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Clopidogrel versus Aspirin Monotherapy in Patients with High Ischemic Risk after PCI : SMART-CHOICE 3 Trial

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On behalf of SMART-CHOICE 3 Investigators

AMERICAN COLLEGE of CARDIOLOGY

Background (I)

- Standard practice has been to recommend indefinite aspirin monotherapy following dual antiplatelet therapy (DAPT) for the prevention of subsequent cardiovascular events among patients undergoing percutaneous coronary intervention (PCI).
- However, data supporting the use of aspirin as a single antiplatelet therapy after DAPT have been debated, and clopidogrel has been proposed as a possibly superior alternative to aspirin.

2024 ESC Guidelines for the management of chronic coronary syndromes

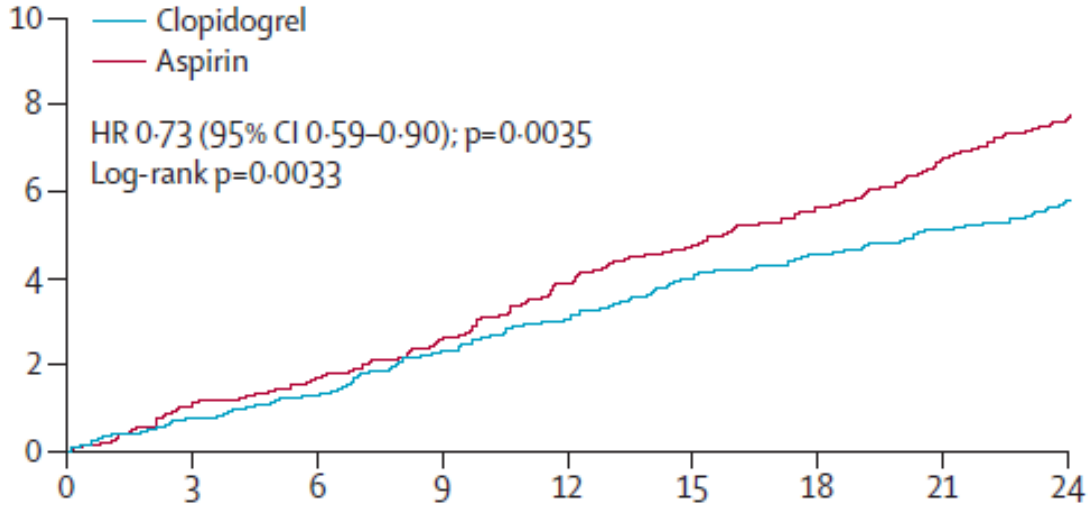
Recommendations	Class[a]	Level[b]
Long-term antithrombotic therapy in patients with chronic coronary syndrome and no clear indication for oral anticoagulation		
In CCS patients with a prior MI or remote PCI, aspirin 75–100 mg daily is recommended lifelong after an initial period of DAPT.[558,559]	I	A
In CCS patients with a prior MI or remote PCI, clopidogrel 75 mg daily is recommended as a safe and effective alternative to aspirin monotherapy.[562,564–566,649]	I	A

Background (II)

HOST-EXAM Trial

Lancet 2021; 397: 2487–96

Primary endpoint: all-cause mortality, MI, stroke, readmission due to ACS, major bleeding



- A trial with an adequate sample size comparing clopidogrel with aspirin, focusing solely on a strict endpoint of hard events, is needed.
- Moreover, targeting patients with a higher risk profile than those enrolled in the previous trial may provide more robust evidence for the superiority of clopidogrel over aspirin and help identify the patients who would benefit the most.

Study Objective

- To ascertain the efficacy and safety of clopidogrel monotherapy compared with aspirin monotherapy beyond the standard duration of DAPT after PCI in patients at high risk of recurrent ischemic events

Working Hypothesis

Clopidogrel monotherapy would be superior to aspirin monotherapy as a long-term maintenance treatment after PCI in preventing recurrent ischemic events.

Study Design

SMART-CHOICE 3 (ClinicalTrials.gov, NCT04418479)

An investigator-initiated, randomized, open-label, multicenter trial at 26 sites in South Korea

5,000 Patients Being Treated with Standard Duration of DAPT at High Risk* of Recurrent Ischemic Events After PCI with DES

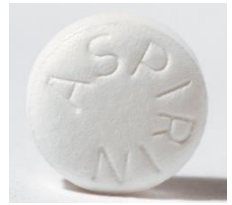
*Previous MI, medication-treated diabetes, complex PCI

Randomization (1:1)
Treatment Strategy of Antiplatelet Monotherapy

Stratified by clinical presentation at the index PCI and participating center

Clopidogrel Monotherapy
N = 2,500

Aspirin Monotherapy
N = 2,500



Enrollment Criteria

INCLUSION

1. Patients were aged 19 years or older.
2. Patients who had undergone successful PCI with DESs
3. Patients who had received a standard duration of DAPT
   - ≥12 months for MI and ≥6 months for any other indication
4. Patients who had no cardiovascular events after the index PCI
5. Patients who at least clinical characteristic (previous MI or medication-treated diabetes) or one complex coronary artery lesion characteristic
   - True bifurcation lesion (Medina 1,1,1/1,0,1/0,1,1) with side branch ≥2.5mm
   - Chronic total occlusion (≥3 months) as target lesion
   - Unprotected LM disease PCI (LM ostium, body, distal LM bifurcation including non-true bifurcation)
   - Long coronary lesions (implanted stent ≥38 mm in length)
   - Multi-vessel PCI (≥2 vessels treated at one PCI session)
   - Multiple stents needed (≥3 more stent per patient)
   - In-stent restenosis lesion as target lesion
   - Severely calcified lesion (encircling calcium in angiography)
   - Ostial coronary lesion (LAD, LCX, RCA)

KEY EXCLUSION

1. Ongoing long-term treatment with oral anticoagulants;
2. Need of DAPT for any reason other than coronary artery disease;
3. Use of single antiplatelet therapy at screening
4. Contraindications to aspirin or clopidogrel
5. Pregnancy or breast feeding
6. Non-cardiac co-morbid conditions are present with life expectancy <2 year or that may result in protocol non-compliance (per site investigator's medical judgment)

Study Organization

Principal Investigator	Joo-Yong Hahn
Steering Committee	Joo-Yong Hahn, Young Bin Song, Kyeong Ho Yun, Jang-Whan Bae, Cheol Whan Lee, Kiyuk Chang, Hyun-Jong Lee, Jin-Ok Jeong
Data Safety and Monitoring Board	Jun-Hee Lee, Sun Woo Kim, So Ree Kim
Clinical Event Adjudication Committee	Sang-Ho Jo, Woo Jin Jang, Hyun Sung Joh
Data Coordination and Management	Clinical Research Institute, Academic-Clinical Research Operation Team, Samsung Medical Center
Sponsor	Dong-A ST

Study Endpoints

Primary Endpoint

- **Major adverse cardiac and cerebrovascular events (MACCE)**
  - A composite of death from any cause, myocardial infarction, or stroke

Secondary Endpoints

- Death from any cause
- Myocardial infarction (4th Universal Definition)
- Stroke
- Definite or probable stent thrombosis (ARC criteria)
- Death from cardiovascular cause
- Death from cardiovascular cause, MI, or stroke
- Bleeding (BARC type 2, 3, or 5)
- Major bleeding (BARC type 3 or 5)
- Upper gastrointestinal clinical event
- Gastrointestinal ulcer or bleeding*
- Net adverse clinical events (MACCE + major bleeding)
- Any revascularization

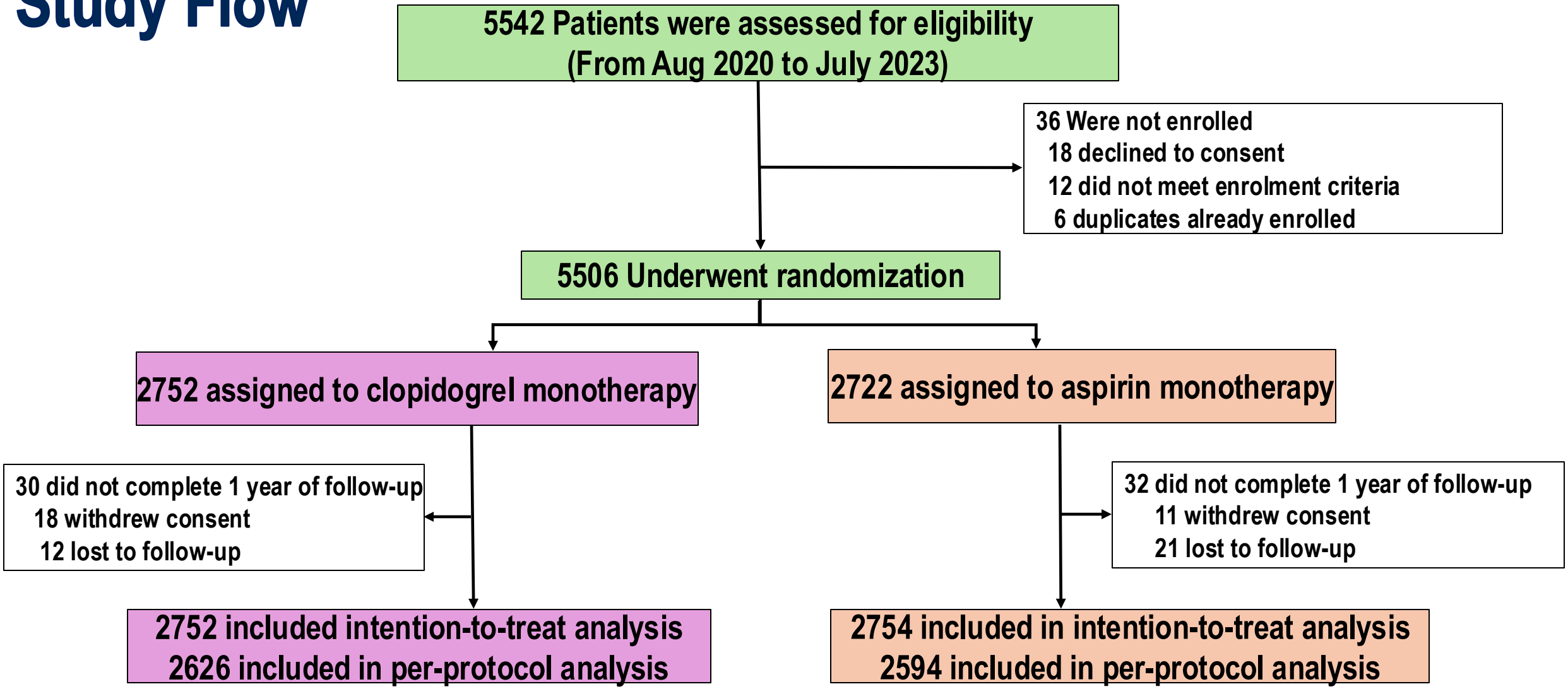
*Composite of overt bleeding of gastroduodenal origin, overt upper gastrointestinal bleeding of unknown origin, occult gastrointestinal bleeding with a documented decrease in hemoglobin concentration of at least 2 g/dL, symptomatic gastroduodenal ulcer or at least five erosions, symptomatic gastro-esophageal reflux disease, upper gastrointestinal obstruction, or perforation

Sample Size Calculation and Statistical Analyses

- Expected annual event rate of the primary end point
  - 4.0% in the aspirin group
  - 3.0% in the clopidogrel group (25% relative risk reduction)
- Accrual time – 3 years
- Additional follow-up time – 1 year after last patient enrollment
- 1:1 randomization
- A total of 5,000 patients would provide a statistical power of 82% with significance level of 0.05 (2-sided).

- When the original target sample size of 5000 patients was reached ahead of the planned accrual period, we decided to continue enrolling patients until the end of the planned recruitment period (ie, a 3-year accrual period).

Study Flow


5542 Patients were assessed for eligibility
(From Aug 2020 to July 2023)
36 Were not enrolled
18 declined to consent
12 did not meet enrolment criteria
6 duplicates already enrolled
5506 Underwent randomization
2752 assigned to clopidogrel monotherapy
2722 assigned to aspirin monotherapy
30 did not complete 1 year of follow-up
18 withdrew consent
12 lost to follow-up
32 did not complete 1 year of follow-up
11 withdrew consent
21 lost to follow-up
2752 included intention-to-treat analysis
2626 included in per-protocol analysis
2754 included in intention-to-treat analysis
2594 included in per-protocol analysis

Protocol Deviations

	Patients (%)
Clopidogrel Monotherapy	N=2752
No protocol violation	2626 (95·4%)
Patient wanted	7 (0·3%)
Judgement by the clinician	32 (1·2%)
Prescription error	0 (0%)
Received other devices (not drug-eluting stent)	87 (3·1%)
Aspirin Monotherapy	N=2754
No protocol violation	2594 (94·2%)
Patient wanted	7 (0·3%)
Judgement by the clinician	64 (2·3%)
Prescription error	4 (0·1%)
Received other devices (not drug-eluting stent)	85 (3·1%)

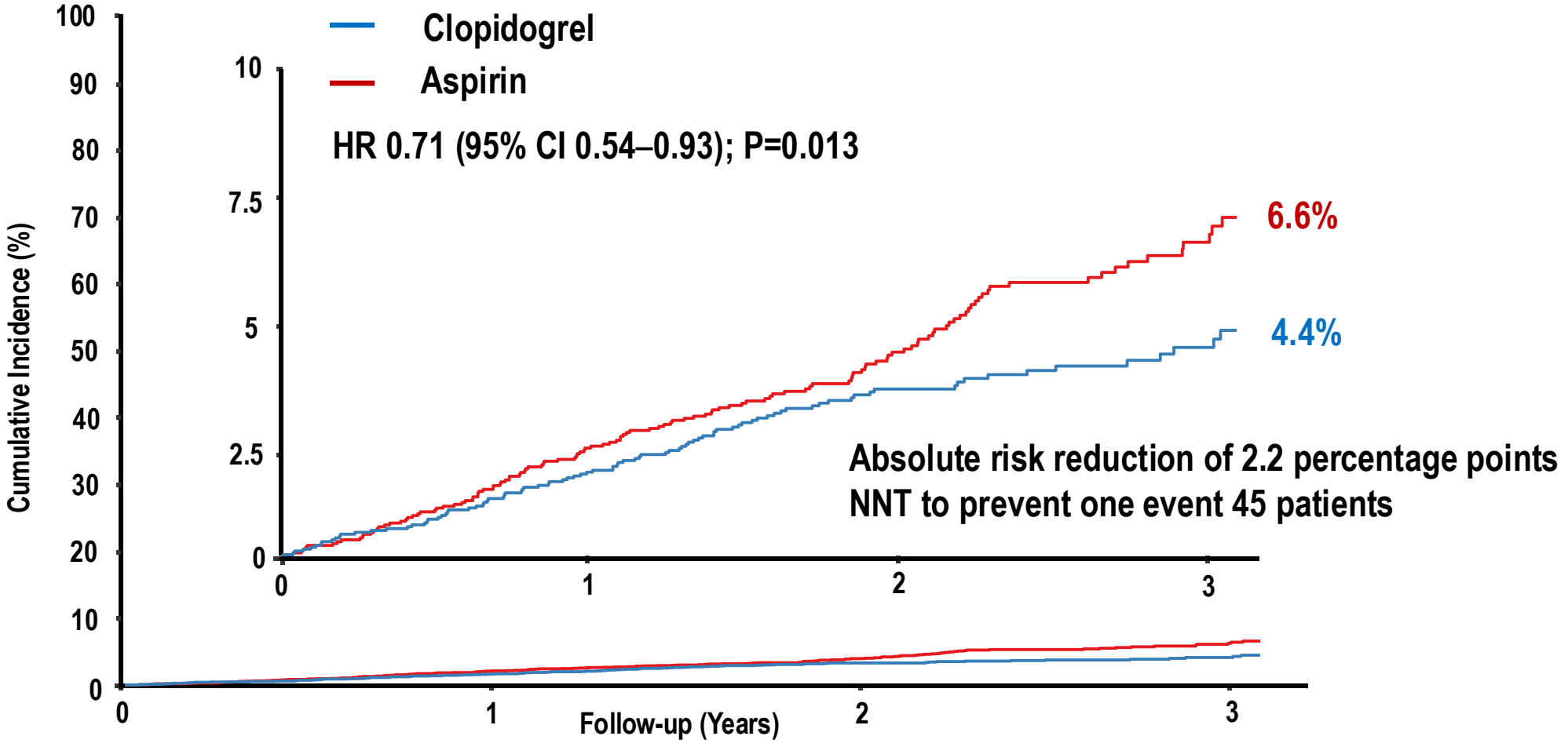
Baseline Patient Characteristics (I)

	Clopidogrel group (n=2752)	Aspirin group (n=2754)
Age, years	66·0 (58·0–73·0)	65·0 (58·0–73·0)
Women	512 (18·6%)	490 (17·8%)
Enrolment criteria		
Previous myocardial infarction	1283 (46·6%)	1269 (46·1%)
Medication-treated diabetes	1039 (37·8%)	1050 (38·1%)
Complex PCI	2113 (76·8%)	2072 (75·2%)
BMI, kg/m²	24·9 (23·0–27·0)	24·8 (23·1–26·9)
Hypertension	1756 (63·8%)	1690 (61·4%)
Dyslipidaemia	1626 (59·1%)	1604 (58·2%)
Current smoking	448 (16·3%)	488 (17·7%)
Chronic kidney disease	242 (8·8%)	260 (9·4%)
Previous stroke	76 (2·8%)	66 (2·4%)
Peripheral vascular disease	23 (0·8%)	22 (0·8%)
Previous history of major bleeding	15 (0·5%)	21 (0·8%)
Left ventricular ejection fraction, %	60·0% (55·0–65·0)	60·0% (55·0–65·0)

Baseline Patient Characteristics (II)

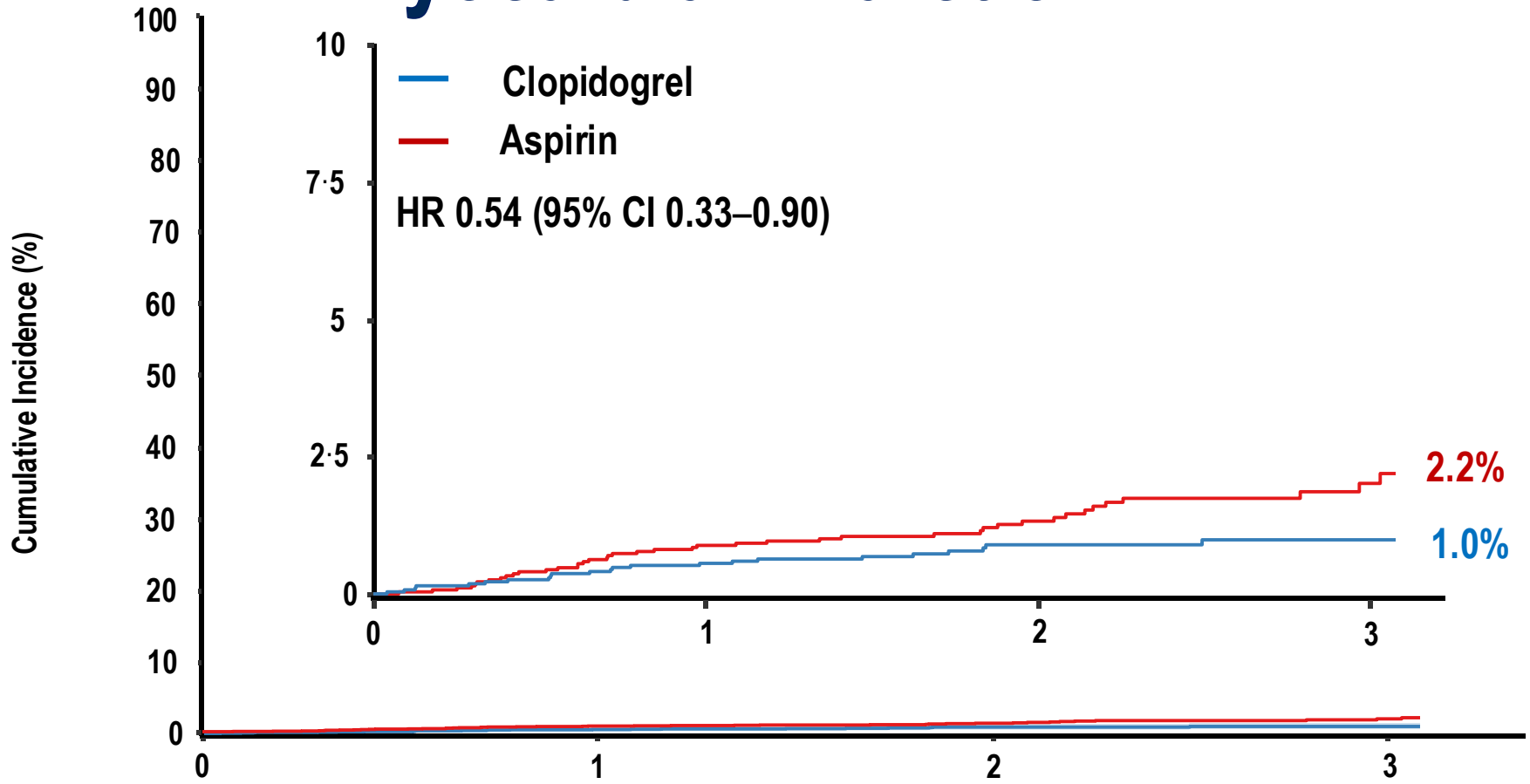
	Clopidogrel group (n=2752)	Aspirin group (n=2754)
High bleeding risk defined by ARC	427 (15·5%)	448 (16·3%)
Time from PCI to randomisation, months	17·3 (12·7–36·1)	17·7 (12·6–36·2)
DAPT regimen before randomisation		
Aspirin plus clopidogrel	1702 (61·8%)	1729 (62·8%)
Aspirin plus prasugrel	304 (11·0%)	341 (12·4%)
Aspirin plus ticagrelor	746 (27·1%)	684 (24·8%)
Medications at randomisation		
Statin	2708 (98·4%)	2714 (98·5%)
Ezetimibe	1717 (62·4%)	1730 (62·8%)
β blocker	1524 (55·4%)	1565 (56·8%)
ACEI or ARB	1755 (63·8%)	1762 (64·0%)
Gastrointestinal protection medication	792 (28·8%)	844 (30·6%)
Proton-pump inhibitor	545 (19·8%)	589 (21·4%)
Potassium-competitive acid blocker	100 (3·6%)	115 (4·2%)
Histamine-2 receptor blocker or others	153 (5·6%)	150 (5·4%)

Primary Endpoint: MACCE



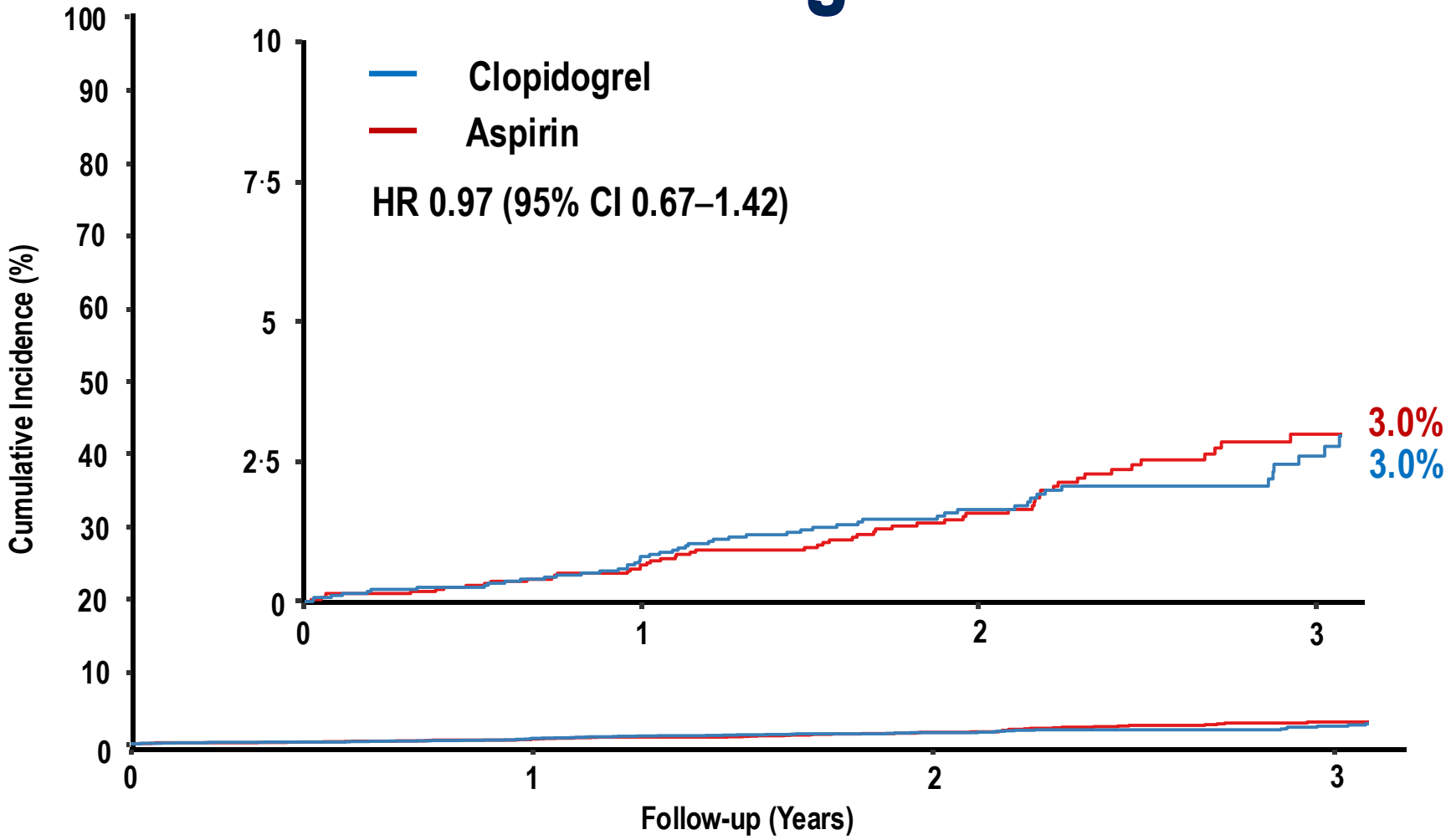
Number at Risk (number censored)				
Aspirin	2754	2642	1573	597
Clopidogrel	2752	2662	1583	602

Myocardial Infarction



Number at Risk (number censored)				
Aspirin	2754	2656	1585	601
Clopidogrel	2752	2668	1593	607

Bleeding



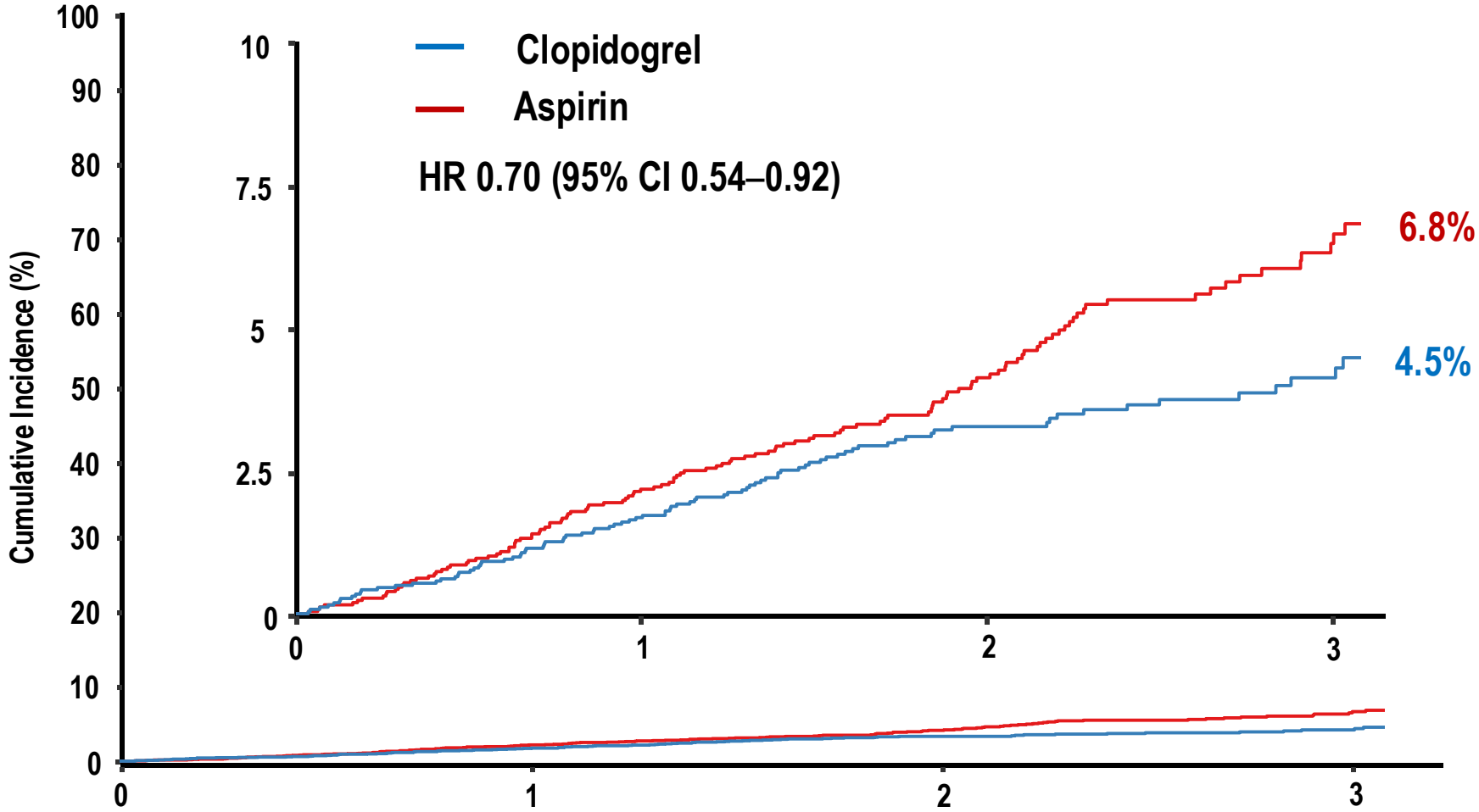
Number at Risk (number censored)				
Aspirin	2754	2660	1580	597
Clopidogrel	2752	2660	1577	599

Secondary End Points

	Clopidogrel group (n=2752)	Aspirin group (n=2754)	Hazard ratio (95% CI)
Death from any cause	50 (2·4% [1·6–3·1])	70 (4·0% [2·9–5·0])	0·71 (0·49–1·02)
Death from cardiovascular cause	33 (1·4% [0·9–2·0])	42 (2·1% [1·4–2·8])	0·79 (0·50–1·24)
Death from non-cardiovascular cause	17 (1·0% [0·4–1·5])	28 (1·9% [1·1–2·6])	0·60 (0·33–1·10)
Stroke	23 (1·3% [0·7–2·0])	29 (1·3% [0·8–1·7])	0·79 (0·46–1·36)
Stent thrombosis	1 (0% [0·0–0·0])	5 (0·2% [0·0–0·4])	0·20 (0·02–1·68)
Death from any cause or MI	71 (3·2% [2·4–4·1])	109 (5·9% [4·7–7·1])	0·65 (0·48–0·87)
Death from cardiovascular cause or MI	54 (2·3% [1·6–3·0])	81 (4·1% [3·1–5·1])	0·66 (0·47–0·94)
Death from cardiovascular cause, MI, or stroke	76 (3·6% [2·7–4·5])	103 (4·9% [3·9–6·0])	0·73 (0·54–0·98)
Major bleeding (BARC type 3 or 5)	26 (1·6% [0·9–2·3])	26 (1·3% [0·8–1·8])	1·00 (0·58–1·73)
Upper gastrointestinal clinical event	58 (2·8% [2·0–3·6])	90 (4·9% [3·7–6·0])	0·65 (0·47–0·90)
Gastrointestinal ulcer or bleeding	24 (1·3% [0·7–1·8])	32 (1·6% [1·0–2·1])	0·76 (0·45–1·29)
Gastrointestinal ulcer	8 (0·6% [0·0–1·1])	15 (0·7% [0·0–1·1])	0·54 (0·23–1·28)
Gastrointestinal bleeding	21 (1·1% [0·6–1·6])	25 (1·4% [0·8–2·0])	0·85 (0·48–1·52)
Net adverse clinical event	111 (5·4% [4·2–6·5])	142 (7·3% [6·0–8·6])	0·78 (0·61–0·99)

Median follow-up period: 2.3 years (IQR 1·6–3·0)

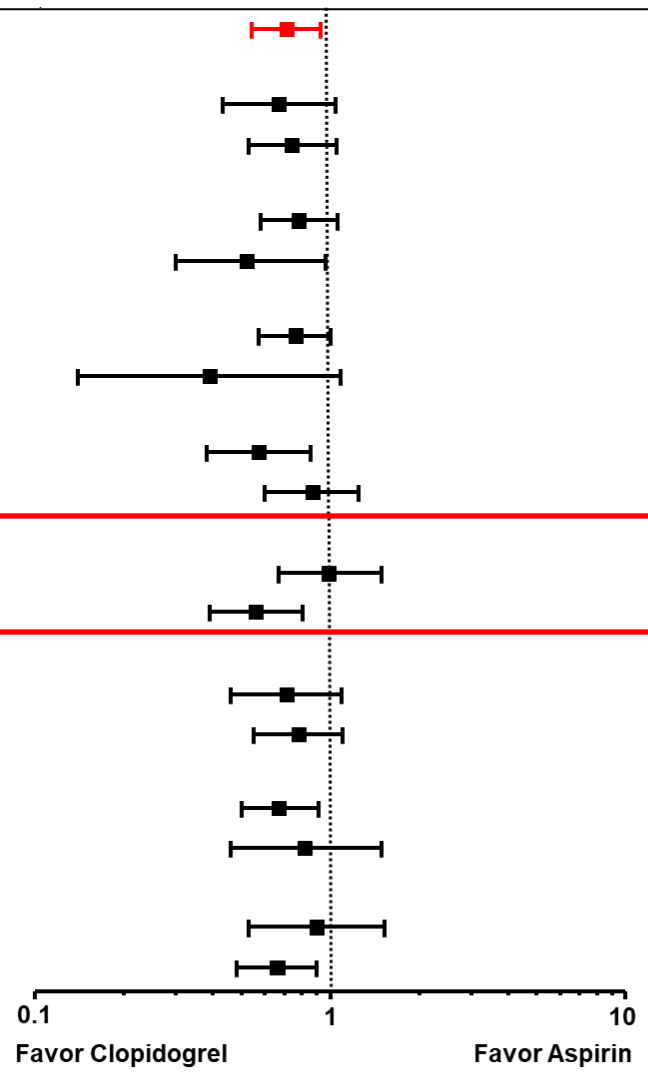
Sensitivity Analysis (Per-Protocol Population)



No.at Risk				
Aspirin	2594	2487	1483	569
Clopidogrel	2626	2540	1500	568

Prespecified Subgroup Analysis

Subgroup	Clopidogrel Monotherapy	Aspirin Monotherapy	Hazard Ratio (95% CI)
All Subjects (n=5506)	92/2752 (4.4%)	128/2754 (6.6%)	0.71 (0.54–0.93)
Age			
≥ 75 years (n=1070)	35/531 (9.3%)	51/539 (13.2%)	0.67 (0.43–1.04)
< 75 years (n=4436)	57/2221 (3.3%)	77/2215 (5.1%)	0.74 (0.53–1.05)
Sex			
Male (n=4504)	76/2240 (4.4%)	98/2264 (6.0%)	0.78 (0.58–1.06)
Female (n=1002)	16/512 (4.3%)	30/490 (9.4%)	0.52 (0.30–0.96)
Duration of DAPT Before Randomization			
> 12 months (n=4766)	86/2384 (4.7%)	113/2382 (6.7%)	0.76 (0.57–1.00)
≤ 12 months (n=740)	6/368 (2.2%)	15/372 (6.2%)	0.39 (0.14–1.08)
Diabetes Mellitus			
Medication-treated diabetes (n=2089)	36/1039 (4.5%)	65/1050 (9.1%)	0.57 (0.38–0.86)
Others (n=3417)	56/1713 (4.3%)	63/1704 (5.1%)	0.87 (0.60–1.25)
Clinical Presentation			
Acute myocardial infarction (n=2552)	48/1283 (5.0%)	49/1269 (5.4%)	0.99 (0.67–1.49)
Non-acute myocardial infarction (n=2954)	44/1469 (3.7%)	79/1485 (7.6%)	0.56 (0.39–0.81)
Bleeding Risk			
High bleeding risk (n=875)	36/427 (9.7%)	56/448 (18.8%)	0.71 (0.46–1.09)
Non-high bleeding risk (n=4631)	56/2325 (3.4%)	72/2306 (4.4%)	0.78 (0.55–1.10)
Anatomical Complexity			
Complex PCI (n=4185)	72/2113 (4.6%)	103/2072 (7.1%)	0.67 (0.50–0.91)
Non-complex PCI (n=1318)	20/638 (3.8%)	25/680 (5.1%)	0.82 (0.46–1.49)
Use of PPI at Randomization			
PPI use (n=1134)	26/545 (6.2%)	31/589 (6.0%)	0.90 (0.53–1.52)
No PPI use (n=4372)	66/2207 (3.9%)	97/2165 (6.7%)	0.66 (0.48–0.90)



Limitations

- The trial had an open-label design, and the allocated group were not masked by the physician. However, we minimized the risk of bias by using an end-point analysis with precisely defined criteria, and by having clinical events adjudicated by a committee.
- The actual event rate was lower than expected, resulting in substantially fewer number of expected events, even though the final sample size was increased by 10% from the original sample size.
- This study exclusively enrolled Korean patients; therefore, the results should be applied with caution to other populations. However, given the high prevalence of intermediate or poor clopidogrel metabolism in the Korean population, clopidogrel might in fact be more effective in populations where reduced-function CYP2C19 alleles are less common.

Conclusion

- Among patients who were at high risk of recurrent ischemic events and completed the standard duration of DAPT following PCI, clopidogrel monotherapy resulted in a lower risk of a composite of death from any cause, myocardial infarction, or stroke than aspirin monotherapy, without increase in bleeding.
- The SMART-CHOICE 3 trial was the first to demonstrate the benefits of clopidogrel monotherapy compared with aspirin monotherapy on a composite of hard endpoints in patients at a high risk of recurrent ischemic events after PCI.

Thank You Very Much!

I would like to thank **patients** enrolled, **research nurses**, **study coordinators**, and **participating investigators**.

SMART-CHOICE 3 Investigators

Name	Center	No. of patients enrolled
Joo-Yong Hahn	Samsung Medical Center	1573
Ki Hong Choi		
Hyeon-Cheol Gwon		
Seung-Hyuk Choi		
Young Bin Song		
Jeong Hoon Yang		
Taek Kyu Park		
Joo Myung Lee		
Yong Hwan Park	Samsung Changwon Hospital	608
Jong-Young Lee	Kangbuk Samsung Hospital	544
Jin-Ok Jeong	Chungnam National University Hospital	258
Chan Joon Kim	Catholic University of Korea Uijeongbu St. Mary's Hospital	237
Kyeong Ho Yun	Wonkwang University Hospital	234
Han Cheol Lee	Pusan National University Hospital	234
Kiyuk Chang	Catholic University of Koea Seoul St. Mary's Hospital	198
Mahn-Won Park	Catholic University of Korea Daejeon St. Mary's Hospital	150

Name	Center	No. of patients enrolled
Jang-Whan Bae	Chungbuk National University Hospital	139
Joon-Hyung Doh	Inje University Ilsan Paik Hospital	135
Byung Ryul Cho	Kangwon National University Hospital	131
Hee-Yeol Kim	Catholic University of Korea Bucheon St. Mary's Hospital	119
Weon Kim	Kyung Hee University Hospital	118
Ung Kim	Yeungnam University Medical Center	106
Seung-Woon Rha	Korea University Guro Hospital	100
Young Joon Hong	Chonnam National University Hospital	98
Hyun-Jong Lee	Bucheon Sejong Hospital	90
Sung Gyun Ahn	Wonju Severance Christian Hospital	82
Doo Il Kim	Inje University Haeundae Paik Hospital	81
Jang Hyun Cho	St Carollo Hospital	76
Sung Ho Her	Catholic University of Korea St. Vincent's Hospital	65
Doo Soo Jeon	Catholic University of Korea Incheon St. Mary's Hospital	51
Seung Hwan Han	Gachon University Gil Medical Center	37
Jin-Bae Lee	Daegu Catholic University Medical Center	22
Cheol Whan Lee	Asan Medical Center	20

THE LANCET

Efficacy and safety of clopidogrel versus aspirin monotherapy in patients at high risk of subsequent cardiovascular event after percutaneous coronary intervention (SMART-CHOICE 3): a randomised, open-label, multicentre trial

Ki Hong Choi, Yong Hwan Park*, Jong-Young Lee, Jin-Ok Jeong, Chan Joon Kim, Kyeong Ho Yun, Han Cheol Lee, Kiyuk Chang, Mahn-Won Park, Jang-Whan Bae, Joon-Hyung Doh, Byung Ryul Cho, Hee-Yeol Kim, Weon Kim, Ung Kim, Seung-Woon Rha, Young Joon Hong, Hyun-Jong Lee, Sung Gyun Ahn, Doo-Il Kim, Jang Hyun Cho, Sung Ho Her, Doo Soo Jeon, Seung Hwan Han, Jin-Bae Lee, Cheol Whan Lee, Danbee Kang, Joo Myung Lee, Taek Kyu Park, Jeong Hoon Yang, Soo-Youn Lee, Seung-Hyuk Choi, Hyeon-Cheol Gwon, Young Bin Song†, Joo-Yong Hahn†, for the SMART-CHOICE 3 investigators‡*