Clinically Driven Revascularization in High-Risk Patients Treated With Ticagrelor Monotherapy After PCI: Insights from the Randomized TWILIGHT Trial.

Brief title: Ticagrelor monotherapy and clinically-driven revascularization

Corresponding author:
Roxana Mehran, MD
Professor of Medicine
Icahn School of Medicine at Mount Sinai
1 Gustav L. Levy Place, Box 1030,
New York, NY 10029
Phone: +1 212 659 9649
Fax: +1 646 537 8547
roxana.mehran@mountsinai.org

Author name	Affiliation	COI
Dominick J. Angiolillo, MD, PHD	Division of Cardiology, University of Florida College of Medicine, Jacksonville, Florida, USA	Dr. Angiolillo declares that he has received consulting fees or honoraria from Abbott, Amgen, AstraZeneca, Bayer, Biosensors, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Daiichi-Sankyo, Eli Lilly, Haemonetics, Janssen, Merck, Novartis, PhaseBio, PLx Pharma, Pfizer, and Sanofi; D.J.A. also declares that his institution has received research grants from Amgen, AstraZeneca, Bayer, Biosensors, CeloNova, CSL Behring, Daiichi-Sankyo, Eisai, Eli Lilly, Gilead, Idorsia, Janssen, Matsutani Chemical Industry Co., Merck, Novartis, and the Scott R. MacKenzie Foundation.
Usman Baber, MD, MS	Department of Cardiology, The University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA	Dr Baber has received honoraria from AstraZeneca and Boston Scientific.
Carlo Briguori, MD, PhD	Mediterranea Cardiocentro, Naples, Italy	None
David J. Cohen, MD, MSc	Cardiovascular Research Foundation, New York, New York, USA St. Francis Hospital, Roslyn, Roslyn, New York, USA	Dr Cohen has received grant support, paid to his institution, and consulting fees from AstraZeneca, Medtronic, and Abbott Vascular; and has received grant support, paid to his institution, from Boston Scientific
Timothy Collier, MSC	Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, United Kingdom	None
George Dangas, MD	The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, New York, USA	Dr Dangas has received consulting fees and advisory board fees from AstraZeneca; has received consulting fees from Biosensors; and previously held stock in Medtronic
Dariusz Dudek, MD, PHD	Jagiellonian University Medical College, Krakow, Poland	None
Javier Escaned, MD, PHD	Hospital Clínico San Carlos IDISCC, Complutense University of Madrid, Madrid, Spain	Dr Escaned has received consulting and lecture fees from Abbott, Philips, Boston Scientific, and Medtronic; and has received lecture fees from Abiomed, Terumo, and Biosensors.
C. Michael Gibson, MD, MSc	Division of Cardiovascular Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA	Dr. Gibson has received grant support and consulting fees from Angel Medical, Bayer, CSL Behring, Janssen Pharmaceuticals, Johnson & Johnson, and Portola Pharmaceuticals; has received consulting fees from The Medicines Company, Eli Lilly, Gilead

		Sciences, Novo Nordisk, WebMD, UpToDate Cardiovascular Medicine, Amarin Pharma, Amgen, Boehringer Ingelheim, Chiesi, Merck, PharmaMar, Sanofi, Somahlution, Verreseon, Boston Scientific, Impact Bio, MedImmume, Medtelligence, MicroPort, the PERT Consortium, and GE Healthcare; holds equity in Inference; serves as chief executive officer of the Baim Institute; and has received grant support, paid to the Baim Institute, from Bristol Myers Squibb and Astra Zeneca
Ya-Ling Han, MD, PhD	General Hospital of Northern Theater Command, No. 83 Wenhua Road, Shenyang 110016, China	None
Kurt Huber, MD	Third Department Medicine, Cardiology and Intensive Care Medicine, Wilhelminen Hospital, and Sigmund Freud University, Medical Faculty, Vienna, Austria	Dr Huber has received lecture fees from AstraZeneca and Bayer
Adnan Kastrati, MD	Deutsches Herzzentrum München, Munich, Germany	Dr. Kastrati is an inventor in a patent application related to drug-eluting stent technology; he also serves in the Data and Safety Monitoring Board of the TARGET IV trial sponsored by the Cardiovascular Research Foundation in New York, USA.
Upendra Kaul, MD	Batra Hospital and Medical Research Centre, New Delhi, India	None
Ran Kornowski, MD	Rabin Medical Center, Petach Tikva, Israel	None
Mitchel Krucoff, MD	Division of Cardiology, Department of Medicine, Duke University Medical Center, Duke Clinical Research Institute, Durham, North Carolina, USA	None
Vijay Kunadian, MBBS, MD	Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University and Freeman Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom	None
Roxana Mehran, MD	The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, New York, USA	Dr. Mehran reports institutional research payments from Abbott, Abiomed, Alleviant Medical, Amgen, AM-Pharma, Arena, AstraZeneca, Atricure, Bayer, Biosensors, Biotronik, Boston Scientific, Bristol-Myers Squibb, CardiaWave,

		CeloNova, Chiesi, Concept Medical, CSL Behring, Cytosorbents, Daiichi Sankyo, Element Science, Faraday, Humacyte, Idorsia Pharmaceuticals, Janssen, Medtronic, Novartis, OrbusNeich, PhaseBio, Philips, Pi-Cardia, PLx Pharma, RenalPro, RM Global, Shockwave, Vivasure, Zoll; personal fees from Cine-Med Research, Novartis, WebMD; Equity <1% in Applied Therapeutics, Elixir Medical, Stel, ControlRad (spouse); Scientific Advisory Board for AMA, ACC (BOT Member), SCAI (Women in Innovations Committee Member), JAMA Associate Editor; Faculty CRF (no fee).
Shamir R. Mehta, MD	Hamilton Health Sciences, Hamilton, Ontario, Canada	Dr Mehta has received grant support from and has served on an executive committee and as site investigator for AstraZeneca
D. Moliterno	Division of Cardiovascular Medicine, University of Kentucky	None
Stuart Pocock, PhD	Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, United Kingdom	None
Gennaro Sardella, MD	Policlinico Umberto I University, Rome, Italy	None
Samantha Sartori, PHD	The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, New York, USA	None
Richard A. Shlofmitz, MD	St. Francis Hospital, Roslyn, Roslyn, New York, USA	None
Samin Sharma, MD	The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, New York, USA	None
Alessandro Spirito, MD	The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, New York, USA	Dr Spirito received a research grant from the Swiss National Science Foundation (SNSF).
Philippe Gabriel Steg, MD	Université Paris-Cité, FACT (French Alliance for Cardiovascular Trials), INSERM_U1148 and AP-HP, Hôpital Bichat, Paris, France	Dr Steg received research grant from Amarin, Bayer, Sanofi and Servier; speaking or consulting fees from Amarin, Amgen, AstraZeneca, Bayer/Janssen, Bristol Myers Squibb, Idorsia, Myokardia, Novartis, Novo Nordisk, PhaseBio, Pfizer, Regeneron, Sanofi and Servier.

Birgit Vogel, MD	The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, New York, USA	None

1

Abstract

Background: Repeat coronary revascularization is a common adverse event after successful percutaneous coronary intervention (PCI). The aim of this analysis was to assess the effects of ticagrelor monotherapy on repeat clinically driven revascularization.

Methods: In the TWILIGHT trial (Ticagrelor With Aspirin or Alone in High-Risk Patients after Coronary Intervention), after 3 months of ticagrelor plus aspirin, high-risk patients were maintained on ticagrelor and randomized to aspirin or placebo for 1 year. The primary endpoint of this analysis was clinically driven revascularization within 12 months after randomization. The key secondary endpoints were major adverse cardiovascular and cerebrovascular events (MACCE), a composite of all-cause death, myocardial infarction, stroke or clinically driven revascularization; and net adverse clinical events (NACE), including the individual components of MACCE and clinically relevant bleeding. The analysis was performed in the per-protocol population.

Results: Among 7,039 patients, ticagrelor monotherapy was associated with a similar 12-month risk of clinically driven revascularization (7.1% vs 6.6%, HR 1.09, 95% CI 0.90-1.30, p-value 0.363) and MACCE (8.9% vs 8.6%, HR 1.04, 95% CI 0.89-1.22), and a lower risk of NACE (12.2% vs 14.6%, HR 0.83 95% CI 0.73-0.94, p-value 0.004) as compared to ticagrelor plus aspirin. These effects were consistent irrespective of the clinical presentation, presence of diabetes and PCI complexity (interaction p-values non- significant).

Conclusions: Among high-risk patients undergoing PCI, ticagrelor monotherapy after 3 months of ticagrelor-based DAPT was associated with a similar risk of clinically driven revascularization and MACCE, and a reduction of NACE (TWILIGHT: NCT02270242).

Key words: ticagrelor monotherapy; percutaneous coronary intervention; repeat revascularization; clinically driven revascularization

Introduction

Despite advances in stent technologies, percutaneous coronary intervention (PCI) techniques and intensive secondary prevention, repeat coronary revascularization after successful PCI remains relatively frequent in clinical practice[1-3]. Even though the impact of this outcome on mortality is still uncertain, repeat revascularization is a matter of concern for patients, clinicians and policy makers given its association with procedural risks, reduced quality of life, and additional use of healthcare resources[4-8].

Repeat revascularization is often triggered by recurrent angina or myocardial ischemia potentially due to a new significant coronary stenosis, which may result from progressive atherosclerosis or from acute changes of a previously stented or a de-novo coronary lesion[5]. Therefore, prevention of repeat revascularization relies on interventions reducing atherosclerotic disease progression or spontaneous acute coronary events[9, 10].

Dual antiplatelet therapy (DAPT) for 6 to 12 months is considered the standard of care in patients undergoing PCI to reduce stent-related and spontaneous ischemic events[9, 11]. In some prior studies, longer DAPT duration has been associated with fewer repeat revascularization[12-14]. Yet, because of the bleeding risk associated with longer DAPT regimens, new antiplatelet strategies have been investigated to optimize ischemic prevention while reducing bleeding complications[15]. The TWILIGHT (Ticagrelor With Aspirin or Alone in High-Risk Patients after Coronary Intervention) trial demonstrated that in patients with high-risk features of ischemic or bleeding events who underwent successful PCI, ticagrelor monotherapy after 3-months of DAPT reduced bleeding without increasing the risk of the composite outcome of all-cause death, non-fatal myocardial infarction (MI) or non-fatal stroke compared to DAPT continuation[16].

The scope of the current analysis was to assess for the first time the effect of ticagrelor monotherapy on repeat clinically driven revascularization in the TWILIGHT trial.

METHODS

Study design

TWILIGHT (NCT02270242) was a randomized, placebo-controlled trial conducted at 187 sites in 11 countries. The rationale, design, and principal results of the trial have been reported previously[16, 17]. In brief, this trial was supported by an investigator-initiated grant from AstraZeneca and was designed, coordinated, and sponsored by the Icahn School of Medicine at Mount Sinai. AstraZeneca provided financial support, supplied ticagrelor for the trial but had no role in the design, collection, analysis, or interpretation of the data. The executive and steering committees were responsible for trial conduct, integrity of data analysis, and reporting of results. National regulatory agencies and Institutional Review Boards or ethics committees of participating centers approved the trial protocol. The safety of trial participants was ensured by an external and independent data and safety monitoring board.

Study population

Patients were eligible for inclusion if they underwent a successful PCI with implantation of at least 1 commercially available drug-eluting stent (DES) and were planned to be prescribed a regimen of ticagrelor plus aspirin by the treating clinician. In addition, the fulfilment of at least 1 clinical and 1 angiographic feature associated with a high risk for ischemic or bleeding events was required for trial inclusion[16, 17]. Clinical high-risk criteria were: age ≥65 years, female sex, troponin-positive acute coronary syndrome, atherosclerotic vascular disease (prior MI, coronary revascularization, or peripheral arterial disease), diabetes mellitus requiring medication, and chronic kidney disease (CKD) defined as estimated glomerular filtration rate <60 ml/min/1.73 m2 or creatinine clearance <60 ml/min. Angiographic high-risk criteria included multivessel coronary artery disease, total stent length >30 mm, thrombotic target lesion, bifurcation lesion requiring 2

stents, obstructive left main or proximal left anterior descending coronary artery lesion, and calcified target lesion requiring debulking devices. Key exclusion criteria were presentation with an ST-segment elevation MI (STEMI), cardiogenic shock, planned coronary revascularization within 90 days from enrollment, prior stroke, need for oral anticoagulation, or contraindication to aspirin or ticagrelor.

Study regimen

All enrolled patients received open-label ticagrelor (90 mg twice daily) and enteric-coated aspirin (81 to 100 mg/day) after the index PCI. At 3 months, patients adherent to this drug regimen and free from relevant adverse events between index PCI and 3 months were randomized 1:1 in a double-blind fashion to aspirin or matching placebo for an additional 12 months (i.e., to 15 months post-PCI)[16, 17]. Relevant adverse events determining ineligibility to randomization included Bleeding Academic Research Consortium (BARC) type 3b or higher bleeding events and ischemic events (stroke, MI, or coronary revascularization). Telephone follow-up occurred at 1 month after randomization, in person visits at 6 and 12 months after randomization.

Clinical endpoints

The primary endpoint of this analysis was repeat revascularization up to 1 year after randomization. Repeat clinically driven revascularization was defined in accordance to the Academic Research Consortium consensus document as any repeat revascularization (PCI or coronary artery bypass graft [CABG]) due to recurrent or symptomatic ischemia associated with a lesion determining a >50% diameter stenosis, or revascularization of a lesion with a ≥70% diameter stenosis even in absence of ischemic signs or symptoms[18]. Diameter stenosis was assessed by an independent coronary angiographic core laboratory with quantitative methods.

Secondary outcomes included target lesion revascularization (TLR); non-TLR target vessel revascularization (TVR); non-TVR; major adverse cardiovascular or cerebrovascular endpoints (MACCE), a composite of death from any causes, non-fatal MI, non-fatal stroke, and repeat revascularization, net adverse clinical events (NACE) including the individual components of MACCE and BARC type 2, 3, or 5 bleeding. MI was defined according to the third universal definition[19]. Detailed definitions of all the outcomes are provided in **supplementary Table 1**. All clinical events were adjudicated by an independent committee blinded to treatment assignment[16, 17].

Statistical analysis

Clinical and procedural characteristics were summarized as mean and standard deviation for continuous variables and frequencies for categorical variables. The cumulative incidence of the primary and secondary endpoints was estimated using the Kaplan-Meier method. Patients without primary endpoints were censored at the time of death, last known contact, or 365 days, whichever came first. Hazard ratios (HRs) and 95% confidence intervals (CIs) were generated using unadjusted Cox proportional hazards models.

Analyses were performed in the per protocol cohort, which included randomized participants who completed all study-related contacts without any major protocol deviations, such as missing intake of at least one dose of the protocol-mandated therapy or non-adherence to the study drug. Non-adherence to study drug (aspirin or placebo) was defined as taking less than 80% of dispensed tablets based on manual pill bottle count at each study visit[16, 17]. The cumulative incidence and HRs for the primary endpoint were assessed in relevant subgroups stratified according to: diabetes, clinical presentation (acute coronary syndrome [ACS] vs chronic coronary syndrome [CCS]) and complex PCI. Index PCI was considered complex in presence of at least one

of the following features: PCI involving ≥3 vessels, ≥3 lesions, left main coronary artery, surgical bypass graft, chronic total occlusion, or total stent length >60 mm, bifurcation with 2 stents implanted or use of atherectomy device.

All analyses were performed using Stata version 18.0 (StataCorp, College Station, Texas).

Results

Population characteristics

Among 9,006 patients enrolled from July 2015 through December 2017, 7,119 underwent randomization at 3 months after the index procedure and 7,039 patients were included in the per-protocol analysis. Of those, 3,524 received at least one dose of ticagrelor plus placebo and 3,515 at least one dose of ticagrelor plus aspirin.

Baseline and procedural characteristics were well balanced between the two groups (**Table 1 and 2**). The mean age was 64 years, women comprised 23.8% of the study population, 36.8% of patients had diabetes, 64.9% presented with acute coronary syndrome and 32.8% underwent a complex PCI. Follow-up was completed in 98.4% of patients and vital status was known in 99.7%.

Treatment effect on repeat revascularization

At 1-year after randomization, repeat revascularization occurred in 246 (7.1%) patients receiving ticagrelor monotherapy and in 227 (6.6%) patients receiving ticagrelor plus aspirin (HR 1.09, 95% CI 0.90-1.30; p-value 0.363) (**Figure 2** and **Figure 3**). TLR was observed in 137 (4.0%) and 126 (3.7%) of patients in the two treatment arms, respectively (HR 1.09, 95% CI 0.86-1.39; p-value 0.489); non-TLR TVR occurred in 34 (1.0%) and 31 (0.9%) patients (HR 1.10, 95% CI 0.68-1.78; p-value 0.713), respectively. Non-TVR was observed in 91 (2.6%) patients assigned to

ticagrelor monotherapy and 86 (2.5%) patients assigned to ticagrelor plus aspirin (HR 1.06, 95% CI 0.79-1.42, p-value 0.710) (**Figure 3**).

The effects of ticagrelor monotherapy versus ticagrelor plus aspirin was consistent in high-risk subgroups, such as patients with diabetes (interaction p-value 0.498), presenting with ACS (interaction p-value 0.183) or undergoing complex PCI (interaction p-value 0.766) (**Figure 4**).

Treatment effect on secondary outcomes

At 12 months after randomization, the composite endpoint of MACCE occurred in 309 (8.9%) patients on ticagrelor monotherapy and 298 (8.6%) patients on ticagrelor plus aspirin (HR 1.04, 95% CI 0.89-1.22, p-value 0.619) (**Figure 3**).

The composite endpoint of NACE was observed in 427 (12.2%) patients on ticagrelor monotherapy and 508 (14.6%) patients on ticagrelor plus aspirin (HR 0.83, 95% CI 0.73-0.94, p-value 0.004).

BARC 2, 3 or 5 bleeding was significantly lower in the ticagrelor monotherapy than in the ticagrelor plus placebo group (3.4% vs 7.1%, HR 0.56, 95% CI 0.45-0.69, p-value <0.001).

DISCUSSION

In this post-hoc analysis of the TWILIGHT trial, we assessed for the first time the effect of ticagrelor monotherapy after 3 months of ticagrelor-based DAPT on centrally adjudicated clinically driven revascularization at 12-month after randomization. We found that ticagrelor monotherapy compared to ticagrelor plus aspirin was associated with similar rates of clinically driven revascularization, TLR, TVR, non-TVR, MACCE and a reduction of NACE and BARC 2, 3 or 5 bleeding.

Despite advances in PCI techniques, stent devices and pharmacological therapy, repeat revascularization after PCI remains a relatively frequent adverse event, associated with increased morbidity and healthcare costs. Previous studies reported that around 50% of repeat revascularizations are due to a recurrent acute coronary syndrome or MI[4, 8, 20]. Thus, the type of antithrombotic regimen prescribed after PCI may play a relevant role in preventing repeat revascularization.

In the current study, the rate of repeat clinically driven revascularization during the 12 months following randomization (i.e. from 3 to 15 months after PCI) was about 7%. This incidence is slightly higher than previously reported rates after current generation DES implantation[2, 21-23], probably because all patients of TWILIGHT had at least one complex angiographic feature. More than half the clinically driven revascularization was a TLR, in keeping with prior reports[2, 8, 21, 22]. We found that the cumulative incidence of repeat revascularization, TLR, non TLR TVR, non-TVR and MACCE – a composite endpoint including clinically driven revascularization - was similar among patients receiving ticagrelor monotherapy and ticagrelor plus aspirin. These results were consistent in higher risk subgroups, such as patients with diabetes, ACS or undergoing complex PCI.

At variance with trials comparing stent devices, studies examining antithrombotic therapies after PCI do not systematically report repeat revascularization. Nonetheless, some randomized controlled trials demonstrated a decrease of repeat revascularization with more potent or prolonged antiplatelet regimens after PCI. Among 2,237 patients with stable CAD, ticagrelor or clopidogrel-based DAPT prescribed according to the level of platelet reactivity was associated with significantly lower rates of urgent revascularization at 6-month as compared to a standard DAPT with clopidogrel (0.3% vs 1.3%)[12]. Similarly, among 19,220 diabetic patients with stable CAD, an extended ticagrelor-based DAPT resulted in a numerical but not significant decrease of repeat

revascularization at 36 months after PCI as compared to aspirin alone (absolute rate difference 0.7%)[13]. The HOST-EXAM extended study reported significantly less revascularization at a median follow-up of 5.8 years with clopidogrel compared to aspirin for chronic maintenance[14]. On the other hand, in the STOP-DAPT 2 trial, clopidogrel monotherapy after 1-month of DAPT was associated with a borderline increase of repeat revascularization when compared to standard DAPT (6.8% vs 5.3% HR 1.31, 95% CI 0.97-1.77, p-value 0.08) [24]**.** Interestingly, in the GLOBAL LEADERS trial, TLR was numerically lower with 1-month of DAPT followed by ticagrelor monotherapy for 23 months than with 12 month DAPT followed by aspirin (4.87% vs 5.54%, relative risk 0.88, 95% CI 0.77–1.01, p-value 0.068) [25].

The main analysis of the TWILIGHT trial demonstrated that in patients with high-risk features of ischemic or bleeding events who underwent successful PCI, ticagrelor monotherapy after 3-months of DAPT reduced clinically relevant bleeding without increasing the risk of the composite outcome of all-cause death, non-fatal myocardial infarction (MI) or non-fatal stroke[16]. The current analysis confirms that such a strategy can effectively prevent clinically driven revascularization. These findings are supported by the existing evidence. Prior studies reported that more than half of repeat revascularizations are due to a recurrent ACS or MI[4, 8, 20], which are frequently associated with acute plaque rupture or erosion and intracoronary thrombus formation[26]. Previous pharmacodynamic investigations showed that ex vivo platelet-dependent thrombus formation is not affected by aspirin withdrawal in presence of a potent $P2Y_{12}$ receptors inhibition[17, 27].

Strategies preventing atherosclerotic progression, erosion or rupture of de-novo or previously stented coronary lesions should be implemented to reduce repeat revascularization. Those include appropriate choice of stent device, advanced stent implantation techniques, use of intracoronary imaging, intensive lipid lowering therapy and treatment of cardiovascular risk factors[9, 28].

Limitations

These results should be interpreted in light of several limitations. First, information on angiographic findings or clinical presentation (ACS or CCS) in patients undergoing clinically repeat revascularization was not available. These findings may not generalize to patients treated with other oral P2Y12 inhibitors, particularly clopidogrel or to patients presenting with STEMI, who were excluded from participation in TWILIGHT. Moreover, the findings apply to patients who were able to adhere to 3 months of DAPT without experiencing any major bleeding or ischemic event.

CONCLUSIONS

Among high-risk patients undergoing PCI, ticagrelor monotherapy following 3 months of DAPT was associated with similar rates of clinically driven revascularization and MACCE and a reduction of NACCE as compared with ticagrelor plus aspirin. These findings support the use of ticagrelor monotherapy after PCI to prevent adequately ischemic events, including repeat revascularization, and to reduce significantly bleeding complications.

References

1. Xaplanteris P, Fournier S, Pijls NHJ, et al. Five-Year Outcomes with PCI Guided by Fractional Flow Reserve. *N Engl J Med*. Jul 19 2018;379(3):250-259. doi:10.1056/NEJMoa1803538
2. Taniwaki M, Stefanini GG, Silber S, et al. 4-year clinical outcomes and predictors of repeat revascularization in patients treated with new-generation drug-eluting stents: a report from the RESOLUTE All-Comers trial (A Randomized Comparison of a Zotarolimus-Eluting Stent With an Everolimus-Eluting Stent for Percutaneous Coronary Intervention). *J Am Coll Cardiol*. Apr 29 2014;63(16):1617-25. doi:10.1016/j.jacc.2013.12.036
3. Nicolas J, Pivato CA, Chiarito M, Beerkens F, Cao D, Mehran R. Evolution of drug-eluting coronary stents: a back-and-forth journey from the bench to bedside. *Cardiovasc Res*. May 2 2023;119(3):631-646. doi:10.1093/cvr/cvac105
4. Arnold SV, Smolderen KG, Kennedy KF, et al. Risk factors for rehospitalization for acute coronary syndromes and unplanned revascularization following acute myocardial infarction. *J Am Heart Assoc*. Feb 9 2015;4(2)doi:10.1161/jaha.114.001352
5. Lamelas P, Belardi J, Whitlock R, Stone GW. Limitations of Repeat Revascularization as an Outcome Measure: JACC Review Topic of the Week. *J Am Coll Cardiol*. Dec 24 2019;74(25):3164-3173. doi:10.1016/j.jacc.2019.10.041
6. Inohara T, Kohsaka S, Miyata H, et al. Prognostic Impact of Subsequent Acute Coronary Syndrome and Unplanned Revascularization on Long-Term Mortality After an Index Percutaneous Coronary Intervention: A Report From a Japanese Multicenter Registry. *J Am Heart Assoc*. Oct 27 2017;6(11)doi:10.1161/jaha.117.006529
7. Palmerini T, Della Riva D, Biondi-Zoccai G, et al. Mortality Following Nonemergent, Uncomplicated Target Lesion Revascularization After Percutaneous Coronary Intervention: An Individual Patient Data Pooled Analysis of 21 Randomized Trials and 32,524 Patients. *JACC Cardiovasc Interv*. May 14 2018;11(9):892-902. doi:10.1016/j.jcin.2018.01.277
8. Parasca CA, Head SJ, Milojevic M, et al. Incidence, Characteristics, Predictors, and Outcomes of Repeat Revascularization After Percutaneous Coronary Intervention and Coronary Artery Bypass Grafting: The SYNTAX Trial at 5 Years. *JACC Cardiovasc Interv*. Dec 26 2016;9(24):2493-2507. doi:10.1016/j.jcin.2016.09.044
9. Lawton JS, Tamis-Holland JE, Bangalore S, 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*. Jan 18 2022;145(3):e18-e114. doi:10.1161/cir.0000000000001038
10. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J*. Jan 7 2019;40(2):87-165. doi:10.1093/eurheartj/ehy394
11. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. Jan 14 2018;39(3):213-260. doi:10.1093/eurheartj/ehx419
12. Zheng YY, Wu TT, Yang Y, et al. Personalized antiplatelet therapy guided by a novel detection of platelet aggregation function in stable coronary artery disease patients undergoing

percutaneous coronary intervention: a randomized controlled clinical trial. *Eur Heart J Cardiovasc Pharmacother*. Jul 1 2020;6(4):211-221. doi:10.1093/ehjcvp/pvz059
13. Steg PG, Bhatt DL, Simon T, et al. Ticagrelor in Patients with Stable Coronary Disease and Diabetes. *N Engl J Med*. Oct 3 2019;381(14):1309-1320. doi:10.1056/NEJMoa1908077
14. Kang J, Park KW, Lee H, et al. Aspirin Versus Clopidogrel for Long-Term Maintenance Monotherapy After Percutaneous Coronary Intervention: The HOST-EXAM Extended Study. *Circulation*. Jan 10 2023;147(2):108-117. doi:10.1161/circulationaha.122.062770
15. Capodanno D, Bhatt DL, Gibson CM, et al. Bleeding avoidance strategies in percutaneous coronary intervention. *Nat Rev Cardiol*. Feb 2022;19(2):117-132. doi:10.1038/s41569-021-00598-1
16. Mehran R, Baber U, Sharma SK, et al. Ticagrelor with or without Aspirin in High-Risk Patients after PCI. *N Engl J Med*. Nov 21 2019;381(21):2032-2042. doi:10.1056/NEJMoa1908419
17. Baber U, Dangas G, Cohen DJ, et al. Ticagrelor with aspirin or alone in high-risk patients after coronary intervention: Rationale and design of the TWILIGHT study. *Am Heart J*. Dec 2016;182:125-134. doi:10.1016/j.ahj.2016.09.006
18. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. May 1 2007;115(17):2344-51. doi:10.1161/circulationaha.106.685313
19. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *J Am Coll Cardiol*. Oct 16 2012;60(16):1581-98. doi:10.1016/j.jacc.2012.08.001
20. Adlam D, Evans N, Malhotra A, et al. Repeat percutaneous coronary revascularization: indications and outcomes in a "real world" cohort. *Catheter Cardiovasc Interv*. Oct 1 2012;80(4):539-45. doi:10.1002/ccd.23395
21. Naidu SS, Krucoff MW, Rutledge DR, et al. Contemporary incidence and predictors of stent thrombosis and other major adverse cardiac events in the year after XIENCE V implantation: results from the 8,061-patient XIENCE V United States study. *JACC Cardiovasc Interv*. Jun 2012;5(6):626-35. doi:10.1016/j.jcin.2012.02.014
22. Raungaard B, Jensen LO, Tilsted HH, et al. Zotarolimus-eluting durable-polymer-coated stent versus a biolimus-eluting biodegradable-polymer-coated stent in unselected patients undergoing percutaneous coronary intervention (SORT OUT VI): a randomised non-inferiority trial. *Lancet*. Apr 18 2015;385(9977):1527-35. doi:10.1016/s0140-6736(14)61794-3
23. Stolker JM, Cohen DJ, Kennedy KF, et al. Repeat revascularization after contemporary percutaneous coronary intervention: an evaluation of staged, target lesion, and other unplanned revascularization procedures during the first year. *Circ Cardiovasc Interv*. Dec 2012;5(6):772-82. doi:10.1161/circinterventions.111.967802
24. Watanabe H, Domei T, Morimoto T, et al. Effect of 1-Month Dual Antiplatelet Therapy Followed by Clopidogrel vs 12-Month Dual Antiplatelet Therapy on Cardiovascular and Bleeding Events in Patients Receiving PCI: The STOPDAPT-2 Randomized Clinical Trial. *Jama*. Jun 25 2019;321(24):2414-2427. doi:10.1001/jama.2019.8145
25. Vranckx P, Valgimigli M, Jüni P, et al. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. *Lancet*. Sep 15 2018;392(10151):940-949. doi:10.1016/s0140-6736(18)31858-0

26. Johnson TW, Räber L, di Mario C, et al. Clinical use of intracoronary imaging. Part 2: acute coronary syndromes, ambiguous coronary angiography findings, and guiding interventional decision-making: an expert consensus document of the European Association of Percutaneous Cardiovascular Interventions. *Eur Heart J*. Aug 14 2019;40(31):2566-2584. doi:10.1093/eurheartj/ehz332
27. Franchi F, Rollini F, Faz G, et al. Pharmacodynamic Effects of Vorapaxar in Prior Myocardial Infarction Patients Treated With Potent Oral P2Y(12) Receptor Inhibitors With and Without Aspirin: Results of the VORA-PRATIC Study. *J Am Heart Assoc*. Apr 21 2020;9(8):e015865. doi:10.1161/jaha.120.015865
28. Räber L, Mintz GS, Koskinas KC, et al. Clinical use of intracoronary imaging. Part 1: guidance and optimization of coronary interventions. An expert consensus document of the European Association of Percutaneous Cardiovascular Interventions. *Eur Heart J*. Sep 14 2018;39(35):3281-3300. doi:10.1093/eurheartj/ehy285

Funding

The TWILIGHT trial was an investigator-initiated trial designed, coordinated, and sponsored by the Icahn School of Medicine at Mount Sinai. Astra Zeneca provided an investigator-initiated grant and supplied ticagrelor for the trial but had no role in the design, collection, analysis, or interpretation of the data.

Figure legends

Figure 1. Cumulative incidence of clinically driven revascularization at 1 year after randomization.

Figure 2. Cumulative incidence of MACCE and NACE at 1 year after randomization.

MACCE: Major adverse cardiovascular and cerebrovascular events; NACE: Net adverse clinical events

Figure 3. Treatment effect on adverse events at 1-year after randomization.

BARC: Bleeding Academic Research Consortium; MACCE: Major adverse cardiovascular and cerebrovascular events; NACE: Net adverse clinical events; TLR: target lesion revascularization; TVR: target vessel revascularization.
#composite of death from any causes, non-fatal MI, non-fatal stroke, and repeat revascularization.
**composite of death from any causes, non-fatal MI, non-fatal stroke, repeat revascularization and BARC type 2, 3, or 5 bleeding*

Figure 4. Treatment effect on clinically driven revascularization at 1-year after randomization in relevant subgroups. PCI was defined complex in presence of at least one of the following: PCI involving ≥3 vessels, ≥3 lesions, left main coronary artery, surgical bypass graft, chronic total occlusion, or total stent length >60 mm, bifurcation with 2 stents implanted or use of atherectomy device

ACS: acute coronary syndrome; PCI: percutaneous coronary intervention

Figure 1.

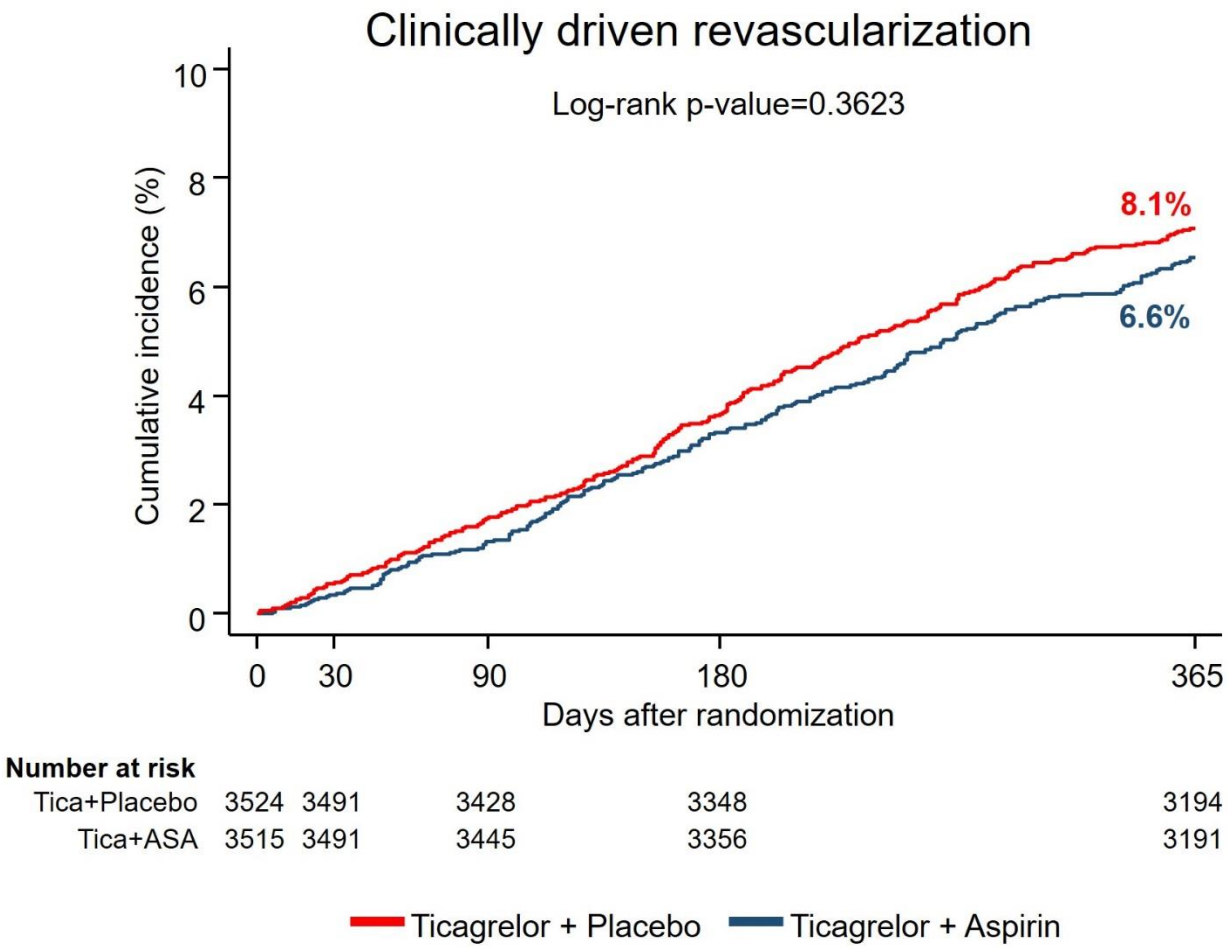
Clinically driven revascularization
Log-rank p-value=0.3623
Cumulative incidence (%)
10
8
6
4
2
0
8.1%
6.6%
0
30
90
180
365
Days after randomization
Number at risk
Tica+Placebo 3524 3491 3428 3348 3194
Tica+ASA 3515 3491 3445 3356 3191
Ticagrelor + Placebo
Ticagrelor + Aspirin

Figure 2

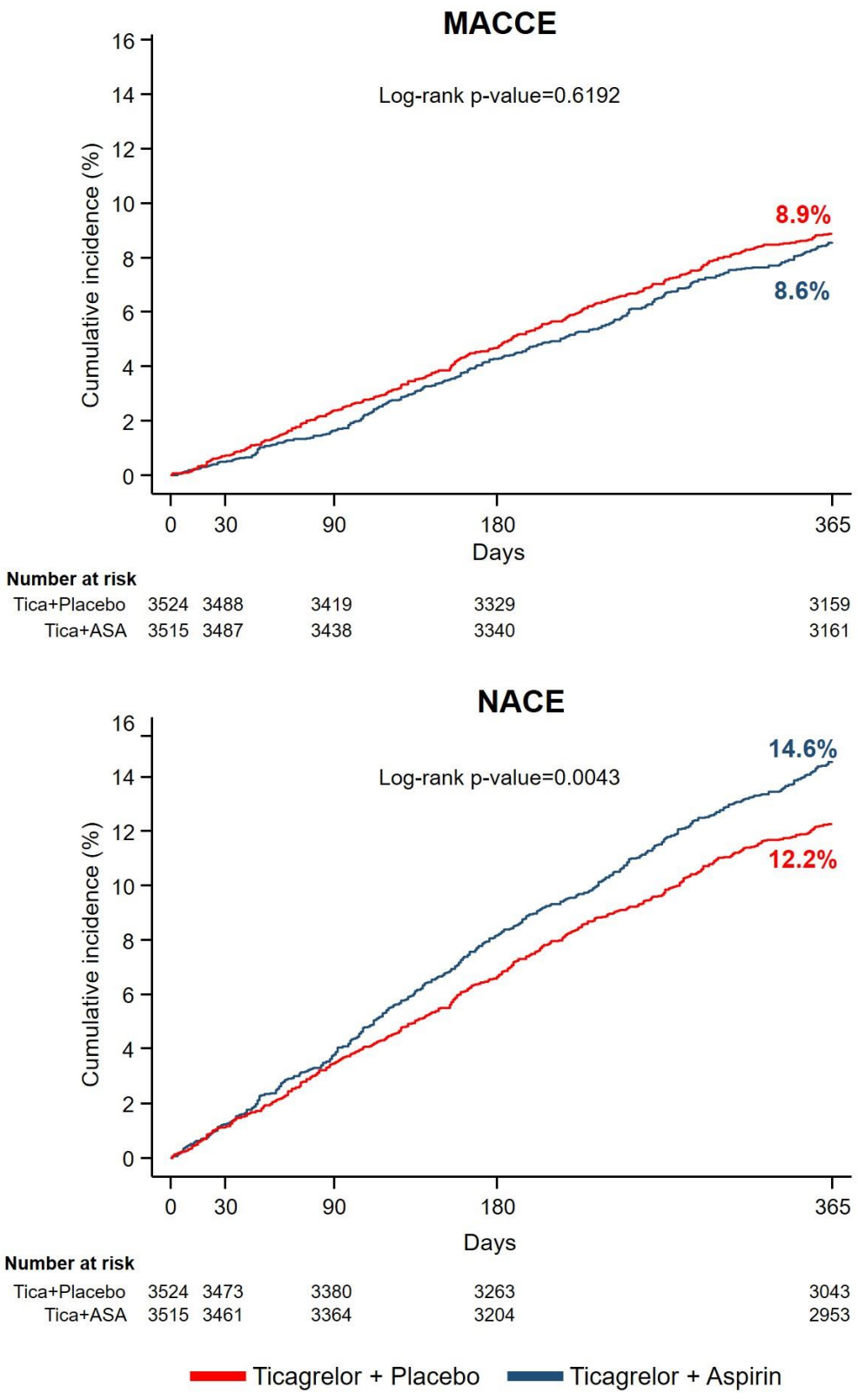
MACCE
Log-rank p-value=0.6192
Cumulative incidence (%)
16
14
12
10
8
6
4
2
0
8.9%
8.6%
0
30
90
180
365
Days
Number at risk
Tica+Placebo 3524 3488 3419 3329 3159
Tica+ASA 3515 3487 3438 3340 3161
NACE
Log-rank p-value=0.0043
Cumulative incidence (%)
16
14
12
10
8
6
4
2
0
14.6%
12.2%
0
30
90
180
365
Days
Number at risk
Tica+Placebo 3524 3473 3380 3263 3043
Tica+ASA 3515 3461 3364 3204 2953
Ticagrelor + Placebo
Ticagrelor + Aspirin

Figure 3

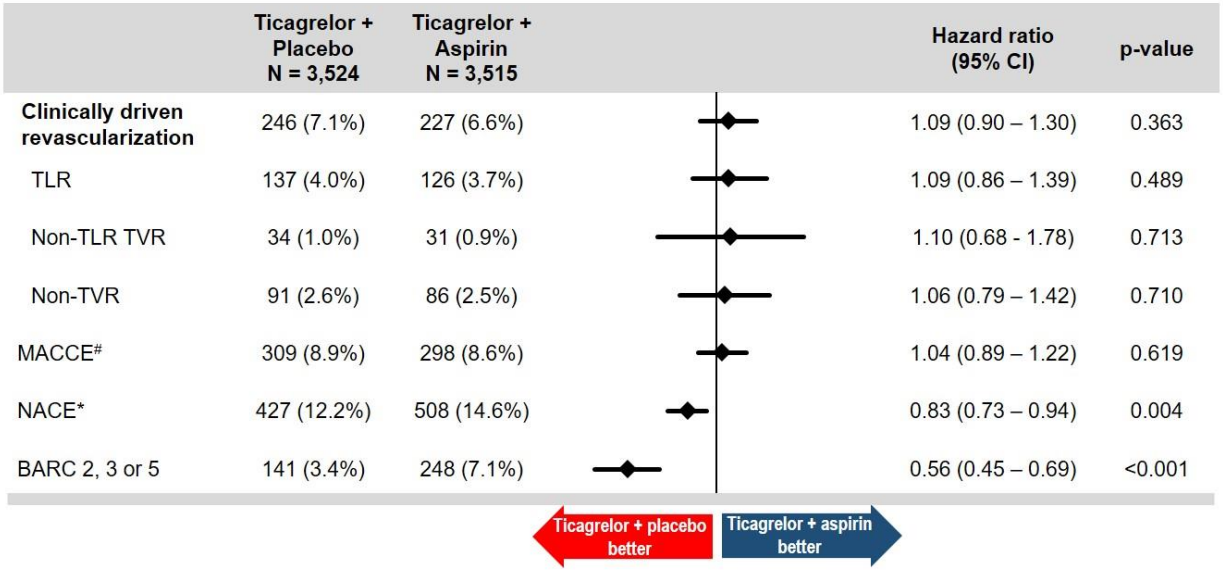
Ticagrelor + Placebo N = 3,524
Ticagrelor + Aspirin N = 3,515
Hazard ratio (95% CI)
p-value
Clinically driven revascularization
246 (7.1%)
227 (6.6%)
1.09 (0.90 – 1.30)
0.363
TLR
137 (4.0%)
126 (3.7%)
1.09 (0.86 – 1.39)
0.489
Non-TLR TVR
34 (1.0%)
31 (0.9%)
1.10 (0.68 - 1.78)
0.713
Non-TVR
91 (2.6%)
86 (2.5%)
1.06 (0.79 – 1.42)
0.710
MACCE#
309 (8.9%)
298 (8.6%)
1.04 (0.89 – 1.22)
0.619
NACE*
427 (12.2%)
508 (14.6%)
0.83 (0.73 – 0.94)
0.004
BARC 2, 3 or 5
141 (3.4%)
248 (7.1%)
0.56 (0.45 – 0.69)
<0.001
Ticagrelor + placebo better
Ticagrelor + aspirin better

Figure 4

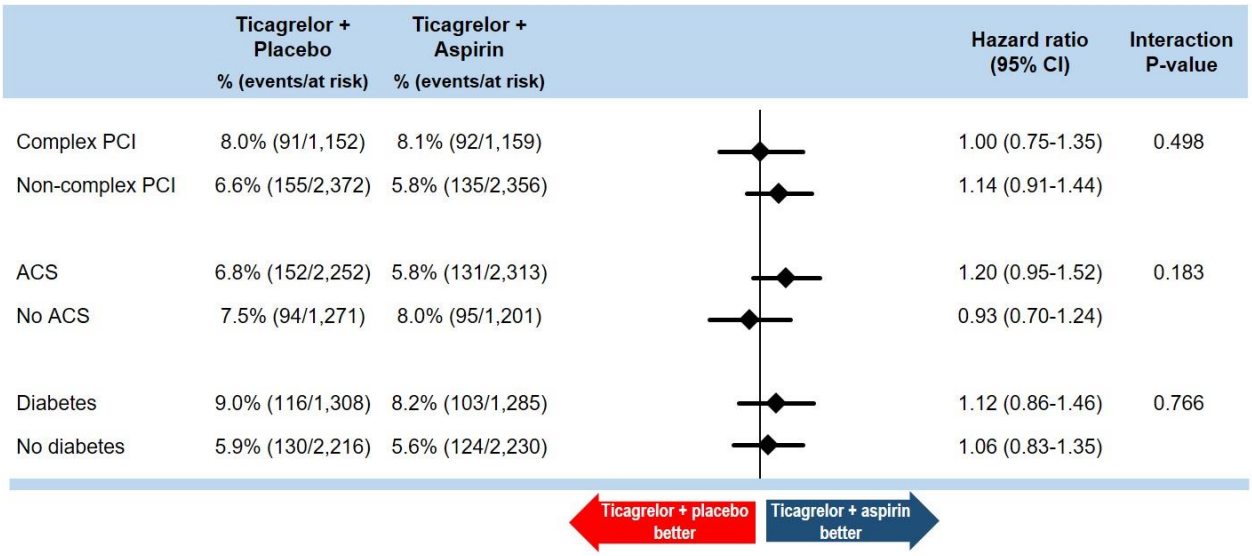
Ticagrelor + Placebo
% (events/at risk)
Ticagrelor + Aspirin
% (events/at risk)
Hazard ratio (95% CI)
Interaction P-value
Complex PCI
8.0% (91/1,152)
8.1% (92/1,159)
1.00 (0.75-1.35)
0.498
Non-complex PCI
6.6% (155/2,372)
5.8% (135/2,356)
1.14 (0.91-1.44)
ACS
6.8% (152/2,252)
5.8% (131/2,313)
1.20 (0.95-1.52)
0.183
No ACS
7.5% (94/1,271)
8.0% (95/1,201)
0.93 (0.70-1.24)
Diabetes
9.0% (116/1,308)
8.2% (103/1,285)
1.12 (0.86-1.46)
0.766
No diabetes
5.9% (130/2,216)
5.6% (124/2,230)
1.06 (0.83-1.35)
Ticagrelor + placebo better
Ticagrelor + aspirin better

Table 1. Baseline characteristics in the per-protocol population.

	Overall N=7,039	Ticagrelor +Placebo N=3,524	Ticagrelor +Aspirin N=3,515	p-value
Age, years	63.9±10.2	63.9±10.1	63.8±10.2	0.789
Female sex	1676 (23.8%)	840 (23.8%)	836 (23.8%)	0.959
Nonwhite race	2165 (30.8%)	1100 (31.2%)	1065 (30.3%)	0.405
BMI, kg/m^2	28.6±5.6	28.6±5.5	28.6±5.6	0.909
Enrolling region				0.962
North America	2939 (41.8%)	1471 (41.7%)	1468 (41.8%)	
Europe	2487 (35.3%)	1241 (35.2%)	1246 (35.4%)	
Asia	1613 (22.9%)	812 (23.0%)	801 (22.8%)	
Diabetes	2593 (36.8%)	1308 (37.1%)	1285 (36.6%)	0.627
Treated with insulin	700 (27.0%)	332 (25.4%)	368 (28.6%)	0.062
Chronic kidney disease	1100 (16.3%)	549 (16.2%)	551 (16.3%)	0.939
Anemia	1311 (19.4%)	668 (19.8%)	643 (19.0%)	0.438
Current smoker	1530 (21.7%)	719 (20.4%)	811 (23.1%)	0.007
Hypercholesterolemia	4260 (60.5%)	2141 (60.8%)	2119 (60.3%)	0.686
Hypertension	5097 (72.4%)	2558 (72.6%)	2539 (72.3%)	0.754
Previous MI	2019 (28.7%)	1011 (28.7%)	1008 (28.7%)	0.991
Previous PCI	2968 (42.2%)	1492 (42.3%)	1476 (42.0%)	0.768
Previous CABG	702 (10.0%)	360 (10.2%)	342 (9.7%)	0.494
Previous major bleed	62 (0.9%)	31 (0.9%)	31 (0.9%)	0.992
Indication for PCI				0.095
Stable CAD	2472 (35.1%)	1271 (36.1%)	1201 (34.2%)	
ACS	4565 (64.9%)	2252 (63.9%)	2313 (65.8%)	

ACS: Acute coronary syndrome**,** BMI: body mass index, CABG: coronary artery bypass graft, CAD: coronary artery disease, MI: myocardial infarction, PCI: percutaneous coronary intervention.

Table 2. Procedural characteristics in the per-protocol population.

	Overall N=7,039	Ticagrelor + placebo N=3,524	Ticagrelor + aspirin N=3,515	p-value
Radial artery access	5132 (72.9%)	2577 (73.1%)	2555 (72.7%)	0.679
Multivessel CAD	4426 (62.9%)	2260 (64.1%)	2166 (61.6%)	0.029
Target vessel				
Left Main	349 (5.0%)	165 (4.7%)	184 (5.2%)	0.286
LAD	3962 (56.3%)	1981 (56.2%)	1981 (56.4%)	0.903
LCX	2265 (32.2%)	1135 (32.2%)	1130 (32.1%)	0.957
RCA	2476 (35.2%)	1237 (35.1%)	1239 (35.2%)	0.897
Number of vessels treated	1.3±0.5	1.3±0.5	1.3±0.5	0.513
Number of lesions treated	1.5±0.7	1.5±0.7	1.5±0.7	0.511
Lesion morphology†				
Moderate/severe calcification	975 (13.9%)	492 (14.0%)	483 (13.7%)	0.789
Bifurcation	856 (12.2%)	430 (12.2%)	426 (12.1%)	0.916
Total occlusion	438 (6.2%)	220 (6.2%)	218 (6.2%)	0.943
Thrombotic	745 (10.6%)	368 (10.4%)	377 (10.7%)	0.700
Total stent length, mm†	39.9±24.3	40.2±24.3	39.6±24.3	0.336
Minimum stent diameter, mm	2.8±0.5	2.8±0.5	2.9±0.5	0.171
Complex PCI‡	2,311 (32.8%)	1,152 (32.7%)	1,159 (33.0%)	0.756

CAD: coronary artery disease, LAD: left anterior descending, LCX: left circumflex, RCA: right coronary artery, PCI: percutaneous coronary intervention

†Assessed by operators

‡PCI involving ≥3 vessels, ≥3 lesions, left main coronary artery, surgical bypass graft, chronic total occlusion, or total stent length >60 mm, bifurcation with 2 stents implanted or use of atherectomy device