10.1161/CIRCULATIONAHA.123.067283

Safety and Efficacy of Ticagrelor Monotherapy in Patients With Acute Coronary Syndromes Undergoing Percutaneous Coronary Intervention: an Individual Patient Data Meta-analysis of TWILIGHT and TICO Randomized Trials

Running title: *Baber et al.; Ticagrelor monotherapy in ACS patients*

Usman Baber, MD[1]; Yangsoo Jang, MD, PhD[2]; Angelo Oliva, MD[3,4]; Davide Cao, MD[3,4]; Birgit Vogel, MD[3]; George Dangas, MD, PhD[3]; Samantha Sartori, PhD[3]; Alessandro Spirito, MD[3]; Kenneth F. Smith, MPH[3]; Mattia Branca, PhD[5]; Timothy Collier, MSc[6]; Stuart Pocock, PhD[6]; Marco Valgimigli, MD, PhD[7,8]; Byeong-Keuk Kim, MD, PhD[9]; Myeong-Ki Hong, MD, PhD[9]; Roxana Mehran, MD[3].

[1]Cardiovascular Disease Section, Department of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK; [2]Bundang CHA Medical Center, CHA University School of Medicine, Seongnam, South Korea; [3]The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York City, NY; [4]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele (MI), Italy; [5]CTU Bern, University of Bern, Bern, Switzerland; [6]Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, United Kingdom; [7]Cardiocentro Ticino Institute, Ente Ospedaliero Cantonale (EOC), Lugano, Switzerland; [8]Department of Biomedical Sciences, University of Italian Switzerland, Lugano, Switzerland; [9]Severance Cardiovascular Hospital, Yonsei University College of Medicine, Seoul, South Korea

Address for Correspondence:

Roxana Mehran, MD
The Zena and Michael A. Wiener Cardiovascular Institute
Icahn School of Medicine at Mount Sinai
1 Gustave L. Levy Place
New York, NY 10029
roxana.mehran@mountsinai.org

*This article is published in its accepted form, it has not been copyedited and has not appeared in an issue of the journal. Preparation for inclusion in an issue of Circulation involves copyediting, typesetting, proofreading, and author review, which may lead to differences between this accepted version of the manuscript and the final, published version.

**This work was presented as an abstract at TCT, October 23-26, 2023

Abstract

Background: Dual antiplatelet therapy (DAPT) with a potent $P2Y_{12}$ Inhibitor coupled with aspirin for 1 year is the recommended treatment for patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI). Alternatively, monotherapy with a $P2Y_{12}$ inhibitor after a short period of DAPT has emerged as a bleeding reduction strategy.

Methods: We pooled individual patient data from randomized trials that included ACS patients undergoing PCI treated with an initial 3-month course of DAPT followed by ticagrelor monotherapy versus continued ticagrelor plus aspirin. Patients sustaining a major ischemic or bleeding event in the first 3 months after PCI were excluded from analysis. The primary outcome was Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding occurring between 3 and 12 months after index PCI. The key secondary endpoint was the composite of death, myocardial infarction (MI), or stroke. Hazard ratios (HR) and 95% confidence intervals (CI) were generated using Cox regression with a one-stage approach in the intention to treat population.

Results: The pooled cohort (N = 7,529) was characterized by a mean age of 62.8 years, 23.2% of patients were female and 55% presented with biomarker positive ACS. Between 3 and 12 months, ticagrelor monotherapy significantly reduced BARC 3 or 5 bleeding as compared with ticagrelor plus aspirin (0.8% vs. 2.1%; HR 0.37, 95% CI 0.24-0.56; $p < 0.001$). Rates of all-cause death, MI, or stroke were not significantly different between groups (2.4% vs. 2.7%; HR 0.91, 95% CI 0.68-1.21; P = 0.515). Findings were unchanged among patients presenting with biomarker positive ACS.

Conclusions: Among ACS patients undergoing PCI who have completed a 3-month course of DAPT, discontinuation of aspirin followed by ticagrelor monotherapy significantly reduced major bleeding without incremental ischemic risk, as compared with ticagrelor plus aspirin.

Clinical Trial Registration: PROSPERO registration number: CRD42023449646 https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=449646

Key Words: Acute Coronary Syndrome, Percutaneous Coronary Intervention, P2Y12 receptor antagonists, Ticagrelor Monotherapy, Bleeding.

Nonstandard Abbreviations and Acronyms

DAPT: dual antiplatelet therapy
ACS: acute coronary syndrome
PCI: percutaneous coronary intervention
CPG: clinical practice guidelines
IPD: individual patient data
RCTs: randomized clinical trials
DES: drug-eluting stent
BARC: Bleeding Academic Research Consortium
TIMI: Thrombolysis In Myocardial Infarction
NACE: net adverse clinical events
HR: Hazard ratios
CI: confidence intervals

Clinical Perspective

What is new?

- We pooled individual data of 7,529 patients presenting with acute coronary syndrome from TICO (Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus eluting Stent for Acute Coronary Syndrome) and TWILIGHT (Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention) trials.
- Among ACS patients treated with a 3-month course of DAPT, ticagrelor monotherapy yields a superior net clinical benefit as compared with ticagrelor plus aspirin by significantly reducing major bleeding without incremental ischemic risk.
- These benefits are preserved across ACS presentations and varying degree of bleeding risk and PCI complexity.

What are the clinical implications?

- Patients with acute coronary syndrome undergoing percutaneous coronary intervention derived a superior clinical benefit from a 3-month course of dual antiplatelet therapy (DAPT) followed by ticagrelor monotherapy as compared with continued DAPT.
- Our findings reinforce guideline recommendations that endorse the withdrawal of aspirin as early as 3 months post-ACS followed by P2Y12 inhibitor monotherapy.

Introduction

Pharmacotherapy consisting of aspirin and an inhibitor of the platelet $P2Y_{12}$ receptor, or dual antiplatelet therapy (DAPT), is indicated for at least one year in all patients presenting with acute coronary syndrome (ACS) treated with percutaneous coronary intervention (PCI).[1,2] Clinical practice guidelines (CPG) advocate the preferential use of the potent $P2Y_{12}$ inhibitors ticagrelor or prasugrel given their established superiority over clopidogrel in preventing recurrent thrombosis.[3,4] Despite the clinical trial evidence and recommendations to the contrary, many high-risk ACS patients are still treated with clopidogrel.[5-7] One reason for this counter-intuitive practice pattern relates to concerns around bleeding, which is not uncommon after PCI. Moreover, bleeding associates with DAPT discontinuation and is independently linked with excess morbidity and mortality.[8-11]

An evolving therapeutic strategy that preserves the benefits of strong $P2Y_{12}$ inhibition yet mitigates bleeding risk involves the early withdrawal of aspirin followed by $P2Y_{12}$ inhibitor monotherapy. To date, at least two clinical trials have examined this approach among ACS patients exclusively with inconsistent results.[12,13] Analogously, subgroup analyses from trials enrolling both stable and acute patients have shown that the effect of ticagrelor monotherapy varies by clinical presentation, comparator antiplatelet regimen and time from PCI.[14,15] Pooled analyses have been limited by lack of patient-level data[16,17] and inclusion of trials that evaluated different $P2Y_{12}$ inhibitors.[18] Accordingly, we sought to further characterize the safety and efficacy of aspirin withdrawal followed by guideline-endorsed $P2Y_{12}$ inhibitor monotherapy with ticagrelor after a 3-month course of DAPT among ACS patients undergoing PCI.

Methods

Study Design and Selection Criteria

We conducted an individual patient data (IPD) meta-analysis of randomized clinical trials (RCTs) comparing ticagrelor monotherapy with ticagrelor plus aspirin in patients with ACS undergoing PCI with drug-eluting coronary stents (DES) implantation. Studies were deemed eligible if ischemic and bleeding events were centrally adjudicated by a clinical event committee and patients were treated with ticagrelor in both experimental (ticagrelor monotherapy) and control (aspirin plus ticagrelor) arms. We excluded RCTs including patients requiring long-term oral anticoagulation and comparing other $P2Y_{12}$ inhibitors different than ticagrelor. Trials needed to have been approved by local medical ethics committees and all patients should have provided written informed consent for inclusion the study. The study protocol was registered in PROSPERO and is available online (CRD42023449646).

Search Strategy and Data Extraction

Studies were identified by a systematic search of databases (PubMed, Embase) and websites (www.ClinicalTrials.gov, www.cardiosource.com, www.escardio.org, www.tctmd.com) from inception onwards and without language restrictions; the detailed search algorithm is provided in the Supplemental Methods. Citations were screened on the basis of title and abstract and potentially eligible reports were retrieved and scrutinized for eligibility in full-text; reasons for exclusion were discussed and discrepancies were resolved by consensus. We reported the number of records identified, included and excluded, and the reasons for exclusions in the PRISMA 2020 Flow diagram for systematic review (Figure S1). The TICO (Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus eluting Stent for Acute Coronary Syndrome) and TWILIGHT (Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention) trials were identified for the inclusion in the analysis and the principal investigators were contacted requesting patient-level data in anonymized electronic data sets. Data were compared with the original publication in order to check completeness and consistency. The principal investigators of included trials were contacted in case of missing information or if queries arose at integrity checks.

Study Population

The experimental strategy tested in both TICO and TWILIGHT involved aspirin withdrawal followed by ticagrelor monotherapy after a 3-month course of DAPT. In TWILIGHT only those patients who remained event-free in the first 3 months after PCI were eligible for randomization while randomization occurred at the time of PCI in TICO. To ensure a homogenous cohort we included all ACS patients randomized at the 3-month study visit in TWILIGHT and applied similar criteria in TICO. Hence, we excluded TICO participants sustaining an ischemic or major bleeding event within the first 3 months post-PCI. With respect to longitudinal follow-up, TWILIGHT and TICO followed patients up to 15 and 12 months post-PCI, respectively. To align follow-up across trials we included all events occurring between the time of DAPT discontinuation in the experimental arm (3 months post-PCI) and 9 months thereafter.

Study Endpoints

The prespecified primary endpoint was major bleeding, defined as the composite of Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding.[19] The prespecified key secondary ischemic endpoint was the composite of all-cause death, myocardial infarction (MI), or stroke. Other secondary outcomes were the individual components of the primary and secondary outcomes, cardiovascular death, stent thrombosis, Thrombolysis In Myocardial Infarction (TIMI) major or minor bleeding, the composite of cardiovascular death, MI, or ischemic stroke, and net adverse clinical events (NACE), defined as composite of all-cause death, MI, stroke, or BARC type 3 or 5 bleeding. The definitions used for endpoints were largely consistent across included trials and are extensively reported in Table S1.

Statistical Analysis

We used a one-step approach to analyze all data simultaneously in the intention-to-treat population, as primary analysis. For longitudinal data we considered all events occurring between the time at which randomly allocated treatment commenced (3 months after PCI) and 9 months thereafter. Time to event outcomes were estimated using the Kaplan-Meier method and observations were censored at the time of death, lost to follow-up or 9 months follow-up, whichever comes first. Baseline characteristics were summarized as means (standard deviation) or median (interquartile range) and percentages for continuous and categorical variables, respectively. Hazard ratios (HR) and 95% confidence intervals (CI) were generated using random effects Cox proportional hazard that included a frailty term (γ) to assess random effects in the trials.[20,21] Frailties are the unmeasured factors that affect trial-specific baseline risk and are distributed as γ random variables with a mean of 1 and variance θ. The variance parameter is interpreted as a metric of heterogeneity in baseline risk between trials. The likelihood ratio test was used to test the significance of the variance parameter. The aspirin plus ticagrelor group was the reference category for all analyses. Superiority testing for the primary endpoint of BARC 3 or 5 bleeding was performed using a conventional 2-sided p-value of 0.05. We prespecified a set of subgroup analyses for the primary and key secondary outcomes according to clinical and procedural characteristics accompanied by tests of interaction. A sensitivity analyses was performed estimating effect sizes from each trial separately and then pooling estimates together using fixed-effects meta-analysis. All statistical analyses were conducted at the Icahn School of Medicine at Mount Sinai in New York with Stata software version 18.0 (StataCorp., College Station, TX, US) and SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina). The data that support the findings of this study are available from the corresponding author upon reasonable request.

Results

Baseline and Procedural Characteristics

A total of 7,529 patients, from 2 randomized trials were included in the present analysis; of these 3,726 (49.5%) patients were randomized to ticagrelor monotherapy and 3,803 (50.5%) received aspirin plus ticagrelor. Among 3,056 patients originally enrolled in TICO trial, 141 (4.6%) were excluded from analysis after harmonization of the study cohort due to occurrence of ischemic or major bleeding events or loss to follow-up within the first 3 months. Therefore, the study cohort consisted of 2,915 (38.7%) patients from TICO and 4,614 (61.3%) patients from TWILIGHT (Figure 1). When stratified according to the study treatment, the two populations were well balanced in terms of baseline and procedural characteristics (Table 1 and 2). Mean age was 62.8 years and 23.2% of participants were female. A total of 31.9% of patients had a diagnosis of diabetes mellitus (7.1% insulin-treated), whereas 16.9% suffered from chronic kidney disease. A prior MI was reported in 16.9% of patients, and 1.6% had a prior stroke. Previous percutaneous or surgical revascularization was performed in 25.4% and 5.6% of patients, respectively. Unstable angina was the most common ACS qualifying event at presentation (45.0%), followed by non-ST-segment elevation MI (41.1%) and ST-segment elevation MI (13.9%). Patients underwent PCI more frequently from radial access (68.6%) with most (76.9%) undergoing single-vessel PCI treated with a median stent length of 32 mm. Baseline and procedural characteristics, stratified according to individual trial are reported in Table S2 and S3.

Primary and Key Secondary Outcomes

The overall association between clinical outcomes and treatment group is shown in Table 3. Between 3 and 12 months after PCI, ticagrelor monotherapy significantly reduced the primary endpoint of BARC 3 or 5 bleeding as compared with aspirin plus ticagrelor (0.8% vs. 2.1%; HR 0.37, 95% CI 0.24-0.56; P-for-superiority < 0.001) (Figure 2A). The risk of the key secondary ischemic endpoint, a composite of death, MI, or stroke, was similar between ticagrelor monotherapy and aspirin plus ticagrelor (2.4% vs. 2.7%; HR 0.91 95% CI 0.68-1.21; P = 0.515) (Figure 2B).

Secondary Outcomes

The risk of MI (HR 0.96, 95% CI 0.67-1.36, P = 0.809), any stroke (HR 0.94, 95% CI 0.43-2.07 P = 0.883), ischemic stroke (HR 0.84, 95% CI 0.35-2.02, P = 0.689), hemorrhagic stroke (HR 3.06, 95% CI 0.32-29.4, P = 0.332), stent thrombosis (definite stent thrombosis: HR 0.73, 95% CI 0.23-2.30, P = 0.589; probable stent thrombosis: HR 2.04, 95% CI 0.19-22.5, P = 0.560) was similar between ticagrelor monotherapy and aspirin plus ticagrelor. No differences were observed for the risk of all-cause death (HR 0.72, 95% CI 0.43-1.22, P = 0.219), cardiovascular death (HR 0.69, 95% CI 0.37-1.29, P = 0.246), and the composite of cardiovascular death, MI, or ischemic stroke (HR 0.89, 95% CI 0.66-1.20, P = 0.439). The risk of TIMI major (HR 0.33, 95% CI 0.18-0.62; P < 0.001), minor (HR 0.45, 95% CI 0.34-0.61; P < 0.001), and major or minor bleeding (HR 0.43, 95% CI 0.33-0.57; P < 0.001) was significantly lower with ticagrelor monotherapy (Figure 2C). Ticagrelor monotherapy significantly reduced the incidence of NACE (3.1% vs. 4.4%; HR 0.71, 95% CI 0.56-0.90, P = 0.004; Figure 2D).

Subgroup and Sensitivity Analysis

The treatment effects for the primary bleeding endpoint and the key secondary ischemic endpoint were consistent across all pre-specified subgroups including: age, sex, diabetes mellitus, chronic kidney disease; clinical presentation; high bleeding risk (HBR), and complex PCI (Figure 3 and 4). A prespecified sensitivity analysis performed estimating effect sizes from each trial separately and then pooling estimates together using fixed-effects meta-analysis yielded consistent results (Figure S2). We performed an additional study-level sensitivity meta-analysis that included ACS patients in the GLOBAL LEADERS Adjudication Sub-StudY (GLASSY) that yielded almost identical treatment effects for BARC 3 or 5 bleeding and death, MI, or stroke (data not shown).[22]

Discussion

We conducted a patient-level pooled analysis involving over 7,500 ACS patients undergoing PCI to examine the effect of $P2Y_{12}$ inhibition with ticagrelor alone after 3 months of DAPT. We found that ticagrelor monotherapy, as compared with ticagrelor plus aspirin, significantly reduces major bleeding without incremental ischemic risk over 9 months. Our results remained consistent when using alternative bleeding definitions and persisted across clinically relevant subgroups, including biomarker positive ACS patients. In aggregate, our findings suggest that ticagrelor monotherapy preserves the ischemic benefits of DAPT while avoiding aspirin-related bleeding thereby yielding a net clinical benefit in the setting of ACS and PCI. Hence, our findings reinforce guideline recommendations that endorse the withdrawal of aspirin as early as 3 months post-ACS followed by $P2Y_{12}$ inhibitor monotherapy.[1]

The primary endpoint of our pooled analysis was BARC type 3 or 5 bleeding, an event that occurred infrequently in both TICO and TWILIGHT thus rendering estimates for this important outcome somewhat imprecise in the original trials.[12,23] We increased analytic power by pooling data and only considering those events that occurred after DAPT was discontinued in the experimental arm. We focused on major bleeding given that the association between BARC type 3 or 5 bleeding and subsequent mortality is large, durable and approximates that of recurrent MI.[8,10] In this context we observed relative and absolute risk reductions in major bleeding with ticagrelor monotherapy of 63% and 1.3%, respectively, yielding a number needed to treat of 76. Our findings also substantiate the safety of aspirin withdrawal and continuation of ticagrelor alone with respect to ischemic events. These findings are concordant with both *in vitro* and *ex vivo* studies showing that aspirin exerts a negligible effect on indices of platelet reactivity and blood thrombogenicity on a background of strong $P2Y_{12}$ inhibitor blockade.[24,25]

In the GLOBAL LEADERS trial ticagrelor monotherapy after one month of DAPT did not reduce site-reported BARC 3 or 5 bleeding over 2 years as compared with a conventional antiplatelet strategy among unselected patients undergoing PCI.[26] However, among ACS patients a significant 27% reduction in major bleeding was observed.[15] The larger effect we detected may reflect differences in endpoint ascertainment (site-reported versus central adjudication) and comparator antiplatelet strategy. Similarly, previous meta-analyses have shown that $P2Y_{12}$ inhibitor monotherapy may serve as a therapeutic alternative to DAPT.[16-18] However, these reports included trials characterized by heterogeneity with respect to background $P2Y_{12}$ inhibitor, timing of DAPT discontinuation, clinical presentation, treatment effect and duration of exposure to $P2Y_{12}$ inhibition in the experimental arm. By contrast, we included a more homogenous ACS cohort treated with a single experimental strategy allowing us to more precisely estimate the effect of ticagrelor monotherapy on both ischemic and bleeding outcomes. These distinctions are relevant as clopidogrel monotherapy did not achieve non-inferiority with respect to ischemic events as compared with DAPT among ACS patients.[13] Our results are also concordant with those of a prior patient-level meta-analysis comprising both stable and acute patients that suggested an accentuated benefit of potent $P2Y_{12}$ inhibition with respect to bleeding as compared with DAPT.[18] We extend these earlier findings to an ACS cohort treated exclusively with ticagrelor monotherapy after

10.1161/CIRCULATIONAHA.123.067283

a uniform 3-month exposure to DAPT. As thrombotic events post ACS tend to occur in the first few months after index presentation, a minimum DAPT duration of at least 3 months is recommended in most patients prior to DAPT discontinuation.[1] The experimental strategy examined in both TICO and TWILIGHT aligns with this therapeutic approach.

Although we examined a bleeding reduction strategy, the 9-month rate of BARC 3 or 5 bleeding in our pooled cohort was only 1.5%, well below the annualized threshold of 4% set forth by the Academic Research Consortium (ARC).[19] Moreover, only 15% of our patients were characterized as HBR using a validated risk model.[27] This distinction is clinically meaningful as the optimal antiplatelet strategy following PCI may vary according to HBR status. Specifically, several studies have shown that a very short (i.e. 1 month) duration of DAPT followed by aspirin or clopidogrel monotherapy is superior to a longer duration of DAPT among HBR patients.[28,29] Conversely, non-HBR ACS patients are more appropriate candidates for strong $P2Y_{12}$ inhibition with or without aspirin. Whether or not selected HBR patients with concomitant high thrombotic risk may also derive a benefit from aspirin withdrawal and potent $P2Y_{12}$ inhibition remains unknown.

Importantly, the experimental strategy examined herein represents one of several DAPT de-escalation approaches as articulated by the ARC.[30] Alternatives include switching from a more to less potent $P2Y_{12}$ inhibitor or reducing the dose of $P2Y_{12}$ inhibitor. With respect to the former, several studies have shown that switching from ticagrelor or prasugrel to clopidogrel after a minimum duration of DAPT, as compared to not switching, reduces bleeding without compromising ischemic efficacy.[31] In regards to the latter, similar benefits were shown by reducing the dose of $P2Y_{12}$ inhibitor while maintaining aspirin.[32] Despite the comparable results when comparing each strategy to conventional DAPT, the relative merits of different de-escalation approaches have not been directly compared. Nonetheless, increased adoption of DAPT de-escalation as an *a priori* therapeutic strategy should enable greater use of ticagrelor or prasugrel over clopidogrel among ACS patients undergoing PCI.

Among the limitations of our study include limited power to detect differences in rare but clinically important endpoints, such as stent thrombosis and stroke. Due to differences in the inclusion criteria across trials TWILIGHT participants displayed a higher burden of thrombotic risk factors compared with TICO patients. However, prior studies have shown that the effect of ticagrelor monotherapy is uniform across different clinical and angiographic risk profiles.[33,34] In addition, while DES choice was at operator's discretion in TWILIGHT all TICO participants received a biodegradable-polymer DES. While these differences may influence baseline thrombotic risk, the effect of ticagrelor monotherapy on ischemic and bleeding outcomes appears uniform across DES platforms.[35] As further limitation, we acknowledge the relatively low number of STEMI patients in our pooled cohort. However, the treatment effect of ticagrelor monotherapy was homogenous across ACS presentations with no evidence of statistical interaction. Finally, our study design precludes inferences regarding earlier discontinuation of DAPT post-PCI or an evaluation of ticagrelor monotherapy versus alternative referent antiplatelet strategies.

In conclusion, our results show that a 3-month course of DAPT followed by ticagrelor monotherapy yields a superior clinical benefit as compared with continued DAPT among ACS patients undergoing PCI.

Acknowledgments

None

Sources of Funding

TICO was supported by the Cardiovascular Research Center, Seoul, South Korea and funded by Biotronik (Bülach, Switzerland). TWILIGHT was an investigator-initiated study sponsored by the Icahn School of Medicine at Mount Sinai and funded by AstraZeneca. The present analysis was funded by AstraZeneca. The Icahn School of Medicine at Mount Sinai has received financial compensation from AstraZeneca for Dr. Roxana Mehran's role as global PI for this study.

Disclosures

Dr. Baber has received honoraria from AstraZeneca and Boston Scientific.Dr. Mehran reports institutional research payments from Abbott, Abiomed, Affluent Medical, Alleviant Medical, Amgen, AM-Pharma, Applied Therapeutics, Arena, AstraZeneca, AtriCure Inc., Biosensors, Biotronik, Boston Scientific, Bristol-Myers Squibb, CardiaWave, CeloNova, Chiesi, Concept Medical, CSL Behring, Cytosorbents, Daiichi Sankyo, Duke, Element Science, Faraday, Humacyte, Idorsia, I-Laser, Janssen, Magenta, MedAlliance, Medscape, Mediasphere, Medtelligence, Medtronic, MJH Healthcare, Novartis, OrbusNeich, Penumbra, PhaseBio, Philips, Pi-Cardia, PLx Pharma, Protembis, RenalPro, RM Global, Shockwave, Transverse Medical, Inc., Vivasure, Zoll; personal fees from Affluent Medical, Cardiovascular Research Foundation (CRF), Daiichi Sankyo Brasil, E.R. Squibb & Sons, Esperion Science/Innovative Biopharma, Europa Group/Boston Scientific, Gaffney Events, Educational Trust, Ionis Pharmaceuticals, J-CalC, Novartis, NovoNordisk, Vectura, VoxMedia, IQVIA, McVeigh Global, Overcome, Primer Healthcare of New Jersey, Radcliffe, SL Solutions, TARSUS

Cardiology, WebMD; Equity <1% in Applied Therapeutics, Elixir Medical, Stel, ControlRad (spouse); no Fees from AMA (Scientific Advisory Board), SCAI (Women in Innovations Committee Member); Faculty CRF; and honoraria from JAMA Cardiology (Associate Editor), ACC (BOT Member, SC Member CTR Program). Dr. Dangas has received consulting fees and advisory board fees from AstraZeneca; has received consulting fees from Biosensors; and previously held stock in Medtronic. Dr. Cao reports consulting fees from Terumo.

All other authors have reported no relationships relevant to the contents of this paper to disclose.

Supplemental Materials

Supplemental Methods

Supplemental Figures S1-2

Supplemental Tables S1-S3

References

1. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, Claeys MJ, Dan GA, Dweck MR, Galbraith M, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. *Eur Heart J*. 2023;44:3720-3826. doi: 10.1093/eurheartj/ehad191
2. Lawton JS, Tamis-Holland JE, Bangalore S, Bates ER, Beckie TM, Bischoff JM, Bittl JA, Cohen MG, DiMaio JM, Don CW, et al. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;145:e18-e114. doi: 10.1161/CIR.0000000000001038
3. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361:1045-1057. doi: 10.1056/NEJMoa0904327
4. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357:2001-2015. doi: 10.1056/NEJMoa0706482
5. Dayoub EJ, Seigerman M, Tuteja S, Kobayashi T, Kolansky DM, Giri J, Groeneveld PW. Trends in Platelet Adenosine Diphosphate P2Y12 Receptor Inhibitor Use and Adherence Among Antiplatelet-Naive Patients After Percutaneous Coronary Intervention, 2008-2016. *JAMA Intern Med*. 2018;178:943-950. doi: 10.1001/jamainternmed.2018.0783
6. Ozaki AF, Jackevicius CA, Chong A, Sud M, Fang J, Austin PC, Ko DT. Hospital-Level Variation in Ticagrelor Use in Patients With Acute Coronary Syndrome. *J Am Heart Assoc*. 2022;11:e024835. doi: 10.1161/JAHA.121.024835
7. Rodwin BA, Lu D, Giaimo A, Annapureddy A, Daggubati R, Curtis J, Sciria CT, Wang TY, Desai NR. Patient and hospital characteristics associated with ticagrelor uptake in acute MI: An analysis of the Chest Pain-MI Registry. *Int J Cardiol*. 2020;304:14-20. doi: 10.1016/j.ijcard.2020.01.029
8. Baber U, Dangas G, Chandrasekhar J, Sartori S, Steg PG, Cohen DJ, Giustino G, Ariti C, Witzenbichler B, Henry TD, 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;9:1349-1357. doi: 10.1016/j.jcin.2016.04.009
9. Mehran R, Baber U, Steg PG, Ariti C, Weisz G, Witzenbichler B, Henry TD, Kini AS, Stuckey T, Cohen DJ, 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;382:1714-1722. doi: 10.1016/S0140-6736(13)61720-1
10. Valgimigli M, Costa F, Lokhnygina Y, Clare RM, Wallentin L, Moliterno DJ, Armstrong PW, White HD, Held C, Aylward PE, et al. Trade-off of myocardial infarction vs. bleeding types on mortality after acute coronary syndrome: lessons from the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) randomized trial. *Eur Heart J*. 2017;38:804-810. doi: 10.1093/eurheartj/ehw525
11. Piccolo R, Oliva A, Avvedimento M, Franzone A, Windecker S, Valgimigli M, Esposito G, Jüni P. Mortality after bleeding versus myocardial infarction in coronary artery disease: a systematic review and meta-analysis. *EuroIntervention*. 2021;17:550-560.
12. Kim BK, Hong SJ, Cho YH, Yun KH, Kim YH, Suh Y, Cho JY, Her AY, Cho S, Jeon DW, et al. Effect of Ticagrelor Monotherapy vs Ticagrelor With Aspirin on Major Bleeding and Cardiovascular Events in Patients With Acute Coronary Syndrome: The TICO Randomized Clinical Trial. *JAMA*. 2020;323:2407-2416. doi: 10.1001/jama.2020.7580

13. Watanabe H, Morimoto T, Natsuaki M, Yamamoto K, Obayashi Y, Ogita M, Suwa S, Isawa T, Domei T, Yamaji K, et al. Comparison of Clopidogrel Monotherapy After 1 to 2 Months of Dual Antiplatelet Therapy With 12 Months of Dual Antiplatelet Therapy in Patients With Acute Coronary Syndrome: The STOPDAPT-2 ACS Randomized Clinical Trial. *JAMA Cardiol*. 2022;7:407-417. doi: 10.1001/jamacardio.2021.5244
14. Baber U, Dangas G, Angiolillo DJ, Cohen DJ, Sharma SK, Nicolas J, Briguori C, Cha JY, Collier T, Dudek D, et al. Ticagrelor alone vs. ticagrelor plus aspirin following percutaneous coronary intervention in patients with non-ST-segment elevation acute coronary syndromes: TWILIGHT-ACS. *Eur Heart J*. 2020;41:3533-3545. doi: 10.1093/eurheartj/ehaa670
15. Vranckx P, Valgimigli M, Odutayo A, Serruys PW, Hamm C, Steg PG, Heg D, Mc Fadden EP, Onuma Y, Benit E, et al. Efficacy and Safety of Ticagrelor Monotherapy by Clinical Presentation: Pre-Specified Analysis of the GLOBAL LEADERS Trial. *J Am Heart Assoc*. 2021;10:e015560. doi: 10.1161/JAHA.119.015560
16. Giacoppo D, Matsuda Y, Fovino LN, D'Amico G, Gargiulo G, Byrne RA, Capodanno D, Valgimigli M, Mehran R, Tarantini G. Short dual antiplatelet therapy followed by P2Y12 inhibitor monotherapy vs. prolonged dual antiplatelet therapy after percutaneous coronary intervention with second-generation drug-eluting stents: a systematic review and meta-analysis of randomized clinical trials. *Eur Heart J*. 2021;42:308-319. doi: 10.1093/eurheartj/ehaa739
17. O'Donoghue ML, Murphy SA, Sabatine MS. 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. *Circulation*. 2020;142:538-545. doi: 10.1161/CIRCULATIONAHA.120.046251
18. Valgimigli M, Gragnano F, Branca M, Franzone A, Baber U, Jang Y, Kimura T, Hahn JY, Zhao Q, Windecker S, et al. P2Y12 inhibitor monotherapy or dual antiplatelet therapy after coronary revascularisation: individual patient level meta-analysis of randomised controlled trials. *BMJ*. 2021;373:n1332. doi: 10.1136/bmj.n1332
19. Urban P, Mehran R, Colleran R, Angiolillo DJ, Byrne RA, Capodanno D, Cuisset T, Cutlip D, Eerdmans P, Eikelboom J, et al. Defining High Bleeding Risk in Patients Undergoing Percutaneous Coronary Intervention. *Circulation*. 2019;140:240-261. doi: 10.1161/CIRCULATIONAHA.119.040167
20. Glidden DV, Vittinghoff E. Modelling clustered survival data from multicentre clinical trials. *Stat Med*. 2004;23:369-388. doi: 10.1002/sim.1599
21. Stefanini GG, Baber U, Windecker S, Morice MC, Sartori S, Leon MB, Stone GW, Serruys PW, Wijns W, Weisz G, et al. Safety and efficacy of drug-eluting stents in women: a patient-level pooled analysis of randomised trials. *Lancet*. 2013;382:1879-1888. doi: 10.1016/s0140-6736(13)61782-1
22. Franzone A, McFadden EP, Leonardi S, Piccolo R, Vranckx P, Serruys PW, Hamm C, Steg PG, Heg D, Branca M, et al. Ticagrelor alone or conventional dual antiplatelet therapy in patients with stable or acute coronary syndromes. *EuroIntervention*. 2020;16:627-633. doi: 10.4244/eij-d-20-00145
23. Mehran R, Baber U, Sharma SK, Cohen DJ, Angiolillo DJ, Briguori C, Cha JY, Collier T, Dangas G, Dudek D, et al. Ticagrelor with or without Aspirin in High-Risk Patients after PCI. *N Engl J Med*. 2019;381:2032-2042. doi: 10.1056/NEJMoa1908419
24. Armstrong PC, Leadbeater PD, Chan MV, Kirkby NS, Jakubowski JA, Mitchell JA, Warner TD. In the presence of strong P2Y12 receptor blockade, aspirin provides little additional inhibition of platelet aggregation. *J Thromb Haemost*. 2011;9:552-561. doi: 10.1111/j.1538-7836.2010.04160.x

25. Baber U, Zafar MU, Dangas G, Escolar G, Angiolillo DJ, Sharma SK, Kini AS, Sartori S, Joyce L, Vogel B, et al. Ticagrelor With or Without Aspirin After PCI: The TWILIGHT Platelet Substudy. *J Am Coll Cardiol*. 2020;75:578-586. doi: 10.1016/j.jacc.2019.11.056
26. Vranckx P, Valgimigli M, Juni P, Hamm C, Steg PG, Heg D, van Es GA, McFadden EP, Onuma Y, van Meijeren C, et al. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. *Lancet*. 2018;392:940-949. doi: 10.1016/S0140-6736(18)31858-0
27. Costa F, van Klaveren D, James S, Heg D, Raber L, Feres F, Pilgrim T, Hong MK, Kim HS, Colombo A, 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;389:1025-1034. doi: 10.1016/S0140-6736(17)30397-5
28. Mehran R, Cao D, Angiolillo DJ, Bangalore S, Bhatt DL, Ge J, Hermiller J, Makkar RR, Neumann FJ, Saito S, et al. 3- or 1-Month DAPT in Patients at High Bleeding Risk Undergoing Everolimus-Eluting Stent Implantation. *JACC Cardiovasc Interv*. 2021;14:1870-1883. doi: 10.1016/j.jcin.2021.07.016
29. Valgimigli M, Frigoli E, Heg D, Tijssen J, Juni P, Vranckx P, Ozaki Y, Morice MC, Chevalier B, Onuma Y, et al. Dual Antiplatelet Therapy after PCI in Patients at High Bleeding Risk. *N Engl J Med*. 2021;385:1643-1655. doi: 10.1056/NEJMoa2108749
30. Capodanno D, Mehran R, Krucoff MW, Baber U, Bhatt DL, Capranzano P, Collet JP, Cuisset T, De Luca G, De Luca L, et al. Defining Strategies of Modulation of Antiplatelet Therapy in Patients With Coronary Artery Disease: A Consensus Document from the Academic Research Consortium. *Circulation*. 2023;147:1933-1944. doi: 10.1161/CIRCULATIONAHA.123.064473
31. Tavenier AH, Mehran R, Chiarito M, Cao D, Pivato CA, Nicolas J, Beerkens F, Nardin M, Sartori S, Baber U, et al. Guided and unguided de-escalation from potent P2Y12 inhibitors among patients with acute coronary syndrome: a meta-analysis. *Eur Heart J Cardiovasc Pharmacother*. 2022;8:492-502. doi: 10.1093/ehjcvp/pvab068
32. Kim HS, Kang J, Hwang D, Han JK, Yang HM, Kang HJ, Koo BK, Rhew JY, Chun KJ, Lim YH, et al. Prasugrel-based de-escalation of dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (HOST-REDUCE-POLYTECH-ACS): an open-label, multicentre, non-inferiority randomised trial. *Lancet*. 2020;396:1079-1089. doi: 10.1016/S0140-6736(20)31791-8
33. Angiolillo DJ, Baber U, Sartori S, Briguori C, Dangas G, Cohen DJ, Mehta SR, Gibson CM, Chandiramani R, Huber K, et al. Ticagrelor With or Without Aspirin in High-Risk Patients With Diabetes Mellitus Undergoing Percutaneous Coronary Intervention. *J Am Coll Cardiol*. 2020;75:2403-2413. doi: 10.1016/j.jacc.2020.03.008
34. Dangas G, Baber U, Sharma S, Giustino G, Mehta S, Cohen DJ, Angiolillo DJ, Sartori S, Chandiramani R, Briguori C, et al. Ticagrelor With or Without Aspirin After Complex PCI. *J Am Coll Cardiol*. 2020;75:2414-2424. doi: 10.1016/j.jacc.2020.03.011
35. Dangas G, Baber U, Sharma S, Giustino G, Sartori S, Nicolas J, Goel R, Mehta S, Cohen D, Angiolillo DJ, et al. Safety and efficacy of ticagrelor monotherapy according to drug-eluting stent type: the TWILIGHT-STENT study. *EuroIntervention*. 2022;17:1330-1339. doi: 10.4244/EIJ-D-21-00721

Table 1. Baseline Clinical Characteristics.

	Overall N=7529	Ticagrelor Monotherapy N=3726 (49.5%)	Aspirin + Ticagrelor N=3803 (50.5%)	p-value
Study ID				
TICO	2915 (38.7%)	1453 (39.0%)	1462 (38.4%)	0.622
TWILIGHT	4614 (61.3%)	2273 (61.0%)	2341 (61.6%)	0.622
Patient Demographics				
Age, years	62.8±10.8	62.7±10.8	63.0±10.8	0.403
Age ≥ 65 Years	3329 (44.2%)	1629 (43.7%)	1700 (44.7%)	0.391
Female sex	1743 (23.2%)	882 (23.7%)	861 (22.6%)	0.289
Height, m	1.7±0.1	1.7±0.1	1.7±0.1	0.783
Weight, kg	77.1±17.8	77.2±17.7	77.1±17.9	0.790
Body mass index	27.1±5.1	27.1±5.0	27.1±5.2	0.987
Geographical region				0.806
Asia	4302 (57.1%)	2146 (57.6%)	2156 (56.7%)	
North America	1799 (23.9%)	882 (23.7%)	917 (24.1%)	
Western Europe	962 (12.8%)	465 (12.5%)	497 (13.1%)	
Eastern Europe	466 (6.2%)	233 (6.3%)	233 (6.1%)	
Medical History				
Diabetes	2398 (31.9%)	1196 (32.1%)	1202 (31.6%)	0.647
Insulin treated diabetes	532 (7.1%)	260 (7.0%)	272 (7.2%)	0.768
Current cigarette smoker	2243 (29.8%)	1061 (28.5%)	1182 (31.1%)	0.013
Hypertension	4571 (60.7%)	2252 (60.4%)	2319 (61.0%)	0.623
Hypercholesterolemia	4146 (55.1%)	2053 (55.1%)	2093 (55.0%)	0.956
Liver Disease	18 (0.2%)	11 (0.3%)	7 (0.2%)	0.323
Peripheral artery disease	262 (5.7%)	130 (5.7%)	132 (5.6%)	0.906
Prior MI	1274 (16.9%)	638 (17.1%)	636 (16.7%)	0.644
Prior PCI	1837 (24.4%)	910 (24.4%)	927 (24.4%)	0.962
Prior CABG	418 (5.6%)	209 (5.6%)	209 (5.5%)	0.827
Prior Stroke	119 (1.6%)	57 (1.5%)	62 (1.6%)	0.727
Prior bleeding	42 (0.6%)	23 (0.6%)	19 (0.5%)	0.493
History of CKD	1228 (16.7%)	585 (16.1%)	643 (17.3%)	0.158
History of chronic lung disease	221 (4.9%)	108 (4.8%)	113 (4.9%)	0.936
Clinical Presentation				
Unstable angina	3390 (45.0%)	1674 (44.9%)	1716 (45.1%)	0.865
Non-STEMI	3091 (41.1%)	1532 (41.1%)	1559 (41.0%)	0.914
STEMI	1048 (13.9%)	520 (14.0%)	528 (13.9%)	0.928
Aspirin on admission	5665 (75.2%)	2813 (75.5%)	2852 (75.0%)	0.613
PRECISE-DAPT*	15.9±9.0	15.8±8.8	16.1±9.2	0.152
PRECISE-DAPT ≥ 25	1042 (15.3%)	503 (14.9%)	539 (15.6%)	0.424
Creatine Clearance, ml/min	85.7 (70.9-101.5)	85.8 (71.2-101.8)	85.7 (70.4-101.1)	0.178
Hemoglobin, g/dl	14.1±1.7	14.1±1.7	14.1±1.7	0.982
LVEF %	54.4±11.3	54.4±11.0	54.3±11.6	0.773

Values are n (%), mean±SD, or median (IQR).
*The PRECISE-DAPT (Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy) score includes 5 items: age, creatinine clearance, white blood cell count, hemoglobin, and history of bleeding.
TICO: Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus-eluting Stent for Acute Coronary Syndrome; TWILIGHT: Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention; MI: myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; CKD: chronic kidney disease; NSTEMI: non-ST segment elevation myocardial infarction; STEMI: ST segment elevation myocardial infarction; LVEF: left ventricular ejection fraction.

Table 2. Baseline Procedural Characteristics.

	Overall N=7529	Ticagrelor Monotherapy N=3726 (49.5%)	Aspirin + Ticagrelor N=3803 (50.5%)	p-value
Radial access	5166 (68.6%)	2548 (68.4%)	2618 (68.8%)	0.670
Femoral access	2351 (31.2%)	1173 (31.5%)	1178 (31.0%)	0.636
Brachial access	1 (0.0%)	0 (0.0%)	1 (0.0%)	1.000
Unfractionated heparin	5715 (75.9%)	2832 (76.0%)	2883 (75.8%)	0.841
LMWH	1031 (13.7%)	508 (13.6%)	523 (13.8%)	0.881
GP IIb/IIIa inhibitors	611 (8.1%)	297 (8.0%)	314 (8.3%)	0.650
Bivalirudin	627 (8.3%)	307 (8.2%)	320 (8.4%)	0.783
Number of vessels treated at index PCI				0.863
1 vessel	5793 (76.9%)	2876 (77.2%)	2917 (76.7%)	
2 vessels	1537 (20.4%)	754 (20.2%)	783 (20.6%)	
3 vessels	193 (2.6%)	94 (2.5%)	99 (2.6%)	
Number of lesions treated at index PCI				0.567
1 lesion	5085 (67.5%)	2513 (67.4%)	2572 (67.6%)	
2 lesions	1899 (25.2%)	934 (25.1%)	965 (25.4%)	
≥3 lesions	520 (6.9%)	269 (7.2%)	251 (6.6%)	
Left anterior descending artery	4351 (57.8%)	2146 (57.6%)	2205 (58.0)%	0.735
Left circumflex artery	2180 (29.0%)	1077 (28.9%)	1103 (29.0%)	0.925
Right coronary artery	2619 (34.8%)	1293 (34.7%)	1326 (34.9%)	0.880
Left main	324 (4.3%)	162 (4.3%)	162 (4.3%)	0.851
Venous or arterial graft	87 (1.2%)	37 (1.0%)	50 (1.3%)	0.192
Bifurcation	1088 (14.5%)	526 (14.1%)	562 (14.8%)	0.415
Bifurcation lesion treated with ≥2 stents	226 (3.0%)	112 (3.0%)	114 (3.0%)	0.983
Thrombus-containing lesion	1773 (23.5%)	880 (23.6%)	893 (23.5%)	0.889
Implanted stents, n	1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.659
Overlapping stents	300 (10.3%)	152 (10.5%)	148 (10.1%)	0.764
Total stent length, mm	32.0 (22.0-48.0)	32.0 (22.0-50.0)	32.0 (22.0-48.0)	0.947
Minimum diameter of all implanted stents, mm	2.9±0.5	2.9±0.5	3.0±0.5	0.504
Maximum diameter of all implanted stents, mm	3.2±0.5	3.2±0.5	3.2±0.5	0.371
ACE-inhibitors or ARBs at randomization	5244 (69.7%)	2613 (70.1%)	2631 (69.2%)	0.372
B-blockers at randomization	5670 (75.3%)	2803 (75.2%)	2867 (75.4%)	0.872
Statins at randomization	7261 (96.4%)	3595 (96.5%)	3666 (96.4%)	0.839
PPI at randomization	2360 (51.1%)	1166 (51.3%)	1194 (51.0%)	0.842

Values are n (%), mean±SD, or median (IQR).
GP: glycoprotein; LMWH: low-molecular-weight heparin; PCI: percutaneous coronary intervention; TIMI: Thrombolysis In Myocardial Infarction; DES: drug-eluting stent; ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; PPI proton pump inhibitor.

10.1161/CIRCULATIONAHA.123.067283

Table 3. Clinical Outcomes of Individual Patient Data Meta-analysis.

	Ticagrelor Monotherapy N=3726 (49.5%)	Aspirin + Ticagrelor N=3803 (50.5%)	HR (95% CI)	p-value
BARC bleeding:				
3 or 5	29 (0.8%)	80 (2.1%)	0.37 (0.24 - 0.56)	<0.001
TIMI bleeding:				
Major	13 (0.4%)	40 (1.1%)	0.33 (0.18 - 0.62)	<0.001
Minor	65 (1.8%)	145 (3.9%)	0.45 (0.34 - 0.61)	<0.001
Major or minor	78 (3.5%)	183 (7.8%)	0.43 (0.33 - 0.57)	<0.001
Death, MI, or stroke	89 (2.4%)	100 (2.7%)	0.91 (0.68 - 1.21)	0.515
Cardiovascular death, MI, or ischemic stroke	80 (2.2%)	92 (2.4%)	0.89 (0.66 - 1.20)	0.439
Death or MI	78 (2.1%)	89 (2.4%)	0.90 (0.66 - 1.21)	0.476
Death:				
All-cause	24 (0.7%)	34 (0.9%)	0.72 (0.43 - 1.22)	0.219
Cardiovascular	17 (0.5%)	25 (0.7%)	0.69 (0.37 - 1.29)	0.246
Non-cardiovascular	7 (0.2%)	9 (0.2%)	0.79 (0.30 - 2.13)	0.647
MI	60 (1.6%)	64 (1.7%)	0.96 (0.67 - 1.36)	0.809
Stroke:				
Any	12 (0.3%)	13 (0.3%)	0.94 (0.43 - 2.07)	0.883
Ischemic	9 (0.2%)	11 (0.3%)	0.84 (0.35 - 2.02)	0.689
Hemorrhagic	3 (0.1%)	1 (0.0%)	3.06 (0.32 - 29.4)	0.332
Stent thrombosis:				
Definite	5 (0.1%)	7 (0.2%)	0.73 (0.23 - 2.30)	0.589
Probable	2 (0.1%)	1 (0.0%)	2.04 (0.19 - 22.5)	0.560
NACE	116 (3.1%)	166 (4.4%)	0.71 (0.56 - 0.90)	0.004

The percentages mentioned above represent K-M rates at 9-month follow-up; HR: hazard ratio; BARC: Bleeding Academy Research Consortium; TIMI=Thrombolysis in Myocardial Infarction; MI: myocardial infarction; NACE=net adverse clinical events (defined as composite of all-cause death, myocardial infarction, stroke, and BARC type 3 or type 5 bleeding).

10.1161/CIRCULATIONAHA.123.067283

Figure Legends

Figure 1. Flow Chart of Patient Inclusion

*Not mutually exclusive. ACS: acute coronary syndrome; MI: myocardial infarction; BARC: Bleeding Academic Research Consortium; DAPT: dual antiplatelet therapy.

Figure 2. Primary and Secondary Clinical Outcomes

Kaplan-Meier estimates and HR for (A) the primary endpoint of Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding; (B) key secondary ischemic endpoint of all-cause death, myocardial infarction, or stroke; (C) Thrombolysis In Myocardial Infarction (TIMI) major or minor bleeding; (D) net adverse clinical events (NACE), defined as composite of all-cause death, myocardial infarction, stroke, or BARC type 3 or 5 bleeding. Kaplan-Meier curves and hazard ratios are from one-stage IPD meta-analysis, according to randomized treatment.

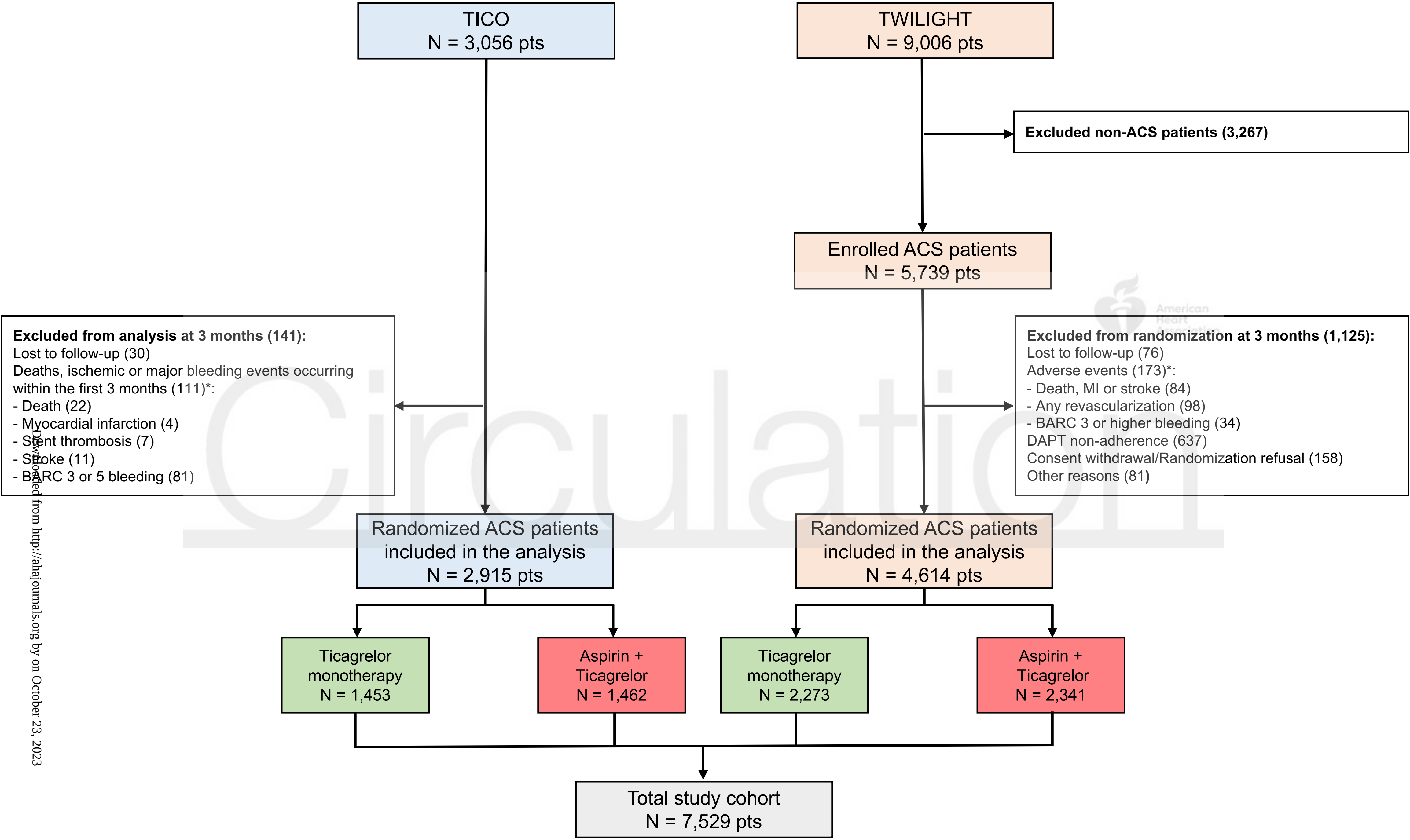
Figure 3. Subgroup Analyses for the Primary Endpoint of Bleeding Academic Research Consortium (BARC) 3 or 5 bleeding

High bleeding risk (HBR) was defined on basis of modified Academic Research Consortium for High Bleeding Risk (ARC-HBR) criteria; major criteria: severe or end-stage chronic kidney disease (CKD) [eGFR < 30 ml/min,] hemoglobin <11 g/dL, previous major bleeding, liver cirrhosis with portal hypertension; HBR minor criteria: age ≥ 75 years, moderate CKD [eGFR 30-60 ml/min], hemoglobin 11-12.9 g/dL for men and 11-11.9 g/dL for women. Complex percutaneous coronary intervention (PCI) was defined as having at least one of the following criteria: 3 vessels treated, ≥ 3 lesions treated, ≥ 3 implanted stents, bifurcation with

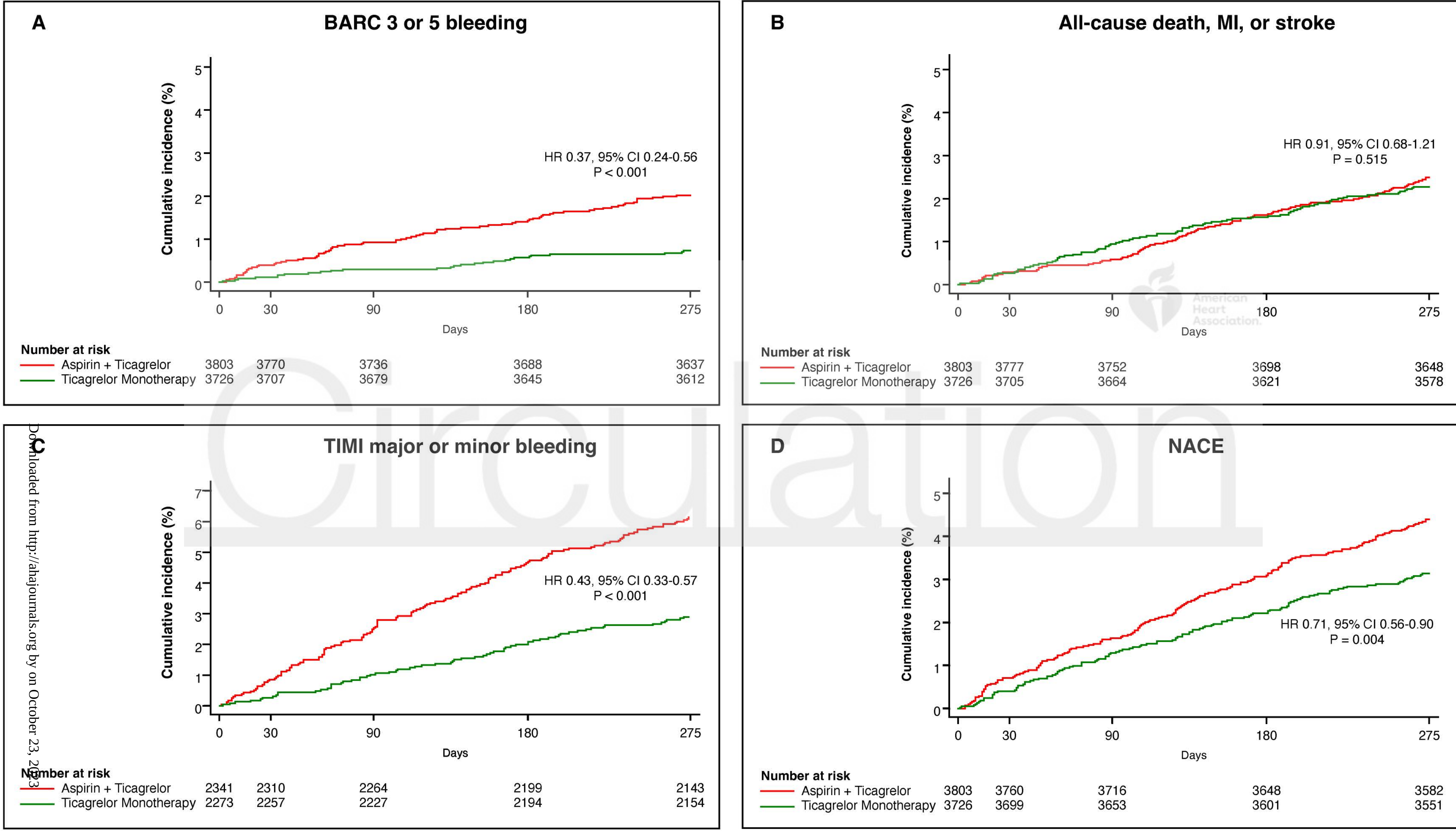
2 stents implanted, total stent length > 60mm. NSTEMI: non-ST segment elevation myocardial infarction; STEMI: ST segment elevation myocardial infarction.

Figure 4. Subgroup Analysis for the Key Secondary Ischemic Endpoint of Death, Myocardial Infarction or Stroke

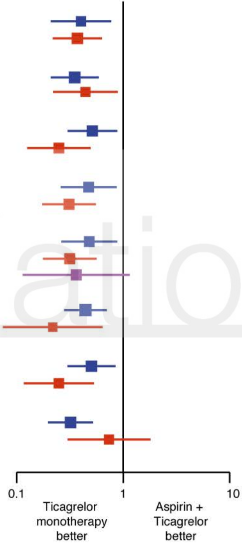
High bleeding risk (HBR) and complex percutaneous coronary intervention (PCI) are defined as described for figure 3.



TICO
N = 3,056 pts
TWILIGHT
N = 9,006 pts
Excluded non-ACS patients (3,267)
Enrolled ACS patients
N = 5,739 pts
Excluded from analysis at 3 months (141):
Lost to follow-up (30)
Deaths, ischemic or major bleeding events occurring within the first 3 months (111)*:
- Death (22)
- Myocardial infarction (4)
- Stent thrombosis (7)
- Stroke (11)
- BARC 3 or 5 bleeding (81)
Excluded from randomization at 3 months (1,125):
Lost to follow-up (76)
Adverse events (173)*:
- Death, MI or stroke (84)
- Any revascularization (98)
- BARC 3 or higher bleeding (34)
DAPT non-adherence (637)
Consent withdrawal/Randomization refusal (158)
Other reasons (81)
Randomized ACS patients included in the analysis
N = 2,915 pts
Randomized ACS patients included in the analysis
N = 4,614 pts
Ticagrelor monotherapy
N = 1,453
Aspirin + Ticagrelor
N = 1,462
Ticagrelor monotherapy
N = 2,273
Aspirin + Ticagrelor
N = 2,341
Total study cohort
N = 7,529 pts


A
BARC 3 or 5 bleeding
Cumulative incidence (%)
HR 0.37, 95% CI 0.24-0.56
P < 0.001
Days
Number at risk
Aspirin + Ticagrelor 3803 3770 3736 3688 3637
Ticagrelor Monotherapy 3726 3707 3679 3645 3612
B
All-cause death, MI, or stroke
Cumulative incidence (%)
HR 0.91, 95% CI 0.68-1.21
P = 0.515
Days
Number at risk
Aspirin + Ticagrelor 3803 3777 3752 3698 3648
Ticagrelor Monotherapy 3726 3705 3664 3621 3578
C
TIMI major or minor bleeding
Cumulative incidence (%)
HR 0.43, 95% CI 0.33-0.57
P < 0.001
Days
Number at risk
Aspirin + Ticagrelor 2341 2310 2264 2199 2143
Ticagrelor Monotherapy 2273 2257 2227 2194 2154
D
NACE
Cumulative incidence (%)
HR 0.71, 95% CI 0.56-0.90
P = 0.004
Days
Number at risk
Aspirin + Ticagrelor 3803 3760 3716 3648 3582
Ticagrelor Monotherapy 3726 3699 3653 3601 3551

Subgroup	Ticagrelor monotherapy No. of events (%)	Aspirin + Ticagrelor No. of events (%)	HR (95% CI)	p-value	Interction p-value
Age					
<65 year	12 (0.6%)	31 (1.5%)	0.39 (0.20 - 0.75)	0.005	0.869
≥65 years	17 (1.1%)	49 (2.9%)	0.36 (0.21 - 0.62)	<0.001	
Sex					
Male	18 (0.6%)	55 (1.9%)	0.34 (0.20 - 0.57)	<0.001	0.604
Female	11 (1.3%)	25 (2.9%)	0.43 (0.21 - 0.87)	0.018	
Diabetes					
No	19 (0.8%)	39 (1.5%)	0.50 (0.29 - 0.86)	0.013	0.108
Yes	10 (0.8%)	41 (3.5%)	0.24 (0.12 - 0.48)	<0.001	
Clinical Presentation					
Biomarker negative ACS	15 (0.9%)	33 (1.9%)	0.46 (0.25 - 0.85)	0.013	0.327
Biomarker positive ACS	14 (0.7%)	47 (2.3%)	0.30 (0.17 - 0.55)	<0.001	
Clinical Presentation					
Unstable angina	15 (0.9%)	33 (1.9%)	0.46 (0.25 - 0.85)	0.013	0.572
NSTEMI	10 (0.7%)	36 (2.3%)	0.28 (0.14 - 0.57)	<0.001	
STEMI	4 (0.8%)	11 (2.1%)	0.37 (0.12 - 1.16)	0.088	
CKD (eGFR < 60 ml/min)					
No	25 (0.8%)	58 (1.8%)	0.43 (0.27 - 0.69)	<0.001	0.229
Yes	4 (1.0%)	21 (4.6%)	0.21 (0.07 - 0.62)	0.004	
HBR					
No	21 (0.7%)	43 (1.5%)	0.49 (0.29 - 0.83)	0.007	0.120
Yes	8 (1.1%)	36 (4.6%)	0.24 (0.11 - 0.52)	<0.001	
Complex PCI					
No	21 (0.7%)	69 (2.3%)	0.31 (0.19 - 0.51)	<0.001	0.113
Yes	8 (1.0%)	11 (1.4%)	0.72 (0.29 - 1.78)	0.474	



Subgroup	Ticagrelor monotherapy No. of events (%)	Aspirin + Ticagrelor No. of events (%)	HR (95% CI)	p-value	Interction p-value
Age					
<65 year	40 (1.9%)	45 (2.2%)	0.89 (0.58 - 1.36)	0.591	0.867
≥65 years	49 (3.0%)	55 (3.3%)	0.93 (0.64 - 1.37)	0.730	
Sex					
Male	69 (2.4%)	72 (2.5%)	0.99 (0.71 - 1.38)	0.968	0.292
Female	20 (2.3%)	28 (3.3%)	0.70 (0.39 - 1.24)	0.216	
Diabetes					
No	50 (2.0%)	50 (1.9%)	1.03 (0.70 - 1.52)	0.882	0.348
Yes	39 (3.3%)	50 (4.2%)	0.78 (0.51 - 1.19)	0.252	
Clinical Presentation					
Biomarker negative ACS	44 (2.6%)	43 (2.5%)	1.05 (0.69 - 1.59)	0.833	0.373
Biomarker positive ACS	45 (2.2%)	57 (2.8%)	0.81 (0.55 - 1.19)	0.279	
Clinical Presentation					
Unstable angina	44 (2.6%)	43 (2.5%)	1.05 (0.69 - 1.59)	0.833	0.623
NSTEMI	42 (2.8%)	52 (3.4%)	0.83 (0.55 - 1.24)	0.356	
STEMI	3 (0.6%)	5 (1.0%)	0.61 (0.15 - 2.56)	0.501	
CKD (eGFR < 60 ml/min)					
No	67 (2.1%)	73 (2.3%)	0.93 (0.66 - 1.29)	0.651	0.948
Yes	21 (5.2%)	25 (5.5%)	0.95 (0.53 - 1.69)	0.854	
HBR					
No	60 (2.1%)	62 (2.1%)	0.98 (0.69 - 1.39)	0.901	0.754
Yes	28 (3.8%)	34 (4.3%)	0.89 (0.54 - 1.46)	0.636	
Complex PCI					
No	64 (2.2%)	78 (2.6%)	0.84 (0.61 - 1.18)	0.317	0.392
Yes	25 (3.2%)	22 (2.8%)	1.13 (0.64 - 2.00)	0.681