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 $P2Y_{12}$ inhibitor lowers thrombotic risk in the setting of acute coronary syndromes (ACS) but increases bleeding. Monotherapy with a potent $P2Y_{12}$ 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 (NSTE-ACS), 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 or stroke was the key secondary outcome.

Findings

Among patients with NSTE-ACS, 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 aspirin (hazard ratio [HR] 0.46; 95% CI 0.36-0.61; $p<0.001$). Analogous rates among patients without NSTE-ACS (n=2,503) were 4.8% and 6.2%, respectively (HR 0.76; 95% CI 0.54-1.06); $p = 0.11$; $p_{interaction} = 0.03$). Rates of all-cause all-cause death, MI or stroke were similar across treatment arms among patients with (4.3% vs. 4.4%; HR 0.97; 95% CI 0.74-1.28; p=0.84) or without (3.1% vs. 3.2%; HR 0.96; 95% CI 0.61-1.49; P=0.85) NSTE-ACS.

Interpretation

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.

Funding

AstraZeneca

Introduction

Compared with aspirin alone, dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ 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 $P2Y_{12}$ 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 $P2Y_{12}$ inhibitor, thus preventing aspirin-related bleeding while maintaining the benefits of $P2Y_{12}$ 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 versus without non-ST segment elevation acute coronary syndromes (NSTE-ACS) who were treated with PCI.[8]

METHODS

Study design and participants

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] 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 ≥ 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.

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. 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.

Randomization and Masking

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. The treatment allocation was double-blind, and patients were given aspirin tablets or matching aspirin placebo tablets with identical appearance.

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. Treatment effects were examined in relation to clinical presentation (NSTE-ACS [n=4614] vs. stable syndromes [n=2503]) with formal interaction testing to assess for effect modification. Sensitivity analyses were performed after stratifying NSTE-ACS by unstable angina (n=2494) and NSTEMI (n=2920).

Role of the funding source

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.

RESULTS

Patient Characteristics

As shown in **Figure 1**, among the 7119 patients randomized in the main TWILIGHT trial, we excluded 2 with missing data as to type of presentation. Among patients presenting with NSTE-ACS (n=4,614, 65% of trial cohort), 2273 were randomized to ticagrelor plus placebo and 2243 received ticagrelor plus aspirin. Among patients without NSTE-ACS, 1,281 were randomized to ticagrelor plus placebo and 1,222 were randomized to ticagrelor plus aspirin. Clinical follow-up was available in 98.4% of subjects.

Compared with patients presenting with stable syndromes, NSTE-ACS patients were younger, more often female with fewer cardiovascular risk factors including prior MI, prior coronary revascularization and less diabetes mellitus (**Supplementary Table 1**). Angiographic features including total stent length and number of treated lesions were similar between patients with and without NSTE-ACS. As shown in **Table 1**, demographic and clinical parameters were well balanced between treatment arms among patients with NSTE-ACS; mean age was 64 years, 25% were female, and approximately 35% had diabetes mellitus. 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 40 mm in both groups.

Bleeding

As shown in **Table 3** and **Figure 2,** among NSTE-ACS patients BARC 2, 3 or 5 bleeding occurred in 81 subjects (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). Among patients without NSTE-ACS a BARC 2, 3 or 5 bleed occurred in 60 patients (4.8%) randomized to ticagrelor plus placebo while it occurred in 75 subjects (6.2%) with ticagrelor plus aspirin (HR 0.76; 95% CI 0.54-1.06; p=0.11). Interaction testing for this outcome displayed a nominal level of significance ($p_{interaction}$ = 0.03). Patterns of risk in relation to clinical presentation were similar with alternative bleeding scales (**Table 3**).

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 (**Table 3**). The treatment effect for all ischemic outcomes was consistent among those with or without NSTE-ACS (all p_{int} >0.1).

Additional Analyses

Figure 3 shows rates of permanent study drug discontinuation between randomized groups stratified by clinical presentation. Among NSTE-ACS patients, one-year rates of study drug discontinuation among patients randomized to ticagrelor plus placebo and ticagrelor plus aspirin were 367 (16.3%) and 397 (17.1%), respectively, (p=0.46). Similar rates were observed between treatment groups among those without NSTE-ACS (18.4% vs. 18.9%; p=0.69). The effect of ticagrelor monotherapy on BARC 2, 3 or 5 bleeding was consistent among patients with unstable angina or NSTEMI (**Supplementary Table 3**). Similar effects were observed for ischemic events.

Discussion

Principal findings from our pre-specified analysis involving 4614 patients with NSTE-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) the bleeding-related benefits of ticagrelor monotherapy were larger in magnitude among patients with versus without NSTE-ACS; and (3) one-year rates of ischemic events, including all-cause death, recurrent MI and definite/probable stent thrombosis, appeared similar between treatment arms irrespective of clinical presentation. 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 $P2Y_{12}$ 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 among NSTE-ACS patients, 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 aspirin 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 $P2Y_{12}$

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] 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 NSTE-ACS versus stable syndromes, although bleeding risk was similar between groups. These patterns suggest that severity of clinical presentation uniquely contributes to recurrent thrombosis and not bleeding following PCI, and are consistent with prior reports highlighting the impact of ACS on post-PCI ischemic and bleeding complications.[13,26] Despite displaying a higher thrombotic risk, ACS patients in the present analysis were also younger with less renal impairment compared to those with stable presentations, suggesting a relatively low-risk bleeding profile. Indeed, one-year rates of BARC 2, 3 or 5 bleeding in the placebo arms were 3.6% and 4.8% among those with versus without NSTE-ACS. The relative effect of aspirin with respect to bleeding may have been amplified in the setting of low versus high bleeding risk, thus accounting for the larger reduction in bleeding observed with ticagrelor monotherapy versus ticagrelor plus aspirin we observed among NSTE-ACS patients.

Despite guideline recommendations to the contrary, clopidogrel remains a commonly prescribed $P2Y_{12}$ inhibitor among patients with ACS, and switching from a potent agent to clopidogrel (i.e. de-escalation) is relatively common after an ACS event.[27] These practice patterns may be driven by bleeding-related safety concerns as patients receiving potent $P2Y_{12}$ inhibitors are usually characterized by a lower risk clinical profile compared with their counterparts treated with clopidogrel.[28] 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 $P2Y_{12}$ 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.[29] 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 $P2Y_{12}$ 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 $P2Y_{12}$ inhibitor monotherapy does not increase cerebrovascular risk as compared to DAPT.[30]

In conclusion, among patients with NSTE-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.

References

1. Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001; **358**(9281): 527-33.

2. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2016; **68**(10): 1082-115.

3. Yeh RW, Kereiakes DJ, Steg PG, et al. Benefits and Risks of Extended Duration Dual Antiplatelet Therapy After PCI in Patients With and Without Acute Myocardial Infarction. *J Am Coll Cardiol* 2015; **65**(20): 2211-21.

4. Valgimigli M, Costa F, Lokhnygina Y, et al. Trade-off of myocardial infarction vs. bleeding types on mortality after acute coronary syndrome: lessons from the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) randomized trial. *European heart journal* 2017; **38**(11): 804-10.

5. Mehran R, Baber U, Steg PG, et al. Cessation of dual antiplatelet treatment and cardiac events after percutaneous coronary intervention (PARIS): 2 year results from a prospective observational study. *Lancet* 2013; **382**(9906): 1714-22.

6. Hahn JY, Song YB, Oh JH, et al. 6-month versus 12-month or longer dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (SMART-DATE): a randomised, open-label, non-inferiority trial. *Lancet* 2018; **391**(10127): 1274-84.

7. Capodanno D, Mehran R, Valgimigli M, et al. Aspirin-free strategies in cardiovascular disease and cardioembolic stroke prevention. *Nature reviews Cardiology* 2018; **15**(8): 480-96.

8. Mehran R, Baber U, Sharma S. Ticagrelor With or Without Aspirin in High-Risk Patients After PCI. *NEJM* 2019.

9. Baber U, Dangas G, Cohen DJ, et al. Ticagrelor with aspirin or alone in high-risk patients after coronary intervention: Rationale and design of the TWILIGHT study. *American heart journal* 2016; **182**: 125-34.

10. Baber U, Dangas G, Chandrasekhar J, et al. Time-Dependent Associations Between Actionable Bleeding, Coronary Thrombotic Events, and Mortality Following Percutaneous Coronary Intervention: Results From the PARIS Registry. *JACC Cardiovasc Interv* 2016; **9**(13): 1349-57.

11. Costa F, van Klaveren D, James S, et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *Lancet* 2017; **389**(10073): 1025-34.

12. Genereux P, Giustino G, Witzenbichler B, et al. Incidence, Predictors, and Impact of Post-Discharge Bleeding After Percutaneous Coronary Intervention. *J Am Coll Cardiol* 2015; **66**(9): 1036-45.

13. Yeh RW, Secemsky EA, Kereiakes DJ, et al. Development and Validation of a Prediction Rule for Benefit and Harm of Dual Antiplatelet Therapy Beyond 1 Year After Percutaneous Coronary Intervention. *Jama* 2016; **315**(16): 1735-49.

14. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation* 2011; **123**(23): 2736-47.

15. Bovill EG, Terrin ML, Stump DC, et al. Hemorrhagic events during therapy with recombinant tissue-type plasminogen activator, heparin, and aspirin for acute myocardial infarction. Results of the Thrombolysis in Myocardial Infarction (TIMI), Phase II Trial. *Annals of internal medicine* 1991; **115**(4): 256-65.

16. An International Randomized Trial Comparing Four Thrombolytic Strategies for Acute Myocardial Infarction. *New England Journal of Medicine* 1993; **329**(10): 673-82.

17. Kaatz S, Ahmad D, Spyropoulos AC, Schulman S, the Subcommittee on Control of A. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. *Journal of Thrombosis and Haemostasis* 2015; **13**(11): 2119-26.

18. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *J Am Coll Cardiol* 2012; **60**(16): 1581-98.

19. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007; **115**(17): 2344-51.

20. Hahn JY, Song YB, Oh JH, et al. Effect of P2Y12 Inhibitor Monotherapy vs Dual Antiplatelet Therapy on Cardiovascular Events in Patients Undergoing Percutaneous Coronary Intervention: The SMART-CHOICE Randomized Clinical Trial. *Jama* 2019; **321**(24): 2428-37.

21. Vranckx P, Valgimigli M, Juni P, et al. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. *Lancet* 2018; **392**(10151): 940-9.

22. Watanabe H, Domei T, Morimoto T, et al. Effect of 1-Month Dual Antiplatelet Therapy Followed by Clopidogrel vs 12-Month Dual Antiplatelet Therapy on Cardiovascular and

Bleeding Events in Patients Receiving PCI: The STOPDAPT-2 Randomized Clinical Trial. *Jama* 2019; **321**(24): 2414-27.

23. Armstrong PC, Leadbeater PD, Chan MV, et al. In the presence of strong P2Y12 receptor blockade, aspirin provides little additional inhibition of platelet aggregation. *J Thromb Haemost* 2011; **9**(3): 552-61.

24. Kirkby NS, Leadbeater PD, Chan MV, Nylander S, Mitchell JA, Warner TD. Antiplatelet effects of aspirin vary with level of P2Y(1)(2) receptor blockade supplied by either ticagrelor or prasugrel. *J Thromb Haemost* 2011; **9**(10): 2103-5.

25. Vilahur G, Segales E, Salas E, Badimon L. Effects of a novel platelet nitric oxide donor (LA816), aspirin, clopidogrel, and combined therapy in inhibiting flow- and lesion-dependent thrombosis in the porcine ex vivo model. *Circulation* 2004; **110**(12): 1686-93.

26. Baber U, Mehran R, Giustino G, et al. Coronary Thrombosis and Major Bleeding After PCI With Drug-Eluting Stents: Risk Scores From PARIS. *J Am Coll Cardiol* 2016; **67**(19): 2224-34.

27. Angiolillo DJ, Rollini F, Storey RF, et al. International Expert Consensus on Switching Platelet P2Y12 Receptor-Inhibiting Therapies. *Circulation* 2017; **136**(20): 1955-75.

28. Sahlen A, Varenhorst C, Lagerqvist B, et al. Contemporary use of ticagrelor in patients with acute coronary syndrome: insights from Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART). *European heart journal Cardiovascular pharmacotherapy* 2016; **2**(1): 5-12.

29. Schupke S, Neumann FJ, Menichelli M, et al. Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes. *N Engl J Med* 2019.

30. Diener HC, Bogousslavsky J, Brass LM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet* 2004; **364**(9431): 331-7.

Figure Legends

Figure 1 Disposition of study participants in TWILIGHT trial

Figure 2 Kaplan-Meier estimates of Bleeding Academic Research Consortium (BARC) 2, 3 or 5 bleeding with ticagrelor plus placebo and ticagrelor plus aspirin among patients presenting with (A) stable syndromes and (B) acute coronary syndromes.

Figure 3 Kaplan-Meier estimates of all-cause death, myocardial infarction or stroke with ticagrelor plus placebo and ticagrelor plus aspirin among patients presenting with (A) stable syndromes and (B) acute coronary syndromes

Figure 4 Rate of Discontinuation of Blinded Study Drug Over One Year in both Non-ACS and NSTE-ACS patients.

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%)	0.82
Nonwhite Race	872 (38.4%)	854 (36.5%)	0.62
Enrolling Region			
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; NSTE ACS- 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
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. Treatment Effects for Bleeding and Ischemic Outcomes Stratified by Clinical Presentation

	Stable syndrome (n=2503)			NSTE-ACS (n=4614)			
	Ticagrelor plus Placebo (n=1281)	Ticagrelor plus Aspirin (n=1222)	HR (95% CI)	Ticagrelor plus Placebo (n=2273)	Ticagrelor plus Aspirin (n=2341)	HR (95% CI)	P_{int}
Bleeding Outcomes							
BARC 2, 3 or 5	60 (4.8%)	75 (6.2%)	0.76 (0.54-1.06)	81 (3.6%)	175 (7.6%)	0.47 (0.36-0.61)	0.027
BARC 3 or 5	17 (1.4%)	20 (1.7%)	0.81 (0.43-1.56)	17 (0.8%)	49 (2.1%)	0.36 (0.20-0.62)	0.056
GUSTO moderate or severe	13 (1.0%)	13 (1.1%)	0.96 (0.44-2.07)	13 (0.6%)	36 (1.6%)	0.37 (0.20-0.70)	0.061
TIMI Major	5 (0.4%)	11 (0.9%)	0.43 (0.15-1.25)	12 (0.5%)	23 (1.0%)	0.53 (0.27-1.08)	0.744
ISTH Major	19 (1.5%)	21 (1.7%)	0.87 (0.47-1.61)	20 (0.9%)	51 (2.2%)	0.40 (0.24-0.67)	0.062
Ischemic Outcomes							
All-cause death, MI or stroke	39 (3.1%)	39 (3.2%)	0.96 (0.61-1.49)	96 (4.3%)	102 (4.4%)	0.97 (0.74-1.28)	0.956
Cardiovascular death, MI or ischemic stroke	36 (2.9%)	35 (2.9%)	0.98 (0.62-1.57)	90 (4.0%)	97 (4.2%)	0.96 (0.72-1.28)	0.923
All-cause death	12 (0.9%)	14 (1.2%)	0.82 (0.38-1.77)	22 (1.0%)	34 (1.5%)	0.67 (0.39-1.14)	0.665
MI	25 (2.0%)	25 (2.1%)	0.96 (0.55-1.66)	70 (3.1%)	72 (3.1%)	1.00 (0.72-1.39)	0.884
Ischemic stroke	5 (0.4%)	2 (0.2%)	2.4 (0.47-12.38)	11 (0.5%)	6 (0.3%)	1.89 (0.70-5.10	0.807
Definite or probable stent thrombosis	6 (0.5%)	6 (0.5%)	0.96 (0.31-2.97)	8 (0.4%)	14 (0.6%)	0.59 (0.25-1.40)	0.501

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

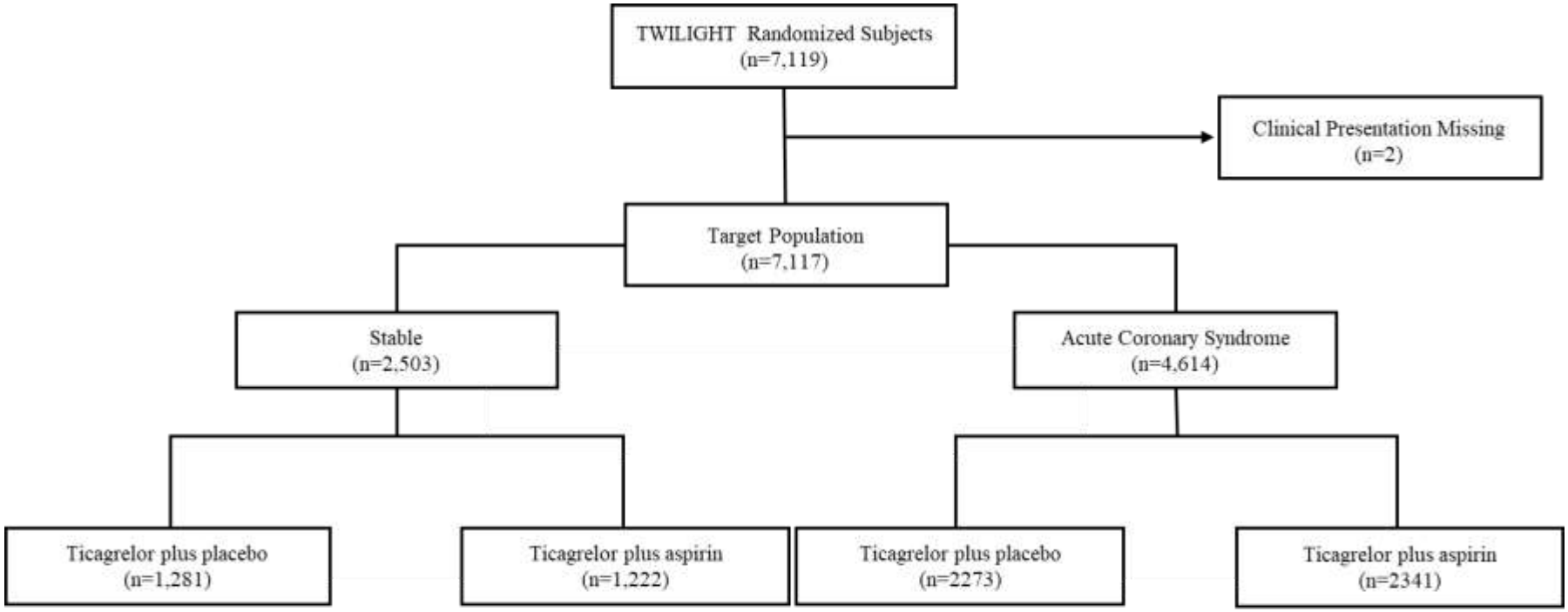
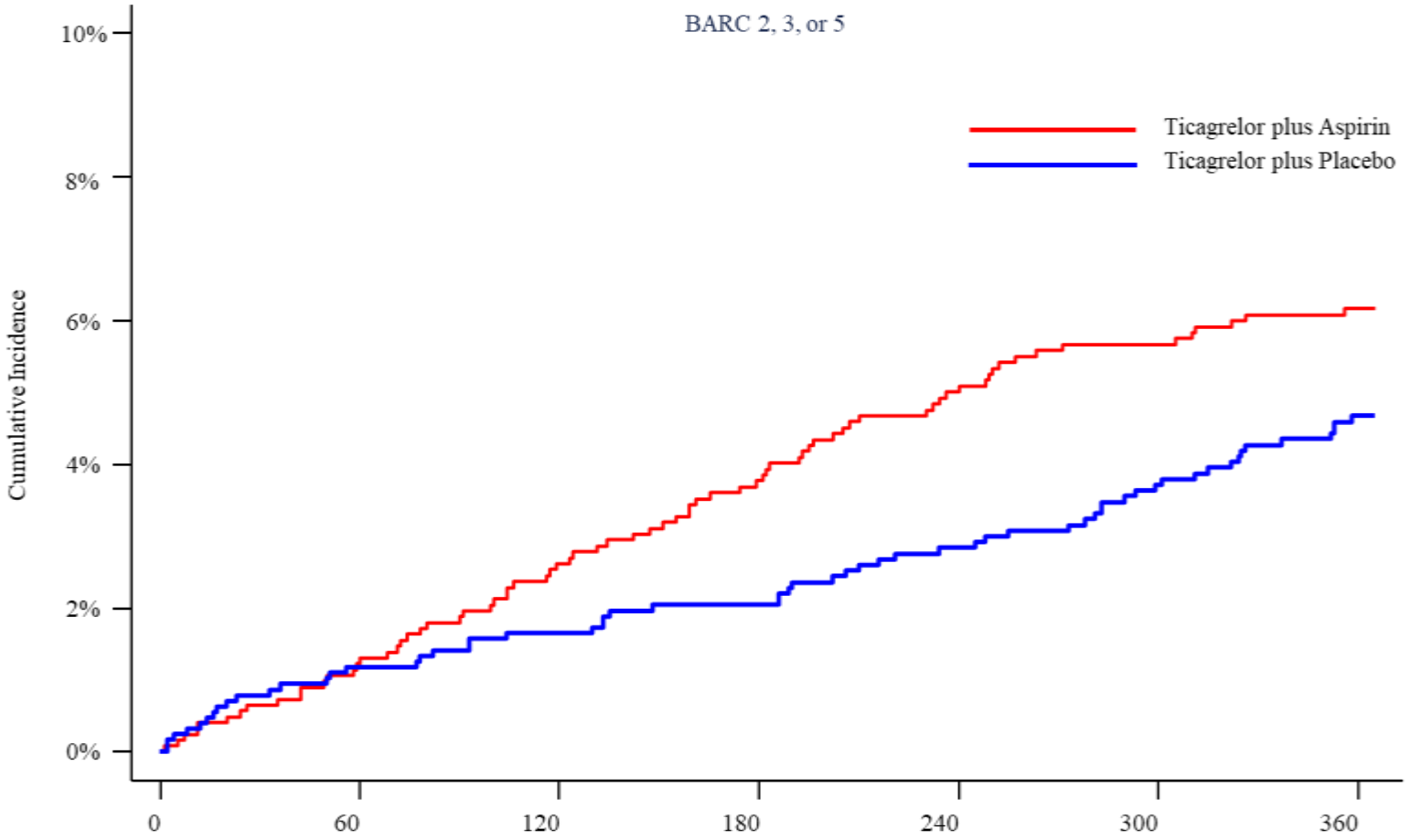
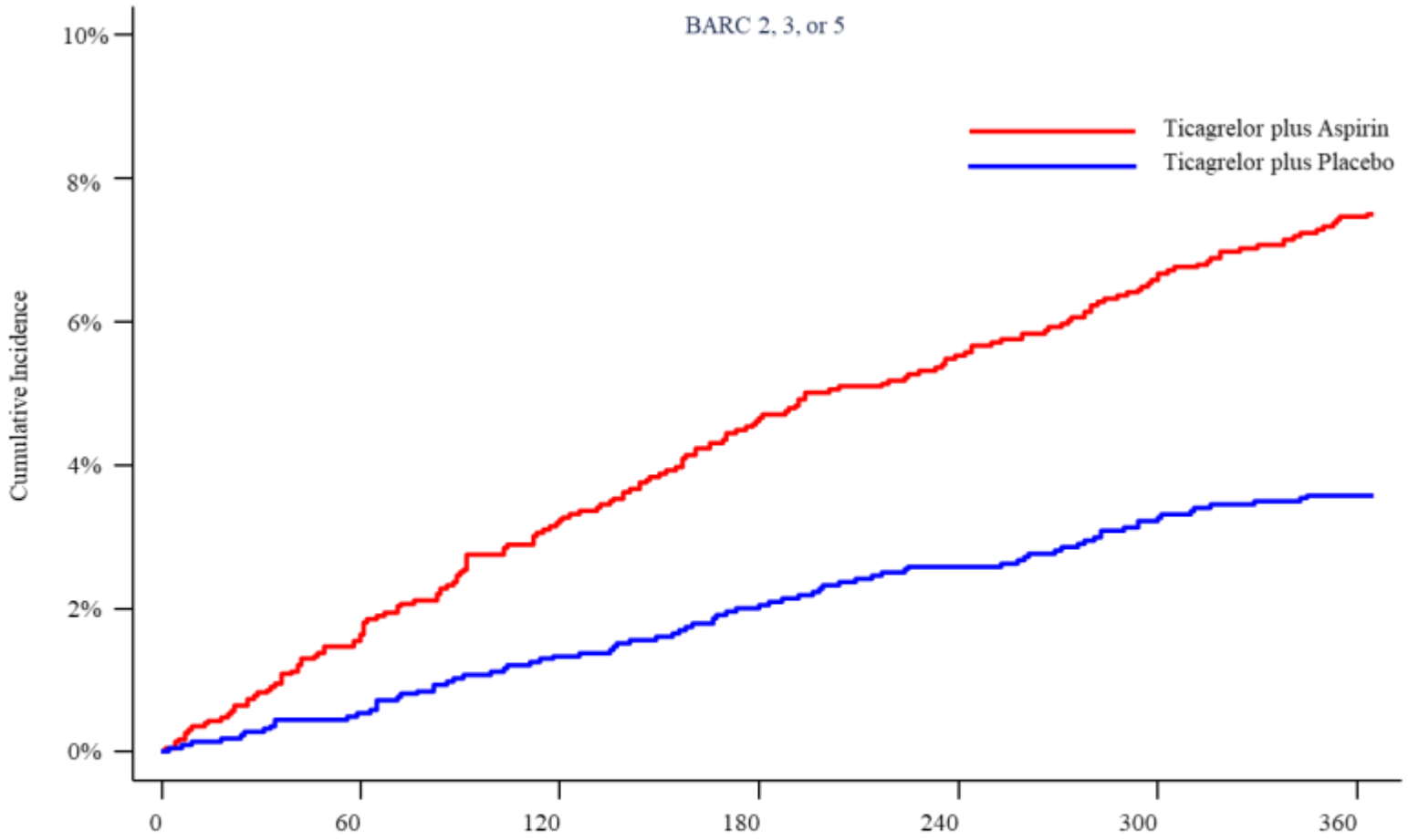


Figure 1 Disposition of study participants in TWILIGHT trial



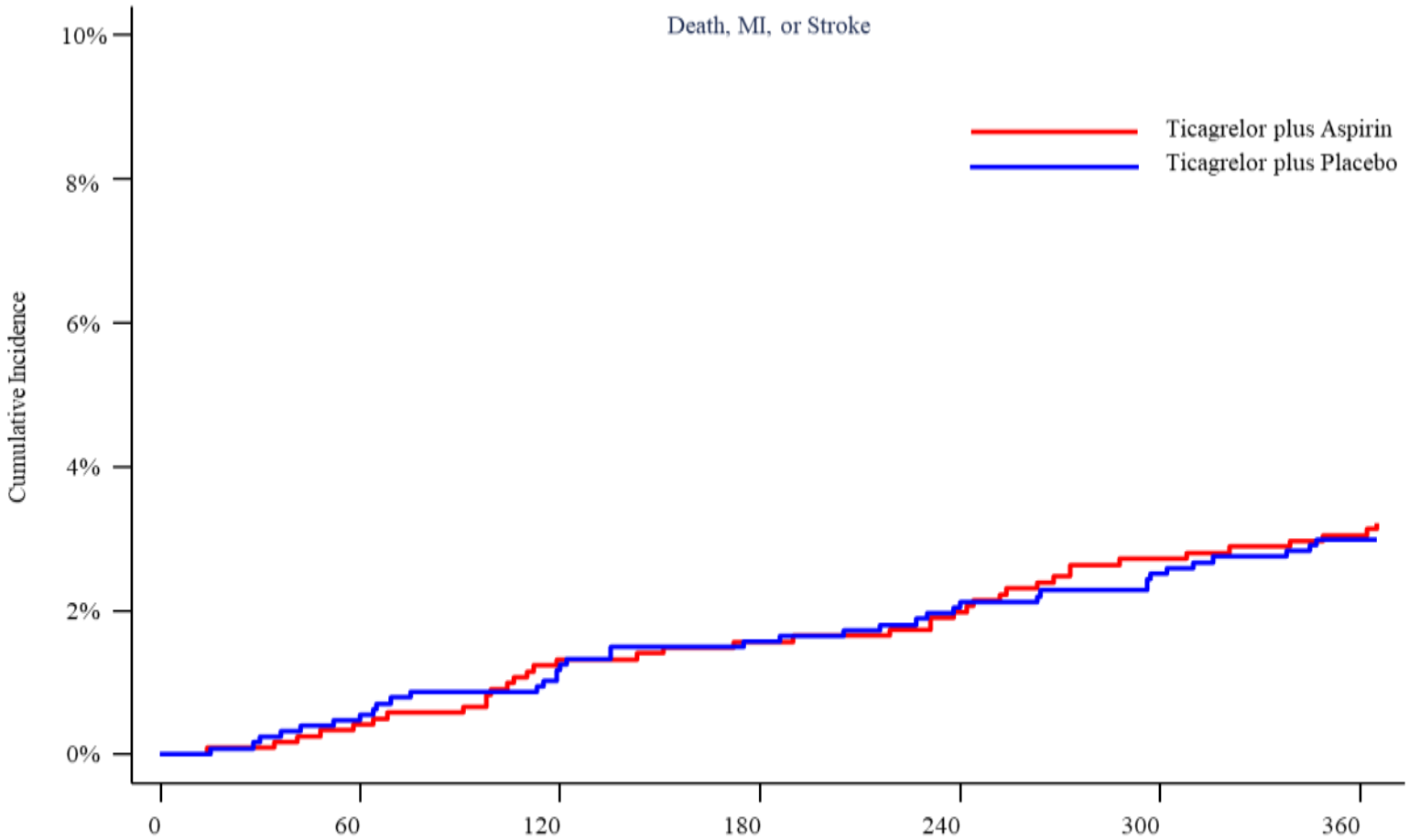
Number at risk							
Ticagrelor plus Aspirin	1225	1203	1181	1166	1147	1133	1121
Ticagrelor plus Placebo	1285	1259	1247	1239	1222	1208	1192

Figure 2a Kaplan-Meier estimates of Bleeding Academic Research Consortium (BARC) 2, 3 or 5 bleeding with ticagrelor plus placebo and ticagrelor plus aspirin among patients presenting with stable syndromes



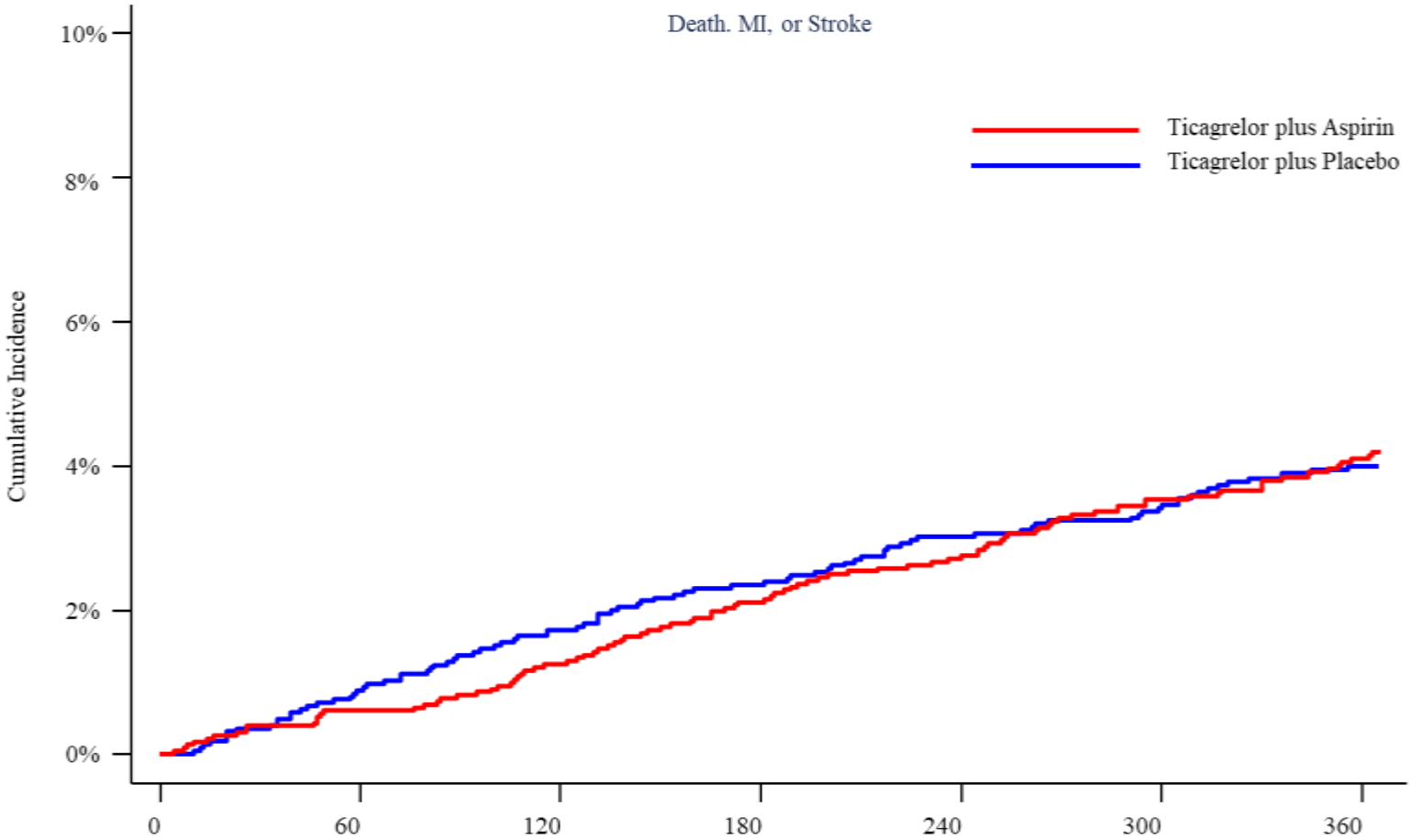
Number at risk							
Ticagrelor plus Aspirin	2338	2285	2240	2197	2160	2129	2095
Ticagrelor plus Placebo	2269	2238	2215	2190	2159	2142	2130

Figure 2b Kaplan-Meier estimates of Bleeding Academic Research Consortium (BARC) 2, 3 or 5 bleeding with ticagrelor plus placebo and ticagrelor plus aspirin among patients presenting with acute coronary syndromes



Number at risk							
Ticagrelor plus Aspirin	1225	1214	1202	1198	1188	1178	1170
Ticagrelor plus Placebo	1285	1285	1258	1250	1238	1231	1221

Figure 3a Kaplan-Meier estimates of all-cause death, myocardial infarction or stroke with ticagrelor plus placebo and ticagrelor plus aspirin among patients presenting with stable syndromes



Number at risk							
Ticagrelor plus Aspirin	2338	2308	2292	2269	2242	2223	2201
Ticagrelor plus Placebo	2269	2235	2215	2195	2167	2158	2143

Figure 3b Kaplan-Meier estimates of all-cause death, myocardial infarction or stroke with ticagrelor plus placebo and ticagrelor plus aspirin among patients presenting with acute coronary syndromes

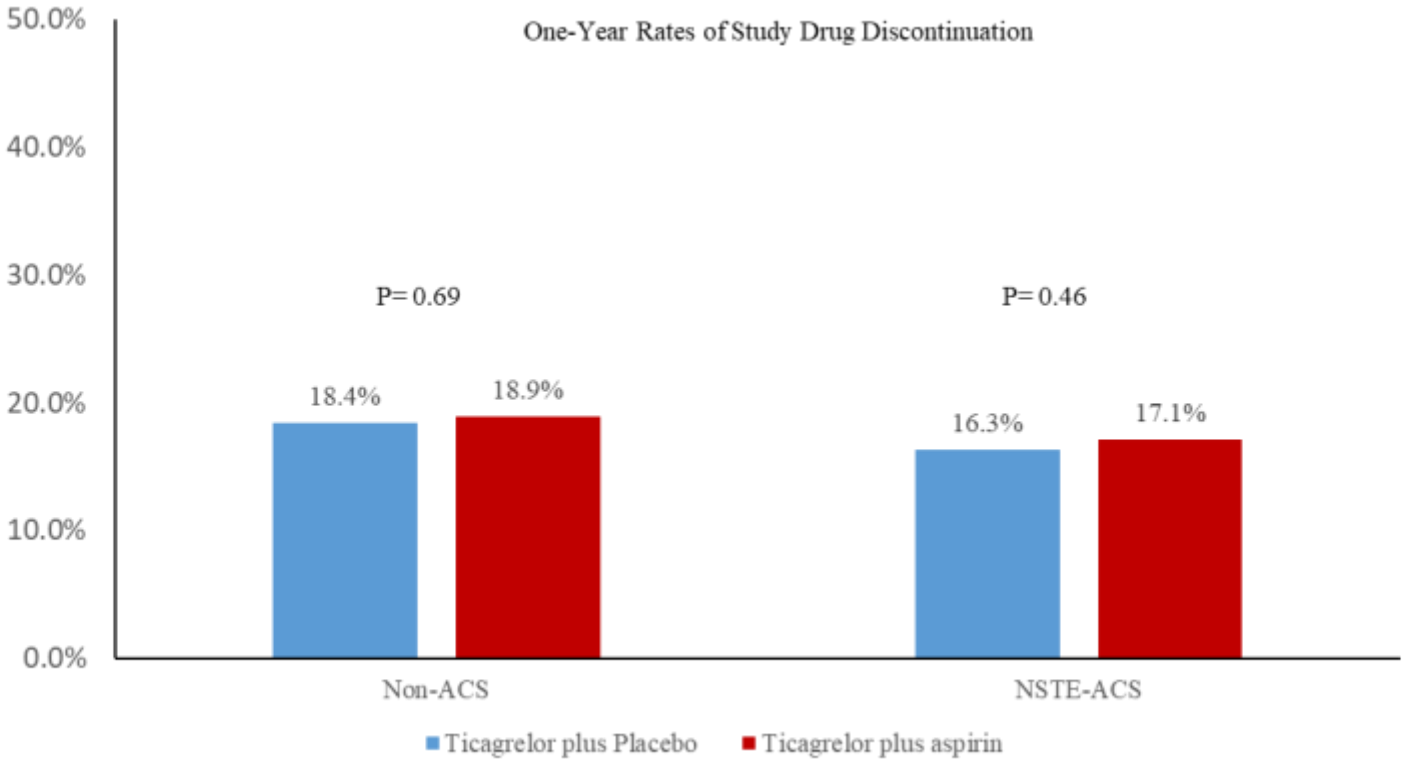


Figure 4 Rate of Discontinuation of Medications at One year Follow Up in both Non-ACS and NSTE-ACS patients.