$P2Y_{12}$ inhibitor or aspirin after percutaneous coronary intervention: individual patient data meta-analysis of randomised clinical trials

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ABSTRACT

OBJECTIVE

To assess the long term comparative effectiveness of $P2Y_{12}$ inhibitor monotherapy compared with aspirin monotherapy in patients after percutaneous coronary intervention (PCI) and discontinuation of dual antiplatelet therapy (DAPT).

DESIGN

Individual participant data (IPD) meta-analysis of randomised clinical trials.

DATA SOURCES

PubMed/Medline, Scopus, Web of Science, and Ovid/Embase.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES

Randomised trials investigating monotherapy with a $P2Y_{12}$ inhibitor or aspirin for secondary prevention of ischaemic events in patients with coronary artery disease who underwent PCI.

DATA EXTRACTION AND SYNTHESIS

Anonymised IPD were extracted and transferred to the coordinating centre by dedicated electronic spreadsheets. Data were primarily combined by mixed effects models (one stage analysis) and complemented with multivariable mixed effects models and two stage analyses based on random effects models. The primary and co-primary outcomes were a composite of major adverse cardiac and cerebrovascular events (MACCE) and major bleeding, respectively. The secondary outcomes included a net composite of adverse cardiac and cerebrovascular events (NACCE), derived from the combination of the primary and co-primary outcomes, and individual ischaemic and bleeding events.

RESULTS

A total of 16 117 patients assigned to $P2Y_{12}$ inhibitor or aspirin monotherapy after PCI and completion of the recommended DAPT regimen (median duration of 12 months) in five randomised trials were included. At a median follow-up of 1351 days (interquartile range 373-1791 days), $P2Y_{12}$ inhibitor monotherapy was associated with a lower risk of MACCE compared with aspirin monotherapy (one stage analysis: hazard ratio 0.77 (95% confidence interval (CI) 0.67 to 0.89), P<0.001; multivariable one stage analysis: adjusted hazard ratio 0.77 (0.67 to 0.89), P<0.001; two stage analysis: hazard ratio 0.77 (0.67 to 0.89), P<0.001), yielding a number needed to treat to benefit of 45.5 (95% CI 31.4 to 93.6). No significant difference in major bleeding (one stage analysis: hazard ratio 1.26 (0.78 to 2.04), P=0.35; multivariable one stage analysis: 1.12 (0.74 to 1.70), P=0.60; two stage analysis: 1.15 (0.69 to 1.92), P=0.59) was observed. NACCE, myocardial infarction, and stroke were lower in patients assigned to a $P2Y_{12}$ inhibitor compared with those assigned to aspirin. These findings were confirmed across multiple sensitivity and subgroup analyses.

CONCLUSIONS

In patients who had undergone PCI and discontinued DAPT, at a follow-up of about 5.5 years, $P2Y_{12}$ inhibitor monotherapy with ticagrelor or clopidogrel was associated with lower MACCE, owing to reduced rates of myocardial infarction and stroke compared with aspirin monotherapy, without a concurrent increased risk of major bleeding.

REVIEW REGISTRATION

PROSPERO CRD42024517983.

WHAT IS ALREADY KNOWN ON THIS TOPIC

In patients who underwent percutaneous coronary intervention (PCI) and completed dual antiplatelet therapy (DAPT), monotherapy with aspirin has been found to reduce the occurrence of major ischaemic events

Some randomised clinical trials have indicated a possible advantage of long term secondary prevention with a $P2Y_{12}$ inhibitor in place of aspirin

WHAT THIS STUDY ADDS

In patients who underwent PCI and completed DAPT, antiplatelet therapy with a $P2Y_{12}$ inhibitor reduced the five year incidence of cardiovascular death, myocardial infarction, or stroke and a net composite outcome including both major ischaemic events and major bleeding compared with aspirin

These findings were confirmed in multiple sensitivity analyses and were driven by significant reductions in myocardial infarction and stroke

Although major bleeding and any bleeding were not significantly different between treatments, substantial between trial heterogeneity was detected

Introduction

In high income countries, percutaneous coronary intervention (PCI) is the most common invasive treatment for coronary artery disease, with an estimated median of 2000 procedures per million inhabitants yearly.[1] After PCI, the secondary prevention of coronary ischaemic events generally requires a period of dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor.[2 3] Upon completion of DAPT, in the absence of an overriding indication for oral anticoagulation, long term aspirin use is the only class I recommended antithrombotic drug in European and North American guidelines.[2 3]

The evidence supporting aspirin as the preferred antiplatelet for secondary prevention derives from studies conducted more than four decades ago.[4 5] The lack of recent evidence raises concerns about relevance to contemporary practice, owing to substantial advancements in alternative antithrombotic drugs, cardiovascular medical treatment, devices, and procedural techniques observed in recent years.[6-8] In contrast, more recent studies conducted in the era of drug eluting stents focused on various combinations of antithrombotic drugs with the objective of reducing secondary coronary ischaemic events in patients with previous PCI.[9-11] In this regard, continuation of DAPT beyond the recommended duration, or dual pathway inhibition with aspirin and low dose rivaroxaban has been shown to lower the risk of non-fatal cardiac or cerebrovascular events compared with aspirin monotherapy at the cost of greater major bleeding events, limiting the adoption of these drugs in selected subsets of patients.[9-11]

The use of monotherapy with a $P2Y_{12}$ inhibitor in place of aspirin has been underexplored in patients after PCI and inconclusively defined by available clinical trials due to limitations in statistical power for major individual ischaemic and haemorrhagic endpoints. In addition, information on patient subgroups that may derive particular benefit or harm from use of a $P2Y_{12}$ inhibitor instead of aspirin is limited. A recent individual participant data (IPD) meta-analysis of patients with established coronary artery disease managed with or without revascularisation showed that $P2Y_{12}$ inhibitor monotherapy was associated with a reduced incidence of major adverse cardiac and cerebrovascular events (MACCE).[12] This improvement, however, translated into a number needed to treat to benefit (NNTB) of 121, implying the need to treat a relatively large number of patients with $P2Y_{12}$ monotherapy in place of aspirin to prevent the occurrence of one MACCE.[12] Moreover, the availability of a maximum follow-up of two years was deemed insufficient to gain long term comparative effectiveness data of $P2Y_{12}$ inhibitors versus aspirin.[12] Since then, substantial new data and long term follow-up information from randomised trials of patients after PCI have become available. These data have enabled the assessment of long term antiplatelet monotherapies for the secondary prevention of coronary ischaemic events in more contemporary study populations and more appropriate time horizons.

We performed an IPD meta-analysis of all available randomised trials of patients who underwent PCI and had discontinued DAPT to assess the long term outcomes of monotherapy with a $P2Y_{12}$ inhibitor or aspirin and explore whether treatment effects were modulated by specific individual characteristics.

Methods

We performed an IPD meta-analysis focusing on patients assigned to monotherapy with a $P2Y_{12}$ inhibitor (clopidogrel, prasugrel, or ticagrelor) or aspirin for long term secondary prevention of cardiovascular ischaemic events after PCI in the context of randomised clinical trials. The study population typically requires transitioning from DAPT to antiplatelet monotherapy because of the long term risk of thrombosis associated with stent implantation and an inherent propensity for coronary artery disease to progress over time.[13-15] The protocol was registered with PROSPERO (CRD42024517983) and the IPD meta-analysis reported in keeping with the Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data (PRISMA-IPD) recommendations (see supplementary table S1).[16] The original trials were approved by ethics committees, and all patients provided written informed consent. In the context of an IPD meta-analysis, new ethical approval was not required.

Data sources and searches

We searched four major electronic databases (Medline through PubMed, Scopus, Web of Science, and Embase through Ovid) from inception to 2 December 2023 for randomised trials that compared $P2Y_{12}$ inhibitor monotherapy with aspirin monotherapy (see supplementary appendix). The search was updated on 1 June 2024. Additionally, we searched major websites with an interest in the specialty, conference proceedings, and archives of registered trials (see supplementary appendix). Two reviewers (DG and FG) independently screened titles and abstracts to identify trials that met the inclusion criteria. Potentially eligible reports underwent independent full text screening under the supervision of a third senior reviewer (MV). Finally, the search strategy was complemented by backwards snowballing of relevant reports identified across the four major databases.

Study selection

Patients were deemed eligible for inclusion in this meta-analysis if they were randomly assigned to monotherapy with an oral $P2Y_{12}$ inhibitor (ie, clopidogrel, prasugrel, or ticagrelor) or aspirin and underwent myocardial revascularisation by PCI. We considered trials planning an initial period of DAPT after PCI, as currently recommended, to be eligible. Their contribution to the analyses was, however, limited to the comparison between a $P2Y_{12}$ inhibitor and aspirin to avoid confounding influences on long term clinical outcomes due to dissimilar baseline risk between patients arising from different DAPT durations. More specifically, we considered the time of DAPT discontinuation as the start of follow-up, therefore excluding patients who were lost to follow-up, died, or experienced a non-fatal major event (ie, myocardial infarction, stroke, stent thrombosis, or major bleeding) during the period preceding the comparison between antithrombotic monotherapies. We excluded trials of patients with an indication for long term oral anticoagulation or assessing antiplatelet drugs different from contemporary $P2Y_{12}$ inhibitors.

Data extraction and quality assessment

The primary investigators of eligible trials agreed to collaborate in the present study. We extracted

anonymised IPD and transferred these to the coordinating centre using dedicated electronic spreadsheets. To assess the completeness and consistency of the extracted data, we compared the gathered information with the original publications and conducted an interactive cross-check with the primary investigators. In general, no relevant inconsistency in the definition of variables collected in the databases was observed. Two investigators (DG and FG) independently assessed the risk of bias using the Cochrane Collaboration's risk of bias 2.0 (RoB 2) tool.[17] Disagreements were resolved by consensus and consultation with a third senior author (MV).

Outcomes

The prespecified primary outcome was a composite of MACCE comprising cardiovascular death, myocardial infarction, or stroke. The prespecified co-primary outcome was major bleeding, primarily defined as type 3 or 5 according to the Bleeding Academic Research Consortium (BARC). Trials conducted before the development of the BARC definitions were, however, pooled by using the study specific definition of major bleeding. The secondary outcomes included a net composite of adverse cardiac and cerebrovascular events (NACCE), derived from the combination of the primary and co-primary outcomes, and the individual outcomes of all cause death, cardiovascular death, myocardial infarction, stroke, ischaemic stroke, haemorrhagic stroke, definite or probable stent thrombosis (Academic Research Consortium definitions), definite stent thrombosis, probable stent thrombosis, major gastrointestinal bleeding, any bleeding, and any gastrointestinal bleeding.

Data synthesis and analysis

Categorical variables were presented as counts and proportions and compared using Pearson's χ^2 or Fisher's exact tests, as appropriate. Continuous variables were presented as medians and interquartile ranges (IQRs) and compared using the Wilcoxon-Mann-Whitney U test based on the results of the Shapiro-Wilk test.

The primary analysis involved the intention-to-treat population. Outcomes at the maximum available follow-up were primarily assessed by mixed effects Cox proportional hazards regression models with a random intercept and a random slope to account for between trial differences in the baseline hazard and heterogenous treatment effects across trials, respectively (one stage analyses).[18 19] Treatment effects were presented as hazard ratios and 95% confidence intervals (CIs). In the ASpirin non-responsiveness and Clopidogrel clinical Endpoint Trial (ASCET), we assumed events to occur at the end of the follow-up period because the time of occurrence of events was not collected in the original database. We described outcomes between treatment groups as counts, cumulative incidences computed by the Kaplan-Meier method, and incidence rates per 100 person years. After excluding patients from ASCET, the cumulative distributions of events from the initiation of antithrombotic monotherapies to five year follow-up (ie, in many patients corresponding to 66 to 78 months after the index PCI) were shown by Kaplan-Meier curves and compared using the log-rank test. The median follow-up time was estimated by the reverse Kaplan-Meier method.[20] We tested for the proportional hazards assumption using the Grambsch-Therneau test and Schoenfeld scaled residuals.[19]

As recommended for IPD meta-analyses, we also assessed outcomes in two stage analyses, in which hazard ratios and 95% CIs were computed by Cox proportional hazards regression within each trial and subsequently combined by random effects models with inverse variance weighting.[21] Firth's correction was used to calculate rare outcomes with monotonic distribution within individual trials.[22] Between trial heterogeneity was formally tested with the Q test and measured by I^2 and τ^2 statistics.[21] We calculated τ^2 using the restricted maximum likelihood estimator.[21] The analyses were replicated with conservative adjustment of the 95% CI of summary estimates using the Hartung-Knapp method.[21]

In a sensitivity analysis, we reassessed outcomes by multivariable mixed effects Cox proportional hazards regression models applied across datasets (n=10) generated by chain equation multiple imputation accounting for the multilevel structure of data.[23] The following variables were included in the multivariable models along with the treatment strategy: age, sex, body mass index, geographical region, index clinical presentation, diabetes, hypertension, hypercholesterolaemia, smoking status, previous myocardial infarction, previous stroke, previous bleeding, peripheral artery disease, estimated glomerular filtration rate, PRECISE-DAPT (PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual AntiPlatelet Therapy) score, use of a proton pump inhibitor, and type of $P2Y_{12}$ inhibitor. We pooled the results across imputed datasets according to the Rubin's rules.[23] One and two stage analyses were replicated in the per protocol population accounting for deviations from the intended antiplatelet monotherapy regimen.

In another sensitivity analysis, considering that 2000 days was the maximum available follow-up, we applied the landmark time point of 1000 days to inspect differences in the distribution of events over time between the treatment groups. We also assessed the primary outcome of MACCE and the co-primary outcome of major bleeding across prespecified subgroups. Treatment-by-subgroup interaction was formally assessed, and multiplicity adjusted for, in the presence of significant P values for interaction. Finally, when we observed statistically significant differences in a major outcome, we computed the NNTB or number needed to treat to harm (NNTH) as described for Cox regression models.[24] Although NNTB and NNTH have known limitations and may oversimplify results, they provide a straightforward measure of the magnitude of treatment effect and usefully complement absolute and relative differences between $P2Y_{12}$ inhibitor and

Table 1 | Baseline characteristics of participants assigned to monotherapy with a $P2Y_{12}$ inhibitor or aspirin after percutaneous coronary intervention in randomised clinical trials. Values are number (percentage) unless stated otherwise

Characteristics	$P2Y_{12}$ inhibitor (n=8075)	Aspirin (n=8042)	P value
Median (IQR) age (years)	65.0 (57.0-73.0)	65.0 (57.0-72.7)	0.88
Women	1931 (23.9)	1909 (23.7)	0.79
Median (IQR) body mass index	25.7 (23.4-28.4)	25.7 (23.4-28.4)	0.76
Region:			
Europe	3817 (47.3)	3772 (46.9)	0.89
North America	143 (1.8)	145 (1.8)	
Eastern Asia	4115 (51.0)	4125 (51.3)	
Diabetes:			
Overall	2311 (28.6)	2295 (28.5)	0.90
Insulin dependent	358 (15.8)	362 (16.2)	0.76
Hypertension	5415 (67.1)	5340 (66.5)	0.38
Hypercholesterolaemia	5185 (67.8)	5201 (68.3)	0.52
Current smoking	2063 (25.5)	2038 (25.3)	0.76
Previous myocardial infarction	2450 (30.4)	2436 (30.3)	0.93
Previous stroke	294 (3.6)	326 (4.1)	0.17
Clinical presentation:			
Chronic coronary syndrome	3567 (44.2)	3607 (44.9)	0.39
Acute coronary syndrome	4508 (55.8)	4435 (55.1)	
Peripheral artery disease	386 (4.8)	449 (5.6)	0.02
Chronic kidney disease	1162 (15.0)	1105 (14.3)	0.23
Median (IQR) creatinine (µmol/L; mg/dL)	79.6 (69.0-92.8); 0.9 (0.8-1.0)	79.6 (69.0-93.0); 0.9 (0.8-1.1)	0.58
Median (IQR) eGFR (mL/min/1.73 m^2)	84.6 (68.4-97.1)	83.9 (68.1-97.1)	0.50
Chronic obstructive pulmonary disease	266 (3.4)	253 (3.3)	0.59
Liver disease	59 (0.8)	51 (0.7)	0.46
Previous bleeding	45 (0.6)	53 (0.7)	0.41
Median (IQR) haemoglobin (g/L; g/dL)	141 (130-151); 14.1 (13.0-15.1)	141 (130-151); 14.1 (13.0-15.1)	0.90
Median (IQR) white blood cell count (×10^9/L)	7.0 (5.7-8.8)	7.0 (5.8-8.7)	0.90
Median (IQR) PRECISE-DAPT score*	15.0 (9.0-23.0)	15.0 (9.0-23.0)	0.65
PRECISE-DAPT score ≥25*	1476 (20.6)	1476 (20.7)	0.85
Aspirin dose:			
Low	7462 (92.4)	7435 (92.5)	0.92
High	613 (7.6)	607 (7.5)	
$P2Y_{12}$ inhibitor:			
Clopidogrel	4728 (58.6)	4732 (58.8)	0.71
Ticagrelor	3347 (41.4)	3310 (41.2)	
Proton pump inhibitor	3314 (42.3)	3273 (41.9)	0.65
Drug eluting stent:			
None	303 (3.9)	301 (3.9)	0.74
First generation	248 (3.2)	264 (3.4)	
Second generation	7150 (92.8)	7102 (92.6)	

eGFR=estimated glomerular filtration rate; IQR=interquartile range; PRECISE-DAPT=PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual AntiPlatelet Therapy.
*Range 0-100 points (scores ≥25 represent high risk of bleeding).

aspirin monotherapies. Analyses were performed using R 4.3.2.

Patient and public involvement

Patients and members of the public were not directly involved as this study was an IPD meta-analysis of randomised trials. Patients and investigators, including several authors of the manuscript, were involved in the original randomised trials.

Results

A total of 16 117 patients from five randomised trials (ASCET, CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events), GLASSY (GLOBAL LEADERS Adjudication Sub-Study), HOST-EXAM (Harmonizing Optimal Strategy for Treatment of coronary artery stenosis-Extended Antiplatelet Monotherapy), STOPDAPT-2 (ShorT and OPtimal Duration of Dual AntiPlatelet Therapy-2 study)) who were assigned to monotherapy with a $P2Y_{12}$ inhibitor or aspirin were included in the study (see supplementary figure S1).[25-31] Supplementary tables S2-S5 report the main characteristics of the original trials. Qualitative assessment of the trials did not raise major concerns (see supplementary figure S2).

Baseline characteristics were well balanced between groups for all the variables of interest except for a higher prevalence of peripheral artery disease in patients receiving aspirin compared with those receiving a $P2Y_{12}$ inhibitor (table 1). The mean age of patients was 65 years (IQR 57-73 years), 23.8% were women, 28.6% had diabetes, and 14.6% had moderate-to-severe chronic kidney disease. Acute coronary syndrome at the index admission—six to 18 months before the comparison between antiplatelet monotherapies in about 95% of patients—was diagnosed in 55.5% of

Table 2 | Clinical outcomes by one stage models in participants assigned to $P2Y_{12}$ inhibitor or aspirin monotherapy after percutaneous coronary intervention in randomised clinical trials

Outcomes	$P2Y_{12}$ inhibitor			Aspirin			Hazard ratio (95% CI)	P value	Adjusted hazard ratio† (95% CI)	P value‡
	No of events/ patients	Cumulative incidence (%)*	Incidence per 100 person years	No of events/ patients	Cumulative incidence (%)*	Incidence per 100 person years				
MACCE	341/8075	7.7	1.49	441/8042	10.0	1.93	0.77 (0.67 to 0.89)	<0.001	0.77 (0.67 to 0.89)	<0.001
Major bleeding	160/8075	3.5	0.70	162/8042	3.8	0.70	1.26 (0.78 to 2.04)	0.35	1.12 (0.74 to 1.70)	0.60
NACCE	458/8075	10.1	2.03	544/8042	12.3	2.41	0.86 (0.75 to 0.98)	0.03	0.85 (0.73 to 0.99)	0.04
Death	347/8075	8.1	1.50	341/8042	8.2	1.46	1.04 (0.88 to 1.23)	0.63	1.04 (0.89 to 1.21)	0.61
Cardiovascular death	147/8075	3.5	0.63	163/8042	4.1	0.70	0.88 (0.68 to 1.13)	0.31	0.90 (0.72 to 1.13)	0.37
Myocardial infarction	131/8075	2.8	0.57	190/8042	3.9	0.82	0.69 (0.55 to 0.87)	0.001	0.69 (0.55 to 0.87)	0.001
Stroke	90/8075	2.3	0.39	135/8042	3.2	0.58	0.67 (0.51 to 0.89)	0.006	0.67 (0.52 to 0.88)	0.004
Ischaemic stroke	59/7763	1.6	0.26	94/7731	2.2	0.42	0.63 (0.45 to 0.87)	0.005	0.64 (0.46 to 0.89)	0.007
Haemorrhagic stroke	25/7763	0.7	0.11	34/7731	0.9	0.15	0.74 (0.44 to 1.26)	0.27	0.76 (0.45 to 1.27)	0.29
Definite or probable stent thrombosis	18/7462	0.3	0.08	30/7435	0.6	0.14	0.55 (0.29 to 1.07)	0.08	0.60 (0.33 to 1.07)	0.08
Definite stent thrombosis	13/7462	0.2	0.06	21/7435	0.4	0.09	0.62 (0.31 to 1.24)	0.18	0.62 (0.31 to 1.24)	0.18
Probable stent thrombosis	5/7462	0.1	0.02	9/7435	0.3	0.04	0.53 (0.18 to 1.60)	0.26	0.48 (0.14 to 1.72)	0.26
Any bleeding	397/8075	7.9	1.79	339/8042	7.3	1.51	1.33 (1.00 to 1.77)	0.05	1.31 (0.98 to 1.75)	0.07
Major gastrointestinal bleeding	73/7763	1.7	0.33	57/7731	1.5	0.25	1.56 (0.72 to 3.36)	0.26	1.49 (0.74 to 2.99)	0.26
Any gastrointestinal bleeding	116/7763	2.6	0.52	104/7731	2.4	0.46	1.21 (0.79 to 1.84)	0.39	1.15 (0.88 to 1.50)	0.31

All models are mixed effects.
CI=confidence interval; MACCE=major adverse cardiac and cerebrovascular events (composite of cardiovascular death, myocardial infarction, or stroke); NACCE=net adverse cardiac and cerebrovascular events (composite of cardiovascular death, myocardial infarction, stroke, or major bleeding).
*Kaplan-Meier method.
†Multivariable adjusted hazard.
‡P value from multivariable models using Wald type test.

patients. The $P2Y_{12}$ inhibitor was clopidogrel in 58.7% of patients and ticagrelor in 41.3% of patients. Overall, 48.9% of patients were enrolled in trials conducted in Europe or North America and 51.1% in trials conducted in eastern Asia.

Primary and co-primary outcomes

Table 2 and figure 1 show the number of events, incidence rates, and summary estimates of MACCE and major bleeding. At a median follow-up of 1351 days (IQR 373-1791 days), the primary MACCE outcome occurred in 341 patients assigned to $P2Y_{12}$ inhibitor monotherapy (1.49 per 100 person years) and 441 patients assigned to aspirin monotherapy (1.93 per 100 person years) (table 2). In the one stage analysis, the reduction in MACCE with $P2Y_{12}$ monotherapy compared with aspirin monotherapy was significant (hazard ratio 0.77, 95% CI 0.67 to 0.89, P<0.001; NNTB 45.5, 95% CI 31.4 to 93.6) (table 2 and figure 1). This finding remained unchanged after multivariable mixed effects model analysis (adjusted hazard ratio 0.77 (0.67 to 0.89), P<0.001) (table 2 and figure 1). The two stage analysis showed consistent results, regardless of adjustment for the summary estimate 95% CI (hazard ratio 0.77 (0.67 to 0.89), P<0.001; hazard ratio 0.77 (0.63 to 0.94), P=0.02), with no between trial heterogeneity (I^2=0%, τ^2=0, P=0.97) (table 3 and figure 1).

The co-primary outcome of major bleeding occurred in 160 patients assigned to $P2Y_{12}$ inhibitor monotherapy (0.70 per 100 person years) and 162 patients assigned to aspirin monotherapy (0.70 per 100 person years) (table 2). Major bleeding did not differ between treatment groups in both univariate one stage (hazard ratio 1.26 (0.78 to 2.04), P=0.35) and multivariable mixed effects model analyses (adjusted hazard ratio 1.12 (0.74 to 1.70), P=0.60) (table 2 and figure 2). The two stage analysis showed consistent findings (hazard ratio 1.15 (0.69 to 1.92), P=0.59) with significant between trial heterogeneity (I^2=69.0%, τ^2=0.165, P=0.01) (table 3 and figure 2).

Secondary outcomes

NACCE occurred in 458 patients assigned to $P2Y_{12}$ inhibitor monotherapy (2.03 per 100 person years) and 544 patients assigned to aspirin monotherapy (2.41 per 100 person years) (table 2 and figure 3). The one stage analysis showed a significant reduction in NACCE associated with $P2Y_{12}$ monotherapy compared with aspirin monotherapy (hazard ratio 0.86 (0.75 to 0.98), P=0.03; NNTB 61.2 (95% CI 34.4 to 505.7)) (table 2 and figure 3). After multivariable mixed effects model analysis, the result remained unchanged (adjusted hazard ratio 0.85 (0.73 to 0.99), P=0.04) (table 2 and figure 3). The two stage analysis was consistent (hazard ratio 0.84 (0.73 to 0.98), P=0.03) and no between trial heterogeneity was detectable (I^2=0%, τ^2=0.006, P=0.43) (table 3 and figure 3).

Table 2 and table 3 also include the individual secondary endpoints. Cardiovascular death was not significantly different between groups (one stage:

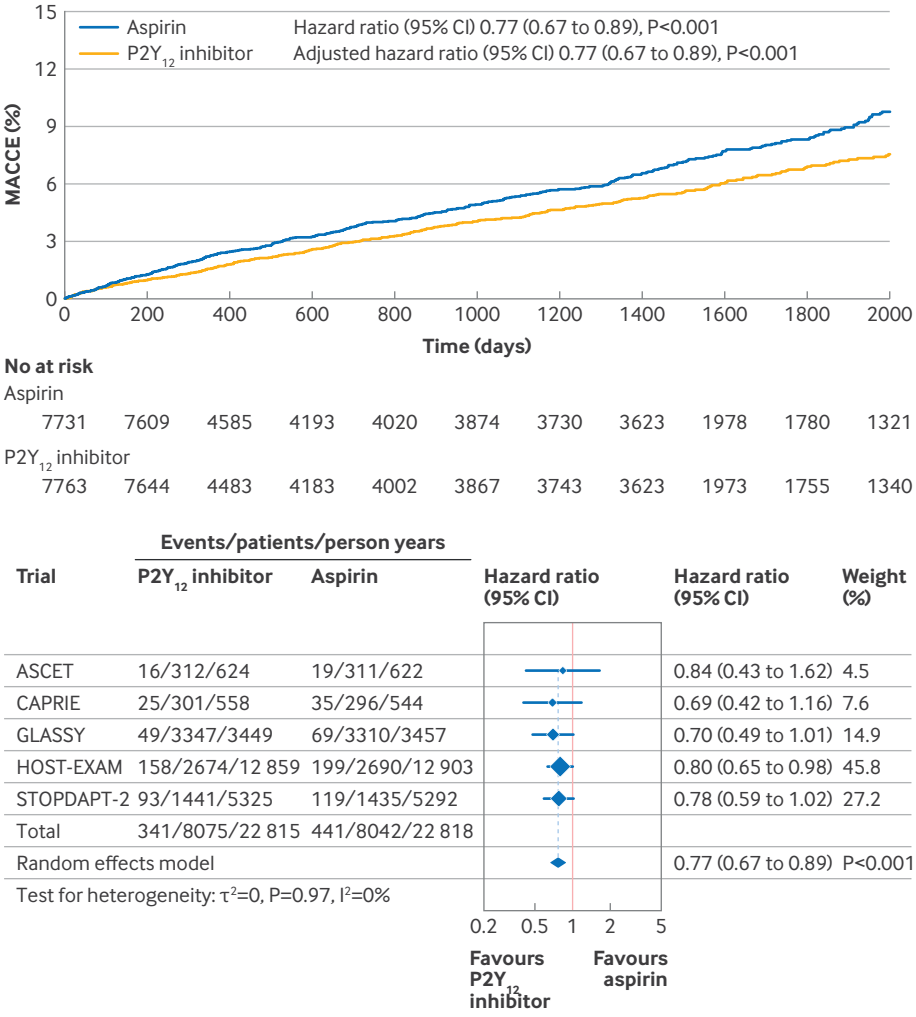

Fig 1 | Primary outcome of MACCE. Cumulative incidences were calculated using Kaplan-Meier method and compared with log-rank test. (Top panel) One stage analysis accounting for differences in baseline hazard and treatment effects across trials. Mixed effects models were used to calculate hazard ratios and 95% CIs and multivariable mixed effects models to calculate adjusted hazard ratios and 95% CIs (sensitivity analysis). The corresponding P values were derived from Wald type testing. (Bottom panel) Two stage analysis by random effects models with inverse variance weighting. CI=confidence interval; ASCET=ASpirin non-responsiveness and Clopidogrel clinical Endpoint Trial; CAPRIE=Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events; GLASSY=GLOBAL LEADERS Adjudication Sub-Study; HOST-EXAM=Harmonizing Optimal Strategy for Treatment of coronary artery stenosis-Extended Antiplatelet Monotherapy; MACCE=major adverse cardiac and cerebrovascular events (composite of cardiovascular death, myocardial infarction, or stroke); STOPDAPT-2=ShorT and OPtimal Duration of Dual AntiPlatelet Therapy-2 Study

hazard ratio 0.88 (0.68 to 1.13), P=0.31; multivariable one stage: adjusted hazard ratio 0.90 (0.72 to 1.13), P=0.37; two stage: hazard ratio 0.91 (0.73 to 1.13), P=0.39; adjusted two stage: hazard ratio 0.91 (0.66 to 1.25), P=0.44) and no between trial heterogeneity was detectable (table 2, table 3, and figure 4). Consistently, all cause death was not significantly different between antiplatelet monotherapies, regardless of the methods used (table 2, table 3, and supplementary figure S3). Myocardial infarction (one stage: hazard ratio 0.69 (0.55 to 0.87), P=0.001; NNTB 84.2 (95% CI 57.8 to 194.7); multivariable one stage: adjusted hazard ratio 0.69 (0.55 to 0.87), P=0.001; two stage: hazard ratio 0.69 (0.55 to 0.86), P=0.001; adjusted two stage: hazard ratio 0.69 (0.50 to 0.95), P=0.03) and stroke (one stage: hazard ratio 0.67 (0.51 to 0.89), P=0.006; NNTB (98.2, 65.1 to 297.9); multivariable one stage: adjusted hazard ratio 0.67 (0.52 to 0.88), P=0.004; two stage: hazard ratio 0.67 (0.51 to 0.88), P=0.003; adjusted two stage: hazard ratio 0.67 (0.46 to 0.98), P=0.04) were significantly reduced in patients assigned to $P2Y_{12}$ inhibitor monotherapy compared with those assigned to aspirin monotherapy (table 2, table 3, figure 5, and figure 6). No between trial heterogeneity was detectable for myocardial infarction and stroke (table 3, figure 5, and figure 6). The analysis of the stroke components showed that ischaemic stroke was significantly reduced in patients assigned to $P2Y_{12}$ inhibitor monotherapy compared with those assigned to aspirin monotherapy, and haemorrhagic stroke was not significantly different between treatment groups (table 2 and table 3). Definite or probable stent thrombosis showed a numerical reduction in patients assigned to $P2Y_{12}$ inhibitor monotherapy

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Table 3 | Clinical outcomes by two stage models in participants assigned to $P2Y_{12}$ inhibitor or aspirin monotherapy after percutaneous coronary intervention in randomised clinical trials

Outcomes	Hazard ratio (95% CI)	P value	Adjusted hazard ratio* (95% CI)	P value†	I^2 (%)	τ^2	P value‡
MACCE	0.77 (0.67 to 0.89)	<0.001	0.77 (0.63 to 0.94)	0.02	0	0	0.97
Major bleeding	1.15 (0.69 to 1.92)	0.59	1.15 (0.56 to 2.37)	0.61	69.0	0.165	0.01
NACCE	0.84 (0.73 to 0.98)	0.03	0.84 (0.68 to 1.05)	0.09	0	0.006	0.43
Death	1.02 (0.88 to 1.19)	0.76	1.02 (0.83 to 1.26)	0.78	0	0	0.84
Cardiovascular death	0.91 (0.73 to 1.13)	0.39	0.91 (0.66 to 1.25)	0.44	0	0	0.85
Myocardial infarction	0.69 (0.55 to 0.86)	0.001	0.69 (0.50 to 0.95)	0.03	0	0	0.80
Stroke	0.67 (0.51 to 0.88)	0.003	0.67 (0.46 to 0.98)	0.04	0	0	0.85
Ischaemic stroke	0.65 (0.47 to 0.89)	0.009	0.65 (0.38 to 1.10)	0.08	0	<0.001	0.74
Haemorrhagic stroke	0.73 (0.43 to 1.23)	0.23	0.73 (0.31 to 1.70)	0.32	0	0	0.71
Definite or probable stent thrombosis	0.67 (0.36 to 1.22)	0.19	0.67 (0.13 to 3.32)	0.39	31.2	<0.001	0.23
Definite stent thrombosis	0.72 (0.35 to 1.51)	0.39	0.72 (0.09 to 5.51)	0.56	37.0	<0.001	0.20
Probable stent thrombosis	0.56 (0.19 to 1.67)	0.30	0.56 (0.19 to 1.67)	0.30	—	—	—
Any bleeding	1.29 (0.95 to 1.75)	0.11	1.29 (0.83 to 1.98)	0.18	79.4	0.087	<0.001
Major gastrointestinal bleeding	1.53 (0.60 to 3.92)	0.38	1.53 (0.33 to 7.05)	0.44	72.8	0.481	0.01
Any gastrointestinal bleeding	1.24 (0.74 to 2.10)	0.41	1.24 (0.53 to 2.90)	0.47	58.6	0.135	0.06

All models are random effects, with and without Hartung-Knapp adjustment of 95% CIs.
CI=confidence interval; MACCE=major adverse cardiac and cerebrovascular events (composite of cardiovascular death, myocardial infarction, or stroke); NACCE=net adverse cardiac and cerebrovascular events (composite of cardiovascular death, myocardial infarction, stroke, or major bleeding).
*Hazard ratio from two stage model with Hartung-Knapp adjustment of CI.
†Wald type test P value from two stage model with Hartung-Knapp adjustment of CI.
‡P value from Q test for heterogeneity.

compared with those assigned to aspirin monotherapy (table 2, table 3, and supplementary figure S4). The difference remained non-statistically significant in the multivariable one stage analysis and two stage analyses (table 2, table 3, and supplementary figure 4). Mild between trial heterogeneity was detected (I^2=31.2%, τ^2<0.001, P=0.23) (table 3 and supplementary figure S4).

Any bleeding was numerically increased in patients assigned to $P2Y_{12}$ inhibitor monotherapy compared with aspirin monotherapy (one stage: hazard ratio 1.33 (1.00 to 1.77), P=0.05; multivariable one stage: adjusted hazard ratio 1.31 (0.98 to 1.75), P=0.07; two stage: hazard ratio 1.29 (0.95 to 1.75), P=0.11) (table 2, table 3, and supplementary figure S5). Significant between trial heterogeneity was detected (I^2=79.4%, τ^2=0.087, P<0.001) (table 3 and supplementary figure S5). Major gastrointestinal bleeding and gastrointestinal bleeding did not differ between antiplatelet monotherapies, regardless of the model used (table 2, table 3, and supplementary figure S6). Significant between trial heterogeneity was detected for both major gastrointestinal bleeding (I^2=72.8%, τ^2=0.481, P=0.01) and any gastrointestinal bleeding (I^2=58.6%, τ^2=0.135, P=0.06) (table 2 and supplementary figure 6).

Landmark analyses

MACCE and major bleeding were assessed by applying the landmark time point of 1000 days (see supplementary table S6) to inspect variations in effects between earlier and later treatment periods. Supplementary figure S7 illustrates the results in terms of MACCE and supplementary figure S8 in terms of major bleeding. Overall, there was no significant heterogeneity between the effects observed within 1000 days since initiation of antiplatelet monotherapy and those within the subsequent period from 1000 to 2000 days (P=0.50 for interaction; P=0.39 for interaction) (see supplementary table S1 and supplementary figures S7 and S8).

Per protocol analyses

After accounting for protocol deviations, including non-adherence to the assigned antiplatelet monotherapy, the results remained overall consistent with those observed in the intention-to-treat population (see supplementary tables S7 and S8 and supplementary figures S9-S11). The assessment of MACCE confirmed a significant reduction with $P2Y_{12}$ inhibitor compared with aspirin (one stage: hazard ratio 0.73 (0.62 to 0.85), P<0.001; multivariable one stage: adjusted hazard ratio 0.73 (0.62 to 0.85), P<0.001; two stage: hazard ratio 0.73 (0.62 to 0.85), P<0.001; two stage adjusted: hazard ratio 0.73 (0.58 to 0.91), P=0.02) driven by significant reductions in myocardial infarction and stroke (see supplementary tables S7 and S8 and supplementary figure S9). The assessment of major bleeding confirmed the absence of significant differences between treatment groups (one stage: hazard ratio 1.05 (0.68 to 1.63), P=0.82; multivariable one stage: adjusted hazard ratio 1.00 (0.67 to 1.50), P=0.99; two stage: hazard ratio 1.07 (0.63 to 1.80), P=0.81; adjusted two stage: hazard ratio 1.07 (0.46 to 2.49), P=0.83) (see supplementary tables S7 and S8 and supplementary figure S10). The assessment of NACCE showed a significant reduction in the $P2Y_{12}$ inhibitor group compared with the aspirin group (one stage: hazard ratio 0.80 (0.70 to 0.92), P=0.002; multivariable one stage: adjusted hazard ratio0.79 (0.69 to 0.91), P=0.001; two stage: hazard ratio 0.80 (0.69 to 0.91), P=0.001; adjusted two stage: hazard ratio 0.80 (0.65 to 0.97), P=0.03) (see supplementary tables S7 and S8 and supplementary figure S11).

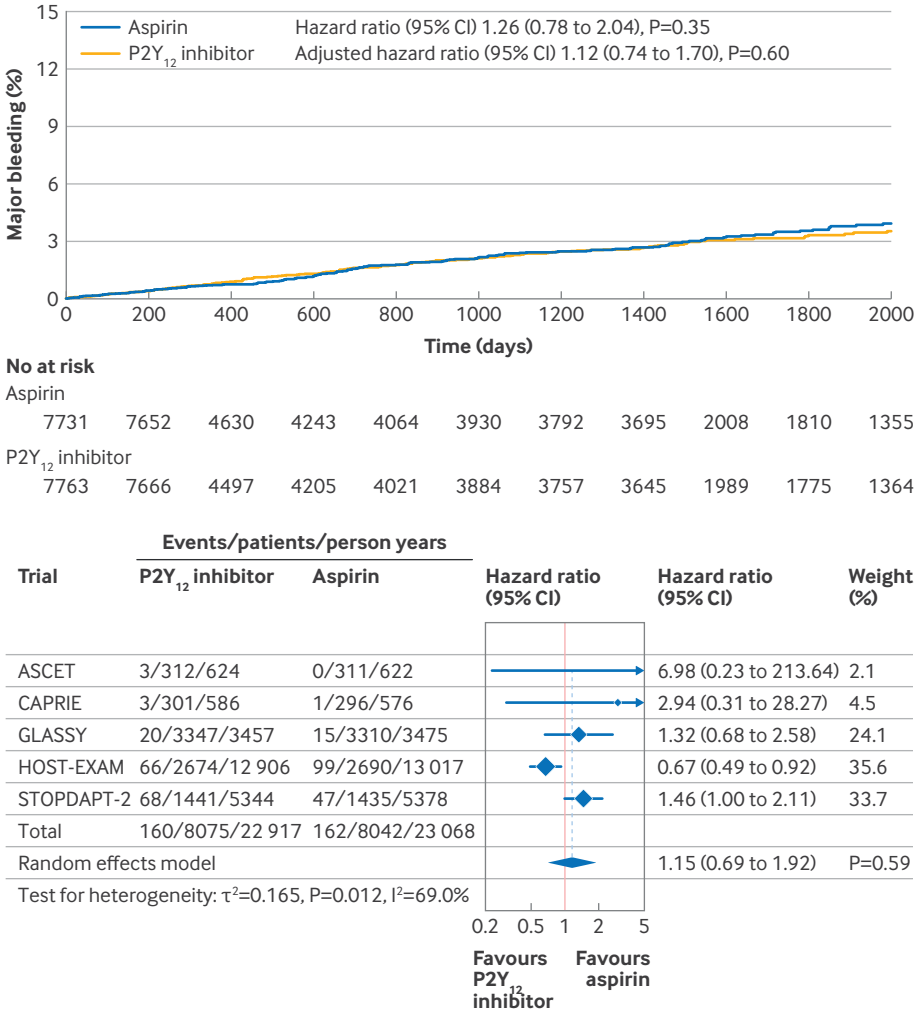

Fig 2 | Co-primary outcome of major bleeding. Cumulative incidences were calculated using Kaplan-Meier method and compared with log-rank test. (Top panel) One stage analysis accounting for differences in baseline hazard and treatment effects across trials. Mixed effects models were used to calculate hazard ratios and 95% CIs and multivariable mixed effects models to calculate adjusted hazard ratios and 95% CIs (sensitivity analysis). The corresponding P values were derived from Wald type testing. (Bottom panel) Two stage analysis by random effects models with inverse variance weighting. ASCET=ASpirin non-responsiveness and Clopidogrel clinical Endpoint Trial; CAPRIE=Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events; CI=confidence interval; GLASSY=GLOBAL LEADERS Adjudication Sub-Study; HOST-EXAM=Harmonizing Optimal Strategy for Treatment of coronary artery stenosis-Extended Antiplatelet Monotherapy; STOPDAPT-2=ShorT and OPtimal Duration of Dual AntiPlatelet Therapy-2 Study

Subgroup and sensitivity analyses

The primary outcome of MACCE was assessed across several prespecified subgroups without significant interaction detected (fig 7). Main biometric (ie, age, sex, and body mass index) and ischaemic risk characteristics (ie, diabetes, smoking status, previous myocardial infarction, and previous stroke), major comorbid conditions associated with coronary artery disease (peripheral artery disease and chronic kidney disease), the geographical region where the trial was conducted (P=0.75 for interaction), and the index clinical presentation (acute or chronic coronary syndrome, P=0.65 for interaction) did not significantly influence the antithrombotic effects of $P2Y_{12}$ inhibitor monotherapy over aspirin monotherapy. Consistently, proton pump inhibitor use (P=0.92 for interaction), aspirin dose (P=0.89 for interaction), and $P2Y_{12}$ inhibitor type (clopidogrel or ticagrelor, P=0.65 for interaction) did not significantly influence the antithrombotic effects of $P2Y_{12}$ inhibitor monotherapy over aspirin monotherapy.

The co-primary outcome of major bleeding was assessed across the same set of prespecified subgroups without observing significant treatment-by-subgroup interaction (fig 8).

The analyses after individually or simultaneously excluding the less contemporary ASCET and CAPRIE trials did not significantly alter the general conclusions in the overall study population (see supplementary tables S9-S11). A post hoc sensitivity analysis excluding the GLASSY trial to combine only patients receiving clopidogrel monotherapy showed largely consistent results (see supplementary table S12).

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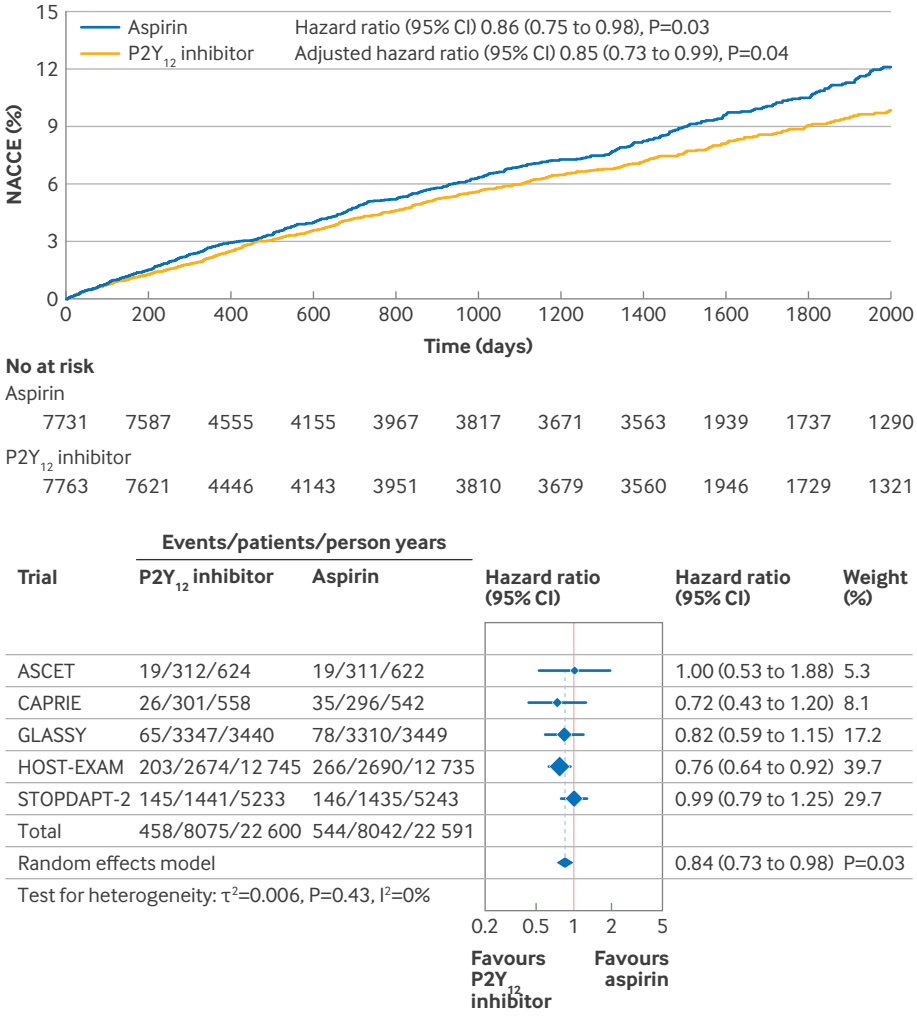

Fig 3 | Key secondary outcome of NACCE. Cumulative incidences were calculated using Kaplan-Meier method and compared with log-rank test. (Top panel) One stage analysis accounting for differences in baseline hazard and treatment effects across trials. Mixed effects models were used to calculate hazard ratios and 95% CIs and multivariable mixed effects models to calculate adjusted hazard ratios and 95% CIs (sensitivity analysis). The corresponding P values were derived from Wald type testing. (Bottom panel) Two stage analysis by random effects models with inverse variance weighting. ASCET=ASpirin non-responsiveness and Clopidogrel clinical Endpoint Trial; CAPRIE=Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events; CI=confidence interval; GLASSY=GLOBAL LEADERS Adjudication Sub-Study; HOST-EXAM=Harmonizing Optimal Strategy for Treatment of coronary artery stenosis-Extended Antiplatelet Monotherapy; NACCE=net adverse cardiac and cerebrovascular events (composite of cardiovascular death, myocardial infarction, stroke, or major bleeding); STOPDAPT-2=ShorT and OPtimal Duration of Dual AntiPlatelet Therapy-2 Study

Discussion

This IPD meta-analysis evaluated the comparative effectiveness of $P2Y_{12}$ inhibitor monotherapy (clopidogrel or ticagrelor) versus aspirin monotherapy in 16 117 patients who underwent PCI and had discontinued DAPT. These patients had the longest available follow-up data in the five eligible randomised clinical trials.

Our data provide evidence of a reduction of non-fatal ischaemic events with $P2Y_{12}$ inhibitor monotherapy compared with aspirin monotherapy for the long term prevention of cardiovascular events after DAPT, without increased major bleeding risk after PCI. Our data add to previous findings because this is the first meta-analysis including exclusively patients who underwent PCI, providing long term follow-up information and relying on IPD from all available PCI trials with contemporary $P2Y_{12}$ inhibitors.[12 32]

$P2Y_{12}$ inhibitor monotherapy was associated with a 23% relative risk reduction in the primary composite endpoint of MACCE (cardiovascular death, myocardial infarction, or stroke), with no between trial heterogeneity or identifiable treatment effect modifiers. Our analysis suggests that the benefit of $P2Y_{12}$ inhibitor was consistent across individual trials and predefined subgroups, including age, sex, geographical region, type of coronary syndrome, diabetes, smoking status, previous myocardial infarction or stroke, peripheral

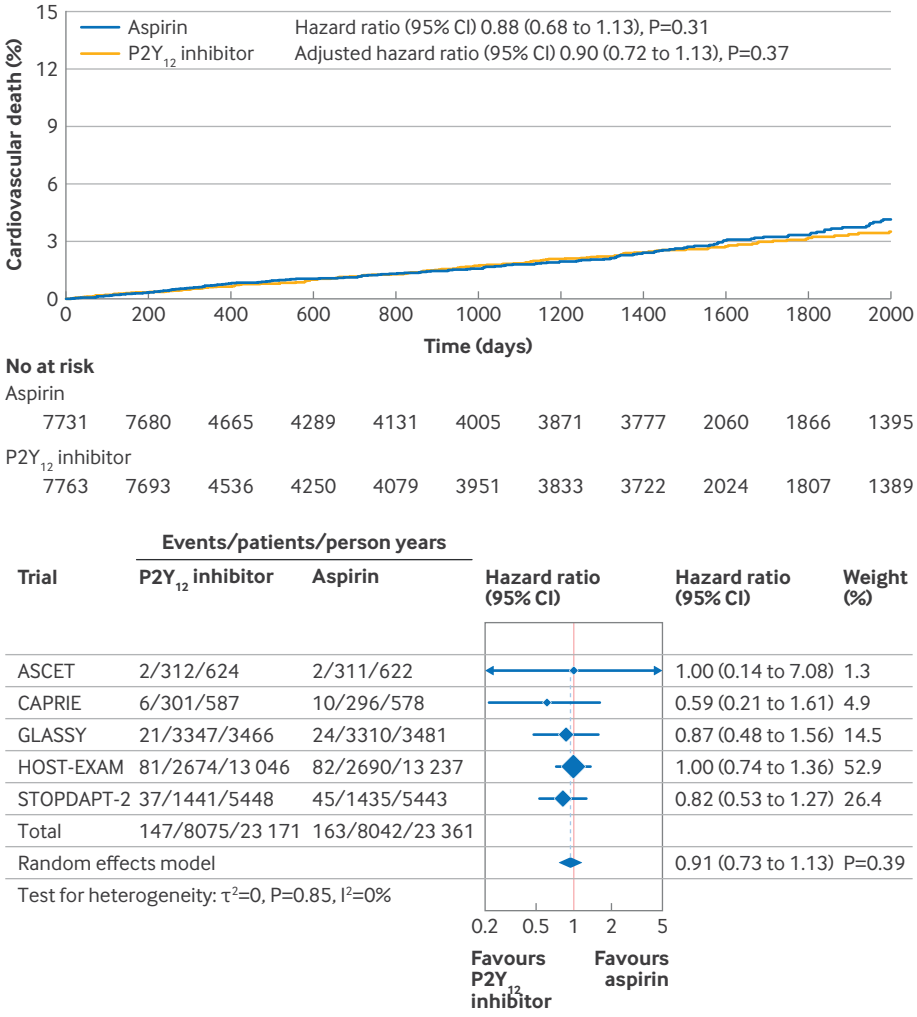

Fig 4 | Cardiovascular death. Cumulative incidences were calculated using the Kaplan-Meier method and compared with log-rank test. Multivariable mixed effects models were used to calculate adjusted hazard ratios and 95% CIs in sensitivity analysis. The corresponding P values were derived from Wald type testing. (Bottom panel) Two stage analysis by random effects models with inverse variance weighting. ASCET=ASpirin non-responsiveness and Clopidogrel clinical Endpoint Trial; CAPRIE=Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events; CI=confidence interval; GLASSY=GLOBAL LEADERS Adjudication Sub-Study; HOST-EXAM=Harmonizing Optimal Strategy for Treatment of coronary artery stenosis-Extended Antiplatelet Monotherapy; MACCE=major adverse cardiac and cerebrovascular events (composite of cardiovascular death, myocardial infarction, or stroke); STOPDAPT-2=ShorT and OPtimal Duration of Dual AntiPlatelet Therapy-2 Study

artery disease, kidney function, bleeding risk, use of a proton pump inhibitor, aspirin dose, and type of $P2Y_{12}$ inhibitor. This benefit came from significantly lower incidences of myocardial infarction and stroke, with no between trial heterogeneity for these components of the primary endpoint separately appraised. The low heterogeneity of treatment effects across trials observed for MACCE, myocardial infarction, and stroke along with the high consistency of results across multiple major clinical settings lend support to the greater antithrombotic effectiveness of a $P2Y_{12}$ inhibitor over aspirin for the long term secondary prevention of ischaemic events after PCI, which should affect guidelines and practice. Evidence for a numerical reduction of definite or probable stent thrombosis with $P2Y_{12}$ inhibitor was only available in three studies (90.6% of the total study population) and reached statistical significance only at multivariable one stage analysis. In this context, these borderline findings may reflect the insufficient sample size to ascertain treatment effects on a rare event, such as late stent thrombosis. Both ischaemic and haemorrhagic strokes contributed numerically to the lower risk of stroke with a $P2Y_{12}$ inhibitor, although only the former endpoint reached statistical significance. The results of this IPD meta-analysis show that treating 46 patients with a $P2Y_{12}$ inhibitor instead of aspirin after DAPT for 2000 days (about 5.5 years) would prevent the occurrence of one MACCE. This treatment effect should be interpreted in the light of aspirin being associated with an NNTB in the range of 30 for MACCE at a mean follow-up of 27 months (about 2.3 years) in patients

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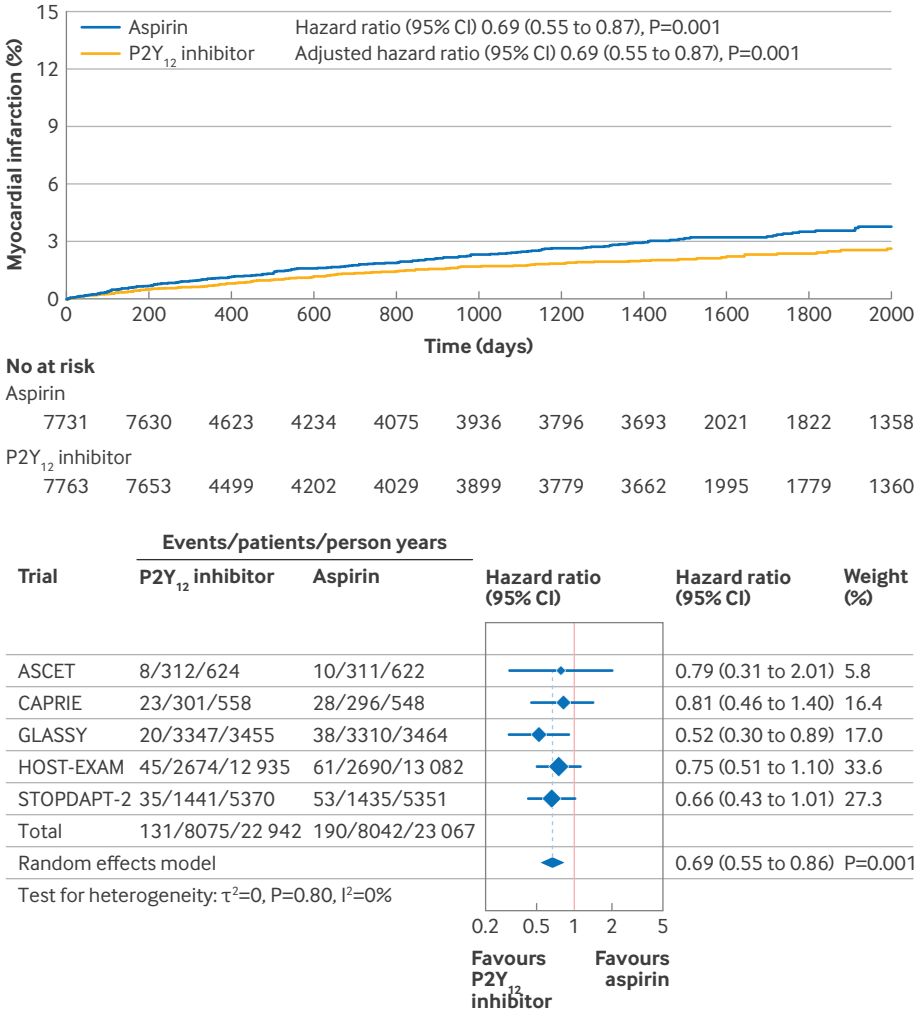

Fig 5 | Myocardial infarction. Cumulative incidences were calculated using the Kaplan-Meier method and compared with log-rank test. Multivariable mixed effects models were used to calculate adjusted hazard ratios and 95% CIs in sensitivity analysis. The corresponding P values were derived from Wald type testing. (Bottom panel) Two stage analysis by random effects models with inverse variance weighting. ASCET=ASpirin non-responsiveness and Clopidogrel clinical Endpoint Trial; CAPRIE=Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events; CI=confidence interval; GLASSY=GLOBAL LEADERS Adjudication Sub-Study; HOST-EXAM=Harmonizing Optimal Strategy for Treatment of coronary artery stenosis-Extended Antiplatelet Monotherapy; MACCE=major adverse cardiac and cerebrovascular events (composite of cardiovascular death, myocardial infarction, or stroke); STOPDAPT-2=ShorT and OPtimal Duration of Dual AntiPlatelet Therapy-2 Study

with previous myocardial infarction compared with placebo.[33] Although no study compared an oral $P2Y_{12}$ inhibitor with placebo, our findings on the comparison of $P2Y_{12}$ inhibitor with aspirin may indirectly result in a treatment effect exceeding the historical benefit magnitude of aspirin compared with placebo, without further enhanced bleeding risk. A landmark analysis suggested that the treatment effect for the primary efficacy composite endpoint of MACCE accrued consistently both within and beyond 1000 days of treatment, and the two year NNTB of about 100 was more advantageous than that reported in a general population of patients with established atherosclerosis in any vascular district.[12]

There was no evidence of increased risk of major bleeding with a $P2Y_{12}$ inhibitor, with moderate to high between trial heterogeneity and no identifiable factors that could influence treatment effect across the predefined subgroups. However, there was a trend towards a higher risk of any bleeding with a $P2Y_{12}$ inhibitor, with borderline statistical non-significance at unadjusted one stage analysis. This finding was associated with significant between trial heterogeneity, likely driven by the observation that all included studies but HOST-EXAM showed an increase of any bleeding with $P2Y_{12}$ inhibitor monotherapy, whereas this endpoint was significantly reduced with a $P2Y_{12}$ inhibitor in the HOST-EXAM trial.[28 29] The reasons for the discrepancy are not clear and additional research is needed to conclusively ascertain the individual conditions influencing the risk of bleeding between $P2Y_{12}$ inhibitor and aspirin monotherapies. Previous

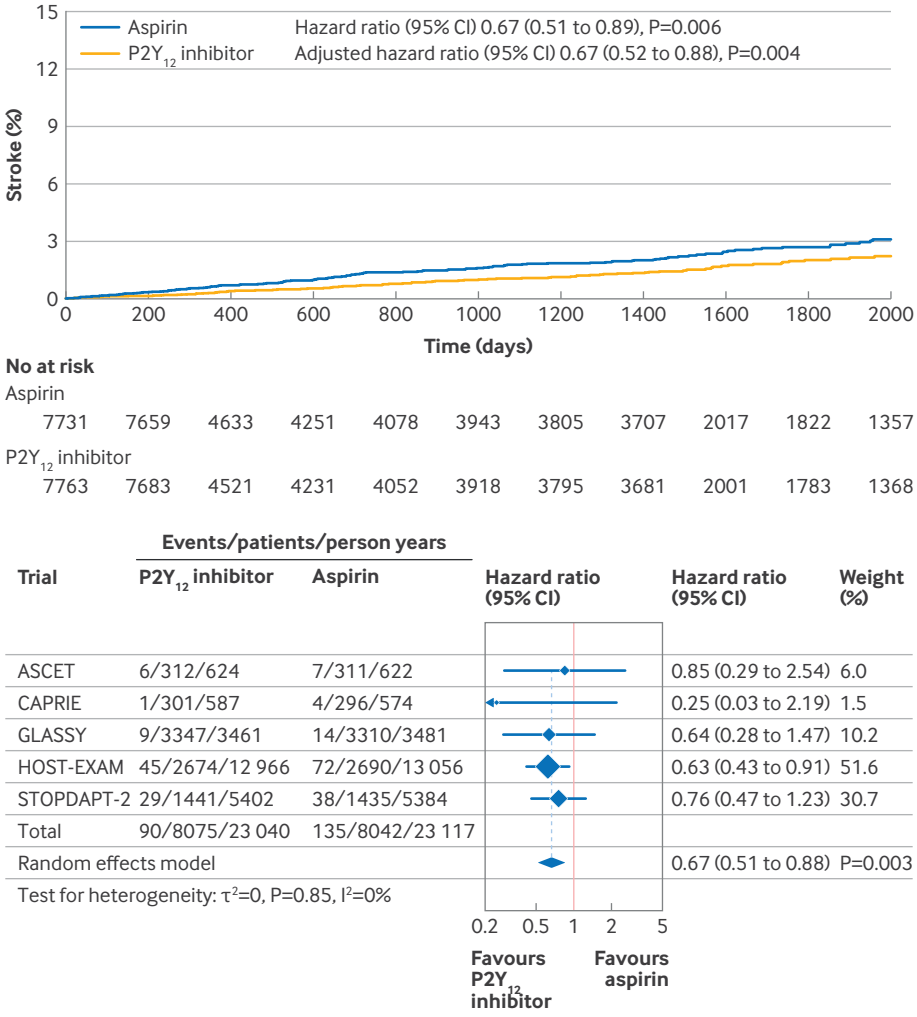

Fig 6 | Stroke. Cumulative incidences were calculated using the Kaplan-Meier method and compared with log-rank test. Multivariable mixed effects models were used to calculate adjusted hazard ratios and 95% CIs in sensitivity analysis. The corresponding P values were derived from Wald type testing. (Bottom panel) Two stage analysis by random effects models with inverse variance weighting. ASCET=ASpirin non-responsiveness and Clopidogrel clinical Endpoint Trial; CAPRIE=Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events; CI=confidence interval; GLASSY=GLOBAL LEADERS Adjudication Sub-Study; HOST-EXAM=Harmonizing Optimal Strategy for Treatment of coronary artery stenosis-Extended Antiplatelet Monotherapy; MACCE=major adverse cardiac and cerebrovascular events (composite of cardiovascular death, myocardial infarction, or stroke); STOPDAPT-2=ShorT and OPtimal Duration of Dual AntiPlatelet Therapy-2 Study

data indicated that $P2Y_{12}$ inhibitor monotherapy may reduce major bleeding or gastrointestinal bleeding owing to the avoidance of gastric mucosal injury compared with long term aspirin treatment.[28 32] In contrast, in our IPD meta-analysis, major and any gastrointestinal bleeding events were not significantly different between treatment groups. Importantly, in subgroup and multivariable analyses, proton pump inhibitor use was not involved in the causal explanation of these findings.

Nevertheless, this residual uncertainty should be interpreted in the context of a reduction of net adverse events with a $P2Y_{12}$ inhibitor and evidence that myocardial infarction and stroke have worse prognostic implications on mortality than non-major bleeding.[34] $P2Y_{12}$ inhibitor monotherapy significantly reduces NACCE compared with aspirin monotherapy, and the standard two stage analysis confirmed this result. After Hartung-Knapp adjustment, reduction in NACCE did not reach the significance threshold, but it is known that this method is generally conservative and sensitive to the amount of heterogeneity.

Long term secondary prevention treatment after PCI

DAPT, consisting of aspirin and an oral $P2Y_{12}$ inhibitor, is the standard of care treatment after PCI. Upon completion of DAPT, which typically occurs from one to several months after the intervention, long term aspirin monotherapy is the single class I recommended treatment after PCI, irrespective of the number, type, and location of implanted coronary stents, if any.[2 3] Multiple studies have investigated a prolonged versus

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Subsets	Events/patients/incidence (%)/ incidence per 100 person years: $P2Y_{12}$ inhibitor	Aspirin	Hazard ratio (95% CI)	P value	P for interaction
Age (years)					
≤65	136/4202/5.3/1.14	171/4187/7.3/1.45	0.84 (0.65 to 1.08)	0.17	0.84
>65	205/3873/10.6/1.88	270/3855/13.0/2.45	0.66 (0.49 to 0.90)	0.008	
Sex					
Women	98/1931/9.3/1.79	103/1909/9.7/1.84	0.94 (0.71 to 1.25)	0.68	0.06
Men	243/6144/7.2/1.40	338/6133/10.1/1.96	0.71 (0.60 to 0.84)	<0.001	
BMI					
<25	178/3275/8.4/1.64	212/3317/9.7/1.89	0.84 (0.68 to 1.03)	0.09	0.31
25-30	127/3415/7.2/1.36	174/3300/10.7/1.98	0.65 (0.51 to 0.83)	0.001	
≥30	30/1289/6.0/1.38	45/1321/7.5/1.94	0.76 (0.42 to 1.38)	0.37	
Region					
Asia	251/4115/7.3/1.38	318/4125/9.4/1.75	0.79 (0.67 to 0.93)	0.005	0.75
Europe	80/3817/10.4/1.84	106/3772/13.6/2.44	0.75 (0.56 to 1.00)	0.05	
North America	10/143/8.0/3.63	17/145/14.0/6.22	0.59 (0.27 to 1.28)	0.18	
Clinical presentation					
Chronic coronary syndrome	138/3567/8.4/1.50	174/3607/10.2/1.86	0.75 (0.58 to 0.97)	0.03	0.65
Acute coronary syndrome	203/4508/7.4/1.49	267/4435/9.9/1.98	0.75 (0.63 to 0.90)	0.002	
Diabetes					
No diabetes	213/5763/7.0/1.37	257/5747/8.5/1.65	0.81 (0.67 to 0.98)	0.03	0.21
Diabetes	128/2311/9.2/1.75	184/2295/13.1/2.55	0.69 (0.55 to 0.86)	0.001	
Smoking status					
Non-current smoker	249/6012/7.6/1.42	339/6004/10.1/1.93	0.72 (0.61 to 0.85)	<0.001	0.31
Current smoker	92/2063/7.8/1.74	102/2038/9.3/1.95	0.91 (0.68 to 1.22)	0.51	
Medical history					
No previous myocardial infarction	201/5622/6.7/1.32	266/5606/9.0/1.74	0.76 (0.63 to 0.91)	0.003	0.76
Previous myocardial infarction	140/2450/9.5/1.85	175/2436/11.7/2.32	0.79 (0.63 to 0.99)	0.04	
No previous stroke	312/7778/7.3/1.43	392/7716/9.3/1.80	0.79 (0.68 to 0.92)	0.002	0.50
Previous stroke	29/294/16.6/3.08	49/326/22.8/4.65	0.59 (0.36 to 0.97)	0.04	
No peripheral artery disease	316/7666/7.4/1.44	410/7578/9.8/1.88	0.76 (0.66 to 0.88)	<0.001	0.42
Peripheral artery disease	25/386/22.1/2.88	31/449/14.1/3.06	0.94 (0.55 to 1.59)	0.81	
No chronic kidney disease	223/6604/6.2/1.18	282/6632/7.7/1.48	0.81 (0.68 to 0.96)	0.02	0.51
Chronic kidney disease	93/1162/15.5/2.72	124/1105/23.3/3.80	0.71 (0.54 to 0.93)	0.01	
PRECISE-DAPT					
<25	170/5693/5.5/1.08	214/5650/7.0/1.37	0.80 (0.65 to 0.99)	0.04	0.81
≥25	114/1476/15.3/2.70	143/1476/17.7/3.31	0.81 (0.62 to 1.06)	0.13	
Proton pump inhibitor					
No proton pump inhibitor	201/4524/7.4/1.40	257/4535/9.4/1.80	0.74 (0.61 to 0.91)	0.003	0.92
Proton pump inhibitor	125/3314/7.7/1.65	163/3273/11.3/2.13	0.76 (0.59 to 0.98)	0.03	
Aspirin dose					
Low	300/7462/7.3/1.39	387/7435/9.4/1.79	0.77 (0.67 to 0.90)	0.001	0.89
High	41/613/9.4/3.47	54/607/14.0/4.63	0.75 (0.50 to 1.12)	0.16	
$P2Y_{12}$ inhibitor					
Clopidogrel	292/4728/7.8/1.51	372/4732/10.1/1.92	0.78 (0.67 to 0.91)	0.001	0.65
Ticagrelor	49/3347/1.5/1.42	69/3310/2.1/2.00	0.70 (0.49 to 1.01)	0.06	

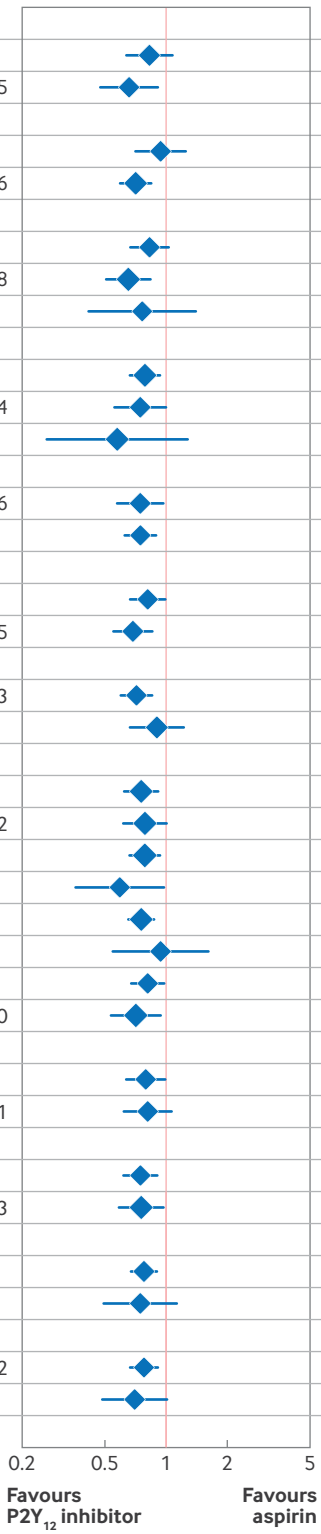

Fig 7 | Subgroup analysis for MACCE. Mixed effects models were used to calculate hazard ratios and 95% CIs (one stage analysis).Corresponding P values were derived from Wald type testing. BMI=body mass index; CI=confidence interval; MACCE=major adverse cardiac and cerebrovascular events; PRECISE-DAPT=PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual AntiPlatelet Therapy

Subsets	Events/patients/incidence (%)/ incidence per 100 person years: $P2Y_{12}$ inhibitor	Aspirin	Hazard ratio (95% CI)	P value	P for interaction
Age (years)					
≤65	39/4202/1.5/0.32	40/4187/1.8/0.33	1.59 (0.67 to 3.73)	0.29	0.85
>65	121/3873/5.9/1.11	122/3855/6.2/1.10	1.00 (0.72 to 1.40)	0.99	
Sex					
Women	46/1931/4.5/0.84	46/1909/4.6/0.81	0.93 (0.48 to 1.81)	0.84	0.72
Men	114/6144/3.2/0.65	116/6133/3.6/0.67	1.46 (0.76 to 2.81)	0.25	
BMI					
<25	80/3275/3.6/0.73	97/3317/4.4/0.86	0.74 (0.45 to 1.22)	0.24	0.06
25-30	62/3415/3.5/0.66	52/3300/3.5/0.58	1.14 (0.79 to 1.65)	0.49	
≥30	16/1289/3.9/0.73	7/1321/0.7/0.30	2.44 (1.00 to 5.93)	0.05	
Region					
Asia	134/4115/3.8/0.73	146/4125/4.2/0.79	0.98 (0.57 to 1.70)	0.95	0.41
Europe	25/3817/1.4/0.57	16/3772/0.4/0.37	1.55 (0.83 to 2.90)	0.17	
North America	1/143/1.2/0.35	0/145/0/0	0.99 (0.80 to 1.24)	0.96	
Clinical presentation					
Chronic coronary syndrome	76/3567/3.9/0.82	74/3607/4.2/0.79	1.13 (0.57 to 2.26)	0.73	0.59
Acute coronary syndrome	84/4508/3.2/0.61	88/4435/3.5/0.64	1.11 (0.70 to 1.75)	0.65	
Diabetes					
No diabetes	99/5763/3.0/0.63	99/5747/3.6/0.63	1.25 (0.76 to 2.05)	0.39	0.86
Diabetes	61/2311/4.6/0.83	63/2295/4.4/0.86	0.86 (0.41 to 1.80)	0.68	
Smoking status					
Non-current smoker	130/6012/3.7/0.74	128/6004/4.0/0.72	1.24 (0.79 to 1.94)	0.35	0.39
Current smoker	30/2063/2.8/0.56	34/2038/3.3/0.64	0.71 (0.40 to 1.27)	0.25	
Medical history					
No previous myocardial infarction	116/5622/3.6/0.76	107/5606/3.7/0.70	1.12 (0.68 to 1.85)	0.65	0.52
Previous myocardial infarction	44/2450/3.2/0.58	55/2436/4.0/0.72	0.81 (0.55 to 1.21)	0.31	
No previous stroke	145/7778/3.3/0.66	144/7716/3.6/0.66	1.44 (0.79 to 2.60)	0.23	0.92
Previous stroke	15/294/7.2/1.60	18/326/9.0/1.66	0.97 (0.47 to 2.01)	0.94	
No peripheral artery disease	142/7666/3.3/0.65	147/7578/3.7/0.67	1.19 (0.76 to 1.85)	0.45	0.74
Peripheral artery disease	18/386/7.1/2.09	15/449/9.5/1.46	1.42 (0.72 to 2.83)	0.31	
No chronic kidney disease	105/6604/2.8/0.55	107/6632/2.9/0.56	1.31 (0.74 to 2.33)	0.36	0.25
Chronic kidney disease	52/1162/8.4/1.53	54/1105/11.2/1.64	0.89 (0.59 to 1.36)	0.59	
PRECISE-DAPT					
<25	85/5693/2.6/0.54	71/5650/2.4/0.45	1.30 (0.74 to 2.29)	0.36	0.17
≥25	65/1476/8.3/1.54	74/1476/9.7/1.70	0.90 (0.64 to 1.27)	0.56	
Proton pump inhibitor					
No proton pump inhibitor	74/4524/2.7/0.51	92/4535/3.5/0.64	1.32 (0.52 to 3.37)	0.56	0.78
Proton pump inhibitor	73/3314/4.7/0.96	56/3273/3.5/0.72	1.21 (0.78 to 1.88)	0.40	
Aspirin dose					
Low	154/7462/3.6/0.71	161/7435/4.0/0.74	1.03 (0.67 to 1.57)	0.91	0.12
High	6/613/1.2/0.50	1/607/0.2/0.08	5.95 (0.72 to 49.43)	0.10	
$P2Y_{12}$ inhibitor					
Clopidogrel	140/4728/3.6/0.72	147/4732/4.0/0.75	1.40 (0.68 to 2.86)	0.36	0.85
Ticagrelor	20/3347/0.6/0.58	15/3310/0.5/0.43	1.32 (0.68 to 2.58)	0.41	

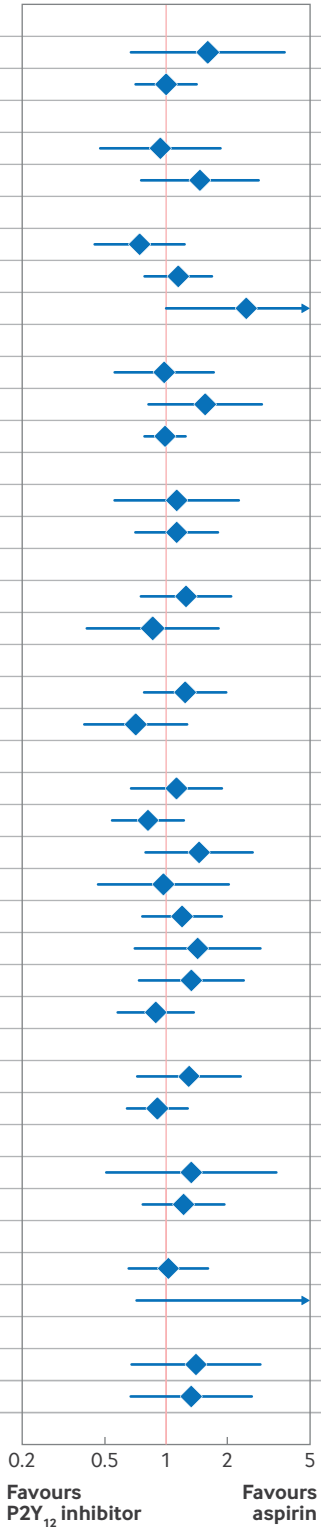

Fig 8 | Subgroup analysis for major bleeding. Prespecified subgroups were explored in terms of the co-primary outcome of major bleeding. Mixed effects models were used to calculate hazard ratios and 95% CIs (one stage analysis). The corresponding P values were derived from Wald type testing. BMI=body mass index; CI=confidence interval; PRECISE-DAPT=PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual AntiPlatelet Therapy

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standard DAPT followed by aspirin monotherapy after PCI.[9 11 35-37]

In the DAPT trial, among relatively unselected patients undergoing PCI who tolerated the recommended post-procedural DAPT, continued treatment with thienopyridine based DAPT for up to 30 months reduced the rates of MACCE (4.3% *v* 5.9%; hazard ratio 0.71 (95% CI 0.59 to 0.85)) compared with aspirin monotherapy.[11] However, the rate of Global Utilisation of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries (GUSTO) moderate or severe bleeding was increased with continued thienopyridine based DAPT (2.5% *v* 1.6%, P=0.001).[11] The corresponding NNTB and NNTH were 63 and 111, respectively. The rates of BARC defined major bleeding were 2.73% with continued thienopyridine based DAPT and 1.54% with aspirin, yielding a NNTH of 84.[11] Consistently, in the PEGASUS-TIMI 54 (PrEvention with TicaGrelor of SecondAry Thrombotic Events in High-RiSk Patients with Prior AcUte Coronary Syndrome-Thrombolysis In Myocardial Infarction Study Group) trial enrolling patients with previous myocardial infarction, three year cumulative incidences of cardiovascular death, myocardial infarction, or stroke were 7.77% in patients assigned to 60 mg of ticagrelor twice daily plus aspirin and 9.04% in patients assigned to aspirin monotherapy (hazard ratio 0.84 (95% CI 0.74 to 0.95)), yielding a NNTB of 79.[9] However, the rate of major bleeding was 2.30% in the ticagrelor based DAPT group and 1.06% in the aspirin monotherapy group (2.32 (1.68 to 3.21)), leading to a NNTH of 81.[9] In the COMPASS-PCI (Rivaroxaban Plus Aspirin Versus Aspirin Alone in Patients With Prior Percutaneous Coronary Intervention) study, in patients with chronic coronary syndrome and previous PCI, at a mean follow-up of 5.4 years, the addition of low dose rivaroxaban to aspirin was associated with fewer composite endpoint of cardiovascular death, myocardial infarction, or stroke compared with aspirin monotherapy (4.0% *v* 5.5%; hazard ratio 0.74 (95% CI 0.61 to 0.88)), yielding a NNTB of 67.[38] However, major bleeding events occurred more frequently in patients assigned to rivaroxaban plus aspirin compared with aspirin monotherapy (3.3% *v* 2.0%; 1.70 (1.40 to 2.05)), yielding a NNTH of 77.[38] Hence, the addition of a $P2Y_{12}$ inhibitor or low dose rivaroxaban to aspirin was shown to be associated with lower risk of MACCE compared with standard aspirin monotherapy after initial DAPT completion at the cost of a clinically relevant higher risk of major bleeding. The unsatisfactory risk-benefit trade-off in all these trials has made novel antiplatelet treatments difficult to implement in contemporary practice, and recommendations of international guidelines have been confined to selected PCI patient populations.[2 3]

Our findings support the use of $P2Y_{12}$ inhibitor monotherapy instead of aspirin after completion of the recommended post-PCI DAPT period to reduce the risk of non-fatal cardiac and cerebrovascular ischaemic events without an identifiable greater risk of major bleeding. Non-major bleeding events might, however, occur more frequently with $P2Y_{12}$ inhibitors.

Limitations of this review

Several limitations should be considered when interpreting the results of this IPD meta-analysis. Firstly, some changes in the original design of some trials were required to create uniform data. Briefly, two trials (ASCET and CAPRIE) also enrolled patients with established coronary artery disease who received medical therapy alone.[25 26] These patients were excluded from the present study. Similarly, in four trials, a few patients who underwent coronary artery bypass grafting before the assessment period for antiplatelet monotherapies were excluded.[25-31] Nevertheless, in the present IPD meta-analysis, the two treatment groups remained well balanced and the results of sensitivity analyses using multivariable models were consistent with those of the univariate one stage primary analysis. Secondly, GLASSY, HOST-EXAM, and STOPDAPT-2 are contemporary trials that used current generation drug eluting stents and implemented modern PCI techniques and medical treatments. As a result, more than 90% of the patients included in the present IPD meta-analysis underwent PCI over the past decade. In contrast, the CAPRIE trial was conducted before the advent of drug eluting stents and the results of pivotal trials on post-PCI DAPT, whereas ASCET was conducted during the era of first generation drug eluting stents. In addition, the ASCET database did not include the time of occurrence of adverse outcomes, requiring the methodological expedient of considering the events as occurring at the end of the available follow-up for analysis. Despite these limitations inherent to ASCET and CAPRIE, the corresponding information was retained to avoid arbitrarily excluding some trials and introducing availability bias.[39] Sensitivity analyses after excluding CAPRIE, ASCET, and both ASCET and CAPRIE yielded entirely consistent results. Thirdly, although the availability of IPD sometimes permits pooling outcomes with uniform definitions, in the present study some differences in definitions could not be overcome as some trials were conducted before the development and validation of more contemporary classifications. Nevertheless, except for major and any bleeding, no significant between trial heterogeneity was noted, indicating that study conclusions were based on effects consistent across trials. Fourthly, devices and PCI guidance techniques showed some differences between early and more contemporary trials. However, the present IPD meta-analysis included only patients with no major complications or adverse events from PCI to initiation of antiplatelet monotherapy (ie, six to 18 months after PCI in almost all patients). Fifthly, differences in the design of original trials led to different maximum duration of antiplatelet monotherapy across patients. However, landmark analyses did not indicate significant differences in treatment effects between the periods of 0 to 1000 days and 1000 to 2000 days. Sixthly, although subgroup analyses are frequently affected by insufficient statistical power for detecting true interaction or may indicate spurious effects requiring an adjustment for multiplicity, the present study relied on a large number

of patients, subgroup analyses were prespecified, and interaction tests did not show significant treatment-by-subgroup interactions regardless of adjustment for repeat statistical testing.[40] Nevertheless, as with most of the studies on coronary artery disease, women were underrepresented. For these reasons, more data in this setting may be required. Moreover, our results may not apply to advanced age, as reduced life expectancy may reduce the long term effects observed in our study. In addition, although the key subset of diabetes did not reveal significant treatment-by-subgroup interaction, further analyses focused on this setting are required to strengthen our general conclusions. Seventhly, ticagrelor monotherapy was investigated in a single study.[27] The treatment effects were, however, consistent between the two investigated $P2Y_{12}$ inhibitors, despite previous evidence indicating that clopidogrel exhibits lower antithrombotic effectiveness and more variable response between individuals than ticagrelor.[41] Nevertheless, the role of the metabolic variability and potency of $P2Y_{12}$ inhibition in the context of long term monotherapy remains unclear. In addition, although the current European Society of Cardiology guidelines on chronic coronary syndrome endorse the use of ticagrelor monotherapy for chronic secondary prevention, the European Medicines Agency considers this indication exclusively for patients with diabetes mellitus. Finally, given that this study did not include patients assigned to prasugrel monotherapy, the results may not apply to this type of $P2Y_{12}$ inhibitor.

Conclusions

In patients who underwent PCI and had completed DAPT, monotherapy with a $P2Y_{12}$ inhibitor, consisting of clopidogrel or ticagrelor, compared with aspirin was associated with lower rates of cardiovascular death, myocardial infarction, or stroke, owing to lower risk of non-fatal cardiac or cerebrovascular events without an increase in major bleeding.

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Contributors: DG, FG, and MV conceived and designed the study. DG, FG, HW, JK, AAP, and MV transferred and validated the original data. DG, FG, and MV combined, managed, analysed, and output the data. DG, FG, HW, TK, JK, KWP, HSK, AAP, DB, SP, RM, and MV interpreted the study results. DG and MV drafted the initial and revised versions of the manuscript. FG, HW, TK, JK, KWP, HSK, AAP, DB, SP, and RM critically revised the manuscript. DG, FG, HW, TK, JK, KWP, HSK, AAP, DB, SP, RM, and MV revised the final version of the manuscript and approved its submission. DG, FG, HW, JK, AAP, and MV ensured the accuracy and integrity of the data. MV is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Ethical approval: Not required.

Data sharing: Data supporting study findings are available from the corresponding author upon reasonable request.

Transparency: The lead author (MV) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: We plan to share the results of this study on multiple social media platforms, including X (formerly Twitter) and LinkedIn. Copies of the manuscript will be sent to contributing centres and the results presented during an upcoming international congress.

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Supplementary information: Additional information