Aspirin versus clopidogrel for chronic maintenance monotherapy after percutaneous coronary intervention (HOST-EXAM): an investigator-initiated, prospective, randomised, open-label, multicentre trial

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Summary

Background Optimal antiplatelet monotherapy during the chronic maintenance period in patients who undergo coronary stenting is unknown. We aimed to compare head to head the efficacy and safety of aspirin and clopidogrel monotherapy in this population.

Methods We did an investigator-initiated, prospective, randomised, open-label, multicentre trial at 37 study sites in South Korea. We enrolled patients aged at least 20 years who maintained dual antiplatelet therapy without clinical events for 6–18 months after percutaneous coronary intervention with drug-eluting stents (DES). We excluded patients with any ischaemic and major bleeding complications. Patients were randomly assigned (1:1) to receive a monotherapy agent of clopidogrel 75 mg once daily or aspirin 100 mg once daily for 24 months. 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 (BARC) bleeding type 3 or greater, in the intention-to-treat population. This trial is registered with ClinicalTrials.gov, NCT02044250.

Findings Between March 26, 2014, and May 29, 2018, we enrolled 5530 patients. 5438 (98·3%) patients were randomly assigned to either the clopidogrel group (2710 [49·8%]) or to the aspirin group (2728 [50·2%]). Ascertainment of the primary endpoint was completed in 5338 (98·2%) patients. During 24-month follow-up, the primary outcome occurred in 152 (5·7%) patients in the clopidogrel group and 207 (7·7%) in the aspirin group (hazard ratio 0·73 [95% CI 0·59–0·90]; p=0·0035).

Interpretation Clopidogrel monotherapy, compared with aspirin monotherapy during the chronic maintenance period after percutaneous coronary intervention with DES significantly reduced the risk of the composite of all-cause death, non-fatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and BARC bleeding type 3 or greater. In patients requiring indefinite antiplatelet monotherapy after percutaneous coronary intervention, clopidogrel monotherapy was superior to aspirin monotherapy in preventing future adverse clinical events.

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Introduction

After percutaneous coronary intervention (PCI), guidelines recommend an initial 6–12 months of dual antiplatelet therapy (DAPT), which is decided on the basis of various factors, including clinical presentation (acute coronary syndrome *vs* chronic coronary syndrome).[1,2] After this period, indefinite maintenance of single antiplatelet therapy is indicated for secondary prevention of atherosclerotic cardiovascular events. Aspirin, a cyclooxygenase pathway inhibitor, is the most widely used antiplatelet agent and is recommended as standard therapy in patients after PCI.[3] The evidence for this recommendation is based on collective analyses of trials done several decades ago that showed benefit of aspirin for secondary prevention of cardiovascular disease.[4,5] However, recent trials in the primary prevention setting found little or no benefit in the prevention of vascular events for aspirin and showed that aspirin might be associated with an increased bleeding risk, including intracranial and gastrointestinal bleeding.[6–8] Clopidogrel, an adenosine diphosphate-receptor blocker, is recommended as an alternative in patients who do not tolerate aspirin therapy.[9] One previous trial in 1996 reported that clopidogrel might have potential benefits in patients with atherosclerotic vascular disease, such as reducing cardiovascular events with a reduced incidence of gastrointestinal complications.[10] However, the trial did not specifically address the post-PCI population and was not done in an era when drug-eluting stents (DES) or high-intensity statins were available. A few registry-based

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Research in context

Evidence before this study

After percutaneous coronary intervention, standard therapy is dual antiplatelet therapy for 6–12 months followed by indefinite duration of antiplatelet monotherapy. Aspirin is the recommendation of choice for antiplatelet monotherapy and clopidogrel is recommended as an alternative in patients who do not tolerate aspirin therapy. However, no trial has specifically studied which antiplatelet agent might be the optimal choice during the chronic maintenance period in a percutaneous coronary intervention population in the drug-eluting stent era. We searched PubMed on March 1, 2021, for articles published in English, with the search terms "single antiplatelet therapy", "chronic maintenance", "secondary prevention", "percutaneous coronary intervention", "aspirin", and "clopidogrel". Our search identified two previous randomised studies that investigated this issue. In the large-scale CAPRIE study, which enrolled patients with atherosclerotic vascular disease, clopidogrel showed a modest benefit over aspirin in reducing future vascular events. In the ASCET study, a smaller study that enrolled patients with stable coronary artery disease on aspirin indicated for long-term single antiplatelet therapy, clinical outcomes were not different between aspirin and clopidogrel use. However, these studies were neither done in a dedicated percutaneous coronary intervention population nor done in the contemporary drug-eluting stent era.

Added value of this study

The HOST-EXAM is the first randomised trial to compare clopidogrel and aspirin monotherapy in patients who received percutaneous coronary intervention with a drug-eluting stent. In 5438 patients, clopidogrel monotherapy was associated with a reduced risk of adverse clinical events (a composite of all-cause death, non-fatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and Bleeding Academic Research Consortium bleeding of type 3 or more during the 24-month follow-up period. Prespecified and post-hoc subgroup analyses also showed that the beneficial effect of clopidogrel monotherapy was consistent in various subgroups without any significant interaction.

Implications of all the available evidence

In patients who received percutaneous coronary intervention and successfully maintained the intended duration of dual antiplatelet therapy, clopidogrel monotherapy was superior to aspirin monotherapy in preventing future adverse clinical events, including both the thrombotic composite and any bleeding.

studies have shown promising results for clopidogrel as an antiplatelet agent in the chronic maintenance period after PCI[11–13] but no randomised trial in the contemporary DES era has specifically addressed which antiplatelet agent might be the optimal choice during the period of indefinite antiplatelet monotherapy in the PCI population.

Therefore, we did the HOST-EXtended Antiplatelet Monotherapy (HOST-EXAM) trial to compare head to head the efficacy and safety of aspirin and clopidogrel monotherapy in patients who received PCI for coronary artery disease and required chronic maintenance antiplatelet therapy.

Methods

Study design

The HOST-EXAM trial was an investigator-initiated, prospective, randomised, open-label, multicentre trial done at 37 study sites in South Korea. Details regarding the trial design have been described previously.[14] All participating centres and trial personnel are listed in the appendix (pp 4–8).

The Seoul National University Hospital Clinical Trial Center and Medical Research Collaborating Center (MRCC) were responsible for the scientific conduct of the trial and an independent analysis of the data. All events were adjudicated by an independent clinical-event committee whose members were unaware of the trial group assignments. Members of the independent clinical-event committee received medical records of adverse events after removal of any reference to the treatment groups. The safety of the patients was overseen by the data and safety monitoring board. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, available in the appendix (pp 46–68).

Participants

Patients aged 20 years or older who underwent PCI with DES and maintained DAPT without any clinical events within 6–18 months after PCI were eligible for this study. Patients with any ischaemic and major bleeding complications (ie, non-fatal myocardial infarction, any repeat revascularisation, readmission due to a cardiovascular cause, and major bleeding) were excluded from randomisation. Antiplatelet therapy before enrolment was composed of aspirin plus any $P2Y_{12}$ inhibitor. We had no restriction regarding the clinical diagnosis at the index PCI period, stenosis location, length, or numbers of lesions or vessels at the time of PCI. Key exclusion criteria were patients with known hypersensitivity or contraindications for clopidogrel, or those who could not cease their current antiplatelet agents for medical, financial, or personal reasons. Other antiplatelet agents, including cilostazol and sarpogrelate hydrochloride, were not permitted during the follow-up period. Detailed inclusion and exclusion criteria of this study are described in the appendix (p 10).

The trial protocol was approved by the institutional review board at each participating site and all patients were required to provide written informed consent at the time of enrolment and randomisation. This study was done 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

In each participating centre, patients were randomly assigned by a web-based application (MRCC IWRS System; software configuration, Apache 2, PHP 5, and mysql 5) developed by the MRCC (Seoul, South Korea), without blocking or stratification methods. Patients who met all the inclusion criteria and none of the exclusion criteria were randomly assigned in consecutive order to either the clopidogrel group (75 mg once daily) or aspirin group (100 mg once daily) in a ratio of 1:1 (figure 1). This study used a web-based electronic case report form with the Pharmaco-epidemiology and Clinical Trial Application X (PhactaX), which was developed by the MRCC. When patients previously using potent $P2Y_{12}$ inhibitors were randomly assigned to the clopidogrel group, clopidogrel 600 mg loading was recommended for ticagrelor users, while prasugrel users switched to clopidogrel 75 mg without a loading dose. Participants and study investigators were not masked to the assigned group.

Procedures

Participants received either clopidogrel (75 mg once daily) or aspirin (100 mg once daily) orally. Clinical follow-up was scheduled at 12 months and 24 months (each with a window of plus or minus 3 months). Any additional visits were at the discretion of attending physicians. On each visit, active surveillance was done for any adverse clinical events, along with the assessment of adherence to the study drug.

Outcomes

The primary endpoint was a composite of all-cause death, non-fatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and major bleeding complications during the 24-month follow-up period. Major bleeding was defined as Bleeding Academic Research Consortium (BARC) type bleeding of least 3. The individual components of the primary endpoint, revascularisation, and minor gastrointestinal complications were analysed as secondary endpoints at 24 months. Interim analysis was not planned and was not done during the follow-up duration. Post-hoc secondary composite endpoints, including the thrombotic composite endpoint (defined as cardiac death, non-fatal myocardial infarction, ischaemic stroke, readmission due to acute coronary syndrome, and definite or probable stent thrombosis) and any bleeding (defined as BARC type ≥2 bleeding), were analysed. Detailed definitions of each clinical event are described in the appendix (pp 13–18). The vital status of all patients was cross-checked through the National Health Insurance Service system of South Korea and the South Korea National Statistics System. The definite cause of death was confirmed by the recorded data classified by the International Classification of Disease, 10th Revision, Clinical Modification codes. Additionally, all source data were checked for at least 80% of the patients in all centres. All serious adverse events, primary endpoints, and secondary endpoints were monitored on site.

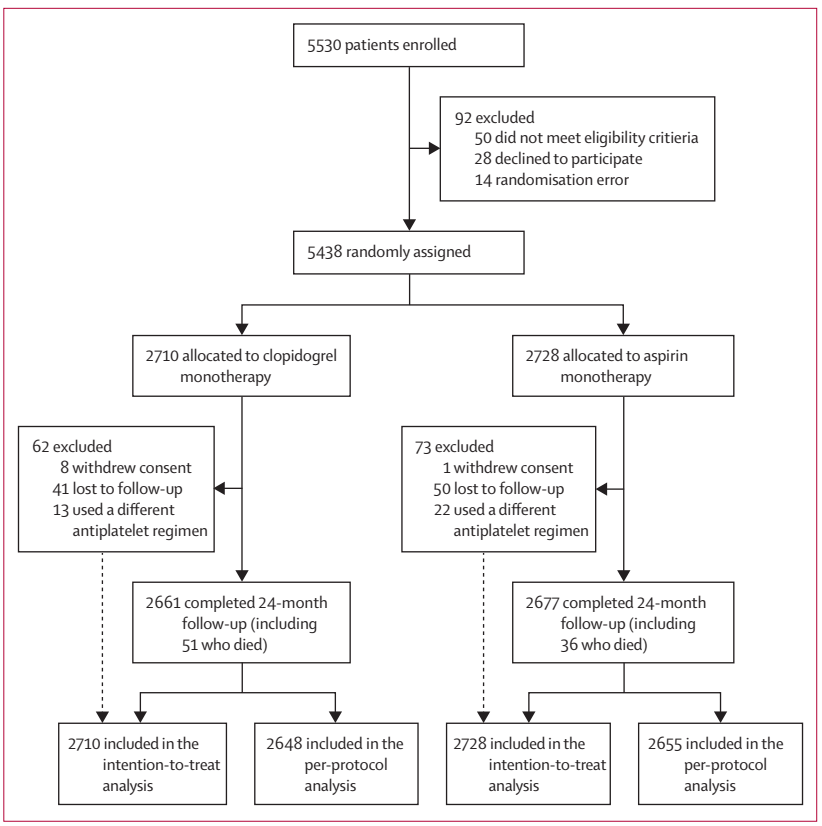

Figure 1: **Trial profile**
Patients who underwent percutaneous coronary intervention with a drug-eluting stent and maintained dual antiplatelet therapy without any clinical events within 6–18 months after the index procedure were eligible for this study and underwent randomisation. The primary efficacy endpoint was analysed during the 24-month follow-up duration in the intention-to-treat population, which included all patients who underwent randomisation.

Statistical analysis

The working hypothesis of our study was that clopidogrel 75 mg once daily would be superior to aspirin 100 mg once daily as a chronic maintenance monotherapy agent. The sample size calculation was based on the assumption that the event rates of the primary endpoint at 24 months would be 9·6% for the clopidogrel group and 12·0% for the aspirin monotherapy group. The specific assumptions and calculations are reported in the appendix (pp 11–12). With a sampling ratio of 1:1 and an estimated rate of follow-up loss as 5% in each group for 24 months,

	Clopidogrel (n=2710)	Aspirin (n=2728)
Age, years	63·5 (10·7)	63·4 (10·7)
Sex		
Female	695 (25·6%)	689 (25·3%)
Male	2015 (74·4%)	2039 (74·7%)
Diabetes*	925 (34·1%)	935 (34·3%)
Insulin-dependent diabetes	55 (2·0%)	62 (2·3%)
Hypertension	1664 (61·4%)	1674 (61·4%)
Dyslipidaemia	1884 (69·5%)	1883 (69·0%)
Current smoker	545 (20·1%)	581 (21·3%)
Chronic kidney disease	356 (13·1%)	337 (12·4%)
Previous myocardial infarction	437 (16·1%)	435 (15·9%)
Previous cerebrovascular accident	120 (4·4%)	133 (4·9%)
Clinical indication of PCI		
Silent ischaemia	58 (2·1%)	70 (2·6%)
Stable angina	688 (25·4%)	701 (25·7%)
Unstable angina	975 (36·0%)	959 (35·2%)
NSTEMI	526 (19·4%)	528 (19·4%)
STEMI	463 (17·1%)	470 (17·2%)
Laboratory results		
White blood cells, cells per μL	6·7 (1·9)	6·8 (1·9)
Haemoglobin, g/dL	13·7 (1·7)	13·8 (1·6)
Creatinine, mg/dL	1·0 (0·7)	1·0 (0·7)
Total cholesterol, mg/dL	136·8 (29·)8	138·2 (30·5)
Triglyceride, mg/dL	126·8 (86·5)	125·2 (70·8)
HDL cholesterol, mg/dL	46·3 (12·0)	46·5 (12·2)
LDL cholesterol, mg/dL	70·7 (23·7)	72·1 (23·2)
HbA_{1c}	6·5 (1·1)	6·5 (1·2)
Days from PCI to randomisation	383 (357–424)	380 (358–421)
DAPT at the randomisation		
Aspirin plus clopidogrel	2218 (81·8%)	2212 (81·1%)
Aspirin plus ticagrelor	266 (9·8%)	268 (9·8%)
Aspirin plus prasugrel	212 (7·8%)	235 (8·6%)
Aspirin plus clopidogrel plus cilostazol	14 (0·5%)	13 (0·5%)
Angiographic data per patient		
Extent of CAD		
One-vessel disease	1367 (50·4%)	1376 (50·4%)
Two-vessel disease	855 (31·5%)	844 (30·9%)
Three-vessel disease	488 (18·0%)	507 (18·6%)
Left main disease	142 (5·2%)	130 (4·8%)
PCI for bifurcation lesion	285 (10·5%)	295 (10·8%)
Two-stenting for bifurcation PCI	46 (1·7%)	42 (1·5%)
PCI for CTO lesion	257 (9·5%)	254 (9·3%)
Number of treated lesions†	1·3 (0·6)	1·3 (0·6)
Mean diameter of implanted stents, mm	3·1 (0·4)	3·1 (0·4)
Minimum diameter of implanted stents, mm	3·0 (0·5)	3·0 (0·5)
Total length of implanted stents, mm	36·1 (24·2)	35·7 (23·6)
Total number of implanted stents	1·5 (0·8)	1·5 (0·8)
Generation of DES		
First generation DES	54 (2·0%)	52 (1·9%)
Second generation DES	2627 (96·9%)	2651 (97·2%)
Unknown generation	29 (1·1%)	25 (0·9%)

Data are n (%), mean (SD), or median (IQR). CAD=coronary artery disease. CTO=chronic total occlusion. DAPT=dual antiplatelet therapy. DES=drug-eluting stent. HbA_{1c}=glycated haemoglobin. NSTEMI=non ST-segment elevation myocardial infarction. PCI=percutaneous coronary intervention. STEMI=ST-segment elevation myocardial infarction. *Diabetes was defined as any type of diabetes. †3562 lesions were treated in the clopidogrel group and 3565 in the aspirin group.

Table 1: **Baseline characteristics of the intention-to-treat population**

5530 patients were needed to ensure a power of at least 80% with a two-sided α of 5%. All patients randomly assigned were included in the primary intention-to-treat analysis and a per-protocol analysis was also done. The intention-to-treat population included all patients randomly assigned to a treatment group and the per-protocol population were those who received the allocated single antiplatelet therapy for the full duration of the 24-month follow-up unless they had an adverse clinical event.

Continuous variables were reported as means (SD) and categorical variables were presented as absolute values and their proportions. Differences between continuous variables were compared by Student's *t* test for independent data. All primary and secondary endpoints were analysed both on intention-to-treat and per-protocol sets and on a per-patient basis. The primary endpoint was analysed by a Cox proportional hazards model and Kaplan-Meier survival curves to estimate the risk of clinical events according to the type of antiplatelet agent. No factor 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 prespecified subgroups, defined according to age (<65 years or ≥65 years), sex (male or female), clinical presentation (acute myocardial infarction or not and acute coronary syndrome or not), renal function, diabetes (defined as being of any type), and complex PCI. Post-hoc subgroup analyses were done to analyse the presence of any interaction between the treatment effect and high bleeding risk, angiographic severity (single vessel disease *vs* multivessel disease), DES generation (first generation DES *vs* second generation DES), duration from index PCI to randomisation, potent $P2Y_{12}$ inhibitor usage before randomisation, and

proton-pump inhibitor usage. The specific definitions of complex PCI and high bleeding risk are shown in the appendix (p 13). Statistical tests were done using SPSS (version 24) and R (version 4.0.4).

This study is registered with ClinicalTrials.gov, NCT02044250.

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 who were event free for 6–18 months after PCI and successfully received the intended duration of DAPT were enrolled from 37 centres. Among these patients, 5438 (98·3%) patients were successfully randomly assigned to aspirin monotherapy (2728 [50·2%]) or clopidogrel monotherapy (2710 [49·8%]; figure 1). During the follow-up period, 35 (0·6%) patients used a different antiplatelet regimen from that of the allocated group, nine (0·2%) patients withdrew informed consent, and 91 (1·7%) patients were lost to follow-up. Ascertainment of the primary endpoint was complete in 5338 (98·2%) patients and vital status cross-checked in all patients who were randomly assigned.

The baseline characteristics of the total population are shown in table 1 and the appendix (p 19). The two groups were well balanced for demographic, clinical, and procedural characteristics, and non-trial-related medications. The mean age was 63·5 years (SD 10·7) and 4054 (74·5%) patients were male and 1384 (25·5%) were female. The clinical diagnosis at the time of PCI was stable angina in 1389 (25·5%) patients, unstable angina in 1934 (35·5%), non-ST segment elevation myocardial infarction in 1054 (19·4%), and ST segment elevation myocardial infarction in 933 (17·2%). Angiographically, 955 (18·3%) had three-vessel disease, 272 (5·0%) had left main disease, and the mean number of stents used for treatment was 1·5 (SD 0·8). The median time from PCI to randomisation was 382 days (IQR 357–422). The DAPT regimen before randomisation was mainly aspirin plus clopidogrel (4430 [81·5%]). The allocated treatment discontinuation rates (for less than 3 months) in the two groups were similar (281 [5·1%] *vs* 272 [4·9%]).

During the 24-month follow-up, the primary endpoint occurred in 152 patients (Kaplan-Meier estimate at 24 months 5·7%) who received clopidogrel monotherapy and in 207 patients (Kaplan-Meier estimate at 24 months 7·7%) who received aspirin monotherapy (hazard ratio [HR] 0·73 [95% CI 0·59–0·90]; p=0·0035) with an absolute risk reduction of 2·0% (95% CI 0·6–3·3; number needed to treat [NNT]=51 patients; table 2; figure 2A).

The incidences of the individual components of the primary endpoint and other secondary endpoints are shown in table 2 and the appendix (pp 23–24). The incidence of all-cause death was similar (51 [1·9%] in the clopidogrel group and 36 [1·3%] in the aspirin group). The specific causes of mortality events are described in the appendix (p 25). The incidence of stroke, readmission due to acute coronary syndrome, and major bleeding were lower in the clopidogrel group than in the aspirin group (table 2; appendix pp 23–24).

The secondary composite thrombotic endpoint of cardiac death, non-fatal myocardial infarction, stroke, readmission due to acute coronary syndrome, or definite or probable stent thrombosis occurred in 99 (3·7%) patients in the clopidogrel group and 146 (5·5%) patients in the aspirin group (HR 0·68 [95% CI 0·52–0·87]; p=0·0028), for a difference in risk of 1·7% (95% CI 0·6–2·8; NNT=59 patients; figure 2B). Any bleeding (BARC type ≥2) occurred in 61 (2·3%) patients in the clopidogrel group and 87 (3·3%) patients in the aspirin group (HR 0·70 [0·51–0·98]; p=0·036), for a difference in risk of 0·9% (0·0–1·8; NNT=111 patients; figure 2C). The individual type of bleeding according to the BARC definition is presented in the appendix (p 26). The incidence of revascularisation and definite or probable stent thrombosis were similar in both groups (table 2).

	Clopidogrel (n=2710)	Aspirin (n=2728)	Hazard ratio (95% CI)*	p value
Primary composite endpoint†	152 (5·7%)	207 (7·7%)	0·73 (0·59–0·90)	0·003
Thrombotic composite endpoint‡	99 (3·7%)	146 (5·5%)	0·68 (0·52–0·87)	0·003
Any bleeding (BARC type ≥2)§	61 (2·3%)	87 (3·3%)	0·70 (0·51–0·98)	0·036
All-cause death¶	51 (1·9%)	36 (1·3%)	1·43 (0·93–2·19)	0·101
Cardiac death	19 (0·7%)	14 (0·5%)	1·37 (0·69–2·73)	0·374
Non-cardiac death	32 (1·2%)	22 (0·8%)	1·47 (0·85–2·52)	0·167
Non-fatal myocardial infarction	18 (0·7%)	28 (1·0%)	0·65 (0·36–1·17)	0·150
Stroke	18 (0·7%)	43 (1·6%)	0·42 (0·24–0·73)	0·002
Ischaemic stroke	14 (0·5%)	26 (1·0%)	0·54 (0·28–1·04)	0·064
Haemorrhagic stroke	4 (0·2%)	17 (0·6%)	0·24 (0·08–0·70)	0·010
Readmission due to ACS	66 (2·5%)	109 (4·1%)	0·61 (0·45–0·82)	0·001
Major bleeding (BARC type ≥3)	33 (1·2%)	53 (2·0%)	0·63 (0·41–0·97)	0·035
Any revascularisation	56 (2·1%)	69 (2·6%)	0·82 (0·57–1·16)	0·261
Target lesion revascularisation	24 (0·9%)	36 (1·4%)	0·67 (0·40–1·12)	0·130
Target vessel revascularisation	37 (1·4%)	48 (1·8%)	0·78 (0·50–1·19)	0·245
Definite or probable stent thrombosis	10 (0·4%)	16 (0·6%)	0·63 (0·29–1·39)	0·251
Any minor gastrointestinal complications	272 (10·2%)	320 (11·9%)	0·85 (0·72–1·00)	0·048

Data are n (%), unless otherwise specified. Clinical endpoints were assessed in the intention-to-treat population at 24 months after randomisation. The percentages shown are Kaplan-Meier estimates. All primary and secondary endpoints and their associated definitions are listed in the appendix (pp 13–18). ACS=acute coronary syndrome. BARC=Bleeding Academic Research Consortium. *The 95% CIs for secondary endpoints have not been adjusted for multiple testing and therefore no clinical inferences can be made from these analyses. †The primary composite endpoint was defined as a composite of all-cause death, non-fatal myocardial infarction, stroke, readmission due to ACS, and major bleeding events (BARC type ≥3). ‡The thrombotic composite endpoint was defined as cardiac death, non-fatal myocardial infarction, ischaemic stroke, readmission due to ACS, and definite or probable stent thrombosis. §The specific types of bleeding events are described in the appendix (p 26). Any bleeding event was defined as BARC type bleeding of 2 or more. ¶The specific causes of death are described in the appendix (p 25).

Table 2: **Clinical outcomes in the intention-to-treat population**

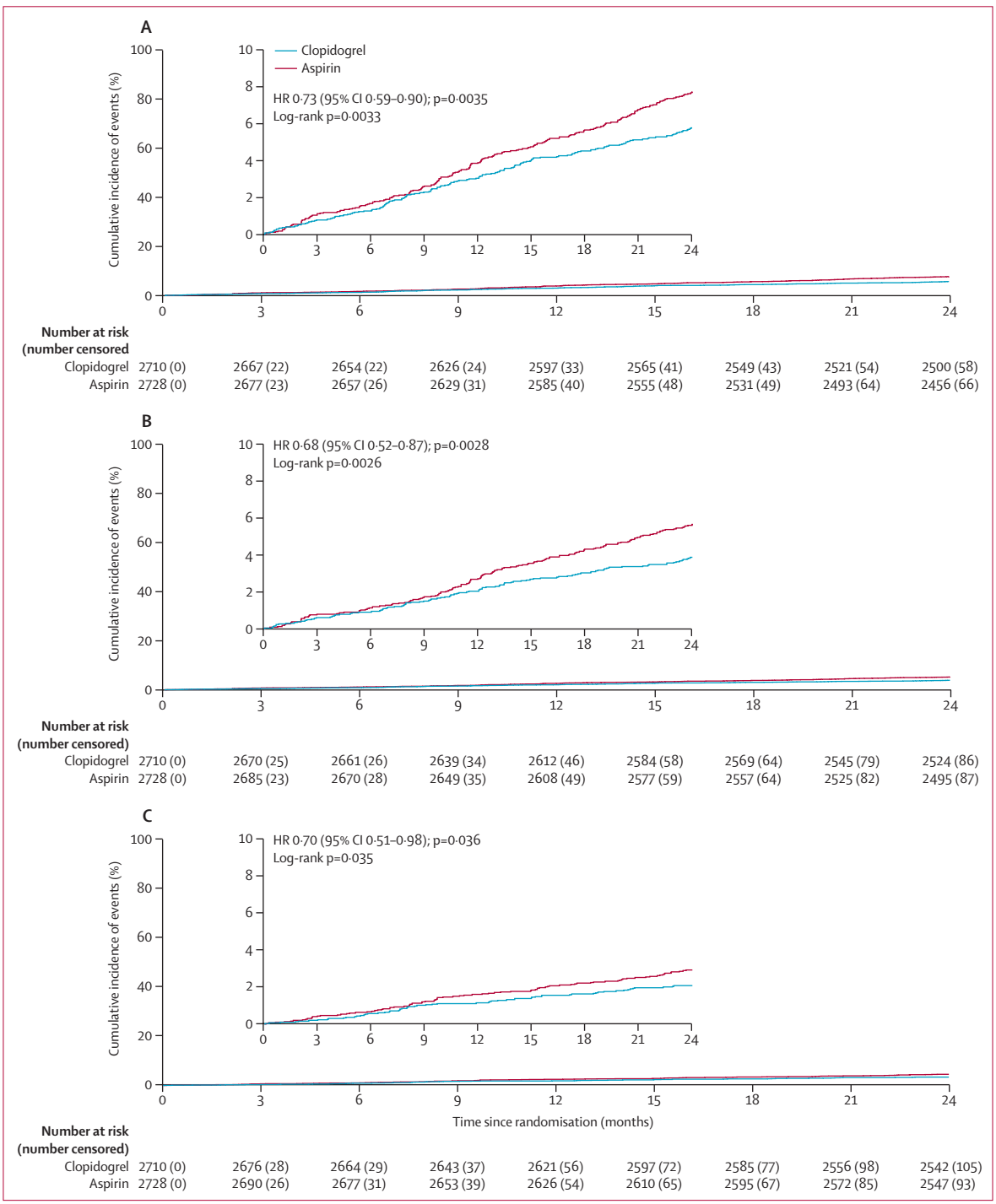

Figure 2: **24-month cumulative incidence of the primary composite outcome and secondary composite outcome**
(A) The cumulative incidence of the primary endpoint, consisting of all-cause death, non-fatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and major bleeding (Bleeding Academic Research Consortium bleeding type 3 or more) complications. (B) The 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) The cumulative incidence of any bleeding events. The HR shown is for clopidogrel monotherapy versus aspirin monotherapy. The inset shows the same data on an enlarged y-axis. HR=hazard ratio.

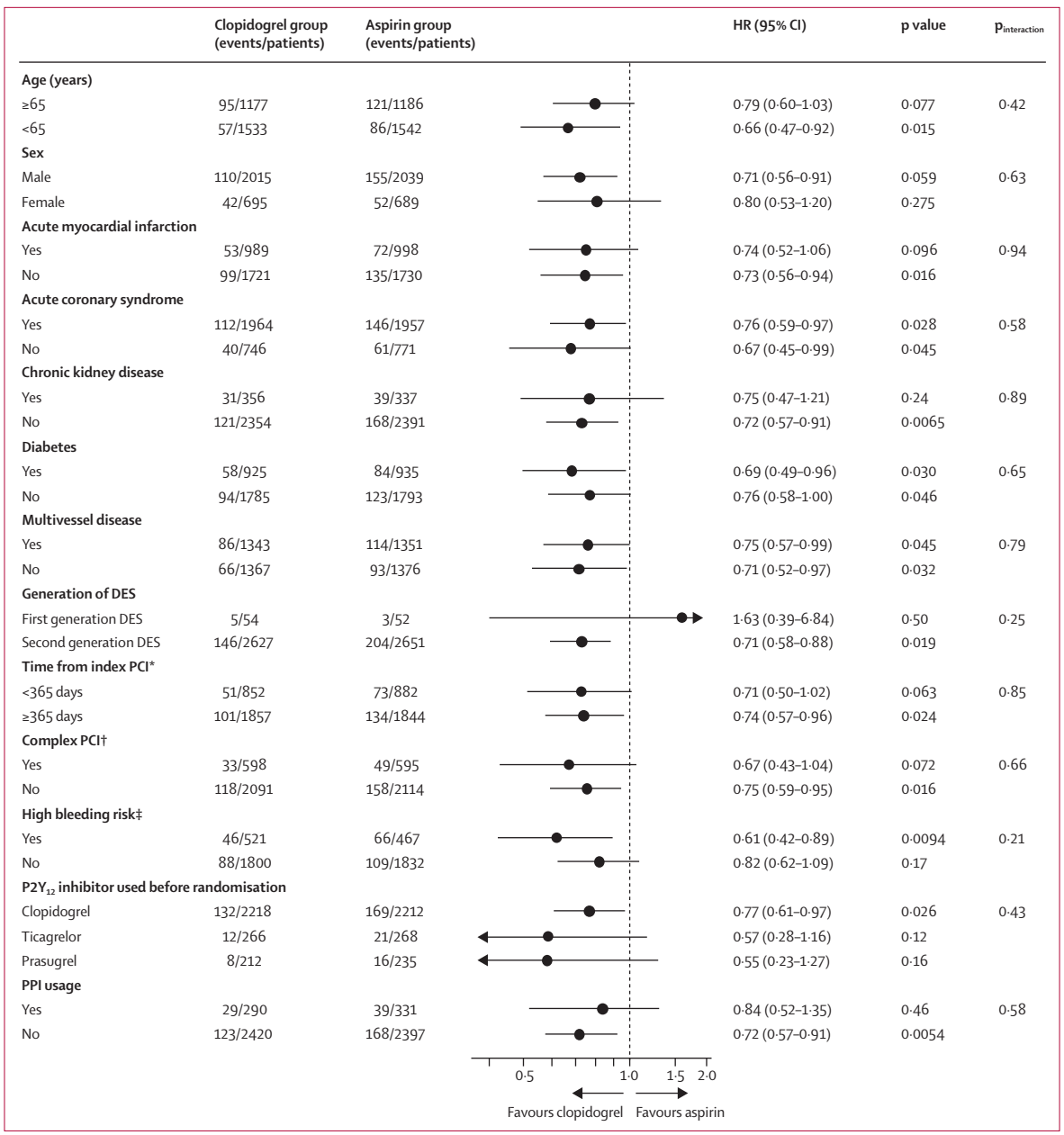

Figure 3: **Primary efficacy endpoint in selected subgroups**

The HRs for the primary efficacy endpoint (a composite of all-cause death, non-fatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and major bleeding complications) in both groups are shown according to prespecified and post-hoc subgroups. HR=hazard ratio. DES=drug-eluting stents. PCI=percutaneous coronary intervention. PPI=proton-pump inhibitor. *1734 patients stopped dual antiplatelet therapy before 12 months, which was similar between both groups (852 [31·4%] vs 882 [32·3%]). Detailed clinical diagnosis of these patients is described in the appendix (p 22). †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. Data were available in 5398 (99·3%) of 5438 patients. ‡High bleeding risk was defined according to the Academic Research Consortium for High Bleeding Risk definition. Data were available in 4620 (85·0%) patients.

Minor gastrointestinal complications such as epigastric soreness, dyspepsia, abdominal pain, nausea, vomiting, diarrhoea, constipation, melena, or haematochezia occurred in 272 (10·2%) patients in the clopidogrel group and 320 (11·9%) patients in the aspirin group (HR 0·85 [0·72–1·00]; p=0·048; table 2).

Regarding the primary endpoint, the beneficial effect of clopidogrel monotherapy compared with aspirin monotherapy was generally consistent across all pre-specified subgroups (figure 3). Also, post-hoc analyses showed no statistically significant interaction between the treatment effect and various subgroups (figure 3).

A similar consistency of effect was observed for the thrombotic composite endpoint and any bleeding (appendix pp 38–41). The per-protocol analyses yielded similar results to the intention-to-treat analyses for the primary study endpoint (HR 0·72 [0·58–0·89]; p=0·002) and the secondary endpoints (appendix pp 36–37).

Discussion

The HOST-EXAM trial is the first large-scale randomised controlled trial to compare clopidogrel with aspirin monotherapy during the chronic maintenance period in patients who received stenting with DES and had successfully completed 6–18 months of DAPT without events. Compared with aspirin, clopidogrel monotherapy was associated with a lower risk of the composite of all-cause death, non-fatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and major bleeding during the 24-month follow-up period. The benefit of clopidogrel monotherapy was observed in both thrombotic and bleeding endpoints. The results were consistent across major patient subgroups, regardless of baseline clinical and angiographic characteristics. Also, post-hoc subgroup analyses reported no significant interaction between the treatment effect and various subgroups, such as the DES generation, duration from index PCI to randomisation, and concomitant medications. Collectively, our results show that clopidogrel monotherapy compared with aspirin monotherapy provides clinical benefit with fewer thrombotic and bleeding events, when given in the chronic maintenance period for patients who received PCI with DES.

Current practice guidelines recommend DAPT as standard therapy after PCI to prevent immediate complications such as stent thrombosis and myocardial infarction. After an intended duration of DAPT, clinicians de-escalate to antiplatelet monotherapy during the chronic maintenance phase for secondary prevention of cardiovascular events. For this purpose, aspirin is recommended and is the mainstay of therapy.[3] Although clopidogrel is used as an alternative to aspirin, especially in those who are intolerant of or allergic to aspirin, few studies have done a head-to-head comparison between aspirin and clopidogrel in patients with stable coronary artery disease. Previously, the CAPRIE trial[10] showed that clopidogrel was moderately more effective than aspirin was in reducing cardiovascular adverse events in patients at risk for vascular events. Subsequent studies[15–17] suggested that the benefit of clopidogrel over aspirin on ischaemic event reduction is increased in higher-risk patients. Several differences exist between the CAPRIE trial and our study. First, the study population of the CAPRIE trial was not a PCI population and thus cannot represent pharmacotherapy in post-PCI patients. Second, the aspirin dose in the CAPRIE trial was 325 mg once daily, whereas our study used 100 mg once daily. Finally, contemporary practice uses DES and high-intensity statins, which were never part of the CAPRIE trial because the trial was done in the early 1990s. Subsequently, a few non-randomised, registry-based studies compared the efficacy and safety of clopidogrel with that of aspirin monotherapy for secondary prevention in patients with stable coronary artery disease, showing promising results for clopidogrel.[11–13] Further, a study-level meta-analysis compared $P2Y_{12}$ inhibitor monotherapy with aspirin monotherapy for secondary prevention and concluded that $P2Y_{12}$ inhibitor monotherapy was associated with a reduced risk of myocardial infarction and a neutral effect on mortality.[18] Collectively, the previous studies raised important hypotheses regarding which antiplatelet monotherapy might yield the best clinical results in the chronic maintenance period after PCI. Our study, which was done in a homogeneous population of stabilised patients after PCI who received DES, confirms these previous findings for the first time in a large-scale randomised study.

Two trials (the STOPDAPT-2 and SMART-CHOICE trials) investigated the feasibility of $P2Y_{12}$ inhibitor monotherapy in patients after PCI. A meta-analysis also reported that 1–3 months of DAPT followed by $P2Y_{12}$ inhibitor monotherapy was associated with a reduced risk of adverse clinical events.[19] However, the major difference between our study and these previous studies is the timepoint at which this regimen was used. Previous trials compared the efficacy and safety of $P2Y_{12}$ inhibitor monotherapy versus DAPT within the first year after PCI, whereas we compared $P2Y_{12}$ inhibitor monotherapy versus aspirin monotherapy 6–18 months post-PCI.

The cumulative event curves seemed to significantly diverge at 9 months. However, we saw a slight separation even in the early phase and a small bump in the clopidogrel group curve around 7–8 months makes it appear as though the curves overlap until 9 months. Without this small bump, we believe that the curves would have looked as though there was a steady separation between the two groups. Additionally, the cumulative incidence of adverse clinical events continuously increased without any plateau effect, implying a constant incidence of clinical events during the chronic maintenance period after PCI with DES. This finding is similar to the event curve that was observed in the DAPT trial, which also enrolled patients who had not had an adverse clinical event within the first year after PCI.[20] Moreover, we found progressive divergence of the cumulative incidence curve between the clopidogrel and aspirin groups, suggesting a continuous benefit of clopidogrel throughout the study period. Compared with the DAPT trial, the event rate in our study was slightly lower despite longer follow-up (18 months *vs* 24 months). This difference can be partially explained by the fact that the DAPT trial had a much higher rate of patients who received early generation DES, whereas 97% of our population was treated with second generation DES. Also, most of the patients in the DAPT study were White, whereas our study was done in an east Asian popu-

lation who are known to have lower rates of thrombotic events compared with those of White people.[21,22]

One interesting finding from our study was that the reduction of adverse clinical events, both ischaemic and bleeding events, did not translate into a reduced risk of death. Regarding the specific cause of death, the trend of mortality rates due to cardiovascular and non-cardiovascular causes were in the opposite direction compared with other non-fatal outcomes, although this finding was not statistically significant. Also, we found numerically more cancer-related deaths in the clopidogrel group than in the aspirin group. This finding could be due to including more patients with unknown cancer before enrolment in the clopidogrel group than in the aspirin group. The protective effect of aspirin in cancer-related death has been suggested in a few previous studies.[23,24] However, in the ASPREE trial,[25] cancer-related mortality occurred more frequently in healthy adults who received aspirin compared to those who received placebo. The influence of aspirin versus clopidogrel on death (including cancer-related deaths) requires further investigation and longer follow-up. We hope that the extended follow-up of the HOST-EXAM trial, the so-called HOST-EXAM Extended study, will bring further insights on the true effect of chronic maintenance monotherapy on death.

Our study has several limitations. First, the open-label design has a potential for bias in outcome reporting and ascertainment. However, all endpoints had a standardised definition and were specifically adjudicated by an independent committee that was unaware of the treatment group. Second, the observed event rate of the primary endpoint was lower than what was anticipated in the sample size calculation, suggesting a possibility of selection bias or under-reporting of events. However, we periodically monitored every participating centre, where imputed data were cross-checked with source documentation in more than 80% of the enrolled patients. Further, the vital status of all patients randomly assigned was double-checked using two national databases that have access to individual mortality information. Another limitation when the rate of the primary endpoint is lower than expected is the possibility of a false-negative result (type II error). However, our findings were significant for both the primary endpoint and secondary composite endpoints and the benefit of clopidogrel was consistent in all prespecified subgroups. Third, phenotypic and genetic testing for clopidogrel was not done and the study population was east Asian patients, which might limit the generalisability of the study. 50–60% of the east Asian population carry loss-of-function mutations of the *CYP2C19* gene causing an attenuated antiplatelet effect of clopidogrel. However, multiple studies have shown that thrombotic event rates are lower in east Asian people compared with in White people, implying that the prognostic value of clopidogrel resistance might be different between ethnicities, a phenomenon termed the east Asian paradox.[26] Furthermore, drug-resistance issues are not confined to only clopidogrel. In our previous study, [27] the prevalence of aspirin resistance (aspirin reactivity unit >550) was 18·0% (164 of 911 patients), similar to 19·7% (180 of 911 patients) for clopidogrel resistance (platelet reactivity unit >275). The clinical significance of clopidogrel resistance is still under debate and current guidelines do not recommend routine platelet function tests in the decision making for personalised treatment approaches.[3] Fourth, the comparison between clopidogrel and aspirin for the secondary endpoints was not adjusted for multiple testing and, therefore, we cannot make any definitive conclusions regarding the secondary endpoints. Fifth, the follow-up duration of 24 months might be too short to give a concrete conclusion, considering the fact that maintenance antiplatelet therapy is administered indefinitely. Therefore, we have launched the HOST-EXAM Extended study, in which we will be extending the median follow-up to 10 years. Finally, our results only apply to those who had 6–18 months of DAPT without any major adverse events. Thus, extrapolation of our results directly to those who use a shorter duration of DAPT, such as 1 month or 3 months, is difficult. Also, we cannot clearly address the optimal antiplatelet agent in patients with atrial fibrillation treated with oral anticoagulants.

In conclusion, among patients who were event free for 6–18 months post-PCI and successfully received the intended duration of DAPT, clopidogrel monotherapy compared with aspirin monotherapy significantly reduced the risk of the composite of all-cause death, non-fatal myocardial infarction, stroke, readmission due to acute coronary syndrome, and BARC type bleeding of 3 or more.

Contributors

B-KK, KWP, E-SS, J-KH, and H-SK conceived and designed the study. JK, T-MR and B-KK acquired the data and participated in data analysis and data interpretation. All authors participated in enrolment of patients and performed clinical follow-up, along with revising the draft critically for important intellectual content. B-KK, JK, and KWP wrote the first draft, reviewed, and revised the manuscript. All authors approved the final version of the manuscript and ensured that the accuracy or integrity of any part of the work is appropriately investigated and resolved. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

H-SK has received research grants or speaker's fees from Medtronic, Abbott Vascular, Edwards Life Science, Boston Scientific, Terumo, Biotronik and Dio, AmGen, Pfizer, AstraZeneca, MSD, Daiichi Sankyo, and Boehringer Ingelheim. B-KK has received institutional research grants from Abbott Vascular and Philips. KWP reports fees from Daiichi Sankyo, AstraZeneca, Sanofi, Bristol-Myers Squibb, Bayer, and Pfizer outside the submitted work. All other authors declare no competing interests.

Data sharing

The HOST-EXAM trial is planning to continue follow-up until 2025. No individual participant data will be available before this. Any relevant inquiries should be sent to the corresponding author.

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References

1 Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: an update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery. *Circulation* 2016; **134:** e123–55.

2 Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the task force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2018; **39:** 213–60.

3 Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J* 2019; **40:** 87–165.

4 Collaboration AT. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002; **324:** 71–86.

5 Baigent C, Blackwell L, Collins R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009; **373:** 1849–60.

6 Gaziano JM, Brotons C, Coppolecchia R, et al. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. *Lancet* 2018; **392:** 1036–46.

7 Bowman L, Mafham M, Wallendszus K, et al. Effects of aspirin for primary prevention in persons with diabetes mellitus. *N Engl J Med* 2018; **379:** 1529–39.

8 McNeil JJ, Wolfe R, Woods RL, et al. Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. *N Engl J Med* 2018; **379:** 1509–18.

9 Smith SC Jr, Benjamin EJ, Bonow RO, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. *Circulation* 2011; **124:** 2458–73.

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

11 Sim DS, Jeong MH, Kim HS, et al. Clopidogrel versus aspirin after dual antiplatelet therapy in acute myocardial infarction patients undergoing drug-eluting stenting. *Korean Circ J* 2020; **50:** 120–29.

12 Park TK, Song YB, Ahn J, et al. Clopidogrel versus aspirin as an antiplatelet monotherapy after 12-month dual-antiplatelet therapy in the era of drug-eluting stents. *Circ Cardiovasc Interv* 2016; **9:** e002816.

13 Lemesle G, Schurtz G, Meurice T, et al. Clopidogrel use as single antiplatelet therapy in outpatients with stable coronary artery disease: prevalence, correlates and association with prognosis (from the CORONOR Study). *Cardiology* 2016; **134:** 11–18.

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

15 Bhatt DL, Chew DP, Hirsch AT, Ringleb PA, Hacke W, Topol EJ. Superiority of clopidogrel versus aspirin in patients with prior cardiac surgery. *Circulation* 2001; **103:** 363–68.

16 Bhatt DL, Marso SP, Hirsch AT, Ringleb PA, Hacke W, Topol EJ. Amplified benefit of clopidogrel versus aspirin in patients with diabetes mellitus. *Am J Cardiol* 2002; **90:** 625–28.

17 Ringleb PA, Bhatt DL, Hirsch AT, Topol EJ, Hacke W. Benefit of clopidogrel over aspirin is amplified in patients with a history of ischemic events. *Stroke* 2004; **35:** 528–32.

18 Chiarito M, Sanz-Sánchez J, Cannata F, et al. Monotherapy with a $P2Y_{12}$ inhibitor or aspirin for secondary prevention in patients with established atherosclerosis: a systematic review and meta-analysis. *Lancet* 2020; **395:** 1487–95.

19 Giacoppo D, Matsuda Y, Fovino LN, et al. Short dual antiplatelet therapy followed by $P2Y_{12}$ inhibitor monotherapy vs. prolonged dual antiplatelet therapy after percutaneous coronary intervention with second-generation drug-eluting stents: a systematic review and meta-analysis of randomized clinical trials. *Eur Heart J* 2021; **42:** 308–19.

20 Mauri L, Kereiakes DJ, Yeh RW, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med* 2014; **371:** 2155–66.

21 Kim BK, Hong SJ, Cho YH, et al. Effect of ticagrelor monotherapy *vs* ticagrelor with aspirin on major bleeding and cardiovascular events in patients with acute coronary syndrome: the TICO randomized clinical trial. *JAMA* 2020; **323:** 2407–16.

22 Kim HS, Kang J, Hwang D, et al. Prasugrel-based de-escalation of dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (HOST-REDUCE-POLYTECH-ACS): an open-label, multicentre, non-inferiority randomised trial. *Lancet* 2020; **396:** 1079–89.

23 Rothwell PM, Fowkes FG, Belch JF, Ogawa H, Warlow CP, Meade TW. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. *Lancet* 2011; **377:** 31–41.

24 Rothwell PM, Wilson M, Price JF, Belch JF, Meade TW, Mehta Z. Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials. *Lancet* 2012; **379:** 1591–601.

25 McNeil JJ, Nelson MR, Woods RL, et al. Effect of aspirin on all-cause mortality in the healthy elderly. *N Engl J Med* 2018; **379:** 1519–28.

26 Kang J, Kim HS. The evolving concept of dual antiplatelet therapy after percutaneous coronary intervention: focus on unique feature of east Asian and "Asian paradox". *Korean Circ J* 2018; **48:** 537–51.

27 Lim WH, Chae IH, Yoon CH, et al. Comparison of dual antiplatelet therapy prescribed as one-pill versus two-pill regimen. A pooled analysis of individual patient data from the three MR-CAPCIS trials. *Thromb Haemost* 2016; **116:** 78–86.