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

Marco Valgimigli,1,2* Felice Gragnano,3* Mattia Branca,4 Anna Franzone,5 Usman Baber,6 Yangsoo Jang,7 Takeda Kimura,8 Joo-Yong Hahn,9 Qiang Zhao,10 Stephan Windecker,2 Charles M Gibson,11 Byeong-Keuk Kim,7 Hirotoshi Watanabe,8 Young Bin Song,9 Yunpeng Zhu,10 Pascal Vranckx,12 Shamir Mehta,13,14 Sung-Jin Hong,7 Kenji Ando,15 Hyeon-Cheol Gwon,9 Patrick W Serruys,16,17 George D Dangas,6 Eugène P McFadden,18,19 Dominick J Angiolillo,20 Dik Heg,4 Peter Jüni,21* Roxana Mehran6*

ABSTRACT

OBJECTIVE
To assess the risks and benefits of P2Y12 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 P2Y12 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 P2Y12 inhibitor monotherapy and 315 (3.27%) with DAPT in the per protocol population (hazard ratio 0.93, 95% confidence interval 0.89 to 1.09; P=0.005 for non-inferiority; P=0.38 for superiority; t2=0.00). The treatment effect was consistent across all subgroups, except for sex (P for interaction=0.02), suggesting that P2Y12 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 P2Y12 inhibitor monotherapy than with DAPT (97 (0.89%) v 197 (1.83%); hazard ratio 0.49, 0.39 to 0.63; P<0.001; t2=0.03), which was consistent across subgroups, except for type of P2Y12 inhibitor (P for interaction=0.02), suggesting greater benefit when a newer P2Y12 inhibitor rather than clopidogrel was part of the DAPT regimen.

CONCLUSIONS
P2Y12 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.
oral P2Y\textsubscript{12} inhibitor preserves the treatment effect of the latter in combination with aspirin.\textsuperscript{11} Previous aggregate data meta-analyses of oral P2Y\textsubscript{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.\textsuperscript{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.\textsuperscript{7} 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\textsubscript{12} inhibitor monotherapy, should be considered depending on the balance between ischaemic risk and bleeding risk.\textsuperscript{15} The American Heart Association/American College of Cardiology guidelines have not yet issued a formal recommendation for this treatment option.\textsuperscript{1}

We did a systematic review and individual participant data meta-analysis of all randomised trials that compared P2Y\textsubscript{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\textsubscript{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.\textsuperscript{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).\textsuperscript{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\textsubscript{12} inhibitor monotherapy versus DAPT. The key safety endpoint was Bleeding Academic Research Consortium (BARC) type 3 or type 5 bleeding.\textsuperscript{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,\textsuperscript{19} 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).\textsuperscript{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 $\tau^2$. 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<sub>12</sub> inhibitor monotherapy in the experimental group. Data were analysed up to the longest available time point with protocol specified P2Y<sub>12</sub> inhibitor monotherapy in the experimental group and DAPT in the control group.

We first tested the non-inferiority of P2Y<sub>12</sub> 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<sub>12</sub> 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. If non-inferiority was met, we pre-specified testing of the superiority of P2Y<sub>12</sub> 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<sub>12</sub> 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<sub>12</sub> 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<sub>12</sub> 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 in 4297 (36.8%), aspirin and prasugrel in 140 (1.2%), aspirin and ticagrelor in 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<sub>12</sub> 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 (c<sup>2</sup>=0.00) (table 2). The same composite endpoint occurred in 303 (2.94%) and 338 (3.36%) patients with P2Y<sub>12</sub> inhibitor monotherapy and DAPT, respectively, in the intention to treat population (hazard ratio 0.90, 0.77
to 1.05; P=0.18), with no between trial heterogeneity (τ²=0.00) (table 2; fig 1).

P2Y12 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 P2Y12 inhibitor monotherapy (0.57% v 0.90%; 0.69, 0.50 to 0.95), with no between trial heterogeneity (τ²=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, 0.68 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 P2Y12 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.
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 P2Y12 inhibitor monotherapy (fig 3). The treatment effects for the primary efficacy endpoint or its components were consistent with respect to clopidogrel or newer P2Y12 inhibitors, consisting of mainly ticagrelor, in the experimental arm (fig 4). In an analysis restricted to trials with monotherapy with newer P2Y12 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 P2Y12 inhibitor monotherapy compared with DAPT (0.89% vs 1.83%; hazard ratio 0.49, 0.39 to 0.63; P<0.001; \( \tau^2=0.03 \)), 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 P2Y12 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 P2Y12 inhibitors; P for interaction=0.02) (supplementary figure G). The use of a newer P2Y12 inhibitor was associated with treatment-by-subgroup interactions for clinical presentation (acute versus chronic coronary syndrome) and type of P2Y12 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 P2Y12 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 P2Y12 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 P2Y12 inhibitor

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**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.**

| Outcome | Intention to treat population | Per protocol population |
|---------|-----------------------------|-------------------------|
|         | P2Y12 inhibitor (n=11,674) | Aspirin + P2Y12 inhibitor (n=11,674) | Hazard ratio (95% CI) | \( \tau^2 \) | P value | P2Y12 inhibitor (n=10,766) | Aspirin + P2Y12 inhibitor (n=11,195) | Hazard ratio (95% CI) | \( \tau^2 \) | 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 | 0.18 |
| 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 |
| 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 (0.61 to 1.60) | 0.79 | 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) | 0.04 | 0.26 | 5 (0.05) | 2 (0.02) | 2.11 (0.40 to 12.09) | 0.00 | 0.16 |
| Definite | 23 (0.24) | 26 (0.28) | 0.85 (0.48 to 1.50) | 0.00 | 0.56 | 17 (0.20) | 25 (0.28) | 0.78 (0.38 to 1.64) | 0.00 | 0.29 |
| Probable | 6 (0.05) | 7 (0.06) | 0.72 (0.23 to 2.26) | 0.03 | 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) | 0.69 (0.39 to 0.63) | 0.00 | 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 (0.31 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 (1.98) | 331 (3.3) | 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 a of 5% corresponding to 90% CIs; other P values are two sided for superiority; 95% CIs are shown.
monotherapy and 173 (1.31%) with DAPT (hazard ratio 0.85, 0.68 to 1.06; P=0.14; $\tau^2=0.00$) 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 P2Y12 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 P2Y12 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 P2Y12 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 ($\tau^2=0.00$) (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 P2Y12 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 P2Y12 inhibitor monotherapy after revascularisation, including 24,096 patients mainly after percutaneous coronary intervention, provides strong evidence that P2Y12 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. P2Y12 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 P2Y12 inhibitor monotherapy...
owing to the lower risk of major adverse cardiovascular events, largely driven by a reduction in cardiovascular death. P2Y12 inhibitor monotherapy was associated with lower bleeding rates consistently across subgroups, although the magnitude of this treatment effect varied by the potency of the P2Y12 inhibitor in the experimental and control groups, which has important implications for practice.

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=P2Y12 inhibitor monotherapy; PCI=percutaneous coronary intervention
### Table 1: Sex stratified analysis for primary endpoint, all cause death, cardiovascular death, myocardial infarction, or stroke in intention to treat population.

| Primary outcome | Female | P2Y12i monotherapy (%) | Male | DAPT (%) | Hazard ratio (95% CI) | P value for interaction | Hazard ratio (95% CI) |
|-----------------|--------|------------------------|------|----------|-----------------------|------------------------|-----------------------|
| Stroke          |        | 59/2717 (2.3)          | 91/2706 (3.6) | 0.02 | 0.64 (0.46 to 0.89) |
|                 |        | 244/8917 (3.1)         | 247/8968 (3.2) | 1.00 | (0.83 to 1.19)     |
| Myocardial infarction | Female | 17/2717 (0.7)          | 39/2706 (1.7) | 0.002 | 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)     |
| All cause mortality | 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)     |
| Death           | 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=P2Y12 inhibitor monotherapy

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**Rationale for P2Y12 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 P2Y12 inhibition on a background of aspirin therapy, has gained consensus.1 4 14 22 However, this approach is poorly standardised and lacks prospective validation.17 An alternative approach consists of early aspirin withdrawal and continuation with P2Y12 inhibitor monotherapy up to 12 months after percutaneous coronary intervention or direct initiation of P2Y12 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.5 9 10 They mostly showed no excess of ischaemic events and lower bleeding rates with P2Y12 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.14

**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 P2Y12 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 P2Y12 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
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 aspirin and clopidogrel. However, confidence intervals were large for this comparison, including both benefit and harm. P2Y_{12} inhibitor monotherapy therefore seems particularly appealing in the choice of 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.12
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. However, all studies implemented blinded central endpoint adjudication, 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. We excluded events occurring while randomised groups received identical DAPT regimens in four 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, and the results remained largely consistent for either ischaemic or bleeding endpoints when stratified on the basis of clinical presentation.

Conclusions
P2Y₁₂ 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 P2Y₁₂ inhibitor, respectively. The data on P2Y₁₂ inhibitor monotherapy compared with DAPT after coronary artery bypass grafting is limited to a single trial and requires further investigation. Prasugrel monotherapy was used in a few patients within one trial and as protocol deviations in another. Four trials mandated the use of ticagrelor monotherapy, and only one trial allowed and stratified randomisation for all three oral P2Y₁₂ inhibitors. The duration of P2Y₁₂ 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, and the results remained largely consistent for either ischaemic or bleeding endpoints when stratified on the basis of clinical presentation.

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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.

AUTHOR AFFILIATIONS

1Cardiocentro Ticino Institute, Ente Ospedaliero Cantonale, Lugano, Switzerland
2Department of Cardiology, Bern University Hospital, University of Bern, Bern, Switzerland
3Department of Translational Medical Sciences, University of Campania Luigi Vanvitelli, Caserta, Italy
4Clinical Trials Unit, Bern, Switzerland
5Department of Advanced Biomedical Sciences, University of Naples Federico II, Naples, Italy
6Icahn School of Medicine at Mount Sinai, New York, NY, USA
7Severance Cardiovascular Hospital, Yonsei University College of Medicine, Seoul, South Korea
8Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan
9Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
10Department of Cardiovascular Surgery, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China
11Division of Cardiology, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA
12Department of Cardiology and Critical Care Medicine, Hartenrctum Hasselt, Jessa Ziekenhuis, Belgium
13Department of Medicine, McMaster University, Hamilton, ON, Canada
14Hamilton Health Sciences, Hamilton, ON, Canada
15Kokura Memorial Hospital, Department of Cardiology, Kitakyushu, Japan
16Department of Cardiology, National University of Ireland Galway, Galway, Ireland
17National Heart and Lung Institute, Imperial College London, London, UK
18Cardiology Core Laboratories and Clinical Trial Management, Rotterdam, Netherlands
19Department of Cardiology, Cork University Hospital, Cork, Ireland
20Division of Cardiology, University of Florida College of Medicine, Jacksonville, FL, USA
21Applied Health Research Centre of the Li Ka Shing Knowledge Institute, Department of Medicine, St Michael’s Hospital, University of Toronto, Toronto, ON, Canada

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PV has received consulting fees or honoraria from AstraZeneca, Bayer AG, Daiichi-Sankyo, and the Medicines Company outside the present work, and his institution has received research grants from Daiichi-Sankyo and Medtronic; PI serves as unpaid member of steering group or executive committee of trials funded by Abbott Vascular, Astra Zeneca, Biotronik, Biosensors, St Jude Medical, Terumo, and the Medicines Company and has received research grants to the institution from Appili Therapeutics, AstraZeneca, Biotronik, Biosensors International, Eli Lilly, and the Medicines Company and served as unpaid member of the selection committee in Switzerland; CMG has received personal fees from Pfizer during the conduct of the study, or honoraria from AstraZeneca, Bayer, Cellelithium, Bioveris, Medtronic, and personal fees from AstraZeneca, Biosensors, Gilead Sciences, Pfizer, and Scios, outside the submitted work; SW has received research and educational grants to the institution from Abbott, Amgen, CMS, Bayer, Boston Scientific, Biotronik, Cardiovalve, CSL Behring, Daiichi Sankyo, Edwards Lifesciences, johnson & johnson, Medtronic, Osprey Medical, PES, Pfizer, and Sanofi, outside the submitted work; RM has received grants from Abbott Laboratories, AstraZeneca, and has other relationships with Dyad Medical, outside the submitted work; HW has received personal fees from Abbott Medical Japan and Daiichi Sankyo, outside the submitted work; YZ has received grants and personal fees from AstraZeneca, personal fees from Novartis and Sanofi, personal fees and non-financial support from Medtronic, and grants and personal fees from ChugaiPharma, outside the submitted work; PWS has received personal fees from Sinomedical, SMT, Philips, Xelitis, Novartis, and Merilife, outside the submitted work; GDD has received grants from AstraZeneca during the conduct of the study and personal fees from Biosensors, grants from Abbott Vascular, Medtronic, Daiichi-Sankyo, and Bayer, and grants and personal fees from Boston Scientific, outside the submitted work; EPMF reports personal fees from Cardialysis BV, Rotterdam, Netherlands, outside the submitted work; DJA has received consulting fees or honoraria from Abbott, Amgen, Arael, AstraZeneca, Bayer, Biosensors, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Daiichi-Sankyo, Eli Lilly, Haemonetics, Janssen, Merck, PhaseBio, Plx Pharma, Pfizer, Sanofi, and the Medicines Company and payments for participation in review activities from CeloNova and St Jude Medical, outside the present work, and his institution has received research grants from Amgen, AstraZeneca, Bayer, Biosensors, CeloNova, CSL Behring, Daiichi-Sankyo, Eisai, Eli Lilly, Gilead, Janssen, MatsuMura Chemical Industry Co, Merck, Novartis, Osprey Medical, Renal Guard Solutions, and Scott R MacKenzie Foundation; 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Bayer, Beth Israel Deaconess, BMC, BSL Behring, DSI, Medtronic, Novartis Pharmaceuticals, and OrbusNeich and personal fees from Abbott Laboratories, Boston Scientific, Medscape/WebMD, Siemens Medical Solutions, PLx Opco Inc/dba PLx Pharma Inc, Roivant Sciences, Sanofi, Medtelligen, and Janssen Scientific Affairs, has other financial relationships with Abbott Laboratories, Abiomed, the Medicine Company, Regeneron Pharmaceuticals, and Bristol Myers Squibb, and has no financial support from and other relationships with Spectranetics/Philips/Volcano Corp and Watermark Research Partners, outside the submitted work, no other relationships or activities that could appear to have influenced the submitted work.

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Data sharing: Requests for data sharing should be sent to the corresponding author at marco.valgimigli@cardiocentro.org.

The manuscript’s guarantor 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 originally planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communication: The investigators will disseminate the study results through their social media outlets, including Twitter, Facebook, and LinkedIn. They will run dedicated #hashtag campaigns (#PSIDENY2, #MonosPY212, #MonosToX) to promote the main findings. The results will be also disseminated through scientific meetings and webinars. Press releases will be prepared for public engagement via general medicine and cardiology blogs and websites on request.

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Web appendix: Supplementary materials