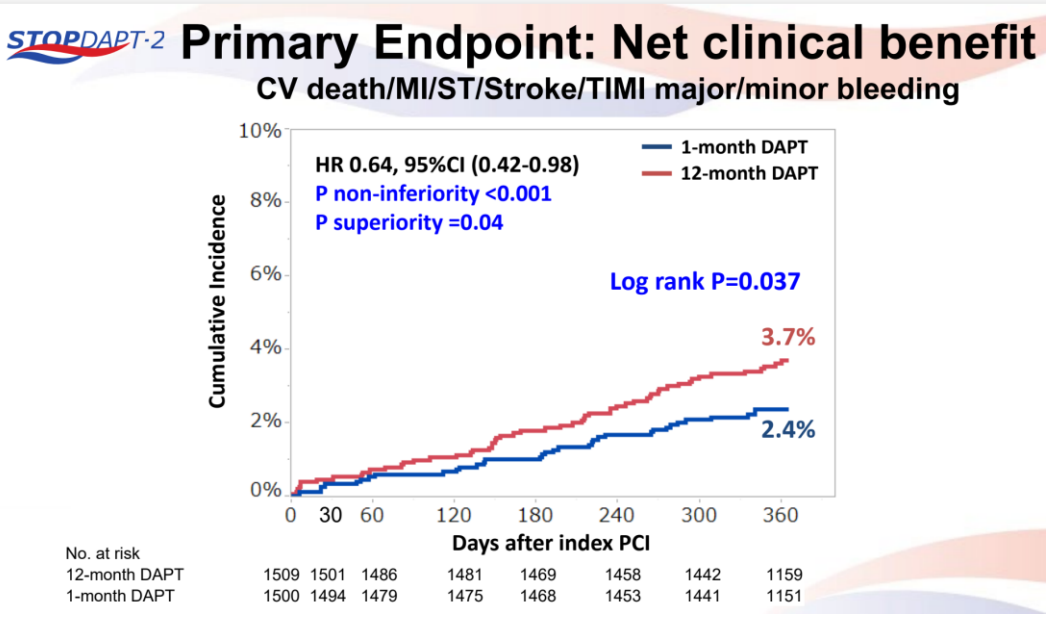
Other secondary endpoints	N	P2Y12 Inhibitor (n = 12,178)	Aspirin (n = 12,147)	HR (95% CI)	P Value
Stroke, n(%)					
Any	24,325	202 (1.06)	239 (1.25)	0.84 (0.70-1.02)	0.076
Ischemic	23,324	178 (0.98)	192 (1.06)	0.93 (0.75-1.13)	0.45
Hemorrhagic	23,324	13 (0.07)	30 (0.17)	0.43 (0.23-0.83)	0.012
Stent thrombosis, n(%)					
Definite	12,503	8 (0.09)	19 (0.21)	0.42 (0.19-0.97)	0.041
Probable	12,503	4 (0.04)	7 (0.08)	0.58 (0.17-1.97)	0.38
Definite or probable	12,503	12 (0.13)	26 (0.28)	0.46 (0.23-0.92)	0.028
Major bleeding	24,325	146 (0.76)	167 (0.87)	0.87 (0.70-1.09)	0.23
Major GI bleeding	23,324	31 (0.17)	46 (0.25)	0.67 (0.43-1.06)	0.089
Any GI bleeding	23,324	99 (0.52)	132 (0.69)	0.75 (0.57-0.97)	0.027
Any bleeding	24,325	646 (3.54)	587 (3.22)	1.10 (0.98-1.23)	0.10
Net adverse clinical events	24,325	785 (4.19)	874 (4.68)	0.89 (0.81-0.98)	0.020

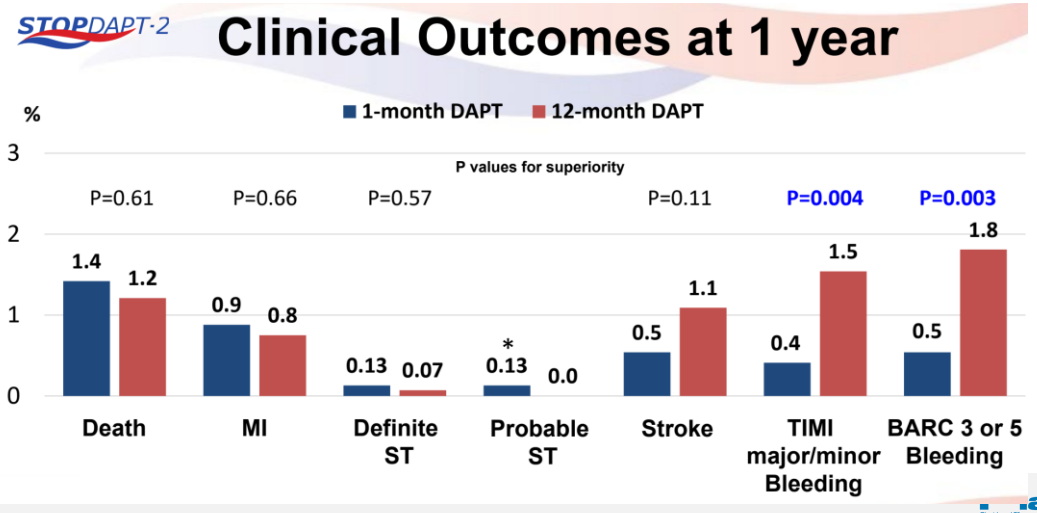
Reference 1. Gragnano F, et al. J Am Coll Cardiol. 2023;82(2):89-105.

STOPDAPT-2: 1M DAPT vs. 12M DAPT

1-month DAPT followed by clopidogrel monotherapy as compared with the standard 12-month DAPT with aspirin and clopidogrel



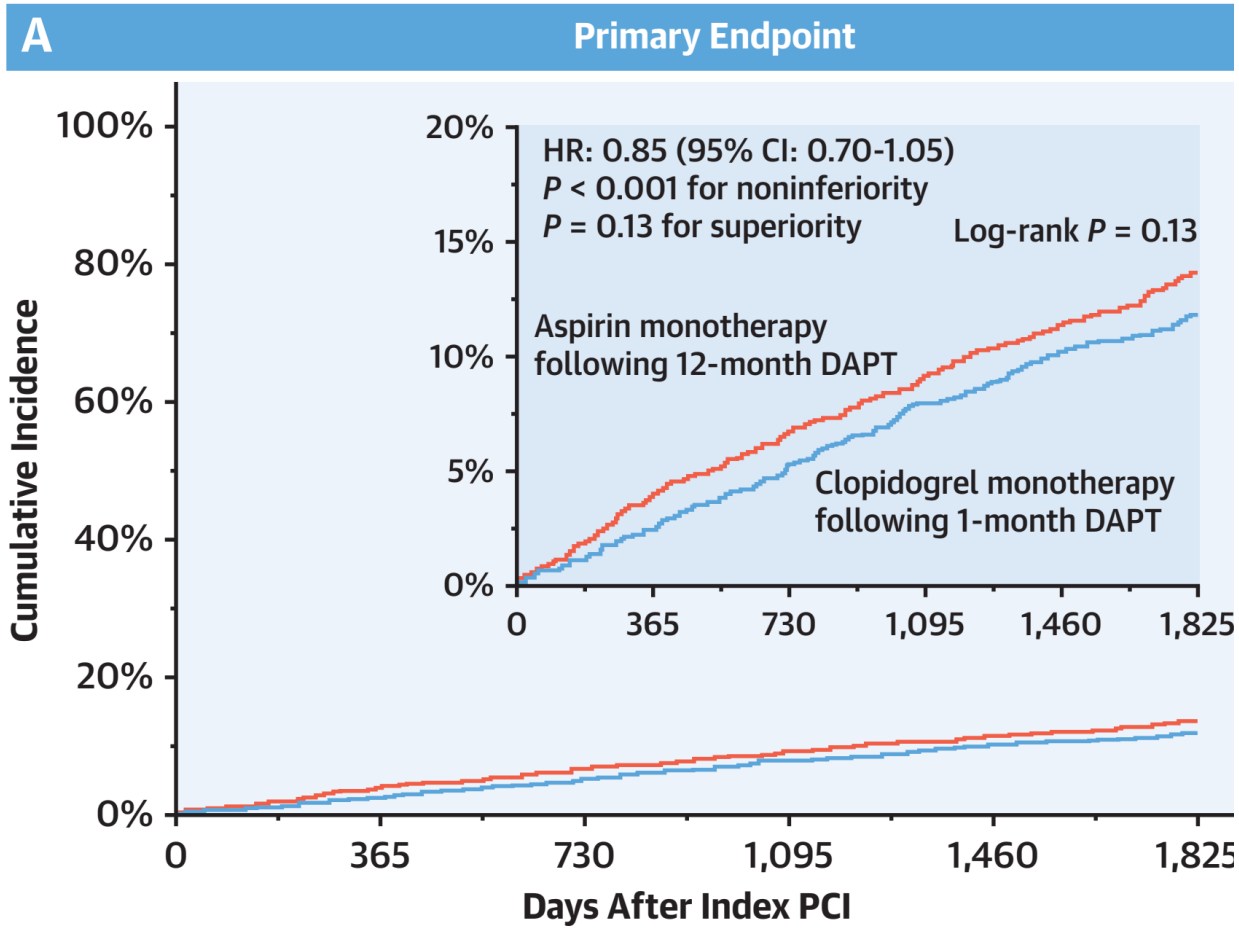


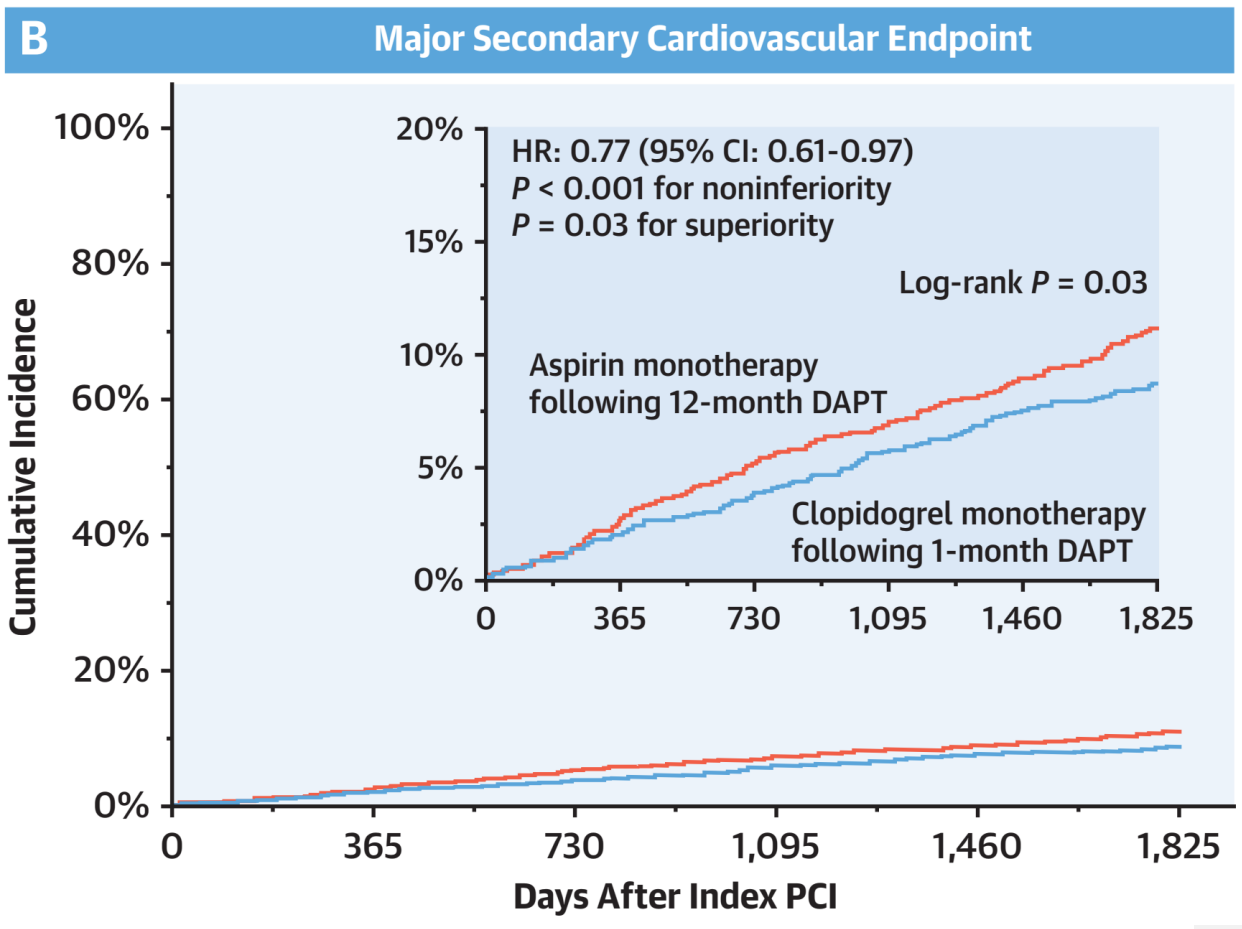


Reference 1. Watanabe H, et al Presented at ACC 2019

STOPDAPT-2: 5 year follow-up

5-Year Time-to-Event Curves for the Primary and Major Secondary Endpoints

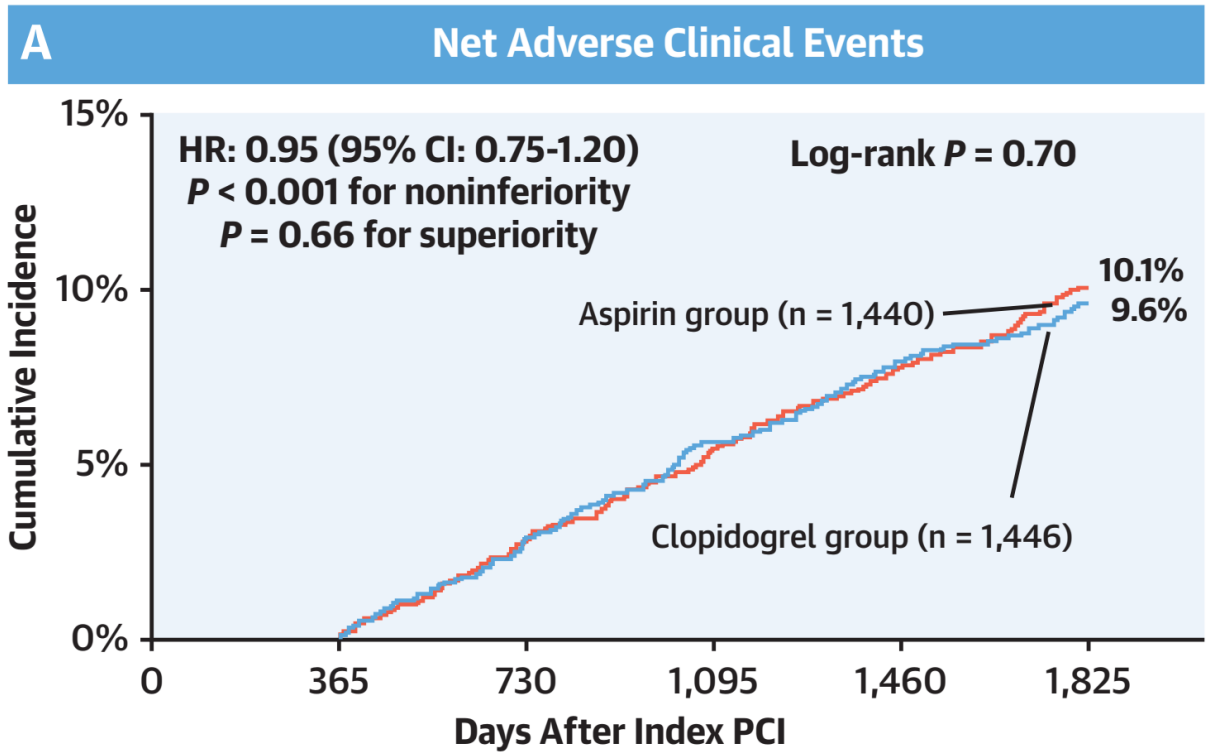


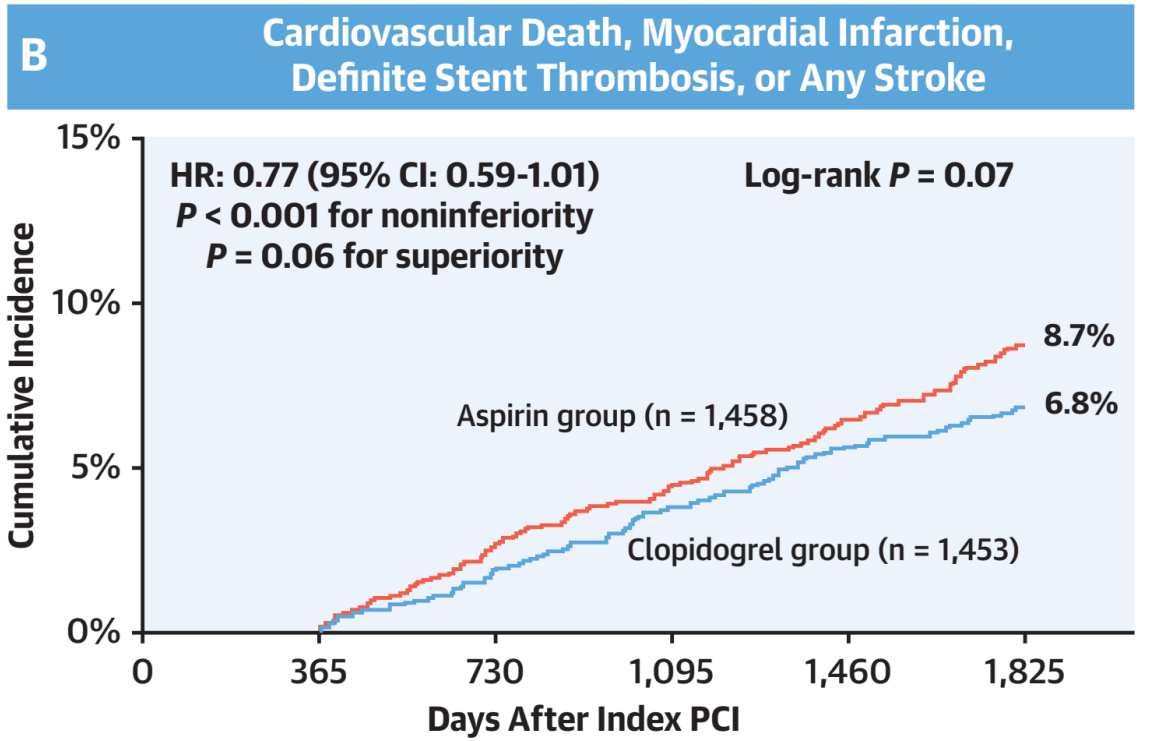


Reference 1. Watanabe H, et al. J Am Coll Cardiol 2024;83:17–31

STOPDAPT-2: 5 year follow-up

Time-to-Event Curves for the Landmark Analysis Beyond 1 Year

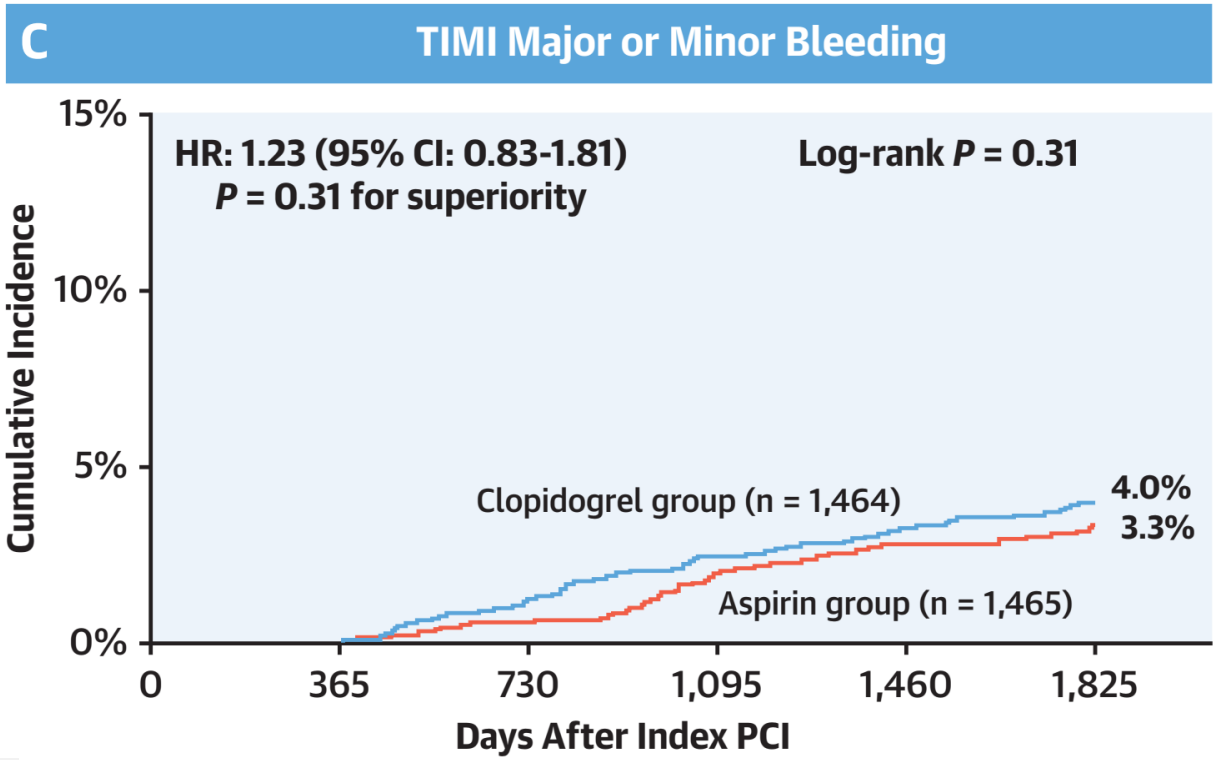




Reference 1. Watanabe H, et al. J Am Coll Cardiol 2024;83:17–31

STOPDAPT-2: 5 year follow-up

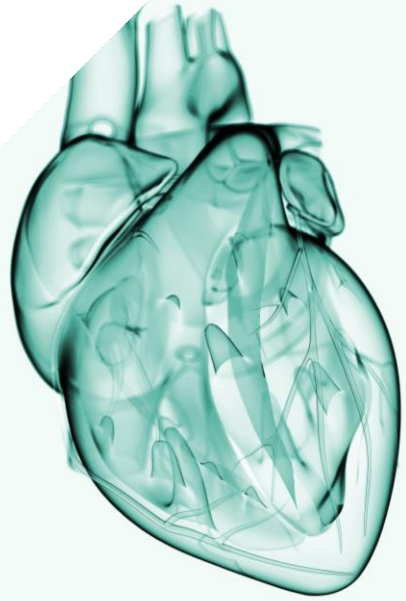
Time-to-Event Curves for the Landmark Analysis Beyond 1 Year



One of the reasons for the numeric increase in major bleeding with clopidogrel monotherapy relative to aspirin monotherapy in the present study might be related to the high prevalence of PPI use (79%), whereas the prescription rate of PPIs in HOST-EXAM was only 11%.[14] The prescription rate of PPIs during follow-up could be lower in the clopidogrel group than in the aspirin group, because physicians might discontinue PPIs at the time of or shortly after the discontinuation of aspirin, which

Reference 1. Watanabe H, et al. J Am Coll Cardiol 2024;83:17–31

Contents



Summary

- Aspirin has been considered the standard of care for maintenance therapy in practice guidelines, but recent studies suggest a potential advantage of clopidogrel over aspirin.
- In particular, the studies have shown a benefit in terms of ischemic risk reduction, but the benefit in terms of bleeding risk is inconclusive.
- Future research may help to determine whether certain factors such as ethnic differences or the use of PPIs play a role in the relative risk of bleeding with clopidogrel versus aspirin as maintenance therapy.