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Ticagrelor Monotherapy Versus Dual-Antiplatelet Therapy After PCI

An Individual Patient-Level Meta-Analysis

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ABSTRACT

OBJECTIVES The aim of this study was to compare ticagrelor monotherapy with dual-antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI) with drug-eluting stents.

BACKGROUND The role of abbreviated DAPT followed by an oral $P2Y_{12}$ inhibitor after PCI remains uncertain.

METHODS Two randomized trials, including 14,628 patients undergoing PCI, comparing ticagrelor monotherapy with standard DAPT on centrally adjudicated endpoints were identified, and individual patient data were analyzed using 1-step fixed-effect models. The protocol was registered in PROSPERO (CRD42019143120). The primary outcomes were the composite of Bleeding Academic Research Consortium type 3 or 5 bleeding tested for superiority and, if met, the composite of all-cause death, myocardial infarction, or stroke at 1 year, tested for noninferiority against a margin of 1.25 on a hazard ratio (HR) scale.

RESULTS Bleeding Academic Research Consortium type 3 or 5 bleeding occurred in fewer patients with ticagrelor than DAPT (0.9% vs. 1.7%, respectively; HR: 0.56; 95% confidence interval [CI]: 0.41 to 0.75; $p < 0.001$). The composite of all-cause death, myocardial infarction, or stroke occurred in 231 patients (3.2%) with ticagrelor and in 254 patients (3.5%) with DAPT (HR: 0.92; 95% CI: 0.76 to 1.10; $p < 0.001$ for noninferiority). Ticagrelor was associated with lower risk for all-cause (HR: 0.71; 95% CI: 0.52 to 0.96; $p = 0.027$) and cardiovascular (HR: 0.68; 95% CI: 0.47 to 0.99; $p = 0.044$) mortality. Rates of myocardial infarction (2.01% vs. 2.05%; $p = 0.88$), stent thrombosis (0.29% vs. 0.38%; $p = 0.32$), and stroke (0.47% vs. 0.36%; $p = 0.30$) were similar.

CONCLUSIONS Ticagrelor monotherapy was associated with a lower risk for major bleeding compared with standard DAPT, without a concomitant increase in ischemic events. (J Am Coll Cardiol Intv 2021;14:444-56) © 2021 by the American College of Cardiology Foundation.

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Dual-antiplatelet therapy (DAPT), including aspirin and an oral $P2Y_{12}$ inhibitor, represents the current standard of care after percutaneous coronary intervention (PCI) with drug-eluting stents to diminish the risk for stent-related and unrelated ischemic events (1,2). However, prolonged DAPT confers a heightened risk for major bleeding, affecting mortality, morbidity, and costs (3,4). Shorter durations (3 or 6 months) of DAPT followed by aspirin alone are associated with lower bleeding risk (5-7). However, this approach may increase the odds of myocardial infarction in patients at risk, such as those with acute coronary syndromes (ACS) and/or multivessel coronary artery disease (8-10).

Given of the central role of platelet $P2Y_{12}$ receptor signaling on thrombotic complications and the established association between aspirin and bleeding, in particular gastrointestinal bleeding (11), an emerging bleeding reduction strategy has been to discontinue aspirin and maintain patients on $P2Y_{12}$ inhibitor monotherapy (12). This novel antithrombotic strategy has been investigated in patients after PCI (10,13-15). However, data are still limited, and the interpretation of available evidence is challenged by variations in patient selection, choice of $P2Y_{12}$ inhibitor, duration of the initial DAPT regimen, timing of randomization, and endpoint ascertainment (adjudicated vs. investigator reported). We therefore performed a systematic review and individual patient data (IPD) analysis of randomized trials to compare the safety and efficacy of ticagrelor monotherapy with standard DAPT among patients undergoing PCI with drug-eluting stents.

METHODS

The protocol was prospectively registered (CRD42019143120); methods and reporting follow the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analyses of IPD (16).

SEARCH STRATEGY AND ELIGIBILITY CRITERIA. We performed a systematic review and IPD meta-analysis of randomized trials that compared ticagrelor monotherapy versus current standard of care consisting of DAPT with aspirin and a $P2Y_{12}$ inhibitor among patients with coronary artery disease who underwent PCI with drug-eluting coronary stents. To qualify for inclusion, trials had to report centrally adjudicated outcome data, including nonfatal ischemic and bleeding events and cause of death. Two investigators (M.V. and A.F.) determined trial eligibility criteria, and a third investigator (R.P.) was involved in case of disagreement. Randomized trials were identified by a search in Ovid MEDLINE, Embase, and 3 web sites (www.tctmd.com, www.escardio.org, and www.cardiosource.com). Reference lists of retrieved papers were hand-searched. There were no language restrictions. The search strategy is provided in the Supplemental Appendix.

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DATA COLLECTION AND QUALITY ASSESSMENT. Data for GLASSY (GLOBAL LEADERS Adjudication Sub-Study) were already available (17,18). We contacted the principal investigator (R.M.) of the single additional study found to be eligible, the TWILIGHT (Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention) trial (15), requesting deidentified IPD. The protocol was finalized on July 9, 2019, before database lock of 1 of the 2 included trials (15), and on July 19, 2019, submitted to PROSPERO, which made it available online on

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)
BARC = Bleeding Academic Research Consortium
CCS = chronic coronary syndrome(s)
CEC = clinical event committee
CI = confidence interval
DAPT = dual-antiplatelet therapy
HR = hazard ratio
IPD = individual patient data
ITT = intention-to-treat
NNTB = number needed to treat for benefit
PCI = percutaneous coronary intervention

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October 29, 2019. A pre-defined selection of variables of interest was generated and their availability in each dataset verified by the corresponding principal investigator. Data were centrally checked for completeness and consistency by the data coordination center (B.K., B.R.d.C., P.J.) and compared with the results of the original publications. Two investigators (A.F., R.P.) independently assessed the quality of included trials using the Cochrane Collaboration's tool for assessing risk for bias (19). Details of study conduct are reported in the Supplemental Appendix. Each trial was approved by its local medical ethics committee, and all patients provided written informed consent. Ad hoc approval before data transfer for one trial (15) was obtained as per local requirement (HS #14-00671).

CROSS-ADJUDICATION. To explore between-trial consistency of clinical event committee (CEC) adjudication, 200 triggers of event adjudication were randomly selected, which suggested either a potential primary outcome event of this study or a potential stent thrombosis. Random sampling was stratified by trial and type of trigger (potential death, myocardial infarction, stroke, bleeding, or stent thrombosis). The narrative of a single trigger could be associated with multiple types of events, and all events associated with the randomly selected triggers in one trial were independently adjudicated under blind conditions by the CEC of the other trial and classified according to the relevant framework specified in the dedicated CEC charter if a specific type of event was confirmed (Supplemental Appendix).

OUTCOMES. Pre-specified primary endpoints were, in hierarchical order, Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding and the composite of all-cause death, myocardial infarction, or stroke throughout the entire duration of the randomized comparison of protocol-mandated ticagrelor monotherapy versus standard DAPT. Secondary endpoints included each component of the primary endpoints, cardiovascular and noncardiovascular mortality, ischemic and/or hemorrhagic stroke, definite and/or probable stent thrombosis, target lesion revascularization, and bleeding according to the BARC, TIMI (Thrombolysis In Myocardial Infarction), or GUSTO (Global Use of Strategies to Open Occluded Arteries) scale (Supplemental Appendix).

DATA ANALYSIS. Baseline and procedural continuous variables were summarized as mean ± SD and categorical variables as counts and percentages. The pre-specified primary analysis was based on a 1-step approach to model the data from both trials simultaneously using a fixed-effect Cox regression model stratified by trial. Pre-specified sensitivity analyses of the primary endpoints were based on a 2-step approach using an inverse-variance fixed-effect model, and a DerSimonian-Laird random-effects model to combine trial-level estimates. Between-trial heterogeneity was estimated from the 2-step fixed-effect model using the I^2 statistic. Treatment effects were derived as hazard ratios (HRs) and 95% confidence intervals (CIs). P values for superiority and 95% CIs are 2 sided. Analyses were done in Stata release 15.1 (StataCorp, College Station, Texas) and R version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria). Further details on data analysis are reported in the Supplemental Appendix.

ROLE OF THE FUNDING SOURCE. There was no industry involvement in the design, analysis, or funding of this study. This study was funded by institutional support from the Department of Cardiology at Bern University Hospital (Bern, Switzerland), which had no role in the data analysis, interpretation, or writing of the report. The first and last authors (M.V., R.M., and P.J.) had full access to the data and had final responsibility for the decision to submit for publication.

RESULTS

We screened 1,093 unique citations. Of these, 459 were judged potentially eligible during screening of titles and abstracts, and 2 were deemed eligible after full text review (Supplemental Figure 1). IPD were sought and obtained for both trials. The Supplemental Appendix describes trial characteristics, patient populations, the definitions used for outcomes, and the risk for bias of included trials (Supplemental Tables 1 to 4). A total of 14,628 participants were included, and 7,308 (50%) were randomly allocated to ticagrelor monotherapy and 7,320 (50%) to standard DAPT using aspirin and ticagrelor (5,604 [76.6%]) or aspirin and clopidogrel (1,716 [23.4%]). The duration of treatment ranged from 11 to 12 months and both studies were sponsored by nonfor-profit organizations (Supplemental Table 1).

PATIENT CHARACTERISTICS. Baseline clinical characteristics were well balanced between groups (**Table 1**). The mean age was 65 years, and 23.7% of the patients were women. The majority of the patients were recruited in Europe (68.5%), 20.3% in North America, and 11.2% in Asia. A total of 4,424 patients (30.2%) had histories of diabetes, and 2,135 (14.6%) had renal failure. Histories of myocardial infarction,

TABLE 1 Baseline Characteristics

	GLASSY		TWILIGHT		Combined	
	Ticagrelor Monotherapy (n = 3,753)	$P2Y_{12}$ Inhibitor Plus Aspirin (n = 3,756)	Ticagrelor Monotherapy (n = 3,555)	$P2Y_{12}$ Inhibitor Plus Aspirin (n = 3,564)	Ticagrelor Monotherapy (n = 7,308)	$P2Y_{12}$ Inhibitor Plus Aspirin (n = 7,320)
Age, yrs	64.9 ± 10.3	64.8 ± 10.3	65.2 ± 10.3	65.1 ± 10.4	65.0 ± 10.3	64.9 ± 10.4
Female	894 (23.8)	875 (23.3)	846 (23.8)	852 (23.9)	1,740 (23.8)	1,727 (23.6)
BMI, kg/m^2	28.0 ± 4.5	27.9 ± 4.5	28.6 ± 5.5	28.5 ± 5.6	28.3 ± 5.1	28.2 ± 5.1
Clinical presentation						
Stable CAD	1,844 (49.1)	1,875 (49.9)	1,281 (36.0)	1,222 (34.3)	3,125 (42.8)	3,097 (42.3)
Unstable angina	486 (12.9)	498 (13.3)	1,249 (35.1)	1,245 (34.9)	1,735 (23.7)	1,743 (23.8)
Non-STEMI	750 (20.0)	731 (19.5)	1,024 (28.8)	1,096 (30.8)	1,774 (24.3)	1,827 (25.0)
STEMI	673 (17.9)	652 (17.4)	0 (0.0)	0 (0.0)	673 (9.2)	652 (8.9)
Medical history						
Diabetes	912 (24.3)	892 (23.7)	1,319 (37.1)	1,301 (36.5)	2,231 (30.5)	2,193 (30.0)
Insulin treatment	262 (7.0)	267 (7.1)	335 (9.4)	374 (10.5)	597 (8.2)	641 (8.8)
Renal failure*	501 (13.4)	489 (13.1)	572 (16.1)	573 (16.1)	1,073 (14.7)	1,062 (14.5)
Current smoking	1,068 (28.5)	1,092 (29.1)	726 (20.4)	822 (23.1)	1,794 (24.6)	1,914 (26.2)
Hypercholesterolemia	2,377 (65.7)	2,455 (67.7)	2,157 (60.7)	2,146 (60.2)	4,534 (63.2)	4,601 (64.0)
Hypertension	2,724 (72.8)	2,712 (72.4)	2,580 (72.6)	2,574 (72.2)	5,304 (72.7)	5,286 (72.3)
Previous MI	861 (23.0)	885 (23.6)	1,020 (28.7)	1,020 (28.6)	1,881 (25.8)	1,905 (26.0)
Previous PCI	1,228 (32.7)	1,279 (34.1)	1,502 (42.3)	1,496 (42.0)	2,730 (37.4)	2,775 (37.9)
Previous CABG	204 (5.4)	238 (6.3)	362 (10.2)	348 (9.8)	566 (7.7)	586 (8.0)
Peripheral artery disease	250 (6.7)	297 (7.9)	245 (6.9)	244 (6.8)	495 (6.8)	541 (7.4)
Previous major bleeding	26 (0.7)	22 (0.6)	31 (0.9)	32 (0.9)	57 (0.8)	54 (0.7)
High bleeding risk	730 (19.5)	724 (19.3)	616 (17.3)	603 (16.9)	1,346 (18.4)	1,327 (18.1)
Use of proton pump inhibitors	2,425 (64.6)	2,351 (62.6)	1,800 (50.6)	1,801 (50.5)	4,225 (57.8)	4,152 (56.7)
Region						
Western Europe	3,002 (80.0)	3,009 (80.1)	915 (25.7)	922 (25.9)	3,917 (53.6)	3,931 (53.7)
Eastern Europe	751 (20.0)	747 (19.9)	336 (9.5)	336 (9.4)	1,087 (14.9)	1,083 (14.8)
North America	0 (0.0)	0 (0.0)	1,484 (41.7)	1,488 (41.8)	1,484 (20.3)	1,488 (20.3)
Asia	0 (0.0)	0 (0.0)	820 (23.1)	818 (23.0)	820 (11.2)	818 (11.2)

Values are mean ± SD or n (%). The denominators for the combined trials are 7,308 and 7,320 in the experimental and control groups, except for clinical presentation (7,307 and 7,319), renal failure (7,155 and 7,172), current smoking (7,306 and 7,318), hypercholesterolemia (7,172 and 7,189), hypertension (7,299 and 7,308), previous MI (7,301 and 7,318), previous PCI (7,306 and 7,318), previous CABG (7,305 and 7,318), previous major bleeding (7,300 and 7,315), and BMI (7,296 and 7,302). High bleeding risk was defined according to a PRECISE-DAPT (Predicting Bleeding Complication in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy) score of 25 or greater. *Defined as estimated glomerular filtration rate <60 ml/min/1.73 m^2.

BMI = body mass index; CABG = coronary artery bypass grafting; CAD = coronary artery disease; GLASSY = GLOBAL LEADERS Adjudication Sub-Study; MI = myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; TWILIGHT = Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention.

PCI, and coronary artery bypass surgery were noted in 3,786 (25.9%), 5,505 (37.6%), and 1,152 (7.9%) patients, respectively. At presentation, the majority of patients (8,404 [57.4%]) had ACS, and 6,222 (42.5%) had chronic coronary syndromes (CCS). Procedural characteristics are shown in **Table 2** and medication adherence data in Supplemental Table 5.

BLEEDING. There was strong evidence for a reduction in the risk for BARC type 3 or 5 bleeding among patients randomly allocated to ticagrelor monotherapy compared with DAPT (0.94% vs. 1.66%; HR: 0.57; 95% CI: 0.42 to 0.76; $p < 0.0001$), for a number needed to treat for benefit (NNTB) of 127 (95% CI: 96 to 223) (**Table 3, Figure 1, Central Illustration**), without between-trial heterogeneity ($I^2 = 0\%$). The treatment effect was mostly consistent across pre-defined subgroups, with a positive treatment-by-subgroup interaction with respect to type of presenting syndrome, left main or proximal left anterior descending coronary artery intervention, and type of DAPT in the control group (Supplemental Figure 2).

Bleeding according to BARC type 2, 3, or 5 occurred in 263 patients (3.60%) with ticagrelor monotherapy compared with 422 patients (5.77%) with DAPT (HR: 0.62; 95% CI: 0.53 to 0.72; $p < 0.0001$; $I^2 = 0\%$; NNTB = 46 [95% CI: 36 to 67]) (**Table 3**). This effect was consistent across other bleeding definitions, including TIMI major and minor bleeding (2.37% and 4.02%, respectively; HR: 0.58; 95% CI: 0.48 to 0.70; $p < 0.0001$; NNTB = 61 [95% CI: 45 to 91]), and for TIMI major and minor bleeding separately (**Table 3**).

ISCHEMIC EVENTS. The coprimary efficacy endpoint of all-cause death, myocardial infarction, or stroke occurred in 231 (3.16%) and 254 (3.47%) patients with

TABLE 2 Procedural Characteristics

	GLASSY		TWILIGHT		Combined	
	Ticagrelor Monotherapy (n = 3,753)	$P2Y_{12}$ Inhibitor Plus Aspirin (n = 3,756)	Ticagrelor Monotherapy (n = 3,555)	$P2Y_{12}$ Inhibitor Plus Aspirin (n = 3,564)	Ticagrelor Monotherapy (n = 7,308)	$P2Y_{12}$ Inhibitor Plus Aspirin (n = 7,320)
PCI performed	3,236 (99.5)	3,240 (99.6)	3,255 (100.0)	3,264 (100.0)	7,291 (99.8)	7,204 (99.8)
Radial access	2,228 (73.0)	2,265 (73.9)	2,200 (73.1)	2,286 (72.6)	5,228 (73.1)	5,251 (73.3)
Patients with treated lesions	3,223 (99.2)	3,227 (99.2)	3,255 (100.0)	3,264 (100.0)	7,278 (99.6)	7,291 (99.6)
Number of lesions treated per patient						
1	2,224 (75.6)	2,218 (75.3)	2,210 (59.4)	2,233 (59.8)	4,234 (67.7)	4,251 (67.8)
2	722 (19.3)	711 (19.0)	1,285 (30.5)	1,290 (30.6)	1,207 (24.8)	1,201 (24.7)
3 or more	177 (4.7)	198 (5.3)	360 (10.1)	341 (9.6)	537 (7.4)	539 (7.4)
Number of vessels treated per patient						
1	3,241 (87.1)	3,243 (87.0)	2,264 (74.9)	2,252 (74.4)	5,205 (81.1)	5,295 (80.9)
2	462 (12.4)	452 (12.1)	790 (22.2)	799 (22.4)	1,252 (17.2)	1,251 (17.2)
3	20 (0.5)	32 (0.9)	101 (2.8)	113 (3.2)	121 (1.7)	145 (2.0)
Presence of lesions treated in vessels						
Left main coronary artery	99 (2.7)	107 (2.9)	166 (4.7)	187 (5.2)	265 (3.6)	294 (4.0)
Left anterior descending coronary artery	1,212 (46.0)	1,221 (46.2)	1,293 (56.1)	2,210 (56.4)	3,205 (50.9)	3,231 (51.2)
Left circumflex coronary artery	1,290 (29.3)	1,298 (29.5)	1,251 (32.4)	1,246 (32.2)	2,241 (30.8)	2,244 (30.8)
Right coronary artery	1,288 (34.6)	1,276 (34.2)	1,243 (35.0)	1,257 (35.3)	2,231 (34.8)	2,233 (34.7)
Target lesion morphology						
Bifurcation	512 (13.7)	533 (14.3)	434 (12.2)	432 (12.1)	946 (13.0)	965 (13.2)
Chronic total occlusion	120 (3.2)	111 (3.0)	222 (6.2)	224 (6.3)	342 (4.7)	335 (4.6)
Venous bypass graft	42 (1.1)	46 (1.2)	62 (1.7)	72 (2.0)	104 (1.4)	118 (1.6)
Total stent length, mm	30.9 ± 20.1	31.1 ± 21.3	40.1 ± 24.2	39.7 ± 24.3	35.4 ± 22.7	35.3 ± 23.2
Minimum stent diameter, mm	2.9 ± 0.5	2.9 ± 0.5	2.8 ± 0.5	2.9 ± 0.5	2.9 ± 0.5	2.9 ± 0.5
Complex PCI	809 (21.7)	805 (21.5)	1,283 (30.5)	1,277 (30.2)	1,292 (25.9)	1,282 (25.8)

Values are n (%) or mean ± SD.
Abbreviations as in Table 1.

ticagrelor monotherapy and DAPT, respectively (HR: 0.92; 95% CI: 0.76 to 1.10; $p < 0.001$ for noninferiority in the per protocol population; $p = 0.32$ for superiority in the intention-to-treat [ITT] population) (**Figure 2, Central Illustration**), again with no between-trial heterogeneity ($I^2 = 0\%$). Ticagrelor monotherapy was associated with a lower risk for all-cause mortality (0.94% vs. 1.34%; HR: 0.71; 95% CI: 0.52 to 0.96; $p = 0.027$) (**Table 3, Figure 3**), with no between-trial heterogeneity ($I^2 = 0\%$). This benefit was driven by a reduction of cardiovascular mortality (0.64% vs. 0.94%; HR: 0.68; 95% CI: 0.47 to 0.99; $p = 0.044$) (**Table 3**). The risks for myocardial infarction (2.01% vs. 2.05%; HR: 0.98; 95% CI: 0.78 to 1.23; $p = 0.88$), stroke (0.47% vs. 0.36%; HR: 1.31; 95% CI: 0.79 to 2.19; $p = 0.30$) and definite or probable stent thrombosis (0.29% vs. 0.38%; HR: 0.75; 95% CI: 0.43 to 1.32; $p = 0.32$) appeared similar (**Table 3**).

The treatment effect was consistent across predefined subgroups (**Figure 4**), and noninferiority was confirmed in the ITT analysis ($p < 0.001$ for noninferiority) (**Table 3**).

ADDITIONAL ANALYSES. Pre-specified sensitivity analyses using 1- and 2-step fixed-effect and random-effects models (**Figures 1B, 2B, and 3B**, Supplemental Figures 3 to 5) and sensitivity analyses including the first 30 days from randomization in GLASSY yielded consistent results with respect to the coprimary bleeding or ischemic endpoint (Supplemental Table 6). A 1-step fixed-effect model for all-cause death including GLASSY and TWILIGHT study population is shown in Supplemental Table 7. Post hoc sensitivity analyses of the coprimary endpoints adjusted for all available patient characteristics at baseline again yielded consistent results (Supplemental Table 8). Cross-adjudication of a randomly selected sample of 100 events for each trial yielded agreement ≥94.5% and kappa values ≥0.86 (Supplemental Table 9).

DISCUSSION

Our collaborative IPD meta-analysis of 2 recent large randomized trials, including a total of 14,628 patients undergoing drug-eluting coronary stent

implantation, provides strong evidence that ticagrelor monotherapy, after a short course of 1- or 3-month DAPT, was associated with a lower risk for major bleeding without any measurable increase in ischemic events compared with standard DAPT. Furthermore, we observed a significant reduction in all-cause mortality among patients randomized to ticagrelor monotherapy, driven mostly by a reduction of cardiovascular death, that requires a cautious interpretation in view of the similar rates of myocardial infarction, stent thrombosis and stroke (**Central Illustration**).

The GLOBAL LEADERS (A Clinical Study Comparing Two Forms of Anti-Platelet Therapy After Stent Implantation) trial was the first trial to assess the risks and benefits of ticagrelor monotherapy after 1 month of DAPT compared with 12-month DAPT followed by aspirin monotherapy (13). The composite of all-cause death or new Q-wave myocardial infarction at 2 years was not significantly reduced with ticagrelor monotherapy, and there were no between-group differences for bleeding endpoints. Irrespective of clinical presentation, patients in the experimental arm received 75 to 100 mg aspirin daily plus 90 mg ticagrelor twice daily for 1 month, followed by ticagrelor monotherapy for 23 months. In the control arm, DAPT with 75 to 100 mg aspirin plus 75 mg clopidogrel daily or with 75 to 100 mg aspirin plus 90 mg ticagrelor twice daily was prescribed for 12 months to patients in stable condition or those with ACS, respectively; they all received aspirin monotherapy for the subsequent 12 months.

GLASSY implemented an independent central adjudication process of both reported events and potential unreported event triggers among 7,585 patients from the 20 participating sites. Results after 24 months suggested noninferiority of the experimental treatment over standard care with respect to the coprimary efficacy endpoint of all-cause death, nonfatal myocardial infarction, nonfatal stroke, or urgent target vessel revascularization. The rates of BARC type 3 or 5 bleeding did not differ between groups at 24 months (18).

The double-blind TWILIGHT trial assigned 7,119 patients after an uneventful 3-month period of DAPT to ticagrelor alone or ticagrelor plus aspirin for 12 months and showed a reduction of BARC type 2, 3, or 5 bleeding with the experimental treatment. The risk for death, myocardial infarction, or stroke was similar at 3.9% in both treatment groups, which fulfilled the pre-defined noninferiority 1.6% absolute risk margin. However, the rate of the ischemic composite endpoint was 50% lower than expected, and the upper margin of the 95% CI entailed up to a 25% risk increase with ticagrelor alone compared with standard DAPT. Moreover, all participants in the control group, including those with CCS, received DAPT in the form of aspirin and ticagrelor (15).

Prior analyses of aggregate data showed higher bleeding risk and no greater ischemic protection with prolonged DAPT compared with $P2Y_{12}$ monotherapy (20,21). However, they included studies with variable type and duration of antiplatelet therapy in the experimental and control arms, hampering a clear translation of these study findings into practice. We

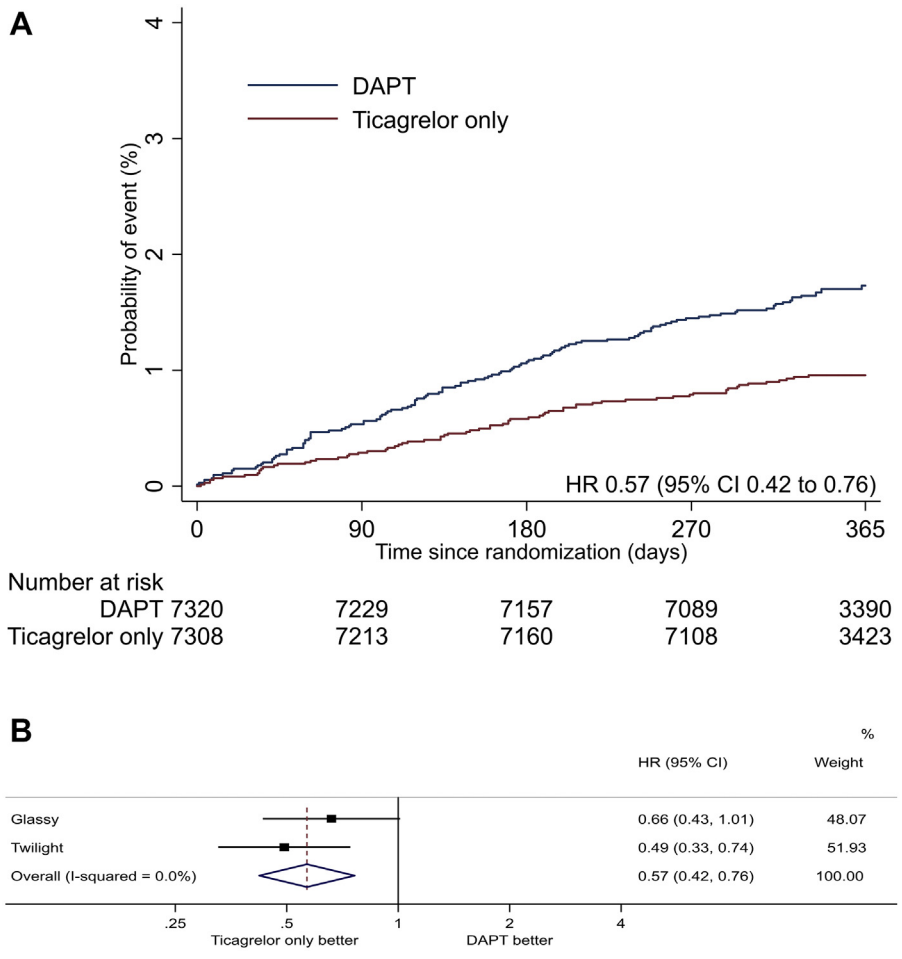
TABLE 3 Outcomes in the Intention-to-Treat Population

	Ticagrelor Monotherapy (n = 7,308)	$P2Y_{12}$ Inhibitor Plus Aspirin (n = 7,320)	HR (95% CI)	p Value
Death				
All cause	69 (0.9)	98 (1.3)	0.71 (0.52–0.96)	0.027
Cardiovascular	47 (0.6)	69 (0.9)	0.68 (0.47–0.99)	0.044
Noncardiovascular	22 (0.3)	28 (0.4)	0.79 (0.45–1.38)	0.40
All-cause death or MI	203 (2.8)	232 (3.2)	0.88 (0.73–1.06)	0.18
MI	147 (2.0)	150 (2.0)	0.98 (0.78–1.23)	0.88
Stroke				
Any	34 (0.5)	25 (0.4)	1.37 (0.81–2.29)	0.24
Ischemic	30 (0.4)	23 (0.3)	1.31 (0.76–2.25)	0.33
Hemorrhagic	3 (0.0)	1 (0.0)	3.01 (0.31–28.92)	0.34
Death, MI, or stroke*	231 (3.2)	253 (3.5)	0.92 (0.77–1.10)	0.34
BARC bleeding				
Type 2, 3, or 5	262 (3.6)	421 (5.8)	0.62 (0.53–0.72)	<0.001
Type 3 or 5*	68 (0.9)	122 (1.7)	0.56 (0.41–0.75)	<0.001
Type 5	2 (0.0)	1 (0.0)	2.01 (0.18–22.13)	0.57
TIMI bleeding				
Major	38 (0.5)	59 (0.8)	0.65 (0.46–0.97)	0.035
Minor	136 (1.9)	239 (3.3)	0.56 (0.46–0.69)	<0.001
Major or minor	173 (2.4)	294 (4.0)	0.58 (0.48–0.70)	<0.001
CABG related	2 (0.0)	3 (0.0)	0.67 (0.11–3.98)	0.66
GUSTO bleeding				
Severe	24 (0.3)	15 (0.2)	1.60 (0.84–3.06)	0.15
Moderate	34 (0.5)	79 (1.1)	0.43 (0.29–0.64)	<0.001
Mild	656 (9.0)	1001 (13.7)	0.63 (0.57–0.70)	<0.001
Moderate or severe	58 (0.8)	91 (1.2)	0.64 (0.46–0.89)	0.007
Stent thrombosis				
Definite	20 (0.3)	25 (0.3)	0.80 (0.45–1.44)	0.46
Probable	1 (0.0)	3 (0.0)	0.33 (0.03–3.21)	0.34
Possible	21 (0.3)	36 (0.5)	0.59 (0.34–1.00)	0.051
Definite or probable	21 (0.3)	28 (0.4)	0.75 (0.43–1.32)	0.32
Any	42 (0.6)	64 (0.9)	0.66 (0.45–0.97)	0.035
Target vessel revascularization	317 (4.3)	313 (4.3)	1.02 (0.87–1.19)	0.82

Values are n (%) unless otherwise indicated. The p values are 2-sided for superiority. Outcome data were obtained after median follow-up period of 11 months (interquartile range: 11 to 11 months) in GLASSY and 12 months (interquartile range: 12 to 12 months) in TWILIGHT. *Coprimary outcomes.

BARC = Bleeding Academic Research Consortium; CI = confidence interval; GUSTO = Global Use of Strategies to Open Occluded Arteries; HR = hazard ratio; TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Table 1.

FIGURE 1 Hazard Ratios for Individual Trials and for the Pooled Population and Kaplan-Meier Estimates for the Coprimary Composite Endpoint of Bleeding Academic Research Consortium Type 3 or 5 in the Intention-to-Treat Population

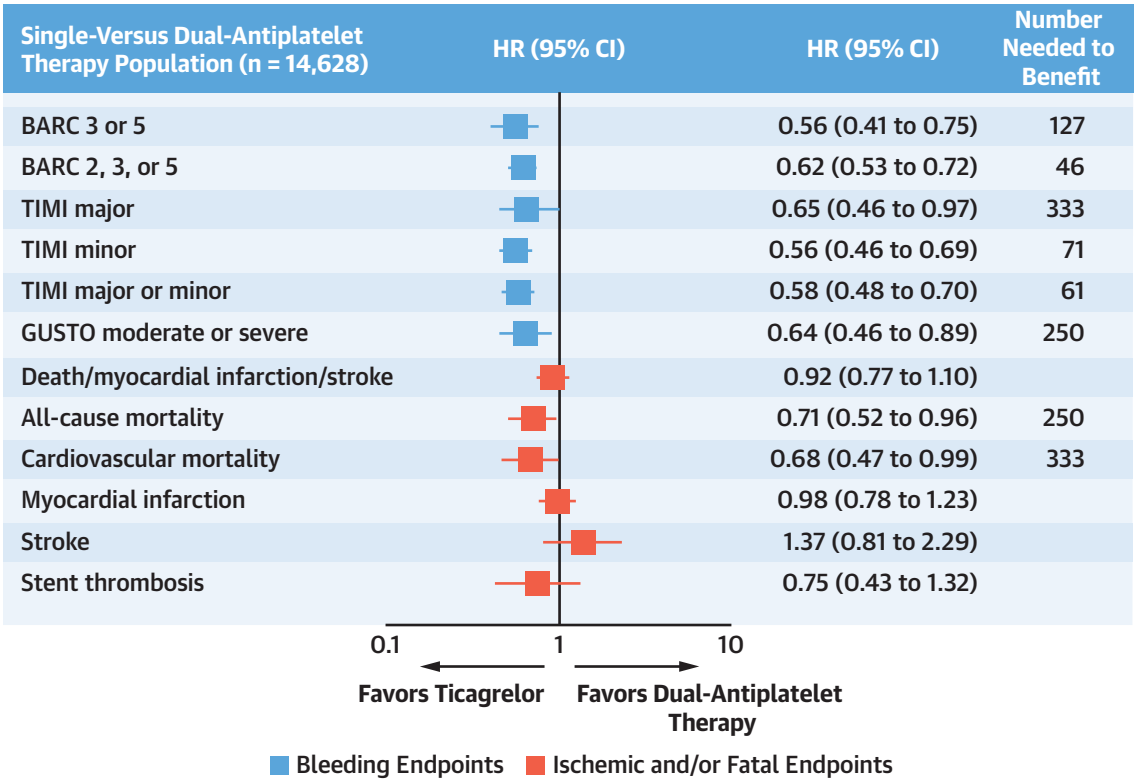


Kaplan-Meier curves and hazard ratios (HRs) from 1-step fixed-effect meta-analysis **(A)** and 2-step fixed-effect meta-analysis **(B)**.
CI = confidence interval; DAPT = dual-antiplatelet therapy; GLASSY = GLOBAL LEADERS Adjudication Sub-Study; TWILIGHT = Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention.

present the first IPD meta-analysis focused on ticagrelor monotherapy, which provides in a large patient cohort important implications for practice.

First, it shows that ticagrelor monotherapy after a short course of DAPT was associated with lower risk for major bleeding compared with standard DAPT duration in an analysis of the pre-specified primary endpoint. These findings were consistent when the TIMI bleeding scale was analyzed among other secondary endpoints. These findings are in contrast to those for other emerging treatment strategies, such as phenotype- or genotype-guided $P2Y_{12}$ inhibitor de-escalation, which were recently explored among patients with ACS, in whom minor but not major bleeding was reduced (22,23). Second, combining IPD from 2 large randomized trials increased power and allowed a more precise quantification of the potential risk and benefit associated with early aspirin discontinuation. Although in our present analysis, noninferiority was established on the basis of a 25% relative margin on an HR scale, the upper limit of the 2-sided 95% CIs of per protocol and ITT analyses excluded a >10% increase in the experimental group compared with standard DAPT. The small residual uncertainty needs to be interpreted against a >40% relative reduction of major bleeding with ticagrelor monotherapy compared with standard DAPT. Third, the impact of

CENTRAL ILLUSTRATION **Bleeding and Ischemic Outcomes in Single Versus Dual-Antiplatelet Therapy Groups**

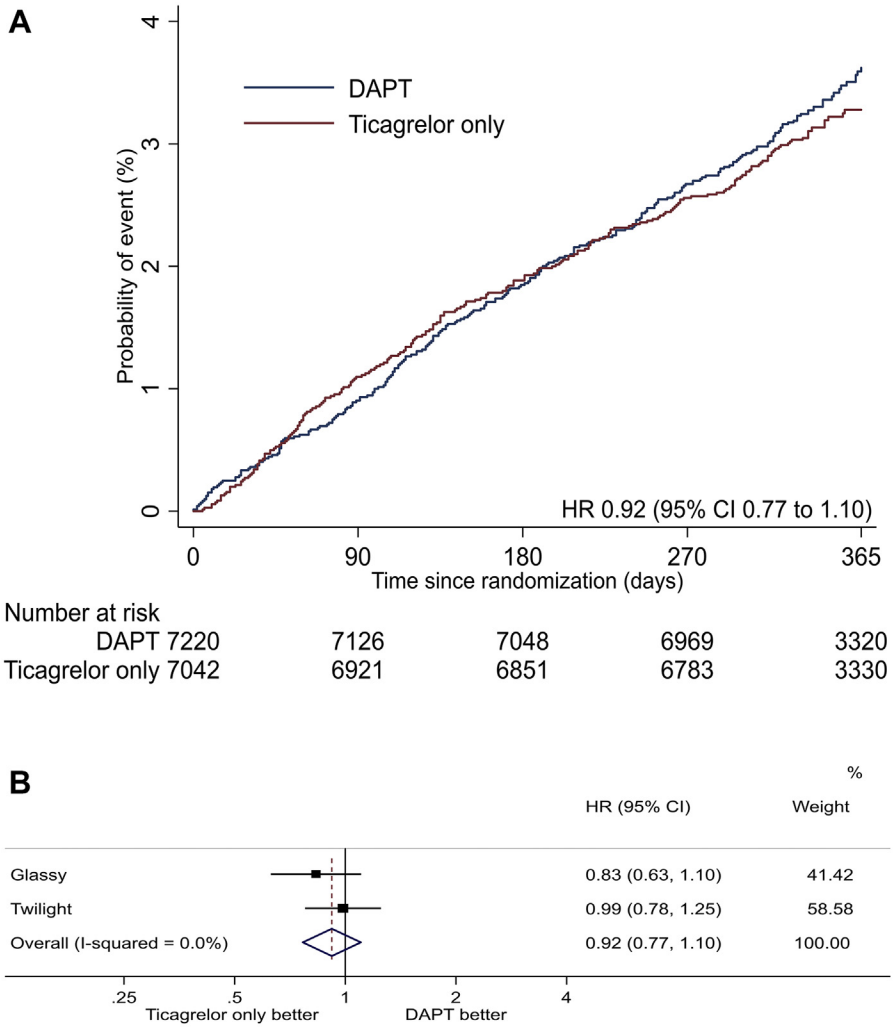


Valgimigli, M. et al. J Am Coll Cardiol Intv. 2021;14(4):444–56.

BARC = Bleeding Academic Research Consortium; CI = confidence interval; GUSTO = Global Use of Strategies to Open Occluded Arteries; HR = hazard ratio; TIMI = Thrombolysis In Myocardial Infarction.

ticagrelor monotherapy on relatively rare but important events, such as all-cause or cardiovascular mortality, could not be adequately tested in a single trial, because of limited statistical precision. We observed a total of 167 fatal events in our combined dataset and found a nominally significant 29% risk reduction of all-cause mortality with ticagrelor monotherapy in the ITT analysis. Although a causal link cannot be established, we speculate that the benefit in terms of all-cause mortality might be related to the observed reduction in nonfatal bleeding, whose impact on survival is associated with several factors: location, severity, timing, anemia, and therapeutic measures undertaken to control it, such as discontinuation of antithrombotic therapy and blood transfusions (24-26). Fourth, our subgroup analysis allows further investigation of the distinct role of type of DAPT in the control arm and presenting syndrome. In both GLOBAL LEADERS and GLASSY, a significant qualitative interaction between BARC type 3 or 5 bleeding was noted with respect to clinical presentation, suggesting lower bleeding risk among patients with ACS but not those with CCS with the experimental treatment (13,18). A treatment-by-subgroup interaction for the type of reference treatment (i.e., aspirin plus ticagrelor among patients with ACS and aspirin and clopidogrel among those with CCS) seemed to account for this observation. However, TWILIGHT alone reported a significant treatment-by-subgroup interaction for presenting syndrome with respect to the primary safety endpoint of BARC type 2, 3, or 5 bleeding and indicated greater bleeding risk reduction among patients with ACS compared with those in stable condition with ticagrelor monotherapy (15). As all patients in TWILIGHT received aspirin plus ticagrelor in the control group, irrespective of presenting syndrome, this observation cannot be attributed to the type of DAPT implemented in the control arm.

FIGURE 2 HRs for Individual Trials and for the Pooled Population and Kaplan-Meier Estimates for the Coprimary Composite Endpoint of All-Cause Death, Nonfatal Myocardial Infarction and Nonfatal Stroke in the per Protocol Population



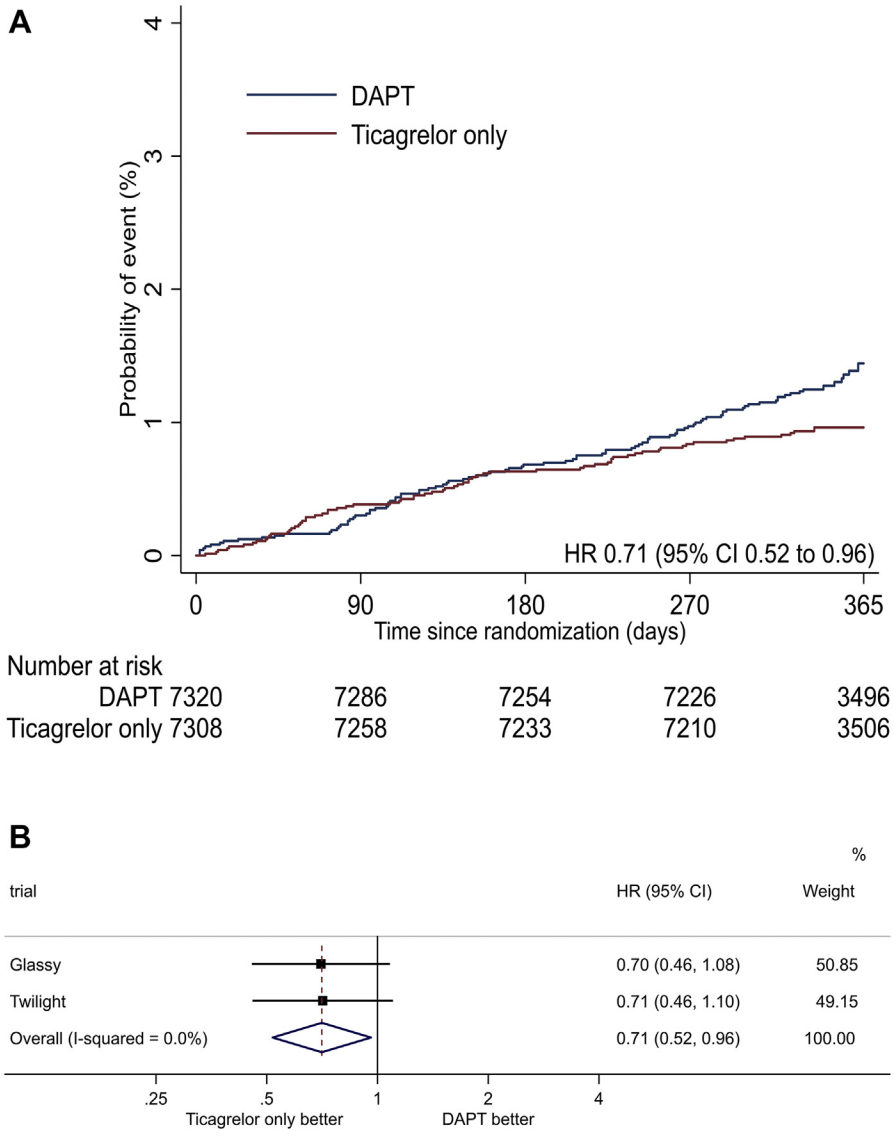
Kaplan-Meier curves and HRs from 1-step fixed-effect meta-analysis **(A)** and 2-step fixed-effect meta-analysis **(B)**. Abbreviations as in Figure 1.

STUDY LIMITATIONS. First, the study is subject to the shortcomings of the original trials. Second, only 2 trials fulfilled the selection criteria. However, the gathered IPD dataset included a large patient population from multiple geographic areas. Consistency of adjudication between the 2 trials was evaluated using 100 randomly selected events from each trial. The consistency of the adjudication and the large number of outcome events make our pooled analysis more robust and credible.

Third, the left censoring of the first 30 days after randomization was introduced for the main analyses for GLASSY because by design all patients received standard DAPT within the first 30-day period. However, sensitivity analyses for both coprimary endpoints, including the 30-day period following randomization in GLASSY, provided consistent results. Fourth, no correction for multiple testing was pre-specified. Therefore, the findings on the mortality benefit with ticagrelor monotherapy are exploratory and need replication in a larger dataset.

Fifth, the 2 trials included different patient populations because GLASSY was designed as all-comers study, whereas TWILIGHT included patients at

FIGURE 3 **HRs for Individual Trials and for the Pooled Population and Kaplan-Meier Estimates for All-Cause Death in the Intention-to-Treat Population**

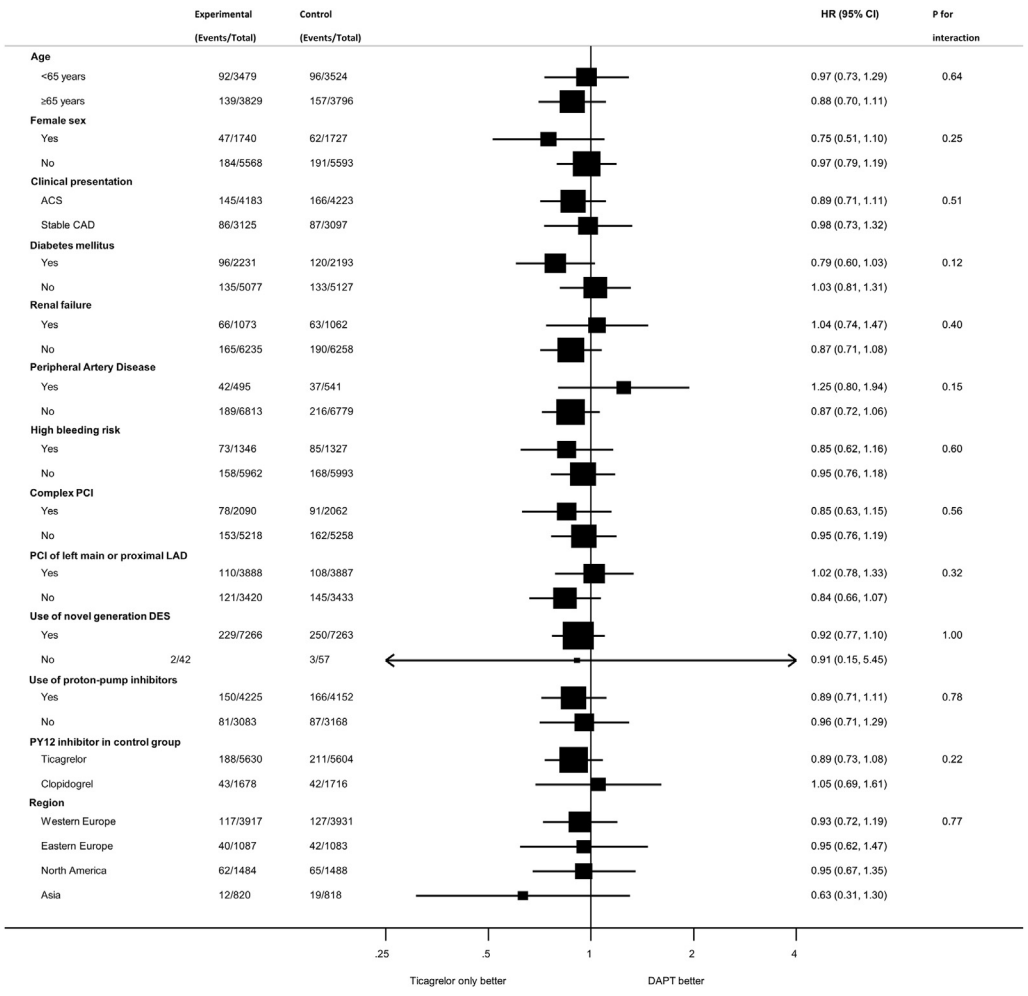


Kaplan-Meier curves and HRs from 1-step fixed-effect meta-analysis **(A)** and 2-step fixed-effect meta-analysis **(B)**. Abbreviations as in Figure 1.

higher risk for ischemic events. Sixth, although the experimental arms in both studies were similar, differences in the type of oral $P2Y_{12}$ inhibitor were present in the control arms (clopidogrel and ticagrelor in GLASSY and ticagrelor only in TWILIGHT). Moreover, although a direct comparison with aspirin monotherapy might be informative about the clinical effectiveness of ticagrelor monotherapy, this could not be performed because of the specific design of included studies.

Seventh, guideline-recommended DAPT duration has quickly evolved since the design of the present studies, and 12- or 15-month DAPT in the control group across all patients in stable condition and those with ACS may no longer be perceived as the current standard of care.

FIGURE 4 Subgroup Analyses for the Composite Coprimary Endpoint of All-Cause Death, Myocardial Infarction, and Stroke in the per-Protocol Population



High bleeding risk was defined on the basis of a PRECISE-DAPT (Predicting Bleeding Complication in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy) score of 25 or greater. ACS = acute coronary syndrome(s); CAD = coronary artery disease; DES = drug-eluting stent(s); LAD = left anterior descending coronary artery; PCI = percutaneous coronary intervention; other abbreviations as in Figure 1.

Finally, although this study supports the use of ticagrelor monotherapy after a short course of DAPT, our data cannot be extrapolated to other $P2Y_{12}$ inhibitors. The findings of ISAR-REACT 5 (Prospective, Randomized Trial of Ticagrelor Versus Prasugrel in Patients With Acute Coronary Syndrome) warrant assessing the risks and benefits of prasugrel monotherapy compared with current standard of care (27). In addition, the competing risk for bleeding and ischemic events after PCI is variable over time, and the safety and efficacy of extended, long-term, ticagrelor monotherapy as well as its application in specific clinical subset (i.e., patients requiring noncardiac surgery) need to be further investigated.

CONCLUSIONS

Compared with conventional DAPT, ticagrelor monotherapy was associated with a lower risk for major bleeding without evidence of a trade-off in terms of an increase in ischemic risk among patients who

underwent drug-eluting stent implantation. The observed benefit in terms of mortality needs further investigation.

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PERSPECTIVES

WHAT IS KNOWN? In patients undergoing PCI, dropping aspirin after a short course of DAPT is emerging as a novel strategy to lessen the risk for bleeding complications while preserving unaffected protection against ischemic events through more potent platelet inhibition.

WHAT IS NEW? This was an IPD meta-analysis of the only 2 studies currently investigating the risks and benefits of a ticagrelor monotherapy treatment strategy after a short course of DAPT compared with a standard DAPT regimen. We found that dropping aspirin shortly after PCI is associated with lower bleeding and mortality risks, without a concomitant increase in cardiovascular ischemic recurrences compared with standard DAPT continuation.

WHAT IS NEXT? Further studies comparing a strategy based on monotherapy with more potent $P2Y_{12}$ inhibitors and standard DAPT are warranted.

REFERENCES

1. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the Task Force for Dual Antiplatelet Therapy in Coronary Artery Disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2018;39:213–60.

2. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease. J Am Coll Cardiol 2016;68:1082–115.

3. Valgimigli M, Costa F, Lokhnygina Y, et al. Trade-off of myocardial infarction vs. bleeding types on mortality after acute coronary syndrome: lessons from the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) randomized trial. Eur Heart J 2017;38:804–10.

4. Mehran R, Pocock S, Nikolsky E, et al. Impact of bleeding on mortality after percutaneous coronary intervention. J Am Coll Cardiol Intv 2011;4:654–64.

5. Navarese EP, Andreotti F, Schulze V, et al. Optimal duration of dual antiplatelet therapy after percutaneous coronary intervention with drug eluting stents: meta-analysis of randomised controlled trials. BMJ 2015;350:h1618.

6. Valgimigli M, Campo G, Monti M, et al. Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting. Circulation 2012;125:2015–26.

7. Valgimigli M, Tebaldi M, Borghesi M, et al. Two-year outcomes after first- or second-generation drug-eluting or bare-metal stent implantation in all-comer patients undergoing percutaneous coronary intervention. J Am Coll Cardiol Intv 2014;7:20–8.

8. Costa F, Van Klaveren D, Feres F, et al. Dual antiplatelet therapy duration based on ischemic and bleeding risks after coronary stenting. J Am Coll Cardiol 2019;73:741–54.

9. Giustino G, Chieffo A, Palmerini T, et al. Efficacy and safety of dual antiplatelet therapy after complex PCI. J Am Coll Cardiol 2016;68:1851–64.

10. Hahn J-Y, Song YB, Oh J-H, et al. 6-Month versus 12-month or longer dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (SMART-DATE): a randomised, open-label, non-inferiority trial. Lancet 2018;391:1274–84.

11. Li L, Geraghty OC, Mehta Z, Rothwell PM. Age-specific risks, severity, time course, and outcome of bleeding on long-term antiplatelet treatment after vascular events: a population-based cohort study. Lancet 2017;390:490–9.

12. Gargiulo G, Windecker S, Vranckx P, Gibson CM, Mehran R, Valgimigli M. A critical appraisal of aspirin in secondary prevention. Circulation 2016;134:1881–906.

13. Vranckx P, Valgimigli M, Jüni P, et al. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. Lancet 2018;392:940–9.

14. Watanabe H, Domei T, Morimoto T, et al. Effect of 1-month dual antiplatelet therapy followed by clopidogrel vs 12-month dual antiplatelet therapy on cardiovascular and bleeding events in patients receiving PCI. JAMA 2019;321:2414–27.

15. Mehran R, Baber U, Sharma SK, et al. Ticagrelor with or without aspirin in high-risk patients after PCI. N Engl J Med 2019;381:2032–42.

16. Stewart LA, Clarke M, Rovers M, et al. Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: thee PRISMA-IPD statement. JAMA 2015;313:1657–65.

17. Leonardi S, Franzone A, Piccolo R, et al. Rationale and design of a prospective substudy of clinical endpoint adjudication processes within an investigator-reported randomised controlled trial in patients with coronary artery disease: the GLOBAL LEADERS Adjudication Sub-Study (GLASSY). BMJ Open 2019;9:e026053.

18. Franzone A, McFadden E, Leonardi S, et al. Ticagrelor alone versus dual antiplatelet therapy from 1 month after drug-eluting coronary stenting. J Am Coll Cardiol 2019;74:2223–34.

19. Higgins JPT, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.

20. Kuno T, Ueyama H, Takagi H, Bangalore S. $P2Y_{12}$ inhibitor monotherapy versus aspirin monotherapy after short-term dual antiplatelet therapy for percutaneous coronary intervention: Insights from a network meta-analysis of randomized trials. Am Heart J 2020;227:82–90.

21. McClure JD, Ramsay JC, Berry C. Pooled analysis of bleeding, major adverse cardiovascular events, and all-cause mortality in clinical trials of time-constrained dual-antiplatelet therapy after percutaneous coronary intervention. J Am Heart Assoc 2020;9:e017109.

22. Claassens DMF, Vos GJA, Bergmeijer TO, et al. A genotype-guided strategy for oral $P2Y_{12}$ inhibitors in primary PCI. N Engl J Med 2019;381:1621–31.

23. Sibbing D, Aradi D, Jacobshagen C, et al. Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial. Lancet 2017;390:1747–57.

24. Valgimigli M, Gagnor A, Calabró P, et al. Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: a randomised multicentre trial. Lancet 2015;385:2465–76.

25. Valgimigli M, Frigoli E, Leonardi S, et al. Radial versus femoral access and bivalirudin versus unfractionated heparin in invasively managed patients with acute coronary syndrome (MATRIX): final 1-year results of a multicentre, randomised controlled trial. Lancet 2018;392:835–48.

26. Stone GW, Witzenbichler B, Guagliumi G, et al. Bivalirudin during primary PCI in acute myocardial infarction. N Engl J Med 2008;358:2218–30.

27. Schüpke S, Neumann F-J, Menichelli M, et al. Ticagrelor or prasugrel in patients with acute coronary syndromes. N Engl J Med 2019;381:1524–34.

KEY WORDS aspirin, DAPT, meta-analysis, $P2Y_{12}$ inhibitors, ticagrelor

APPENDIX For a list of SIDNEY collaborators, supplemental methods, the assembled dataset, the search strategy, a reference list of included trials, further details on data analysis, supplemental tables, figures, and references, please see the online version of this paper.