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Ticagrelor or Clopidogrel Monotherapy vs Dual Antiplatelet Therapy After Percutaneous Coronary Intervention

A Systematic Review and Patient-Level Meta-Analysis

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IMPORTANCE Among patients undergoing percutaneous coronary intervention (PCI), it remains unclear whether the treatment efficacy of $P2Y_{12}$ inhibitor monotherapy after a short course of dual antiplatelet therapy (DAPT) depends on the type of $P2Y_{12}$ inhibitor.

OBJECTIVE To assess the risks and benefits of ticagrelor monotherapy or clopidogrel monotherapy compared with standard DAPT after PCI.

DATA SOURCES MEDLINE, Embase, TCTMD, and the European Society of Cardiology website were searched from inception to September 10, 2023, without language restriction.

STUDY SELECTION Included studies were randomized clinical trials comparing $P2Y_{12}$ inhibitor monotherapy with DAPT on adjudicated end points in patients without indication to oral anticoagulation undergoing PCI.

DATA EXTRACTION AND SYNTHESIS Patient-level data provided by each trial were synthesized into a pooled dataset and analyzed using a 1-step mixed-effects model. The study is reported following the Preferred Reporting Items for Systematic Review and Meta-Analyses of Individual Participant Data.

MAIN OUTCOMES AND MEASURES The primary objective was to determine noninferiority of ticagrelor or clopidogrel monotherapy vs DAPT on the composite of death, myocardial infarction (MI), or stroke in the per-protocol analysis with a 1.15 margin for the hazard ratio (HR). Key secondary end points were major bleeding and net adverse clinical events (NACE), including the primary end point and major bleeding.

RESULTS Analyses included 6 randomized trials including 25 960 patients undergoing PCI, of whom 24 394 patients (12 403 patients receiving DAPT; 8292 patients receiving ticagrelor monotherapy; 3654 patients receiving clopidogrel monotherapy; 45 patients receiving prasugrel monotherapy) were retained in the per-protocol analysis. Trials of ticagrelor monotherapy were conducted in Asia, Europe, and North America; trials of clopidogrel monotherapy were all conducted in Asia. Ticagrelor was noninferior to DAPT for the primary end point (HR, 0.89; 95% CI, 0.74-1.06; *P* for noninferiority = .004), but clopidogrel was not noninferior (HR, 1.37; 95% CI, 1.01-1.87; *P* for noninferiority > .99), with this finding driven by noncardiovascular death. The risk of major bleeding was lower with both ticagrelor (HR, 0.47; 95% CI, 0.36-0.62; *P* < .001) and clopidogrel monotherapy (HR, 0.49; 95% CI, 0.30-0.81; *P* = .006; *P* for interaction = 0.88). NACE were lower with ticagrelor (HR, 0.74; 95% CI, 0.64-0.86, *P* < .001) but not with clopidogrel monotherapy (HR, 1.00; 95% CI, 0.78-1.28; *P* = .99; *P* for interaction = .04).

CONCLUSIONS AND RELEVANCE This systematic review and meta-analysis found that ticagrelor monotherapy was noninferior to DAPT for all-cause death, MI, or stroke and superior for major bleeding and NACE. Clopidogrel monotherapy was similarly associated with reduced bleeding but was not noninferior to DAPT for all-cause death, MI, or stroke, largely because of risk observed in 1 trial that exclusively included East Asian patients and a hazard that was driven by an excess of noncardiovascular death.

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Supplemental content

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Group Information: The Single Versus Dual Antiplatelet Therapy (Sidney-3) Collaboration members are listed in Supplement 1.

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Dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor is recommended after percutaneous coronary intervention (PCI) to reduce the risk of cardiovascular ischemic events.[1,2] However, prolonged DAPT use is associated with an increased risk of bleeding.[3-5] Studies with an abbreviated DAPT duration followed by aspirin monotherapy have reported lower bleeding but higher ischemic risks, especially in patients with acute coronary syndrome (ACS) or complex PCI, compared with standard DAPT.[6-8] Aspirin cessation and continuation of the $P2Y_{12}$ inhibitor after a short course of DAPT has been more recently investigated.[9-14] A patient-level meta-analysis including 23 308 patients undergoing coronary revascularization showed that $P2Y_{12}$ inhibitor monotherapy, after 1- to 3-month DAPT, was associated with a similar risk of death, myocardial infarction (MI), 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 efficacy of $P2Y_{12}$ inhibitor monotherapy might differ depending on the type of $P2Y_{12}$ inhibitor. Clopidogrel is associated with large interindividual platelet response variability, and up to 30% of patients have high residual platelet reactivity while receiving treatment and a greater risk of subsequent cardiovascular events.[16]

In a 2022 randomized clinical trial including 4169 patients with ACS undergoing implantation of current-generation drug-eluting stents, clopidogrel monotherapy after 1 to 2 months of DAPT failed to show noninferiority to conventional DAPT for the net clinical benefit. Furthermore, clopidogrel was associated with a substantial increase in the rate of MI.[17]

Therefore, we updated a patient-level meta-analysis[15] to reflect the totality of available evidence from randomized clinical trials that compared $P2Y_{12}$ inhibitor monotherapy with DAPT in patients who underwent PCI to ascertain whether the efficacy of monotherapy depends on the type of $P2Y_{12}$ inhibitor.

Key Points

Question Are ticagrelor or clopidogrel monotherapy after percutaneous coronary intervention (PCI) and 1 to 3 month dual antiplatelet therapy (DAPT) similarly effective and safer compared with standard DAPT?

Findings This systematic review and individual patient data meta-analysis including 6 randomized clinical trials with 25 960 patients found that ticagrelor monotherapy was noninferior to DAPT for death, myocardial infarction, or stroke and superior for major bleeding. Clopidogrel monotherapy was associated with reduced bleeding but was not noninferior for death, myocardial infarction, or stroke.

Meaning These findings suggest that ticagrelor monotherapy was similarly effective and safer than DAPT and that clopidogrel was not noninferior to DAPT for ischemic protection, but the current evidence base is inadequate and further trials are needed.

Methods

The protocol for this systematic review and individual patient data meta-analysis was prospectively registered with PROSPERO (identifier: CRD42022347824). Methods and reporting follow the Preferred Reporting Items for Systematic Review and Meta-Analyses of Individual Participant Data (PRISMA-IPD).[18] Each trial was approved by local ethics committees. All patients provided written informed consent for inclusion in each trial.

Search Strategy and Selection Criteria

We performed a systematic review and patient-level meta-analysis of randomized clinical trials comparing $P2Y_{12}$ inhibitor monotherapy with DAPT in patients undergoing PCI without an indication for long-term oral anticoagulation on centrally adjudicated end points. A previous search[15] was updated using identical methods and including unique citations from June 16, 2020, to September 10, 2023 (eAppendix 1 in Supplement 1).

Data Extraction and Quality Assessment

Data from 5 trials[9-13] were available from a previous analysis (eAppendix 2 in Supplement 1).[15,19] For 1 additional trial,[17] the dataset was obtained and pooled with other trials. Data were checked for integrity and completeness, and the clean data were analyzed. Two investigators (F.G. and M.B.) independently assessed the risk of bias using the revised Cochrane risk-of-bias tool (ROB 2).[20] Disagreements were solved by discussion and, if unsolved, by consulting a third investigator (M.V.).

Outcomes

The primary end point was the composite of all-cause death, MI, or stroke. The key secondary end points were major bleeding, defined as Bleeding Academic Research Consortium type 3 or 5, and net adverse clinical events (NACE), defined as the composite of the primary end point and major bleeding. Outcome data were analyzed throughout the duration of the randomized comparison of protocol-mandated $P2Y_{12}$ inhibitor monotherapy vs DAPT. Nonfatal components and disease-specific mortality were centrally adjudicated in each trial by an independent clinical events committee; the original adjudication data were used for this analysis. Other secondary end points are described in eAppendix 3 in Supplement 1.

Statistical Analysis

We did a 1-step meta-analysis to model patient-level data from available trials using a mixed-effects Cox regression model with baseline hazards stratified by trial and a random slope to account for variation between trials in treatment efficacy.[21] Treatment effects were expressed as hazard ratios (HRs) and 95% CIs. The extent of heterogeneity was estimated by the variance of the random slope τ^2. We used I^2 to estimate between-trial heterogeneity. Primary analyses were conducted separately for ticagrelor and clopidogrel monotherapy. We first tested for noninferiority of ticagrelor monotherapy and of clopidogrel monotherapy for the primary end point, each at a 1-sided $\alpha = .025$. If noninferiority was met for either drug, we prespecified to test for superiority of the monotherapy with this drug for the primary

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end point at a 2-sided α = .025. The noninferiority margin was prespecified at 1.15 on an HR scale,[15] which preserves 50% of the treatment effect of aspirin vs control reported in patients with prior MI for the composite of vascular death, MI, or stroke.[22] Noninferiority analyses were performed in the per-protocol populations, which excluded patients violating enrollment criteria 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 efficacy depended on the type of $P2Y_{12}$ inhibitor used in the experimental group. In the primary per-protocol analysis, we report a 1-sided *P* value for noninferiority; for all other analyses, we report 2-sided *P* values for superiority and 2-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 after randomization during the initial 1- to 3-month DAPT phase, 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 group. Data were analyzed up to the longest available time point with protocol-specified $P2Y_{12}$ inhibitor monotherapy in the experimental group and DAPT in the control group. Prespecified subgroup and sensitivity analyses were conducted. Further details are reported in eAppendix 4 in Supplement 1. Analyses were conducted using Stata version 16.1 (StataCorp) and R version 3.6.1 (R Project for Statistical Computing).

Results

Study Selection

We identified 6450 unique citations, of which 7 were judged potentially eligible, and 1 was eligible for inclusion after full-text review.[17] Of 6 studies[9-14] that were already available from a previous analysis, 1 study of 334 patients undergoing coronary artery bypass grafting[14] was excluded to ensure consistent assessment of treatment efficacy in patients after PCI. The study selection flow diagram is provided in eFigure 1 in Supplement 1. Patient-level data were sought and obtained for 6 eligible trials[9-13,17] (eTable 1 and eTable 2 in Supplement 1). The end point definitions were largely consistent across trials (eTable 3 in Supplement 1). All studies were sponsored by not-for-profit organizations. The risk of bias was judged as low in 1 trial[10] and revealed some concerns in 5 unblinded trials[9,11-13,17] (eTable 4 in Supplement 1).

We obtained data for 26 750 participants (eFigure 2 in Supplement 1). We excluded 203 patients due to premature study termination or death occurring during the initial DAPT phase, which was common to both study groups in 5 trials,[9,11-13,17] and 587 patients from 1 study[10] owing to lack of approval for data sharing by Chinese regulatory authorities.

Study Population

A total of 25 960 patients were available for the intention-to-treat analysis, including 12 960 patients assigned to $P2Y_{12}$ inhibitor monotherapy and 13 000 patients assigned to DAPT. A total of 8790 patients receiving ticagrelor monotherapy, 4110 patients receiving clopidogrel monotherapy, and 60 patients receiving prasugrel monotherapy were compared with 8791, 4144, and 65 participants treated with DAPT, respectively. The per-protocol analysis excluded 1566 patients (6.03%) not fulfilling the prespecified criteria, and included 8292 patients receiving ticagrelor monotherapy (vs 8480 patients receiving DAPT), 3654 patients receiving clopidogrel monotherapy (vs 3860 patients receiving DAPT), and 45 patients receiving prasugrel monotherapy (vs 63 patients receiving DAPT) (eFigure 2 in Supplement 1). The median (range) treatment duration was 334 (300-334) days.

Baseline characteristics of the ticagrelor or clopidogrel monotherapy groups were well-balanced compared with the DAPT groups (**Table 1**; eTable 5 in Supplement 1). The mean (SD) age was 64 (11) years with ticagrelor and 67 (11) years with clopidogrel, and female patients comprised 23% of participants in both groups. Among patients receiving ticagrelor monotherapy, 29.9% of patients had diabetes and 15.4% of patients had chronic kidney disease, while among patients receiving clopidogrel monotherapy, 35.4% of patients had diabetes and 24.8% of patients had chronic kidney disease. The qualifying event for inclusion was an ACS in 64.8% of patients in the ticagrelor monotherapy group and 63.1% of patients in the clopidogrel monotherapy group. Ticagrelor monotherapy was compared with aspirin and ticagrelor in 80.4% of patients and with aspirin and clopidogrel in 19.6% of patients, whereas clopidogrel monotherapy was exclusively compared with aspirin and clopidogrel. Comparisons of baseline characteristics of patients included in trials testing ticagrelor or clopidogrel monotherapy are shown in eTable 6 and eTable 7 in Supplement 1. Clinical characteristics and outcomes of patients assigned to prasugrel monotherapy or DAPT are described in eTable 8 and eTable 9 in Supplement 1.

Ticagrelor Monotherapy vs DAPT

Ticagrelor monotherapy was noninferior to DAPT in the per-protocol analysis (cumulative incidence of the primary end point of death, MI, or stroke at 12 months, 3.00% vs 3.46%; HR, 0.89; 95% CI, 0.74-1.06; $\tau^2 < 0.001$, *P* for noninferiority = .004; *P* for superiority = .19) and the intention-to-treat analysis (cumulative incidence of the primary end point, 3.01% vs 3.49%; HR, 0.89; 95% CI, 0.74-1.06; $\tau^2 < 0.001$; *P* for noninferiority = .004; *P* for superiority = .18) (**Table 2** and **Figure 1**). In intention-to-treat analyses, we found evidence that ticagrelor was associated with a reduced risk of all-cause death compared with DAPT (cumulative incidence, 0.94% vs 1.44%; HR, 0.72; 95% CI, 0.54-0.97; $\tau^2 < 0.001$; *P* = .03), whereas there was no significant association of ticagrelor with cardiovascular death (cumulative incidence, 0.61% vs 0.92%; HR, 0.70; 95% CI, 0.49-1.01; $\tau^2 < 0.001$; *P* = .06). The risk of major bleeding

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Table 1. Baseline Characteristics in Patients With Ticagrelor or Clopidogrel Monotherapy or DAPT

Characteristic	Ticagrelor monotherapy (n = 8790)	Aspirin + $P2Y_{12}$ inhibitor (n = 8791)	*P* value	Clopidogrel monotherapy (n = 4110)	Aspirin + $P2Y_{12}$ inhibitor (n = 4144)	*P* value
Study						
Franzone et al,[9] 2019	3753 (42.7)	3756 (42.7)	.98	0	0	NA
Hahn et al,[12] 2019	273 (3.1)	263 (3.0)	.66	1122 (27.3)	1143 (27.6)	.79
Watanabe et al,[11] 2019	0	0	NA	1496 (36.4)	1507 (36.4)	.98
Watanabe et al,[17] 2022	0	0	NA	1492 (36.3)	1494 (36.0)	.82
Kim et al,[13] 2020	1499 (17.1)	1505 (17.1)	.92	0	0	NA
Mehran et al,[10] 2019	3265 (37.1)	3267 (37.2)	.99	0	0	NA
Age						
No.	8790	8791	NA	4110	4144	NA
Mean (SD), y	64.2 (10.5)	64.2 (10.5)	.94	67.1 (11.2)	67.2 (11.2)	.90
≥65 y	4357(49.6)	4317 (49.1)	.55	2568 (62.5)	2570 (62.0)	.67
Sex						
No.	8790	8791	NA	4110	4144	NA
Female sex	2028 (23.1)	1981 (22.5)	.40	972 (23.6)	989 (23.9)	.82
Male sex	6762 (76.9)	6810 (77.5)		3138 (76.4)	3155 (76.1)	
Height						
No.	8781	8785	NA	4108	4141	NA
Mean (SD), m	1.7 (0.1)	1.7 (0.1)	>.99	1.6 (0.1)	1.6 (0.1)	.43
Weight						
No.	8784	8784	NA	4110	4142	NA
Mean (SD), kg	80.2 (17.3)	80.1 (17.0)	.65	65.1 (12.4)	65.0 (12.2)	.70
BMI						
No.	8781	8782	NA	4108	4141	NA
Mean (SD)	27.7 (5.0)	27.7 (5.0)	.74	24.3 (3.5)	24.3 (3.4)	.90
Geographic region						
No.	8790	8791	NA	4110	4144	NA
Asia	2302 (26.2)	2289 (26.0)	.82	4110 (100)	4144 (100)	NA
North America	1484 (16.9)	1488 (16.9)	.95	0	0	NA
Western Europe	3917 (44.5)	3931 (44.7)	.84	0	0	NA
Eastern Europe	1087 (12.4)	1083 (12.2)	.93	0	0	NA
Comorbidities, No./total No. (%)						
Diabetes	2624/8789 (29.9)	2578/8791 (29.3)	.44	1455/4107 (35.4)	1438/4144 (34.7)	.49
Insulin-treated diabetes	618/8591 (7.2)	652/8601 (7.6)	.33	164/3425 (4.8)	192/3429 (5.6)	.13
Current cigarette smoker	2395/8787 (27.3)	2508/8789 (28.5)	.06	1172/4109 (28.5)	1070/4141 (25.8)	.006
Hypercholesterolemia	5543/8654 (64.1)	5616/8660 (64.8)	.27	2599/4106 (63.3)	2631/4137 (63.6)	.78
Hypertension	6017/8781 (68.5)	6002/8779 (68.4)	.83	2803/4109 (68.2)	2869/4144 (69.2)	.32
Liver disease	15/8517 (0.2)	8/8528 (0.1)	.14	10/2988 (0.3)	6/3001 (0.2)	.31
PAD	489/7272 (6.7)	539/7271 (7.4)	.11	136/4108 (3.3)	151/4143 (3.6)	.41
Previous MI	1901/8783 (21.6)	1907/8789 (21.7)	.93	357/4109 (8.7)	331/4143 (8.0)	.25
Previous PCI	2790/8788 (31.7)	2832/8788 (32.2)	.50	796/4108 (19.4)	818/4143 (19.7)	.67
Previous CABG	571/8787 (6.5)	594/8789 (6.8)	.49	41/4108 (1.0)	58/4143 (1.4)	.09
Prior stroke	164/8784 (1.9)	168/8789 (1.8)	.83	233/4108 (5.7)	261/4144 (6.3)	.23
Prior bleeding	58/8782 (0.7)	54/8786 (0.6)	.70	82/4107 (2.0)	85/4143 (2.1)	.86
History of CKD	1333/8648 (15.4)	1353/8657 (15.6)	.70	1018/4109 (24.8)	1022/4144 (24.7)	.91
Chronic lung disease	358/6947 (5.2)	373/6954 (5.4)	.58	66/2988 (2.2)	81/3001 (2.7)	.22
Clinical presentation						
No.	8789	8791	NA	4110	4142	NA
CCS	3097 (35.2)	3081 (35.0)	.79	1515 (36.9)	1514 (36.6)	.77
ACS						
Any	5692 (64.8)	5710 (65.0)	NA	2595 (63.1)	2628 (63.4)	NA
Unstable angina	2092 (36.7)	2120 (37.1)	.68	826 (31.8)	866 (32.9)	.39
Non-STEMI	2314 (40.7)	2323 (40.7)	.99	528 (20.4)	557 (21.2)	.45
STEMI	1286 (22.6)	1267 (22.2)	.61	1241 (47.8)	1205 (45.9)	.16

(continued)

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Table 1. Baseline Characteristics in Patients With Ticagrelor or Clopidogrel Monotherapy or DAPT (continued)

Characteristic	Ticagrelor monotherapy (n = 8790)	Aspirin + $P2Y_{12}$ inhibitor (n = 8791)	*P* value	Clopidogrel monotherapy (n = 4110)	Aspirin + $P2Y_{12}$ inhibitor (n = 4144)	*P* value
Aspirin on admission, No./total No. (%)	6167/8789 (70.2)	6185/8790 (70.4)	.78	250/1122 (22.3)	257/1141 (22.5)	.89
PRECISE-DAPT[a]						
No.	8340	8374	NA	4054	4099	NA
Mean (SD)	16.3 (8.8)	16.3 (8.9)	.83	17.1 (10.9)	17.2 (10.9)	.56
PRECISE-DAPT ≥25, No./total No. (%)	1336/8340 (16.0)	1342/8374 (16.0)	.99	786/4054 (19.4)	787/4099 (19.2)	.83
Creatinine clearance (MDRD)						
No.	8647	8657	NA	4070	4110	NA
Median (IQR), mL/min/1.73 m^2	83.5 (69.7-98.3)	82.9 (68.9-98.2)	.16	90.5 (73.9-108.4)	90.6 (74.3-107.4)	.61
Hemoglobin						
No.	8485	8500	NA	4073	4106	NA
Mean (SD), g/dL	14.1 (1.6)	14.1 (1.7)	.55	13.7 (1.9)	13.7 (2.8)	.97
LVEF						
No.	4269	4242	NA	3747	3800	NA
Mean (SD), %	54.0 (10.8)	54.1 (11.1)	.62	58.7 (10.8)	58.8 (10.7)	.63

Abbreviations: ACS, acute coronary syndrome; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CABG, coronary artery bypass grafting; CCS, chronic coronary syndrome; CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; LVEF, left ventricular ejection fraction; MDRD, Modification of Diet in Renal Disease; MI, myocardial infarction; NA, not applicable; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

SI conversion factor: To convert creatinine clearance to milliliters per second per meter squared, multiply by 0.0167; to convert hemoglobin to grams per liter, multiply by 10.

[a] The PRECISE-DAPT score includes 5 items: age, creatinine clearance, white blood cell count, hemoglobin, and history of bleeding.

was more than halved with ticagrelor (cumulative incidence, 0.94% vs 2.00%; HR, 0.47; 95% CI, 0.36-0.62; $\tau^2 = 0.053$; $P < .001$) compared with DAPT (Figure 1), yielding a number needed to treat to benefit of 94. NACE were lower with ticagrelor monotherapy than DAPT (cumulative incidence, 3.84% vs 5.25%; HR, 0.74; 95% CI, 0.64-0.86; $\tau^2 = 0.056$; $P < .001$), with a number needed to treat to benefit of 73.

Clopidogrel Monotherapy vs DAPT

Clopidogrel monotherapy did not meet noninferiority to DAPT in the per-protocol analysis (cumulative incidence of the primary end point, 2.76% vs 2.07%; HR, 1.37; 95% CI, 1.01-1.87; $\tau^2 = 0.034$; *P* for noninferiority > .99; *P* for superiority = .04) and the intention-to-treat analysis (cumulative incidence of the primary end point, 2.90% vs 2.38%; HR, 1.24; 95% CI, 0.94-1.63; $\tau^2 = 0.14$; *P* for noninferiority > .99; *P* for superiority = .13) (**Table 3** and **Figure 2**). In intention-to-treat analyses, the risks of all-cause death (cumulative incidence, 1.31% vs 0.97%; HR, 1.33; 95% CI, 0.87-2.03; $\tau^2 < 0.001$; $P = .19$) and cardiovascular death (cumulative incidence, 0.44% vs 0.61%; HR, 0.72; 95% CI, 0.38-1.33; $\tau^2 < 0.001$; $P = .29$) did not differ significantly. The risk of major bleeding was lower with clopidogrel monotherapy (cumulative incidence, 0.59% vs 1.20%; HR, 0.49; 95% CI, 0.30-0.81; $\tau^2 = 0.415$; $P = .006$; number needed to treat to benefit, 163) and the risk of NACE was similar (cumulative incidence, 3.29% vs 3.28%; HR, 1.00; 95% CI, 0.78-1.28; $\tau^2 = 0.079$; $P = .99$) compared with DAPT (Figure 2).

Treatment Efficacy by Type of $P2Y_{12}$ Inhibitor

After multivariable adjustment for observed differences, there was evidence for an interaction with the type of $P2Y_{12}$ inhibitor monotherapy (ie, ticagrelor or clopidogrel) for the primary end point of death, MI, or stroke in the per-protocol and intention-to-treat analyses. An interaction was also found for type of $P2Y_{12}$ inhibitor with the composite of death or MI, all-cause death alone, and NACE in the per-protocol and intention-to-treat analyses (eFigure 3 and eFigure 4 in Supplement 1).

Subgroup and Sensitivity Analyses

Prespecified subgroup analyses of the primary composite end point suggested variation in the efficacy of ticagrelor monotherapy by sex and diabetes, whereas the treatment efficacy was consistent for clopidogrel monotherapy compared with DAPT (eFigures 5-8 in Supplement 1). The absolute risk difference in the primary end point with clopidogrel monotherapy vs DAPT was greater in patients with ACS than in those undergoing elective PCI. The relative risk increase in the primary end point with clopidogrel monotherapy vs DAPT was similar in patients with acute and chronic coronary syndrome, with negative interaction testing in the intention-to-treat and per-protocol analyses.

Results for the primary and key secondary end points remained consistent in prespecified sensitivity analyses (eFigures 9-12 and eTables 10-17 in Supplement 1). Results were also consistent when monotherapy with a newer $P2Y_{12}$ inhibitor (ticagrelor or prasugrel) was compared with DAPT and when ticagrelor monotherapy was exclusively compared with ticagrelor plus aspirin (eFigure 13, eFigure 14, eTable 18, and eTable 19 in Supplement 1).

The leave-one-out analysis of the clopidogrel trials highlighted that STOPDAPT-2 ACS was the primary driver of the observed risk, and when we excluded that trial, the signal of harm

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Table 2. Clinical Outcomes in Patients With Ticagrelor Monotherapy or DAPT

Outcome	Intention-to-treat population						Per-protocol population					
	Events, No. (%)						Events, No. (%)					
	Ticagrelor monotherapy (n = 8790)	Aspirin + $P2Y_{12}$ inhibitor (n = 8791)	HR (95% CI)	τ^2	I^2, %	*P* value	Ticagrelor monotherapy (n = 8292)	Aspirin + $P2Y_{12}$ inhibitor (n = 8480)	HR (95% CI)	τ^2	I^2, %	*P* value
Death, MI, or stroke[a]	238 (3.01)	269 (3.49)	0.89 (0.74-1.06)	<0.001	0	.18	224 (3.00)	258 (3.46)	0.89 (0.74-1.06)	0.005	9.8	.19
Death or MI	212 (2.66)	246 (3.21)	0.86 (0.72-1.04)	<0.001	0	.12	200 (2.65)	239 (3.22)	0.85 (0.71-1.03)	<0.001	0	.10
Death												
All cause	78 (0.94)	108 (1.44)	0.72 (0.54-0.97)	<0.001	0	.03	78 (0.99)	104 (1.43)	0.77 (0.57-1.03)	<0.001	0	.08
Cardiovascular	50 (0.61)	70 (0.92)	0.70 (0.49-1.01)	<0.001	0	.06	50 (0.65)	68 (0.92)	0.74 (0.51-1.06)	<0.001	0	.10
Noncardiovascular	24 (0.28)	33 (0.46)	0.73 (0.43-1.23)	<0.001	0	.24	24 (0.30)	32 (0.46)	0.78 (0.46-1.32)	<0.001	0	.35
Myocardial infarction	146 (1.85)	156 (2.00)	0.94 (0.75-1.18)	0.005	5.6	.58	134 (1.80)	152 (2.01)	0.90 (0.72-1.14)	0.072	54.2	.39
Stroke												
Any	33 (0.44)	28 (0.33)	1.18 (0.71-1.96)	<0.001	0	.52	31 (0.43)	24 (0.29)	1.33 (0.78-2.26)	<0.001	0	.30
Ischemic	28 (0.38)	26 (0.31)	1.08 (0.63-1.84)	0.097	35.1	.78	27 (0.38)	22 (0.27)	1.26 (0.72-2.21)	<0.001	0	.42
Hemorrhagic	4 (0.05)	1 (0.01)	4.01 (0.45-35.87)	<0.001	0	.21	3 (0.04)	1 (0.01)	3.08 (0.32-29.57)	<0.001	0	.33
Stent thrombosis												
Definite	21 (0.28)	25 (0.34)	0.80 (0.44-1.44)	<0.001	0	.46	17 (0.24)	24 (0.34)	0.72 (0.38-1.33)	<0.001	0	.29
Probable	3 (0.03)	6 (0.07)	0.50 (0.13-2.01)	<0.001	0	.33	3 (0.04)	6 (0.07)	0.51 (0.13-2.06)	<0.001	0	.35
Definite or probable	24 (0.31)	31 (0.41)	0.78 (0.46-1.32)	<0.001	0	.35	20 (0.28)	30 (0.41)	0.68 (0.38-1.19)	<0.001	0	.18
BARC bleeding												
2, 3 or 5	251 (3.21)	409 (5.16)	0.61 (0.52-0.71)	0.045	63.9	<.001	240 (3.24)	397 (5.18)	0.61 (0.52-0.72)	0.034	56.0	<.001
3 or 5	78 (0.94)	164 (2.00)	0.47 (0.36-0.62)	0.053	37.2	<.001	74 (0.94)	146 (1.85)	0.52 (0.39-0.68)	0.070	41.7	<.001
5	2 (0.02)	2 (0.02)	1.00 (0.14-7.11)	<0.001	0	>.99	2 (0.02)	2 (0.02)	1.02 (0.14-7.27)	<0.001	0	.97
TIMI bleeding												
Major	39 (0.47)	77 (0.94)	0.51 (0.34-0.74)	0.396	73.7	<.001	39 (0.50)	69 (0.88)	0.58 (0.39-0.85)	0.333	69.7	.006
Minor	134 (1.78)	236 (2.97)	0.56 (0.45-0.69)	<0.001	0	<.001	130 (1.82)	224 (2.92)	0.57 (0.46-0.71)	<0.001	0	<.001
Major or minor	172 (2.25)	309 (3.90)	0.55 (0.46-0.66)	0.040	58.5	<.001	168 (2.31)	290 (3.79)	0.57 (0.47-0.69)	0.080	61.6	<.001
NACE	306 (3.84)	410 (5.25)	0.74 (0.64-0.86)	0.056	66.0	<.001	288 (3.82)	381 (5.06)	0.77 (0.66-0.90)	0.047	59.8	.001

Abbreviations: BARC, Bleeding Academy Research Consortium; DAPT, dual antiplatelet therapy; HR, hazard ratio; 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.

[a] *P* for noninferiority = .004 of ticagrelor monotherapy vs DAPT in per-protocol population.

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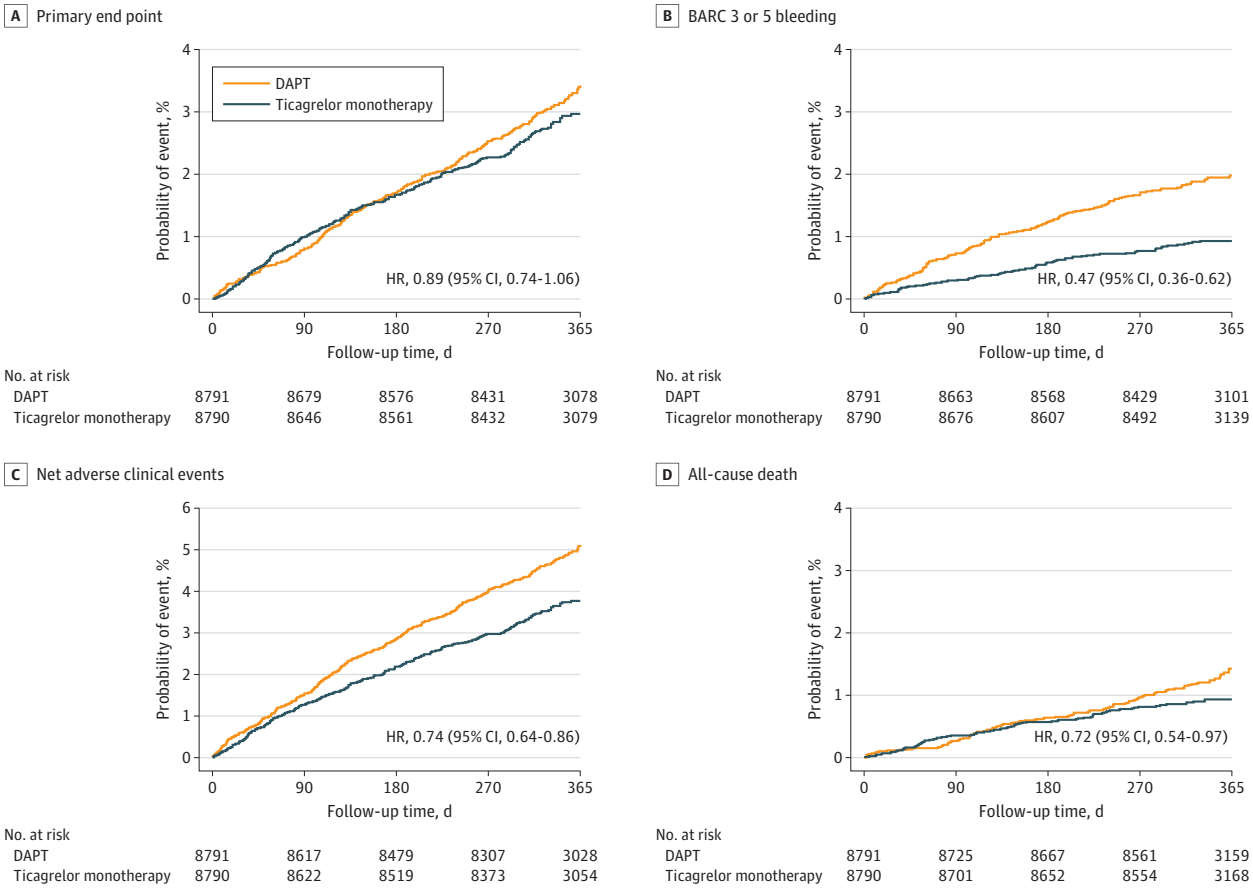
Figure 1. Kaplan-Meier Estimates for Clinical Outcomes in Patients Receiving Ticagrelor Monotherapy or Dual Antiplatelet Therapy (DAPT)



BARC indicates Bleeding Academic Research Consortium; HR, hazard ratio.

with clopidogrel monotherapy decreased (from HR, 1.37; 95% CI, 1.01-1.87; to HR, 1.13; 95% CI, 0.77-1.65) (eFigure 15 in Supplement 1). Stratified analyses of the per-protocol effect of clopidogrel monotherapy vs DAPT by clinical presentation in 2-step random-effects models are shown in eFigure 16 and eFigure 17 in Supplement 1.

In a post hoc landmark analysis of ticagrelor trials (eFigure 18 in Supplement 1), the treatment efficacies of ticagrelor monotherapy for the primary end point and bleeding were consistent within and beyond 6 months after aspirin discontinuation. In a post hoc landmark analysis of clopidogrel trials (eFigure 19 in Supplement 1), the higher risk for the primary end point with clopidogrel monotherapy vs DAPT was entirely concentrated in the early post-PCI period (within 6 months of aspirin discontinuation) and appeared similar thereafter; clopidogrel monotherapy was associated with consistently reduced post-PCI bleeding over time.

Discussion

This updated systematic review and patient-level meta-analysis of 6 randomized clinical trials, including 25 960 patients who underwent PCI, provides evidence that the treatment efficacy of $P2Y_{12}$ inhibitor monotherapy compared with DAPT continuation varied depending on the type of $P2Y_{12}$ inhibitor. Ticagrelor monotherapy, after a short course of DAPT, was noninferior for the composite of all-cause death, MI, or stroke and superior for the prevention of major bleeding and their combined appraisal in the NACE end point compared with DAPT continuation. Conversely, clopidogrel monotherapy, after a short course of DAPT, did not meet noninferiority in intention-to-treat or per-protocol analyses and was associated with a significantly higher risk of death, MI, or stroke in a per-protocol analysis. Subgroup analyses by type of $P2Y_{12}$ inhibitor monotherapy provided evidence of a qualitative interaction for the composites of death, MI, or stroke, death or MI, and all-cause death alone, suggesting similar efficacy for ticagrelor and harm for clopidogrel monotherapy compared with DAPT.

A prolonged DAPT regimen was associated with superior outcomes in selected patients for the prevention of cardiovascular events compared with abbreviated DAPT regimens followed by aspirin monotherapy after PCI.[6-8] However, prolonged DAPT increases bleeding risk, which offsets the anticipated ischemic benefits in patients with high bleeding or low ischemic risks.[3-5] Guidelines recommend DAPT duration be guided by ischemic and bleeding risks assessment[1,2];

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Table 3. Clinical Outcomes in Patients With Clopidogrel Monotherapy or DAPT

Outcome	Intention-to-treat population						Per-protocol population					
	Events, No. (%)						Events, No. (%)					
	Clopidogrel monotherapy (n = 4110)	Aspirin + $P2Y_{12}$ inhibitor (n = 4144)	HR (95% CI)	τ^2	I^2, %	*P* value	Clopidogrel monotherapy (n = 3654)	Aspirin + $P2Y_{12}$ inhibitor (n = 3860)	HR (95% CI)	τ^2	I^2, %	*P* value
Death, MI, or stroke[a]	110 (2.90)	90 (2.38)	1.24 (0.94-1.63)	0.140	68.7	.13	94 (2.76)	73 (2.07)	1.37 (1.01-1.87)	0.034	31.1	.04
Death or MI	87 (2.30)	69 (1.81)	1.27 (0.93-1.75)	0.187	69.3	.13	75 (2.2)	60 (1.67)	1.33 (0.95-1.87)	0.056	37.5	.10
Death												
All cause	50 (1.31)	38 (0.97)	1.33 (0.87-2.03)	<0.001	0	.19	46 (1.34)	30 (0.82)	1.64 (1.03-2.59)	<0.001	0	.04
Cardiovascular	17 (0.44)	24 (0.61)	0.72 (0.38-1.33)	<0.001	0	.29	17 (0.49)	18 (0.48)	1.03 (0.53-2.00)	<0.001	0	.93
Noncardiovascular	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	68.8	.32	32 (0.95)	31 (0.88)	1.11 (0.67-1.81)	0.127	37.9	.69
Stroke												
Any	24 (0.61)	22 (0.59)	1.10 (0.62-1.97)	0.307	51.0	.74	20 (0.57)	14 (0.41)	1.51 (0.76-2.99)	<0.001	0	.24
Ischemic	17 (0.44)	19 (0.51)	0.90 (0.47-1.73)	0.186	30.5	.76	15 (0.43)	11 (0.33)	1.40 (0.64-3.04)	<0.001	0	.40
Hemorrhagic	4 (0.1)	2 (0.05)	2.02 (0.37-11.02)	<0.001	0	.42	3 (0.08)	2 (0.05)	1.59 (0.27-9.51)	<0.001	0	.61
Stent thrombosis												
Definite	7 (0.19)	3 (0.09)	2.35 (0.61-9.1)	<0.001	0	.22	2 (0.07)	2 (0.05)	1.05 (0.15-7.43)	<0.001	0	.96
Probable	1 (0.03)	0	NA	NA	NA	NA	1 (0.03)	0	NA	NA	NA	NA
Definite or probable	8 (0.22)	3 (0.09)	2.69 (0.71-10.14)	<0.001	0	.14	3 (0.09)	2 (0.05)	1.57 (0.26-9.42)	<0.001	0	.62
BARC bleeding												
2, 3 or 5	52 (1.36)	107 (2.78)	0.49 (0.35-0.68)	0.001	1.0	<.001	43 (1.25)	101 (2.81)	0.47 (0.33-0.67)	0.062	36.5	<.001
3 or 5	23 (0.59)	47 (1.20)	0.49 (0.30-0.81)	0.415	65.5	.006	20 (0.57)	43 (1.17)	0.50 (0.29-0.85)	0.438	64.0	.01
5	2 (0.05)	3 (0.07)	0.67 (0.11-4.02)	<0.001	0	.66	2 (0.05)	3 (0.08)	0.71 (0.12-4.23)	<0.001	0	.70
TIMI bleeding												
Major	7 (0.18)	20 (0.52)	0.35 (0.15-0.83)	0.002	0.4	.02	6 (0.17)	17 (0.48)	0.35 (0.14-0.90)	<0.001	0	.03
Minor	3 (0.07)	10 (0.25)	0.30 (0.08-1.10)	<0.001	0	.07	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	61.5	.99	107 (3.14)	105 (2.92)	1.09 (0.83-1.42)	<0.001	0	.54

Abbreviations: BARC, Bleeding Academy Research Consortium; DAPT, dual antiplatelet therapy; HR, hazard ratio; 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.

[a] *P* for noninferiority >.99 of clopidogrel monotherapy vs DAPT in per-protocol population.

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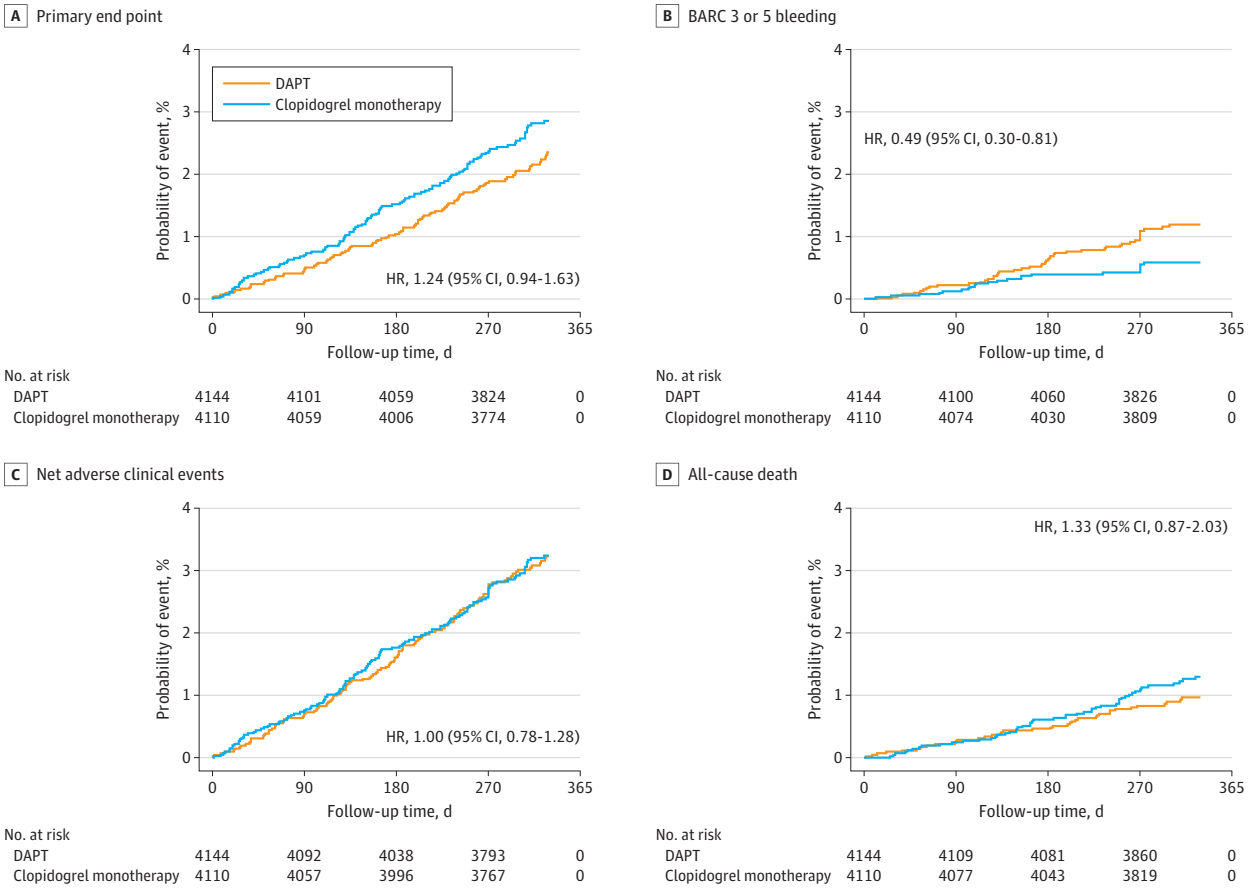
Figure 2. Kaplan-Meier Estimates for Clinical Outcomes in Patients Receiving Clopidogrel Monotherapy or Dual Antiplatelet Therapy (DAPT)



BARC indicates Bleeding Academic Research Consortium; HR, hazard ratio.

however, they do not provide clear guidance on which treatment should be preferred for the large segment of patients in whom both risks are similar.

Given the central role of platelet $P2Y_{12}$ receptor signaling on thrombotic complications and the established association between aspirin and bleeding (particularly gastrointestinal bleeding),[23-25] discontinuation of aspirin instead of the $P2Y_{12}$ inhibitor could be a bleeding reduction strategy that preserves ischemic protection.[25-27] Recent trials have investigated $P2Y_{12}$ inhibitor monotherapy, mainly using ticagrelor or clopidogrel, after a short course of DAPT.[9-14] When singularly appraised, each trial has limitations inherent to study design, study power, or both, hampering definitive conclusions for practice.[9-14] Aggregate data meta-analyses have shown similar ischemic and lower bleeding risks with $P2Y_{12}$ inhibitor monotherapy compared with DAPT continuation but did not investigate the role of the type of $P2Y_{12}$ inhibitor after DAPT cessation, to our knowledge.[28,29] In a prior patient-level meta-analysis, there was no evidence of treatment effect heterogeneity between clopidogrel and newer $P2Y_{12}$ inhibitors.[15] However, only 2586 patients (22.2%) received clopidogrel monotherapy, whereas 9048 patients (77.8%) underwent monotherapy with newer $P2Y_{12}$ inhibitors.[15]

This updated meta-analysis includes almost twice as many patients with clopidogrel.[15] Clopidogrel monotherapy was associated with a significant 37% higher risk of the primary end point compared with aspirin and clopidogrel in the per-protocol analysis. All 3 components of the primary end point were numerically more frequent with clopidogrel monotherapy than DAPT. These results were consistent across subgroups, but an appraisal of absolute risks suggests that the signal of harm may be more relevant in patients with ACS. Conversely, the observed bleeding benefit associated with clopidogrel monotherapy and the null finding for NACE suggest that this strategy is associated with a trade-off of ischemic and bleeding events and might be justified in patients with high bleeding risk.[4]

Our patient-level meta-analysis provides evidence that aspirin discontinuation 1 to 3 months after PCI followed by ticagrelor monotherapy was safer than and at least as effective as standard DAPT. Noninferiority was established based on a 15% relative margin on the HR scale for the primary end point; the upper limits of the 2-sided 95% CI of both per-protocol and intention-to-treat analyses were compatible with a relative risk increase not greater than 6% compared with DAPT. The residual possibility of a small risk needs to be interpreted against

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the 53% relative reduction of major bleeding and 26% relative reduction of NACE. In addition, we observed a nominally significant 28% lower risk of mortality with ticagrelor monotherapy. The mortality benefit might be related to the substantial reduction in major bleeding.[30,31]

Patients with high platelet reactivity while using clopidogrel are frequent[16] and incur increased risk of thrombotic complications after PCI.[16,32] Patients with high platelet reactivity while using clopidogrel might experience an even higher risk when aspirin is withdrawn and no or minimal antiplatelet treatment effect persists. Ticagrelor exerts a more profound and consistent $P2Y_{12}$ receptor inhibition than clopidogrel.[16] The lack of pharmacodynamic or genetic data in our study prevent us from assessing whether high platelet reactivity while using clopidogrel or *CYP2C19* genotypes explains the differential treatment outcomes with ticagrelor or clopidogrel monotherapy. The trials investigating clopidogrel monotherapy were conducted in Japan or Korea. East Asian patients have a higher frequency of *CYP2C19* loss-of-function alleles[33] and may therefore be more prone to no or poor response to clopidogrel. On the other hand, East Asian populations have a lower incidence of ischemic heart disease and a decreased risk of post-PCI atherothrombotic complications compared with White populations.[33] In a global trial of patients at high bleeding risk, abbreviated DAPT was noninferior to standard DAPT for ischemic events and superior for bleeding.[4,34] Although the choice of the type of monotherapy was left to the discretion of the investigators and randomization was not stratified by type of antiplatelet monotherapy, clopidogrel monotherapy was used in 53.9% of patients in the abbreviated therapy group, apparently not leading to an overall signal of harm compared with standard DAPT, in contrast to what was observed in the STOPDAPT-2 ACS study by Watanabe et al.[17]

In a post-hoc landmark analysis, the harm with clopidogrel monotherapy compared with DAPT was limited to the early post-PCI period (ie, first 6 months). Therefore, our findings remain consistent with the possibility that clopidogrel monotherapy remains an appealing option in the long term after PCI, as suggested by the OPT-BIRISK trial.[35] Ticagrelor monotherapy was associated with beneficial effects on mortality, regardless of its postulated cardiovascular vs noncardiovascular cause, whereas clopidogrel monotherapy was associated with a higher mortality rate compared with DAPT, owing to an excess of noncardiovascular events. It remains unclear whether this finding on clopidogrel reflects chance or a loss of protective effects of aspirin beyond its antiplatelet activity in clopidogrel-treated but not in ticagrelor-treated patients. Ticagrelor, unlike clopidogrel and similar to aspirin, has been associated with pleiotropic outcomes that seem to be unrelated to platelet inhibition.[36]

This analysis has several strengths. Combining patient-level data from 6 large trials allowed a precise quantification of the risks and benefits associated with aspirin withdrawal on a background therapy of ticagrelor or clopidogrel after PCI. For this purpose, we left-censored all clinical events that occurred during the initial DAPT phase, which was identical in both experimental and control groups in 5 trials and, if included, might have biased treatment estimates toward the null. Although this approach may limit the generalizability of our primary analysis, our findings were corroborated by multiple sensitivity analyses, which suggested that the observed outcome was robust after the inclusion or exclusion of patients who experienced nonfatal events during the initial DAPT phase.

Limitations

The study has some limitations and is subject to the shortcomings of the original trials, including the open-label design in 5 trials.[9-13,17] However, all studies implemented independent event adjudication, and end point definitions were largely consistent across trials. Prasugrel monotherapy was underrepresented in our dataset and allowed only in 1 trial, which stratified randomization by the intended $P2Y_{12}$ inhibitor.[12] In a leave-one-out analysis, the harm with clopidogrel monotherapy was not significant and less pronounced after removal of the STODAPT-2 ACS trial. Clopidogrel monotherapy was not noninferior to standard DAPT mainly because of an excess of noncardiovascular deaths, which remains unexplained. Although the signal of harm with clopidogrel monotherapy was more relevant in patients with ACS on an absolute basis, our study could not provide conclusive evidence on whether clinical presentation influences the treatment effect. While the evidence for ticagrelor monotherapy derived from global trial populations of diverse ethnicities, clopidogrel monotherapy vs DAPT has only been studied in East Asian populations, to our knowledge.

Conclusions

In this systematic review and patient-level meta-analysis including patients undergoing PCI, ticagrelor monotherapy after 1 to 3 months of DAPT was noninferior to standard DAPT for the composite of all-cause death, MI, or stroke and superior for major bleeding and NACE. Clopidogrel monotherapy after 1 to 3 months of DAPT was associated with similarly reduced major bleeding but was not noninferior to standard DAPT for all-cause death, MI, or stroke and did not decrease NACE, largely because of risk seen in 1 trial that exclusively included East Asian patients and a hazard that was driven by an excess of noncardiovascular death.

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Data Sharing Statement: See Supplement 2.

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