Circulation

ORIGINAL RESEARCH ARTICLE

The Safety and Efficacy of Aspirin Discontinuation on a Background of a $P2Y_{12}$ Inhibitor in Patients After Percutaneous Coronary Intervention

A Systematic Review and Meta-Analysis

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BACKGROUND: Dual antiplatelet therapy with aspirin and a $P2Y_{12}$ inhibitor has been shown to reduce the risk of major adverse cardiovascular events (MACE) compared with aspirin alone after percutaneous coronary intervention (PCI) or acute coronary syndrome but with increased risk of bleeding. The safety of discontinuing aspirin in favor of $P2Y_{12}$ inhibitor monotherapy remains disputed.

METHODS: A meta-analysis was conducted from randomized trials (2001–2020) that studied discontinuation of aspirin 1 to 3 months after PCI with continued $P2Y_{12}$ inhibitor monotherapy compared with traditional dual antiplatelet therapy. Five trials were included; follow-up duration ranged from 12 to 15 months after PCI. Primary bleeding and MACE outcomes were the prespecified definitions in each trial.

RESULTS: The study population included 32 145 patients: 14 095 (43.8%) with stable coronary artery disease and 18 046 (56.1%) with acute coronary syndrome. In the experimental arm, background use of a $P2Y_{12}$ inhibitor included clopidogrel in 2649 (16.5%) and prasugrel or ticagrelor in 13 408 (83.5%) patients. In total, 820 patients experienced a primary bleeding outcome and 937 experienced MACE. Discontinuation of aspirin therapy 1 to 3 months after PCI significantly reduced the risk of major bleeding by 40% compared with dual antiplatelet therapy (1.97% versus 3.13%; hazard ratio [HR], 0.60 [95% CI, 0.45–0.79]), with no increase observed in the risk of MACE (2.73% versus 3.11%; HR, 0.88 [95% CI, 0.77–1.02]), myocardial infarction (1.08% versus 1.27%; HR, 0.85 [95% CI, 0.69–1.06]), or death (1.25% versus 1.47%; HR, 0.85 [95% CI, 0.70–1.03]). Findings were consistent among patients who underwent PCI for an acute coronary syndrome, in whom discontinuation of aspirin after 1 to 3 months reduced bleeding by 50% (1.78% versus 3.58%; HR, 0.50 [95% CI, 0.41–0.61]) and did not appear to increase the risk of MACE (2.51% versus 2.98%; HR, 0.85 [95% CI, 0.70–1.03]).

CONCLUSIONS: Discontinuation of aspirin with continued $P2Y_{12}$ inhibitor monotherapy reduces risk of bleeding when stopped 1 to 3 months after PCI. An increased risk of MACE was not observed after discontinuation of aspirin, including in patients with acute coronary syndrome.

Key Words: anticoagulants ■ aspirin ■ dual anti-platelet therapy ■ percutaneous coronary intervention ■ platelet aggregation inhibitor

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Clinical Perspective

What Is New?

- Although trials have shown that discontinuation of aspirin in favor of P2Y$_{12}$ inhibitor monotherapy reduces the risk of bleeding compared with traditional dual antiplatelet therapy, it remains disputed whether this strategy increases the risk of major adverse cardiovascular events after percutaneous coronary intervention.
- The current meta-analysis across randomized trials demonstrated that discontinuation of aspirin therapy 1 to 3 months after percutaneous coronary intervention significantly reduced the risk of major bleeding by 40% compared with dual antiplatelet therapy and did not appear to increase the risk of major adverse cardiovascular events (hazard ratio, 0.88 [95% CI, 0.77–1.02]), myocardial infarction (hazard ratio, 0.85 [95% CI, 0.69–1.06]), or death (hazard ratio, 0.85 [95% CI, 0.70–1.03]).

What Are the Clinical Implications?

- A strategy of stopping aspirin 1 to 3 months after percutaneous coronary intervention with continued use of a P2Y$_{12}$ inhibitor reduces the risk of bleeding when compared with traditional dual antiplatelet therapy with aspirin and a P2Y$_{12}$ inhibitor.
- This strategy does not appear to increase risk of major adverse cardiovascular events.
- When considering the clinical implications, clinicians should consider the eligibility criteria for the individual trials included in this meta-analysis.

Nearly 2 decades ago, addition of the P2Y$_{12}$ inhibitor clopidogrel on a background of aspirin therapy was shown to reduce the risk of major adverse cardiovascular events (MACE) in patients after a non–ST-segment–elevation acute coronary syndrome (ACS) but with increased risk of major and minor bleeding.[1] More potent P2Y$_{12}$ inhibition with prasugrel and ticagrelor subsequently has been shown to reduce the risk of MACE further when compared with clopidogrel on a background of aspirin after ACS, but again with increased risk of major and minor bleeding.[2,3] Although the optimal duration of dual antiplatelet therapy (DAPT) has remained controversial, more prolonged use of a P2Y$_{12}$ inhibitor on a background of aspirin reduces risk of recurrent cardiac events in secondary prevention, but increases the risk of bleeding.[4–6]

Although several trials have evaluated the duration of use of a P2Y$_{12}$ inhibitor on a background of continued aspirin, there has been growing interest in the concept of discontinuing aspirin in favor of monotherapy with a P2Y$_{12}$ inhibitor. Supporting the concept, in patients with a recent atherosclerotic event, clopidogrel monotherapy has been shown to reduce the risk of MACE and reduce the risk of gastrointestinal bleeding when compared head to head with aspirin monotherapy.[7] For patients with an indication for an oral anticoagulant after percutaneous coronary intervention (PCI), discontinuation of aspirin with continued use of a P2Y$_{12}$ inhibitor and oral anticoagulant has been shown to reduce the risk of bleeding without a clear signal toward increased risk of MACE.[8] However, in the absence of a concomitant oral anticoagulant, there has been hesitation to discontinue aspirin in favor of monotherapy with a P2Y$_{12}$ inhibitor.

Because individual trials have been relatively underpowered to examine the relative risk of MACE when aspirin is discontinued for patients on DAPT, we conducted a meta-analysis of published randomized trials to examine the efficacy and safety of stopping aspirin in favor of monotherapy with a P2Y$_{12}$ inhibitor 1 to 3 months after PCI when compared with traditional DAPT.

METHODS

Study Selection

A computerized literature search was conducted from 2001 until March 2020 of the MEDLINE, PubMed, Cochrane, Embase, and clinicaltrials.gov databases to identify randomized clinical trials that compared a strategy of aspirin discontinuation with continued use of a P2Y$_{12}$ inhibitor versus DAPT with aspirin and a P2Y$_{12}$ inhibitor in patients after PCI with an indication of either stable coronary artery disease (CAD) or ACS. Abstracts presented at major scientific meetings were reviewed. Bleeding and MACE outcomes were required to be reported with follow-up time of at least 6 months. Search terms included but were not restricted to "with or without aspirin," "duration of dual antiplatelet therapy," "aspirin duration," "ticagrelor/clopidogrel/prasugrel/antiplatelet monotherapy," and "P2Y$_{12}$ inhibitor monotherapy" (Table I in the Data Supplement). Studies were excluded if patients were to be treated with anticoagulant therapy; if they were duplicative, were observational, or used a crossover design; or if the method of allocation was not random (Figure I in the Data Supplement). Two investigators (Drs O'Donoghue and Sabatine) independently reviewed studies considered for inclusion in the meta-analysis. Because the current meta-analysis was based on data extracted from previously published research, the data and study materials are available to other researchers for purposes of reproducing the results or replicating the procedure and the analytic methods are outlined in the following.

The primary safety and efficacy outcomes were the primary bleeding and MACE outcomes that were prespecified in each trial (Table 1). Additional outcomes including death, myocardial infarction (MI), stroke, and major bleeding (Bleeding Academic Research Consortium 3 or 5)[9] are reported. Stent thrombosis is reported as Academic Research Consortium definite or probable definition[10] (data from GLOBAL LEADERS are reported as Academic Research Consortium definite). All trials included in the meta-analysis stated that written informed consent was obtained for all participants.

Table 1. Randomized Trials of $P2Y_{12}$ Inhibitor Monotherapy Versus Dual Antiplatelet Therapy Included in the Meta-Analysis

Trial Name	Blind	Study Population	Intervention	Control	Sample Size	Primary Bleeding End Point	Primary Cardiovascular End Point	Follow-Up Time
GLOBAL LEADERS[11,14]	Open label	ACS (47%) or stable CAD after DES	Ticagrelor monotherapy after month 1	Clopidogrel (stable CAD) or ticagrelor (ACS) + ASA 75 to 100 mg daily	15 968	BARC 3 or 5 bleeding (site-reported)	All-cause death or MI (adjudicated new Q wave)	12 months*
SMART CHOICE[15]	Open label	ACS (58%) or stable CAD after DES	Any $P2Y_{12}$ inhibitor monotherapy after month 3	Any $P2Y_{12}$ inhibitor + ASA 100 mg daily	2993	BARC 2 to 5 bleeding	All-cause death, MI, or stroke	12 months
STOPDAPT-2[16]	Open label	ACS (38%) or stable CAD after DES	Clopidogrel monotherapy after month 1	Clopidogrel + ASA 81 to 200 mg daily after month 1	3045 (3009 in ITT)	TIMI major or minor bleeding	Cardiovascular death, MI, stroke, or definite stent thrombosis†	12 months
TWILIGHT[17]	Double blind	NSTE-ACS or stable CAD after DES	Ticagrelor monotherapy after month 3	Ticagrelor + ASA 81 to 100 mg daily	7119	BARC 2, 3, or 5 bleeding	All-cause death, MI, or stroke	Month 15 (randomized at month 3)
TICO[18]	Open label	ACS (STEMI or NSTE-ACS) after DES	Ticagrelor monotherapy after month 3	Ticagrelor + ASA 100 mg daily	3056	TIMI major bleeding	All-cause death, MI, stroke, stent thrombosis, or target vessel revascularization	12 months

ASA indicates acetylsalicylic acid; ACS, acute coronary syndrome; BARC, Bleeding Academic Research Consortium; CAD, coronary artery disease; DES, drug-eluting stent; GLOBAL LEADERS, GLOBAL LEADERS: A Clinical Study Comparing Two Forms of Antiplatelet Therapy After Stent Implantation; TIMI, Thrombolysis in Myocardial Infarction; ITT, intention to treat; MI, myocardial infarction; NSTE-ACS, non–ST-segment–elevation acute coronary syndrome; SMART CHOICE, Smart Angioplasty Research Team: Comparison Between P2Y12 Antagonist Monotherapy Versus Dual Antiplatelet Therapy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents; STEMI, ST-segment–elevation myocardial infarction; STOPDAPT-2, Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent; TICO, Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus Stent for Acute Coronary Syndrome; TIMI, Thrombolysis in Myocardial Infarction; and TWILIGHT, Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention.

*Follow-up duration in GLOBAL LEADERS was restricted to the first 12 months since $P2Y_{12}$ inhibitor use was discontinued at month 12 in the control arm. ACS substudy analysis was based on landmark analysis at month 1 through month 12 when ASA was discontinued in the intervention arm.

†The primary outcome for STOPDAPT-2 was a composite of both efficacy and bleeding outcomes and was therefore not used for this analysis.

Statistical Analyses

A meta-analysis was conducted for each outcome extracted based on published data using random effects models. Heterogeneity across trials was assessed by the Cochran Q statistic and I^2 for heterogeneity. Hazard ratios (HRs) with 95% CIs are reported. A sensitivity analysis was conducted restricted to those patients with an index diagnosis of ACS.[11] Risk of bias assessments were performed for each trial with the Cochrane Collaboration tool.[12,13] This included assessments of the randomization process, blinding, withdrawal of consent, loss to follow-up, and outcome reporting assessments (Table II in the Data Supplement). All statistical analyses were performed using Stata 16.0 (College Station, TX). All tests were 2-sided, with $P<0.05$ considered significant.

RESULTS

A total of 1655 records were screened and 5 trials fulfilled all inclusion criteria (Figure I in the Data Supplement).[14–18] The 5 trials enrolled patients after PCI with an indication of either stable CAD or ACS; the TICO trial (Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus Stent for Acute Coronary Syndrome) exclusively enrolled patients with ACS (ST-segment–elevation MI or non–ST-segment–elevation ACS)[18] (Table 1). The key features of each trial included in the meta-analysis are displayed in Table 1, including the study populations, treatment arms, primary outcomes, and follow-up duration. Additional considerations regarding the studies selected are noted in the Data Supplement. Table 2 shows the pooled baseline characteristics across studies. A total of 32 145 patients were included across the 5 trials, of whom 14 095 (43.8%) underwent PCI for a diagnosis of stable CAD and 18 046 (56.1%) underwent PCI for a diagnosis of ACS. Background use of a $P2Y_{12}$ inhibitor in the experimental arm consisted of clopidogrel in 2649 (16.5%) patients and prasugrel or ticagrelor in 13 408 (83.5%). Overall, baseline characteristics were well balanced across randomized treatment arms, and there was a high prevalence of comorbid conditions including hypertension (69.9%), hyperlipidemia (64.2%), diabetes mellitus (30.4%), previous MI (19.9%), chronic kidney disease (13.1%), and current tobacco use (26.0%). In total, 820 patients experienced a primary bleeding outcome and 937 experienced a MACE.

Table 2. Baseline Characteristics Across Clinical Trials Pooled in Aggregate Across Randomized Treatment Arms

	GLOBAL LEADERS (n=15 968)	SMART CHOICE (n=2993)	STOPDAPT-2 (n=3009)	TWILIGHT (n=7119)	TICO (n=3056)	Pooled Population (n=32 145), n (%)
Age, y, mean (SD)	64.6 (10.3)	64.5 (10.7)	68.6 (10.7)	65.1 (10.3)	61.0 (11.0)	64.7 (10.6)
Female, %	23.3	26.6	22.3	23.9	20.5	7507 (23.4)
Diabetes mellitus, %	25.3	37.5	38.5	36.8	27.3	9774 (30.4)
Smoking, %	26.1	26.4	23.6	21.7	37.4	8360 (26.0)
Hypertension, %	73.4	61.5	73.8	72.4	50.4	22 471 (69.9)
Hyperlipidemia, %	67.4	45.2	74.6	60.4	NR	18 667 (64.2)
Chronic kidney disease, %	13.6	3.2	5.5	16.1	20.3	4199 (13.1)
Previous myocardial infarction, %	23.2	4.2	13.5	28.7	3.7	6396 (19.9)
Indication for percutaneous coronary intervention						
Acute coronary syndrome, %	46.9	58.2	38.2	64.8	100	18 046 (56.1)
Stable coronary artery disease, %	53.1	41.8	61.8	35.2	0	14 095 (43.8)

Values are percentages unless otherwise noted. TICO was excluded from the denominator for pooled population for hyperlipidemia because these data were not reported. GLOBAL LEADERS indicates GLOBAL LEADERS: A Clinical Study Comparing Two Forms of Antiplatelet Therapy After Stent Implantation; NR, not reported; SMART CHOICE, Smart Angioplasty Research Team: Comparison Between P2Y12 Antagonist Monotherapy Versus Dual Antiplatelet Therapy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents; STOPDAPT-2, Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent; TICO, Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus Stent for Acute Coronary Syndrome; and TWILIGHT, Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention.

Discontinuation of aspirin therapy 1 to 3 months after PCI significantly reduced the risk of bleeding by 40% when compared with continued DAPT (HR, 0.60 [95% CI, 0.45–0.79]; P<0.001; I^2=64.6%; Table 3). When restricted only to Bleeding Academic Research Consortium 3 or 5 bleeding, aspirin discontinuation reduced the risk of these major bleeds by 40% (HR, 0.60 [95% CI, 0.42–0.86]; P=0.005; I^2=63.0%). Of note, significant heterogeneity across trials was observed for the bleeding outcomes, although all the individual trial results were directionally consistent (Figure 1). When we examined efficacy outcomes, discontinuation of aspirin did not appear to increase the risk of MACE (HR, 0.88 [95% CI, 0.77–1.02]; P=0.09; I^2=11.8%). Discontinuation of aspirin also did not appear to increase the risk of all-cause mortality (HR, 0.85 [95% CI, 0.70–1.03]; P=0.09; I^2=0.0%), MI (HR, 0.85 [95% CI, 0.69–1.06]; P=0.14; I^2=3.5%), or stroke (HR, 1.08 [95% CI, 0.67–1.74]; P=0.74; I^2=48.6%). Stent thrombosis was infrequent (147 events), and aspirin discontinuation was not associated with a statistically significant increase in the risk (HR, 1.17 [95% CI, 0.84–1.63]; P=0.35; I^2=0.0%; Table 3).

Consistent results were observed when restricted to only those patients who underwent PCI for an index

Table 3. Safety and Efficacy of P2Y$_{12}$ Inhibitor Monotherapy Versus Dual Antiplatelet Therapy in Patients After Percutaneous Coronary Intervention

Outcome*	P2Y$_{12}$ Inhibitor Monotherapy (n=16 057), n (%)	Aspirin + P2Y$_{12}$ Inhibitor (n=16 088), n (%)	Hazard Ratio (95% CI)
Primary bleeding outcome	317 (1.97)	503 (3.13)	0.60 (0.45–0.79)
Major bleeding (BARC 3 or 5 bleeding)	196 (1.22)	291 (1.81)	0.60 (0.42–0.86)
Primary major adverse cardiovascular event outcome	438 (2.73)	499 (3.11)	0.88 (0.77–1.02)
Death	200 (1.25)	236 (1.47)	0.85 (0.70–1.03)
Myocardial infarction	173 (1.08)	203 (1.27)	0.85 (0.69–1.06)
Stroke	95 (0.59)	89 (0.55)	1.08 (0.67–1.74)
Stent thrombosis (ARC definite or probable)	80 (0.50)	67 (0.42)	1.17 (0.84–1.63)

ARC indicates Academic Research Consortium; BARC, Bleeding Academic Research Consortium; GLOBAL LEADERS: A Clinical Study Comparing Two Forms of Antiplatelet Therapy After Stent Implantation; SMART CHOICE, Smart Angioplasty Research Team: Comparison Between P2Y12 Antagonist Monotherapy Versus Dual Antiplatelet Therapy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents; TICO, Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus Stent for Acute Coronary Syndrome; and TWILIGHT, Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention.

*For GLOBAL LEADERS, the myocardial infarction outcome is restricted to new Q-wave myocardial infarction. For SMART CHOICE, the BARC 3 or 5 outcome includes BARC 4 bleeding. In TWILIGHT, the stroke outcome is restricted to ischemic stroke and stent thrombosis is restricted to ARC definite and the per-protocol population was used for all major adverse cardiovascular event outcomes (n=7039). For TICO, BARC 3 or 5 bleeding is not reported; therefore, the data reflect Thrombolysis in Myocardial Infarction major bleeding.

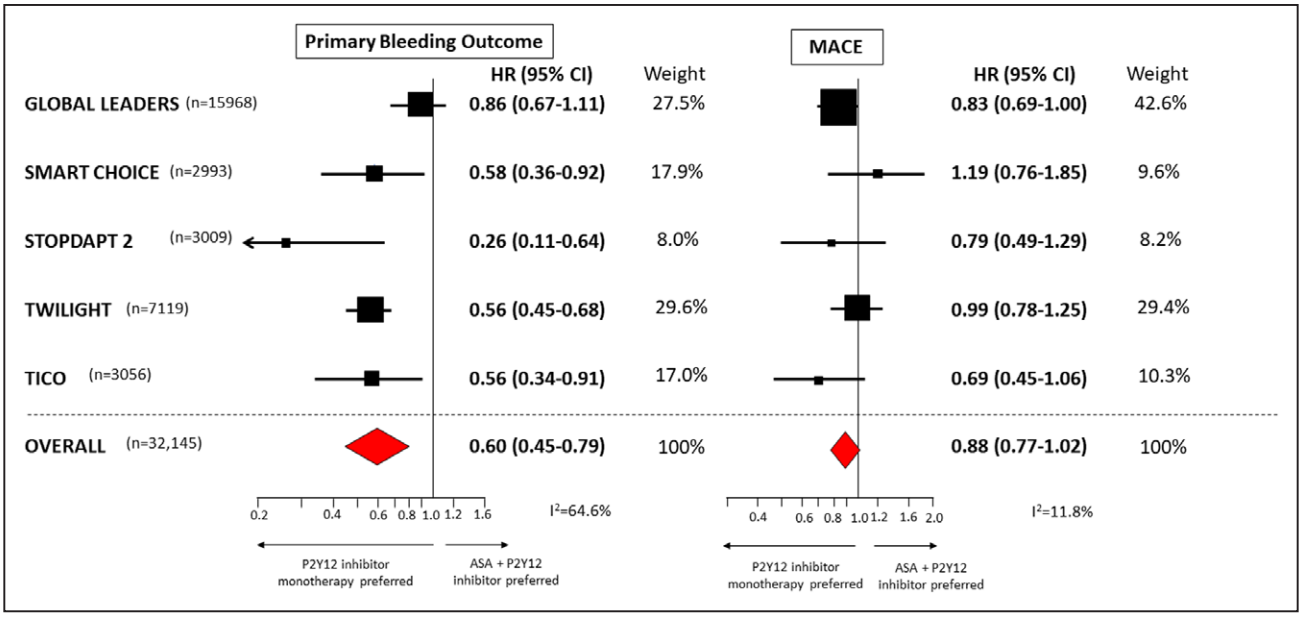

Figure 1. The relative hazard of bleeding and MACE for patients treated with $P2Y_{12}$ monotherapy versus dual antiplatelet therapy starting 1 to 3 months after percutaneous coronary intervention.

Size of data markers is weighted based on the inverse variance. ASA indicates acetylsalicylic acid; GLOBAL LEADERS, GLOBAL LEADERS: A Clinical Study Comparing Two Forms of Antiplatelet Therapy After Stent Implantation; HR, hazard ratio; MACEs, major adverse cardiovascular events; SMART CHOICE, Smart Angioplasty Research Team: Comparison Between P2Y12 Antagonist Monotherapy Versus Dual Antiplatelet Therapy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents; STOPDAPT-2, Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent; TICO, Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus Stent for Acute Coronary Syndrome; and TWILIGHT, Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention.

diagnosis of ACS (n=16 898; Table II in the Data Supplement). Of those patients enrolled with ACS, 4070 (24.1%) were enrolled with ST-segment–elevation MI. Among patients who had been hospitalized with ACS, discontinuation of aspirin after 1 to 3 months reduced bleeding by 50% (HR, 0.50 [95% CI, 0.41–0.61]; $P<0.001$; $I^2=0.0\%$) and did not appear to increase risk of MACE (HR, 0.85 [95% CI, 0.70–1.03]; $P=0.09$; $I^2=2.9\%$; Figure 2).

Funnel plots to assess for selection bias were not analyzed owing to the small number of studies included in the meta-analysis, thereby limiting test power.[19] Overall, there was concern about possible risk of bias because of the open-label nature of 4 of the 5 included trials (Table III in the Data Supplement). Unadjudicated investigator-reported events were included from GLOBAL LEADERS, which was an open-label trial. GLOBAL LEADERS and STOPDAPT-2 (Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent) did not include data from patients who withdrew consent, thereby introducing possible risk of bias. The number of patients excluded on this basis was small (n=23 in GLOBAL LEADERS; n=36 in STOPDAPT-2). GLOBAL LEADERS used clopidogrel in the control arm for patients with stable CAD (based on practice guidelines) and ticagrelor in the experimental arm; therefore, patients with stable CAD in GLOBAL LEADERS varied between treatment arms both by choice of $P2Y_{12}$ inhibitor and presence of aspirin. Although this decision was by experimental design, it introduces risk of bias in terms of interpretability of study results because 2 treatment factors differed between arms in this trial.

DISCUSSION

The current findings indicate that discontinuation of aspirin 1 to 3 months after PCI with continued $P2Y_{12}$ inhibitor monotherapy leads to a marked reduction in the risk of bleeding when compared with traditional DAPT. In this data set of 32 145 patients of whom 937 experienced MACE, an increased risk of MACE was not observed for patients randomized to $P2Y_{12}$ inhibitor monotherapy. These findings were consistent in patients hospitalized with ACS in addition to those with more stable coronary disease.

Although multiple studies have explored the optimal duration of DAPT after PCI, most trials have evaluated a strategy of $P2Y_{12}$ inhibitor discontinuation on a background of lifelong aspirin use. To that end, in patients after ACS, a strategy of a more prolonged course of DAPT with aspirin and a $P2Y_{12}$ inhibitor has been shown to reduce risk of MACE, but with increased risk of bleeding.[4,5] In contrast, some studies have supported the concept that a $P2Y_{12}$ inhibitor can be discontinued safely several months after PCI with continued use of aspirin in lower risk patients with stable CAD.

Although aspirin has been long believed to be the cornerstone of antiplatelet therapy, there exists

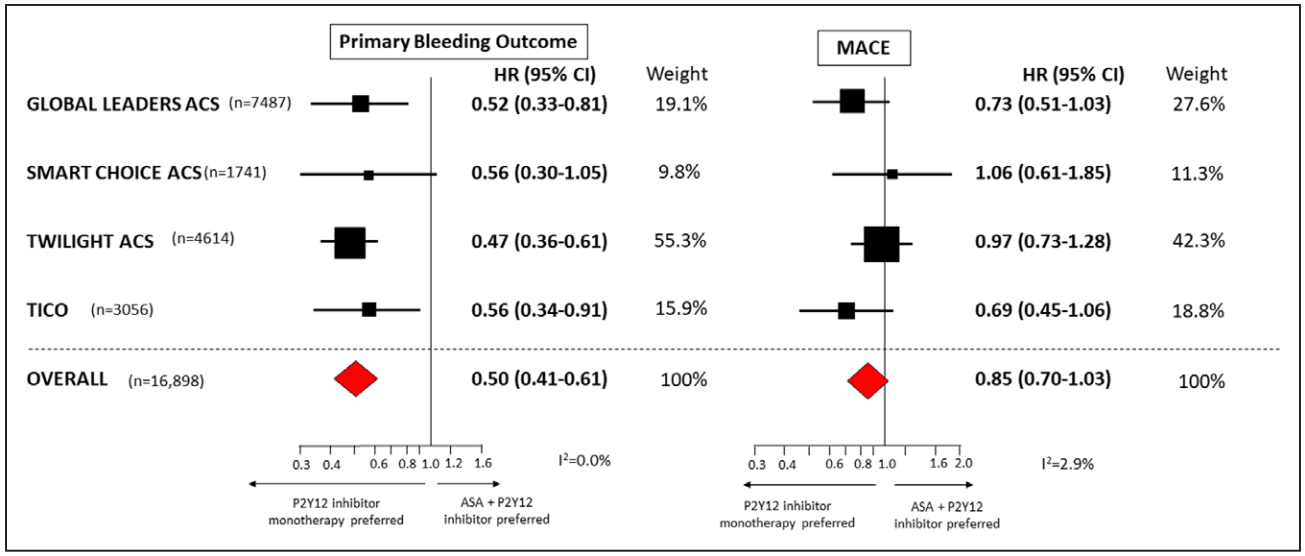

Figure 2. The relative hazard of bleeding and MACE for patients treated with $P2Y_{12}$ monotherapy versus dual antiplatelet therapy starting 1 to 3 months after ACS.

Size of data markers is weighted based on the inverse variance. ACS indicates acute coronary syndrome; ASA, acetylsalicylic acid; GLOBAL LEADERS, GLOBAL LEADERS: A Clinical Study Comparing Two Forms of Antiplatelet Therapy After Stent Implantation; HR, hazard ratio; MACE, major adverse cardiovascular events; SMART CHOICE, Smart Angioplasty Research Team: Comparison Between P2Y12 Antagonist Monotherapy Versus Dual Antiplatelet Therapy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents; TICO, Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus Stent for Acute Coronary Syndrome; and TWILIGHT, Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention.

rationale for a strategy of preferentially discontinuing its use in favor of a $P2Y_{12}$ inhibitor. Despite its cardiovascular efficacy in secondary prevention, aspirin is known to increase the risk of bleeding complications, including gastrointestinal bleeding and intracranial hemorrhage.[20] Placebo-controlled studies of aspirin were primarily conducted before the advent of other established medical therapies, including statins and $P2Y_{12}$ inhibitors. To that end, blockade of the $P2Y_{12}$ receptor may also interfere with thromboxane A_2–induced adenosine diphosphate release. When aspirin was compared head to head with clopidogrel in the CAPRIE trial (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events), clopidogrel monotherapy was shown to reduce the risk of cardiovascular death, MI, or stroke when compared with aspirin in patients with a recent atherosclerotic event.[7] Although overall bleeding rates were comparable between groups, clopidogrel exhibited a lower risk of gastrointestinal bleeding when compared with aspirin.[7] In patients with acute stroke or transient ischemic attack, the more potent $P2Y_{12}$ inhibitor ticagrelor did not reduce the risk of MACE or bleeding when compared with low-dose aspirin, but ticagrelor monotherapy reduced the secondary end point of stroke.[21]

Further supporting the concept that aspirin can be discontinued safely in the presence of concomitant therapies, early discontinuation of aspirin after PCI with continued use of a $P2Y_{12}$ inhibitor has been shown to reduce the risk of bleeding in patients with an indication for anticoagulant therapy without a clear increase in the risk of MACE.[7] However, anticoagulant drugs have independently been shown to reduce risk of MACE and stent thrombosis, thereby providing greater reassurance that a $P2Y_{12}$ inhibitor without aspirin may be adequate in this setting.[22] It is known that clopidogrel exhibits significant interpatient variability in its pharmacodynamic response,[23] thereby increasing concerns that aspirin discontinuation could contribute to an excess of cardiovascular events in patients treated with clopidogrel in the absence of an anticoagulant. There has therefore been an unmet need to evaluate the safety and efficacy of aspirin discontinuation in favor of monotherapy with a $P2Y_{12}$ inhibitor in patients who are not on an anticoagulant.

The current findings from >30 000 patients with >800 bleeding outcomes and >900 MACE provide some degree of reassurance that aspirin can be discontinued safely 1 to 3 months after PCI in patients who continue monotherapy with a $P2Y_{12}$ inhibitor and who are similar in terms of eligibility to the patients enrolled across the included studies. Not only was bleeding, including major bleeding, significantly reduced, but there was no evidence of any increase in the risk of MACE, with the upper bound of the 95% CI excluding an increase of >2% and a point estimate <1 (0.88). To that end, it has been hypothesized that bleeding may lead to discontinuation of all antiplatelet strategies and therefore place the patient at excess risk of MACE. The number of stent thrombosis and stroke events was relatively low (147 and 184 events, respectively) and therefore the CIs for the effect of aspirin discontinuation were wide, precluding ruling out a clinically important excess. However, the point estimates for MACE, MI, and all-cause mortality were overall reassuring.

There remain unanswered questions and limitations that warrant consideration. Because they were not compared directly, the optimal choice of P2Y$_{12}$ inhibitor in a patient prescribed monotherapy cannot be determined, although previous studies have demonstrated that prasugrel and ticagrelor reduce the risk of MACE when compared with clopidogrel in patients after ACS on a background of aspirin. Because interpatient variability in response to clopidogrel exists,[24,25] it remains unknown whether genotyping or platelet function testing should be utilized for patients being considered for clopidogrel monotherapy. If a patient is treated with a P2Y$_{12}$ inhibitor as monotherapy after PCI, it is unclear whether this strategy should be continued indefinitely beyond 12 to 15 months and whether aspirin can be discontinued safely earlier than 1 to 3 months after PCI.

As with any meta-analysis, there were differences among the 5 trials in terms of their study design including the use of blinding, choice of antiplatelet therapies across treatment arms, and timing of randomization. However, general consistency in the results was seen across studies and study populations were broadly similar. Also, individual patient-level data were not used for this analysis but would be unlikely to provide incremental information beyond data extracted from previously published reports. Patient selection is a factor in any clinical trial raising questions about widespread generalizability. One cannot exclude that some patients who were deemed to be higher risk by study investigators were excluded from study participation, which is reflected by the fact that event rates across the trials were generally lower than those observed in all-comer PCI registries. To that end, in the TWILIGHT trial (Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention), patients were not randomized until 3 months after PCI, so one cannot exclude that further patient selection occurred during this time period. However, the exclusion criteria did not exclude patients with an interim ischemic or bleeding event unless they were actively bleeding or believed to be at extreme bleeding risk.[17] Nonetheless, the trials included in this meta-analysis included a wide range of patients with stable and unstable coronary disease and baseline characteristics reflect the presence of multiple cardiovascular risk factors.

In summary, this large meta-analysis across randomized trials demonstrates that a strategy of stopping aspirin 1 to 3 months after PCI with continued use of a P2Y$_{12}$ inhibitor reduces the risk of bleeding when compared with traditional DAPT with aspirin and a P2Y$_{12}$ inhibitor. There was no apparent increase in the risk of MACE for patients randomized to P2Y$_{12}$ inhibitor monotherapy. When considering the clinical implications, clinicians should always consider the eligibility criteria for the individual trials included in this meta-analysis and recognize that patient selection by study physicians may play a role.

ARTICLE INFORMATION

Received February 10, 2020; accepted May 20, 2020.

The Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/circulationaha.120.046251.

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Disclosures

Dr O'Donoghue has received research grants to the TIMI Study Group at Brigham and Women's Hospital from Amgen, AstraZeneca, GlaxoSmithKline, Merck, Medicines Company, Eisai, and Janssen and has received consulting fees from Novartis, Janssen, Amgen, AstraZeneca, and CRICO. S.A. Murphy reports grants to the TIMI Study Group at Brigham and Women's Hospital from Abbott Laboratories, Amgen, AstraZeneca, Critical Diagnostics, Daiichi-Sankyo, Eisai, Genzyme, Gilead, GlaxoSmithKline, Intarcia, Janssen Research and Development, Medicines Company, MedImmune, Merck, Novartis, Pfizer, Poxel, Roche Diagnostics, and Takeda; and personal fees from Amgen. Dr Sabatine has received research grants to the TIMI Study Group at his institution and personal fees for consulting from AstraZeneca, Amgen, Intarcia, Janssen Research and Development, Medicines Company, MedImmune, Merck, and Novartis; research grants to the TIMI Study Group at his institution from Bayer, Daiichi-Sankyo, Eisai, GlaxoSmithKline, Pfizer, Poxel, Quark Pharmaceuticals, and Takeda; and personal fees for consulting from Anthos Therapeutics, Bristol Myers Squibb, CVS Caremark, DalCor, Dyrnamix, Esperion, IFM Therapeutics, and Ionis. Dr Sabatine is also a member of the TIMI Study Group, which has also received institutional research grant support through his institute from Abbott, Aralez, Roche, and Zora Biosciences.

Supplemental Materials

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