Clopidogrel versus aspirin for secondary prevention of coronary artery disease: a systematic review and individual patient data meta-analysis

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Summary

Background Aspirin monotherapy is recommended indefinitely for patients with established coronary artery disease (CAD). The aim of this individual patient level meta-analysis was to provide a comprehensive evaluation of the comparative efficacy and safety of clopidogrel versus aspirin monotherapy in patients with established CAD, most of whom had undergone percutaneous coronary intervention or had acute coronary syndrome.

Methods We conducted a systematic search in PubMed, Scopus, Web of Science, and Embase to identify randomised trials published from database inception to April 12, 2025, comparing clopidogrel monotherapy with aspirin monotherapy in patients with established CAD who had discontinued or never started dual antiplatelet therapy. Randomised trials featuring an initial phase of dual antiplatelet therapy were eligible for inclusion in this individual patient data meta-analysis. In the main analysis, we used semi-parametric shared log-normal frailty models (one-stage analysis), including a random intercept to account for differences in the baseline hazard across trials, and a random slope to account for between-trial differences in treatment effects. The primary efficacy endpoint was a composite of cardiovascular death, myocardial infarction, or stroke (major adverse cardiovascular or cerebrovascular events [MACCE]); the primary safety endpoint was major bleeding. This study is registered with PROSPERO (CRD42025645594).

Findings Seven randomised trials including 28 982 patients (14 507 assigned to clopidogrel; 14 475 assigned to aspirin) with a median follow-up of 2·3 years (IQR 1·1–4·0) were eligible and included. At 5·5 years, MACCE was less common in patients assigned to clopidogrel than in patients assigned to aspirin (929 events [2·61 per 100 patient-years] *vs* 1062 events [2·99 per 100 patient-years]; hazard ratio 0·86 [95% CI 0·77–0·96]; p=0·0082). Mortality and major bleeding (256 events [0·71 per 100 patient-years] with clopidogrel *vs* 279 events [0·77 per 100 patient-years] with aspirin; 0·94 [0·74–1·21]; p=0·64) did not differ.

Interpretation These findings add to the evidence that clopidogrel monotherapy is superior to aspirin monotherapy for MACCE prevention with no increase in the risk of bleeding, and support the preferential use of clopidogrel over aspirin for secondary prevention in patients with established CAD.

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Introduction

Aspirin monotherapy is recommended indefinitely for patients with established coronary artery disease (CAD).[1–3] However, the body of evidence that has supported the long-term use of aspirin monotherapy for decades is largely based on small studies performed before the advent of modern pharmacotherapies and revascularisation strategies.[4–6] Among the studies supporting this indication, a few continued aspirin for more than 2 years and none for more than 4 years, a few disentangled acute treatment effects of aspirin from chronic effects by initiating aspirin at a different timepoint to the qualifying coronary event, and none appraised the long-term treatment risks by systematically ascertaining the whole spectrum of clinically relevant bleeding.[4–6] In a meta-analysis of 16 high-quality secondary prevention trials, of which only six included patients who had a myocardial infarction and, of those six, only two had mean continuous treatment durations of longer than 2 years, aspirin versus no aspirin was associated with a 20% lower risk of major coronary events and a two-times higher risk of major bleeding.[7] However, major bleeding data were collected in only five trials overall, and in none of the six trials of patients with CAD.[7] In a seminal aggregate data meta-analysis of 287 studies, major extracranial bleeding was not reported by any of the studies assessing aspirin in the chronic phase following the CAD qualifying event;

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Research in context

Evidence before this study

We searched MEDLINE (via PubMed), Scopus, Web of Science, Embase (via Ovid), and five websites (www.tctmd.com, www.pcronline.org, www.crtonline.org, www.escardio.org, and www.heart.org), without language restrictions, from database inception to April 12, 2025, for randomised trials that compared clopidogrel versus aspirin monotherapy in patients with coronary artery disease (CAD) who discontinued or never started dual antiplatelet therapy. The following search terms were used: "aspirin", "acetylsalicylic acid", "$P2Y_{12}$ inhibitor", "clopidogrel", "prasugrel", "ticagrelor", "atherosclerosis", "coronary artery disease", "percutaneous coronary intervention", "coronary artery bypass grafting", "myocardial infarction", "stroke", and "peripheral artery disease". Previous evidence on the comparative efficacy and safety of the two antiplatelet strategies has been inconsistent and limited by insufficient statistical power of individual trials and heterogeneity across trial designs and objectives. Earlier meta-analyses suggested a potential advantage of $P2Y_{12}$ inhibitors over aspirin for cardiovascular event prevention; however, their findings were limited by the pooled evaluation of different $P2Y_{12}$ inhibitors (eg, clopidogrel and ticagrelor) and the inclusion of mixed atherosclerotic disease populations or selected cohorts of patients treated with percutaneous coronary intervention. In addition, previous analyses did not incorporate extended follow-up data from earlier studies or recent evidence from the STOPDAPT-3 trial and the SMART-CHOICE 3 trial, which together compared clopidogrel and aspirin in a total of 11 339 patients with CAD. Moreover, although clinical factors associated with poor response to clopidogrel have been identified, their influence on the comparative outcomes of long-term monotherapy with clopidogrel versus aspirin in stable CAD remains unexamined.

Added value of this study

We analysed patient-level data from all available randomised trials comparing clopidogrel and aspirin monotherapy for secondary prevention in patients with established CAD, irrespective of the initial clinical presentation (acute or chronic coronary syndrome) and treatment strategy (percutaneous coronary intervention, coronary artery bypass grafting, or medical therapy alone). Clopidogrel monotherapy was associated with a reduced risk of major adverse cardiovascular and cerebrovascular events, driven primarily by lower rates of myocardial infarction and stroke. There were no differences between the two strategies in the risk of major bleeding, any bleeding, or gastrointestinal bleeding. Treatment effects were consistent across all prespecified subgroups, including individuals with clinical features associated with poor responsiveness to clopidogrel, as defined by the ABCD-GENE score, evaluated both individually and in combination.

Implications of all the available evidence

This comprehensive synthesis of available evidence indicates that, in patients with CAD, long-term clopidogrel monotherapy offers superior protection against major cardiovascular and cerebrovascular events compared with aspirin, without an excess risk of bleeding. The superior efficacy of clopidogrel versus aspirin was consistent across multiple key subgroups, including individuals with clinical features predictive of poor clopidogrel responsiveness, supporting the generalisability of these findings to the broad spectrum of patients with CAD. These results support a preference for clopidogrel over aspirin for chronic antiplatelet monotherapy for patients with stable CAD. The widespread availability, generic formulation, and affordability of clopidogrel further supports its potential for extensive adoption in clinical practice.

therefore, the safety of aspirin for patients with CAD was derived by a single trial of acute myocardial infarction with 35 days of follow-up.[8]

The use of clopidogrel monotherapy, a $P2Y_{12}$ inhibitor, as an alternative to aspirin monotherapy is recommended, although inconsistently, across guidelines for the management of patients with peripheral artery disease.[9–12] Recently the focus has shifted to the role of clopidogrel monotherapy in patients with CAD.[2] Previous meta-analyses, which investigated the aggregate effects of clopidogrel or ticagrelor monotherapy compared with aspirin, showed that $P2Y_{12}$ inhibitor monotherapy has the potential to lower the risk of cardiovascular events in patients with established atherosclerosis.[13–15] However, the evidence base regarding long-term ticagrelor monotherapy is limited,[16,17] and up to 30% of patients have a reduced pharmacodynamic response to clopidogrel,[18] which might have hindered its broader adoption without concomitant prescription of aspirin. New clopidogrel studies[19,20] and extended follow-up analyses from earlier trials[21,22] have become available, setting the foundations for the reappraisal of long-term $P2Y_{12}$ inhibitor monotherapy with clopidogrel for patients with CAD. In this systematic review and individual patient level meta-analysis, we captured the available evidence on the comparative outcomes of clopidogrel versus aspirin for patients with CAD, with a focus on the consistency of the treatment effects across a broad spectrum of clinically identifiable patient subsets.

Methods

Overview

To compare the efficacy and safety of clopidogrel monotherapy versus aspirin monotherapy for secondary prevention in patients with established CAD, we conducted a systematic review and individual patient data meta-analysis of randomised trials including this patient population. Trials featuring an initial phase of dual antiplatelet therapy (DAPT) after randomisation

were eligible for inclusion; however, their contribution was limited to the protocol-specified comparison of clopidogrel and aspirin monotherapy after the exclusion of patients who had early trial termination, died, or had myocardial infarction, stroke, stent thrombosis, or major bleeding during the initial DAPT phase. Randomised trials that included patients on chronic oral anticoagulation were included only if less than 20% of participants required long-term treatment after randomisation.

The results of this individual patient data meta-analysis are reported according to the PRISMA individual participant data guidelines (appendix pp 6–11).[23] The study protocol was prospectively registered in PROSPERO (CRD42025645594).

Eligible randomised controlled trials were identified through a systematic search of MEDLINE (via PubMed), Scopus, Web of Science, and Embase (via Ovid) electronic databases, and websites of cardiology societies (www.tctmd.com, www.pcronline.org, www.crtonline.org, www.escardio.org, www.heart.org) from database inception to March 1, 2025. The search was updated on April 12, 2025. The search strategy used for each database, along with the number of retrieved records, is illustrated in the appendix (pp 12–16). No language restrictions were imposed, and no clinical setting was excluded. Two investigators conducted these searches and extracted the data (DG and FG). Any disagreements were resolved through collegial discussion involving a third investigator (MV).

Outcomes

The primary efficacy outcome was major adverse cardiovascular or cerebrovascular events (MACCE), defined as a composite of cardiovascular death, myocardial infarction, or stroke. The primary safety outcome was major bleeding, defined as Bleeding Academic Research Consortium type 3 or 5 when available or, if not available, using trial-specific definitions. The key secondary endpoint was net adverse cardiac or cerebrovascular events, defined as a composite of cardiovascular death, myocardial infarction, stroke, or major bleeding. Additional secondary endpoints were all-cause death, cardiovascular death, myocardial infarction, stroke (any type, ischaemic, or haemorrhagic), stent thrombosis (definite or probable), any bleeding, major gastrointestinal bleeding, and any gastrointestinal bleeding. In each trial, events were adjudicated by the original clinical events committee.

Data extraction and quality assessment

The principal investigators of eligible trials participated in the collaborative project and provided anonymised individual patient data via dedicated electronic spreadsheets. For each trial, data completeness and consistency were evaluated by a comparison between the supplied datasets and the data reported in the original manuscripts, and by a cross-validation of previously reported and unreported variables with the investigators. Two investigators (DG and FG) independently assessed the risk of bias using the Risk of Bias 2.0 tool, and any disagreements were resolved through collegial discussion including a third investigator (MV). The certainty of evidence for the coprimary and key secondary outcomes was assessed using the GRADE framework. Publication bias was not formally assessed because the total number of included trials was fewer than ten. All trials were approved by ethics committees, and all patients provided written informed consent for participation in the original trials.

See **Online** for appendix

Statistical analysis

Categorical variables were summarised as n (%) and compared using Pearson's χ^2 or Fisher's exact test, as appropriate. Continuous variables were presented as mean (SD) or median (IQR) and compared using the Welch *t* test or the Wilcoxon–Mann–Whitney *U* test based on the distribution.

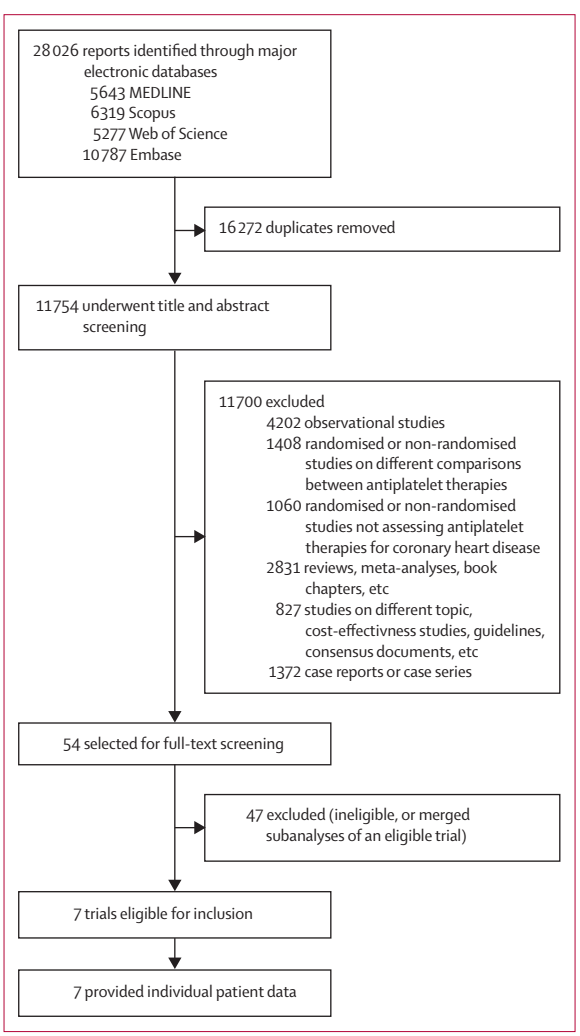

Figure 1: **PRISMA flow diagram**

	Clopidogrel (n=14 507)	Aspirin (n=14 475)	p value
Age, years	65·5 (58·0–74·9)	65·5 (57·0–74·5)	0·42
Sex	..	..	0·40
Male	11 430 (78·8%)	11 346 (78·4%)	..
Female	3077 (21·2%)	3129 (21·6%)	..
BMI, kg/m²	24·5 (22·5–26·8)	24·5 (22·5–26·7)	0·70
Region	..	..	0·92
Asia	9672 (66·7%)	9679 (66·9%)	..
Europe	2530 (17·4%)	2520 (17·4%)	..
North America	2305 (15·9%)	2276 (15·7%)	..
Diabetes*	4689 (32·5%)	4691 (32·6%)	0·89
Hypertension	8834 (60·9%)	8630 (59·6%)	0·027
Hypercholesterolaemia†	8291 (59·6%)	8244 (59·4%)	0·78
Current smoker	3346 (23·1%)	3393 (23·4%)	0·45
Previous myocardial infarction	7384 (50·9%)	7299 (50·4%)	0·42
Previous stroke*	1079 (7·5%)	1060 (7·4%)	0·70
Clinical presentation	..	..	0·48
Acute coronary syndrome	9896 (68·2%)	9930 (68·6%)	..
Chronic coronary syndrome	4611 (31·8%)	4545 (31·4%)	..
Myocardial ischaemia treatment‡	..	..	0·020
Percutaneous coronary intervention	10 229/14 413 (71·0%)	10 207/14 385 (71·0%)	..
Medical therapy alone	3687/14 413 (25·6%)	3607/14 385 (25·1%)	..
Coronary artery bypass grafting	356/14 413 (2·5%)	377/14 385 (2·6%)	..
Percutaneous coronary intervention and coronary artery bypass grafting	141/14 413 (1·0%)	194/14 385 (1·3%)	..
Type of device used in percutaneous coronary intervention†	..	..	0·35
Second-generation drug-eluting stent	9407/10 016 (93·9%)	9404/10 024 (93·8%)	..
First-generation drug-eluting stent	90/10 016 (0·9%)	115/10 024 (1·1%)	..
Bioresorbable vascular scaffold, bare-metal stent, plain balloon angioplasty, or other	491/10 016 (4·9%)	479/10 024 (4·8%)	..
Drug-eluting stent of unknown generation	28/10 016 (0·3%)	26/10 024 (0·3%)	..
Peripheral artery disease§	1058 (7·3%)	1094 (7·6%)	0·39
Chronic kidney disease¶	2046 (20·3%)	2028 (20·1%)	0·74
Estimated glomerular filtration rate (mL/min per 1·73 m²)	80·2 (63·5–99·4)	80·6 (63·6–99·5)	0·57
Previous bleeding events‖	127 (1·2%)	113 (1·1%)	0·37
Haemoglobin (g/dL)	13·9 (12·6–15·0)	13·9 (12·6–14·9)	0·69
Aspirin dose	..	..	0·76
Low (≤100 mg per day)	Not applicable	9769 (67·5%)	..
High (>100 mg per day)	Not applicable	4706 (32·5%)	..
Proton pump inhibitor	4517/14 169 (31·9%)	4920/14 143 (34·8%)	<0·0001

Data shown are median (IQR) or n (%), unless otherwise stated. Observed imbalances might in part reflect the exclusion of patients who had early trial termination, died, or had myocardial infarction, stroke, stent thrombosis, or major bleeding during the initial dual antiplatelet therapy phase in the STOPDAPT-219 and STOPDAPT-317 trials. *94 missing values in the clopidogrel group, 90 missing values in the aspirin group. †593 missing values in the clopidogrel group, 592 missing values in the aspirin group. ‡Data were not available for 94 patients in the clopidogrel group and 90 patients in the aspirin group. †Of 10 370 patients in the clopidogrel group who underwent percutaneous coronary intervention alone or with coronary artery bypass grafting, data were unavailable for 354 patients, and of 10 401 patients in the aspirin group who underwent percutaneous coronary intervention alone or with coronary artery bypass grafting, data were unavailable for 377 patients. §100 missing values in the clopidogrel group, 95 missing values in the aspirin group. ¶4425 missing values in the clopidogrel group, 4387 missing values in the aspirin group. ||4336 missing values in the clopidogrel group, 4294 missing values in the aspirin group.

Table 1: **Baseline characteristics across all included trials**

The primary analysis was conducted on the intention-to-treat population. Outcomes at the longest available follow-up were primarily evaluated using semi-parametric shared log-normal frailty models, including a random intercept (mixed-effects models) to account for differences in the baseline hazard across trials, and a random slope to account for between-trial differences in treatment effects (one-stage analyses). Treatment effects were expressed as hazard ratios (HRs) with 95% CIs. Time zero for time-to-event analyses was defined according to the protocol-specified start of the comparison between clopidogrel and aspirin monotherapy in each trial. For the

CAPRIE,[24] CADET,[25] ASCET,[26] HOST-EXAM,[21] and SMART-CHOICE 3 trials,[19] time zero coincided with randomisation. For the STOPDAPT-2 trial,[22] time zero corresponded to 12 months post-randomisation; and for the STOPDAPT-3 trial,[20] it corresponded to 1 month post-randomisation, as per the original trial protocols.

Outcomes were also assessed with two-stage analyses, in which trial-level HRs and 95% CIs were computed by Cox proportional hazards regression and subsequently combined by random-effects models with inverse-variance weighting. Firth's correction was applied when rare outcomes in smaller trials led to monotone likelihood, corresponding to complete separation. Between-trial heterogeneity was assessed by the *Q* test and quantified by the I^2 and τ^2 statistics. The restricted maximum likelihood estimator was used to compute τ^2. For the two-stage analyses, summary estimates were further assessed after conservative adjustment of the 95% CI of summary estimates using the Hartung–Knapp method. We conducted a post-hoc trial sequential analysis to assess whether the results were conclusive for the primary efficacy outcome of MACCE on the basis of the relative risk reduction observed at the one-stage analysis, a two-sided α of 0·050, and a β of 0·10. Monitoring boundaries were based on the Lan–DeMets implementation of the O'Brien–Fleming α-spending and β-spending functions.

To investigate possible temporal differences in event occurrence between the treatment groups, a sensitivity analysis was performed using a 1000-day landmark (chosen because it approximates the median follow-up in the pooled dataset). The coprimary efficacy and safety outcomes were assessed across prespecified subgroups. Treatment-by-subgroup interaction was tested and the corresponding p values reported. If one or more interaction p values were significant, an additional analysis applying the Benjamini–Hochberg method was prespecified to account for multiplicity. As prespecified, one-stage and two-stage analyses were replicated in the per-protocol population. An additional prespecified analysis was conducted to evaluate whether the clinical factors of the ABCD-GENE score,[27] which have been identified as independent predictors of impaired responsiveness to clopidogrel, influenced the comparative efficacy and safety of clopidogrel versus aspirin monotherapy. Based on the original derivation study, an ABCD-GENE score threshold of 10 (measured on a continuous scale) was used to stratify patients into lower and higher risk categories.[27] Bayesian random-effects estimates with 95% credible intervals and 95% prediction intervals for clinical outcomes were also assessed to complement frequentist analyses (appendix p 40).

Analyses were performed using R, version 4.3.2. Detailed information on the statistical analysis is reported in the appendix (pp 4–5).

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.

	Clopidogrel		Aspirin		HR (95% CI)	p value	Adjusted HR (95% CI)	Adjusted p value
	Number of events/number of patients (Kaplan–Meier estimate)	Events per 100 person-years	Number of events/number of patients (Kaplan–Meier estimate)	Events per 100 person-years				
MACCE	929/14 507 (10·7%)	2·61	1062/14 475 (12·9%)	2·99	0·86 (0·77–0·96)	0·0082	0·84 (0·75–0·94)	0·0021
Major bleeding	256/14 507 (3·4%)	0·71	279/14 475 (3·9%)	0·77	0·94 (0·74–1·21)	0·64	1·00 (0·76–1·32)	0·99
NACCE	1116/14 507 (12·9%)	3·16	1247/14 475 (15·3%)	3·54	0·89 (0·81–0·98)	0·023	0·87 (0·79–0·96)	0·0051
Death	713/14 507 (9·4%)	1·96	723/14 475 (10·1%)	1·98	0·99 (0·89–1·09)	0·79	0·99 (0·89–1·10)	0·82
Cardiovascular death	430/14 507 (5·1%)	1·18	435/14 475 (5·8%)	1·19	0·98 (0·84–1·13)	0·74	0·96 (0·83–1·11)	0·58
Myocardial infarction	356/14 507 (3·9%)	0·99	457/14 475 (5·1%)	1·27	0·76 (0·66–0·89)	0·0004	0·75 (0·65–0·88)	0·0003
Stroke	264/14 507 (3·4%)	0·73	316/14 475 (4·0%)	0·88	0·79 (0·66–0·96)	0·018	0·84 (0·71–0·98)	0·032
Ischaemic stroke	218/14 008 (2·7%)	0·62	253/13 973 (3·1%)	0·72	0·80 (0·65–0·98)	0·032	0·86 (0·71–1·03)	0·092
Haemorrhagic stroke	35/14 008 (0·7%)	0·10	46/13 973 (0·8%)	0·13	0·77 (0·49–1·19)	0·23	0·78 (0·50–1·21)	0·27
Definite or probable stent thrombosis	22/9672 (0·3%)	0·08	33/9679 (0·5%)	0·12	0·63 (0·36–1·11)	0·11	0·63 (0·35–1·14)	0·13
Definite stent thrombosis	17/9672 (0·2%)	0·06	22/9679 (0·3%)	0·08	0·77 (0·39–1·50)	0·44	0·78 (0·41–1·50)	0·46
Probable stent thrombosis	5/9672 (0·1%)	0·02	11/9679 (0·2%)	0·04	0·39 (0·13–1·16)	0·090	0·41 (0·14–1·21)	0·11
Any bleeding	780/14 507 (8·8%)	2·21	760/14 475 (8·8%)	2·14	1·04 (0·86–1·26)	0·69	1·07 (0·87–1·31)	0·54
Major gastrointestinal bleeding	110/14 008 (1·5%)	0·31	111/13 973 (1·7%)	0·31	0·98 (0·58–1·64)	0·93	1·03 (0·60–1·77)	0·91
Any gastrointestinal bleeding	220/14 008 (2·8%)	0·63	242/13 973 (3·1%)	0·69	0·93 (0·71–1·22)	0·60	0·97 (0·73–1·27)	0·80

Percentages are Kaplan–Meier estimates of cumulative incidence at 2000 days (longest available follow-up). For patients in the ASCET trial, event timing was unavailable and was assumed to occur at the end of follow-up, as prespecified in the protocol. ASCET patients are included in the table estimates but excluded from the graphical representation in figures, as stated in the figure legends. One-stage analyses were performed by Cox models with a random intercept (accounting for differences in the baseline hazard across trials) and a random slope (accounting for between-trial differences in treatment effects). HR=hazard ratio. MACCE=major adverse cardiovascular or cerebrovascular events. NACCE=net adverse cardiovascular or cerebrovascular events.

Table 2: **Clinical outcomes by one-stage analyses**

Results

Among 11754 unique records, 54 studies were deemed potentially eligible based on title and abstract screening (figure 1). After further review, seven randomised trials (ASCET,[26] CADET,[25] CAPRIE,[24] HOST-EXAM,[21] STOPDAPT-2,[22] STOPDAPT-3,[20] and SMART-CHOICE 3[19]) were deemed eligible and included in the analysis. After the exclusion of 262 patients assigned to clopidogrel and 289 assigned to aspirin who had adverse events during the initial DAPT phase, data from a total of 28 982 patients were extracted, validated, and combined (14 507 patients assigned to clopidogrel monotherapy and 14 475 to aspirin monotherapy; table 1). The main trial-level characteristics are described in the appendix (pp 17–29). The risk of bias assessment showed no significant concerns across trials (appendix p 54). A summary of GRADE ratings for certainty of evidence across coprimary and secondary outcomes is reported in the appendix (pp 30–33). Information on missing data is provided in the appendix (pp 34–35); detailed ethnicity data were not collected.

The median follow-up duration across all included trials was 2·3 years (IQR 1·1–4·0). At the longest available follow-up of 5·5 years, MACCE was lower in the clopidogrel monotherapy group than in the aspirin monotherapy group in the one-stage analysis (929 events [2·61 per 100 patient-years] *vs* 1062 events [2·99 per 100 patient-years]; HR 0·86 [95% CI 0·77–0·96]; p=0·0082; table 2; figure 2). These results were consistent in the multivariable one-stage analysis (adjusted HR 0·84 [0·75–0·94]; p=0·0021; table 2). The two-stage analysis confirmed the superior efficacy of clopidogrel monotherapy, both without (0·86 [0·77–0·95]; p=0·0040)

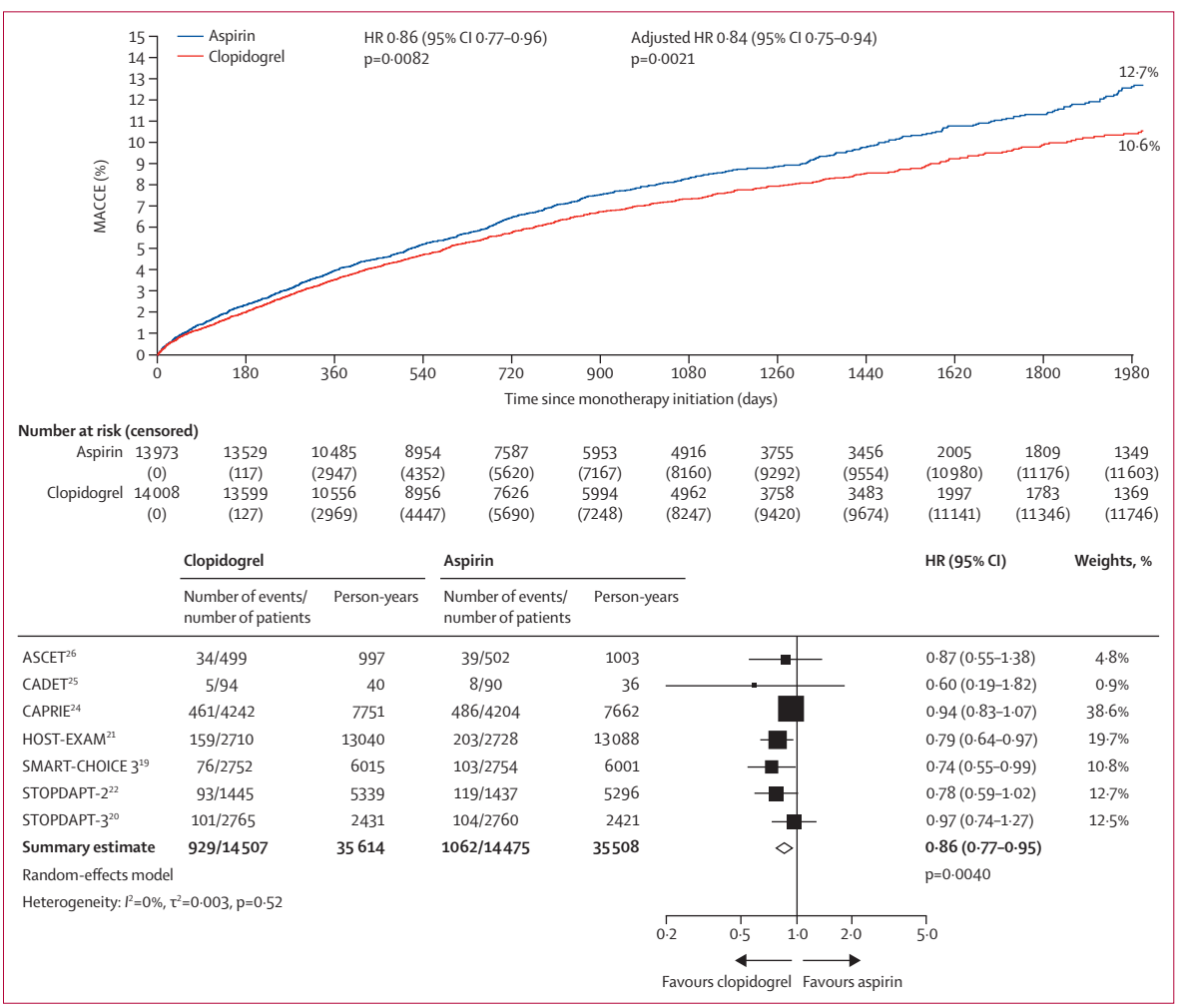

Figure 2: **Analysis of the primary efficacy outcome of MACCE**

The upper panel illustrates the cumulative distribution of the primary efficacy outcome of MACCE, defined as a composite of cardiovascular death, myocardial infarction, or stroke. The rates are computed by the Kaplan–Meier method. Patients enrolled in the ASCET trial[26] were excluded from the graphical representation as the timing of events was unavailable; in the analyses, these events were assumed to occur at the end of follow-up. HR and 95% CI were computed by mixed-effects models (one-stage analysis). Adjusted HRs and 95% CIs were computed by multivariable mixed-effects models as a sensitivity analysis. The lower panel shows the results of the two-stage analysis by random-effects models with inverse-variance weighting. HR=hazard ratio. MACCE=major adverse cardiovascular or cerebrovascular events.

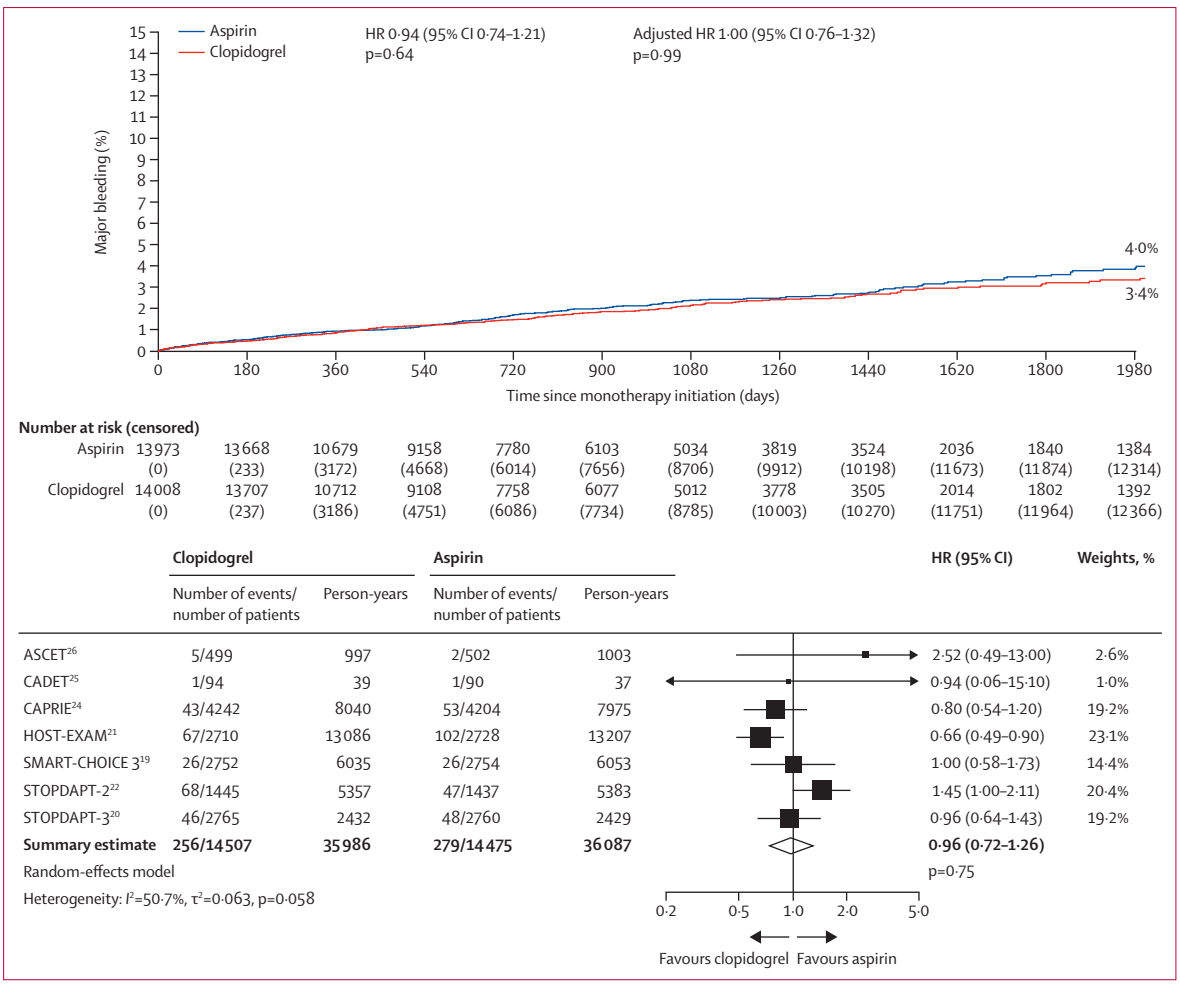

Figure 3: **Analysis of the primary safety outcome of major bleeding**
The upper panel illustrates the cumulative distribution of the primary safety outcome of major bleeding. The rates are computed by the Kaplan–Meier method. Patients enrolled in the ASCET trial[26] were excluded from the graphical representation as the timing of events was unavailable; in the analyses, these events were assumed to occur at the end of follow-up. HR and 95% CIs were computed by mixed-effects models (one-stage analysis). Adjusted HRs and 95% CIs were computed by multivariable mixed-effects models as a sensitivity analysis. The lower panel shows the results of the two-stage analysis by random-effects models with inverse-variance weighting. HR=hazard ratio.

and with CI adjustment (0·86 [0·75–0·98]; p=0·028). No significant between-trial heterogeneity was detected (I^2=0%; τ^2=0·003; p=0·52; appendix pp 36–37; figure 2). Trial sequential analyses showed robust evidence of superiority for the primary efficacy endpoint of MACCE with clopidogrel compared with aspirin (appendix p 55).

Major bleeding did not differ with clopidogrel monotherapy compared with aspirin monotherapy in the one-stage analysis (256 events [0·71 per 100 patient-years] *vs* 279 events [0·77 per 100 patient-years]; HR 0·94 [95% CI 0·74–1·21]; p=0·64; table 2; figure 3). Moderate between-trial heterogeneity was detected (I^2=50·7%; τ^2=0·063; p=0·058), primarily driven by a divergent direction of treatment effects in the HOST-EXAM[21] and STOPDAPT-2[22] trials, which contributed the highest relative weights to the pooled analysis (HOST-EXAM 23·1%, STOPDAPT-2 20·4%; figure 3, appendix pp 36–37).

The key secondary outcome of net adverse cardiac or cerebrovascular events was lower in patients assigned to clopidogrel monotherapy compared with aspirin monotherapy (1116 events [3·16 per 100 patient-years] *vs* 1247 events [3·54 per 100 patient-years]; HR 0·89 [95% CI 0·81–0·98]; p=0·023; table 2; appendix p 56). The results were consistent in the multivariable one-stage analysis (adjusted HR 0·87 [0·79–0·96]; p=0·0051) and two-stage analysis (HR 0·89 [0·80–0·98]; p=0·015). No significant between-trial heterogeneity was observed (I^2=1·9%; τ^2=0·003; p=0·41; appendix pp 36–37).

Cardiovascular and all-cause death did not differ between treatment groups (table 2; appendix pp 36–37, 57–58). The incidence of myocardial infarction was lower in the clopidogrel monotherapy group than the aspirin monotherapy group (table 2; appendix p 59). No significant between-trial heterogeneity was detected (I^2=0·7%;

	Clopidogrel			Aspirin			HR (95% CI)	$p_{interaction}$
	Number of events/ number of patients	Kaplan–Meier estimate, %	Incidence per 100 person-years of follow-up	Number of events/ number of patients	Kaplan–Meier estimate, %	Incidence per 100 person-years of follow-up		
Age, years								0·58
≤65	316/6956	6·8%	1·72	383/7024	9·1%	2·09	0·82 (0·70–0·96)	
>65	613/7551	15·0%	3·55	679/7451	17·1%	3·96	0·87 (0·76–1·00)	
Sex								0·54
Female	219/3077	12·2%	2·80	248/3129	13·5%	3·11	0·91 (0·76–1·09)	
Male	710/11430	10·3%	2·55	814/11346	12·7%	2·96	0·85 (0·74–0·97)	
BMI, kg/m²								0·18
<25	453/7592	10·7%	2·56	492/7634	12·0%	2·73	0·92 (0·80–1·05)	
≥25 to <30	345/5295	10·2%	2·44	425/5149	14·0%	3·16	0·78 (0·67–0·90)	
≥30	123/1428	13·0%	3·92	130/1487	12·6%	3·93	0·70 (0·46–1·07)	
Region								0·43
Asia	429/9672	7·8%	1·60	529/9679	10·0%	1·97	0·82 (0·70–0·95)	
Europe	265/2530	14·4%	5·86	280/2520	16·1%	6·22	0·94 (0·79–1·11)	
North America	235/2305	15·1%	5·51	253/2276	16·2%	6·02	0·92 (0·77–1·09)	
Coronary syndrome								0·22
Chronic	353/4611	12·7%	2·96	428/4545	15·4%	3·64	0·79 (0·68–0·92)	
Acute	576/9896	9·6%	2·43	634/9930	11·5%	2·67	0·91 (0·78–1·06)	
Diabetes								0·24
No	601/9724	10·0%	2·49	659/9694	11·6%	2·73	0·90 (0·81–1·01)	
Yes	323/4689	12·2%	2·82	395/4691	15·5%	3·48	0·79 (0·65–0·96)	
Current smoker								0·28
No	722/11161	10·9%	2·61	810/11082	12·8%	2·90	0·88 (0·78–1·01)	
Yes	207/3346	10·1%	2·59	261/3393	13·1%	3·29	0·78 (0·65–0·94)	
Previous myocardial infarction								0·084
No	298/7123	7·4%	1·64	388/7176	10·1%	2·12	0·77 (0·66–0·91)	
Yes	631/7384	14·0%	3·63	674/7299	15·5%	3·91	0·92 (0·82–1·02)	
Previous stroke								0·75
No	766/13334	9·6%	2·29	873/13325	11·6%	2·62	0·85 (0·76–0·96)	
Yes	158/1079	27·5%	7·37	181/1060	30·7%	8·25	0·82 (0·66–1·02)	
Peripheral artery disease								0·50
No	817/13349	10·1%	2·44	906/13286	12·1%	2·72	0·86 (0·76–0·98)	
Yes	107/1058	28·8%	5·09	148/1094	23·2%	6·88	0·78 (0·59–1·02)	
Chronic kidney disease								0·54
No	301/8036	6·8%	1·30	363/8060	8·3%	1·57	0·85 (0·72–1·00)	
Yes	158/2046	14·2%	3·44	200/2028	20·2%	4·38	0·78 (0·62–0·97)	
Proton pump inhibitor								0·29
No	674/9652	11·0%	2·65	771/9223	13·2%	3·12	0·82 (0·73–0·92)	
Yes	228/4517	9·6%	2·46	254/4920	12·3%	2·57	0·98 (0·72–1·33)	
Aspirin dose								0·23
Low	434/9766	7·8%	1·62	537/9769	10·0%	2·00	0·83 (0·72–0·95)	
High	495/4741	15·0%	5·66	525/4706	16·2%	6·06	0·93 (0·82–1·05)	
Oral anticoagulation								0·97
No	917/14158	10·7%	2·60	1047/14102	12·9%	2·91	0·86 (0·77–0·96)	
Yes	12/349	3·5%	3·91	15/373	4·1%	5·77	0·85 (0·40–1·82)	
ABCD–GENE score								0·43
≤10	876/13980	10·4%	2·53	1005/13958	12·7%	2·91	0·86 (0·77–0·96)	
>10	53/527	23·6%	5·52	57/517	21·1%	5·77	1·11 (0·59–2·09)	

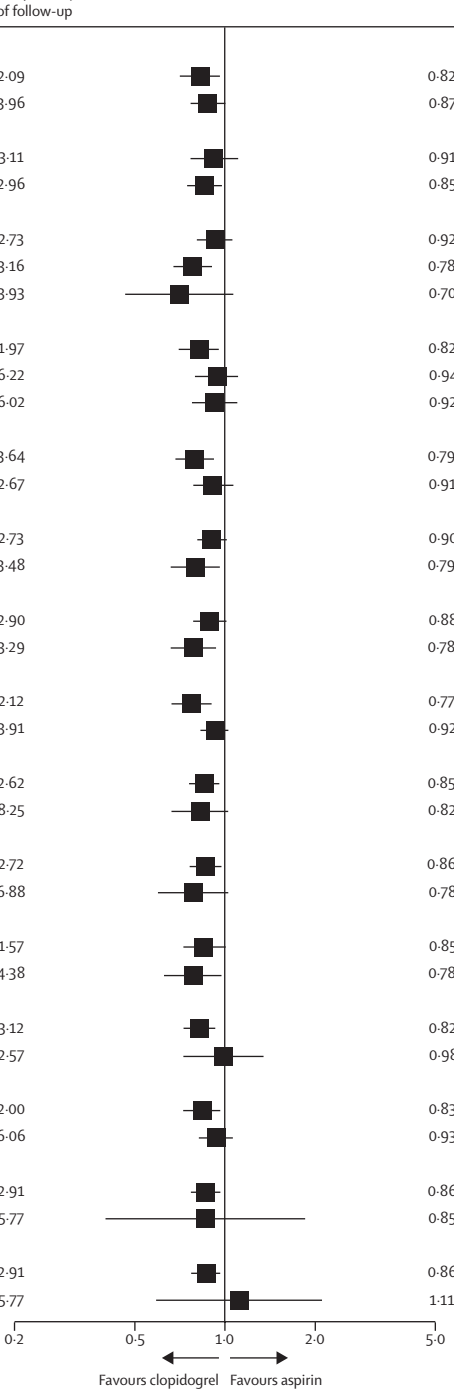

Figure 4: **Subgroup analysis for MACCE**
The Kaplan–Meier estimates refers to the maximum available follow-up of 2000 days. HRs and 95% CIs were computed by mixed-effects models (one-stage analysis). Unadjusted $p_{interaction}$ values formally describe the heterogeneity of treatment effects between or across subgroups. Low-dose aspirin was defined as ≤100 mg per day, high-dose aspirin as >100 mg per day. HR=hazard ratio. MACCE=major adverse cardiovascular or cerebrovascular events.

τ^2<0·001, p=0·42; appendix pp 36–37). The incidence of stroke was lower in patients with clopidogrel than in those with aspirin (table 2; appendix p 60). No significant between-trial heterogeneity was observed (I^2=0%; τ^2=0·012; p=0·42). Stent thrombosis was not significantly different between treatment groups (appendix p 59).

Any bleeding, major gastrointestinal bleeding, and any gastrointestinal bleeding did not differ between treatment groups across all statistical approaches (table 2, appendix pp 36–37, 62–63). High heterogeneity was detected for these outcomes (appendix 36–37, 62–63).

The treatment effect for MACCE was consistent across multiple key subgroups, including clinical determinants known to be independent predictors of impaired clopidogrel response, assessed in isolation or in combination (figure 4). Major bleeding was assessed across the same set of prespecified subgroups, and no significant interactions were detected, with the only exception of proton pump inhibitor use at discharge ($p_{interaction}$=0·0072; appendix p 64). After adjustment for multiplicity, the interaction p value was no longer significant ($p_{interaction}$=0·11).

MACCE and major bleeding were assessed using prespecified the 1000-day landmark (appendix pp 38–39, 66–67) to explore potential variations between earlier and later treatment periods. No significant heterogeneity was observed between treatment effects within the first 1000 days and the subsequent period from 1000 to 2000 days after initiation of antiplatelet monotherapy (($p_{interaction}$=0·16 for MACCE; $p_{interaction}$=0·60 for major bleeding). A 2-year landmark analysis was performed as a sensitivity analysis and yielded similar results (data not shown).

The analyses conducted in the per-protocol population provided consistent results (appendix pp 40–41). There was no evidence of a reduced treatment effect with clopidogrel compared with aspirin with respect to myocardial infarction or stroke in patients presumed to have poor response to clopidogrel according to an integrated analysis of clinical features (appendix p 68).

Results remained consistent in post-hoc sensitivity analyses that were conducted after the exclusion of patients on oral anticoagulation; stratifying trials by timing and definition of the initial DAPT phase; stratifying trials by geographical region; excluding the ASCET[26] trial (due to the lack of timing of clinical events); and stratifying patients by DAPT status before antiplatelet monotherapy (appendix pp 43–53). Results also remained consistent in a post-hoc analysis stratifying patients by treatment strategy for myocardial ischaemia (data not shown).

Discussion

This individual patient data meta-analysis, which integrates all relevant randomised clinical trials, provides the most comprehensive evaluation to date of the comparative efficacy and safety of clopidogrel versus aspirin monotherapy in patients with established CAD, most of whom had undergone percutaneous coronary intervention (PCI) or had acute coronary syndrome, who never started DAPT or discontinued DAPT.

The primary results of this analysis show that, over a follow-up period exceeding 5 years, clopidogrel monotherapy was associated with greater efficacy than aspirin for the long-term prevention of cardiovascular and cerebrovascular events, with no associated excess risk of bleeding. These findings are consistent with, and extend, previous analyses conducted in more heterogeneous populations, including patients with different $P2Y_{12}$ inhibitors,[13] patients treated with non-coronary atherosclerotic disease,[15] or cohorts limited to the post-PCI setting.[14] The additional value of this meta-analysis lies in several crucial aspects: the inclusion of two recent large-scale randomised trials contributing an additional 11 031 patients,[19,20] the availability of longer-term follow-up data from earlier trials,[21,22] the exclusive focus on clopidogrel (which remains the most widely prescribed, accessible, and reimbursed $P2Y_{12}$ inhibitor globally in patients with stable CAD across both high-income and low-income countries), and the confirmation of superiority of clopidogrel in a trial sequential analysis (to our knowledge, the first conducted in this domain). Our analysis shows an entirely consistent treatment effect of clopidogrel across all predefined subgroups, including clinical variables (eg, age, BMI, chronic kidney disease, and diabetes) identified as independent predictors of impaired responsiveness to clopidogrel.[27]

The relative risk reduction in the primary efficacy endpoint of MACCE observed with clopidogrel compared with aspirin was primarily driven by a reduction in myocardial infarction and stroke events. The significant anti-ischaemic benefit of clopidogrel was not offset by an increase in bleeding events, an observation that contrasts with findings from other studies evaluating alternative antithrombotic strategies to aspirin monotherapy.[28–32]

To the best of our knowledge, clopidogrel monotherapy is the only antiplatelet treatment that has consistently demonstrated greater efficacy than aspirin without compromising safety. The incidence of gastrointestinal bleeding was nearly identical between clopidogrel and aspirin. Therefore, the preferential use of clopidogrel over aspirin should be based on its superior efficacy, rather than on improved gastrointestinal safety, which was primarily observed in earlier trials conducted in settings with limited use of proton pump inhibitors and higher-dose aspirin.[26]

In this individual patient data meta-analysis, the results for MACCE were robust and consistent across all analytical approaches. Treatment effects were consistent across all prespecified subgroups, including age, sex, BMI, geographical region, clinical presentation, diabetes, and aspirin dose. These findings support the broad generalisability of the conclusions across diverse patient populations.

The superior efficacy of clopidogrel over aspirin observed in our meta-analysis should be interpreted in

view of the known interindividual variability in clopidogrel responsiveness.[18] Several studies have shown that carriers of *CYP2C19* loss-of-function alleles, present in up to 30% of individuals with European or African ancestry and up to 50% of individuals with east Asian ancestry, exhibit higher platelet reactivity and worse cardiovascular outcomes during clopidogrel therapy compared with non-carriers.[18] In our dataset, genetic data were limited to a subset of patients in a single trial,[19] precluding direct evaluation of the effect of *CYP2C19* alleles on the comparison between clopidogrel and aspirin. However, existing evidence suggests that the clinical relevance of *CYP2C19* polymorphisms is context-dependent, exerting prognostic effect in the early phase of acute coronary syndromes but not thereafter or in stable CAD.[33] Notably, in prespecified subgroup analyses, we found no interaction when patients were stratified by clinical factors known to influence clopidogrel responsiveness (eg, age, BMI, renal function, and diabetes) either individually or in combination.[27] Treatment effects with respect to the primary efficacy and all secondary endpoints, including myocardial infarction or stroke, remained consistent across subgroups with presumed high and low likelihood of poor responsiveness to clopidogrel.

Our findings are in agreement with a genetic substudy conducted in one of the included trials[19] and with previous observations in patients with chronic stroke.[34] Long-term clopidogrel treatment might be less affected than acute treatment with clopidogrel by poor drug responsiveness, which has so far been investigated only shortly after clopidogrel treatment initiation.[35] Aspirin, like clopidogrel, is subject to interindividual variability in antiplatelet effect, with a proportion of patients exhibiting aspirin resistance (a phenomenon that might be exacerbated with enteric-coated formulations and other clinical factors shown to affect clopidogrel response).

We did not observe a difference in mortality or cardiovascular mortality between groups, which is consistent with the finding that no antithrombotic treatment has been associated with mortality reduction when assessed in the post-acute phase of CAD.[29]

Some limitations should be considered when interpreting the results of this individual patient data meta-analysis. First, the inclusion of trials with differing designs, populations, and timing of monotherapy initiation could introduce clinical and methodological heterogeneity; however, we addressed this through individual-level data modelling to ensure robustness of the pooled estimates. Endpoint definitions varied across trials, reflecting differences in study periods and protocols; however, the general consistent direction of treatment effect regardless of endpoint definitions supports the robustness of our findings. The absence of heterogeneity across trials for any of the analysed efficacy endpoint is reassuring. Because patients who had early ischaemic or bleeding events during the initial DAPT phase were either not eligible for randomisation or excluded from the present analysis, our findings only apply to patients who completed an uneventful course of DAPT. Second, some differences in trial design contributed to variability in the duration of antiplatelet monotherapy across studies. However, landmark analyses indicated no significant difference in outcomes between treatment periods. Third, although subgroup analyses are often limited by insufficient statistical power and risk of false positive findings, our study benefits from a large sample size, prespecified subgroup definitions, and adjustment for multiplicity in the presence of significant interactions. Fourth, approximately two-thirds of the study cohort were of east Asian ethnicity. Although east Asian patients have a higher prevalence of *CYP2C19* allelic variants associated with reduced clopidogrel response, the superior efficacy of clopidogrel over aspirin was confirmed in this population, with no significant heterogeneity by geographical region. The absence of effect modification by clinical determinants of poor responsiveness to clopidogrel might at least partly reflect the attenuated prognostic relevance of these factors in the chronic phase of CAD, particularly in east Asian cohorts.[36] Additional trials in non-Asian populations are warranted. Fifth, none of the included trials assessed patient genotype, preventing analysis of the genetic component of the ABCD-GENE score.[27] Yet, no heterogeneity in treatment effects was observed when patients were stratified according to the clinical factors included in the score, either in isolation or in combination. Nevertheless, neither the ABCD-GENE score nor the cutoff of 10 points have ever been validated without genotype information, and we cannot exclude the possibility that access to *CYP2C19* genetic variant data or platelet function testing results would have allowed better risk stratification of our patients.[18] Sixth, although patients treated with coronary artery bypass grafting were included in the present analysis, their relative proportion was small and additional dedicated trials in this setting are warranted. Finally, both clopidogrel and aspirin are available as generic medications; however, clopidogrel carries an incremental cost compared with aspirin in many countries. Studies assessing the cost-effectiveness of clopidogrel versus aspirin in diverse health-care systems are needed to better inform clinical and policy decisions.

In conclusion, this study integrating data from all relevant available trials as of this date shows that, in patients with established CAD, clopidogrel monotherapy lowered the risk of MACCE (primarily by reducing the risk of myocardial infarction and stroke) compared with aspirin monotherapy, without an increase in major or any bleeding. The treatment effects were highly consistent across subgroups, including patients with clinical factors associated with impaired clopidogrel response. These findings support the consideration of clopidogrel as the preferred long-term antiplatelet strategy instead of aspirin in patients with established CAD.

Contributors

MV designed the study; accessed, verified, analysed, and interpreted the data; and drafted and approved the final version of the manuscript. DG accessed, verified, analysed, and interpreted the data and revised and approved the final version of the manuscript. FG accessed, verified, and interpreted the data and revised and approved the final version of the manuscript. KHC, TK, HW, H-SK, JK, KWP, A-ÅP, MW, DLB, PC, DJA, RM, YBS, and J-YH interpreted the data and revised and approved the final version of the manuscript. All authors had access to all the included data and had final responsibility for the decision to submit for publication.

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Data sharing

Anonymised individual patient data are stored at Cardiocentro Ticino institute, Lugano, Switzerland, with the exception of data from the CAPRIE trial, which are available at the Vivli platform (see https://vivli.org for more information). Requests should be addressed to marco.valgimigli@eoc.ch. The analytic code, individual trial protocols (which were individually previously published), study protocol (available at PROSPERO: CRD42025645594), and individual study case report forms can be requested via email to marco.valgimigli@eoc.ch.

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