P2Y12 inhibitor monotherapy or dual antiplatelet therapy after coronary revascularisation: individual patient level meta-analysis of randomised controlled trials

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ABSTRACT

OBJECTIVE

To assess the risks and benefits of $P2Y_{12}$ inhibitor monotherapy compared with dual antiplatelet therapy (DAPT) and whether these associations are modified by patients' characteristics.

DESIGN

Individual patient level meta-analysis of randomised controlled trials.

DATA SOURCES

Searches were conducted in Ovid Medline, Embase, and three websites (www.tctmd.com, www.escardio.org, www.acc.org/cardiosourceplus) from inception to 16 July 2020. The primary authors provided individual participant data.

ELIGIBILITY CRITERIA

Randomised controlled trials comparing effects of oral $P2Y_{12}$ monotherapy and DAPT on centrally adjudicated endpoints after coronary revascularisation in patients without an indication for oral anticoagulation.

MAIN OUTCOME MEASURES

The primary outcome was a composite of all cause death, myocardial infarction, and stroke, tested for non-inferiority against a margin of 1.15 for the hazard ratio. The key safety endpoint was Bleeding Academic Research Consortium (BARC) type 3 or type 5 bleeding.

RESULTS

The meta-analysis included data from six trials, including 24 096 patients. The primary outcome occurred in 283 (2.95%) patients with $P2Y_{12}$ inhibitor monotherapy and 315 (3.27%) with DAPT in the per protocol population (hazard ratio 0.93, 95% confidence interval 0.79 to 1.09; P=0.005 for non-inferiority; P=0.38 for superiority; τ^2=0.00) and in 303 (2.94%) with $P2Y_{12}$ inhibitor monotherapy and 338 (3.36%) with DAPT in the intention to treat population (0.90, 0.77 to 1.05; P=0.18 for superiority; τ^2=0.00). The treatment effect was consistent across all subgroups, except for sex (P for interaction=0.02), suggesting that $P2Y_{12}$ inhibitor monotherapy lowers the risk of the primary ischaemic endpoint in women (hazard ratio 0.64, 0.46 to 0.89) but not in men (1.00, 0.83 to 1.19). The risk of bleeding was lower with $P2Y_{12}$ inhibitor monotherapy than with DAPT (97 (0.89%) *v* 197 (1.83%); hazard ratio 0.49, 0.39 to 0.63; $P<0.001$; τ^2=0.03), which was consistent across subgroups, except for type of $P2Y_{12}$ inhibitor (P for interaction=0.02), suggesting greater benefit when a newer $P2Y_{12}$ inhibitor rather than clopidogrel was part of the DAPT regimen.

CONCLUSIONS

$P2Y_{12}$ inhibitor monotherapy was associated with a similar risk of death, myocardial infarction, or stroke, with evidence that this association may be modified by sex, and a lower bleeding risk compared with DAPT.

REGISTRATION

PROSPERO CRD42020176853.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Aggregate data meta-analyses comparing P2Y12 inhibitor monotherapy with dual antiplatelet therapy (DAPT) in patients undergoing coronary revascularisation have been conducted

They generally showed similar risks of ischaemic events and lower risks of bleeding with P2Y12 inhibitor monotherapy than with DAPT

Previous meta-analyses did not account for the initial DAPT phase, usually common to both experimental and control groups, and almost invariably failed to provide information on subgroups of interest

WHAT THIS STUDY ADDS

P2Y12 inhibitor monotherapy was associated with a similar risk of fatal and ischaemic events and lower rates of major bleeding compared with DAPT

P2Y12 inhibitor monotherapy may be particularly beneficial among female patients, owing to an association with lower cardiovascular mortality

Aspirin cessation from one to three months after coronary revascularisation and continuation with P2Y12 inhibitor monotherapy may be warranted instead of continuation of DAPT, especially in women

Introduction

Inhibition of platelet $P2Y_{12}$ receptor signalling plays a central role in the secondary prevention of cardiac or cerebrovascular thrombotic complications.[1-3] Oral $P2Y_{12}$ inhibitors have mainly been investigated in combination with aspirin after coronary revascularisation.[2-4] In this context, robust evidence shows that dual antiplatelet therapy (DAPT), consisting of aspirin and an oral $P2Y_{12}$ inhibitor, mitigates the incidence of ischaemic events but increases the risk of major bleeding compared with aspirin alone.[1 2] A few studies have assessed oral $P2Y_{12}$ inhibitor monotherapy as an alternative to conventional DAPT.[5-10] However, none was powered to assess whether withdrawal of aspirin and continuation with an oral $P2Y_{12}$ inhibitor preserves the treatment effect of the latter in combination with aspirin.[11] Previous aggregate data meta-analyses of oral $P2Y_{12}$ inhibitor monotherapy studies included events occurring during the initial DAPT phase, which was identical in both experimental and control regimens in most studies, and have therefore not conclusively ascertained the risks and benefits of aspirin withdrawal; nor did they explore the consistency of treatment effects across subgroups.[12-14] Therefore, concerns remain that removal of aspirin after a short course of DAPT may, from that moment onwards, be associated with a higher risk of ischaemic events, especially among patients with high risk features.[3] As a reflection of the residual uncertainties about the trade-off between risks and benefits of aspirin withdrawal in this setting, the 2020 European Society of Cardiology guidelines for the management of acute coronary syndromes in patients presenting without ST segment elevation state that discontinuation of aspirin after a three to six month course of DAPT, and continuation with $P2Y_{12}$ inhibitor monotherapy, should be considered depending on the balance between ischaemic risk and bleeding risk.[15] The American Heart Association/American College of Cardiology guidelines have not yet issued a formal recommendation for this treatment option.[1]

We did a systematic review and individual participant data meta-analysis of all randomised trials that compared $P2Y_{12}$ inhibitor monotherapy with DAPT among patients who underwent coronary revascularisation, with a focus on the preservation of the treatment effect after aspirin removal, and investigated its consistency across predefined subgroups.

Methods

We conducted a systematic review and individual participant data meta-analysis to answer the following PICOS question: in patients who have undergone percutaneous or surgical revascularisation for stable or unstable coronary artery disease, is $P2Y_{12}$ inhibitor monotherapy at least similarly effective for a composite of fatal and cardiovascular ischaemic endpoints and, if so, safer for bleeding endpoints, compared with DAPT among randomised trials that reported centrally adjudicated outcome data?

We excluded trials including patients with a concomitant indication for oral anticoagulation under the rationale that concomitant oral anticoagulation further increases the risk of bleeding and mitigates the risk of ischaemic recurrences after aspirin withdrawal, and long term DAPT is no longer considered a valid standard of care in this setting.[16] We implemented no further restrictions for study selection, such as the number of participants or duration of follow-up. Methods and reporting follow the guidelines of the Preferred Reporting Items for a Systematic Review and Meta-analysis of Individual Participant Data (PRISMA-IPD).[17] The study protocol was prospectively registered on PROSPERO (international prospective register of systematic reviews) and is available online (www.crd.york.ac.uk/prospero, CRD42020176853).

Search strategy

Two investigators (MV, FG) determined trial eligibility criteria; a third investigator (RM) was involved in case of disagreement. Randomised trials were identified by a search in Ovid Medline, Embase, and three websites (www.tctmd.com, www.escardio.org, www.acc.org/cardiosourceplus). Reference lists of retrieved articles were hand searched. We imposed no language restrictions. The search strategy is provided in the appendix.

Outcome measures

The pre-specified primary efficacy endpoint was the composite of all cause death, myocardial infarction, and stroke throughout the duration of the randomised comparison of protocol mandated $P2Y_{12}$ inhibitor monotherapy versus DAPT. The key safety endpoint was Bleeding Academic Research Consortium (BARC) type 3 or type 5 bleeding.[18] Other secondary endpoints are shown in the appendix. The outcome definitions were largely consistent among the included trials (supplementary methods).

Data extraction and quality assessment

We contacted the principal investigators of the eligible trials, requesting individual participant data to be provided in an anonymised electronic dataset (supplementary methods). We checked data for completeness and consistency and compared them with the results of the original publications. We contacted the principal investigators of the included trials in case of missing data or when queries emerged during the integrity checks. Once queries had been resolved, the clean data were uploaded to the main study dataset. For one trial,[10] 587 (8.2%) patients were excluded from this analysis owing to the lack of approval to share the data from the country's legal and regulatory authorities. Two investigators (MV, FG) independently assessed the quality of included trials by using the Cochrane Collaboration's tool for assessing the risk of bias 2 (supplementary table D).[19] Disagreements were resolved first by discussion and then by consulting a third investigator (RM) for arbitration. Each trial had been approved by its local medical ethics committee, and all patients had provided written informed consent.

Data synthesis

We pre-specified a one step approach to model the data from all trials simultaneously using a mixed effect Cox regression model with baseline hazards stratified by trial and a random intercept to account for variation between trials in treatment effect. Treatment effects were derived as hazard ratios and 95% confidence intervals. We quantified the heterogeneity of the treatment effect between trials by using the variance of the random slope τ^2. Pre-specified sensitivity analyses were based on a two step approach using a DerSimonian-Laird random effects model to combine trial level estimates. We used I^2 to estimate between trial heterogeneity for the two step model.

All primary analyses were conducted with censoring of events that occurred during the initial DAPT phase, if present, common to both experimental and treatment groups, and included only events occurring after the time when the protocol specified the change from DAPT to $P2Y_{12}$ inhibitor monotherapy in the experimental group. Data were analysed up to the longest available time point with protocol specified $P2Y_{12}$ inhibitor monotherapy in the experimental group and DAPT in the control group.

We first tested the non-inferiority of $P2Y_{12}$ inhibitor monotherapy compared with DAPT on the primary efficacy endpoint at a one sided α of 0.05 and a non-inferiority margin of 1.15 on the hazard ratio scale. Under the rationale that aspirin was omitted in the experimental arm of $P2Y_{12}$ inhibitor monotherapy, while being continued in the DAPT group, we chose this non-inferiority margin because it represents 50% of the treatment effect of aspirin compared with placebo or standard care observed by the Antithrombotic Trialists' Collaboration in patients with previous myocardial infarction for the composite endpoint of vascular death, myocardial infarction, and stroke.[11] If non-inferiority was met, we pre-specified testing of the superiority of $P2Y_{12}$ inhibitor monotherapy at a two sided α of 0.05. We did superiority analyses in the intention to treat population and the non-inferiority analysis in the per protocol population. We reported the one sided P value for non-inferiority only for the primary per protocol analysis; for all remaining analyses, we reported two sided P values for superiority and two sided 95% confidence intervals to allow conventional interpretation of the results. The per protocol population was pre-specified and excluded ineligible patients (that is, those violating inclusion/exclusion criteria) and/or those who never received allocated treatment strategy. We pre-specified a set of subgroup analyses for the primary efficacy endpoint and the key safety endpoint according to age, sex, clinical presentation, diabetes mellitus, history of chronic kidney disease, peripheral artery disease, bleeding risk, complexity of percutaneous coronary intervention, left main or left anterior descending percutaneous intervention, type of revascularisation (percutaneous or surgical), type of $P2Y_{12}$ inhibitor in the comparator and experimental therapies, use of proton pump inhibitor, and geographical region, accompanied by tests of interaction. Further details on data analysis are reported in the appendix.

Patient and public involvement

Patients and public were not directly involved in this individual participant data meta-analysis. However, we acknowledge their contribution in performing included clinical trials and disseminating research findings.

Results

Study selection

We screened 13 240 unique citations. Of these, 820 were judged potentially eligible during screening of titles and abstracts, and six were deemed eligible after full text review (supplementary figure A). We sought and obtained individual participant data for all eligible trials. The appendix describes trial characteristics and patient populations (supplementary tables A and B). The definitions used for outcomes were largely consistent across trials (supplementary table C), and the risk of bias assessment identified some concerns for five of six trials related to the open label allocation of the treatment assignment (supplementary table D). All six studies were sponsored by academic organisations.

We considered 24 096 participants for the primary analysis, of whom 12 037 (50%) were randomly allocated to $P2Y_{12}$ inhibitor monotherapy and 12 059 (50%) to DAPT. We excluded 788 (3.3%) patients owing to premature study termination or death before the time point at which each study protocol specified the implementation of $P2Y_{12}$ inhibitor monotherapy in the experimental group (four trials) or owing to lack of approval to share the data from the Chinese legal and regulatory authorities for 8.2% of the patients recruited in one trial. Therefore, 23 308 patients were available for the intention to treat analysis, including 11 634 (49.9%) patients assigned to P2Y12 inhibitor monotherapy (clopidogrel in 2586 (22.2%), prasugrel in 92 (0.8%), ticagrelor in 8956 (77.0%)) and 11 674 (50.1%) to DAPT (aspirin and clopidogrel 4297 (36.8%), aspirin and prasugrel 140 (1.2%), aspirin and ticagrelor 7237 (62.0%)). A total of 1347 (5.8%) participants were excluded from the per protocol population (supplementary figure B). The median treatment duration was 334 days (range 9-12 months).

Patient characteristics

Baseline clinical characteristics were balanced between groups (table 1 and supplementary table E). The mean age was 65 years, and 5423 (23.3%) patients were female. A total of 7419 (31.8%) patients had a history of diabetes, and 3823 (16.6%) had chronic kidney failure. History of myocardial infarction, percutaneous coronary intervention, or coronary artery bypass surgery was noted in 4438 (19.0%), 6959 (30.3%), and 1250 (5.4%) patients, respectively. At presentation, most patients (13 966; 59.9%) had an acute coronary syndrome. Procedural characteristics are shown in supplementary tables E and F.

Efficacy endpoints

The composite endpoint of all cause death, myocardial infarction, and stroke occurred in 283 (2.95%) patients with $P2Y_{12}$ inhibitor monotherapy and 315 (3.27%) patients with DAPT in the per protocol population, fulfilling non-inferiority (P=0.005 for non-inferiority with one sided α of 5%), but not superiority (hazard ratio 0.93, 95% confidence interval 0.79 to 1.09; P=0.38), with no between trial heterogeneity (τ^2=0.00) (table 2). The same composite endpoint occurred in 303 (2.94%) and 338 (3.36%) patients with $P2Y_{12}$ inhibitor monotherapy and DAPT, respectively, in the intention to treat population (hazard ratio 0.90, 0.77

Table 1 | Baseline characteristics. Values are numbers (percentages) unless stated otherwise

Characteristics	Primary study population (n=23 308)	$P2Y_{12}$ inhibitor (n=11 634)	Aspirin + $P2Y_{12}$ inhibitor (n=11 674)	Difference (95% CI)	P value
Study ID:					
DACAB	334 (1.4)	166 (1.4)	168 (1.4)	0.0% (−0.3% to 0.3%)	0.95
GLASSY	7509 (32.2)	3753 (32.3)	3756 (32.2)	0.1% (−1.1% to 1.3%)	0.90
SMART-CHOICE	2926 (12.6)	1455 (12.5)	1471 (12.6)	−0.1% (−0.9% to 0.8%)	0.84
STOPDAPT-2	3003 (12.9)	1496 (12.9)	1507 (12.9)	−0.1% (−0.9% to 0.8%)	0.92
TICO	3004 (12.9)	1499 (12.9)	1505 (12.9)	−0.0% (−0.9% to 0.9%)	>0.99
TWILIGHT	6532 (28.0)	3265 (28.1)	3267 (28.0)	0.1% (−1.1% to 1.2%)	0.89
Mean (SD) age, years	64.8 (10.6) (n=23 308)	64.8 (10.6) (n=11 634)	64.9 (10.6) (n=11 674)	−0.1 (−0.3 to 0.2)	0.58
Age ≥65 years	12 194 (52.3)	6094 (52.4)	6100 (52.3)	0.1% (−1.2% to 1.4%)	0.85
Female sex	5423 (23.3)	2717 (23.4)	2706 (23.2)	0.2% (−0.9% to 1.3%)	0.75
Mean (SD) height, m	1.7 (0.1) (n=22 951)	1.7 (0.1) (n=11 455)	1.7 (0.1) (n=11 496)	0.0 (−0.0 to 0.0)	0.32
Mean (SD) weight, kg	76.6 (17.3) (n=22 958)	76.7 (17.3) (n=11 461)	76.5 (17.2) (n=11 497)	0.2 (−0.3 to 0.6)	0.42
Mean (SD) body mass index	26.9 (4.8) (n=22 948)	26.9 (4.8) (n=11 455)	26.9 (4.8) (n=11 493)	0.0 (−0.1 to 0.1)	0.79
Geographical region:					0.99
Asia	10 318 (44.3)	5146 (44.2)	5172 (44.3)	−0.1% (−1.3% to 1.2%)	0.91
North America	2972 (12.8)	1484 (12.8)	1488 (12.7)	0.0% (−0.8% to 0.9%)	0.98
Western Europe	7848 (33.7)	3917 (33.7)	3931 (33.7)	−0.0% (−1.2% to 1.2%)	>0.99
Eastern Europe	2170 (9.3)	1087 (9.3)	1083 (9.3)	0.1% (−0.7% to 0.8%)	0.87
Diabetes mellitus	7419/23 304 (31.8)	3744/11 630 (32.2)	3675/11 674 (31.5)	0.7% (−0.5% to 1.9%)	0.24
Insulin treated diabetes	1543/21 104 (7.3)	746/10 547 (7.1)	797/10 557 (7.5)	−0.5% (−1.2% to 0.2%)	0.18
Current cigarette smoker	6271/23 299 (26.9)	3134/11 630 (26.9)	3137/11 669 (26.9)	0.1% (−1.1% to 1.2%)	0.91
Hypercholesterolaemia	14 695/23 030 (63.8)	7298/11 494 (63.5)	7397/11 536 (64.1)	−0.6% (−1.9% to 0.6%)	0.32
Hypertension	16 005/23 286 (68.7)	7985/11 624 (68.7)	8020/11 662 (68.8)	−0.1% (−1.3% to 1.1%)	0.90
Liver disease	33/20 048 (0.2)	21/10 013 (0.2)	12/10 035 (0.1)	0.1% (−0.0% to 0.2%)	0.11
Peripheral artery disease	1323/20 267 (6.5)	633/10 114 (6.3)	690/10 153 (6.8)	−0.5% (−1.2% to 0.1%)	0.12
Previous myocardial infarction	4438/23 297 (19.0)	221/11 626 (19.1)	2217/11 671 (19.0)	0.1% (−0.9% to 1.1%)	0.83
Previous PCI	6959/22 966 (30.3)	3440/11 464 (30.0)	3519/11 502 (30.6)	−0.6% (−1.8% to 0.6%)	0.33
Previous CABG	1250/23 300 (5.4)	606/11 629 (5.2)	644/11 671 (5.5)	−0.3% (−0.9% to 0.3%)	0.29
Previous stroke	733/23 298 (3.1)	343/11 626 (3.0)	390/11 672 (3.3)	−0.4% (−0.8% to 0.1%)	0.09
Previous bleeding	265/23 291 (1.1)	132/11 623 (1.1)	133/11 668 (1.1)	0.0% (−0.3% to 0.3%)	0.97
History of chronic kidney disease	3823/23 031 (16.6)	1892/11 491 (16.5)	1931/11 540 (16.7)	−0.3% (−1.2% to 0.7%)	0.58
Chronic lung disease	826/17 238 (4.8)	403/8609 (4.7)	423/8629 (4.9)	−0.2% (−0.9% to 0.4%)	0.49
Clinical presentation:	(n=23 305)	(n=11 633)	(n=11 672)		0.53
Chronic coronary syndrome	9339 (40.1)	4685 (40.3)	4654 (39.9)	0.4% (−0.9% to 1.7%)	0.53
Acute coronary syndrome	13 966 (59.9)	6948 (59.7)	7018 (60.1)	−0.4% (−1.7% to 0.9%)	0.53
Unstable angina	5579 (39.9)	2752 (39.6)	2827 (40.3)	−0.7% (−2.3% to 1.0%)	0.41
Non-STEMI	5122 (36.7)	2543 (36.6)	2579 (36.7)	−0.1% (−1.7% to 1.5%)	0.86
STEMI	3265 (23.4)	1653 (23.8)	1612 (23.0)	0.8% (−0.6% to 2.2%)	0.25
Aspirin on admission	13 182/20 301 (64.9)	6581/10 137 (64.9)	6601/10 164 (64.9)	0.0% (−1.3% to 1.3%)	0.97
Mean (SD) PRECISE-DAPT score*	16.7 (9.7) (n=22 018)	16.7 (9.6) (n=10 972)	16.8 (9.7) (n=11 046)	−0.1 (−0.3 to 0.2)	0.55
PRECISE-DAPT score ≥25	3928/22 018 (17.8)	1941/10 972 (17.7)	1987/11 046 (18.0)	−0.3% (−1.3% to 0.7%)	0.56
Median (IQR) creatinine clearance (MDRD), mL/min	84.4 (70.0-100.0) (n=22 961)	84.7 (70.1-100.2) (n=11 455)	84.2 (69.7-99.8) (n=11 506)	0.2 (−2.2 to 2.6)	0.19
Mean (SD) haemoglobin, g/dL	19.8 (27.3) (n=22 639)	19.8 (26.9) (n=11 295)	19.9 (27.6) (n=11 344)	−0.1 (−0.8 to 0.6)	0.74
Mean (SD) LVEF, %	56.4 (11.1) (n=13 742)	56.3 (11.0) (n=6851)	56.4 (11.2) (n=6891)	−0.1 (−0.5 to 0.3)	0.64

ACS=acute coronary syndrome; CABG=coronary artery bypass grafting; CCS=chronic coronary syndrome; LVEF=left ventricular ejection fraction; MDRD=Modification of Diet in Renal Disease; PCI=percutaneous coronary intervention; STEMI=ST-segment elevation myocardial infarction.

*Includes five items: age, creatinine clearance, white blood cell count, haemoglobin, and history of bleeding.

to 1.05; P=0.18), with no between trial heterogeneity (τ^2=0.00) (table 2; fig 1).

$P2Y_{12}$ inhibitor monotherapy was not associated with a lower risk of all cause death (0.98% with monotherapy versus 1.40% with DAPT; hazard ratio 0.80, 0.62 to 1.03), but the risk of cardiovascular death was lower with $P2Y_{12}$ inhibitor monotherapy (0.57% *v* 0.90%; 0.69, 0.50 to 0.95), with no between trial heterogeneity (τ^2=0.00). The risks of myocardial infarction (1.64% with monotherapy versus 1.79% with DAPT; hazard ratio 0.93, 0.75 to 1.14), stroke (0.51% *v* 0.41%; 1.10, 0.73 to 1.64), definite stent thrombosis (0.24% *v* 0.28%; 0.85, 0.48 to 1.50), and definite or probable stent thrombosis (0.27% *v* 0.34%; 0.81, 0.49 to 1.37) did not differ (table 2).

The treatment effect for the primary ischaemic endpoint was consistent across most of the predefined subgroups, in both intention to treat and per protocol analyses (fig 2). We observed a treatment-by-subgroup interaction with sex (P for interaction=0.02), suggesting that $P2Y_{12}$ inhibitor monotherapy lowers the risk of the primary ischaemic endpoint in women (hazard ratio 0.64, 0.46 to 0.89) but not in men (1.00, 0.83 to 1.19) (fig 2). This corresponded to a number needed to treat to benefit of 72 (95% confidence interval 42 to 250) in women but no benefit in men. These findings remained consistent in the per protocol analysis (supplementary figure C). When the components of the primary efficacy endpoint were stratified by sex, a treatment-by-sex interaction existed

Table 2 | Clinical outcomes in intention to treat and per protocol populations. Values are number of events/number of patients at risk (% cumulative incidence) unless stated otherwise

	Intention to treat population					Per protocol population				
Outcome	P2Y$_{12}$ inhibitor (n=11 634)	Aspirin + P2Y$_{12}$ inhibitor (n=11 674)	Hazard ratio (95% CI)	τ^2	P value	P2Y$_{12}$ inhibitor (n=10 766)	Aspirin + P2Y$_{12}$ inhibitor (n=11 195)	Hazard ratio (95% CI)	τ^2	P value
Death, MI, or stroke*	303 (2.94)	338 (3.36)	0.90 (0.77 to 1.05)	0.00	0.18	283 (2.95)	315 (3.27)	0.93 (0.79 to 1.09)	0.00	0.38
Death or MI	259 (2.49)	299 (3.0)	0.87 (0.74 to 1.03)	0.00	0.10	245 (2.53)	287 (2.99)	0.88 (0.74 to 1.05)	0.00	0.15
Death:										
All cause	107 (0.98)	137 (1.40)	0.80 (0.62 to 1.03)	0.00	0.08	107 (1.05)	128 (1.36)	0.88 (0.68 to 1.15)	0.01	0.35
Cardiovascular	61 (0.57)	90 (0.90)	0.69 (0.50 to 0.95)	0.00	0.03	61 (0.61)	83 (0.86)	0.77 (0.56 to 1.08)	0.00	0.13
Non-cardiovascular	42 (0.38)	42 (0.46)	1.03 (0.67 to 1.58)	0.15	0.89	42 (0.40)	41 (0.46)	1.10 (0.71 to 1.70)	0.19	0.66
MI	167 (1.64)	181 (1.79)	0.93 (0.75 to 1.14)	0.01	0.47	153 (1.61)	177 (1.81)	0.89 (0.72 to 1.10)	0.01	0.28
Stroke:										
Any	51 (0.51)	45 (0.41)	1.10 (0.73 to 1.64)	0.09	0.65	45 (0.48)	34 (0.32)	1.32 (0.84 to 2.08)	0.00	0.22
Ischaemic	38 (0.39)	36 (0.33)	1.01 (0.63 to 1.60)	0.07	0.98	35 (0.39)	27 (0.26)	1.27 (0.76 to 2.11)	0.00	0.35
Haemorrhagic	6 (0.05)	2 (0.02)	2.53 (0.49 to 13.0)	0.00	0.26	5 (0.05)	2 (0.02)	2.21 (0.40 to 12.09)	0.00	0.36
Stent thrombosis:										
Definite	23 (0.24)	26 (0.28)	0.85 (0.48 to 1.50)	0.00	0.56	17 (0.20)	25 (0.28)	0.72 (0.38 to 1.33)	0.00	0.29
Probable	6 (0.05)	7 (0.06)	0.72 (0.23 to 2.26)	0.00	0.57	4 (0.04)	7 (0.06)	0.51 (0.13 to 2.06)	0.00	0.34
Possible	27 (0.26)	48 (0.52)	0.56 (0.35 to 0.90)	0.00	0.02	27 (0.28)	47 (0.53)	0.59 (0.37 to 0.94)	0.00	0.03
Definite or probable	27 (0.27)	32 (0.34)	0.81 (0.49 to 1.37)	0.00	0.43	21 (0.23)	31 (0.34)	0.68 (0.38 to 1.19)	0.00	0.17
Any	52 (0.52)	79 (0.85)	0.65 (0.46 to 0.92)	0.00	0.02	47 (0.51)	77 (0.86)	0.61 (0.42 to 0.88)	0.00	0.008
BARC bleeding:										
2, 3, or 5	295 (2.91)	493 (4.76)	0.59 (0.51 to 0.69)	0.00	<0.001	277 (2.93)	475 (4.76)	0.60 (0.52 to 0.70)	0.00	<0.001
3 or 5	97 (0.89)	197 (1.83)	0.49 (0.39 to 0.63)	0.03	<0.001	91 (0.90)	176 (1.71)	0.53 (0.41 to 0.69)	0.03	<0.001
5	3 (0.03)	5 (0.06)	0.67 (0.11 to 4.02)	0.00	0.66	3 (0.04)	5 (0.06)	0.69 (0.11 to 4.12)	0.00	0.68
TIMI bleeding:										
Major	44 (0.45)	93 (0.94)	0.47 (0.33 to 0.68)	0.29	<0.001	44 (0.48)	82 (0.87)	0.55 (0.38 to 0.79)	0.20	0.001
Minor	136 (1.43)	242 (2.4)	0.56 (0.45 to 0.69)	0.00	<0.001	132 (1.48)	230 (2.37)	0.57 (0.46 to 0.71)	0.00	<0.001
Major or minor	179 (1.88)	331 (3.33)	0.53 (0.45 to 0.64)	0.04	<0.001	175 (1.96)	309 (3.25)	0.56 (0.47 to 0.68)	0.04	<0.001
NACE	384 (3.69)	504 (4.94)	0.76 (0.67 to 0.87)	0.02	<0.001	359 (3.71)	460 (4.71)	0.81 (0.70 to 0.93)	0.01	0.002

BARC=Bleeding Academy Research Consortium; MI=myocardial infarction; NACE=net adverse clinical events, defined as composite of all cause death, myocardial infarction, stroke, and BARC type 3 or type 5 bleeding; TIMI=Thrombolysis in Myocardial Infarction.

*P value for non-inferiority=0.005 in per protocol population; non-inferiority testing was performed on one sided α of 5% corresponding to 90% CIs; other P values are two sided for superiority; 95% CIs are shown.

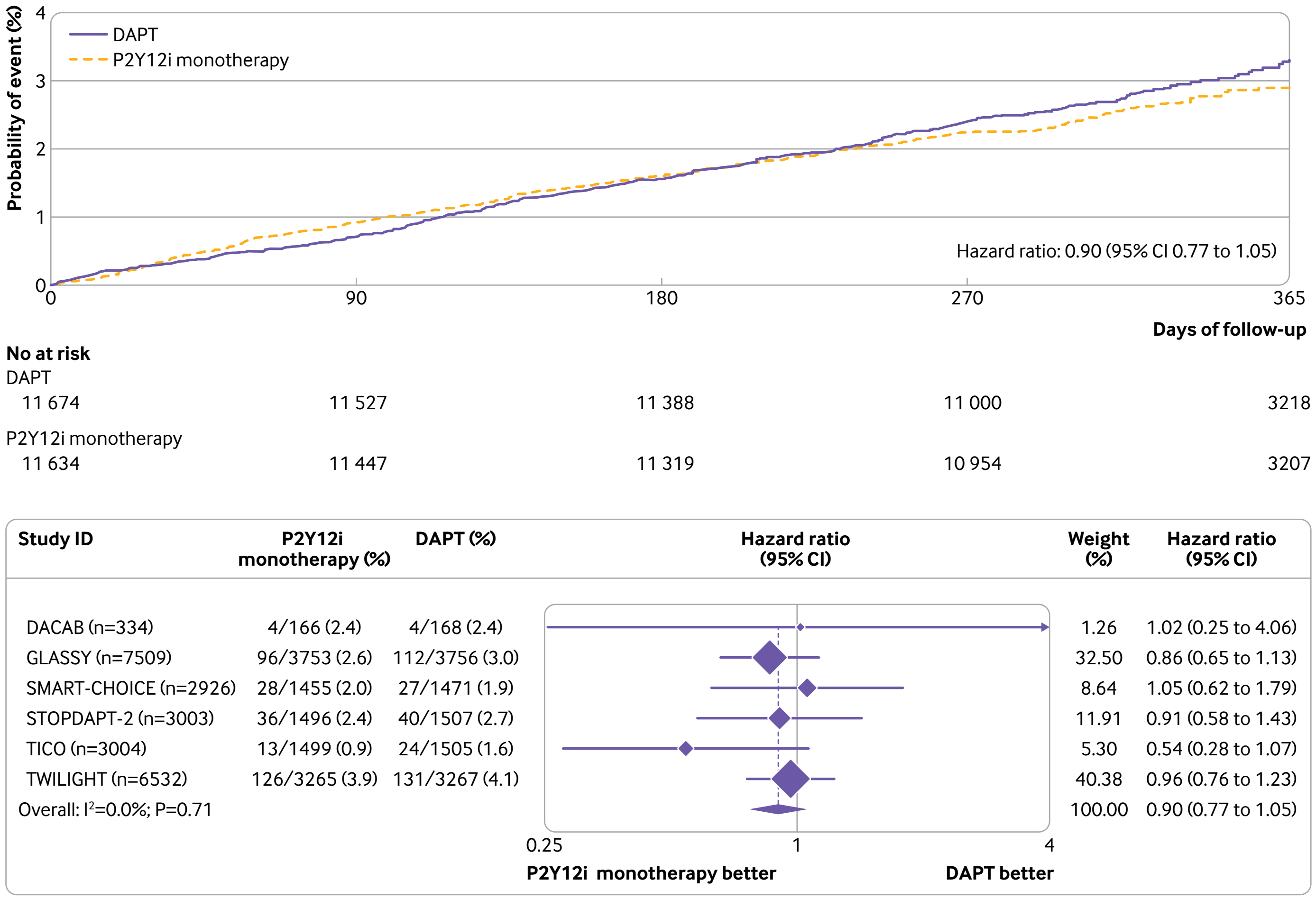
for all cause death (P for interaction=0.02) attributable to cardiovascular death (P for interaction=0.02), which was markedly reduced among women (hazard ratio 0.31, 0.15 to 0.65) but not men (0.86, 0.59 to 1.25) with P2Y$_{12}$ inhibitor monotherapy (fig 3). The treatment effects for the primary efficacy endpoint or its components were consistent with respect to clopidogrel or newer P2Y$_{12}$ inhibitors, consisting of mainly ticagrelor, in the experimental arm (fig 4). In an analysis restricted to trials with monotherapy with newer P2Y$_{12}$ inhibitors, the effect of monotherapy was consistent across subgroups except for sex (P for interaction=0.02) (supplementary figure D). In an analysis restricted to trials with monotherapy with clopidogrel, the effect of monotherapy was consistent across all subgroups (supplementary figure E).

Safety endpoints

We found strong evidence for a reduction in the risk of BARC type 3 or type 5 bleeding among patients randomly allocated to P2Y$_{12}$ inhibitor monotherapy compared with DAPT (0.89% *v* 1.83%; hazard ratio 0.49, 0.39 to 0.63; P<0.001; τ^2=0.03), for a number needed to treat to benefit of 111 (77 to 200) over a median treatment duration of 334 days (table 2; fig 5). The treatment effect was consistent across pre-defined subgroups (supplementary figure F), with the exception of a treatment-by-subgroup interaction for type of P2Y$_{12}$ inhibitor in the control group (hazard ratio 0.77 (0.50 to 1.18) for clopidogrel and 0.41 (0.30 to 0.55) for newer P2Y$_{12}$ inhibitors; P for interaction=0.02) (supplementary figure F). The use of a newer P2Y$_{12}$ inhibitor was associated with treatment-by-subgroup interactions for clinical presentation (acute versus chronic coronary syndrome) and type of P2Y$_{12}$ inhibitor in the control group (supplementary figure G). Clopidogrel monotherapy provided consistent treatment effects across pre-defined subgroups (supplementary figure H). The rates of other bleeding endpoints or net adverse clinical events were reduced with P2Y$_{12}$ inhibitor monotherapy (table 2).

Pre-specified sensitivity analyses

Sensitivity analyses including the initial DAPT phase after randomisation, which was identical in both treatment groups in four trials, yielded no difference for the composite ischaemic endpoint, with attenuated absolute and relative bleeding benefits with P2Y$_{12}$ inhibitor monotherapy (supplementary table H). Additional sensitivity analyses excluding patients who experienced non-fatal ischaemic events (supplementary tables I and J), bleeding events (supplementary tables K and L), or any of these events (supplementary table M) during the initial DAPT phase provided consistent findings. All cause death occurred in 144 (0.98%) patients with P2Y$_{12}$ inhibitor



No at risk

	0	90	180	270	365
DAPT	11 674	11 527	11 388	11 000	3218
P2Y12i monotherapy	11 634	11 447	11 319	10 954	3207

Study ID	P2Y12i monotherapy (%)	DAPT (%)	Weight (%)	Hazard ratio (95% CI)
DACAB (n=334)	4/166 (2.4)	4/168 (2.4)	1.26	1.02 (0.25 to 4.06)
GLASSY (n=7509)	96/3753 (2.6)	112/3756 (3.0)	32.50	0.86 (0.65 to 1.13)
SMART-CHOICE (n=2926)	28/1455 (2.0)	27/1471 (1.9)	8.64	1.05 (0.62 to 1.79)
STOPDAPT-2 (n=3003)	36/1496 (2.4)	40/1507 (2.7)	11.91	0.91 (0.58 to 1.43)
TICO (n=3004)	13/1499 (0.9)	24/1505 (1.6)	5.30	0.54 (0.28 to 1.07)
TWILIGHT (n=6532)	126/3265 (3.9)	131/3267 (4.1)	40.38	0.96 (0.76 to 1.23)
Overall: I^2=0.0%; P=0.71			100.00	0.90 (0.77 to 1.05)

Fig 1 | Hazard ratios for individual trials and for pooled population and Kaplan-Meier estimates for primary endpoint of all cause death, myocardial infarction, or stroke in intention to treat population. Kaplan-Meier curves and hazard ratios from one step, fixed effect meta-analysis (top) and two step, fixed effect meta-analysis (bottom). DAPT=dual antiplatelet therapy; P2Y12i=P2Y$_{12}$ inhibitor monotherapy

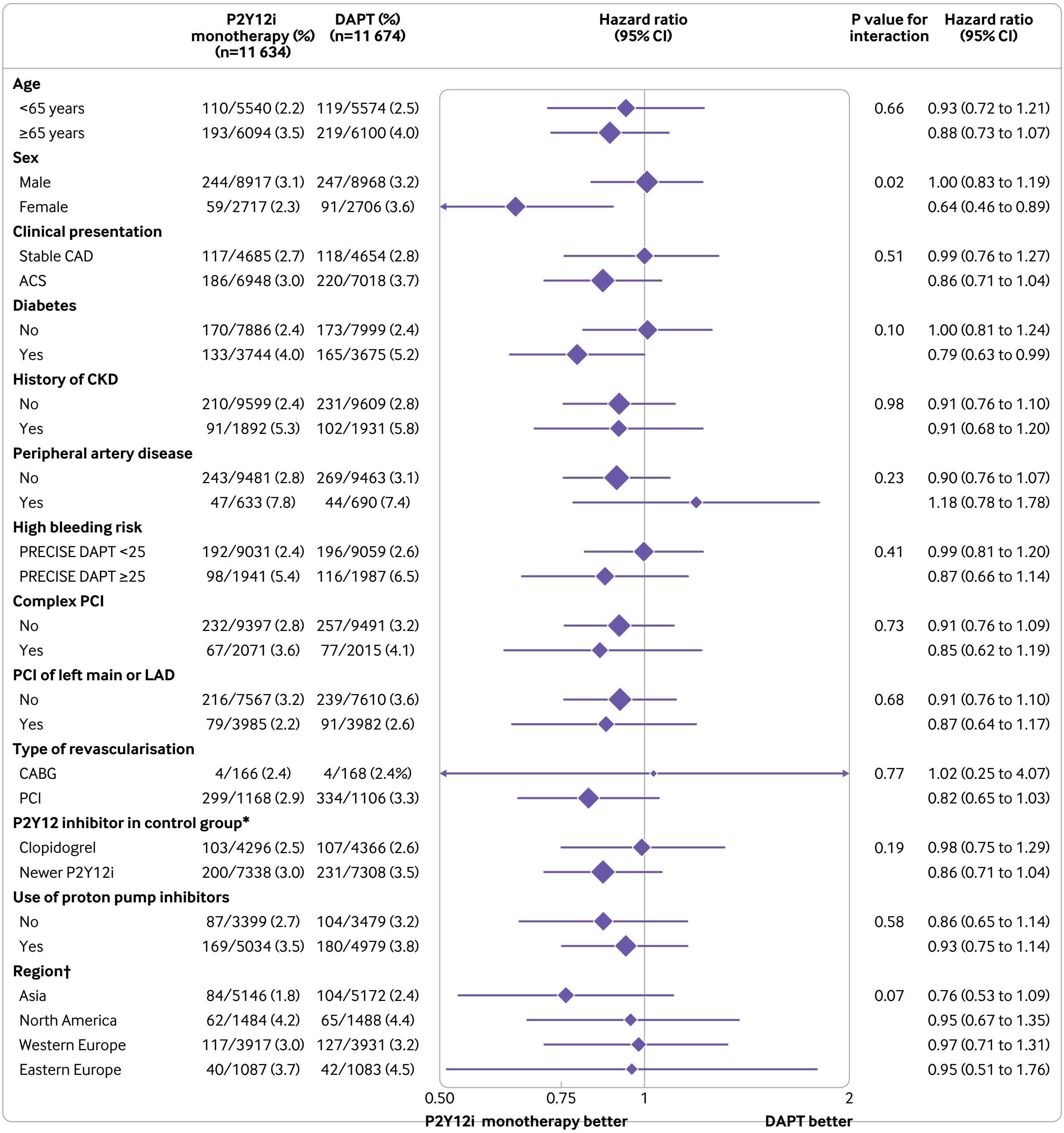
monotherapy and 173 (1.31%) with DAPT (hazard ratio 0.85, 0.68 to 1.06; P=0.14; τ^2=0.00) when GLOBAL LEADERS instead of GLASSY was pooled with the other trials. An on-treatment analysis, excluding one trial due to lack of information,[9] showed no excess of ischaemic events and lower bleeding risk with P2Y$_{12}$ inhibitor monotherapy (supplementary table N).

Additional post hoc analyses

The composite endpoint of all-cause death, myocardial infarction, and stroke, censoring events that occurred nine months after the start of P2Y$_{12}$ inhibitor monotherapy in the experimental arm (to achieve a uniform length of follow-up across trials), occurred in 259 (2.28%) and 240 (2.28%) patients with P2Y$_{12}$ inhibitor monotherapy and in 284 (2.49%) and 262 (2.39%) with DAPT in the intention to treat (hazard ratio 0.92, 0.77 to 1.08; P=0.31 for superiority) and per protocol (0.95, 0.80 to 1.13; P=0.58 for superiority) populations, respectively, with no between trial heterogeneity (τ^2=0.00) (supplementary table O). We observed no treatment-by-subgroup interaction with body weight for the primary efficacy endpoint when both sexes were appraised separately, suggesting consistent benefit with P2Y$_{12}$ inhibitor monotherapy among women but not men, irrespective of body weight (supplementary figure I). The treatment-by-sex interaction testing for the primary outcome in each included study is shown in supplementary figure J.

Discussion

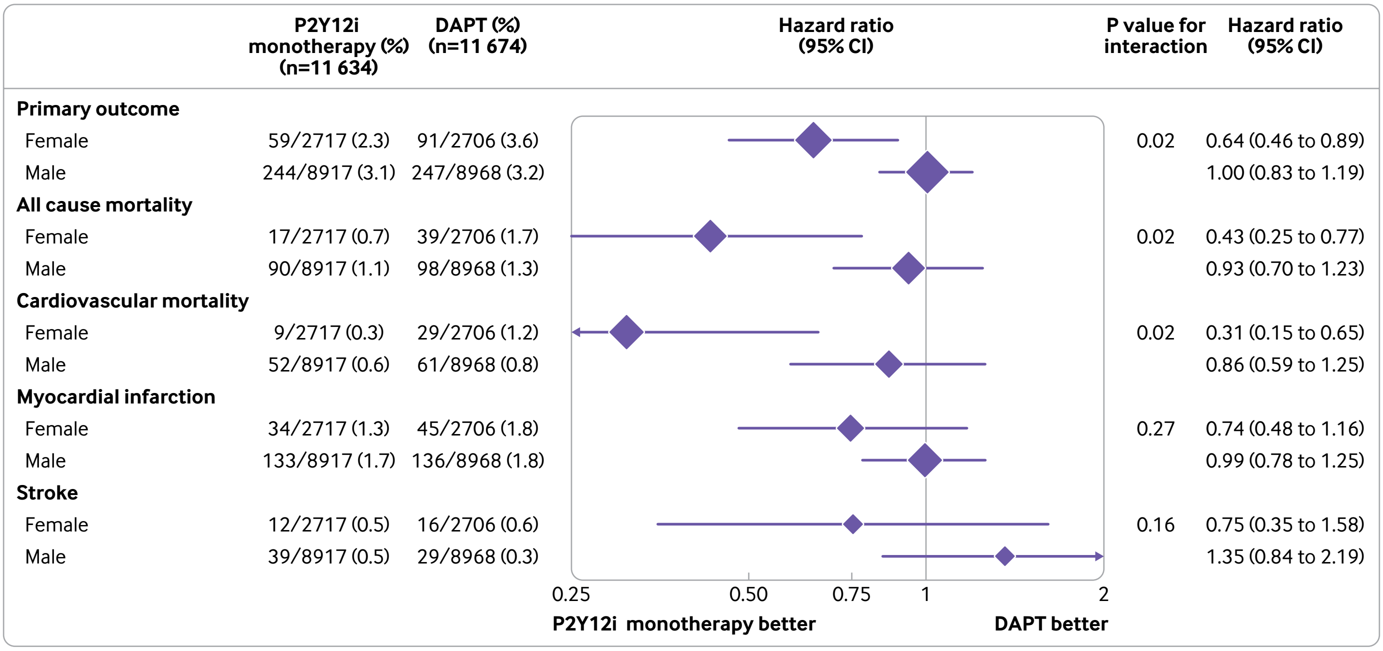
Our individual participant data meta-analysis of the totality of available randomised studies investigating P2Y$_{12}$ inhibitor monotherapy after revascularisation, including 24 096 patients mainly after percutaneous coronary intervention, provides strong evidence that P2Y$_{12}$ inhibitor monotherapy is non-inferior to DAPT. We chose a non-inferiority margin that preserved half of the treatment effect of aspirin observed in the historical aspirin trials,[11] under the rationale that the experimental arm consists of aspirin withdrawal and that the treatment effect of DAPT versus placebo is not known. P2Y$_{12}$ inhibitor monotherapy was associated with a lower risk of major bleeding and net adverse clinical events compared with DAPT. The main findings were corroborated by all sensitivity analyses. Our analysis suggests that female patients may derive particular benefit from P2Y$_{12}$ inhibitor monotherapy



	P2Y12i monotherapy (%) (n=11 634)	DAPT (%) (n=11 674)	P value for interaction	Hazard ratio (95% CI)
Age				
<65 years	110/5540 (2.2)	119/5574 (2.5)	0.66	0.93 (0.72 to 1.21)
≥65 years	193/6094 (3.5)	219/6100 (4.0)		0.88 (0.73 to 1.07)
Sex				
Male	244/8917 (3.1)	247/8968 (3.2)	0.02	1.00 (0.83 to 1.19)
Female	59/2717 (2.3)	91/2706 (3.6)		0.64 (0.46 to 0.89)
Clinical presentation				
Stable CAD	117/4685 (2.7)	118/4654 (2.8)	0.51	0.99 (0.76 to 1.27)
ACS	186/6948 (3.0)	220/7018 (3.7)		0.86 (0.71 to 1.04)
Diabetes				
No	170/7886 (2.4)	173/7999 (2.4)	0.10	1.00 (0.81 to 1.24)
Yes	133/3744 (4.0)	165/3675 (5.2)		0.79 (0.63 to 0.99)
History of CKD				
No	210/9599 (2.4)	231/9609 (2.8)	0.98	0.91 (0.76 to 1.10)
Yes	91/1892 (5.3)	102/1931 (5.8)		0.91 (0.68 to 1.20)
Peripheral artery disease				
No	243/9481 (2.8)	269/9463 (3.1)	0.23	0.90 (0.76 to 1.07)
Yes	47/633 (7.8)	44/690 (7.4)		1.18 (0.78 to 1.78)
High bleeding risk				
PRECISE DAPT <25	192/9031 (2.4)	196/9059 (2.6)	0.41	0.99 (0.81 to 1.20)
PRECISE DAPT ≥25	98/1941 (5.4)	116/1987 (6.5)		0.87 (0.66 to 1.14)
Complex PCI				
No	232/9397 (2.8)	257/9491 (3.2)	0.73	0.91 (0.76 to 1.09)
Yes	67/2071 (3.6)	77/2015 (4.1)		0.85 (0.62 to 1.19)
PCI of left main or LAD				
No	216/7567 (3.2)	239/7610 (3.6)	0.68	0.91 (0.76 to 1.10)
Yes	79/3985 (2.2)	91/3982 (2.6)		0.87 (0.64 to 1.17)
Type of revascularisation				
CABG	4/166 (2.4)	4/168 (2.4%)	0.77	1.02 (0.25 to 4.07)
PCI	299/1168 (2.9)	334/1106 (3.3)		0.82 (0.65 to 1.03)
P2Y12 inhibitor in control group*				
Clopidogrel	103/4296 (2.5)	107/4366 (2.6)	0.19	0.98 (0.75 to 1.29)
Newer P2Y12i	200/7338 (3.0)	231/7308 (3.5)		0.86 (0.71 to 1.04)
Use of proton pump inhibitors				
No	87/3399 (2.7)	104/3479 (3.2)	0.58	0.86 (0.65 to 1.14)
Yes	169/5034 (3.5)	180/4979 (3.8)		0.93 (0.75 to 1.14)
Region†				
Asia	84/5146 (1.8)	104/5172 (2.4)	0.07	0.76 (0.53 to 1.09)
North America	62/1484 (4.2)	65/1488 (4.4)		0.95 (0.67 to 1.35)
Western Europe	117/3917 (3.0)	127/3931 (3.2)		0.97 (0.71 to 1.31)
Eastern Europe	40/1087 (3.7)	42/1083 (4.5)		0.95 (0.51 to 1.76)

Fig 2 | Subgroup analyses for primary endpoint of all cause death, myocardial infarction, or stroke in intention to treat population. High bleeding risk was defined on basis of PRECISE-DAPT score ≥25. *P value obtained by merging within study and across study interactions (owing to design of trials). †European regions pooled together and within study and across study interactions merged owing to trial designs. ACS=acute coronary syndrome; CABG=coronary artery bypass grafting; CAD=coronary artery disease; CKD=chronic kidney disease; DAPT=dual antiplatelet therapy; LAD=left anterior descending artery; P2Y12i=P2Y$_{12}$ inhibitor monotherapy; PCI=percutaneous coronary intervention

owing to the lower risk of major adverse cardiovascular events, largely driven by a reduction in cardiovascular death. P2Y$_{12}$ inhibitor monotherapy was associated with lower bleeding rates consistently across subgroups, although the magnitude of this treatment effect varied by the potency of the P2Y$_{12}$ inhibitor in the experimental and control groups, which has important implications for practice.



	P2Y12i monotherapy (%) (n=11 634)	DAPT (%) (n=11 674)	P value for interaction	Hazard ratio (95% CI)
Primary outcome				
Female	59/2717 (2.3)	91/2706 (3.6)	0.02	0.64 (0.46 to 0.89)
Male	244/8917 (3.1)	247/8968 (3.2)		1.00 (0.83 to 1.19)
All cause mortality				
Female	17/2717 (0.7)	39/2706 (1.7)	0.02	0.43 (0.25 to 0.77)
Male	90/8917 (1.1)	98/8968 (1.3)		0.93 (0.70 to 1.23)
Cardiovascular mortality				
Female	9/2717 (0.3)	29/2706 (1.2)	0.02	0.31 (0.15 to 0.65)
Male	52/8917 (0.6)	61/8968 (0.8)		0.86 (0.59 to 1.25)
Myocardial infarction				
Female	34/2717 (1.3)	45/2706 (1.8)	0.27	0.74 (0.48 to 1.16)
Male	133/8917 (1.7)	136/8968 (1.8)		0.99 (0.78 to 1.25)
Stroke				
Female	12/2717 (0.5)	16/2706 (0.6)	0.16	0.75 (0.35 to 1.58)
Male	39/8917 (0.5)	29/8968 (0.3)		1.35 (0.84 to 2.19)

Fig 3 | Sex stratified analysis for primary endpoint, all cause death, cardiovascular death, myocardial infarction, or stroke in intention to treat population. DAPT=dual antiplatelet therapy; P2Y12i=P2Y$_{12}$ inhibitor monotherapy

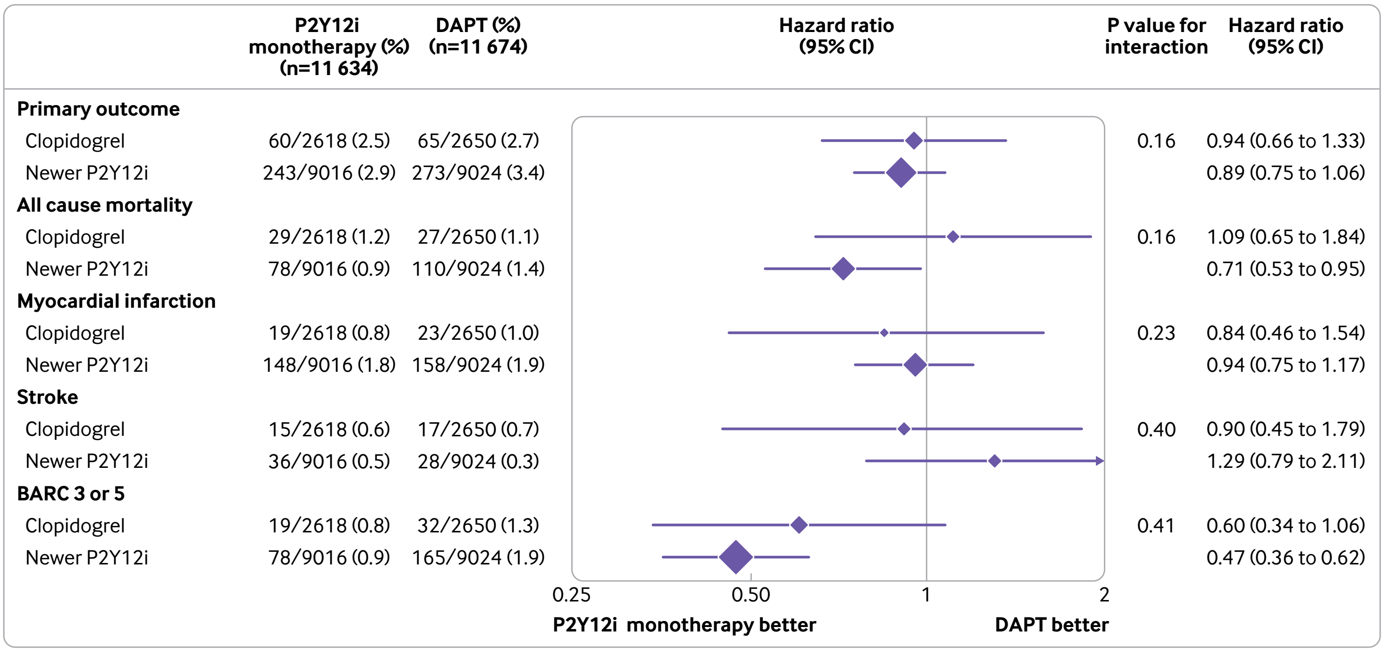
Rationale for P2Y$_{12}$ inhibitor monotherapy after coronary revascularisation

A six to 12 month DAPT regimen is endorsed with a class I recommendation after percutaneous coronary intervention, irrespective of the clinical presentation or revascularisation techniques, and after coronary artery bypass grafting in patients with myocardial infarction.[12] This reflects the robust evidence indicating lower ischaemic risk with DAPT compared with aspirin monotherapy. However, DAPT invariably confers a heightened risk of major bleeding affecting mortality and morbidity,[2 20 21] and its use requires careful assessment of the trade-off between risks and anticipated benefits. An individualised approach to the DAPT regimen, modulating the duration of P2Y$_{12}$ inhibition on a background of aspirin therapy, has gained consensus.[1 2 4 22] However, this approach is poorly standardised and lacks prospective validation.[1 2] An alternative approach consists of early aspirin withdrawal and continuation with P2Y$_{12}$ inhibitor monotherapy up to 12 months after percutaneous coronary intervention or direct initiation of P2Y$_{12}$ inhibitor monotherapy after coronary artery bypass grafting.[5-10] Trials examining this approach were generally powered for non-inferiority with respect to ischaemic endpoints,[6 7 10] based on arbitrary non-inferiority margins, and/or superiority with respect to bleeding or net adverse clinical events, including a combination of ischaemic and bleeding endpoints.[6 9 10] They mostly showed no excess of ischaemic events and lower bleeding rates with P2Y$_{12}$ inhibitor monotherapy instead of DAPT. However, the imprecisions around the composite or individual ischaemic endpoint estimates entailed the loss of the entire treatment effect observed in historical aspirin trials.[11]

Comparison with previous meta-analyses on aggregate data and implications for clinicians

Previous aggregate data meta-analyses have not conclusively quantified the risks and benefits of aspirin withdrawal in comparison with DAPT after coronary revascularisation, because they included events occurring during the initial DAPT phase, which was identical in both experimental and control regimens and might have biased treatment estimates towards the null.[12 14] Both ischaemic events and bleeding events are known to cluster within the first month after revascularisation.[23-25] In our analysis, we censored 30.6% of all primary composite endpoints, 44.4% of cardiovascular deaths, 77.5% of definite stent thromboses, and 52.0% of BARC type 3 or type 5 bleeding events in the included trials. These events had occurred during the initial DAPT phase, which was identical in both treatment groups. In addition, our individual participant data enabled us to investigate the consistency of treatment effects across subgroups of interest. Specifically, we collected in our assembled dataset patient and procedural characteristics affecting ischaemic and/or bleeding outcomes aiming at determining whether P2Y$_{12}$ inhibitor monotherapy could be associated with potential harm in high ischaemic risk subsets or whether the bleeding benefit was confined to patients at high risk of bleeding.

Our individual participant data meta-analysis provides confidence that aspirin withdrawal one to three months after percutaneous coronary intervention and continuation with P2Y$_{12}$ inhibitor monotherapy also consistently preserves ischaemic protection compared with DAPT in patients at higher ischaemic risk, such as those with diabetes or acute coronary syndromes or receiving a complex intervention or an



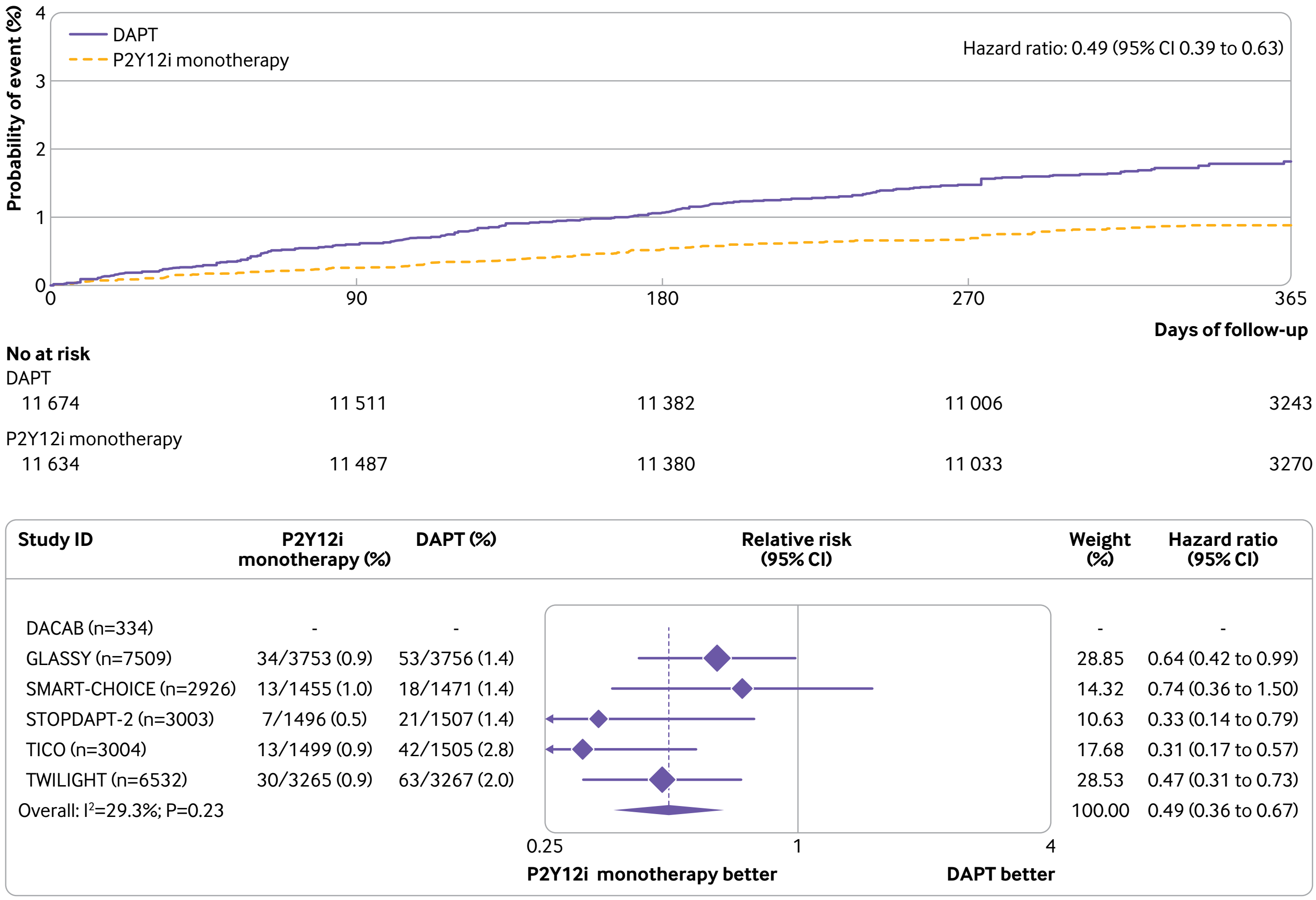
	P2Y12i monotherapy (%) (n=11 634)	DAPT (%) (n=11 674)	P value for interaction	Hazard ratio (95% CI)
Primary outcome				
Clopidogrel	60/2618 (2.5)	65/2650 (2.7)	0.16	0.94 (0.66 to 1.33)
Newer P2Y12i	243/9016 (2.9)	273/9024 (3.4)		0.89 (0.75 to 1.06)
All cause mortality				
Clopidogrel	29/2618 (1.2)	27/2650 (1.1)	0.16	1.09 (0.65 to 1.84)
Newer P2Y12i	78/9016 (0.9)	110/9024 (1.4)		0.71 (0.53 to 0.95)
Myocardial infarction				
Clopidogrel	19/2618 (0.8)	23/2650 (1.0)	0.23	0.84 (0.46 to 1.54)
Newer P2Y12i	148/9016 (1.8)	158/9024 (1.9)		0.94 (0.75 to 1.17)
Stroke				
Clopidogrel	15/2618 (0.6)	17/2650 (0.7)	0.40	0.90 (0.45 to 1.79)
Newer P2Y12i	36/9016 (0.5)	28/9024 (0.3)		1.29 (0.79 to 2.11)
BARC 3 or 5				
Clopidogrel	19/2618 (0.8)	32/2650 (1.3)	0.41	0.60 (0.34 to 1.06)
Newer P2Y12i	78/9016 (0.9)	165/9024 (1.9)		0.47 (0.36 to 0.62)

Fig 4 | **Primary endpoint or its components and key safety endpoint stratified by use of clopidogrel or newer P2Y$_{12}$ inhibitors in experimental arm of intention to treat population. BARC=Bleeding Academy Research Consortium; DAPT=dual antiplatelet therapy**

intervention in critical coronary segments, such as left main or left anterior descending coronary arteries. The treatment effect was consistent irrespective of the choice of P2Y$_{12}$ inhibitor monotherapy. However, ticagrelor was over-represented and prasugrel was under-represented among the newer P2Y$_{12}$ inhibitors, and clopidogrel monotherapy was tested only in Asian populations in comparison with a combination of aspirin and clopidogrel. We ran several sensitivity analyses, which suggested that the observed overall treatment effect was robust and reproducible despite the inclusion or exclusion of patients who experienced non-fatal events during the initial DAPT phase. We also did confirmatory analyses in the per protocol and on-treatment populations, which were either previously not conducted or conducted inconsistently across trials. The observation of a possible benefit of P2Y$_{12}$ inhibitor monotherapy on cardiovascular mortality, apparently confined to female patients, deserves attention. Given the number of pre-specified subgroups of interest and the lack of correction for multiplicity, this finding remains hypothesis generating. Each of the six included trials observed lower hazards of the composite ischaemic endpoint with P2Y$_{12}$ inhibitor monotherapy compared with DAPT in female rather than male patients, even though none of them individually showed a positive treatment-by-sex interaction. The effect on mortality does not seem to be explained by a reduction in major bleeding events with P2Y$_{12}$ inhibitor monotherapy, as both relative and absolute risk reductions for major bleeding were entirely consistent across sexes. Whether between sex disparity in bleeding management, as previously observed,[26] may contribute to explaining our findings remains to be investigated. Given that the risks and benefits of aspirin may be affected by weight,[27] its role was separately appraised in men and women. Our data do not support the hypothesis that weight accounts for the observed heterogeneity in the treatment benefit across sexes.

The treatment effect with P2Y$_{12}$ inhibitor monotherapy on bleeding varied in magnitude according to the potency of P2Y$_{12}$ inhibitor in the experimental and/or control groups and was apparently null when monotherapy with a newer P2Y$_{12}$ inhibitor was compared with aspirin and clopidogrel. However, confidence intervals were large for this comparison, including both benefit and harm. P2Y$_{12}$ inhibitor monotherapy therefore seems particularly appealing when newer P2Y$_{12}$ inhibitors, rather than clopidogrel, are clinically favoured. In all other subgroup analyses, we found benefits with respect to major bleeding events irrespective of baseline risks and across the entire spectrum of included patients. Taken together, this suggests that the recent guideline statements that P2Y$_{12}$ inhibitor monotherapy should be considered after a short course of DAPT, depending on the balance between the ischaemic and bleeding risk, is therefore no longer supported by the totality of evidence.[15]

Our findings are poorly informative on the choice of antithrombotic treatment after coronary artery bypass grafting.[5] Firstly, only a small trial powered for angiographic endpoints was available for inclusion. Secondly, limited and controversial evidence is available on the value of DAPT after surgical revascularisation in patients with chronic coronary syndrome.[1 2 28] Despite supportive evidence from subgroups of large trials after acute coronary syndrome for clopidogrel or ticagrelor,[29 30] a DAPT regimen remains inconsistently implemented in practice.[1 2]



No at risk

	0	90	180	270	365
DAPT	11 674	11 511	11 382	11 006	3243
P2Y12i monotherapy	11 634	11 487	11 380	11 033	3270

Study ID	P2Y12i monotherapy (%)	DAPT (%)	Weight (%)	Hazard ratio (95% CI)
DACAB (n=334)	-	-	-	-
GLASSY (n=7509)	34/3753 (0.9)	53/3756 (1.4)	28.85	0.64 (0.42 to 0.99)
SMART-CHOICE (n=2926)	13/1455 (1.0)	18/1471 (1.4)	14.32	0.74 (0.36 to 1.50)
STOPDAPT-2 (n=3003)	7/1496 (0.5)	21/1507 (1.4)	10.63	0.33 (0.14 to 0.79)
TICO (n=3004)	13/1499 (0.9)	42/1505 (2.8)	17.68	0.31 (0.17 to 0.57)
TWILIGHT (n=6532)	30/3265 (0.9)	63/3267 (2.0)	28.53	0.47 (0.31 to 0.73)
Overall: I^2=29.3%; P=0.23			100.00	0.49 (0.36 to 0.67)

Fig 5 | Hazard ratios for individual trials and for pooled population and Kaplan-Meier estimates for key safety endpoint of Bleeding Academic Research Consortium (BARC) type 3 or type 5 bleeding in intention to treat population. Kaplan-Meier curves and hazard ratios from one step, fixed effect meta-analysis (top) and two step, fixed effect meta-analysis (bottom). DAPT=dual antiplatelet therapy

Limitations of study

The results of this individual participant data meta-analysis should be interpreted in view of several limitations. The analysis is subject to the shortcomings of the original trials, including an open label design in five of the six studies.[5-9] However, all studies implemented blinded central endpoint adjudication,[31] and endpoint definitions were largely consistent across trials. Cardiac instead of cardiovascular death was analysed in one trial because vascular death was not independently adjudicated.[9] We excluded events occurring while randomised groups received identical DAPT regimens in four trials.[6-9] However, sensitivity analyses including the initial DAPT phase following randomisation provided consistent results. No correction for multiple testing was pre-specified. Therefore, the lower risk of composite ischaemic endpoints with $P2Y_{12}$ inhibitor monotherapy in women is exploratory and needs prospective validation. The choice of $P2Y_{12}$ inhibitor monotherapy requires further investigation. Prasugrel monotherapy was used in a few patients within one trial and as protocol deviations in another.[7 8] Four trials mandated the use of ticagrelor monotherapy,[5 6 9 10] one study mandated clopidogrel monotherapy,[8] and only one trial allowed and stratified randomisation for all three oral $P2Y_{12}$ inhibitors.[7] The duration of $P2Y_{12}$ inhibitor monotherapy ranged from nine to 12 months across the included trials. However, findings were consistent after censoring of events that occurred beyond nine months. Finally, six rather than 12 month DAPT is recommended after percutaneous coronary intervention in patients with chronic coronary syndrome. However, 12 month DAPT remains the standard of care in many centres across the world in patients with chronic coronary syndrome,[32] and the results remained largely consistent for either ischaemic or bleeding endpoints when stratified on the basis of clinical presentation.

Conclusions

$P2Y_{12}$ inhibitor monotherapy was associated with similar risks of death, myocardial infarction, or stroke and lower risks of major bleeding compared with DAPT. We found evidence that these associations may be modified by sex and type of $P2Y_{12}$ inhibitor, respectively. The data on $P2Y_{12}$ inhibitor monotherapy compared with DAPT after coronary artery bypass grafting is limited to a single trial and requires further investigation. Our results, based on the totality of the available evidence, support a paradigm shift in antithrombotic management and question the central role of DAPT beyond one to three months after percutaneous coronary intervention.

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Web appendix: Supplementary materials