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

Usman Baber, Yangsoo Jang, Angelo Oliva, Davide Cao, Birgit Vogel, George Dangas, Samantha Sartori, Alessandro Spirito, Kenneth F. Smith, Mattia Branca, Timothy Collier, Stuart Pocock, Marco Valgimigli, Byeong-Keuk Kim, Myeong-Ki Hong and Roxana Mehran

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. The study is registered with PROSPERO (CRD42023449646).

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 and stroke were comparable between groups (2.4% vs. 2.7%; HR 0.91 95% CI 0.68-1.2; P = 0.52). 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.

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.[8-10]

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.[11,12] 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.[13,14] Pooled analyses have been limited by lack of patient-level data[15,16] and inclusion of trials that evaluated different $P2Y_{12}$ inhibitors.[17] 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 acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI) with drug-eluting coronary stents 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. 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.

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 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 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.[18] The prespecified key secondary ischemic endpoint was the composite of all-cause death, myocardial infarction (MI) and 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 and ischemic stroke, and the net adverse clinical events (NACE), defined as composite of all cause death, myocardial infarction, stroke, and BARC 3 or 5 bleeding. The definitions

used for endpoints were largely consistent across included trials and are extensively reported in **Supplementary Table 1**.

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 commences (e.g., 3-month 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) and percentages for continuous and categorical variables, respectively. Hazard ratios (HR) and 95% confidence intervals (CI) were generated using Cox regression with trial included as a stratification variable. 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.

Results

Baseline and procedural characteristics

A total of 7,529 patients, from 2 randomized trials were included in the present IPD-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 acute coronary syndrome qualifying event at the presentation (45.0%), followed by NSTEMI (41.1%) and STEMI (13.9%). Patients underwent PCI more frequently from radial access (68.6%); one-vessel (76.9%) and one-lesion (67.5%) were more commonly treated during index PCI with a median of 1.0 DES (total stent length 32.0 mm, IQR 22.0-48.0; minimum diameter 2.9±0.5 mm; maximum diameter 3.2±0.5 mm), Baseline and procedural characteristics, stratified according to individual trial are reported in **Supplemental Table 2 and 3.**

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 0.68-1.2; P = 0.515) (**Figure 2B**).

Secondary outcomes

The incidence of MI (HR 0.96, 95% CI 0.67-1.36, P = 0.809), 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 difference was 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; **Figure 2C**) was significantly lower with ticagrelor monotherapy. Ticagrelor monotherapy significantly reduced also 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 effect for the primary safety endpoint and the key secondary ischemic endpoint was 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 (**Supplemental Figure 1**).

Discussion

We conducted a patient-level pooled analysis involving over 7500 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. Importantly, our findings were unchanged among high-risk biomarker positive ACS patients. In aggregate, our results 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.[11,19] 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.[20,21]

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.[22] However, among ACS patients a significant 27% reduction in major bleeding was observed.[14] 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.[15-17] However, these reports included trials characterized by heterogeneity with respect to background $P2Y_{12}$ inhibitor, timing of DAPT discontinuation, clinical presentation and treatment effect. 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.[12] Moreover, 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).[18] Moreover, only 15% of our patients were characterized as HBR using a validated risk model.[23] 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.[24,25] 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.[26] 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.[27] In regards to the latter, similar benefits were shown by reducing the dose of $P2Y_{12}$ inhibitor while maintaining aspirin.[28] 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.[29,30] 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.[31] 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.

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. 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. 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
12. 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
13. 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
14. 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
15. 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

16. 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
17. 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
18. 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
19. 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
20. 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
21. 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
22. 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

23. 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
24. 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
25. 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
26. 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
27. 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

28. 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

29. 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

30. 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

31. 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

Figure legend

Figure 1. Flow chart of patients inclusion *Not mutually exclusive.

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, and 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, and BARC 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.

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 2.

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

	Overall N=7529	Ticagrelor monotherapy N=3726 (49.5%)	Aspirin + Ticagrelor N=3803 (50.5%)	p-value
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	0 (0.0%)	0 (0.0%)	0 (0.0)%	N/A
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

Commented [AO1]: Missing data

	Overall N=7529	Ticagrelor monotherapy N=3726 (49.5%)	Aspirin + Ticagrelor N=3803 (50.5%)	p-value
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: percutenous coronary intervention; TIMI: Thrombolysis In Myocardial Infarction; DES: drug-eluting stent; ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; PPI proton pump inhibitor.

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).

Figure 1. Flow chart of patients inclusion

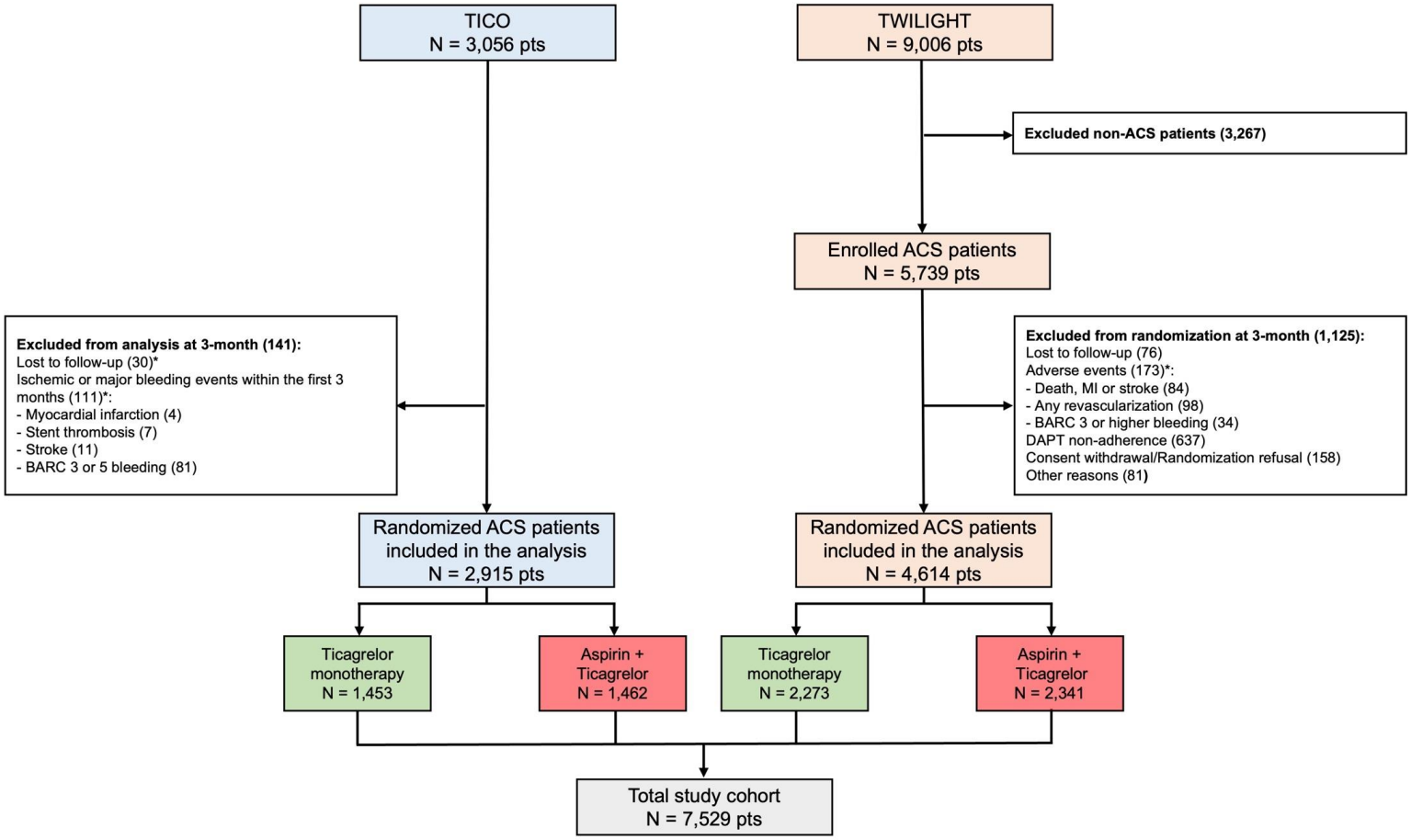

Figure 2. Primary and secondary clinical outcomes

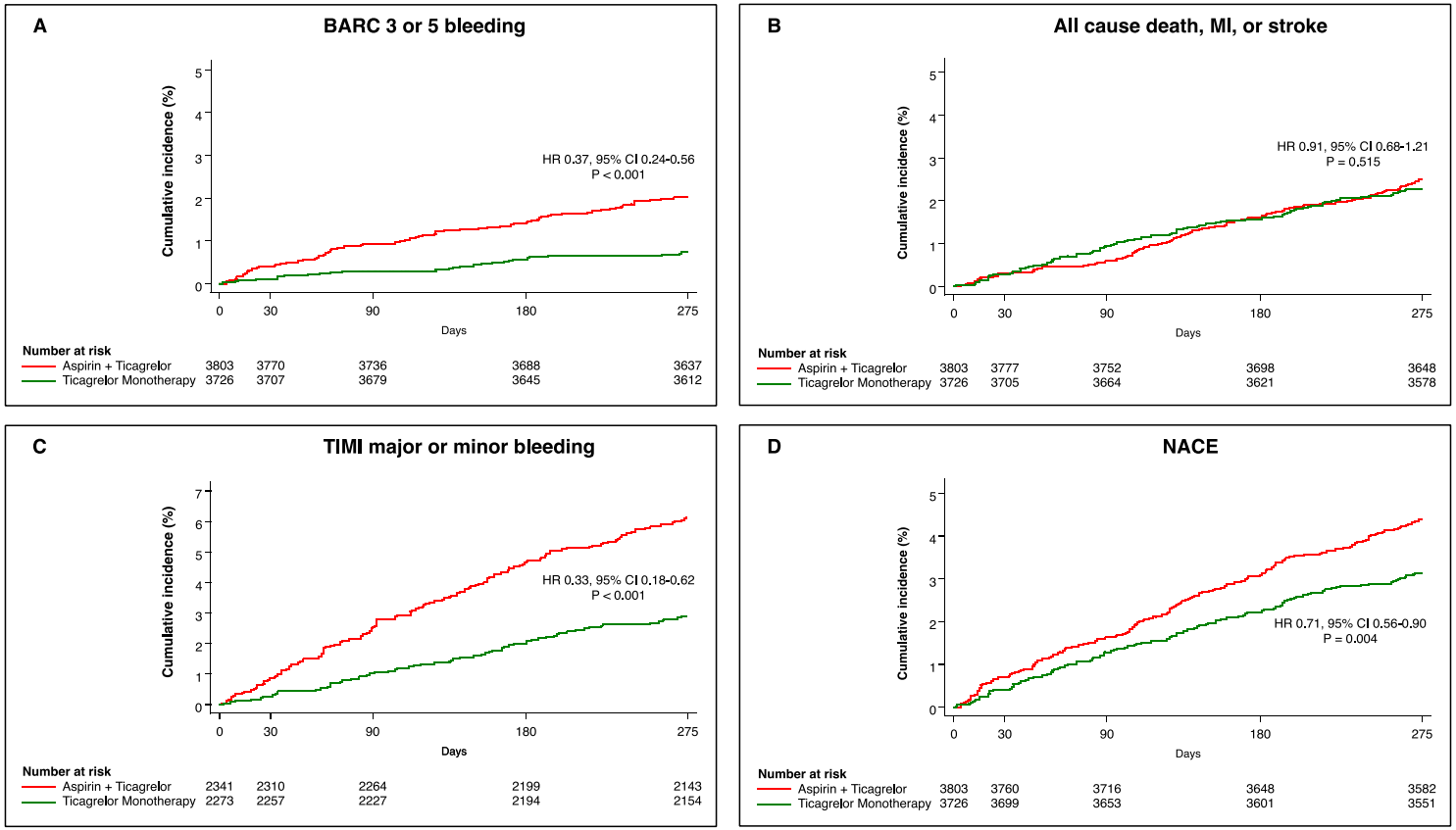

Figure 3. Subgroup analyses for the primary endpoint of Bleeding Academic Research Consortium (BARC) 3 or 5 bleeding

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					
Unstable angina	15 (0.9%)	33 (1.9%)	0.46 (0.25 - 0.85)	0.013	0.327
STEMI / NSTEMI	14 (0.7%)	47 (2.3%)	0.30 (0.17 - 0.55)	<0.001	
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	

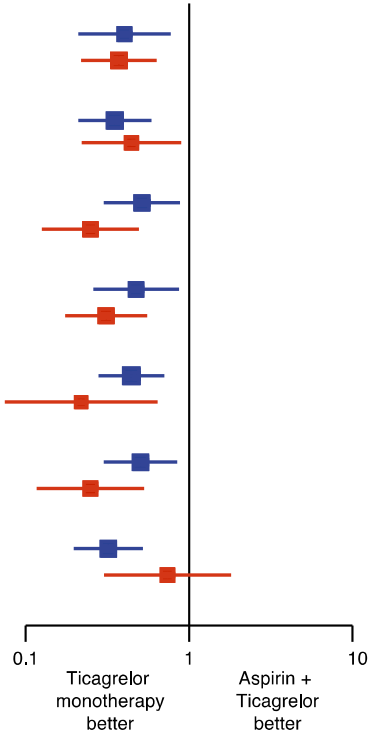

Figure 4. Subgroup analysis for the key secondary ischemic endpoint of death, myocardial infarction or stroke

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%)	0.50 (0.29 - 0.86)	0.882	0.348
Yes	39 (3.3%)	50 (4.2%)	0.78 (0.51 - 1.19)	0.252	
Clinical Presentation					
Unstable angina	44 (2.6%)	43 (2.5%)	1.05 (0.69 - 1.59)	0.833	0.373
STEMI / NSTEMI	45 (2.2%)	57 (2.8%)	0.81 (0.55 - 1.19)	0.279	
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