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

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Summary

Background The optimal strategy for long-term antiplatelet maintenance for patients who underwent percutaneous coronary intervention (PCI) remains uncertain. This study aimed to compare the efficacy and safety of clopidogrel versus aspirin monotherapy in patients who completed a standard duration of dual antiplatelet therapy (DAPT) following PCI with drug-eluting stents.

Methods In this multicentre, randomised, open-label trial, patients aged 19 years or older at high risk of recurrent ischaemic events (previous myocardial infarction at any time before enrolment, medication-treated diabetes, or complex coronary lesions) who completed a standard duration of DAPT after PCI were randomly assigned (1:1) to receive clopidogrel (75 mg once a day) or aspirin (100 mg once a day) oral monotherapy at 26 sites in South Korea. The primary endpoint was the cumulative incidence of a composite of death from any cause, myocardial infarction, or stroke, assessed in the intention-to-treat population. Adverse events were captured as part of the secondary endpoints. This trial is registered with ClinicalTrials.gov (NCT04418479). It is closed to accrual and extended follow-up is ongoing.

Findings Between Aug 10, 2020, and July 31, 2023, 5542 patients were assessed for eligibility and 5506 were randomly assigned (2752 to clopidogrel monotherapy and 2754 to aspirin monotherapy). The median time between PCI and randomisation was 17·5 months (IQR 12·6–36·1 months). During a median follow-up period of 2·3 years (IQR 1·6–3·0), the primary endpoint occurred in 92 patients in the clopidogrel group and 128 patients in the aspirin group (Kaplan–Meier estimated 3-year incidence 4·4% [95% CI 3·4–5·4] *vs* 6·6% [5·4–7·8]; hazard ratio 0·71 [95% CI 0·54–0·93]; p=0·013). Death from any cause occurred in 50 patients in the clopidogrel group and 70 in the aspirin group (2·4% [1·6–3·1] *vs* 4·0% [2·9–5·0] at 3 years; 0·71 [0·49–1·02]); myocardial infarction in 23 patients in the clopidogrel group and 42 in the aspirin group (1·0% [0·6–1·4] *vs* 2·2% [1·4–2·9] at 3 years; 0·54 [0·33–0·90]); and stroke in 23 in the clopidogrel group and 29 in the aspirin group (1·3% [0·7–2·0] *vs* 1·3% [0·8–1·7] at 3 years; 0·79 [0·46–1·36]). There was no difference in the risk of bleeding between the clopidogrel and aspirin groups (3·0% [2·0–3·9] *vs* 3·0% [2·2–3·9] at 3 years; 0·97 [0·67–1·42]). Clopidogrel was not associated with a higher incidence of any adverse event compared with aspirin.

Interpretation Among patients who were at high risk of recurrent ischaemic events and who completed the standard duration of DAPT following PCI, clopidogrel monotherapy, compared with aspirin monotherapy, significantly reduced the cumulative incidence of a composite of death from any cause, myocardial infarction, and stroke, without an apparent increase in the risk of bleeding.

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Introduction

Since the development and adoption of drug-eluting stents, numerous studies have explored strategies for dual antiplatelet therapy (DAPT), particularly during the first year after percutaneous coronary intervention (PCI).[1,2] However, long-term maintenance of antiplatelet therapy

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See Online for appendix

Research in context

Evidence before this study

After percutaneous coronary intervention (PCI) with a current-generation drug-eluting stent, dual antiplatelet therapy (DAPT) remains a cornerstone strategy to prevent recurrent ischaemic events in patients with coronary artery disease. After completion of a standard duration of DAPT, indefinite aspirin monotherapy is recommended for secondary prevention, but the optimal long-term antiplatelet strategy after PCI remains uncertain. We searched PubMed for relevant publications in English up to Feb 28, 2025, using the terms "single antiplatelet therapy", "long-term maintenance", "secondary prevention", "percutaneous coronary intervention", "drug-eluting stent", "aspirin", "clopidogrel", and "$P2Y_{12}$ inhibitor". We identified three randomised clinical trials comparing outcomes with aspirin versus $P2Y_{12}$ inhibitor monotherapy in patients treated with PCI after standard DAPT. The HOST-EXAM trial showed that clopidogrel monotherapy, compared with aspirin monotherapy, significantly reduced the incidence of adverse clinical events after standard DAPT maintenance following PCI with a drug-eluting stent. A landmark analysis of the GLOBAL LEADERS trial compared outcomes in patients treated with ticagrelor versus aspirin monotherapy beyond 1 year after PCI. During the second year, the ischaemic composite endpoint (all-cause death, any myocardial infarction, or stroke) was lower with ticagrelor monotherapy than with aspirin monotherapy, but Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding was numerically higher in the ticagrelor group. The 1-year landmark analysis of the STOPDAPT-2 trial showed that clopidogrel was numerically, but not significantly, superior to aspirin for cardiovascular events (cardiovascular death, myocardial infarction, definite stent thrombosis, or stroke) without a difference in major bleeding.

Added value of this study

SMART-CHOICE 3 was a large randomised trial comparing clopidogrel monotherapy against aspirin monotherapy for long-term maintenance therapy in patients with a high ischaemic risk (previous myocardial infarction, medication-treated diabetes, or complex coronary artery lesions) who completed a standard duration of DAPT after PCI. Clopidogrel monotherapy was associated with a significantly reduced risk of major adverse cardiac and cerebrovascular events, particularly myocardial infarction, compared with aspirin monotherapy. To our knowledge, SMART-CHOICE 3 is the first trial to show a benefit of clopidogrel monotherapy over aspirin monotherapy on a hard ischaemic endpoint after PCI. There was no difference in the incidence of BARC type 2, 3, or 5 bleeding between the clopidogrel and aspirin groups. The risk of upper gastrointestinal clinical events was lower in the clopidogrel group than in the aspirin group.

Implications of all the available evidence

Among patients with coronary artery disease who were at high risk of recurrent ischaemic events and completed the standard duration of DAPT after PCI, clopidogrel monotherapy was associated with a reduced risk of a composite of death from any cause, myocardial infarction, or stroke compared with aspirin monotherapy, without an increase in major bleeding. This trial adds to previous evidence supporting clopidogrel monotherapy as an alternative to aspirin for long-term secondary prevention in PCI patients at high risk of ischaemic events, by demonstrating that clopidogrel offers enhanced protection against ischaemic events without an apparent increase in bleeding.

after the initial phase of DAPT might be crucial for the lifelong management of patients undergoing PCI. Standard practice has been to recommend indefinite aspirin monotherapy following DAPT for the prevention of subsequent cardiovascular events in patients who have had a PCI.[3] These recommendations were largely based on a meta-analysis published in 2009, in which aspirin was associated with a 12% reduction in serious vascular events compared with control.[4] Data supporting the use of aspirin as a single antiplatelet therapy after DAPT in patients undergoing PCI have been debated, and clopidogrel has been proposed as a possibly superior alternative to aspirin,[5] as noted in the 2024 European Society of Cardiology guidelines for the management of chronic coronary syndromes.[6] However, only one trial, HOST-EXAM,[7] has provided data on a direct comparison of clopidogrel versus aspirin after DAPT in patients who underwent PCI. Although HOST-EXAM showed the superiority of clopidogrel monotherapy compared with aspirin monotherapy in preventing thrombotic and bleeding events, a trial with an adequate sample size comparing clopidogrel with aspirin, focusing solely on a strict endpoint of hard events, is necessary. Moreover, targeting patients with a higher risk profile than those enrolled in the HOST-EXAM trial could provide more robust evidence for the superiority of clopidogrel over aspirin and help identify the patients who would benefit the most.

Therefore, the Smart Angioplasty Research Team: Choice of Optimal Anti-Thrombotic Strategy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents (SMART-CHOICE) 3 trial was conducted 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 ischaemic events.

Methods

Study design and participants

SMART-CHOICE 3 was an investigator-initiated, multicentre, prospective, randomised, open-label trial conducted in South Korea. Details regarding the

participating centres and investigators are provided in the appendix (pp 3–5). Patients were eligible for enrolment if they were aged 19 years or older, had undergone successful PCI with a drug-eluting stent, had received a standard duration of DAPT (≥12 months for myocardial infarction and ≥6 months for any other event requiring PCI), had no cardiovascular events after PCI, and had at least one complex coronary artery lesion characteristic or clinical characteristic associated with a high risk of recurrent ischaemic events (ie, previous myocardial infarction or medication-treated diabetes). Complex coronary artery lesions were defined as true bifurcation lesions according to the Medina classification system, with a side branch diameter of at least 2·5 mm; a chronic total occlusion; unprotected left main coronary artery disease; long coronary artery lesions with an expected stent length of at least 38 mm; multivessel PCI involving at least two major epicardial coronary arteries that were treated at the same time; a lesion requiring multiple stents (at least three implanted stents); in-stent restenosis; severely calcified lesions; or ostial lesions of a major epicardial coronary artery. Exclusion criteria included ongoing long-term treatment with oral anticoagulants; use of DAPT for any reason other than coronary artery disease; use of single antiplatelet therapy at screening; or contraindications to aspirin or clopidogrel. Details of the inclusion and exclusion criteria are provided in the appendix (pp 6–7).

The institutional review board of Samsung Medical Center (Seoul, South Korea; approval number 2020-03-031; date of approval June 1, 2020) and the institutional review board of each participating centre approved the trial protocol. All patients provided written informed consent before randomisation. The study protocol and statistical analysis plan are in the appendix (pp 44–101). An independent data and safety monitoring board reviewed safety data from the study and provided recommendations for adverse events or serious adverse events, protocol deviation, and follow-up case reports. The event adjudication process was conducted by an independent clinical event adjudication committee (appendix p 3) composed of interventional cardiologists who did not participate in this study. All reported events (primary and secondary endpoints) were reviewed in a blinded manner to minimise bias and ensure objective assessment. Each case was independently reviewed by three committee members, and discrepancies were resolved through discussion and majority vote. All authors vouched for the accuracy and completeness of the data and the fidelity of the trial to the protocol.

This trial is registered with ClinicalTrials.gov, NCT04418479, and is closed to accrual. Patient follow-up is ongoing and expected to continue for 5 years.

Randomisation and masking

Using a web-based randomisation procedure (Apache 2, PHP 5.3, and MySOL5; S-Soft, Seoul, South Korea) with computer-generated block randomisation (with a block size of four), patients were randomly assigned in a 1:1 ratio to clopidogrel monotherapy (clopidogrel group) or aspirin monotherapy (aspirin group) with stratification according to clinical presentation at the index PCI (myocardial infarction or any other event requiring PCI) and participating centre. Participants and study investigators were not masked to group allocation.

Procedures

After randomisation, DAPT was immediately changed to the allocated medication. Participants were given either clopidogrel (75 mg once a day) or aspirin (100 mg once a day) orally. Clinical follow-up was done at 6 months (with a window of ±30 days) and 12 months (±30 days) from randomisation, and annually thereafter (±90 days). All participants were scheduled to be followed up until 12 months after the enrolment of the last patient. If in-person visits were unavailable, telephone interviews were conducted. At each visit, active surveillance through patient history reviews, physical examinations, and additional tests if necessary were done for any adverse clinical events, including ischaemic and bleeding outcomes, along with an assessment of adherence to the study drug. As an exploratory analysis, the steering committee decided to perform *CYP2C19* genotype testing in patients assigned to clopidogrel monotherapy if they agreed to genetic analysis from Aug 27, 2021. Details of the study protocol and measurements including *CYP2C19* genotype testing are provided in the appendix (pp 15–16).

Outcomes

The primary endpoint was the cumulative incidence of major adverse cardiac and cerebrovascular events (MACCE; a composite of death from any cause, myocardial infarction [defined according to the Fourth Universal Definition of Myocardial Infarction[8]], or stroke [defined as a sudden onset of neurological signs or symptoms fitting a focal or multifocal vascular territory within the brain, spinal cord, or retina[9]]) during follow-up. The vital status of all patients was cross-checked using the Korean National Health Insurance Service system. Secondary endpoints included the individual components of the primary endpoint; death from cardiovascular causes (defined as sudden cardiac death; death due to acute myocardial infarction, heart failure, cardiogenic shock, or other cardiovascular causes; or any unknown death without an undisputed non-cardiac cause); definite or probable stent thrombosis (according to Academic Research Consortium criteria);[10] major bleeding (defined as Bleeding Academic Research Consortium [BARC] type 3 or 5); bleeding (BARC type 2, 3, or 5);[11] target-lesion revascularisation; target-vessel revascularisation; any revascularisation; upper gastrointestinal clinical events (a composite of overt bleeding of gastroduodenal origin, overt upper gastrointestinal bleeding of unknown origin,

occult gastrointestinal bleeding with a documented decrease in haemoglobin concentration of at least 2 g/dL, symptomatic gastroduodenal ulcer or at least five erosions, symptomatic gastro-oesophageal reflux disease, upper gastrointestinal obstruction, or perforation); gastrointestinal ulcer or bleeding; symptomatic gastro-oesophageal reflux disease; net adverse clinical events (defined as MACCE plus BARC type 3 or 5 bleeding); and medical costs. Medical costs are not reported in this paper and a subsequent publication is planned to report the results of the cost-effectiveness analysis. All primary and secondary endpoints and their associated definitions are listed in the appendix (pp 8–14). Adverse events were captured as part of the secondary endpoints. A high risk of bleeding was defined according to the Academic Research Consortium criteria.[12]

Statistical analysis

The working hypothesis of this study was that clopidogrel monotherapy would be superior to aspirin monotherapy as a long-term maintenance treatment after PCI. Assuming an annual MACCE incidence of 4% with aspirin monotherapy, we chose a sample size of 5000, which provided 82% power to detect a 25% lower incidence of MACCE with clopidogrel monotherapy (assumed annual MACCE incidence 3%), with a two-sided type I error of 0·05, using the log-rank test, given an anticipated accrual time of 3 years, follow-up duration of 1 year from final patient enrolment, and a dropout rate of 2·5%. This estimate was based on previous trials that evaluated the rates of MACCE in patients who completed the standard duration of DAPT and were at high risk of recurrent ischaemic events.[13–15] When the original target sample size of 5000 patients was reached ahead of the planned accrual period, investigators debated whether to stop or extend patient enrolment. A blind analysis of the entire dataset, conducted without interim analyses by treatment group, indicated that the actual event rates were lower than expected. On the advice of the data and safety monitoring board and in consultation with the trial statisticians, we decided to continue enrolling patients until the end of the planned recruitment period (ie, a 3-year accrual period) rather than performing adaptive sample size recalculations. This approach aligned with the principles outlined in the International Council for Harmonisation E9 guidelines, which permit such extensions when based on prespecified criteria unrelated to treatment effect.

All analyses were done on an intention-to-treat basis. A per-protocol sensitivity analysis (ie, all patients with no protocol violations; appendix pp 18–19) was also done. The cumulative incidence of the primary and secondary endpoints was estimated using the Kaplan–Meier method. Hazard ratios (HRs) and 95% CIs were calculated using Cox proportional hazards models. All models were adjusted for clinical presentation (myocardial infarction or any other event requiring PCI) and participating centre as stratification factors. The proportional hazards assumption was satisfied for all endpoints (p>0·05) according to the Schoenfeld residual tests, except death from any cause (p=0·01). However, further diagnostic evaluations, including difference in β plots, showed no influential outliers or systematic deviations affecting the hazard estimates for death from any cause. Data from patients who did not have a primary endpoint during follow-up were censored at the time of the last known contact or at 3 years (75th percentile of the follow-up period), whichever came first. As part of the sensitivity analysis, a competing-risk analysis using the Fine–Gray subdistribution hazard model was done for the secondary endpoints, considering death from a non-cardiovascular cause (for death from cardiovascular cause) or death from any cause (for other secondary endpoints) as a competing event.[16] We also performed a permutation test with 5000 resampling iterations to empirically estimate the type I error rate. Additional details regarding the statistical analysis are provided in the appendix (pp 17–19, 87–101). There was no adjustment for multiple testing and multiplicity of outcomes for the number of comparisons. The p values for secondary

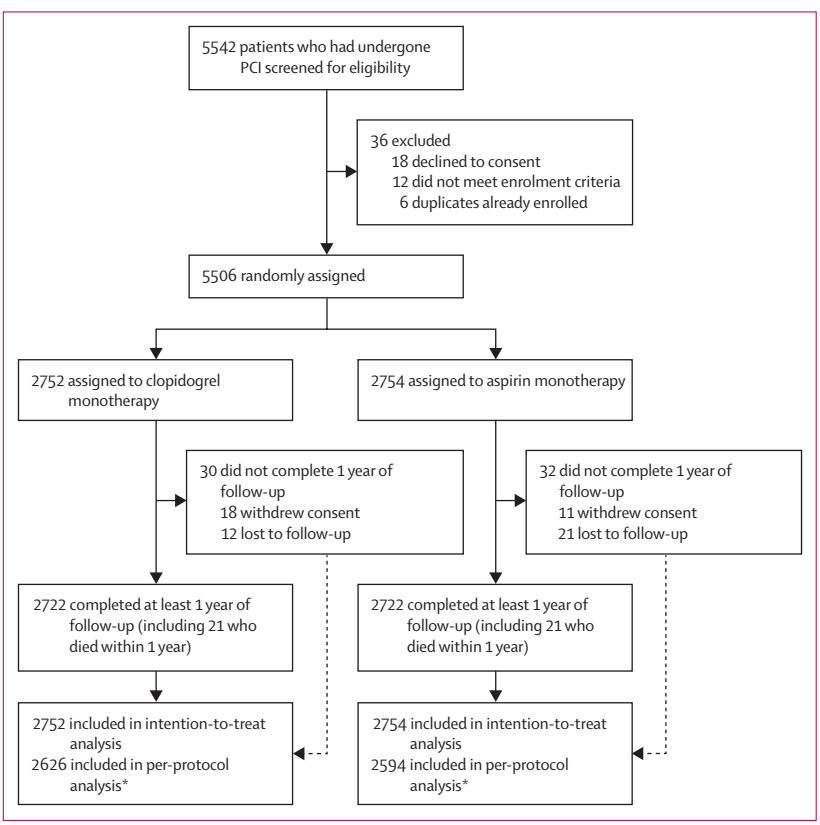

Figure 1: **Trial profile**
In accordance with the protocol, the primary endpoint was assessed at 1 year after the last patient was enrolled, with all patients having a minimum of 12 months of follow-up. The primary analysis was done in the intention-to-treat population. PCI=percutaneous coronary intervention. *126 patients in the clopidogrel group and 160 in the aspirin group deviated from the protocol and were not included in the per-protocol analysis.

endpoints were not presented to avoid misinterpretation of statistical significance. All probability values were two-sided, and p <0·05 was considered statistically significant.

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 Aug 10, 2020, and July 31, 2023, 5542 patients who completed the standard duration of DAPT and who were at high risk of recurrent ischaemic events after PCI at 26 sites in South Korea were screened for eligibility, and 5506 were randomly assigned to receive either clopidogrel monotherapy (2752 patients) or aspirin monotherapy (2754 patients; figure 1). The last patient was randomly assigned on July 31, 2023, and the database was locked on Oct 31, 2024. We did not collect data on race or ethnicity because all enrolled patients were Korean.

Assessment of the primary endpoint at least 1 year after randomisation was completed in 5444 (98·9%) patients (2722 [98·9%] in the clopidogrel group and 2722 [98·8%] in the aspirin group; figure 1). 3906 (70·9%) patients died within or completed 2 years of follow-up, 1918 (34·8%) died within or completed 3 years of follow-up, and 1334 (24·2%) died or had follow-up beyond 3 years, with consideration of the window period. During the follow-up period, 286 (5·2%) patients deviated from the study protocol (126 [4·6%] in the clopidogrel group and 160 [5·8%] in the aspirin group). Details regarding the reasons for protocol violations are summarised in the appendix (p 26), and the medications used during the study period are shown in the appendix (pp 27–28).

The demographics and clinical characteristics at baseline were well balanced between the treatment groups (table 1). The median age of included patients was 65·0 years (IQR 58·0–73·0), 1002 (18·2%) patients were female, 2247 (40·8%) had diabetes (2089 [37·9%] had medication-treated diabetes), and 2552 (46·3%) underwent PCI for acute myocardial infarction (1330 [24·2%] with non-ST-segment elevation myocardial infarction and 1222 [22·2%] with ST-segment elevation myocardial infarction). At randomisation (not at the index PCI), 875 (15·9%) patients had a high risk of bleeding. The median time between PCI and randomisation was 17·5 months (IQR 12·6–36·1; appendix p 20). 3147 (57·2%) patients had angiographically confirmed multivessel disease, and 4185 (76·0%) patients underwent PCI for complex coronary artery lesions (appendix pp 29–30). The baseline clinical and procedural characteristics of patients without protocol violations are provided in the appendix (pp 31–34). No significant differences were noted in the

	Clopidogrel group (n=2752)	Aspirin group (n=2754)
Age, years	66·0 (58·0–73·0)	65·0 (58·0–73·0)
Sex*		
Male	2240 (81·4%)	2264 (82·2%)
Female	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)
Diagnosis at index PCI		
Chronic coronary syndrome	672 (24·4%)	662 (24·0%)
Unstable angina	797 (29·0%)	823 (29·9%)
Non-ST-segment elevation myocardial infarction	678 (24·6%)	652 (23·7%)
ST-segment elevation myocardial infarction	605 (22·0%)	617 (22·4%)
Hypertension	1756 (63·8%)	1690 (61·4%)
Diabetes	1119 (40·7%)	1128 (41·0%)
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)
Haemoglobin concentration, g/dL	13·8 (1·7)	13·8 (1·7)
Platelet count, ×10³ cells per L	216·6 (66·6)	215·6 (61·3)
Estimated glomerular filtration rate§, mL/min per 1·73 m²	86·7 (19·5)	86·2 (19·9)
LDL cholesterol concentration, mmol/L	1·55 (0·57)	1·56 (0·56)
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)
≤12 months of DAPT before randomisation	368 (13·4%)	372 (13·5%)
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%)
ACE inhibitor 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%)

Data are mean (SD), median (IQR), or n (%). ACE=angiotensin-converting enzyme. ARB=angiotensin receptor blocker. ARC=Academic Research Consortium. DAPT=dual antiplatelet therapy. PCI=percutaneous coronary intervention. *Only biological sex was reported. †Defined as kidney damage (pathological abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies) or an estimated glomerular filtration rate of less than 60 mL/min per 1·73 m². ‡Data on left ventricular ejection fraction were available for 2436 (88·5%) patients in the clopidogrel group and 2434 (88·4%) in the aspirin group. §The estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease method.

Table 1: **Baseline patient characteristics**

initial, follow-up, and delta complete blood cell count between the two groups (appendix p 35).

The median follow-up of the total population was 2·3 years (IQR 1·6–3·0), with no significant difference between the clopidogrel group (2·2 years [1·6–2·9]) and aspirin group (2·3 years [1·6–3·0]; p=0·86). The primary endpoint occurred in 92 of 2752 patients in the clopidogrel group and 128 of 2754 patients in the aspirin group (Kaplan–Meier estimated 3-year incidence 4·4% [95% CI 3·4–5·4] in the clopidogrel group *vs* 6·6% [5·4–7·8] in the aspirin group; HR 0·71 [95% CI 0·54–0·93]; p=0·013) with an absolute risk reduction of 2·2 percentage points (number needed to treat to prevent one event 45 patients; table 2, figure 2A). In the permutation test, the empirical type I error rate was 1·7% (p=0·017). Death from any cause occurred in 50 patients in the clopidogrel group and 70 patients in the aspirin group (2·4% [1·6–3·1] *vs* 4·0% [2·9–5·0] at 3 years; HR 0·71 [95% CI 0·49–1·02]; figure 2B); myocardial infarction occurred in 23 patients in the clopidogrel group and 42 patients in the aspirin group (1·0% [0·6–1·4] *vs* 2·2% [1·4–2·9] at 3 years; 0·54 [0·33–0·90]; figure 2C); and stroke occurred in 23 patients in the clopidogrel group and 29 in the aspirin group (1·3% [0·7–2·0] *vs* 1·3% [0·8–1·7] at 3 years; 0·79 [0·46–1·36]; figure 2D). Specific causes of death are listed in the appendix (p 36). Both BARC type 2, 3, or 5 bleeding and major bleeding (BARC type 3 or 5) were similar across the two groups (table 2, figure 3). Upper gastrointestinal clinical events were less frequent in the clopidogrel group than in the aspirin group (table 2).

Sensitivity analyses in the per-protocol population yielded consistent results for the primary endpoint of MACCE (HR 0·70 [95% CI 0·54–0·92]; appendix pp 21, 37) and the secondary endpoint of major bleeding (0·95 [0·54–1·67]; appendix pp 22, 37). A

	Clopidogrel group (n=2752)	Aspirin group (n=2754)	Hazard ratio (95% CI)
Primary endpoint			
Major adverse cardiac and cerebrovascular events*	92 (4·4% [3·4–5·4])	128 (6·6% [5·4–7·8])	0·71 (0·54–0·93), p=0·013
Secondary endpoints			
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)
Myocardial infarction†	23 (1·0% [0·6–1·4])	42 (2·2% [1·4–2·9])	0·54 (0·33–0·90)
Stroke	23 (1·3% [0·7–2·0])	29 (1·3% [0·8–1·7])	0·79 (0·46–1·36)
Ischaemic stroke	20 (1·0% [0·5–1·5])	25 (1·1% [0·6–1·6])	0·79 (0·44–1·43)
Haemorrhagic stroke	3 (0·3% [0·0–0·8])	4 (0·2% [0·0–0·3])	0·74 (0·17–3·30)
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 myocardial infarction	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 myocardial infarction	54 (2·3% [1·6–3·0])	81 (4·1% [3·1–5·1])	0·66 (0·47–0·94)
Death from cardiovascular cause, myocardial infarction, or stroke	76 (3·6% [2·7–4·5])	103 (4·9% [3·9–6·0])	0·73 (0·54–0·98)
Death from cardiovascular cause, myocardial infarction, or stent thrombosis	54 (2·3% [1·6–3·0])	81 (4·1% [3·1–5·1])	0·66 (0·47–0·94)
Bleeding (BARC type 2, 3, or 5)	53 (3·0% [2·0–3·9])	55 (3·0% [2·2–3·9])	0·97 (0·67–1·42)
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)
Gastro-oesophageal reflux disease	23 (1·0% [0·6–1·5])	47 (2·6% [1·7–3·4])	0·49 (0·30–0·81)
Net adverse clinical event¶	111 (5·4% [4·2–6·5])	142 (7·3% [6·0–8·6])	0·78 (0·61–0·99)
Target-lesion revascularisation	32 (1·7% [1·0–2·3])	40 (2·0% [1·3–2·7])	0·80 (0·50–1·27)
Target-vessel revascularisation	42 (2·2% [1·4–2·9])	50 (2·6% [1·8–3·4])	0·84 (0·56–1·27)
Any revascularisation	81 (4·2% [3·1–5·2])	87 (4·5% [3·4–5·5])	0·94 (0·69–1·27)

Values are n (Kaplan–Meier estimated % at 3 years [95% CI]) or hazard ratio (95% CI). The database for the analysis was locked on Oct 31, 2024. Clinical endpoints were evaluated in the intention-to-treat population during the overall study period (ie, from the time of randomisation to the day of the first occurrence of a primary endpoint event, the day of the last office visit or telephone follow-up, or the day of death during follow-up). BARC=Bleeding Academic Research Consortium. *Composite of death from any cause, myocardial infarction, or stroke. †Defined according to the Fourth Universal Definition. ‡Defined according to Academic Research Consortium criteria (definite or probable). §Composite of overt bleeding of gastroduodenal origin, overt upper gastrointestinal bleeding of unknown origin, occult gastrointestinal bleeding with a documented decrease in haemoglobin concentration of at least 2 g/dL, symptomatic gastroduodenal ulcer or at least five erosions, symptomatic gastro-oesophageal reflux disease, upper gastrointestinal obstruction, or perforation. ¶Composite of death from any cause, myocardial infarction, stroke, or major bleeding (BARC type 3 or 5).

Table 2: **Primary and secondary endpoints in the intention-to-treat population**

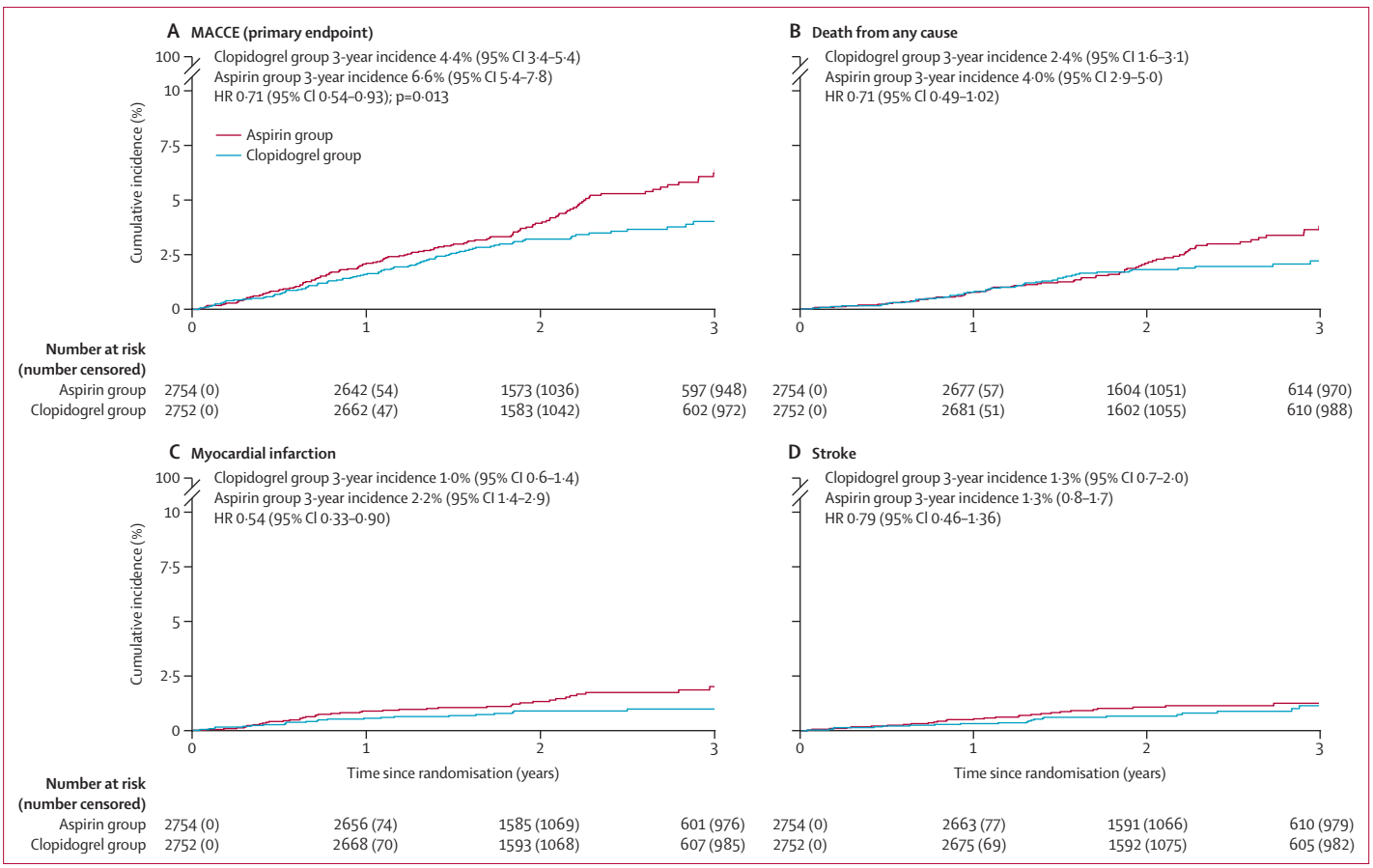

***Figure 2*: Cumulative incidence of MACCE (A), death from any cause (B), myocardial infarction (C), and stroke (D) at 3 years**
Note: y-axes are broken. HR=hazard ratio. MACCE=major adverse cardiac and cerebrovascular events.

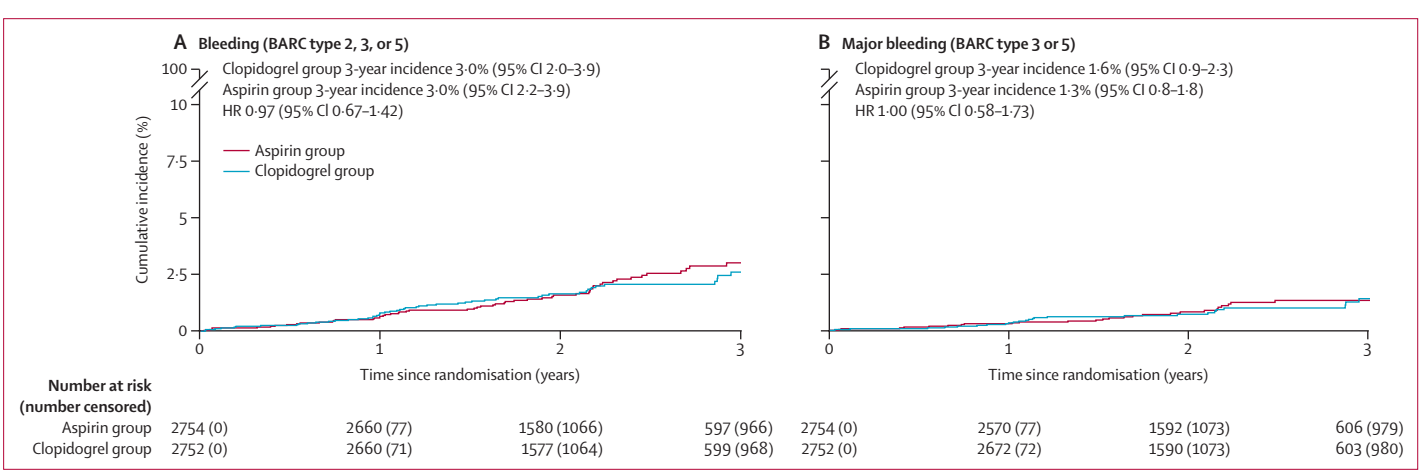

***Figure 3*: Cumulative incidence of BARC type 2, 3, or 5 bleeding (A) and BARC type 3 or 5 bleeding (B) at 3 years**
Note: y-axes are broken. HR=hazard ratio. BARC=Bleeding Academic Research Consortium.

landmark analysis at 2 years of follow-up showed consistent benefits of clopidogrel over aspirin with regard to MACCE, although the difference between the two groups was more prominent beyond 2 years (appendix p 23). A competing-risk analysis for secondary endpoints consistently showed similar results (appendix p 38). We also conducted sensitivity analyses restricted to patients with complete follow-up over 1, 2, and 3 years. In participants with at least 1 year of follow-up, the overall HR for MACCE in the clopidogrel group compared with

	Clopidogrel group		Aspirin group		Hazard ratio (95% CI)	$p_{interaction}$
	n/N	3-year cumulative incidence, % (95% CI)*	n/N	3-year cumulative incidence, % (95% CI)*		
Age (years)						**0·70**
≥75 (n=1070)	35/531	9·3% (5·6–12·9)	51/539	13·2% (9·3–17·0)	0·67 (0·43–1·04)	
<75 (n=4436)	57/2221	3·3% (2·4–4·2)	77/2215	5·1% (3·8–6·3)	0·74 (0·53–1·05)	
Sex						**0·21**
Male (n=4504)	76/2240	4·4% (3·3–5·5)	98/2264	6·0% (4·7–7·3)	0·78 (0·58–1·06)	
Female (n=1002)	16/512	4·3% (2·0–6·6)	30/490	9·4% (5·4–13·1)	0·52 (0·30–0·96)	
Duration of DAPT before randomisation (>12 months *vs* ≤12 months)						**0·20**
>12 months (n=4766)	86/2384	4·7% (3·6–5·8)	113/2382	6·7% (5·3–8·0)	0·76 (0·57–1·00)	
≤12 months (n=740)	6/368	2·2% (0·3–4·1)	15/372	6·2% (2·6–9·6)	0·39 (0·14–1·08)	
Duration of DAPT before randomisation (>18 months *vs* ≤18 months)						**0·16**
>18 months (n=2685)	55/1330	5·2% (3·7–6·6)	67/1335	7·0% (5·2–8·9)	0·85 (0·59–1·21)	
≤18 months (n=2821)	37/1422	3·6% (2·2–5·0)	61/1399	6·0% (4·4–7·6)	0·57 (0·38–0·86)	
Diabetes						**0·12**
Medication-treated diabetes (n=2089)	36/1039	4·5% (2·8–6·1)	65/1050	9·1% (6·6–11·6)	0·57 (0·38–0·86)	
Others (n=3417)	56/1713	4·3% (3·1–5·5)	63/1704	5·1% (3·8–6·4)	0·87 (0·60–1·25)	
Renal function						**0·59**
Chronic kidney disease (n=502)	26/242	12·7% (7·8–17·3)	38/260	22·3% (14·7–29·3)	0·95 (0·56–1·60)	
No chronic kidney disease (n=5004)	66/2510	3·6% (2·6–4·6)	90/2494	4·9% (3·8–6·0)	0·72 (0·52–0·99)	
Clinical presentation						**0·04**
Myocardial infarction (n=2552)	48/1283	5·0% (3·4–6·6)	49/1269	5·4% (3·8–7·0)	0·99 (0·67–1·49)	
No myocardial infarction (n=2954)	44/1469	3·7% (2·6–4·9)	79/1485	7·6% (5·8–9·5)	0·56 (0·39–0·81)	
Bleeding risk†						**0·62**
High bleeding risk (n=875)	36/427	9·7% (6·6–12·7)	56/448	18·8% (13·3–24·0)	0·71 (0·46–1·09)	
No high bleeding risk (n=4631)	56/2325	3·4% (2·4–4·4)	72/2306	4·4% (3·3–5·4)	0·78 (0·55–1·10)	
Anatomical complexity						**0·52**
Complex PCI (n=4185)	72/2113	4·6% (3·3–5·7)	103/2072	7·1% (5·6–8·6)	0·67 (0·50–0·91)	
Non-complex PCI (n=1318)	20/638	3·8% (2·1–5·6)	25/680	5·1% (3·0–7·2)	0·82 (0·46–1·49)	
Use of PPI at randomisation						**0·32**
PPI use (n=1134)	26/545	6·2% (3·6–8·8)	31/589	6·0% (3·9–8·1)	0·90 (0·53–1·52)	
No PPI use (n=4372)	66/2207	3·9% (2·8–4·9)	97/2165	6·7% (5·2–8·1)	0·66 (0·48–0·90)	
BMI						**0·84**
≥25 kg/m² (n=2617)	41/1323	4·1% (2·7–5·4)	53/1294	5·7% (4·0–7·2)	0·79 (0·53–1·20)	
<25 kg/m² (n=2698)	50/1340	4·8% (3·3–6·3)	68/1358	7·3% (5·4–9·3)	0·74 (0·52–1·07)	
Type of $P2Y_{12}$ inhibitor before randomisation						**0·51**
Clopidogrel (n=3431)	62/1702	4·8% (3·5–6·1)	93/1729	7·5% (5·8–9·1)	0·68 (0·49–0·94)	
Ticagrelor or prasugrel (n=2075)	30/1050	3·7% (2·2–5·2)	35/1025	5·2% (3·3–7·0)	0·89 (0·54–1·46)	
Left ventricular function‡						**0·80**
Reduced function (n=203)	10/104	10·6% (4·1–16·8)	12/99	17·5% (5·8–27·7)	1·02 (0·41–2·56)	
Preserved function (n=4667)	72/2332	4·2% (3·1–5·3)	97/2335	6·0% (4·7–7·4)	0·74 (0·55–1·01)	
All patients (n=5506)	**92/2752**	**4·4% (3·4–5·4)**	**128/2754**	**6·6% (5·4–7·8)**	**0·71 (0·54–0·93)**	**NA**

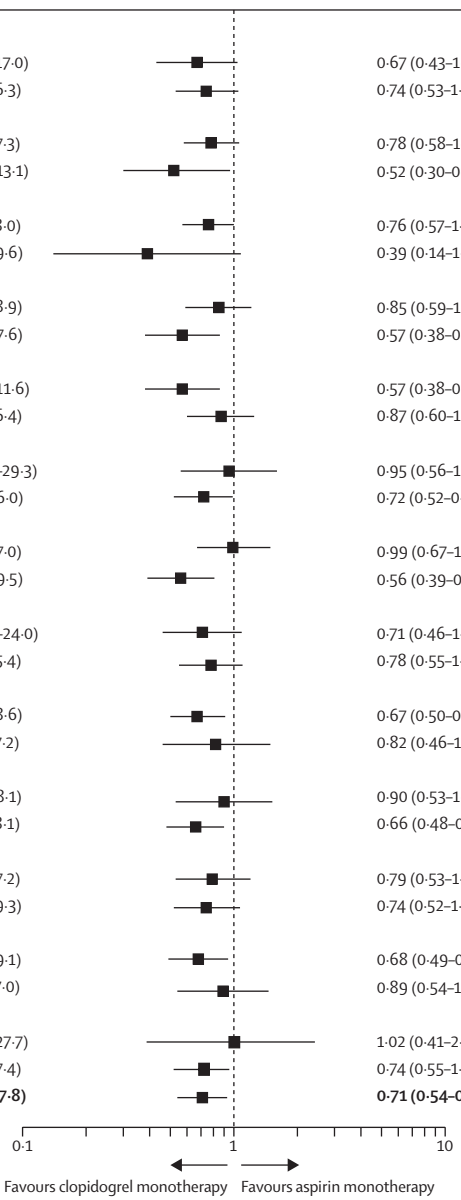

Figure 4: **Subgroup analysis for MACCE (primary endpoint) at 3 years**
DAPT=dual antiplatelet therapy. MACCE=major adverse cardiac and cerebrovascular events. NA=not applicable. PCI=percutaneous coronary intervention. PPI=proton-pump inhibitor. *Percentages (95% CI) are estimated 3-year cumulative incidence from Kaplan–Meier analysis. †Defined according to Academic Research Consortium criteria. ‡Left ventricular function was assessed by ejection fraction from echocardiography; an ejection fraction of 40% or less was defined as reduced function.

the aspirin group was 0·70 (95% CI 0·53–0·92). Among patients with at least 2 years of follow-up, the overall HR was 0·71 (0·54–0·93). Similarly, in patients with at least 3 years of follow-up, the overall HR was 0·73 (0·56–0·97).

The effects of clopidogrel monotherapy on the primary endpoint were generally consistent across the prespecified subgroups (figure 4). There was significant interaction between the treatment effect of clopidogrel monotherapy and clinical presentation for the risk of MACCE ($p_{interaction}$=0·04). Among patients without previous myocardial infarction, the clopidogrel group had a lower estimated cumulative incidence of MACCE at 3 years than the aspirin group (HR 0·56 [95% CI 0·39–0·81]). Conversely, in patients with previous myocardial infarction, the risk of MACCE did not differ between the two groups (0·99 [0·67–1·49]). A

similar incidence of major bleeding between the clopidogrel and aspirin groups was consistently observed across all prespecified subgroups (appendix p 24).

In the exploratory subgroup analysis of patients allocated to the clopidogrel group who underwent *CYP2C19* genotype testing for clopidogrel effectiveness (n=731), there was no significant difference in the risk of the primary endpoint in patients with rapid or normal metabolism versus patients with intermediate or poor metabolism of clopidogrel (appendix p 25).

Discussion

Among patients at high risk of recurrent ischaemic events who underwent PCI and completed a standard duration of DAPT, clopidogrel monotherapy was superior to aspirin monotherapy in reducing MACCE in the present study. This difference was mainly driven by a reduction in myocardial infarction in the clopidogrel group versus the aspirin group. No apparent differences were observed in the overall incidence of bleeding or major bleeding between the groups.

After PCI, most patients require DAPT within 1 year. However, single antiplatelet therapy will typically cover a much longer duration during lifelong management. Nevertheless, evidence regarding the preferred antiplatelet monotherapy following the standard duration of DAPT has been limited due to the scarcity of randomised trials, and the indefinite use of aspirin after discontinuation of $P2Y_{12}$ inhibitors remains the cornerstone of secondary prevention for these patients.[3,17] Thus far, very few relevant randomised trials have compared clopidogrel and aspirin monotherapy. The CAPRIE study[14] found that long-term administration of clopidogrel in patients with atherosclerotic vascular disease was more effective than aspirin in reducing the composite risk of vascular death, myocardial infarction, or ischaemic stroke. However, that study was not dedicated to the population undergoing PCI, but included patients who had recently had an ischaemic stroke or myocardial infarction, in addition to patients with symptomatic peripheral artery disease. Additionally, the enrolled patients were not stabilised and did not receive systematic DAPT before clopidogrel or aspirin monotherapy, and the aspirin dose used was 300 mg, which far exceeded the currently recommended dose. The trial was also conducted during the early 1990s, and hence the included population did not reflect contemporary practices such as PCI with current-generation drug-eluting stent and advanced pharmacotherapy. The HOST-EXAM trial[7] showed that clopidogrel monotherapy, compared with aspirin monotherapy, significantly reduced net adverse clinical events among patients undergoing PCI. These results are in line with the results of the SMART-CHOICE 3 trial. However, SMART-CHOICE 3 differs from HOST-EXAM in several features. First, our study exclusively enrolled patients at a high risk of recurrent ischaemic events, whereas the HOST-EXAM trial enrolled patients without restrictions on patient risk profile or lesion complexity. The cumulative incidences of death from cardiovascular causes and of non-fatal myocardial infarction were much higher in the SMART-CHOICE 3 trial than in the HOST-EXAM trial.[7] Second, MACCE was chosen as our primary endpoint to focus on clinically meaningful ischaemic events; the primary endpoint of the HOST-EXAM trial was broader, including readmission due to acute coronary syndrome as well as both ischaemic and bleeding events. To our knowledge, 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 who completed the standard duration of DAPT and were at a high risk of recurrent ischaemic events after PCI.

There are several plausible explanations for the superiority of clopidogrel to aspirin in the present study. First, the $P2Y_{12}$ receptor is a central mediator of the haemostatic response and plays a central role in the enhancement of the efficiency of platelet activation by other agonists, including thromboxane A_2.[18,19] Moreover, in a randomised crossover study in patients with stents who had received at least 6-month DAPT, clopidogrel monotherapy was associated with greater platelet inhibition and lower coagulation activity than aspirin monotherapy.[20] Clopidogrel also has been shown to have beneficial effects beyond platelet inhibition by reducing leukocyte activity and platelet–leukocyte interactions.[21] This anti-inflammatory effect could contribute to a reduction in MACCE with clopidogrel monotherapy. Second, we exclusively enrolled patients at high risk of recurrent ischaemic events. In an ancillary study of the STOPDAPT-2 trial,[22] clopidogrel was suggested as a possible alternative to aspirin, with a borderline ischaemic benefit beyond 1 year after PCI. However, that study population had relatively low ischaemic risk. These findings highlight the importance of risk stratification, as the results of SMART-CHOICE 3 suggest that clopidogrel is more beneficial for patients with higher ischaemic risk. A secondary analysis of the STOPDAPT-3 trial also did not show superiority of clopidogrel monotherapy over aspirin monotherapy beyond 1 month and up to 1 year after PCI.[23] However, differences in study design and the preceding antiplatelet regimen before randomisation preclude a direct comparison between the STOPDAPT-3 trial and the SMART-CHOICE 3 trial. Third, the risk of bleeding, either major or clinically relevant bleeding, was not significantly different between the groups in the present study. These results are consistent with those of previous observational studies and meta-analyses of randomised trials.[13,24] On the contrary, ticagrelor monotherapy was associated with fewer ischaemic events but more bleeding events compared with aspirin monotherapy during the second

year after PCI, although these results were derived from a post-hoc subanalysis.[25] Furthermore, an increased risk of death from any cause with clopidogrel treatment, a concern raised by previous studies,[7,15] was not observed in this trial. In addition, the absence of a difference in the incidence of gastrointestinal bleeding between clopidogrel and aspirin might result from a low proportion of patients with a high bleeding risk and relatively frequent use of gastrointestinal protection medication. These results were consistent with those observed in the CAPRIE trial.[14] Taken together, these data suggest that clopidogrel monotherapy is a promising option in the stabilised period following PCI.

Unexpectedly, the benefit of clopidogrel monotherapy in preventing MACCE events was greater in patients without previous myocardial infarction than in those with previous myocardial infarction. Patients without previous myocardial infarction had a similar or even higher risk profile than those with previous myocardial infarction in the present study (appendix pp 39–42) and thus might derive greater benefit from clopidogrel monotherapy. There might have been a selection bias as investigators excluded patients who had previous myocardial infarction and were considered to be at very high risk for recurrent ischaemic events. However, the findings that clopidogrel monotherapy showed a greater benefit in patients without previous myocardial infarction compared with those with previous myocardial infarction could be due to chance as a consequence of multiple comparisons. In the current study, the Kaplan–Meier curves for death due to any cause started to diverge at 2 years after randomisation. However, these results appear to be due to a decrease in the slope of the survival curve in the clopidogrel group starting at 2 years, rather than a sudden increase in the aspirin group. When examining the primary endpoint, the survival curves began to separate within 1 year after randomisation and continued to diverge up to 3 years. Late separation of survival curves has occasionally been observed in randomised trials—for example, at nearly 3 years in the IMPROVE-IT trial[26] and 9 months in the HOST-EXAM trial[7]—especially when the event in question occurred less frequently than expected.

This study had several limitations. First, because the trial had an open-label design, the allocated groups were not masked by the physician. We minimised the risk of potential bias by choosing a composite primary outcome that is not subject to investigator bias (death from any cause, myocardial infarction, or stroke), using an endpoint analysis with precisely defined criteria, and having the clinical outcomes assessed by blinded independent clinical event committee. Nevertheless, the open-label design might have influenced prescribing behaviours, as clinicians might, for example, have been more inclined to initiate gastrointestinal protective medications for patients receiving aspirin. Second, the actual event rate was lower than expected, resulting in only around half the number of expected events, even though the final sample size was increased by 10% from the original sample size. Moreover, we did not have an adaptive design, and the requirements or criteria for an increase in sample size were not prespecified. Consequently, there was a relatively high risk of a type I error, although a permutation test showed that the empirical type I error rate was low. The current study provides some, rather than strong, evidence on the superiority of clopidogrel over aspirin, but the clinically meaningful absolute risk reduction of 2·2 percentage points and favourable number needed to treat (45 patients) provided relevant clinical insights for the selection of single antiplatelet regimen in the long-term maintenance period after PCI. Third, in the present study, the proportion of patients with high bleeding risk was low because this trial was focused on patients with a high risk of recurrent ischaemic events. This under-representation of patients with high bleeding risk might have contributed to the small number of overall bleeding events observed in our study. Furthermore, chronic kidney disease and high bleeding risk were not specified in our enrolment criteria, although these characteristics also increase the risk of ischaemic events after PCI. However, patients with chronic kidney disease or high bleeding risk are likely to receive abbreviated antiplatelet therapy rather than standard DAPT after PCI, and did not meet our enrolment criteria in many cases. Fourth, this study exclusively enrolled Korean patients; therefore, the results should be applied with caution to other populations. However, among patients in the clopidogrel monotherapy group who underwent genotyping, no difference in the primary endpoint was observed between carriers and non-carriers of the reduced-function *CYP2C19* allele. Given the high prevalence of intermediate or poor clopidogrel metabolism in the Korean population,[27] clopidogrel might in fact be more effective in populations where reduced-function *CYP2C19* alleles are less common. In addition, previous studies have suggested that east Asians have a lower incidence of major adverse cardiac events than do non-east Asians,[28] although the available evidence is contradictory.[25] Fifth, multiple testing and multiplicity of outcomes were not adjusted to account for the number of comparisons. Therefore, we do not present p values for secondary endpoints to avoid misinterpretation of statistical significance, and the results of secondary endpoints should be interpreted with caution. Sixth, there was no specific antiplatelet treatment strategy for patients requiring new PCI or initiation of anticoagulation during the follow-up in the present study, and these patients were managed according to the discretion of the physician, in alignment with contemporary guidelines. Seventh, the median duration of DAPT before randomisation was 17·5 months, which is longer than the current recommendation. However, clinical practice data

indicate that the duration of DAPT exceeds 12 months in a substantial proportion of patients, especially after complex PCI.[29] In addition, patients undergoing complex PCI might not have been considered to be at high risk at the time of enrolment, given that the impact of PCI complexity as a risk factor appears to diminish after 1 year. A recent substudy from the HOST-EXAM trial showed that the benefit of clopidogrel monotherapy over aspirin monotherapy was consistent, regardless of PCI complexity.[30] Therefore, a longer duration between PCI and randomisation might have contributed, at least partly, to the lower-than-expected event rate in the present study. Eighth, a high proportion of patients received clopidogrel rather than prasugrel or ticagrelor as a $P2Y_{12}$ inhibitor for DAPT before randomisation. This finding could be explained by several factors: the inclusion of patients without previous myocardial infarction, a median time from the index PCI to randomisation exceeding 12 months, and the absence of superiority of potent $P2Y_{12}$ inhibitors in randomised studies in east Asia.[31] Finally, women were under-represented in our study cohort, comprising only 18·2% of the study population. Findings from trials with under-representation of women might not be broadly generalisable to women.[32] Further research is needed to assess whether the observed benefits of clopidogrel monotherapy are independent of sex.

In conclusion, among patients who were at high risk of recurrent ischaemic 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, and can be considered as a preferable alternative to aspirin monotherapy for long-term maintenance in these patients.

Contributors

All authors participated in the study design and enrolment of patients and contributed to clinical follow-up. KHC, YHP, YBS, and J-YH participated in data analysis and data interpretation. KHC wrote the first draft, and YBS and J-YH revised the manuscript. KHC, YBS, and J-YH accessed and verified all the underlying data. All authors approved the final version of the manuscript, had full access to all the data in the study, and accept final responsibility for the decision to submit for publication.

Declaration of interests

J-YH reports funding from the South Korean National Evidence-based Healthcare Collaborating Agency, the South Korean Ministry of Health & Welfare, Abbott Vascular, Biosensors, Biotronik, Boston Scientific, Daiichi Sankyo, Dong-A ST, Hanmi Pharmaceutical, and Medtronic. YBS reports funding from the Korean Society of Cardiology and Microport. KHC reports funding from the Korean Society of Cardiology and Abbott Vascular. JML reports funding from Abbott Vascular, Boston Scientific, and Terumo Corporation; and consulting fees from Abbott Vascular, Boston Scientific, and Pulse Medical. All other authors declare no competing interests.

Data sharing

Patient-level data collected for this study will not be made publicly available but will be available for data sharing upon request for collaboration on specific projects. Any relevant inquiries should be sent to the corresponding author. The protocol and statistical analysis plan of the SMART-CHOICE 3 trial are provided in the appendix (pp 44–86 for protocol and pp 87–101 for statistical analysis plan).

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