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Ticagrelor or clopidogrel monotherapy versus dual antiplatelet therapy after coronary revascularisation: an individual patient data meta-analysis of randomised controlled trials

Marco Valgimigli,* Felice Gragnano,* Mattia Branca, Anna Franzone, Usman Baber, Takeshi Kimura, Yangsoo Jang, Joo-Yong Hahn, Qiang Zhao, Stephan Windecker, Charles M Gibson, Hirotoshi Watanabe, Byeong-Keuk Kim, Young Bin Song, Yunpeng Zhu, Pascal Vranckx, Shamir Mehta, Kenji Ando, Sung-Jin Hong, Hyeon-Cheol Gwon, Patrick W Serruys, George D Dangas, Eùgene P McFadden, Dominick J Angiolillo, Dik Heg, Paolo Calabrò, Peter Jüni,* Roxana Mehran* on behalf of the Single Versus Dual Antiplatelet Therapy (Sidney-3) Collaboration

Cardiocentro Ticino Institute, Ente Ospedaliero Cantonale, Lugano, Switzerland (Prof M. Valgimigli, MD, PhD); **Department of Cardiology, Bern University Hospital, University of Bern, Bern, Switzerland** (Prof M. Valgimigli, MD, PhD, Prof S. Windecker, MD); **Department of Translational Medical Sciences, University of Campania Luigi Vanvitelli, Caserta, Italy** (Dr F. Gragnano, MD, PhD, Prof P. Calabrò, MD, PhD); **Clinical Trials Unit, Bern, Switzerland** (Dr M. Branca, PhD, Dr D. Heg, PhD); **Department of Advanced Biomedical Sciences, University of Naples Federico II, Naples, Italy** (Dr A. Franzone, MD, PhD); **Icahn School of Medicine at Mount Sinai, New York, NY, USA** (Dr U. Baber, MD, Prof R. Mehran, MD, Prof G.D. Dangas, MD); **Kyoto University Graduate School of Medicine, Department of Cardiovascular Medicine, Kyoto, Japan** (Prof T. Kimura, MD, Dr H. Watanabe, MD); **Severance Cardiovascular Hospital, Yonsei University College of Medicine, Seoul, South Korea** (Prof Y. Jang, MD, PhD, Dr B.-K. Kim, MD, Dr Sung-Jin Hong, MD); **Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea** (Prof J.-Y. Hahn, MD, Dr Y.B. Song, MD, Dr H.-C. Gwon, MD); **Department of Cardiovascular Surgery, Ruijin Hospital Shanghai Jiao Tong University School of Medicine, Shanghai, China** (Prof Q. Zhao, MD, PhD,

Dr Y. Zhu, MD); **Division of Cardiology, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA** (Prof C.M. Gibson, MD); **Department of Cardiology and Critical Care Medicine, Hartcentrum Hasselt, Jessa Ziekenhuis, Belgium** (Prof P. Vranckx, MD, PhD); **Department of Medicine, McMaster University, Hamilton, Canada; Hamilton Health Sciences, Hamilton, Canada** (Prof S. Mehta, MD); **Kokura Memorial Hospital, Department of Cardiology, Kitakyushu, Japan** (Dr K. Ando, MD); **Department of Cardiology, National University of Ireland Galway, Galway, Ireland; NHLI, Imperial College London, London, UK** (Prof P.W. Serruys, MD); **Cardialysis Core Laboratories and Clinical Trial Management, Rotterdam, Netherlands; Department of Cardiology, Cork University Hospital, Cork, Ireland** (Dr E.P. McFadden, MD); **Division of Cardiology, University of Florida College of Medicine, Jacksonville, FL, USA** (Prof D.J. Angiolillo, MD, PhD); **Applied Health Research Centre of the Li Ka Shing Knowledge Institute, Department of Medicine, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada** (Dr P. Jüni, MD, PhD).

**: Equally contributing*

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Address for correspondence: Prof. Marco Valgimigli, Cardiocentro Ticino Institute, Ente Ospedaliero Cantonale, 6900 Lugano, Switzerland, Phone: 0041 091 805 31 11, Fax: 0041 091 805 31 11, Email: marco.valgimigli@eoc.ch

Summary

Background $P2Y_{12}$ inhibitor monotherapy is associated with similar fatal or non-fatal cardiovascular events and lower bleeding compared with dual antiplatelet therapy (DAPT). However, it remains unclear if the treatment effect differs depending on the type of $P2Y_{12}$ inhibitor.

Methods We performed a patient-level meta-analysis of randomised trials comparing $P2Y_{12}$ inhibitor monotherapy with DAPT after coronary revascularisation (PROSPERO, CRD42022347824). The primary endpoint was the non-inferiority of the composite of all-cause death, myocardial infarction, or stroke of ticagrelor or clopidogrel monotherapy versus DAPT at per-protocol analysis with a 1·15 margin for the hazard ratio (HR). Key secondary endpoints were Bleeding Academic Research Consortium (BARC) 3 or 5 bleeding and net adverse clinical events (including the primary endpoint and BARC 3 or 5 bleeding). Data were combined in a one-step mixed-effects meta-analysis.

Findings We identified and obtained data from seven trials including 26294 patients, of whom 24728 (DAPT=12571; ticagrelor=8458; clopidogrel=3654; prasugrel=45) were retained in the per-protocol analysis. Ticagrelor was non-inferior (HR 0·89, 95% CI 0·74-1·06, $p_{non\text{-}inferiority}$=0·004), whereas clopidogrel was not non-inferior (HR 1·37, 1·01-1·87, $p_{non\text{-}inferiority}$>0·99) to DAPT for the primary endpoint. There was evidence of treatment-by-type of $P2Y_{12}$ inhibitor monotherapy interaction for the primary endpoint ($p_{interaction}$=0·016), suggesting benefit with ticagrelor and harm with clopidogrel compared with DAPT. Risk of BARC 3 or 5 bleeding was lower with both ticagrelor (HR 0·47, 95% CI 0·36-0·62, p<0·001) and clopidogrel monotherapy (HR 0·49, 0·30-0·81, p=0·006; $p_{interaction}$=0·93). Net adverse clinical events were lower with ticagrelor (HR 0·75, 95% CI 0·64-0·87, p<0·001) but not with clopidogrel monotherapy (HR 1·00, 0·78-1·28, p=0·991; $p_{interaction}$=0·029).

Interpretation Ticagrelor but not clopidogrel monotherapy is non-inferior to DAPT for the risk of all-cause death, myocardial infarction, or stroke and is associated with lower net adverse clinical events compared with DAPT. The Risk of bleeding was lower with both ticagrelor and clopidogrel monotherapy than DAPT.

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Key words: $P2Y_{12}$ inhibitors – Aspirin – DAPT – Meta-analysis

INTRODUCTION

Dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor is recommended after coronary revascularisation to reduce the risk of cardiovascular ischaemic events.[1,2] However, prolonged DAPT is associated with an increased risk of bleeding.[3–5] Studies with an abbreviated DAPT duration followed by aspirin monotherapy showed lower bleeding but higher ischaemic risks, especially in patients with acute coronary syndrome or complex percutaneous coronary intervention (PCI) compared with standard DAPT.[6–8] Aspirin instead of $P2Y_{12}$ inhibitor cessation after a short course of DAPT has been more recently investigated.[9–14] A patient-level meta-analysis including 23308 patients undergoing coronary revascularisation showed that $P2Y_{12}$ inhibitor monotherapy, after 1- to 3-month DAPT, was associated with a similar risk of all-cause death, myocardial infarction, or stroke and a lower risk of major bleeding compared with standard DAPT.[15] However, the relatively small number of patients treated with clopidogrel monotherapy prevented conclusive evidence on whether the treatment effect of $P2Y_{12}$ inhibitor monotherapy might differ depending on the type of $P2Y_{12}$ inhibitor. Clopidogrel is associated with great inter-individual platelet response variability and 5-10% of patients are unresponsive to the treatment due to loss-of-function mutation homozygosity,[16] granting a *boxed warning* to the drug label by the U.S. Food and Drug Administration (FDA).

In a recent randomised trial including 4169 patients with acute coronary syndrome undergoing implantation of current-generation drug-eluting stents, clopidogrel monotherapy after 1 to 2 months of DAPT failed to attest non-inferiority to conventional DAPT for the net clinical benefit and was associated with a substantial increase in the rate of myocardial infarction.[17]

We conducted an updated individual participant data meta-analysis of the totality of available evidence from randomised trials that compared $P2Y_{12}$ inhibitor monotherapy with DAPT in patients who underwent coronary revascularisation to ascertain whether the treatment effect of monotherapy is modified by the type of $P2Y_{12}$ inhibitor.

METHODS

The protocol was prospectively registered with PROSPERO, number CRD42022347824. Methods and reporting follow the guidelines of the Preferred Reporting Items for a Systematic Review and Meta-analysis of Individual Participant Data (PRISMA-IPD) (**Table S1, appendix**).[18]

Search strategy and eligibility criteria

We performed a systematic review and individual participant data meta-analysis of randomised trials that compared $P2Y_{12}$ inhibitor monotherapy with DAPT in patients who underwent percutaneous or surgical coronary revascularisation on centrally adjudicated endpoints.

A previous search[15] was updated including unique citations from June 16, 2020, to June 22, 2022. Two investigators (FG, MB) assessed trial eligibility; a third investigator (MV) was consulted in case of disagreement. Randomised trials were identified by searches in Ovid Medline, EMBASE, and two websites (www.tctmd.com, and www.escardio.org) without language restrictions (**Supplemental methods, appendix**). Reference lists of collected articles were searched for additional trials.

Data collection and quality assessment

We contacted the principal investigators of eligible trials to request patient-level data in anonymised datasets. Data of six trials were available from a previous analysis.[15] For one additional study,[17] the dataset was obtained and pooled with other trials. Data were checked for integrity and completeness. Queries were solved with the principal investigators and the clean data were analysed. Two investigators (FG, MB) independently assessed the risk of bias using the revised version of the Cochrane risk-of-bias tool (RoB 2).[19] Disagreements were solved by discussion and, if unsolved, by consulting a third investigator (MV). Each trial had been approved by local ethics committees. All patients had provided written informed consent for inclusion in each trial.

Outcomes

The primary endpoint was the composite of all-cause death, myocardial infarction, or stroke. The key secondary endpoints were Bleeding Academic Research Consortium (BARC) 3 or 5 bleeding and net adverse clinical events, defined as the composite of the primary endpoint and BARC 3 or 5 bleeding. Outcome data were analysed throughout the duration of the randomised comparison of protocol-mandated $P2Y_{12}$ inhibitor monotherapy versus DAPT. Non-fatal components and disease-specific mortality were centrally adjudicated. Other secondary endpoints are described in the **appendix** (**Supplemental methods**).

Data analysis

We used a one-step meta-analysis to model individual patient data from available trials using a mixed-effects Cox regression model with baseline hazards stratified by trial, a random intercept to account for variation between trials in baseline risk, and a random slope to account for variation between trials in treatment effect. Treatment effects were expressed as hazard ratios (HRs) and 95% CIs. The extent of heterogeneity was estimated by assessing the variance of the random slope τ^2. We prespecified sensitivity analyses using a two-step approach with a DerSimonian-Laird random-effects model to combine trial-level estimates. Primary analyses were conducted separately for ticagrelor monotherapy and clopidogrel monotherapy. We first tested the non-inferiority of ticagrelor monotherapy and of clopidogrel monotherapy for the primary endpoint, each at one-sided alpha of 0·025. If the non-inferiority was met for either drug, we prespecified to test the superiority of the monotherapy with this drug for the primary endpoint at a two-sided alpha of 0·025. The prespecified non-inferiority margin was set at 1·15 on a HR scale,[15] which preserves 50% of the treatment effect of aspirin versus control reported in patients with prior myocardial infarction for the composite of vascular death, myocardial infarction, or stroke.[20] Non-inferiority analyses were performed in the per-protocol populations, which excluded patients violating enrolment criteria and/or who never received the assigned treatment. Superiority analyses were conducted in the intention-to-treat populations. All analyses were accompanied by interaction tests

to determine whether the treatment effect depends on the type of $P2Y_{12}$ inhibitor used in the experimental arm. In the primary per-protocol analysis, we report the one-sided p-value for non-inferiority; for all other analyses, we report two-sided p-values for superiority and two-sided 95% CIs to allow a conventional interpretation of the results. For descriptive purposes, we also estimated the cumulative incidence of events at 12 months after initiation of $P2Y_{12}$ inhibitor monotherapy using the Kaplan-Meier method without stratification by trial. As we anticipated a low number of patients assigned to prasugrel monotherapy, results for prasugrel were reported for descriptive purposes only. We censored all events that occurred during the initial DAPT phase, if present, and we only counted events that occurred after the time point at which the protocol specified the transition from DAPT to $P2Y_{12}$ inhibitor monotherapy in the experimental arm. 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. Three prespecified sensitivity analyses (i) included events that occurred during the initial DAPT phase, (ii) excluded patients that experienced non-fatal events during the initial DAPT phase, and (iii) censored all patients nine months after the start of $P2Y_{12}$ inhibitor monotherapy in the experimental group. An additional sensitivity analysis for overall mortality was performed including the GLOBAL LEADERS dataset[21] instead of GLASSY. Prespecified subgroup analyses of the primary endpoint were conducted. Methods to derive numbers needed to treat to benefit, and further details on the analysis are reported in the **appendix** (**Supplemental methods**).

Role of the funding source

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RESULTS

We identified 4110 unique citations, of which 4 were judged potentially eligible, and one was eligible for inclusion after full-text review, in addition to the six studies that were already available from a previous analysis (**Figure 1**). Patient-level data were sought and obtained for all eligible trials **(Tables S2-S3, appendix**). The endpoint definitions were largely consistent across trials (**Table S4, appendix**). All studies were sponsored by non-for-profit organisations. The risk of bias was judged as low in one trial and revealed some concerns in six unblinded trials (**Table S5, appendix**).

We obtained data for 27084 participants (**Figure S1, appendix**); 203 patients were excluded due to premature study termination or death occurring during the initial DAPT phase, which was common to both study arms in five trials,[9,11–13,17] and 587 patients from one study[10] owing to lack of approval for data sharing by Chinese regulatory authorities.

A total of 26294 patients were available for the primary intention-to-treat analysis, including 13126 assigned to $P2Y_{12}$ inhibitor monotherapy and 13168 assigned to DAPT. A total of 8956 patients on ticagrelor monotherapy, 4110 on clopidogrel monotherapy, and 60 on prasugrel monotherapy were compared with 8959, 4144, and 65 participants treated with DAPT, respectively. The per-protocol analysis excluded 1566 (5·95%) patients not fulfilling the prespecified criteria, mainly due to failure to implement the assigned treatment (**Figure S1, appendix**). The median treatment duration was 334 days (range: 10-12 months).

Baseline characteristics of the ticagrelor or clopidogrel monotherapy groups were well-balanced compared with the DAPT groups (**Table 1 and Table S6, appendix**). Mean age was 64 years with ticagrelor and 67 years with clopidogrel, and females comprised 23% of participants in both groups. Diabetes or chronic kidney disease was reported in 30·1% and 15·2% of cases receiving ticagrelor monotherapy and 35·4% and 24·8% of cases receiving clopidogrel monotherapy, respectively. Among patients assigned to ticagrelor monotherapy, the qualifying event for inclusion was an acute coronary syndrome in 64·7% of cases, whereas 35·3% of participants suffered from chronic coronary syndrome. The corresponding figures for acute and chronic coronary syndrome

at presentation in the clopidogrel monotherapy group were 63·1% and 36·9%, respectively. Ticagrelor monotherapy was compared with aspirin and ticagrelor or with aspirin and clopidogrel in 80·8% and 19·2% of the patients, respectively, whereas clopidogrel monotherapy was exclusively compared with aspirin and clopidogrel. Clinical characteristics of patients assigned to prasugrel monotherapy or aspirin and prasugrel are described in **Table S7** (**appendix**).

Ticagrelor monotherapy was non-inferior to DAPT in per-protocol (cumulative incidence at 12 months, 2·98% vs 3·42%, HR 0·89, 95% CI 0·74-1·06, τ^2<0·001, $p_{non\text{-}inferiority}$=0·004; $p_{superiority}$=0·194) and intention-to-treat (2·99% vs 3·45%, HR 0·89, 95% CI 0·75-1·06, τ^2<0·001, $p_{non\text{-}inferiority}$=0·004; $p_{superiority}$=0·182) analyses of the composite endpoint of all-cause death, myocardial infarction, or stroke (**Table 2, Figure 2**).

In intention-to-treat analyses, we found evidence that ticagrelor was associated with a reduced risk of all-cause death compared with DAPT (0·92% vs 1·42%, HR 0·72, 95% CI 0·54-0·97, τ^2<0·001, p=0·029), whereas the evidence for an association with cardiovascular death was weaker and did not reach conventional levels of statistical significance (0·60% vs 0·91%, HR 0·70, 0·49-1·01, τ^2<0·001, p=0·057). The risks of myocardial infarction (1·83% vs 1·97%, HR 0·94, 95% CI 0·75-1·17, τ^2<0·001, p=0·579), stroke (0·45% vs 0·32%, HR 1·18, 0·71-1·96, τ^2<0·001, p=0·516), and definite or probable stent thrombosis (0·30% vs 0·40%, HR 0·78, 0·46-1·32, τ^2<0·001, p=0·350) did not differ between the groups. The risk of BARC 3 or 5 bleeding was more than halved with ticagrelor (0·92% vs 1·96%, HR 0·47, 95% CI 0·36-0·62, τ^2=0·053, p<0·001) compared with DAPT (**Figure 2**), yielding a number needed to treat to benefit of 96. The net adverse clinical events were lower with ticagrelor monotherapy (3·80% vs 5·18%, HR 0·75, 95% CI 0·64-0·87, τ^2=0·047, p<0·001), with a number needed to treat to benefit of 77.

Clopidogrel monotherapy did not meet non-inferiority to DAPT in the per-protocol (2·76% vs 2·07%, HR 1·37, 95% CI 1·01-1·87, τ^2=0·034, $p_{non\text{-}inferiority}$>0·99; $p_{superiority}$=0·042) and intention-to-treat analyses (2·90 vs· 2·38%; HR 1·24, 95% CI 0·94-1·63, τ^2=0·140, $p_{non\text{-}inferiority}$>0·99; $p_{superiority}$=0·134) for the composite endpoint of all-cause death, myocardial infarction, or stroke (**Table 3, Figure 3**). In intention-to-treat analyses, the risks of all-cause death (1·31% vs 0·97%, HR 1·33, 95% CI 0·87-

2·03, τ^2<0·001, p=0·187), cardiovascular death (0·44% vs 0·61%, HR 0·72, 0·38-1·33, τ^2<0·001, p=0·293), myocardial infarction (1·07% vs 0·86%, HR 1·26, 0·79-2·01, τ^2=0·419, p=0·323), stroke (0·61% vs 0·59%, HR 1·10, 0·62-1·97, τ^2=0·307, p=0·742), and definite or probable stent thrombosis (0·22% vs 0·09%, HR 2·69, 0·71-10·14, τ^2<0·001, p=0·144) did not significantly differ. The risk of BARC 3 or 5 bleeding was lower with clopidogrel monotherapy (0·59% vs 1·20%, HR 0·49, 95% CI 0·30-0·81, τ^2=0·415, p=0·006; number needed to treat to benefit=163) (**Figure 3**) and the risk of net adverse clinical events was similar (3·29% vs 3·28%, HR 1·00, 0·78-1·28, τ^2=0·079, p=0·991) compared with DAPT.

Clinical outcomes in patients with prasugrel monotherapy or DAPT are shown in **Table S8**.

There was evidence for an interaction with the type of monotherapy (i.e., ticagrelor or clopidogrel) for the primary endpoint of all-cause death, myocardial infarction, or stroke, the composite of death or myocardial infarction, all-cause death alone, and net adverse clinical events in per-protocol and intention-to-treat analyses (**Figure 4 and Figure S2, appendix**).

Subgroup analyses of the composite endpoint of all-cause death, myocardial infarction, or stroke suggested variation in the effect of ticagrelor monotherapy by sex and diabetes, whereas the treatment effect was consistent for clopidogrel monotherapy compared with DAPT (**Figure 5 and Figures S3-S5, appendix**).

Prespecified sensitivity analyses

Results for the primary and key secondary endpoints remained consistent after inclusion of events occurring during the initial DAPT phase, right censoring events nine months after the start of $P2Y_{12}$ inhibitor monotherapy, exclusion of patients with non-fatal ischaemic events, bleeding events or both during the initial DAPT phase, and in two-step random-effects models (**Figures S6-S9, Table S9-S15, appendix**). The incidence of all-cause death was 0·92% with ticagrelor and 1·36% with DAPT (HR 0·77, 95% CI 0·60-0·98, τ^2<0·001, p=0·033) when GLOBAL LEADERS was included in the analysis instead of GLASSY.

DISCUSSION

The results of this updated individual patient data meta-analysis of the totality of available trials, including 26294 patients who underwent coronary revascularisation, provide evidence that the treatment effects of $P2Y_{12}$ inhibitor monotherapy compared with DAPT continuation vary depending on the type of $P2Y_{12}$ inhibitor. Ticagrelor monotherapy, after a short course of DAPT, was non-inferior for the composite of all-cause death, myocardial infarction, or stroke and superior for the prevention of major bleeding and their combined appraisal in the net adverse clinical event endpoint compared with DAPT continuation. Clopidogrel monotherapy, after a short course of DAPT, did not meet non-inferiority in intention-to-treat and per-protocol analyses, and was associated with a significantly higher risk of all-cause death, myocardial infarction, or stroke in a per-protocol analysis. Subgroup analyses by type of $P2Y_{12}$ inhibitor monotherapy (ticagrelor or clopidogrel) suggested a qualitative interaction for the composites of all-cause death, myocardial infarction, or stroke, death or myocardial infarction, and all-cause death alone, suggesting a benefit of ticagrelor and harm of clopidogrel monotherapy.

A prolonged DAPT regimen has proven superior for the prevention of combined cardiovascular fatal or non-fatal endpoints when compared with abbreviated DAPT regimens followed by aspirin monotherapy.[6–8] However, prolonged DAPT increases bleeding risk, which offsets the anticipated ischaemic benefits in patients with high bleeding or low ischaemic risks.[3–5] Guidelines recommend DAPT duration be guided by ischaemic and bleeding risks assessment;[1,2] however, they do not provide clear guidance on which treatment strategy should be preferred for the large segment of patients in whom both risks are similar.

Given the central role of platelet $P2Y_{12}$ receptor signalling on thrombotic complications and the established association between aspirin and bleeding (particularly gastrointestinal bleeding),[22] discontinuation of aspirin but not of the $P2Y_{12}$ inhibitor could be a bleeding reduction strategy that preserves ischaemic protection.[23,24] Recent trials investigated $P2Y_{12}$ inhibitor monotherapy, mainly using ticagrelor or clopidogrel, rather than aspirin monotherapy after a short course of DAPT.[9–14] When singularly appraised, each of these trials suffers from limitations inherent to study design,

study power, or both, hampering definitive conclusions for practice.[9–14] Aggregate data meta-analyses have shown similar ischaemic and lower bleeding risks with $P2Y_{12}$ inhibitor monotherapy compared with DAPT continuation but did not investigate the role of type of $P2Y_{12}$ inhibitor after DAPT cessation.[25,26] In a prior individual patient data meta-analysis,[15] there was no evidence of treatment effect heterogeneity between clopidogrel and newer $P2Y_{12}$ inhibitors. However, only 2586 patients (22.2%) received clopidogrel monotherapy, whereas 9048 patients (77.8%) underwent monotherapy with newer $P2Y_{12}$ inhibitors.[15]

The current updated meta-analysis includes almost twice as many patients with clopidogrel monotherapy than previously.[15] We observed that clopidogrel monotherapy after 1 to 3 months of DAPT was associated with a non-significant 24% and significant 37% higher risk of the primary endpoint in intention-to-treat and per-protocol analyses, respectively, compared with DAPT using aspirin and clopidogrel. All three components of the primary endpoint, namely all-cause death, myocardial infarction, and stroke, were numerically more frequent with clopidogrel than DAPT, especially in per-protocol analyses. These results remained consistent across several prespecified subgroups, but an appraisal of absolute risks suggests that the signal of harm may be particularly relevant in patients with acute coronary syndromes. Conversely, the observed bleeding benefit associated with clopidogrel monotherapy and the resulting null effect on net adverse clinical events suggests that this treatment strategy might be justified in selected patients in whom bleeding concerns far exceed concerns about ischaemic risk.

Our individual patient data meta-analysis provides evidence that aspirin discontinuation 1 to 3 months after coronary revascularisation followed by ticagrelor monotherapy is safer and at least as effective as standard DAPT. Non-inferiority was established based on a 15% relative margin on the HR scale for the primary endpoint; the upper limits of the two-sided 95% CIs of both per-protocol and intention-to-treat analyses was compatible with a relative risk increase up to 6% compared with DAPT. This residual possibility of a small risk increase needs to be interpreted against the observed 50% relative reduction of major bleeding and 25% relative reduction of net adverse clinical events. In addition, we observed a nominally significant 28% reduction in overall mortality

with ticagrelor monotherapy. The mortality benefit might be related to the substantial reduction in major bleeding, which has a well-known prognostic effect on mortality.[27,28] Aspirin at daily doses >80 mg inhibits the endothelial release of prostacyclin, which reduces platelet reactivity and may contribute synergistically in vivo to the antiplatelet effects of $P2Y_{12}$ inhibitors.[29] The observation of more pronounced benefits with ticagrelor monotherapy on the primary composite endpoint in females or patients with diabetes remains hypothesis-generating. In the latest update of the Antithrombotic Trialists' Collaboration,[20] among 4961 patients with diabetes from nine trials, aspirin was associated with only a non-significant 7% proportional reduction in serious vascular events, which remained consistent, however, with the reduction of about one quarter observed overall.

Our findings are consistent with the combined analysis of the four pivotal trials on dual antithrombotic treatment compared with triple therapy after PCI or acute coronary syndrome in patients with an indication to oral anticoagulation.[30] In these studies, clopidogrel was used in more than 90% of the patients and early aspirin withdrawal was associated with greater risks of myocardial infarction and stent thrombosis.[30]

The reasons why concomitant administration of aspirin appears critical with clopidogrel but not ticagrelor remain speculative. In a sizable proportion of patients, the conversion of clopidogrel into clopidogrel active metabolite is absent or suboptimal, leading to large variability in treatment response, including no measurable effects on platelet aggregation.[16] Early aspirin withdrawal in clopidogrel non-responders implies no or minimal antiplatelet treatment effect from a few months after coronary revascularisation onwards. Ticagrelor, similarly to prasugrel, exerts a more profound and consistent $P2Y_{12}$ receptor inhibition than clopidogrel.[31] The very small number of patients treated with prasugrel monotherapy and the lack of pharmacodynamic data in our study prevent conclusively assessing whether, irrespective of the type of $P2Y_{12}$ inhibitor used, higher on-treatment residual $P2Y_{12}$-related platelet reactivity explains the differential treatment effects with ticagrelor or clopidogrel monotherapy.

This analysis has several strengths. Combining patient-level data from seven large trials allowed a precise quantification of the risks and benefits associated with aspirin withdrawal on a background

therapy of either ticagrelor or clopidogrel. For this purpose, we left-censored all clinical events that occurred during the initial DAPT phase, which was identical in both experimental and control arms in five trials and, if included, might have biased treatment estimates towards the null. Our findings were corroborated by multiple sensitivity analyses, which suggested that the observed treatment effect was robust after inclusion or exclusion of patients who experienced non-fatal events during the initial DAPT phase.

The current meta-analysis should be interpreted in view of possible limitations. The study is subject to the shortcomings of the original trials, including the open-label design in six trials.[9–14,17] Of note, all studies implemented independent events adjudication and endpoint definitions were largely consistent across trials. This analysis offers limited information on the choice of antiplatelet therapy after coronary artery bypass grafting. Only a small study testing ticagrelor monotherapy and powered for angiographic endpoints was eligible.[14] Further investigations are warranted to assess the effects of different antiplatelet strategies in this setting. The duration of the comparison between $P2Y_{12}$ inhibitor monotherapy and DAPT varied between 9 and 12 months across studies. However, findings were consistent after right censoring follow-up at 9 months to achieve uniform duration. Prasugrel monotherapy was under-represented in our dataset and allowed only in one trial with stratified randomisation for $P2Y_{12}$ inhibitors.[12] Therefore, no conclusions can be drawn regarding this strategy.

In conclusion, monotherapy with ticagrelor but not with clopidogrel was associated with non-inferior risk of all-cause death, myocardial infarction, or stroke and a lower risk of net adverse clinical events compared with DAPT. The risk of major bleeding was reduced to a similar extent with both ticagrelor and clopiodogrel monotherapy compared with DAPT continuation. Data on prasugrel monotherapy are limited and inconclusive. Our findings, based on available randomised evidence, suggest that the treatment effect of $P2Y_{12}$ inhibitor monotherapy, after a short-term DAPT, varies depending on the type of $P2Y_{12}$ inhibitor. Whether the on-treatment degree and consistency of $P2Y_{12}$ receptor inhibition, achieved with different drugs, explain our findings requires further investigations.

RESEARCH IN CONTEXT

Evidence before this study

We searched Ovid Medline, EMBASE, and two websites (www.tctmd.com, www.escardio.org) without language restrictions for randomised trials reported up to June 22, 2022, that compared $P2Y_{12}$ monotherapy with dual antiplatelet therapy (DAPT) after coronary revascularisation. Most of the evidence showed similar risk of ischaemic events and lower risk of bleeding with $P2Y_{12}$ inhibitor monotherapy compared with conventional DAPT. However, individual trials were not designed to assess whether the treatment effect was modified by the type of $P2Y_{12}$ inhibitor. A previous patient-level data meta-analysis of six trials observed that $P2Y_{12}$ inhibitor monotherapy was associated with a similar risk of death, myocardial infarction, or stroke and a lower risk of bleeding compared with DAPT, irrespective of baseline risks and type of $P2Y_{12}$ inhibitor. At variance with this evidence, in the subsequent STOPDAPT-2 ACS trial, clopidogrel monotherapy after 1- to 2-month DAPT failed to attest non-inferiority to standard DAPT in patients undergoing drug-eluting stent implantation for acute coronary syndrome. These findings questioned the role of clopidogrel monotherapy after a short DAPT, particularly in high-risk subsets, and raised uncertainties as to whether the treatment effect of $P2Y_{12}$ inhibitor monotherapy could depend on the type of $P2Y_{12}$ inhibitor.

Added value of this study

This updated individual participant data meta-analysis included all available randomised controlled trials assessing the efficacy and safety of $P2Y_{12}$ inhibitor monotherapy versus standard DAPT in patients who underwent coronary revascularisation on centrally adjudicated endpoints, with a focus on whether the treatment e ect of aspirin removal could depend on the type of the $P2Y_{12}$ antagonist. Our analysis, including 26294 patients, provides evidence, for the first time, that the treatment effect of $P2Y_{12}$ inhibitor monotherapy depends on the type of $P2Y_{12}$ inhibitor used after aspirin withdrawal. We observed that ticagrelor monotherapy was non-inferior for the primary

endpoint of all-cause death, myocardial infarction, or stroke and superior for major bleeding and net adverse clinical events compared with DAPT. There was no signal of greater ischaemic risk for the primary endpoint with ticagrelor monotherapy across the prespecified subgroups, whereas females and patients with diabetes might derive significant benefits with ticagrelor monotherapy than DAPT. Clopidogrel monotherapy was inferior to DAPT in the per-protocol analysis and failed to reach non-inferiority to DAPT in the intention-to-treat analysis. Clopidogrel monotherapy, while reducing major bleeding to similar extent to ticagrelor monotherapy compared with DAPT, was not associated with a lower risk of net adverse clinical events.

Implications of all the available evidence

Our study supports the use of ticagrelor monotherapy, from 1 to 3 months after DAPT, to reduce the risk of major bleeding and net adverse events compared with standard 12-month DAPT after coronary revascularisation. Clopidogrel monotherapy after a few months of DAPT does not provide similar protection from recurrent cardiovascular events compared with aspirin and clopidogrel continuation and might be justified only in selected patients in whom concerns over bleeding prevail on ischaemic risks.

Contributors

MV and RM, conceived, designed, and interpreted the study, drafted the manuscript, revised and approved the final manuscript. FG and PJ designed the study, analysed and interpreted data, revised and approved the final manuscript. MB and DH analysed and interpreted data, revised and approved the final manuscript. AF, UB, TK, YJ, J-YH, QZ, SW, CMG, B-KK, HW, YBS, YZ, PWS, GDD, EPMF, DJA, PV, SRM, S-JH, KA, H-CG, and PC designed the study, interpreted data, revised and approved the final manuscript.

Declaration of interests

MV reports personal fees from Astra Zeneca, grants and personal fees from Terumo, personal fees from Alvimedica/CID, personal fees from Abbott Vascular, personal fees from Daiichi Sankyo, personal fees from Bayer, personal fees from CoreFLOW, personal fees from IDORSIA PHARMACEUTICALS LTD, personal fees from Universität Basel | Dept. Klinische Forschung, personal fees from Bristol Myers Squib SA, personal fees from Medscape, personal fees from Biotronik, personal fees from Novartis, outside the submitted work.

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Data sharing

Requests for data sharing should be sent to the corresponding author at marco.valgimigli@eoc.ch

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FIGURE TITLE AND LEGEND

Figure 1. Study selection. PRISMA individual participant data flow diagram. IPD=individual participant data.

Figure 2. Kaplan-Meier estimates for clinical outcomes in patients receiving ticagrelor monotherapy or DAPT.

(A) All-cause death, myocardial infarction, or stroke (primary endpoint). (B) BARC type 3 or 5 bleeding. (C) Net adverse clinical events. (D) All-cause death. DAPT=dual antiplatelet therapy.

Figure 3. Kaplan-Meier estimates for clinical outcomes in patients receiving clopidogrel monotherapy or DAPT.

(A) All-cause death, myocardial infarction, or stroke (primary endpoint). (B) BARC type 3 or 5 bleeding. (C) Net adverse clinical events. (D) All-cause death. DAPT=dual antiplatelet therapy.

Figure 4. Primary endpoint or its components and key secondary endpoints stratified by the use of ticagrelor or clopidogrel monotherapy in the per-protocol population.

BARC=Bleeding Academy Research Consortium; CV=cardiovascular; DAPT=dual antiplatelet therapy; MI=myocardial infarction; NACE=net adverse clinical events; P2Y12i=P2Y12 inhibitor.

Figure 5. Treatment effect of ticagrelor monotherapy across subgroups for the primary endpoint in the intention-to-treat population.

*European regions pooled together and within study and across study interactions merged owing to trial designs.

ACS=acute coronary syndrome; CAD=coronary artery disease; CKD=chronic kidney disease; DAPT=dual antiplatelet therapy; LAD=left anterior descending artery; PCI=percutaneous coronary intervention.

Table 1. Baseline characteristics in patients with ticagrelor or clopidogrel monotherapy or DAPT.

	Ticagrelor monotherapy (N=8956)	Aspirin + $P2Y_{12}$ inhibitor (N=8959)	p value	Clopidogrel monotherapy (N=4110)	Aspirin + $P2Y_{12}$ inhibitor (N=4144)	p value
Study ID						
DACAB	166 (1·9%)	168 (1·9%)	0·956	0 (0·0%)	0 (0·0%)	-
GLASSY	3753 (41·9%)	3756 (41·9%)	0·988	0 (0·0%)	0 (0·0%)	-
SMART-CHOICE	273 (3·0%)	263 (2·9%)	0·661	1122 (27·3%)	1143 (27·6%)	0·786
STOPDAPT-2	0 (0·0%)	0 (0·0%)	-	1496 (36·4%)	1507 (36·4%)	0·982
STOPDAPT-2 ACS	0 (0·0%)	0 (0·0%)	-	1492 (36·3%)	1494 (36·1%)	0·819
TICO	1499 (16·7%)	1505 (16·8%)	0·920	0 (0·0%)	0 (0·0%)	-
TWILIGHT	3265 (36·5%)	3267 (36·5%)	>0·99	0 (0·0%)	0 (0·0%)	-
Age, years (SD)	(n=8956) 64·2 ± 10·5	(n=8959) 64·2 ± 10·5	0·959	(n=4110) 67·1 ± 11·2	(n=4144) 67·2 ± 11·2	0·896
Age ≥65 years	4431/8956 (49·5%)	4393/8959 (49·0%)	0·560	2568/4110 (62·5%)	2570/4144 (62·0%)	0·666
Female sex	2060/8956 (23·0%)	2015/8959 (22·5%)	0·416	972/4110 (23·6%)	989/4144 (23·9%)	0·818
Height, meters (SD)	(n=8781) 1·7 ± 0·1	(n=8785) 1·7 ± 0·1	0·997	(n=4108) 1·6 ± 0·1	(n=4141) 1·6 ± 0·1	0·425
Weight, kg (SD)	(n=8784) 80·2 ± 17·3	(n=8784 80·1 ± 17·0	0·654	(n=4110) 65·1 ± 12·4	(n=4142) 65·0 ± 12·2	0·697
Mean BMI, kg/m2 (SD)	(n=8781) 27·7 ± 5·0	(n=8782) 27·7 ± 5·0	0·736	(n=4108) 24·3 ± 3·5	(n=4141) 24·3 ± 3·4	0·899
Geographic region	n=8956	n=8959		n=4110	n=4144	
Asia	2468 (27·6%)	2457 (27·4%)	0·854	4110 (100·0%)	4144 (100·0%)	-
North America	1484 (16·6%)	1488 (16·6%)	0·952	0 (0·0%)	0 (0·0%)	-
Western Europe	3917 (43·7%)	3931 (43·9%)	0·857	0 (0·0%)	0 (0·0%)	-
Eastern Europe	1087 (12·1%)	1083 (12·1%)	0·927	0 (0·0%)	0 (0·0%)	-
Diabetes mellitus	2699/8955 (30·1%)	2653/8959 (29·6%)	0·441	1455/4107 (35·4%)	1438/4144 (34·7%)	0·489
Insulin-treated diabetes	618/8591 (7·2%)	652/8601 (7·6%)	0·332	164/3425 (4·8%)	192/3429 (5·6%)	0·130
Current cigarette smoker	2452/8953 (27·4%)	2567/8957 (28·7%)	0·058	1172/4109 (28·5%)	1070/4141 (25·8%)	0·006
Hypercholesterolaemia	5667/8820 (64·3%)	5737/8828 (65·0%)	0·307	2599/4106 (63·3%)	2631/4137 (63·6%)	0·778
Hypertension	6139/8947 (68·6%)	6129/8947 (68·5%)	0·872	2803/4109 (68·2%)	2869/4144 (69·2%)	0·319
Liver disease	15/8517 (0·2%)	8/8528 (0·1%)	0·143	10/2988 (0·3%)	6/3001 (0·2%)	0·312
PAD	516/7438 (6·9%)	565/7439 (7·6%)	0·122	136/4108 (3·3%)	151/4143 (3·6%)	0·408

Previous MI	1961/8949 (21·9%)	1960/8957 (21·9%)	0·960	357/4109 (8·7%)	331/4143 (8·0%)	0·251
Previous PCI	2790/8788 (31·7%)	2832/8788 (32·2%)	0·497	796/4108 (19·4%)	818/4143 (19·7%)	0·674
Previous CABG	571/8953 (6·4%)	594/8957 (6·6%)	0·491	41/4108 (1·0%)	58/4143 (1·4%)	0·094
Prior stroke	177/8950 (2·0%)	194/8957 (2·2%)	0·377	233/4108 (5·7%)	261/4144 (6·3%)	0·230
Prior bleeding	58/8948 (0·6%)	54/8954 (0·6%)	0·702	82/4107 (2·0%)	85/4143 (2·1%)	0·859
History of CKD	1336/8814 (15·2%)	1359/8825 (15·4%)	0·655	1018/4109 (24·8%)	1022/4144 (24·7%)	0·906
Chronic lung disease	363/7113 (5·1%)	379/7122 (5·3%)	0·558	66/2988 (2·2%)	81/3001 (2·7%)	0·220
Clinical presentation	n=8955	n=8959		n=4110	n=4142	
CCS	3160 (35·3%)	3136 (35·0%)	0·691	1515 (36·9%)	1514 (36·6%)	0·771
ACS	5795 (64·7%)	5823 (65·0%)		2595 (63·1%)	2628 (63·4%)	
Unstable angina	2189 (37·8%)	2228 (38·3%)	0·593	826 (31·8%)	866 (33·0%)	0·391
Non-STEMI	2320 (40·0%)	2328 (40·0%)	0·955	528 (20·3%)	557 (21·2%)	0·453
STEMI	1286 (22·2%)	1267 (21·8%)	0·575	1241 (47·8%)	1205 (45·9%)	0·157
Aspirin on admission	6318/8955 (70·6%)	6336/8958 (70·7%)	0·794	250/1122 (22·3%)	257/1141 (22·5%)	0·890
PRECISE-DAPT (SD)*	(n=8340) 16·3 ± 8·8	(n=8374) 16·3 ± 8·9	0·825	(n=4054) 17·1 ± 10·9	(n=4099) 17·2 ± 10·9	0·563
PRECISE-DAPT ≥25	(n=8340) 1336 (16·0%)	1342/8374 (16·0%)	0·991	786/4054 (19·4%)	787/4099 (19·2%)	0·829
Creatinine clearance (MDRD), ml/min (IQR)	(n=8811) 83·5 (69·7; 98·4)	(n=8823) 83·0 (69·0; 98·2)	0·167	(n=4070) 90·5 (73·9; 108·4)	(n=4110) 90·6 (74·3; 107·4)	0·608
Haemoglobin, g/dl (SD)	(n=8650) 14·1 ± 1·6	(n=8667) 14·1 ± 1·7	0·643	(n=4073) 13·7 ± 1·9	(n=4106) 13·7 ± 2·8	0·970
LVEF, % (SD)	(n=4435) 54·2 ± 10·8	(n=4409) 54·3 ± 11·1	0·685	(n=3747) 58·7 ± 10·8	(n=3800) 58·8 ± 10·7	0·633

Data expressed as n (%) or means ± standard deviations (SD) or median (interquartile range [IQR]).
*The PRECISE-DAPT score includes 5 items: age, creatinine clearance, white-blood-cell count, haemoglobin, and history of bleeding.

ACS=acute coronary syndrome; BMI=body-mass index; CABG=coronary artery bypass grafting; CCS=chronic coronary syndrome; CKD=chronic kidney disease; g/dl=grams per deciliter; LVEF=left ventricular ejection fraction; ml/min=milliliter per minute; MDRD=Modification of Diet in Renal Disease; MI=myocardial infarction; PAD=peripheral artery disease; PCI=percutaneous coronary intervention; STEMI=ST-segment elevation myocardial infarction.

Table 2. Clinical outcomes in patients with ticagrelor monotherapy or DAPT.

	Intention-to-treat population					Per-protocol population				
Outcome	**Ticagrelor monotherapy (N=8956)**	**Aspirin + $P2Y_{12}$ inhibitor (N=8959)**	**HR (95% CI)**	**Tau²**	**p value**	**Ticagrelor monotherapy (N=8458)**	**Aspirin + $P2Y_{12}$ inhibitor (N=8648)**	**HR (95% CI)**	**Tau²**	**p value**
Death, MI, or stroke*	242 (2·99%)	273 (3·45%)	0·89 (0·75-1·06)	<0·001	0·182	228 (2·98%)	262 (3·42%)	0·89 (0·74-1·06)	<0·001	0·194
Death or MI	214 (2·62%)	250 (3·18%)	0·86 (0·71-1·03)	<0·001	0·099	202 (2·61%)	243 (3·19%)	0·85 (0·70-1·02)	<0·001	0·084
Death										
All cause	78 (0·92%)	110 (1·42%)	0·72 (0·54-0·97)	<0·001	0·029	78 (0·97%)	106 (1·41%)	0·77 (0·57-1·03)	<0·001	0·080
Cardiovascular	50 (0·60%)	71 (0·91%)	0·70 (0·49-1·01)	<0·001	0·057	50 (0·63%)	69 (0·91%)	0·74 (0·51-1·06)	<0·001	0·103
Non-cardiovascular	24 (0·27%)	34 (0·46%)	0·73 (0·43-1·23)	<0·001	0·237	24 (0·29%)	33 (0·46%)	0·78 (0·46-1·32)	<0·001	0·348
Myocardial infarction	148 (1·83%)	158 (1·97%)	0·94 (0·75-1·17)	<0·001	0·579	136 (1·78%)	154 (1·99%)	0·90 (0·72-1·14)	0·040	0·392
Stroke										
Any	35 (0·45%)	28 (0·32%)	1·18 (0·71-1·96)	<0·001	0·516	33 (0·45%)	24 (0·29%)	1·33 (0·78-2·26)	<0·001	0·299
Ischaemic	28 (0·37%)	21 (0·24%)	1·24 (0·70-2·21)	0·096	0·461	27 (0·37%)	19 (0·23%)	1·36 (0·75-2·47)	0·002	0·314
Haemorrhagic	3 (0·03%)	1 (0·01%)	3·01 (0·31-28·91)	<0·001	0·340	3 (0·04%)	1 (0·01%)	3·07 (0·32-29·56)	<0·001	0·331
Stent thrombosis										
Definite	21 (0·27%)	25 (0·33%)	0·80 (0·44-1·44)	<0·001	0·46	17 (0·24%)	24 (0·33%)	0·72 (0·38-1·33)	<0·001	0·293
Probable	3 (0·03%)	6 (0·07%)	0·50 (0·13-2·01)	<0·001	0·329	3 (0·04%)	6 (0·07%)	0·51 (0·13-2·06)	<0·001	0·346
Definite or probable	24 (0·30%)	31 (0·40%)	0·78 (0·46-1·32)	<0·001	0·350	20 (0·27%)	30 (0·40%)	0·68 (0·38-1·19)	<0·001	0·175
BARC bleeding										
2, 3 or 5	251 (3·14%)	409 (5·05%)	0·61 (0·52-0·71)	0·045	<0·001	240 (3·16%)	397 (5·06%)	0·61 (0·52-0·72)	0·034	<0·001
3 or 5	78 (0·92%)	164 (1·96%)	0·47	0·053	<0·00	74 (0·92%)	146 (1·81%)	0·52	0·070	<0·00

			(0·36-0·62)		1			(0·39-0·68)		1
5	2 (0·03%)	2 (0·04%)	1·00 (0·14-7·11)	<0·001	>0·99	2 (0·03%)	2 (0·04%)	1·04 (0·15-7·35)	<0·001	0·972
TIMI bleeding										
Major	41 (0·52%)	80 (1·02%)	0·51 (0·35-0·75)	0·297	<0·001	41 (0·55%)	72 (0·95%)	0·58 (0·39-0·85)	0·235	0·005
Minor	134 (1·74%)	238 (2·97%)	0·56 (0·45-0·69)	<0·001	<0·001	130 (1·78%)	226 (2·92%)	0·57 (0·46-0·71)	<0·001	<0·001
Major or minor	174 (2·26%)	314 (3·97%)	0·55 (0·45-0·66)	0·040	<0·001	170 (2·32%)	295 (3·87%)	0·57 (0·47-0·69)	0·055	<0·001
NACE	310 (3·80%)	414 (5·18%)	0·75 (0·64-0·87)	0·047	<0·001	292 (3·78%)	385 (4·99%)	0·77 (0·66-0·90)	0·037	0·001

*P value for non-inferiority=0.004 of ticagrelor monotherapy versus DAPT in per-protocol population.

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 3 or 5 bleeding; TIMI=Thrombolysis in Myocardial Infarction.

Table 3. Clinical outcomes in patients with clopidogrel monotherapy or DAPT.

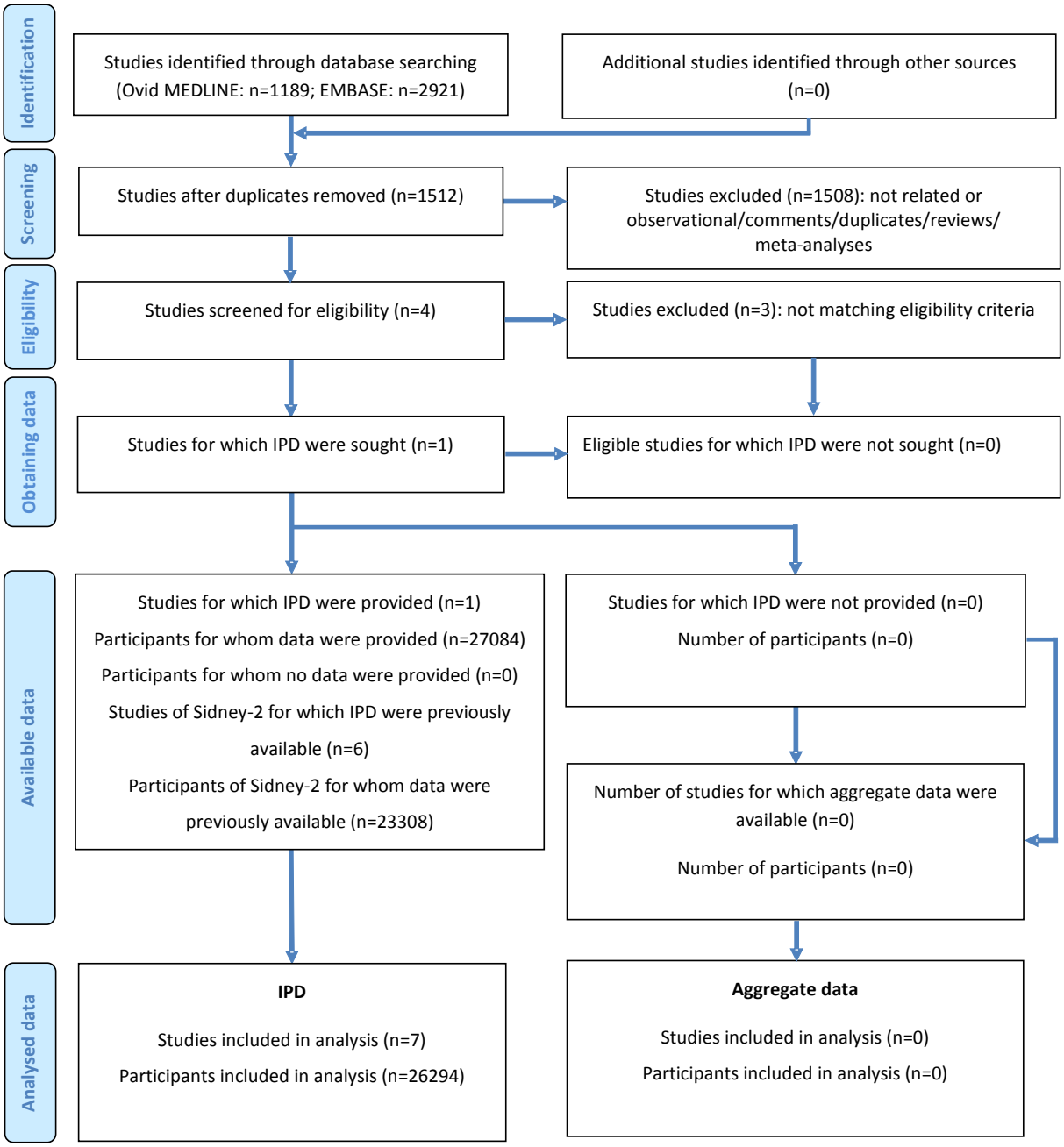
	Intention-to-treat population					Per-protocol population				
Outcome	**Clopidogrel monotherapy (N=4110)**	**Aspirin + $P2Y_{12}$ inhibitor (N=4144)**	**HR (95% CI)**	**Tau^2**	**p value**	**Clopidogrel monotherapy (N=3654)**	**Aspirin + $P2Y_{12}$ inhibitor (N=3860)**	**HR (95% CI)**	**Tau^2**	**p value**
Death, MI, or stroke*	110 (2·90%)	90 (2·38%)	1·24 (0·94-1·63)	0·140	0·134	94 (2·76%)	73 (2·07%)	1·37 (1·01-1·87)	0·034	0·042
Death or MI	87 (2·30%)	69 (1·81%)	1·27 (0·93-1·75)	0·187	0·132	75 (2·2%)	60 (1·67%)	1·33 (0·95-1·87)	0·056	0·096
Death										
All cause	50 (1·31%)	38 (0·97%)	1·33 (0·87-2·03)	<0·001	0·187	46 (1·34%)	30 (0·82%)	1·64 (1·03-2·59)	<0·001	0·036
Cardiovascular	17 (0·44%)	24 (0·61%)	0·72 (0·38-1·33)	<0·001	0·293	17 (0·49%)	18 (0·48%)	1·03 (0·53-2·00)	<0·001	0·926
Non-cardiovascular	33 (0·87%)	14 (0·37%)	2·38 (1·27-4·44)	<0·001	0·007	29 (0·84%)	12 (0·34%)	2·52 (1·29-4·95)	<0·001	0·007
Myocardial infarction	40 (1·07%)	32 (0·86%)	1·26 (0·79-2·01)	0·419	0·323	32 (0·95%)	31 (0·88%)	1·11 (0·67-1·81)	0·127	0·690
Stroke										
Any	24 (0·61%)	22 (0·59%)	1·10 (0·62-1·97)	0·307	0·742	20 (0·57%)	14 (0·41%)	1·51 (0·76-2·99)	<0·001	0·237
Ischaemic	17 (0·44%)	19 (0·51%)	0·90 (0·47-1·73)	0·186	0·756	15 (0·43%)	11 (0·33%)	1·40 (0·64-3·04)	<0·001	0·402
Haemorrhagic	4 (0·1%)	2 (0·05%)	2·02 (0·37-11·02)	<0·001	0·417	3 (0·08%)	2 (0·05%)	1·59 (0·27-9·51)	<0·001	0·612
Stent thrombosis										
Definite	7 (0·19%)	3 (0·09%)	2·35 (0·61-9·1)	<0·001	0·215	2 (0·07%)	2 (0·05%)	1·05 (0·15-7·43)	<0·001	0·963
Probable	8 (0·22%)	3 (0·09%)	2·69 (0·71-10·14)	<0·001	0·144	3 (0·09%)	2 (0·05%)	1·57 (0·26-9·42)	<0·001	0·619
Definite or probable	8 (0·22%)	3 (0·09%)	2·69 (0·71-10·14)	<0·001	0·144	3 (0·09%)	2 (0·05%)	1·57 (0·26-9·42)	<0·001	0·619
BARC bleeding										
2, 3 or 5	52 (1·36%)	107 (2·78%)	0·49 (0·35-0·68)	0·001	<0·001	43 (1·25%)	101 (2·81%)	0·47 (0·33-0·67)	0·062	<0·001
3 or 5	23 (0·59%)	47 (1·20%)	0·49	0·415	0·006	20 (0·57%)	43 (1·17%)	0·50	0·438	0·011

			(0·30-0·81)					(0·29-0·85)		
5	2 (0·05%)	3 (0·07%)	0·67 (0·11-4·02)	<0·001	0·663	2 (0·05%)	3 (0·08%)	0·71 (0·12-4·23)	<0·001	0·703
TIMI bleeding										
Major	7 (0·18%)	20 (0·52%)	0·35 (0·15-0·83)	0·002	0·017	6 (0·17%)	17 (0·48%)	0·35 (0·14-0·90)	<0·001	0·029
Minor	3 (0·07%)	10 (0·25%)	0·3 (0·08-1·10)	<0·001	0·069	2 (0·06%)	10 (0·26%)	0·21 (0·05-0·97)	<0·001	0·045
Major or minor	10 (0·26%)	30 (0·77%)	0·33 (0·16-0·68)	<0·001	0·003	8 (0·23%)	27 (0·74%)	0·30 (0·14-0·65)	<0·001	0·003
NACE	125 (3·29%)	126 (3·28%)	1·00 (0·78-1·28)	0·079	0·991	107 (3·14%)	105 (2·92%)	1·09 (0·83-1·42)	<0·001	0·540

*P value for non-inferiority >0.99 of clopidogrel monotherapy versus DAPT in per-protocol population.

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 3 or 5 bleeding; TIMI=Thrombolysis in Myocardial Infarction.

Figure 1


Identification
Screening
Eligibility
Obtaining data
Available data
Analysed data
Studies identified through database searching (Ovid MEDLINE: n=1189; EMBASE: n=2921)
Additional studies identified through other sources (n=0)
Studies after duplicates removed (n=1512)
Studies excluded (n=1508): not related or observational/comments/duplicates/reviews/ meta-analyses
Studies screened for eligibility (n=4)
Studies excluded (n=3): not matching eligibility criteria
Studies for which IPD were sought (n=1)
Eligible studies for which IPD were not sought (n=0)
Studies for which IPD were provided (n=1)
Participants for whom data were provided (n=27084)
Participants for whom no data were provided (n=0)
Studies of Sidney-2 for which IPD were previously available (n=6)
Participants of Sidney-2 for whom data were previously available (n=23308)
Studies for which IPD were not provided (n=0)
Number of participants (n=0)
Number of studies for which aggregate data were available (n=0)
Number of participants (n=0)
IPD
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Participants included in analysis (n=26294)
Aggregate data
Studies included in analysis (n=0)
Participants included in analysis (n=0)

Figure 2

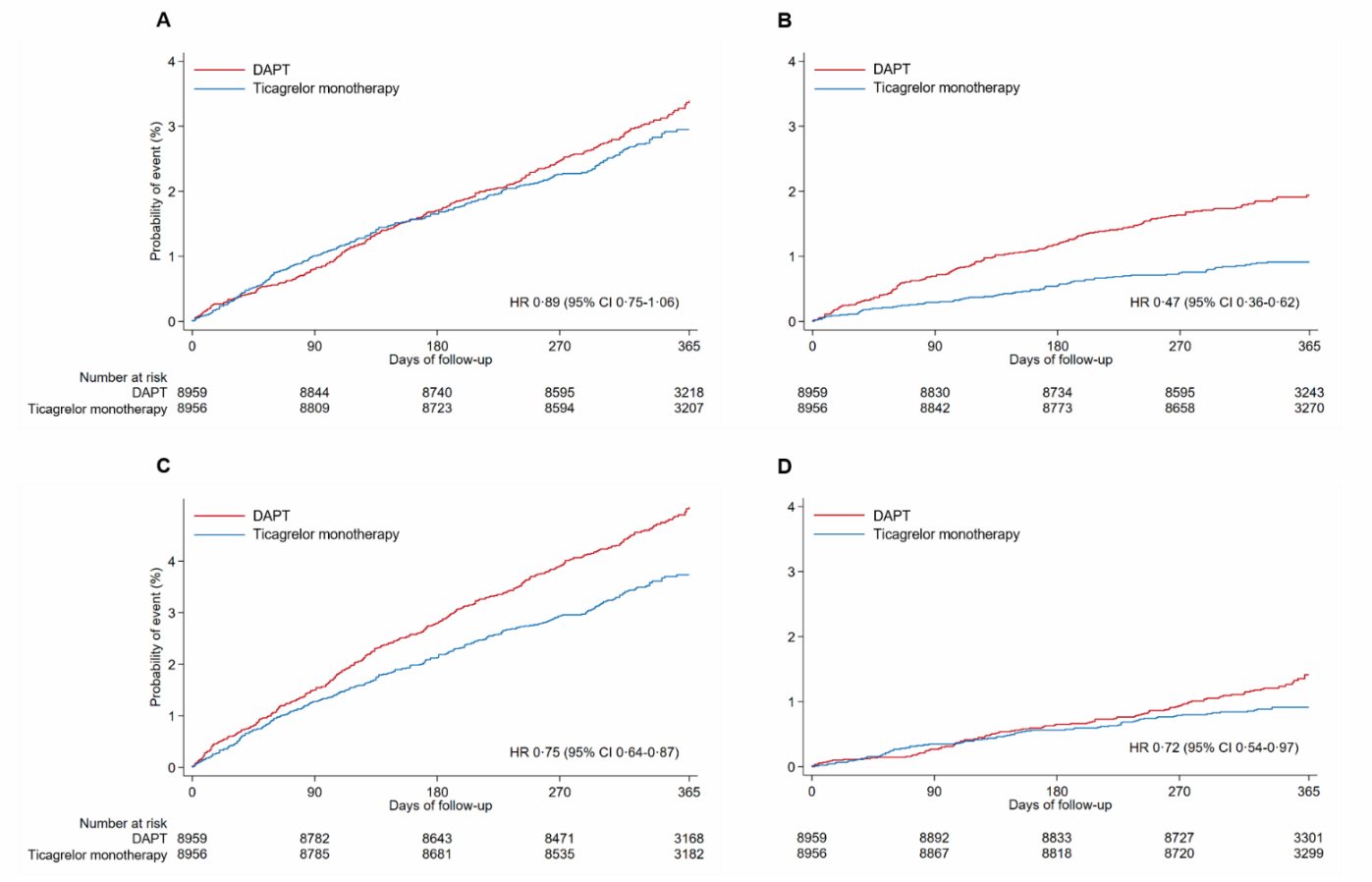
A
DAPT
Ticagrelor monotherapy
Probability of event (%)
HR 0·89 (95% CI 0·75-1·06)
Days of follow-up
Number at risk
DAPT 8959 8844 8740 8595 3218
Ticagrelor monotherapy 8956 8809 8723 8594 3207
B
DAPT
Ticagrelor monotherapy
HR 0·47 (95% CI 0·36-0·62)
Days of follow-up
8959 8830 8734 8595 3243
8956 8842 8773 8658 3270
C
DAPT
Ticagrelor monotherapy
Probability of event (%)
HR 0·75 (95% CI 0·64-0·87)
Days of follow-up
Number at risk
DAPT 8959 8782 8643 8471 3168
Ticagrelor monotherapy 8956 8785 8681 8535 3182
D
DAPT
Ticagrelor monotherapy
HR 0·72 (95% CI 0·54-0·97)
Days of follow-up
8959 8892 8833 8727 3301
8956 8867 8818 8720 3299

Figure 3

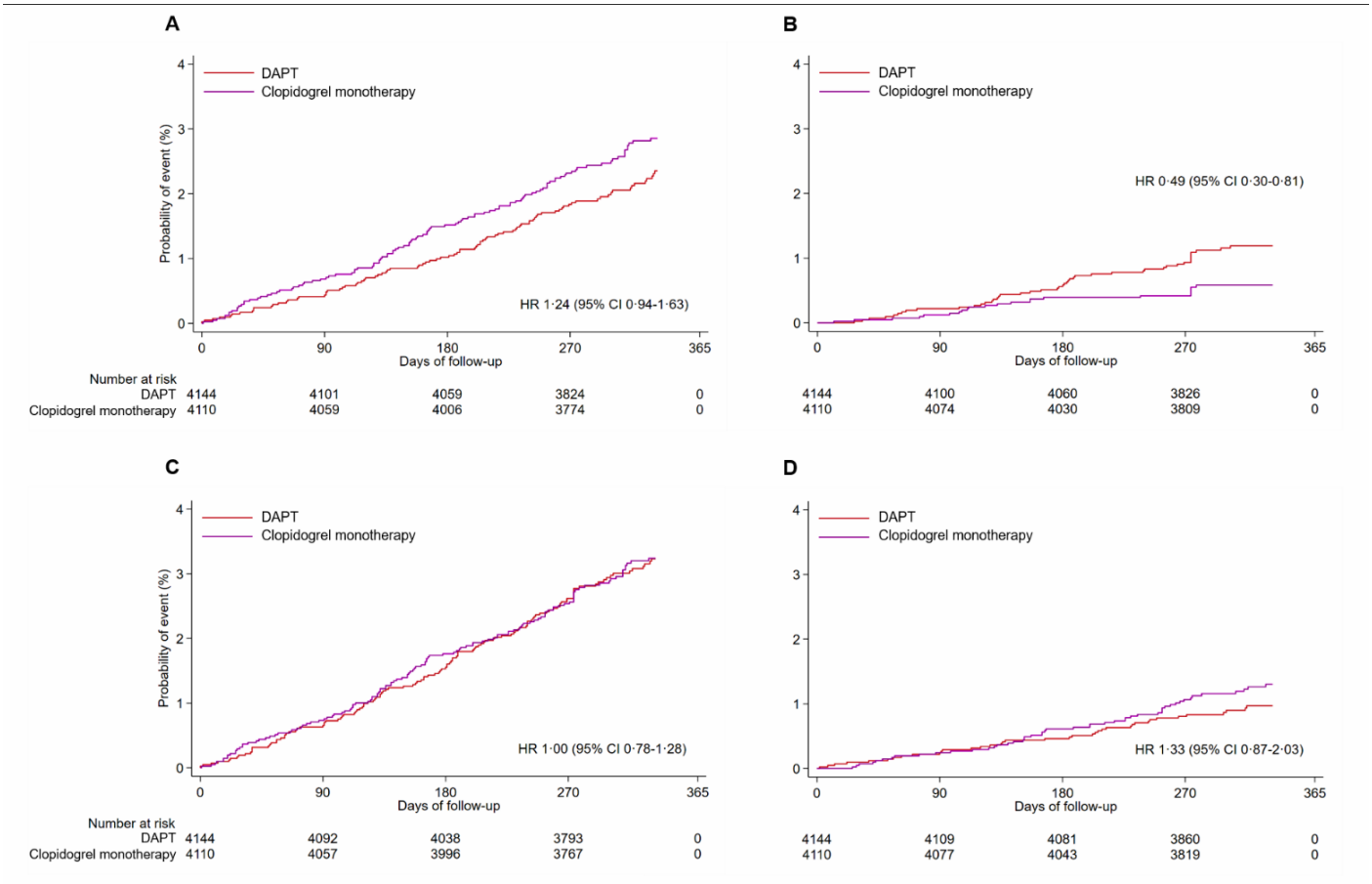
A
DAPT
Clopidogrel monotherapy
Probability of event (%)
HR 1·24 (95% CI 0·94-1·63)
Days of follow-up
Number at risk
DAPT 4144 4101 4059 3824 0
Clopidogrel monotherapy 4110 4059 4006 3774 0
B
DAPT
Clopidogrel monotherapy
HR 0·49 (95% CI 0·30-0·81)
Days of follow-up
4144 4100 4060 3826 0
4110 4074 4030 3809 0
C
DAPT
Clopidogrel monotherapy
Probability of event (%)
HR 1·00 (95% CI 0·78-1·28)
Days of follow-up
Number at risk
DAPT 4144 4092 4038 3793 0
Clopidogrel monotherapy 4110 4057 3996 3767 0
D
DAPT
Clopidogrel monotherapy
HR 1·33 (95% CI 0·87-2·03)
Days of follow-up
4144 4109 4081 3860 0
4110 4077 4043 3819 0

Figure 4

	P2Y12i monotherapy (N=12112)	DAPT (N=12508)	HR (95% CI)	p value for interaction
Primary outcome				
Ticagrelor monotherapy	228 (2·98)	262 (3·42)	0·89 (0·74-1·06)	0·016
Clopidogrel monotherapy	94 (2·76)	73 (2·07)	1·37 (1·01-1·87)	
Death or MI				
Ticagrelor monotherapy	202 (2·61)	243 (3·19)	0·85 (0·70-1·02)	0·022
Clopidogrel monotherapy	75 (2·2)	60 (1·67)	1·33 (0·95-1·87)	
All-cause mortality				
Ticagrelor monotherapy	78 (0·97)	106 (1·41)	0·75 (0·56-1·01)	0·005
Clopidogrel monotherapy	46 (1·34)	30 (0·82)	1·64 (1·03-2·59)	
CV Death				
Ticagrelor monotherapy	50 (0·63)	69 (0·91)	0·74 (0·52-1·07)	0·399
Clopidogrel monotherapy	17 (0·49)	18 (0·48)	1·03 (0·53-2·00)	
MI				
Ticagrelor monotherapy	136 (1·78)	154 (1·99)	0·90 (0·71-1·13)	0·465
Clopidogrel monotherapy	32 (0·95)	31 (0·88)	1·11 (0·67-1·81)	
Stroke				
Ticagrelor monotherapy	33 (0·45)	24 (0·29)	1·41 (0·83-2·39)	0·887
Clopidogrel monotherapy	20 (0·57)	14 (0·41)	1·51 (0·76-2·99)	
BARC 3 or 5				
Ticagrelor monotherapy	74 (0·94)	146 (1·85)	0·52 (0·39-0·68)	0·930
Clopidogrel monotherapy	20 (0·57)	43 (1·17)	0·50 (0·29-0·85)	
Definite or probable stent thrombosis				
Ticagrelor monotherapy	20 (0·28)	30 (0·42)	0·68 (0·38-1·19)	0·388
Clopidogrel monotherapy	3 (0·09)	2 (0·05)	1·57 (0·26-9·38)	
NACE				
Ticagrelor monotherapy	292 (3·78)	385 (4·99)	0·77 (0·66-0·90)	0·029
Clopidogrel monotherapy	107 (3·14)	105 (2·92)	1·09 (0·83-1·42)	

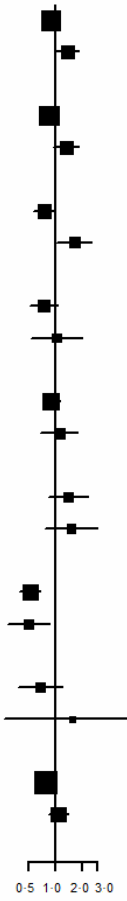

Figure 5

	Ticagrelor monotherapy (N=8956)	DAPT (N=8959)	HR (95% CI)	p value for interaction
Age				
< 65 years	96/4525 (2·4%)	105/4566 (2·6%)	0·93 (0·70-1·22)	0·610
≥ 65 years	146/4431 (3·5%)	168/4393 (4·2%)	0·86 (0·69-1·08)	
Sex				
Male	198/6896 (3·2%)	202/6944 (3·3%)	0·99 (0·81-1·20)	0·021
Female	44/2060 (2·2%)	71/2015 (3·7%)	0·61 (0·42-0·88)	
Clinical presentation				
Stable CAD	85/3160 (2·9%)	86/3136 (2·9%)	0·98 (0·73-1·32)	0·590
ACS	157/5795 (3·0%)	187/5823 (3·7%)	0·85 (0·69-1·05)	
Diabetes				
No	144/6256 (2·5%)	140/6306 (2·4%)	1·04 (0·83-1·31)	0·026
Yes	98/2699 (3·9%)	133/2653 (5·5%)	0·72 (0·56-0·94)	
History of CKD				
No	172/7478 (2·5%)	195/7466 (3·0%)	0·89 (0·72-1·09)	0·760
Yes	68/1336 (5·6%)	73/1359 (5·9%)	0·93 (0·67-1·29)	
Peripheral artery disease				
No	186/6922 (2·8%)	211/6874 (3·3%)	0·88 (0·72-1·07)	0·120
Yes	43/516 (8·6%)	37/565 (7·4%)	1·28 (0·83-1·99)	
High bleeding risk				
PRECISE DAPT < 25	162/7004 (2·6%)	169/7032 (2·8%)	0·97 (0·78-1·20)	0·440
PRECISE DAPT ≥ 25	67/1336 (5·2%)	80/1342 (6·4%)	0·84 (0·61-1·16)	
Complex PCI				
No	176/6946 (2·8%)	198/6988 (3·2%)	0·89 (0·73-1·10)	0·810
Yes	60/1827 (3·6%)	69/1787 (4·2%)	0·86 (0·61-1·22)	
PCI of left main or LAD				
No	170/5864 (3·2%)	195/5898 (3·7%)	0·88 (0·72-1·08)	0·950
Yes	65/3012 (2·3%)	70/2982 (2·6%)	0·92 (0·65-1·29)	
Use of proton-pump inhibitors				
No	86/3337 (2·7%)	101/3403 (3·2%)	0·87 (0·65-1·16)	0·660
Yes	140/3847 (3·7%)	146/3788 (4·0%)	0·94 (0·75-1·19)	
Region*				
Asia	23/2468 (0·9%)	39/2457 (1·8%)	0·59 (0·35-0·98)	0·106
North America	62/1484 (4·2%)	65/1488 (4·4%)	0·95 (0·67-1·35)	
Western Europe	117/3917 (3·0%)	127/3931 (3·2%)	0·97 (0·71-1·31)	
Eastern Europe	40/1087 (3·7%)	42/1083 (4·5%)	0·95 (0·51-1·76)