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*

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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

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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

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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

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,

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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.

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Supplemental Materials

Supplemental Methods

Supplemental Figures S1-2

Supplemental Tables S1-S3

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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.

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 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
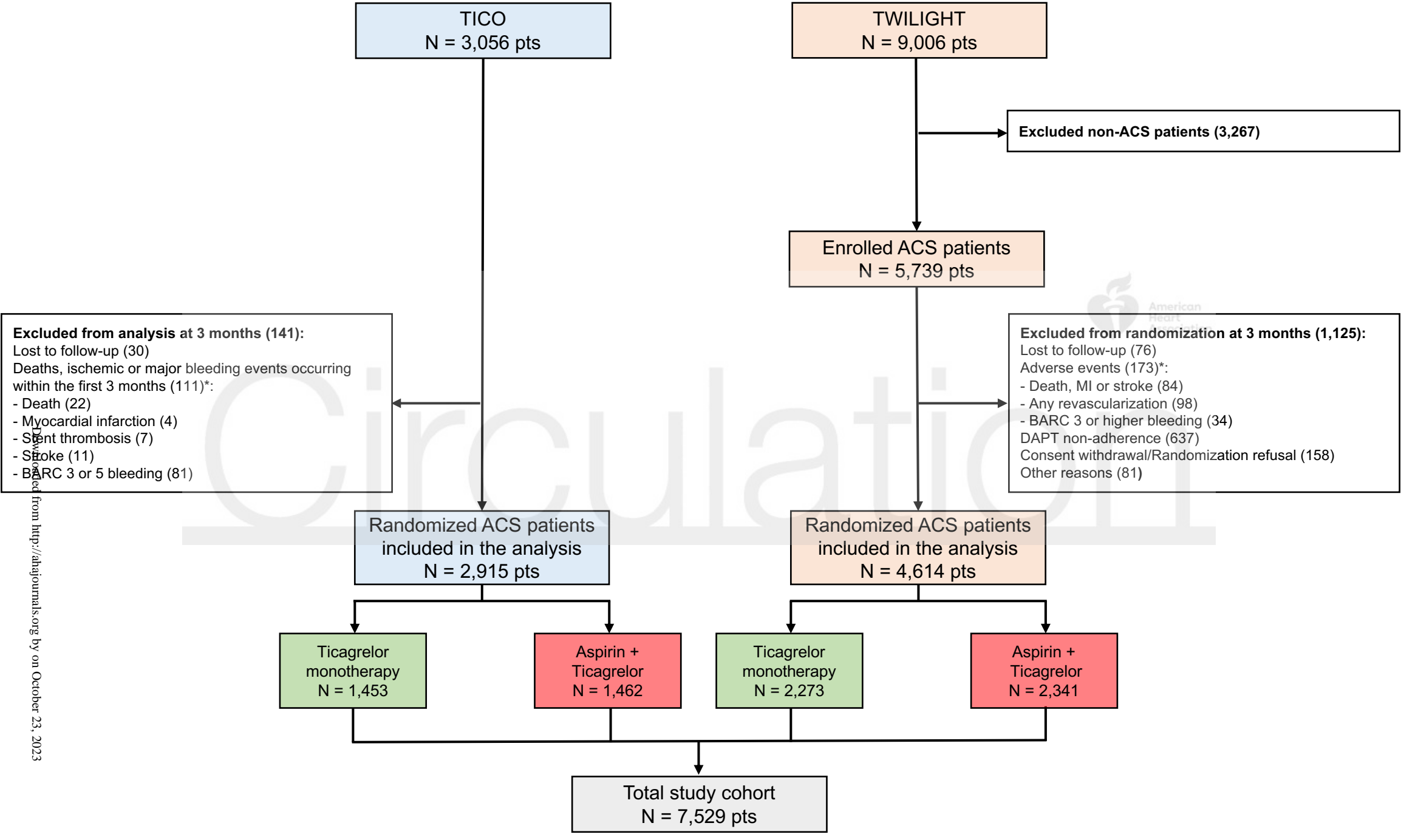
Excluded from analysis at 3 months (141):
Lost to follow-up (30)
Deaths, ischemic or major bleeding events occurring
within the first 3 months (111)*:
- Death (22)
- Myocardial infarction (4)
- Stent thrombosis (7)
- Stroke (11)
- BARC 3 or 5 bleeding (81)

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
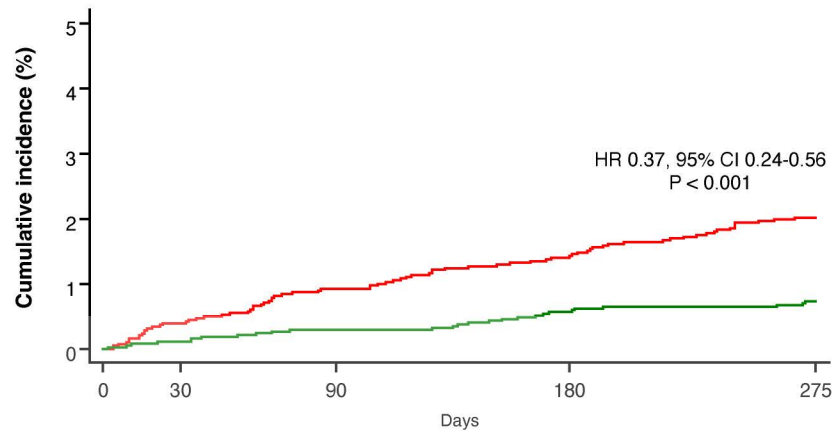
Number at risk
Aspirin + Ticagrelor   3803   3770   3736   3688   3637
Ticagrelor Monotherapy 3726   3707   3679   3645   3612

B All-cause death, MI, or stroke

Cumulative incidence (%)

HR 0.91, 95% CI 0.68-1.21
P = 0.515

Days
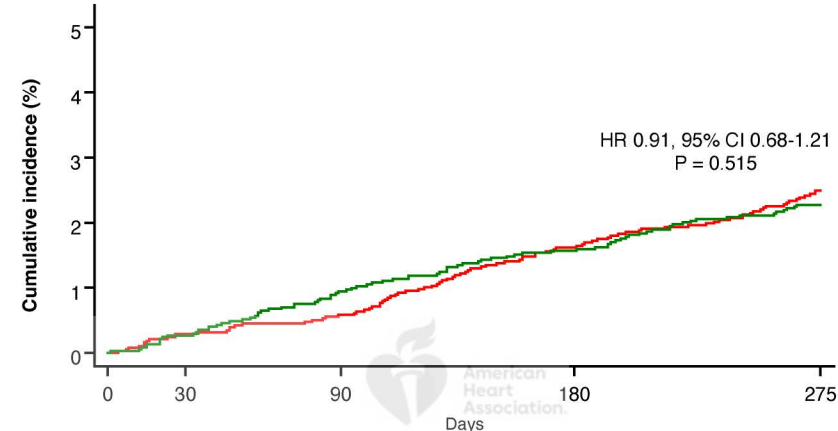
Number at risk
Aspirin + Ticagrelor   3803   3777   3752   3698   3648
Ticagrelor Monotherapy 3726   3705   3664   3621   3578

C TIMI major or minor bleeding

Cumulative incidence (%)

HR 0.43, 95% CI 0.33-0.57
P < 0.001

Days
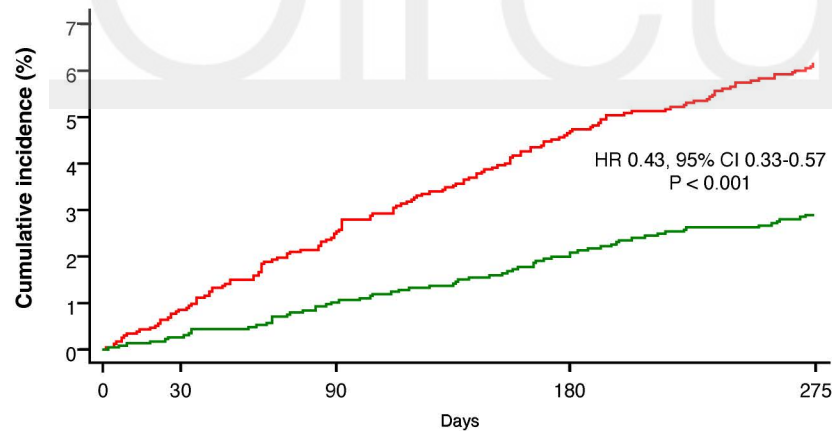
Number at risk
Aspirin + Ticagrelor   2341   2310   2264   2199   2143
Ticagrelor Monotherapy 2273   2257   2227   2194   2154

D NACE

Cumulative incidence (%)

HR 0.71, 95% CI 0.56-0.90
P = 0.004

Days
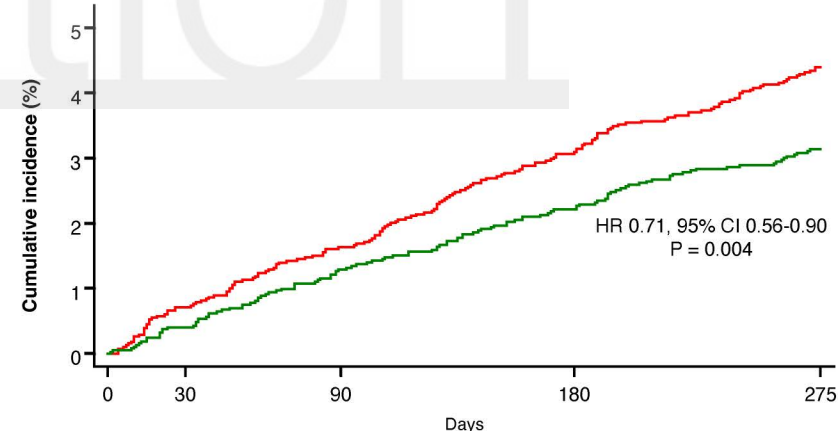
Number at risk
Aspirin + Ticagrelor   3803   3760   3716   3648   3582
Ticagrelor Monotherapy 3726   3699   3653   3601   3551

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

0.1   1   10

Ticagrelor monotherapy better   Aspirin + Ticagrelor better

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	

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