Aspirin versus clopidogrel for chronic maintenance monotherapy after percutaneous coronary intervention: 10-year follow-up of the HOST-EXAM trial

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Summary

Background The long-term clinical outcomes of clopidogrel monotherapy versus aspirin monotherapy after percutaneous coronary intervention (PCI) remain uncertain. We conducted a 10-year follow-up of the HOST-EXAM trial to assess the very long-term effects of clopidogrel versus aspirin monotherapy in this setting.

Methods In HOST-EXAM, patients who had completed dual antiplatelet therapy without clinical events for 6–18 months after PCI were randomly assigned to receive clopidogrel 75 mg once daily or aspirin 100 mg once daily. This study is an investigator-initiated 10-year extended follow-up of the HOST-EXAM trial. The primary endpoint was a composite of all-cause death, non-fatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and Bleeding Academic Research Consortium type ≥3 bleeding. The primary analysis was done in the intention-to-treat population. The study is registered with ClinicalTrials.gov (NCT02044250) and is complete.

Findings From March 26, 2014, to May 29, 2018, 5530 patients were enrolled and 5438 were randomly assigned to the aspirin group (n=2728) or the clopidogrel group (n=2710). Clinical follow-up status was ascertained on May 1, 2025, resulting in a median follow-up duration of 10·5 years (IQR 9·4–11·4) after PCI and a completion rate of 92·8%. Clopidogrel was associated with a lower rate of the primary composite endpoint than aspirin (Kaplan–Meier estimate 25·4% for the clopidogrel group *vs* 28·5% for the aspirin group; hazard ratio 0·86 [95% CI 0·77–0·96]; log-rank p=0·0050). Clopidogrel was also associated with a lower rate of the thrombotic endpoint (17·3% *vs* 20·0%; log-rank p=0·0024) and bleeding endpoint (9·1% *vs* 10·8%; log-rank p=0·020). All-cause mortality was similar between groups.

Interpretation During 10 years of follow-up, clopidogrel monotherapy, compared with aspirin monotherapy, was associated with lower rates of the primary composite, ischaemic, and bleeding outcomes, but not all-cause mortality after PCI. These findings support consideration of clopidogrel as an alternative to aspirin for long-term antiplatelet monotherapy during the chronic maintenance phase after PCI.

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Introduction

After completion of dual antiplatelet therapy (DAPT), antiplatelet monotherapy is recommended for long-term secondary prevention of major adverse cardiovascular events after percutaneous coronary intervention (PCI). Although aspirin has traditionally been the agent of choice,[1,2] recent trials and meta-analyses have reported superiority of clopidogrel monotherapy over aspirin monotherapy for secondary prevention in this setting.[3–6] However, because secondary prevention after PCI is typically continued lifelong, follow-up beyond 5 years is needed to better understand the effects of antiplatelet monotherapy. Therefore, we report the prespecified long-term follow-up of the HOST-EXAM trial, with outcomes assessed at 10 years to evaluate the comparative long-term effects of clopidogrel monotherapy versus aspirin monotherapy.

Methods

Study design and participants

Details regarding the design of the HOST-EXAM trial have been described previously.[7] Briefly, HOST-EXAM was an investigator-initiated, prospective, randomised, open-label, multicentre trial done at 37 study sites in South Korea. Details of the participating centres and investigators are provided in the appendix (pp 5–8). The randomised antiplatelet treatment strategy was mandated during the initial 24-month follow-up after enrolment, whereas antiplatelet therapy during the post-trial follow-up was at the discretion of the treating physician. Patients aged 20 years or older who underwent PCI with drug-eluting stents and maintained DAPT without any clinical events for 6–18 months after PCI were eligible for enrolment in the HOST-EXAM trial.[3,7]

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed, MEDLINE, and the Cochrane Library for randomised controlled trials and meta-analyses comparing P2Y12 inhibitor monotherapy with aspirin monotherapy for long-term secondary prevention after percutaneous coronary intervention (PCI), published from database inception to Dec 31, 2025, using the keywords "clopidogrel", "aspirin", "antiplatelet monotherapy", "percutaneous coronary intervention", "drug-eluting stent", and "secondary prevention", with no language restrictions. Evidence from randomised trials before this study was limited to studies with short or intermediate duration of follow-up. The STOPDAPT-2 and SMART-CHOICE 3 trials reported lower rates of clinical events with clopidogrel than with aspirin, and a 2025 individual patient data meta-analysis reported that clopidogrel monotherapy was superior to aspirin monotherapy for prevention of major adverse cardiovascular or cerebrovascular events. Nevertheless, no randomised trial had previously assessed antiplatelet monotherapy beyond 5 years after PCI.

Added value of this study

This study reports the 10-year follow-up of the HOST-EXAM randomised trial, providing the longest randomised comparison of antiplatelet monotherapy after PCI with drug-eluting stents. Clopidogrel monotherapy was associated with sustained reductions in the primary composite endpoint compared with aspirin monotherapy over 10 years, extending the longest previous randomised follow-up of 5 years. The cumulative long-term benefit was reflected in a lower number needed to treat at 10 years compared with that at 2 years. Treatment adherence was higher in the clopidogrel group than in the aspirin group, in which gastrointestinal discomfort was a common cause of treatment discontinuation, highlighting the role of tolerability in long-term therapy.

Implications of all the available evidence

Combined with data from previous randomised trials and meta-analyses, our results strengthen the evidence supporting the superiority of clopidogrel monotherapy over aspirin monotherapy for long-term secondary prevention after PCI. The continued divergence of the event curves and the decreasing number needed to treat over time suggests that the clinical benefit of clopidogrel is cumulative. The totality of contemporary evidence suggests that the role of aspirin as the first-line lifelong antiplatelet therapy after PCI warrants reconsideration, especially in health-care systems where clopidogrel is accessible and inexpensive.

The Seoul National University Hospital Clinical Trial Center and the Medical Research Collaborating Center were responsible for the scientific conduct of the trial. All events were adjudicated by an independent clinical events committee whose members were unaware of the treatment assignments. Members of the independent clinical events committee received medical records of adverse events after removal of any reference to the treatment groups. This study was conducted in accordance with the standards specified in the International Council for Harmonization Guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki.

Randomisation and masking

Randomisation was done by a web-based application (Medical Research Collaborating Center Interactive Web Response System) developed by the Medical Research Collaborating Center (Seoul, South Korea), without blocking or stratification. Enrolled patients were randomly assigned in a 1:1 ratio to either the clopidogrel group or the aspirin group. Randomisation was performed by an independent research coordinator to ensure allocation concealment. Detailed inclusion and exclusion criteria are described in the appendix (p 12). Patients and study investigators were not masked to treatment assignment. Clinical data were recorded in web-based electronic case report forms developed by the Medical Research Collaborating Center.

Procedures

According to the randomisation assignment, patients received either clopidogrel (75 mg once daily) or aspirin (100 mg once daily). Clinical follow-up was scheduled annually for up to 10 years after randomisation. During the follow-up period, active surveillance was done for any prespecified adverse clinical events, along with assessment of adherence to the study drug. For patients who did not visit the outpatient clinic, telephone follow-up was permitted. Additionally, vital status was cross-checked through the National Health Insurance Service system of South Korea and the South Korea National Statistics System.

Outcomes

The trial endpoints and definitions were identical to those of the HOST-EXAM trial.[3] The primary endpoint was a composite of all-cause death, non-fatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and major bleeding events. Major bleeding was defined as type ≥3 bleeding according to the Bleeding Academic Research Consortium (BARC). Secondary composite endpoints included the thrombotic composite endpoint (defined as cardiovascular 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). The individual components of the primary composite endpoint and of the secondary

composite endpoints were also analysed as secondary endpoints. For mortality cases, the cause of death was confirmed by the recorded data classified by the codes from the ICD-10 Clinical Modification guideline. Detailed definitions of each clinical event are described in the appendix (pp 13–19).

Statistical analysis

The working hypothesis of the HOST-EXAM trial was that clopidogrel would be superior to aspirin as a chronic maintenance monotherapy agent, which required 5530 patients to ensure at least 80% power with a two-sided α of 0·05 based on the assumed event rates. The current study was an extended follow-up of this population; therefore, no additional sample size calculation was done. The primary analysis was done on an intention-to-treat basis and included all randomly assigned patients. As a sensitivity analysis, outcomes were also assessed in the per-protocol population, which included all patients who received the allocated single antiplatelet therapy throughout follow-up unless an adverse clinical event occurred.

Continuous variables were reported as mean (SD), and categorical variables were presented as counts and proportions. Differences between continuous variables were compared by Student's *t* test for independent data. The primary composite endpoint was analysed by a Cox proportional hazards model and Kaplan–Meier curves to estimate the risk of clinical events according to the type of antiplatelet agent. No variables other than the trial group were used for stratification. Event-free survival with incomplete follow-up was counted as censored data for all time-to-event analyses. A Cox proportional hazards model was used for analysis of subgroups, defined according to age (<65 years or ≥65 years), sex (male or female), BMI (≥25 kg/m² or <25 kg/m²), renal function, diabetes,

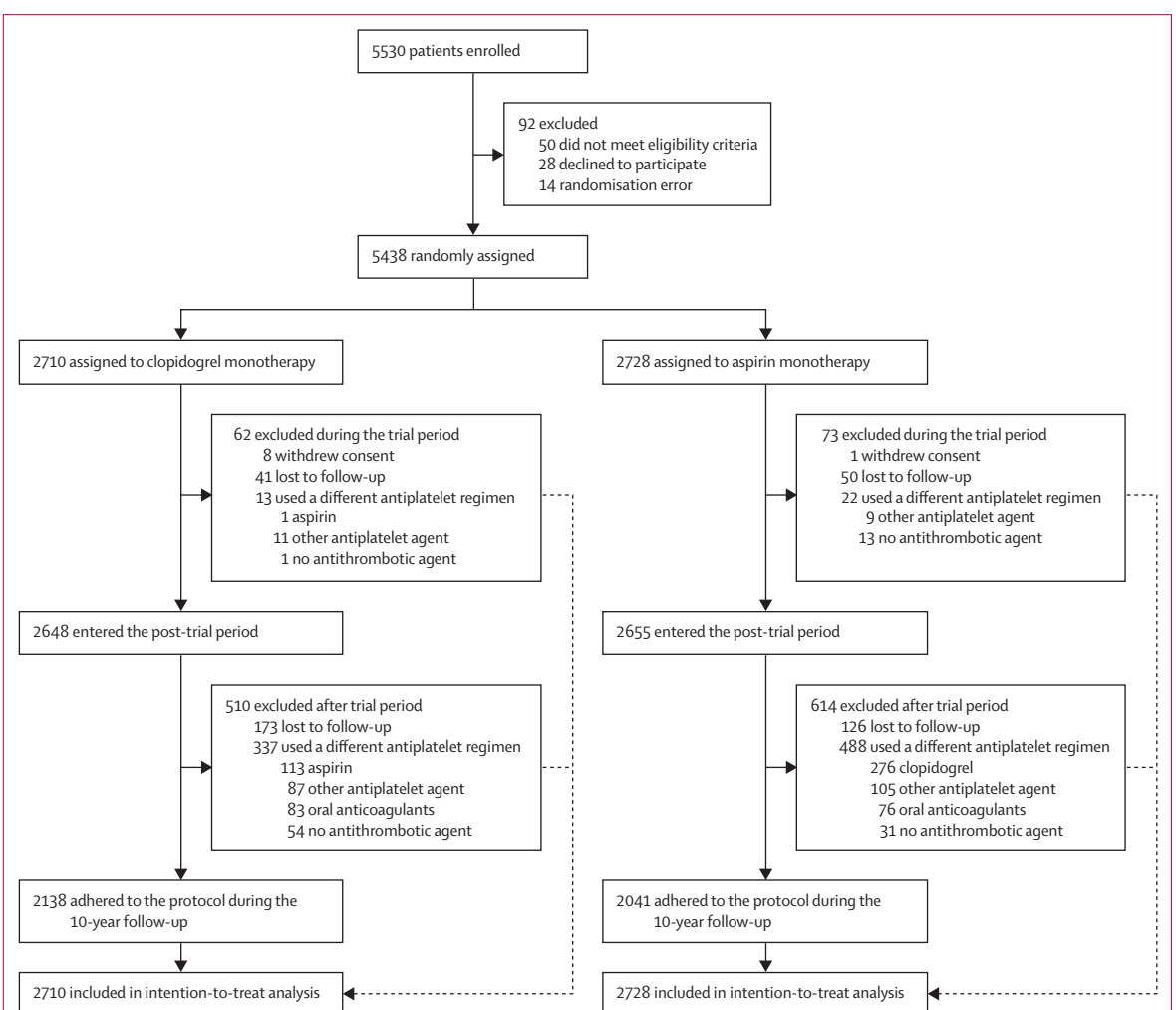
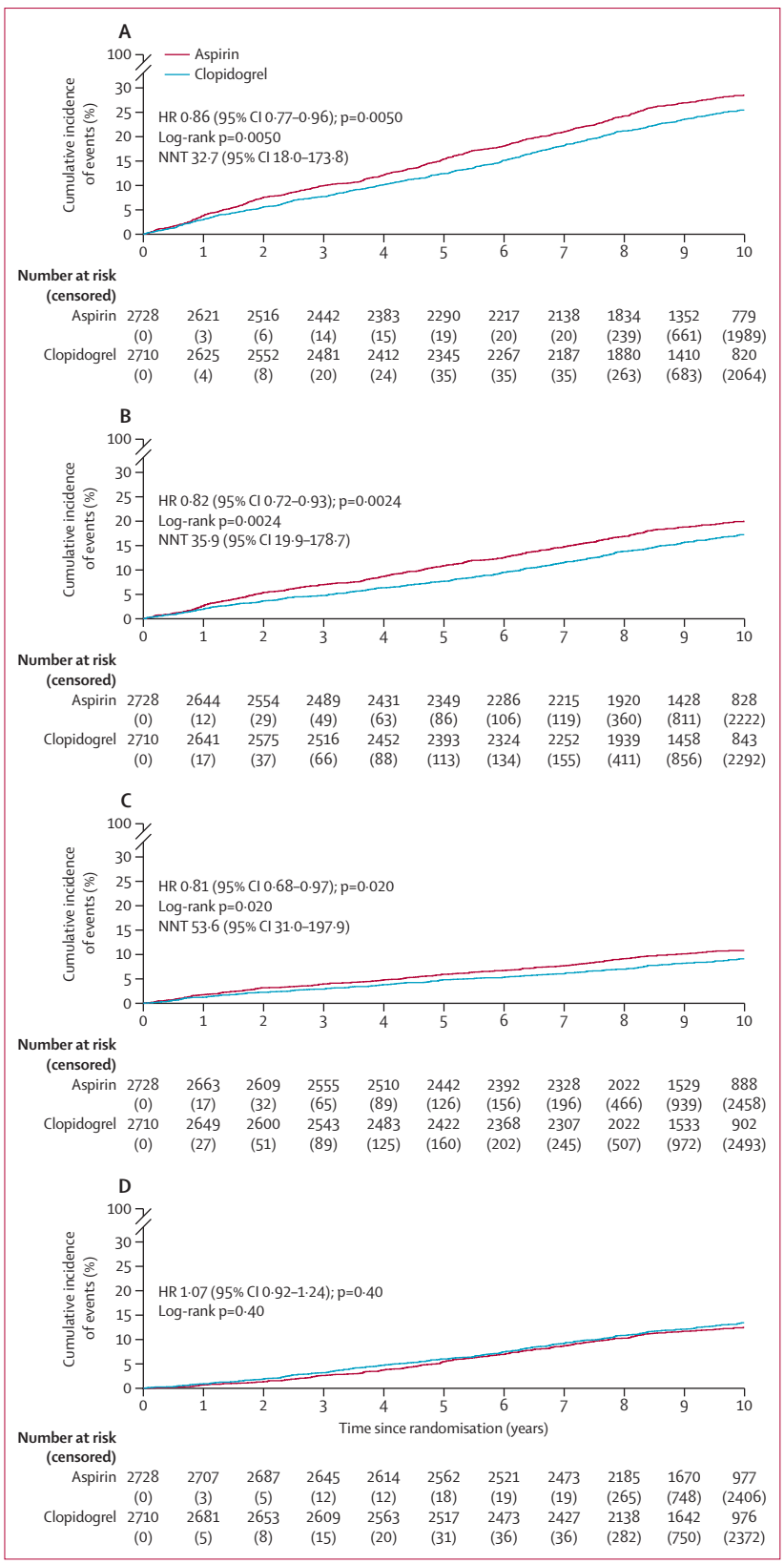


Figure 1: **Trial profile**
Patients who underwent PCI with a drug-eluting stent and maintained dual antiplatelet therapy without any clinical events within 6–18 months after the index PCI were eligible for enrolment in the HOST-EXAM trial. Patients were followed up for up to 10 years. The primary endpoint was analysed in the intention-to-treat population. PCI=percutaneous coronary intervention.



clinical presentation (acute myocardial infarction or not, acute coronary syndrome or not), complex PCI, and high bleeding risk. The specific definitions of complex PCI and high bleeding risk are shown in the appendix (pp 13–14). Statistical tests were done using SPSS version 24 and R version 4.3.3. All p values were two-sided, and $p<0·05$ was considered statistically significant. This study is registered with ClinicalTrials.gov (NCT02044250), and is complete.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between March 26, 2014, and May 29, 2018, 5530 patients were enrolled, of whom 5438 remained event-free for 6–18 months after PCI, successfully received the intended duration of DAPT, and were randomly assigned to either clopidogrel monotherapy (n=2710) or aspirin monotherapy (n=2728; figure 1). Clinical and angiographic characteristics were well matched between groups (appendix pp 20–22). Clinical events during the 10-year follow-up period were collected up to May 1, 2025. The median duration of follow-up was 10·5 years (IQR 9·4–11·4) after PCI and 10·7 years (IQR 9·8–11·5) in survivors. Among the total population, nine patients withdrew informed consent, 390 patients were lost to follow-up (including 91 patients who were lost to follow-up in the in-trial period), and 860 patients used a different antithrombotic strategy during the follow-up period, leaving 4179 (76·8%) of 5438 patients in the per-protocol population. Information on adverse clinical outcomes, including vital status, was complete in 2496 (92·1%) of 2710 patients in the clopidogrel group and 2552 (93·5%) of 2728 patients in the aspirin group, corresponding to outcome ascertainment in 5048 (92·8%) of 5438 patients overall.

During the follow-up period, the primary composite endpoint occurred in 646 patients (Kaplan–Meier estimate 25·4%) who received clopidogrel monotherapy, and in 739 patients (Kaplan–Meier estimate 28·5%) who

Figure 2: **Cumulative incidence of the primary composite endpoint, secondary composite endpoints, and all-cause death in the intention-to-treat population**

(A) Cumulative incidence of the primary composite endpoint, consisting of all-cause death, non-fatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and major bleeding (Bleeding Academic Research Consortium type ≥3 bleeding). (B) Cumulative incidence of the secondary composite thrombotic endpoint, consisting of cardiac death, non-fatal myocardial infarction, ischaemic stroke, readmission due to acute coronary syndrome, or definite or probable stent thrombosis. (C) Cumulative incidence of any bleeding. (D) Cumulative incidence of all-cause death. HRs are for clopidogrel monotherapy versus aspirin monotherapy. NNTs are shown only when the absolute risk difference excludes zero. HR=hazard ratio. NNT=number needed to treat.

	Clopidogrel (n=2710)	Aspirin (n=2728)	Hazard ratio (95% CI)	p value	Absolute risk reduction (95% CI)	Number needed to treat (95% CI)
Primary composite endpoint*	646 (25·4%)	739 (28·5%)	0·86 (0·77–0·96)	0·0050	3·1 (0·6 to 5·6)	32·7 (18·0–173·8)
Thrombotic composite endpoint†	418 (17·3%)	506 (20·0%)	0·82 (0·72–0·93)	0·0024	2·8 (0·6 to 5·0)	35·9 (19·9–178·7)
Any bleeding (BARC type ≥2)‡	217 (9·1%)	270 (10·8%)	0·81 (0·68–0·97)	0·020	1·7 (0·0 to 3·4)	..
All-cause death§	338 (13·4%)	322 (12·5%)	1·07 (0·92–1·24)	0·40	–0·9 (–2·8 to 0·9)	..
Cardiovascular death	167 (7·1%)	171 (6·9%)	0·99 (0·80–1·23)	0·95	–0·1 (–1·6 to 1·4)	..
Non-cardiovascular death	171 (6·9%)	151 (6·0%)	1·15 (0·93–1·43)	0·21	–0·9 (–2·3 to 0·5)	..
Non-fatal myocardial infarction	85 (3·6%)	105 (4·2%)	0·82 (0·62–1·09)	0·17	0·6 (–0·5 to 1·7)	..
Stroke	110 (4·6%)	154 (6·4%)	0·72 (0·56–0·92)	0·0081	1·8 (0·4 to 3·1)	57·2 (32·7–228·5)
Ischaemic stroke	85 (3·6%)	104 (4·3%)	0·81 (0·61–1·08)	0·16	0·8 (–0·4 to 1·9)	..
Haemorrhagic stroke	25 (1·0%)	50 (2·1%)	0·50 (0·31–0·81)	0·0050	1·1 (0·4 to 1·8)	92·5 (55·5–279·1)
Readmission due to acute coronary syndrome	208 (8·7%)	277 (11·0%)	0·75 (0·63–0·90)	0·0017	2·3 (0·6 to 4·0)	42·9 (24·8–158·5)
Percutaneous coronary intervention	157 (6·8%)	207 (8·5%)	0·76 (0·62–0·93)	0·0084	1·7 (0·1 to 3·2)	59·1 (30·9–690·3)
Coronary artery bypass surgery	5 (0·2%)	8 (0·3%)	0·62 (0·20–1·90)	0·41	0·1 (–0·2 to 0·4)	..
Medical treatment	46 (1·8%)	62 (2·4%)	0·74 (0·51–1·09)	0·13	0·6 (–0·2 to 1·4)	..
Major bleeding (BARC type ≥3)	133 (5·6%)	190 (7·7%)	0·71 (0·57–0·88)	0·0019	2·1 (0·7 to 3·5)	47·5 (28·3–148·4)

Data are n (%), unless otherwise specified. Number needed to treat is shown only when the 95% CI for the absolute risk reduction excludes 0. BARC=Bleeding Academic Research Consortium. *Primary composite endpoint is defined as a composite of all-cause death, non-fatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and major bleeding (BARC type ≥3). †Thrombotic composite endpoint is defined as cardiac death, non-fatal myocardial infarction, ischaemic stroke, readmission due to acute coronary syndrome, and definite or probable stent thrombosis. ‡Any bleeding defined as any BARC type ≥2 bleeding events. §The specific causes of mortality events are described in the appendix (pp 23–24).

Table: **Clinical outcomes during the 10-year follow-up in the intention-to-treat population**

received aspirin monotherapy (hazard ratio [HR] 0·86 [95% CI 0·77–0·96]; log-rank p=0·0050). The number needed to treat to prevent one primary endpoint event was 33. The secondary thrombotic endpoint occurred in 418 (17·3%) patients in the clopidogrel group and 506 (20·0%) patients in the aspirin group (HR 0·82 [95% CI 0·72–0·93]; log-rank p=0·0024). The benefit in thrombotic events was primarily driven by lower rates of non-fatal stroke and readmission due to acute coronary syndrome in the clopidogrel group. Any bleeding (BARC type ≥2) occurred in 217 (9·1%) patients in the clopidogrel group and 270 (10·8%) patients in the aspirin group (HR 0·81 [95% CI 0·68–0·97]; log-rank p=0·020). The difference in bleeding outcomes was primarily driven by BARC type 3 bleeding rather than type 2 bleeding. There was no significant difference in the risk of all-cause death between the two groups (13·4% *vs* 12·5%; HR 1·07 [95% CI 0·92–1·24]; log-rank p=0·399). The Kaplan–Meier curves for the endpoints are shown in figure 2. Among other secondary endpoints, the risks of stroke, readmission due to acute coronary syndrome, and major bleeding were lower in the clopidogrel group (table). Cause of mortality and type of bleeding according to the BARC definition are presented in the appendix (pp 23–25).

In a landmark analysis conducted 2 years after randomisation, the event rates for the primary and secondary composite endpoints were numerically lower in the clopidogrel group but the difference was not statistically significant. All-cause death was similar between groups (appendix pp 26, 37–40).

The effect of clopidogrel versus aspirin monotherapy on the primary composite endpoint was generally consistent across prespecified subgroups (figure 3). A significant interaction was observed in the subgroup analysis according to chronic kidney disease, showing a larger reduction in risk among patients with chronic kidney disease. Subgroup analyses of the secondary composite endpoints are shown in the appendix (pp 41–43).

A per-protocol analysis was done including patients who completed the follow-up and adhered to the assigned medication, excluding those who discontinued the allocated medication before a clinical event or during follow-up. A total of 4179 patients (2138 [78·9%] in the clopidogrel group and 2041 [74·8%] in the aspirin group) were included in the analysis, and adherence to the allocated medication was higher in the clopidogrel group (p<0·0004). The reasons for discontinuation of the study drug are presented in the appendix (p 27), showing that gastrointestinal discomfort and minor bleeding were more common in the aspirin group. Baseline characteristics and clinical outcomes of patients included in and excluded from the per-protocol population are shown in the appendix (pp 28–36). Clopidogrel monotherapy yielded results similar to those in the intention-to-treat analysis; however, the effect estimate was larger in the per-protocol analysis for the primary composite endpoint (24·0% *vs* 29·8%; HR 0·76 [95% CI 0·67–0·86]; log-rank p<0·0001), and secondary composite endpoints (thrombotic composite endpoint: 15·5% *vs* 21·0%; 0·69 [0·60–0·81]; log-rank p<0·0001; bleeding endpoint: 8·6% *vs* 11·3%; 0·73 [0·59–0·89];

log-rank p=0·0024). The number needed to treat was 17, which was lower than in the intention-to-treat analysis. The clinical benefit of clopidogrel in the per-protocol analysis was driven by a lower rate of non-fatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and major bleeding. The Kaplan–Meier curves for the endpoints are shown in the appendix (pp 44–47). A landmark analysis 2 years after randomisation in the per-protocol analysis also showed similar results to those in the intention-to-treat population; however, the relative risk reduction was larger than in the intention-to-treat analysis (appendix pp 48–51). Additional sensitivity analyses and subgroup analyses according to prespecified subgroups are shown in the appendix (pp 52–61).

Discussion

Patients after PCI require lifelong antiplatelet monotherapy after completion of DAPT. Aspirin has traditionally been the treatment of choice in this clinical setting. However, recent randomised trials and meta-analyses have reported that clopidogrel monotherapy is superior to aspirin monotherapy in the chronic maintenance phase of secondary prevention.[3,5,6,8] Although, the longest follow-up reported in these studies is up to 5 years.[8] The current report presents the final

	Number of events/number of patients		Hazard ratio (95% CI)	p value	$p_{interaction}$
	Clopidogrel group	Aspirin group			
Age (years)					
≥65	410/1177	459/1186	0·88 (0·77–1·00)	0·056	0·60
<65	236/1534	280/1541	0·83 (0·70–0·98)	0·034	
Sex					
Male	471/2015	523/2039	0·89 (0·79–1·01)	0·068	0·30
Female	175/695	216/689	0·78 (0·64–0·96)	0·017	
BMI ≥25 kg/m²					
Yes	245/1221	288/1178	0·80 (0·68–0·95)	0·011	0·21
No	376/1390	415/1445	0·92 (0·80–1·06)	0·26	
Acute myocardial infarction					
Yes	236/989	260/998	0·90 (0·76–1·08)	0·26	0·49
No	410/1721	479/1730	0·84 (0·73–0·95)	0·0079	
Acute coronary syndrome					
Yes	471/1964	511/1957	0·90 (0·80–1·02)	0·11	0·17
No	228/746	175/771	0·77 (0·63–0·93)	0·0080	
Multivessel disease					
Yes	369/1343	412/1352	0·88 (0·76–1·01)	0·068	0·68
No	277/1367	326/1376	0·84 (0·71–0·98)	0·031	
Diabetes					
Yes	265/935	305/925	0·85 (0·72–1·00)	0·054	0·87
No	382/1785	434/1793	0·87 (0·75–0·99)	0·040	
Chronic kidney disease					
Yes	136/356	174/337	0·69 (0·55–0·87)	0·0013	0·041
No	510/2354	565/2391	0·90 (0·80–1·01)	0·083	
Proton pump inhibitor					
Yes	80/290	110/331	0·80 (0·60–1·07)	0·13	0·57
No	566/2420	629/2397	0·87 (0·78–0·98)	0·019	
Complex PCI*					
Yes	145/598	184/595	0·74 (0·60–0·92)	0·0068	0·13
No	498/2091	551/2114	0·90 (0·80–1·02)	0·090	
High bleeding risk†					
Yes	219/521	231/467	0·79 (0·66–0·95)	0·013	0·19
No	355/1800	385/1832	0·93 (0·80–1·07)	0·31	

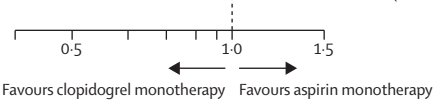


Figure 3: **Subgroup analysis of the primary composite endpoint in the intention-to-treat population**
Hazard ratios for the primary composite endpoint (all-cause death, non-fatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and major bleeding [Bleeding Academic Research Consortium type ≥3]) in the two groups are shown according to prespecified subgroups. *Complex PCI was defined as having at least one of the following features: three vessels treated, three or more stents implanted, three or more lesions treated, bifurcation with two stents implanted, total stent length greater than 60 mm, or chronic total occlusion. †High bleeding risk was defined according to the Academic Research Consortium for High Bleeding Risk definition. PCI=percutaneous coronary intervention.

10-year follow-up results from the HOST-EXAM programme. To the best of our knowledge, this is the first study to assess 10-year clinical outcomes of antiplatelet monotherapy following PCI with drug-eluting stents and provides the longest follow-up currently available comparing clopidogrel monotherapy versus aspirin monotherapy in the secondary prevention setting. Our data show that clopidogrel continued to be superior to aspirin in terms of the primary composite, thrombotic, and bleeding endpoints up to 10 years. The number needed to treat to prevent a net adverse clinical event during follow-up was 33 in the intention-to-treat population and 17 in the per-protocol population. The reduction in clinical events was primarily driven by a lower incidence of readmission due to acute coronary syndrome within the thrombotic composite endpoint. For bleeding events, the lower rate of BARC type 3 bleeding, including haemorrhagic stroke, mainly drove the reduction in bleeding. All-cause death was similar between the two groups. A landmark analysis at 2 years after randomisation showed continued divergence of the clinical event curves beyond 2 years and subgroup analyses showed consistent effects with no significant interactions between the treatment and specific subgroups.

Antiplatelet therapy is a cornerstone of secondary prevention in patients with atherosclerotic cardiovascular disease and is generally indicated indefinitely.[1,2] Among antiplatelet agents, the potential benefit of clopidogrel monotherapy over aspirin was first suggested in the CAPRIE trial.[9] Although, the findings of CAPRIE did not substantially change clinical practice, largely owing to the modest absolute benefit with borderline statistical significance, heterogeneity across subgroups, the inclusion of a non-PCI population, and the high cost of clopidogrel as a patented agent at that time. However, the substantial reduction in the cost of clopidogrel over the past three decades, together with the positive long-term results from the current study, warrants a reappraisal of the benefits of clopidogrel over aspirin. Moreover, considering the current life expectancy and average age of patients with coronary artery disease undergoing PCI, which is typically around 60 years,[3,10,11] we can anticipate that these patients will likely require antiplatelet monotherapy for at least a decade, if not longer. Therefore, confirming the long-term benefits of antiplatelet monotherapy is essential to lifelong post-PCI pharmacotherapy. The short-term to mid-term benefits of clopidogrel over aspirin monotherapy were confirmed in two large-scale randomised clinical trials, the HOST-EXAM trial and the SMART-CHOICE 3 trial.[3,5] Both trials reported reductions in clinical events with clopidogrel monotherapy during the chronic maintenance phase after PCI during 2–3 years of follow-up after randomisation. In a 2025 individual patient data meta-analysis, clopidogrel was associated with lower rates of major adverse cardiac and cerebrovascular events at 5·5 years, with no significant differences in mortality and major bleeding for secondary prevention of coronary artery disease.[6] Incorporating these new data, the 2024 European guidelines now give clopidogrel a class I, level A recommendation for long-term maintenance in post-PCI secondary prevention.[1]

Despite recent changes in clinical guidelines and the positive primary results from randomised comparisons and meta-analyses, the longest follow-up available for clopidogrel versus aspirin monotherapy is approximately 5 years. Because secondary prevention is required indefinitely, further evidence on the long-term benefits of clopidogrel is needed. After the initial HOST-EXAM trial, we reported the mid-term results of the HOST-EXAM extended study, which showed consistent and continuous benefits of clopidogrel up to 5 years.[8] Similar findings were reported in the 5-year results of the STOPDAPT-2 trial, which suggested that clopidogrel might be an alternative to aspirin in the maintenance phase after PCI. One major limitation of the STOPDAPT-2 trial 5-year data is that they derive from an extension of a study that compared different antiplatelet strategies immediately after PCI (ie, clopidogrel monotherapy following 1 month of DAPT in the clopidogrel group *vs* aspirin monotherapy following 12 months of DAPT in the aspirin group), which introduced selection bias in the comparison of monotherapies beyond 1–5 years. The results therefore did not represent a direct comparison of antiplatelet monotherapy after completion of DAPT in patients with stabilised coronary artery disease.[4] Also, along with the HOST-EXAM trial and SMART-CHOICE 3 trial, all trials were conducted in east Asian cohorts, which limits the generalisability to non-Asian populations. In the current study, we compared clopidogrel versus aspirin monotherapy in patients with stabilised coronary artery disease over an extended follow-up. Maintaining long-term follow-up is challenging and has been achieved in only a few clinical trials. Among these, the SYNTAX trial compared only mortality events between PCI and coronary artery bypass surgery for coronary artery disease.[12] Compared with SYNTAX, our study evaluated a broader spectrum of adverse events, including both ischaemic and bleeding outcomes, with robust clinical follow-up and outcome ascertainment of 92·8% of patients.

The per-protocol analysis should be interpreted with caution because such analyses are prone to bias. In particular, treatment discontinuation can be influenced by non-medical factors. Nevertheless, our findings from the per-protocol analysis support the benefit of clopidogrel over aspirin. Based on the per-protocol analyses of previous results, the event rate of the primary composite endpoint at 2 years from the HOST-EXAM trial was 5·4% for the clopidogrel group versus 8·7% for the aspirin group. This event rate increased to 12·8%

versus 16·9% (clopidogrel *vs* aspirin) in the 5-year mid-term follow-up results, and in the current 10-year follow-up to 24·0% versus 29·8% (clopidogrel *vs* aspirin).[3,8] The number needed to treat decreased accordingly from 45 patients in the 2-year follow-up to 24 patients in the 5-year follow-up, and to 17 patients in the current analysis. The continued gradual decrease in the number needed to treat underscores the cumulative benefit of clopidogrel monotherapy over aspirin.

Several points from our study warrant discussion. First, no significant difference in all-cause mortality was observed between the two treatment groups. Clopidogrel monotherapy was associated with a lower risk of both thrombotic and bleeding events, yet this benefit did not translate into a reduction in long-term mortality. Although clopidogrel monotherapy is superior at preventing non-fatal myocardial infarction and stroke, these events might not result in immediate mortality in the modern era of rapid revascularisation and intensive secondary prevention. Unlike the acute phase after a vascular event (eg, acute myocardial infarction), during which antiplatelet therapy can be lifesaving, the marginal benefit of one agent over another in the chronic maintenance phase might be too small to alter overall survival in patients with multiple comorbidities. Second, protocol adherence was higher in the clopidogrel group, and the treatment effect associated with clopidogrel was more pronounced in the per-protocol population. During the 10-year follow-up, 350 (12·9%) patients in the clopidogrel group used a different antithrombotic medication, compared with 510 (18·7%) in the aspirin group. Non-adherence to aspirin is common for various reasons, including nuisance bruising, clinically relevant bleeding events, or gastrointestinal discomfort, which might contribute to adverse clinical outcomes.[13–15] In our study, gastrointestinal discomfort and physician-initiated switches in the aspirin group led to a higher incidence of discontinuation. Third, although the open-label design might have introduced some subjectivity in reporting gastrointestinal symptoms, gastrointestinal intolerance is a well established side-effect of aspirin, whereas the observed higher adherence in the clopidogrel group suggests better tolerability with long-term use. These findings challenge the traditional preference for routine aspirin use, suggesting that current treatment strategies might warrant reconsideration.[16,17]

Although not covered in our study, an important issue in long-term follow-up is perioperative antiplatelet management. Existing perioperative guidelines were formulated within a DAPT framework or for patients receiving aspirin monotherapy.[18] Therefore, future research is needed on perioperative antiplatelet management in patients receiving clopidogrel monotherapy.

This study has several limitations that should be noted. First, this was an extended follow-up of a randomised trial in which no antiplatelet regimen was mandated after the 2-year trial period. Physician discretion in antiplatelet selection could have been influenced by multiple factors. In fact, 18·7% of the aspirin group and 12·9% of the clopidogrel group changed their antiplatelet regimen during follow-up. Although a per-protocol analysis was done to reflect the actual agents used, exclusion of some patients might introduce bias. This limitation could preclude definitive conclusions, as the data do not represent a randomised comparison over a 10-year period, but only during the first 2 years. Second, because the HOST-EXAM trial cohort was entirely east Asian, the generalisability of these results to other populations might be limited, particularly given the high prevalence of CYP2C19 loss-of-function alleles and the routine use of imaging-guided PCI in this region. Regarding the issue of clopidogrel resistance, previous studies have shown that the prevalence of intermediate or poor metabolisers for clopidogrel is higher in east Asian populations.[19] None of the previous randomised clinical trials investigated potential interactions between clopidogrel metabolising phenotypes and clinical outcomes.[3–5] Although clopidogrel appears to be superior to aspirin, whether the results are influenced by metaboliser status remains unknown. However, clopidogrel resistance has mainly been associated with acute outcomes, whereas its association with outcomes in the chronic maintenance phase remains unclear.[20,21] Third, the open-label design of the HOST-EXAM trial could potentially introduce bias in the adjudication of certain clinical endpoints, such as readmission due to acute coronary syndrome, which might be more susceptible to physician discretion than harder endpoints. However, to minimise this potential bias, all suspected clinical events were strictly adjudicated by an independent clinical events committee. In addition, our additional analysis showed that a substantial majority (70·3%) of these readmissions due to acute coronary syndrome required urgent revascularisation, suggesting that these events represented clinically significant ischaemic episodes rather than subjective overdiagnosis. Fourth, we did not systematically collect data on the temporary discontinuation of study medications due to urgent or elective non-study-related invasive procedures. Given that periprocedural management of antiplatelet agents can affect both ischaemic and bleeding risks, the lack of this information might represent a confounding factor. However, given the consistency of findings from previous studies, it is unlikely that these unrecorded interruptions would materially alter the primary conclusions of our study. Fifth, adjustment for multiple testing across multiple outcomes was not done. Therefore, the statistical significance of secondary endpoints should be interpreted with caution. Sixth, the under-representation of women (1348 [25·4%] of 5438) in our study cohort might limit the generalisability of the findings. Seventh, a small proportion of the total population (104 [1·9%] of 5438 patients) received PCI with a first-generation drug-eluting stent. However, previous studies have shown no difference between new-generation and first-generation drug-eluting stents, particularly beyond the first year after PCI.[22]

In conclusion, among stabilised patients who underwent PCI with a drug-eluting stent, clopidogrel monotherapy was associated with significantly lower risk of the primary composite endpoint (all-cause death, non-fatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and BARC type ≥3 bleeding) than aspirin monotherapy over 10 years of follow-up. This clinical benefit was consistent across both thrombotic and bleeding endpoints, with no significant difference observed in all-cause death. These findings suggest that clopidogrel might be considered as a preferred agent for long-term antiplatelet monotherapy during the chronic maintenance phase after PCI.

Contributors

H-SK, KWP, JK, and H-MY conceptualised the study. JK, H-MY, E-SS, S-WR, J-WB, NHL, H-JY, YHC, UK, S-YK, S-HK, J-KH, KWP, and H-SK curated the data. JK, SP, and H-MY did the formal analysis. H-SK, KWP, and H-MY acquired the funding. E-SS, S-WR, J-WB, and J-KH did the investigation and methodology. E-SS, S-WR, J-WB, NHL, H-JY, YHC, UK, S-YK, S-HK, and J-KH were responsible for the project administration. NHL, H-JY, YHC, UK, S-YK, and S-HK were responsible for supervision and validation. JK, SP, and H-MY wrote the original draft. H-SK and KWP performed the manuscript revisions. JK, SP, H-MY, KWP, and H-SK accessed and verified the data. All authors had access to all the included data and were responsible for the decision to submit for publication.

Declaration of interests

H-SK reports research grants or speaker's fees from Daiichi Sankyo, Boston Scientific, Terumo, Biotronik, Dio, Medtronic, Abbott Vascular, Edwards Life Science, Amgen, and Boehringer Ingelheim. KWP reports speaker's fees from Daiichi Sankyo, Novartis, Amgen, InnoN Pharmaceutical, and DaeWoong Pharmaceutical, unrelated to the submitted work. All other authors declare no competing interests.

Data sharing

Any relevant inquiry should be emailed to H-SK or KWP. Upon publication of this trial, de-identified individual participant data and additional documents (eg, study protocol, statistical analysis plan, informed consent forms, and a data dictionary defining each field) will be available for sharing, subject to approval by the steering committee.

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