Ticagrelor Alone Versus Ticagrelor plus Aspirin Following PCI in Patients with Non-ST-Segment Elevation Acute Coronary Syndromes:

TWILIGHT-ACS

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Abstract

Background

Dual antiplatelet therapy (DAPT) with aspirin plus a P2Y₁₂ inhibitor lowers thrombotic risk in the setting of acute coronary syndromes (ACS) among but increases bleeding. Monotherapy with a potent P2Y₁₂ inhibitor may lower aspirin-related bleeding while preserving ischemic benefit.

Methods

In this pre-specified analysis of the Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention (TWILIGHT) trial we analyzed 4,614 patients (65% of the overall trial population) presenting with non ST-elevation ACS (NSTEMI), including unstable angina or non ST-elevation myocardial infarction (NSTEMI), who underwent percutaneous coronary intervention (PCI) with drug eluting stents (DES). After 3 months of DAPT with ticagrelor plus aspirin, adherent and event-free patients were randomized in a double-blind manner to ticagrelor plus placebo versus ticagrelor plus aspirin for 12 months. The primary outcome was Bleeding Academic Research Consortium (BARC) type 2, 3 or 5 bleeding while the composite of all-cause death, myocardial infarction ([MI](#)) or stroke was the key secondary outcome.

Results

Over 12 months of treatment after randomization, BARC 2, 3 or 5 bleeding occurred in 81 patients (3.6%) randomized to ticagrelor plus placebo and 175 (7.6%) patients randomized to ticagrelor plus ASA (hazard ratio [HR] 0.46; 95% CI 0.36-0.61; p<0.001). BARC 3 or 5 bleeding was also significantly reduced (0.8% vs. 2.1%; HR 0.36, 95% CI 0.20-0.62; p<0.001). There were no differences in all-cause death, MI or stroke (4.3%

vs. 4.4%; HR 0.97; 95% CI 0.74-1.28; p=0.84). In stratified analyses, the treatment effects were consistent among patients presenting with unstable angina versus NSTEMI.

Conclusions

Among NSTE-ACS patients undergoing PCI with DES who have completed an initial 3-month course of DAPT, ticagrelor monotherapy significantly reduced bleeding without increasing ischemic events compared with ticagrelor plus aspirin.

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Introduction

Compared with aspirin alone, dual antiplatelet therapy (DAPT) with aspirin and a P2Y₁₂ inhibitor lowers recurrent atherothrombotic events among patients with acute coronary syndromes (ACS) undergoing percutaneous coronary intervention (PCI) with drug eluting stents (DES).¹ While practice guidelines recommend 6 to 12 months of DAPT following PCI in the setting of ACS, reductions in thrombotic events continue to accrue with longer durations.¹⁻⁴ The unavoidable consequence to DAPT-related ischemic benefit, however, is an increased risk of bleeding. Importantly, hemorrhagic complications after PCI also reduce adherence to DAPT, which may further increase thrombotic risk.⁵ Hence, identifying strategies that lower bleeding while also preserving ischemic efficacy have emerged as a clinical priority with respect to post-PCI pharmacotherapy.

In the setting of PCI, shortening the duration of DAPT by early withdrawal of P2Y₁₂ inhibition has emerged as a bleeding reduction strategy. However, while this approach appears feasible in low-risk patients with stable coronary syndromes it led to increased risk of MI in the setting of STEMI.⁶ An alternative approach for patients with ACS involves withdrawal of aspirin with continuation of a potent P2Y₁₂ inhibitor, thus preventing aspirin-related bleeding while maintaining the benefits of P2Y₁₂ platelet inhibition.⁷ Accordingly, we conducted a pre-specified subgroup analysis in the Ticagrelor With Aspirin or Alone in High-Risk Patients after Coronary Intervention (TWILIGHT) trial in order to examine the effect of ticagrelor monotherapy versus ticagrelor plus aspirin among patients with non-ST segment elevation acute coronary syndromes (NSTEMI-ACS) who were treated with PCI.⁸

METHODS

Trial Design and Oversight

TWILIGHT was a randomized, placebo-controlled trial conducted in 187 sites across 11 countries. The trial rationale, design and principal results have been reported previously.⁹ The Icahn School of Medicine at Mount Sinai designed and sponsored the trial, which was supported by an investigator-initiated grant from AstraZeneca. The executive and steering committees were responsible for trial conduct, integrity of data analysis, and reporting of results. National regulatory agencies and institutional review boards or ethics committees of participating centers approved the trial protocol. An independent data safety monitoring board provided external oversight to ensure safety of all trial participants. AstraZeneca provided financial support and supplied ticagrelor for the trial but had no role in the design, collection, analysis, or interpretation of the data.

Trial Population

Patients undergoing successful PCI with at least 1 drug-eluting stent whom the treating clinician intended to discharge on ticagrelor plus aspirin were eligible to participate. Trial inclusion required the presence of at least 1 clinical and 1 angiographic feature associated with a high risk of ischemic or bleeding events.¹⁰⁻

¹³ Clinical criteria included age $\geq$ 65 years, female sex, troponin positive acute coronary syndrome, atherosclerotic vascular disease (prior MI, coronary revascularization or peripheral arterial disease), diabetes mellitus requiring

medication, or chronic kidney disease (estimated glomerular filtration rate < 60 ml/min/1.73m² or creatinine clearance < 60 cc/min). Angiographic criteria included multi-vessel coronary artery disease, total stent length > 30 mm, thrombotic target lesion, bifurcation lesion requiring 2 stents, obstructive left main or proximal left anterior descending lesion, or calcified target lesion requiring atherectomy. Key exclusion criteria included presentation with STEMI, cardiogenic shock, need for oral anticoagulation, or contraindication to aspirin or ticagrelor. For purposes of the present analysis, only those patients presenting with NSTEMI, unstable angina or non-ST elevation myocardial infarction (NSTEMI), were included (n=4,614).

Trial Regimen

All enrolled patients received open-label ticagrelor (90 mg twice daily) and enteric-coated aspirin (81-100 mg daily) after the index PCI. After 3 months, patients without major adverse events were randomized 1:1 in a double-blind fashion to aspirin or matching placebo for an additional 12 months with continuation of open-label ticagrelor. Patients who sustained Bleeding Academic Research Consortium (BARC) type 3b or higher bleeds or ischemic events (stroke, myocardial infarction, or coronary revascularization) between enrollment and 3 months were not eligible for randomization. Non-adherence to ticagrelor or aspirin also rendered patients ineligible for randomization. Randomization was performed using a secure web-based system; an independent statistician not involved with the trial generated the allocation sequence, which was stratified by site with randomly varying block sizes of 4, 6 or 8. Follow-up

occurred 1 month after randomization via phone and in-person at 6 and 12 months after randomization. After 12 months of protocol-mandated therapy, patients were switched to a standard-of-care antiplatelet regimen at the discretion of their treating physician followed by final telephone follow-up 3 months later.

Outcomes

The primary endpoint was the time to first occurrence of BARC type 2, 3 or 5 bleeding between randomization and 1 year. The key secondary endpoint was the time to first occurrence of all-cause death, myocardial infarction, or stroke. Secondary bleeding endpoints included BARC types 3 or 5 bleeding;¹⁴ Thrombolysis in Myocardial Infarction (TIMI) major or minor bleeding;¹⁵ Global Use of Strategies to Open Occluded Arteries (GUSTO) moderate, severe, or life-threatening bleeding;¹⁶ or major bleeding as defined by the International Society of Thrombosis or Hemostasis (ISTH).¹⁷ Other secondary endpoints included cardiovascular death, non-fatal myocardial infarction, ischemic stroke and definite or probable stent thrombosis. Myocardial infarction was defined according to the third universal definition, and revascularization and stent thrombosis were classified according to the Academic Research Consortium.^{18,19} All clinical events were adjudicated by an external blinded independent committee.

Statistical Analyses

Clinical and procedural characteristics are summarized by randomized group using means (standard deviation) and frequencies for continuous and categorical variables, respectively. The cumulative incidence rates for both

primary and secondary endpoints were estimated using the Kaplan-Meier method. Patients without a primary endpoint between randomization and 1 year were censored at the time of death, last known contact, or 365 days, whichever came first. Hazard ratios and 95% confidence intervals (CI) were generated using Cox proportional hazards models. All analyses were performed using the intention to treat approach. As a sensitivity analysis, treatment effects were estimated according to presentation with unstable angina and NSTEMI with formal interaction testing to assess for effect modification. Exploratory analyses were performed to examine the associations between clinical presentation (NSTEMI vs. unstable angina) with the primary outcome of BARC 2, 3 or 5 bleeding and the composite outcome of all-cause death, MI or stroke. In these analyses, hazard ratios and 95% CI were generated from Cox proportional hazards models after adjusting for: treatment allocation, diabetes mellitus, smoking status, moderate to severe target lesion calcification, left main or proximal left anterior descending artery target vessel, prior myocardial infarction, prior coronary revascularization, peripheral arterial disease, estimated glomerular filtration rate, serum hemoglobin, multivessel coronary artery disease.

RESULTS

Patient Characteristics

As shown in **Figure 1**, among the 7119 patients randomized in in the main TWILIGHT trial, we excluded 2503 due to stable presentation and 2 with missing data as to type of

presentation. Hence, a final cohort of 4,614 subjects comprised the present analysis (65% of the overall trial population), including 2273 randomized to ticagrelor plus placebo and 2243 randomized to ticagrelor plus aspirin. Clinical follow-up was available in 98.4% of subjects.

Demographic and clinical parameters were well balanced between treatment arms; mean age was 64 years, 25% were female, and approximately 35% had diabetes mellitus (**Table 1**). Current smoking was less frequent among those randomized to ticagrelor plus placebo versus ticagrelor plus aspirin (23.3% versus 26.6%; $p=0.02$). **Table 2** shows that procedural parameters were well balanced across the two treatment arms. Multivessel CAD was present in 60% of patients; radial arterial access was used in the majority of procedures and mean total stent length was approximately 40mm in both groups. Rates of permanent ticagrelor discontinuation at one year were 12.2% and 13.6% among those randomized to ticagrelor plus placebo versus ticagrelor plus ASA, respectively ($p=0.15$). Analogous results for blinded study drug discontinuation were 16.3% and 17.1%, respectively ($p=0.46$).

Bleeding

As shown in **Table 3** and **Figure 1** BARC 2, 3 or 5 bleeding occurred in 81 patients (3.6%) randomized to ticagrelor plus placebo versus 175 patients (7.6%) randomized to ticagrelor plus aspirin (HR 0.46; 95% CI 0.36-0.61; $p < 0.001$). This effect size is comparable to that observed in the overall trial cohort, as previously reported.⁸ One-year BARC 3 or 5 bleeding rates were 0.8% and 2.1%, respectively, (HR 0.36; 95% CI 0.20 to 0.62). The treatment effect was consistent across different bleeding scales.

Ischemic Events

As shown in **Table 3** and **Figure 2**, the composite outcome of all-cause death, MI, or stroke occurred in 96 patients (4.3%) randomized to ticagrelor plus placebo versus 102 patients (4.4%) randomized to ticagrelor plus aspirin (HR 0.97; 95% CI, 0.74 to 1.28). This effect is similar to that observed in the overall cohort, as previously reported.⁸ Rates of all-cause death (1.0% vs. 1.5%), MI (3.1% vs. 3.1%), ischemic stroke (0.5% vs. 0.2%) and definite or probable stent thrombosis (0.4% vs. 0.6%) were similar (all p-value >0.1) (**Table 3**).

Additional Analyses

Stratified analyses by clinical presentation are shown in **Table 4** and **Figure 3**. The effect of ticagrelor monotherapy on the primary and key secondary outcomes was consistent among patients with unstable angina or NSTEMI with no evidence of effect modification. Results in **Supplementary Table 1** show that the severity of clinical presentation (NSTEMI versus unstable angina) was not significantly associated with increased bleeding while a 2-fold higher risk for ischemic events was observed after adjustment.

Discussion

Principal findings from our pre-specified analysis involving 4614 patients with NSTEMI-ACS randomized in the TWILIGHT trial include: (1) ticagrelor monotherapy, as compared with ticagrelor plus ASA, reduced the incidence of clinically relevant BARC 2, 3 or 5 bleeding as well as more severe BARC 3 or 5 bleeding over one year follow-up by 54% and 64%, respectively; (2) one-year rates of ischemic events, including all-cause death, recurrent MI and definite/probable stent thrombosis, appeared similar between the two arms; (3) treatment effects with respect to ischemic and bleeding outcomes were consistent among patients presenting with unstable angina or NSTEMI and (4) severity of ACS presentation was independently associated with increased risk for thrombotic, but not bleeding, events. In aggregate, these results suggest that the clinical benefits of ticagrelor monotherapy observed in the main TWILIGHT trial cohort are well preserved among patients presenting with an ACS.⁸

Several previous trials have examined the impact of P2Y₁₂ inhibitor monotherapy after a minimal duration of DAPT on post-PCI outcomes.²⁰⁻²² However, these studies were characterized by relatively low-risk or all-comer cohorts, limited number of ACS patients and open-label designs. In contrast, TWILIGHT participants were enriched with clinical and angiographic features associated with an increased risk for ischemic or bleeding complications after PCI. Since over 250 BARC 2, 3 or 5 bleeding events were observed, this subgroup analysis was also adequately powered to detect significant and precise estimates with respect to bleeding. Moreover, while variable levels of adherence across study arms observed in prior studies may have attenuated any

bleeding-related advantage of ASA withdrawal, we observed comparable rates of study drug (i.e. aspirin and matching placebo) discontinuation in our double-blind design.

Consistent with previously reported findings from the overall study cohort, ticagrelor monotherapy was not associated with an increased risk of all-cause death, MI or stroke in ACS patients enrolled in TWILIGHT.⁸ We now extend these earlier findings by demonstrating a similar pattern for the individual endpoint components as well as for other ischemic events such as cardiovascular death, MI and definite/probable stent thrombosis. Similarly, no differences in the composite outcome of death or Q-wave MI were observed between ticagrelor monotherapy and a conventional antiplatelet strategy of DAPT followed by aspirin alone among ACS patients enrolled in the GLOBAL LEADERS trial.²¹ Our results, coupled with earlier observations, suggest that following a short period of DAPT the antithrombotic effect of ticagrelor monotherapy may be sufficient that the need for concomitant long-term ASA is obviated, even in the high-risk ACS patients we studied.

Experimental studies provide a physiologic basis and biological rationale for the lack of incremental thrombosis upon aspirin withdrawal while maintaining ticagrelor alone. For example, pharmacodynamic investigations have shown that aspirin provides limited additional platelet inhibition in platelets isolated from healthy volunteers treated with potent P2Y₁₂ inhibitors.^{23,24} Other experimental studies conducted in animals using a variety of thrombogenic stimuli suggest a limited effect of aspirin in reducing thrombus formation on a background of ongoing P2Y₁₂ blockade.^{25,26} Our findings are concordant with and extend earlier *in vitro* and *ex vivo* observations to a high-risk human population undergoing PCI with DES.

Rates of ischemic events were marginally higher among patients presenting with NSTEMI versus unstable angina, although bleeding risk was similar between groups. These patterns were unchanged after multivariable adjustment and suggest that severity of ACS presentation uniquely contributes to recurrent thrombosis and not bleeding following PCI. These results are consistent with prior reports from registry-based and trial cohorts highlighting the impact of ACS on post-PCI ischemic and bleeding complications.^{13,27} Importantly, the effect of ticagrelor monotherapy with respect to ischemic outcomes appeared uniform across ACS presentation type.

Despite guideline recommendations to the contrary, clopidogrel remains a commonly prescribed P2Y₁₂ inhibitor among patients with ACS, and switching from a potent agent to clopidogrel (i.e. de-escalation) is relatively common after an ACS event.^{28,29} These practice patterns may be driven by bleeding-related safety concerns as patients receiving potent P2Y₁₂ inhibitors are usually characterized by a lower risk clinical profile compared with their counterparts treated with clopidogrel.³⁰ Considered in this context, our findings are particularly relevant since ticagrelor monotherapy may enable high-risk ACS patients to realize the long-term benefits of potent P2Y₁₂ inhibition (as endorsed by practice guidelines), while avoiding aspirin-related bleeding complications.

Although pre-specified, our findings should be considered hypothesis-generating and warrant dedicated, prospective confirmation. Our findings may not generalize to patients treated with clopidogrel or prasugrel after ACS.³¹ However, TWILIGHT was designed to examine the impact of placebo versus aspirin on post-PCI outcomes and in this regard the effect of aspirin withdrawal appears consistent across levels of clinical

risk. In support of this concept, several modest-sized trials enrolling relatively low-risk patients reported similar findings to ours after withdrawing aspirin while continuing clopidogrel alone following 1-3 months of DAPT.^{20,22} The safety and efficacy of P2Y₁₂ inhibitor monotherapy in STEMI patients was not addressed by the present study, since these patients were excluded from participation in TWILIGHT. Power was limited to detect rare, yet clinically important event differences, including stent thrombosis or stroke. Although differences were not statistically significant, the incidence of stroke was numerically higher among patients receiving placebo versus aspirin. However, other studies have shown that P2Y₁₂ inhibitor monotherapy does not increase cerebrovascular risk as compared to DAPT.³²

In conclusion, among patients with NSTEMI-ACS undergoing PCI who remained event-free after 3 months of DAPT, ticagrelor monotherapy significantly reduced bleeding without increasing ischemic events as compared with standard therapy with ticagrelor plus aspirin.

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Table 1. Baseline Clinical Characteristics in non-ST-elevation Acute Coronary Syndrome Patients

	Ticagrelor plus Placebo (n=2273)	Ticagrelor plus Aspirin (n=2341)	p-value
Age, years	64.2 ± 10.5	64.2 ± 10.6	0.99
Female Sex, n (%)	580 (25.5%)	581 (24.8%)	
Nonwhite Race	872 (38.4%)	854 (36.5%)	0.62
Enrolling Region			0.82
North America	882 (38.8%)	917 (39.2%)	
Europe	698 (30.7%)	730 (31.2%)	
Asia	693 (30.5%)	694 (29.7%)	
Body mass index (kg/m ²)	28.4 ± 5.5	28.4 ± 5.7	0.85
Diabetes Mellitus, n (%)	810 (35.6%)	804 (34.3%)	0.36
Insulin requiring, n (%)	221 (9.7%)	237 (10.1%)	0.47
Current smoking, n (%)	528 (23.3%)	622 (26.6%)	0.02
Hypertension, n (%)	1534 (67.5%)	1577 (67.4%)	0.95
Peripheral arterial disease, n (%)	130 (5.7%)	132 (5.6%)	0.91
Prior myocardial infarction, n (%)	578 (25.4%)	589 (25.2%)	0.83
Prior PCI, n (%)	778 (34.2%)	805 (34.4%)	0.91
Prior CABG, n (%)	201 (8.8%)	199 (8.5%)	0.68
Prior major bleeding, n (%)	21 (0.9%)	17 (0.7%)	0.46
Chronic kidney disease, n (%)	321 (14.6%)	341 (15.1%)	0.68
Anemia, n (%)	435 (19.9%)	441 (19.5%)	0.76

PCI- percutaneous coronary intervention; CABG – coronary artery bypass graft; NSTEMI- Non-ST elevation acute coronary syndrome

Table 2. Baseline Procedural Variables in Non-ST-Elevation-Acute Coronary Syndrome Patients

	Ticagrelor plus Placebo (n=2273)	Ticagrelor plus Aspirin (n=2341)	p-value
Multivessel CAD	1409 (61.9%)	1392 (59.5%)	0.08
Target Vessel			
Left Main	117 (5.2%)	120 (5.1%)	0.97
Left Anterior Descending	1311 (57.7%)	1368 (58.4%)	0.60
Left Circumflex	742 (32.6%)	771 (32.9%)	0.83
Right Coronary Artery	795 (34.9%)	795 (33.9%)	0.47
Radial Artery Access	1743 (76.7%)	1786 (76.3%)	0.78
Stent length (mm)	40.5 ± 24.5	39.8 ± 24.6	0.35
Minimal Stent Diameter (mm)	578 (25.4%)	589 (25.2%)	0.83
Number of lesions treated	1.5 ± 0.7	1.5 ± 0.7	0.52
Lesion Morphology*			
Moderate to severe calcification	272 (12.0%)	278 (11.9%)	0.92
Bifurcation	285 (12.5%)	294 (12.6%)	0.98
Total Occlusion	128 (5.6%)	143 (6.1%)	0.49
Thrombotic	338 (14.9%)	361 (15.4%)	0.60

*Lesion features were site-reported
[CAD Coronary artery disease](#)

Table 3. Clinical Outcomes Over One Year by Randomized Group

	Ticagrelor plus Placebo (n=2273)	Ticagrelor plus Aspirin (n=2341)	HR (95% CI)	p-value
Bleeding Outcomes				
BARC 2, 3 or 5	81 (3.6%)	175 (7.6%)	0.47 (0.36-0.61)	<0.001
BARC 3 or 5	17 (0.8%)	49 (2.1%)	0.36 (0.20-0.62)	<0.001
GUSTO moderate or severe	13 (0.6%)	36 (1.6%)	0.37 (0.20–0.70)	0.002
TIMI Major	12 (0.5%)	23 (1.0%)	0.54 (0.27-1.08)	0.08
ISTH Major	20 (0.9%)	51 (2.2%)	0.40 (0.24-0.67)	0.001
Ischemic Outcomes				
All-cause death, MI or stroke	96 (4.3%)	102 (4.4%)	0.97 (0.74-1.28)	0.84
Cardiovascular death, MI or ischemic stroke	90 (4.0%)	97 (4.2%)	0.96 (0.72-1.28)	0.77
All-cause death	22 (1.0%)	34 (1.5%)	0.67 (0.39-1.14)	0.14
MI	70 (3.1%)	72 (3.1%)	1.00 (0.72-1.40)	0.99
Ischemic stroke	11 (0.5%)	6 (0.3%)	1.89 (0.70-5.1)	0.21
Definite or probable stent thrombosis	8 (0.4%)	14 (0.6%)	0.59 (0.25-1.40)	0.23

BARC = Bleeding Academic Research Consortium; TIMI = Thrombolysis in Myocardial Infarction; GUSTO = Global Utilization of Streptokinase and TPA for Occluded Arteries; ISTH = International Society on Thrombosis and Haemostasis; MI = myocardial infarction. Events are expressed as Kaplan-Meier estimates of time to first event (%).

Table 4. Stratified Analysis According to Presentation with Unstable Angina or NSTEMI

	Unstable Angina (n=2494)			NSTEMI (n=2120)			
	Ticagrelor plus Placebo (n=1249)	Ticagrelor plus Aspirin (n=1245)	HR (95% CI)	Ticagrelor plus Placebo (n=1024)	Ticagrelor plus Aspirin (n=1096)	HR (95% CI)	P _{int}
BARC 2, 3 or 5	44 (3.6%)	90 (7.3%)	0.47 (0.33-0.68)	37 (3.7%)	85 (7.9%)	0.46 (0.31-0.67)	0.90
All-cause death, MI or stroke	51 (4.1%)	45 (3.7%)	1.13 (0.75-1.68)	45 (4.5%)	57 (5.3%)	0.85 (0.58-1.26)	0.33

BARC = Bleeding Academic Research Consortium; MI = myocardial infarction.

Supplementary Table 1. Associations Between Clinical Presentation and Bleeding and Ischemic Outcomes

	BARC 2, 3 or 5 Bleeding
	NSTEMI vs. Unstable Angina
Unadjusted	1.06 (0.83-1.36)
Age, Sex Adjusted	1.09 (0.86-1.40)
Multivariable Adjusted*	1.3 (0.91-1.87)
	All-Cause Death, MI or Stroke
	NSTEMI vs. Unstable Angina
Unadjusted	1.26 (0.95-1.66)
Age, Sex Adjusted	1.3 (0.98-1.71)
Multivariable Adjusted*	2.2 (1.44-3.3)