Ticagrelor with or without Aspirin in High-Risk Patients with Diabetes Mellitus undergoing Percutaneous Coronary Intervention

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Brief Title: Diabetes Mellitus Substudy of the TWILIGHT Trial

Disclosures: Dr. Angiolillo reports receiving grant support, consulting fees, and honoraria from Amgen, Aralez, Bayer, Biosensors, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Daiichi Sankyo, Eli Lilly, Janssen, Merck, and Sanofi, consulting fees and honoraria from Haemonetics, PhaseBio, PLx Pharma, Pfizer, and the Medicines Company, grant support and fees for review activities from CeloNova, fees for review activities from St. Jude Medical, and grant support from CSL Behring, Eisai, Gilead, Idorsia Pharmaceuticals, Matsutani Chemical Industry, Novartis, Osprey Medical, and RenalGuard Solutions; Dr. Baber reports receiving honoraria from AstraZeneca, Boston Scientific and Amgen Inc.; Dr. Dangas reports receiving consulting fees and advisory board fees from AstraZeneca, consulting fees from Biosensors, and previously holding stock in Medtronic; Dr. Cohen reports receiving grant support, paid to his institution, and consulting fees from AstraZeneca, Medtronic, Abbott Vascular, and Boston Scientific; and grant support, paid to his institution from AstraZeneca; Dr. Mehta reports receiving grant support from and serving on an executive committee and as site investigator for AstraZeneca; Dr. Gibson reports receiving grant support and consulting fees from Angel Medical, Bayer, CSL Behring, Janssen Pharmaceuticals, Johnson & Johnson, and Portola Pharmaceuticals, consulting fees from the Medicines Company, AstraZeneca, Eli Lilly, Gilead Sciences, Novo Nordisk, WebMD, UpToDate Cardiovascular Medicine, Amarin Pharma, Amgen, Boehringer Ingelheim, Chiesi, Merck, PharmaMar, Sanofi, Somahlution, Verreseon Corporation, Boston Scientific, Impact Bio, MedImmume, Medtelligence, MicroPort, PERT Consortium, and GE Healthcare, holding equity in nference, serving as chief executive officer of Baim Institute, and receiving grant support, paid to Baim Institute, from Bristol-Myers Squibb; Dr. Huber reports receiving lecture fees from AstraZeneca and Bayer; Dr. Weisz reports receiving grant support and advisory board fees from Corindus, advisory board fees from and holding equity in Filterlex, serving on advisory board for and holding options in Trisol, serving on advisory board for and holding options in Magenta, serving on advisory board for and holding options in Intratech, and receiving institutional grant support from Abbott, Ancora, CSI, and ShockWave; Dr. Kunadian reports receiving consulting fees/honoraria from Bayer, Amgen, Daiichi Sankyo, Abbott Vascular, AstraZeneca and major institutional research grant from AstraZeneca; Dr. Oldroyd reports receiving grant support and lecture fees from AstraZeneca and lecture fees from Biosensors, Abbott Vascular and GE; Dr. Escaned reports receiving consulting fees and lecture fees from Abbott, Philips, Boston Scientific, and Medtronic, and lecture fees from Abiomed, Terumo, and Biosensors; Dr. Sharma reports relationships with Abbott Vascular (speaker bureau), Boston Scientific (speaker bureau and advisory board), and Cardiovascular Systems, Inc (speaker bureau); Dr. Mehran reports receiving consulting fees from Abbott Vascular, Boston Scientific, Medscape/WebMD, Siemens Medical Solutions, Phillips/Volcano/Spectranetics, Roviant Sciences, Sanofi Italy, Bracco Group, Janssen, and AstraZeneca, grant support, paid to her institution, from Bayer, CSL Behring, DSI, Medtronic, Novartis Pharmaceuticals, OrbusNeich, Osprey Medical, PLC/RenalGuard, and Abbott Vascular, grant support and advisory board fees, paid to her institution, from BMS, fees for serving on a data and safety monitoring board from Watermark Research Funding, advisory fees and lecture fees from Medintelligence (Janssen), and lecture fees from Bayer. All other authors report no conflicts of interest.
Source of Funding: Investigator-initiated grant from AstraZeneca

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ABSTRACT

Background: $P2Y_{12}$ inhibitor monotherapy with ticagrelor after a brief period of dual antiplatelet therapy can reduce bleeding without increasing ischemic harm after percutaneous coronary intervention (PCI). The impact of this approach among patients with diabetes mellitus (DM) remains unknown.

Objectives: To examine the effect of ticagrelor monotherapy versus ticagrelor plus aspirin among patients with DM undergoing PCI.

Methods: This was a pre-specified analysis of the DM cohort in the TWILIGHT trial. After 3 months of ticagrelor plus aspirin, patients were maintained on ticagrelor and randomized to aspirin or placebo for 1 year. The primary endpoint was Bleeding Academic Research Consortium (BARC) 2, 3 or 5 bleeding. The composite ischemic endpoint was all-cause death, myocardial infarction, or stroke.

Results: Patients with DM comprised 37% (n=2620) of the randomized cohort and were characterized by more frequent comorbidities and a higher prevalence of multivessel disease. The incidence of BARC 2, 3 or 5 bleeding was 4.5% and 6.7% among patients with DM randomized to ticagrelor plus placebo versus ticagrelor plus aspirin (HR 0.65; 95% CI 0.47-0.91; p=0.012). Ticagrelor monotherapy was not associated with an increase in ischemic events compared with ticagrelor plus aspirin (4.6% vs 5.9%; HR 0.77; 95% CI 0.55 to 1.09; p=0.14). In the overall trial population, there was no significant interaction between DM status and treatment group for the primary bleeding or ischemic endpoints.

Conclusions: Compared with ticagrelor plus aspirin, the effect of ticagrelor monotherapy in reducing the risk of clinically relevant bleeding without any increase in ischemic events was consistent among patients with or without DM undergoing PCI.

Key words: Diabetes mellitus; ticagrelor monotherapy; aspirin; bleeding; thrombosis

ClinicalTrials.gov number: **NCT02270242**

CONDENSED ABSRACT

In this pre-specified analysis of the TWILIGHT trial, the clinical impact of $P2Y_{12}$ inhibitor monotherapy with ticagrelor after a brief period of dual antiplatelet therapy in patients with diabetes mellitus (DM) undergoing percutaneous coronary intervention (PCI) was analyzed. Patients with DM comprised 37% (n=2620) of the randomized trial cohort and were characterized by more frequent comorbid risk factors and a higher prevalence of multivessel disease. Compared with ticagrelor plus aspirin, the effect of ticagrelor monotherapy in reducing the risk of clinically relevant bleeding without any increase in ischemic events was consistent among patients with or without DM undergoing PCI.

LIST OF ABBREVIATIONS

ACS: Acute coronary syndrome
BARC: Bleeding Academic Research Consortium
DAPT: Dual antiplatelet therapy
DM: Diabetes mellitus
GUSTO: Global Use of Strategies to Open Occluded Arteries
ISTH: International Society of Thrombosis or Hemostasis
MI: Myocardial infarction
PCI: Percutaneous coronary intervention

STEMI: ST-segment elevation myocardial infarction
TIMI: Thrombolysis in Myocardial Infarction

INTRODUCTION

Dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor is the standard of care for the prevention of thrombotic complications in patients undergoing percutaneous coronary interventions (PCI) [1]. However, such ischemic benefit occurs at the expense of enhanced bleeding, the risk of which increases in a graded fashion with prolonged exposure to DAPT [1, 2]. In light of the adverse prognosis associated with bleeding, there has been much attention toward identifying antithrombotic regimens that can reduce the risk of bleeding while maintaining efficacy post-PCI [3, 4]. Among these, maintaining $P2Y_{12}$ inhibitor monotherapy, after a brief period of DAPT, has emerged as a promising bleeding reduction strategy in a number of investigations [5]. Recently, the Ticagrelor With Aspirin or Alone in High-Risk Patients after Coronary Intervention (TWILIGHT) trial showed that among high-risk PCI patients, after 3 months of DAPT, $P2Y_{12}$ inhibitor monotherapy with ticagrelor reduced bleeding without increasing ischemic harm [6]. As such, there is considerable interest in understanding the benefit of this antithrombotic strategy in patient cohorts who are at particularly high-risk for adverse events.

Patients with diabetes mellitus (DM) have been associated with an increased risk for both ischemic and bleeding complications post-PCI [7, 8]. A number of factors which commonly affect patients with DM contribute to these observations, including the complexity of coronary interventions, endothelial dysfunction, concomitant comorbidities, and dysregulation of hemostatic and thrombotic processes [7, 8]. Importantly, the prevalence of DM (mostly type 2) in the past decade has increased by 30% globally, an observation also reflected in PCI trials wherein DM is a more frequently encountered risk factor, and is projected to markedly increase in the upcoming decades [9]. These observations highlight the importance of defining optimal

post-PCI pharmacotherapy in patients with DM. Accordingly, we conducted a pre-specified analysis in the TWILIGHT trial in order to examine the effect of ticagrelor monotherapy versus ticagrelor plus aspirin among patients with DM.

METHODS

Trial Design and Oversight

TWILIGHT was a randomized, placebo-controlled trial conducted at 187 sites in 11 countries. The trial rationale, design and principal results have been reported previously [5, 10]. The Icahn School of Medicine at Mount Sinai designed and sponsored the trial, which was supported by an investigator-initiated grant from AstraZeneca. AstraZeneca provided financial support and 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. An independent data safety monitoring board provided external oversight to ensure safety of all trial participants.

Trial Population

Patients undergoing successful PCI with at least 1 drug-eluting stent whom the treating clinician intended to discharge on ticagrelor plus aspirin were eligible to participate. Trial inclusion required the presence of at least 1 clinical and 1 angiographic feature associated with a high risk of ischemic or bleeding events [5, 10]. Clinical criteria included age ≥65 years, female sex, troponin positive acute coronary syndrome (ACS), atherosclerotic vascular disease (prior myocardial infarction, coronary revascularization or peripheral arterial disease), DM requiring medication, and chronic kidney disease (estimated glomerular filtration rate <60 ml/min/1.73m^2

or creatinine clearance <60 cc/min). Angiographic criteria included multi-vessel coronary artery disease, total stent length >30 mm, thrombotic target lesion, bifurcation lesion requiring 2 stents, obstructive left main or proximal left anterior descending lesion, and calcified target lesion requiring debulking devices. Key exclusion criteria included presentation with an ST elevation myocardial infarction (STEMI), cardiogenic shock, prior stroke, need for oral anticoagulation, or contraindication to aspirin or ticagrelor. The presence of DM was based upon physician diagnosis as serum glucose and hemoglobin A1c were not routinely collected as part of the TWILIGHT study.

Trial Regimen

All enrolled patients received open-label ticagrelor (90 mg twice daily) and enteric-coated aspirin (81-100 mg daily) after the index PCI. After 3 months, patients without major bleeding or ischemic events were randomized 1:1 in a double-blind fashion to aspirin or matching placebo for an additional 12 months with continuation of open-label ticagrelor. Patients sustaining Bleeding Academic Research Consortium (BARC) type 3b or higher bleeds or ischemic events (stroke, myocardial infarction, or coronary revascularization) between enrollment and 3 months were not eligible for randomization. Non-adherence to ticagrelor or aspirin also rendered patients ineligible for randomization. Randomization was performed using a secure web-based system; an independent statistician not involved with the trial generated the allocation sequence, which was stratified by site with randomly varying block sizes of 4, 6 or 8. Follow-up occurred 1 month after randomization via telephone and in-person at 6 and 12 months after randomization. After 12 months of protocol-mandated therapy, patients were switched to a standard-of-care antiplatelet regimen at the discretion of their treating physician followed by final telephone follow-up 3 months later.

Outcomes

The primary endpoint was the composite of BARC type 2, 3 or 5 bleeding between randomization and 1 year; the key secondary endpoint was the composite of all-cause death, myocardial infarction (MI), or stroke [5, 10]. Secondary bleeding endpoints included BARC types 3 or 5 bleeding; Thrombolysis in Myocardial Infarction (TIMI) major or minor bleeding; Global Use of Strategies to Open Occluded Arteries (GUSTO) moderate, severe, or life-threatening bleeding; or major bleeding as defined by the International Society of Thrombosis or Hemostasis (ISTH) [11-14]. Other secondary endpoints included cardiovascular death, non-fatal MI, ischemic stroke and definite or probable stent thrombosis. MI was defined according to the third universal definition, and revascularization and stent thrombosis were classified according to the Academic Research Consortium [15, 16]. All clinical events were adjudicated by an independent committee, blinded to treatment assignment.

Statistical Analyses

Clinical and procedural characteristics are summarized by randomized group using means (standard deviation) and frequencies for continuous and categorical variables, respectively. The cumulative incidence of both primary and secondary endpoints was estimated using the Kaplan-Meier method. Patients without a primary endpoint between randomization and 1 year were censored at the time of death, last known contact, or 365 days, whichever came first. Hazard ratios and 95% confidence intervals (CI) were generated using Cox proportional hazards models. Analyses of bleeding were performed using the intention-to-treat cohort, while ischemic outcomes were analyzed using the per protocol cohort [5, 10]. Treatment effects were estimated according to presence of DM with formal interaction testing to assess for effect modification. Exploratory subgroup analyses were performed to examine the associations between treatment

group and clinical presentation (acute coronary syndrome vs stable coronary artery disease), and type of glucose lowering treatment (insulin vs non-insulin) with respect to both the primary bleeding and secondary ischemic outcome. Moreover, an exploratory intention-to-treat analysis of net adverse clinical events including BARC 3 or 5 bleeding, death, MI, or stroke was performed. All analyses were performed using Stata version 16.0 (College Station, Texas).

RESULTS

Patient Characteristics

As shown in **Supplemental Figure 1**, among the 7119 patients randomized in the main TWILIGHT trial, 36.8% (n=2620) presented with DM. Of these, 1319 were randomized to ticagrelor plus placebo and 1301 to ticagrelor plus aspirin. Insulin-treated DM status represented 27.1% (n=709) of the DM cohort; 72.9% (n=1911) were non-insulin treated DM, most of whom were on an oral glucose lowering agent with or without non-insulin injectable therapy (n=1718) while the rest were diet-controlled (n=129); in 2.4% (n=64) of patients treatment was unknown. Clinical follow-up was complete in 98.4% of subjects. Patients with DM were more likely to be from North America and of non-white race, and had more risk factors and multivessel coronary artery disease compared with non-DM patients (**Supplemental Table 1**). **Table 1** shows the demographic and clinical characteristics of the DM cohort, which were well balanced between treatment arms, except for current smoking status. Mean age was 64.8 years, 23.6% were female, and 61.6% presented with an ACS. Procedural parameters were also well balanced across the two treatment arms (**Table 2**). Radial arterial access was used in 69.5% of procedures, 68.6% had multivessel disease and mean total stent length was approximately 39.5mm in both groups. Rates of permanent ticagrelor discontinuation at one year were 12.9% and 15.3% among those randomized to ticagrelor plus placebo versus ticagrelor plus aspirin, respectively (p=0.08).

Analogous results for blinded study drug discontinuation were 18.5% and 20.1%, respectively (p=0.33).

Bleeding events

As shown in **Table 3** and **Figure 1**, in the cohort of patients with DM, the primary outcome of BARC 2, 3 or 5 bleeding occurred in 58 patients (4.5%) randomized to ticagrelor plus placebo versus 86 patients (6.7%) randomized to ticagrelor plus aspirin (HR, 0.65; 95% CI, 0.47-0.91; p=0.01). One-year BARC 3 or 5 bleeding rates were 1.1% and 3.1%, respectively (HR 0.34; 95% CI 0.19 to 0.63; p=0.001). This treatment effect was consistent across different bleeding scales, including TIMI, GUSTO and ISTH (**Table 3**). In the overall trial population, interaction testing between DM status and treatment group for bleeding endpoints was non-significant with the exception of GUSTO moderate-severe bleeding where a nominal p-value of 0.03 was obtained (**Table 3**).

Ischemic Events

As shown in **Table 4** and **Figure 2**, the composite outcome of all-cause death, MI, or stroke occurred in 59 patients (4.6%) randomized to ticagrelor plus placebo versus 75 patients (5.9%) randomized to ticagrelor plus aspirin (HR 0.77; 95% CI, 0.55 to 1.09; p=0.14). Respective rates of all-cause death (1.3% vs. 2.0%), MI (3.1% vs. 4.1%), ischemic stroke (0.6% vs 0.4%) and definite/probable stent thrombosis (0.5% vs. 0.7%) were similar between treatment groups (all p-values >0.1) (**Table 4**). In the overall trial population, there was no significant interaction between DM status and treatment group with respect to ischemic endpoints (**Table 4**).

Additional Analyses

The effect of ticagrelor monotherapy on the primary and key secondary outcomes was consistent among patients presenting with an ACS or stable CAD (**Supplemental Table 2**).

Similarly, outcomes were also consistent irrespective of DM management (insulin vs non-insulin) (**Supplemental Table 3**). Finally, an analysis of net adverse clinical events (composite of BARC 3 or 5 bleeding, death, MI, or stroke) significantly favored a ticagrelor monotherapy strategy (5.4% vs 8.7%; HR 0.61; 95% CI, 0.45 to 0.82; p=0.001; interaction p-value 0.004) (**Figure 3; Supplemental Table 4**).

DISCUSSION

The key findings from our pre-specified analysis assessing clinical outcomes in patients with DM (n=2620) randomized in the TWILIGHT trial, following 3 months of adherence to DAPT post-PCI without experiencing major bleeding or ischemic events, include: (1) ticagrelor monotherapy, as compared with ticagrelor plus aspirin, reduced the incidence of clinically relevant BARC 2, 3 or 5 bleeding as well as more severe BARC 3 or 5 bleeding over one year of follow-up by 35% and 66%, respectively; (2) ticagrelor monotherapy was associated with a non-significant 23% reduction in one-year rate of all-cause death, MI, or stroke; and (3) the treatment effects with respect to ischemic and bleeding outcomes were consistent among DM patients irrespective of treatment (insulin vs non-insulin) and clinical presentation (ACS vs stable CAD)(**Central Illustration**). Overall, these results demonstrate that the clinical benefits and safety of ticagrelor monotherapy observed in the main TWILIGHT trial cohort are preserved among patients with DM. These findings are noteworthy in light of the high-risk profile for both ischemic and bleeding complications of this ever-growing cohort of patients [7, 8]. In particular, after 3 months of DAPT, the number of DM patients needed to treat with ticagrelor monotherapy compared with ticagrelor plus aspirin to prevent a net adverse clinical event at one-year was 30.

The impact of $P2Y_{12}$ inhibitor monotherapy after a minimal duration (1-3 months) of DAPT on post-PCI outcomes has been investigated in prior trials [17-19]. However, these

studies had open-label designs and were characterized by relatively low-risk or all-comer cohorts. In contrast, TWILIGHT required participants to be enriched with both clinical and angiographic features associated with an increased risk for ischemic or bleeding complications post-PCI [5, 10]. DM was a key clinical inclusion criterion for the trial [5, 10]. In light of its frequent association with high-risk anatomic features, the prevalence of DM in our trial was high (36.8% of the study population). The prevalence of DM was similarly high (37.5% and 39%) in prior randomized studies of $P2Y_{12}$ monotherapy conducted in Asia [18-19], while this was lower (25.3%) in a study mostly represented by Western Europeans [17]. Indeed, significant recruitment from North America in TWILIGHT, where the prevalence of DM is high, allowed for enrichment of the study population with this high-risk cohort of interest. To date, only one prior analysis assessing the impact of $P2Y_{12}$ inhibitor monotherapy in patients with DM has been reported but which failed to show any differences on clinical outcomes (ischemic or bleeding) [20]. However, these findings need to be interpreted in the context of a trial which did not meet its pre-defined key safety and efficacy endpoints [17].

Withdrawal of aspirin, after 3 months of DAPT, and maintain patients on ticagrelor monotherapy did not result in an increase in ischemic events in the present analysis, an important finding given the well-established associations between DM and systemic atherothrombosis. On the contrary, most ischemic endpoints, including all-cause death, cardiovascular death, MI, stroke and definite/probable stent thrombosis, were numerically lower with ticagrelor monotherapy compared with ticagrelor plus aspirin. These observations provide reassurance regarding the safety of the TWILIGHT regimen (ticagrelor monotherapy after a 3 month period of DAPT) even in a population such as DM notoriously known for being at high risk for thrombotic complications [7, 8].

Prior studies comparing $P2Y_{12}$ inhibitors in high-risk patients undergoing PCI have consistently shown the newer generation agents (i.e., prasugrel and ticagrelor) to be associated with better clinical outcomes compared with clopidogrel [21]. These findings were corroborated in pre-specified analysis conducted in patients with DM, in whom the ischemic benefit appeared to be enhanced [22, 23]. These findings have been attributed not only to the higher baseline risk of DM patients allowing for more potent $P2Y_{12}$ inhibitors to show a greater magnitude of treatment effect, but also due to the greater prevalence of impaired response to clopidogrel among patients with DM [24, 25]. A number of mechanisms may contribute to impaired clopidogrel response in patients with DM including impaired drug metabolism, leading to reduced generation of clopidogrel's active metabolite [26]. Of note, in addition to an increase in markers sensitive to cyclooxygenase-1 (COX-1) blockade, aspirin withdrawal has also shown to be associated with an increase in $P2Y_{12}$ reactivity in clopidogrel-treated patients with DM [27]. These considerations would therefore caution against a strategy of aspirin withdrawal and maintaining clopidogrel monotherapy as a bleeding reduction strategy in patients with DM.

Despite the ischemic benefits of the more potent $P2Y_{12}$ inhibitors compared with clopidogrel in patients undergoing PCI, these occurred at the expense of increased bleeding, including among patients with DM [21-23]. In fact, these trials were conducted on a background of aspirin therapy which could have contributed to the enhanced bleeding associated with prolonged concomitant treatment with a potent $P2Y_{12}$ inhibitor [4]. These clinical findings may be explained by a number of pharmacodynamic investigations specifically addressing the role of aspirin in the presence of alternative antithrombotic treatment regimens, including potent $P2Y_{12}$ blockade [28-32]. In particular, in vitro investigations conducted in platelets from healthy volunteers treated with potent $P2Y_{12}$ inhibitors showed that aspirin provides limited additional

platelet inhibition [28, 29]. Experimental studies conducted in animals suggest a limited effect of aspirin in reducing thrombus formation on a background of $P2Y_{12}$ blockade [30]. Most recently, experimental studies conducted in humans, including a pharmacodynamic investigation from the TWILIGHT trial, showed that while aspirin withdrawal is associated with an increase in markers sensitive to COX-1 blockade, this did not affect markers of $P2Y_{12}$ signaling or ex vivo platelet-dependent thrombus formation [31, 32]. Collectively, these observations from both in vitro and ex vivo investigations suggest that synergism between the COX-1 and $P2Y_{12}$ pathways may be less relevant in the presence of more potent $P2Y_{12}$ inhibition [27-32].

Patients with DM have a peculiar platelet biology that may impact pharmacologic response to antiplatelet agents [7, 8]. In fact, platelets from patients with DM are characterized by high turnover rates which can contribute to inadequate levels of sustained platelet inhibition with once daily aspirin regimens, potentially limiting its ischemic benefits [33]. These observations have suggested that antiplatelet agents with twice-daily administration may be more desirable in DM patients and may explain the enhanced ischemic benefits of ticagrelor in patients with DM with history of MI or prior PCI, from this analysis and others [23, 34-36]. Moreover, DM patients are characterized by heterogeneity in the degree of absorption of aspirin, leading to variability in its antiplatelet effects, and they may also be more vulnerable to gastrointestinal bleeding induced by aspirin due to the presence of vascular disease impairing mucosal integrity [37, 38]. Importantly, bleeding post-PCI is a marker of adverse prognosis, including increasing the risk of ischemic events [3, 4]. Collectively, these observations provide a potential mechanistic explanation for the clinical findings in the cohort of DM patients in the TWILIGHT trial in which we observed that discontinuation of aspirin and maintaining potent $P2Y_{12}$ blockade

with ticagrelor significantly reduced clinically relevant bleeding without any offsetting increase in ischemic events.

Study limitations

Although our analysis was pre-specified, randomization was not stratified by DM status and we did not account for multiplicity thereby increasing the chance for a type 1 error. Moreover, while nominal p-values of 0.05 and 0.03 were obtained for the primary ischemic endpoint and the secondary endpoint of GUSTO moderate to severe bleeding, respectively, these results should be interpreted with caution in the context of an underpowered subgroup analysis. In addition, our analysis for net adverse clinical events was not pre-specified and exploratory in nature. Accordingly, our results should be considered hypothesis-generating rather than conclusive inference and warrant dedicated, prospective confirmation. Moreover, we did not collect hemoglobin A1c levels or have other measures of DM severity or its medical control to better characterize the DM subgroup. Our findings may not generalize to patients treated with other oral $P2Y_{12}$ inhibitors, particularly clopidogrel. The safety and efficacy of $P2Y_{12}$ inhibitor monotherapy in DM patients with STEMI was not addressed by the present study, since these patients were excluded from participation in TWILIGHT. Ultimately, limitations of the parent trial, including the lack of power to detect differences in the risk of important yet rare clinical events (e.g., stent thrombosis and stroke), applicability of the findings not to all enrolled participants but to those patients who were able to adhere to 3 months of DAPT without experiencing any bleeding or ischemic event, which might have altered the risk-benefit calculation for considering ticagrelor monotherapy, also apply to the current analysis.

CONCLUSIONS

Compared with ticagrelor plus aspirin, the effect of ticagrelor monotherapy in reducing the risk of clinically relevant bleeding without any increase in ischemic events was consistent among patients with or without DM undergoing PCI. These findings support such a bleeding avoidance strategy, which can be implemented without any signals for harm even in high-risk patients such as those with DM.

CLINICAL PERSPECTIVES

Competency in Patient Care: In patients undergoing PCI, prolonging the duration of DAPT with aspirin and a $P2Y_{12}$ inhibitor with ticagrelor enhances the risk of bleeding complications. The risk of bleeding can be reduced by a strategy of ticagrelor monotherapy, following 3 months of DAPT, without incurring any increased risk of ischemic events, including among patients with DM.

Translational Outlook: Further prospective studies selectively conducted in patients with DM undergoing PCI are needed to confirm the benefits of a ticagrelor monotherapy strategy after a brief period of DAPT and to expand the generalizability of this strategy to patients with STEMI since these patients were excluded from participation in TWILIGHT.

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FIGURE LEGENDS

Figure 1. Bleeding in patients with DM at one year after randomization. Kaplan–Meier estimates of the incidence of BARC type 2, 3 or 5 bleeding 1 year after randomization (intention-to-treat population). The HR shown is for ticagrelor plus placebo versus ticagrelor plus aspirin. BARC = Bleeding Academic Research Consortium; CI = confidence interval; DM = diabetes mellitus; HR = hazard ratio.

Figure 2. Ischemic events in patients with DM at one year after randomization. Kaplan–Meier estimates of the incidence of death from any cause, nonfatal myocardial infarction or nonfatal stroke 1 year after randomization (per-protocol population). The per-protocol population included patients who underwent randomization and had no major deviations from the protocol. The HR shown is for ticagrelor plus placebo versus ticagrelor plus aspirin. CI = confidence interval; DM = diabetes mellitus; HR = hazard ratio; MI = myocardial infarction.

Figure 3. Net adverse clinical events in patients with DM at one year after randomization. Kaplan–Meier estimates of the incidence of net adverse clinical events (composite of BARC 3 or 5 bleeding, death, MI or stroke) 1 year after randomization (intention-to-treat population). CI = confidence interval; DM = diabetes mellitus; HR = hazard ratio; MI = myocardial infarction; NACE = net adverse clinical events

Central illustration. Ticagrelor with or without Aspirin after PCI in DM. Following 3 months of adherence to DAPT post-PCI in the absence of major bleeding or ischemic events, this pre-specified analysis assessing clinical outcomes in patients with DM (n=2620) randomized in the TWILIGHT trial showed that ticagrelor monotherapy, as compared with ticagrelor plus aspirin, reduced the incidence of clinically relevant BARC 2, 3 or 5 bleeding as well as more severe BARC 3 or 5 bleeding over one year of follow-up by 35% and 66%, respectively.

Ticagrelor monotherapy was associated with a non-significant 23% reduction in one-year rate of all-cause death, MI or stroke. The number of DM patients needed to treat with ticagrelor monotherapy compared with ticagrelor plus aspirin to prevent a net adverse clinical event (composite of BARC 3 or 5 bleeding, death, MI or stroke) at one year was 30. BARC = Bleeding Academic Research Consortium; CI = confidence interval; DAPT = dual antiplatelet therapy; DM = diabetes mellitus; HR = hazard ratio; MI: myocardial infarction; NNT = number needed to treat; PCI = percutaneous coronary intervention

Table 1. Baseline clinical characteristics

Clinical Parameters	Overall DM N = 2620	Tica + Placebo N = 1319 (50.3%)	Tica + Aspirin N = 1301 (49.7%)	p-value
Age, years	64.8 ± 10.1	64.8 ± 9.9	64.8 ± 10.2	0.95
Female sex	618 (23.6%)	308 (23.4%)	310 (23.8%)	0.77
Nonwhite race	972 (37.1%)	493 (37.4%)	479 (36.8%)	0.77
BMI, kg/m^2	29.8 ± 6.0	29.8 ± 5.9	29.8 ± 6.0	0.79
Enrolling Region				0.27
North America	1186 (45.3%)	613 (46.5%)	573 (44.0%)	
Europe	773 (29.5%)	371 (28.1%)	402 (30.9%)	
Asia	661 (25.2%)	335 (25.4%)	326 (25.1%)	
Glucose-lowering treatment				0.054
Insulin	709 (27.1%)	335 (25.4%)	374 (28.8%)	
Non-insulin	1911 (72.9%)	984 (74.6%)	927 (71.2%)	
Chronic kidney disease	534 (21.1%)	256 (20.3%)	278 (22.0%)	0.28
Anemia	645 (25.6%)	323 (25.6%)	322 (25.6%)	1.00
Current smoker	474 (18.1%)	219 (16.6%)	255 (19.6%)	0.045
Hypercholesterolemia	1745 (66.6%)	875 (66.3%)	870 (66.9%)	0.77
Hypertension	2136 (81.5%)	1067 (80.9%)	1069 (82.2%)	0.40
Peripheral arterial disease	221 (8.4%)	117 (8.9%)	104 (8.0%)	0.42
Previous MI	767 (29.3%)	385 (29.2%)	382 (29.4%)	0.92
Previous PCI	1192 (45.5%)	595 (45.1%)	597 (45.9%)	0.69
Previous CABG	330 (12.6%)	179 (13.6%)	151 (11.6%)	0.97

Multivessel CAD	1798 (68.6%)	915 (69.4%)	883 (67.9%)	0.41
Previous major bleed	24 (0.9%)	12 (0.9%)	12 (0.9%)	0.97
Indication for PCI				0.84
Stable CAD	1006 (38.4%)	509 (38.6%)	497 (38.2%)	
ACS	1614 (61.6%)	810 (61.4%)	804 (61.8%)	

DM = diabetes mellitus; Tica = ticagrelor; BMI = body mass index; MI = myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft; CAD = coronary artery disease; ACS = acute coronary syndrome

Table 2. Baseline procedural characteristics

Procedural Parameters	Overall DM N = 2620	Tica + Placebo N = 1319 (50.3%)	Tica + Aspirin N = 1301 (49.7%)	p-value
Radial artery access	1820 (69.5%)	920 (69.8%)	900 (69.2%)	0.75
Multivessel CAD	1798 (68.6%)	915 (69.4%)	883 (67.9%)	0.41
Target vessel				
Left Main	123 (4.7%)	54 (4.1%)	69 (5.3%)	0.14
LAD	1454 (55.5%)	730 (55.3%)	724 (55.7%)	0.88
LCX	889 (33.9%)	450 (34.1%)	439 (33.7%)	0.84
RCA	917 (35.0%)	460 (34.9%)	457 (35.1%)	0.89
Number of vessels treated	1.3 ± 0.5	1.3 ± 0.5	1.3 ± 0.5	0.45
Number of lesions treated	1.5 ± 0.8	1.5 ± 0.7	1.6 ± 0.8	0.28
Lesion Morphology[†]				
Moderate/severe calcification	409 (15.6%)	217 (16.5%)	192 (14.8%)	0.23
Bifurcation	305 (11.6%)	152 (11.5%)	153 (11.8%)	0.85
Total Occlusion	173 (6.6%)	79 (6.0%)	94 (7.2%)	0.20
Thrombotic	200 (7.6%)	100 (7.6%)	100 (7.7%)	0.92
Total stent length, mm[‡]	39.5 ± 24.0	39.4 ± 23.4	39.7 ± 24.6	0.71
Minimum stent diameter, mm	2.8 ± 0.5	2.8 ± 0.5	2.8 ± 0.5	0.86

DM = diabetes mellitus; Tica = ticagrelor; LAD = left anterior descending; LCX = left circumflex; RCA = right coronary artery

[†]Lesion morphology assessed by operators.

[‡]Stent length calculated by operator.

Table 3. Bleeding events in patients with and without DM at one year after randomization

Variable	DM patients (N = 2620)				Non-DM patients (N = 4499)				Interaction p-value
	Tica + Placebo (N = 1319)	Tica + Aspirin (N = 1301)	Hazard ratio (95% CI)	p-value	Tica + Placebo (N = 2236)	Tica + Aspirin (N = 2263)	Hazard ratio (95% CI)	p-value	
	no. of patients (%)				*no. of patients (%)*				
Bleeding outcomes*									
BARC 2, 3 or 5	58 (4.5%)	86 (6.7%)	0.65 (0.47 – 0.91)	0.01	83 (3.8%)	164 (7.3%)	0.50 (0.39 – 0.66)	<0.001	0.23
BARC 3 or 5	14 (1.1%)	40 (3.1%)	0.34 (0.19 – 0.63)	0.001	20 (0.9%)	29 (1.3%)	0.70 (0.39 – 1.23)	0.22	0.09
TIMI minor or major	58 (4.5%)	86 (6.7%)	0.65 (0.47 – 0.91)	0.01	83 (3.8%)	164 (7.3%)	0.50 (0.39 – 0.66)	<0.001	0.23
GUSTO moderate or severe	9 (0.7%)	30 (2.3%)	0.29 (0.14 – 0.62)	0.001	17 (0.8%)	19 (0.9%)	0.91 (0.47 – 1.74)	0.77	0.03
ISTH major	18 (1.4%)	40 (3.1%)	0.44 (0.25 – 0.77)	0.004	21 (1.0%)	32 (1.4%)	0.66 (0.38 – 1.15)	0.15	0.30

DM = diabetes mellitus; Tica = ticagrelor; CI = confidence interval; BARC = Bleeding Academic Research Consortium; TIMI = Thrombolysis in Myocardial Infarction; GUSTO = Global Utilization of Streptokinase and TPA for Occluded Arteries; ISTH = International Society on Thrombosis and Hemostasis

*Bleeding outcomes were performed in the intention-to-treat cohort

The percentages mentioned above represent K-M rates at 12 months after randomization.

Table 4. Ischemic events in patients with and without DM at one year after randomization

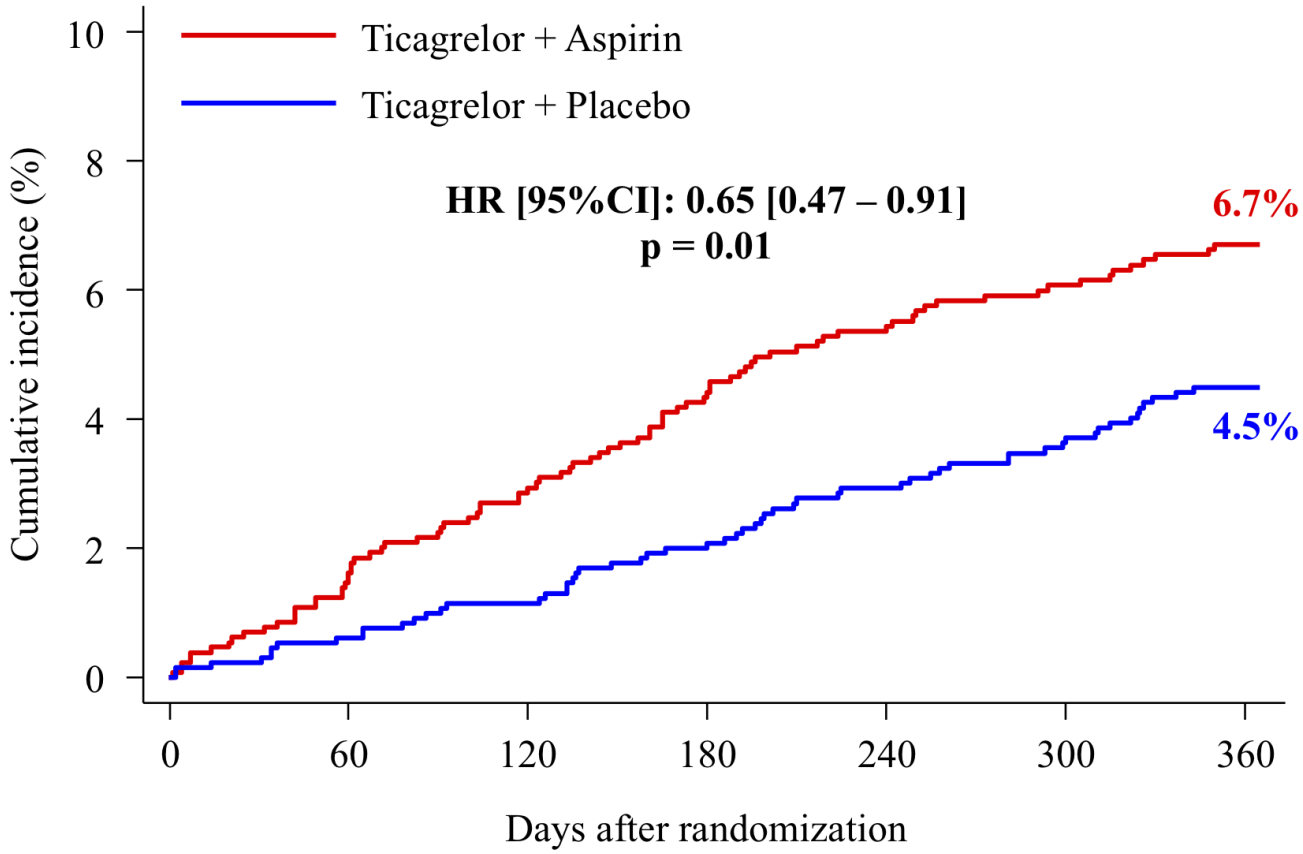
Variable	DM patients (N = 2593)				Non-DM patients (N = 4446)				Interaction p-value
	Tica + Placebo (N = 1308)	Tica + Aspirin (N = 1285)	Hazard ratio (95% CI)	p-value	Tica + Placebo (N = 2216)	Tica + Aspirin (N = 2230)	Hazard ratio (95% CI)	p-value	
	no. of patients (%)				*no. of patients (%)*				
Ischemic outcomes^									
Death, MI or stroke	59 (4.6%)	75 (5.9%)	0.77 (0.55 – 1.09)	0.14	76 (3.5%)	62 (2.8%)	1.24 (0.89 – 1.73)	0.21	0.05
Cardiovascular death, MI or ischemic stroke	57 (4.4%)	70 (5.5%)	0.80 (0.56 – 1.13)	0.21	69 (3.2%)	60 (2.7%)	1.16 (0.82 – 1.64)	0.39	0.14
All-cause death	17 (1.3%)	25 (2.0%)	0.67 (0.36 – 1.23)	0.20	17 (0.8%)	20 (0.9%)	0.85 (0.45 – 1.63)	0.64	0.59
Cardiovascular death	15 (1.2%)	19 (1.5%)	0.78 (0.39 – 1.53)	0.47	11 (0.5%)	18 (0.8%)	0.62 (0.29 – 1.30)	0.21	0.65
MI	40 (3.1%)	52 (4.1%)	0.75 (0.50 – 1.14)	0.18	55 (2.5%)	43 (2.0%)	1.29 (0.87 – 1.92)	0.21	0.07
Ischemic stroke	8 (0.6%)	5 (0.4%)	1.58 (0.52 – 4.82)	0.42	8 (0.4%)	3 (0.1%)	2.69 (0.71 – 10.1)	0.14	0.55
Stent thrombosis (definite/probable)	6 (0.5%)	9 (0.7%)	0.66 (0.23 – 1.84)	0.42	8 (0.4%)	10 (0.5%)	0.81 (0.32 – 2.04)	0.65	0.77

DM = diabetes mellitus; Tica = ticagrelor; CI = confidence interval; MI = myocardial infarction

^Ischemic outcomes were performed in the per-protocol cohort

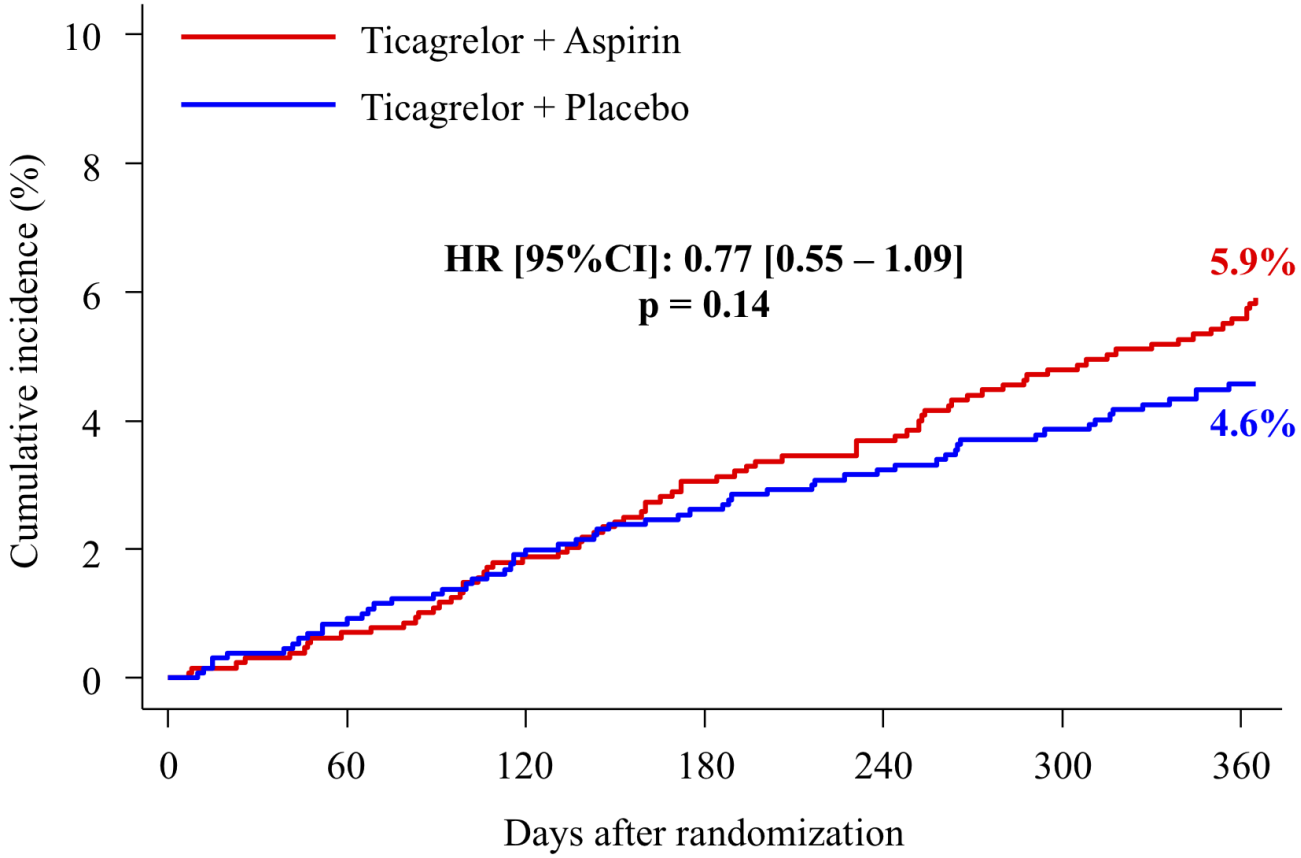
The percentages mentioned above represent K-M rates at 12 months after randomization.

BARC 2, 3 or 5 bleeding (DM cohort)

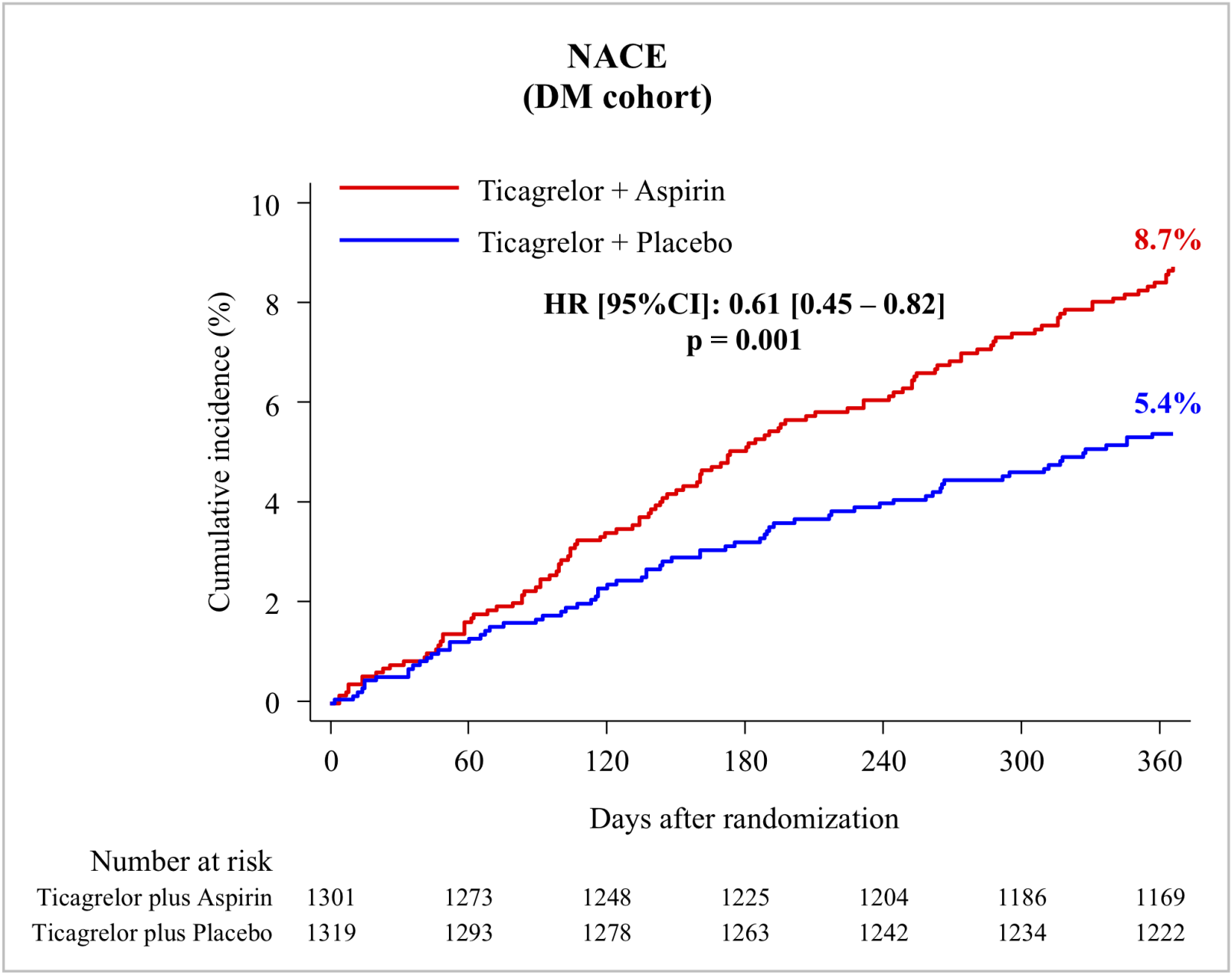


Number at risk							
Ticagrelor plus Aspirin	1301	1274	1250	1223	1200	1184	1169
Ticagrelor plus Placebo	1319	1297	1285	1270	1246	1233	1221

All-cause mortality, non-fatal MI or non-fatal stroke (DM cohort)



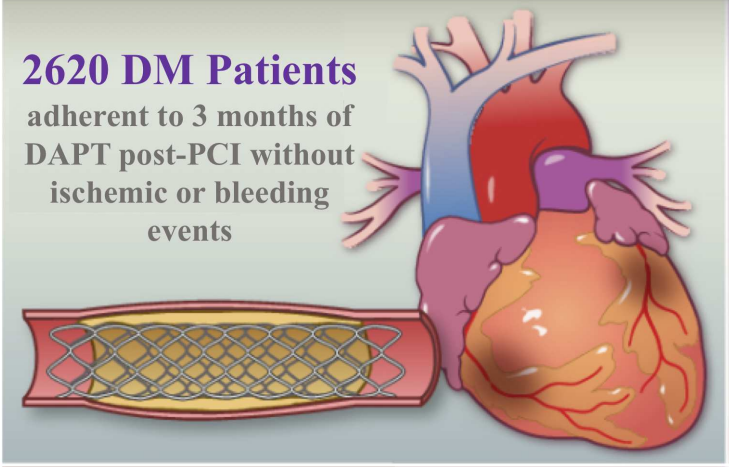
Number at risk							
Ticagrelor plus Aspirin	1285	1269	1252	1235	1219	1204	1190
Ticagrelor plus Placebo	1308	1288	1273	1261	1242	1234	1223


NACE
(DM cohort)
Ticagrelor + Aspirin
Ticagrelor + Placebo
8.7%
HR [95%CI]: 0.61 [0.45 – 0.82]
p = 0.001
5.4%
Cumulative incidence (%)
0
2
4
6
8
10
0
60
120
180
240
300
360
Days after randomization
Number at risk
Ticagrelor plus Aspirin 1301 1273 1248 1225 1204 1186 1169
Ticagrelor plus Placebo 1319 1293 1278 1263 1242 1234 1222

Ticagrelor with or without Aspirin after PCI in DM

Pre-defined cohort analysis from the multicenter, double-blind, randomized TWILIGHT trial

2620 DM Patients
adherent to 3 months of DAPT post-PCI without ischemic or bleeding events



	Ticagrelor (90 mg twice daily) + Placebo (N=1319)	Ticagrelor (90 mg twice daily) + Aspirin (81–100 mg daily) (N=1301)
BARC 2, 3 or 5 bleeding in 12 months	4.5%	6.7%
	HR 0.65; 95% CI 0.47-0.91; p=0.012	
BARC 3 or 5 bleeding in 12 months	1.1%	3.1%
	HR 0.34; 95% CI 0.19-0.63; p=0.001	

Ticagrelor monotherapy was not associated with an increase in ischemic events (all-cause death, MI or stroke) compared to ticagrelor plus aspirin (4.6% vs 5.9%; HR 0.77, 95% CI 0.55 to 1.09; p=0.14)

Net adverse clinical events (composite of BARC 3 or 5 bleeding, death, MI or stroke) favored ticagrelor monotherapy (5.4% vs 8.7%; HR 0.61, 95% CI 0.45 to 0.82; p=0.001) with a NNT of 30

Supplementary Table 1. Baseline clinical and procedural characteristics

Variables	**Randomized patients N = 7119**	**DM patients N = 2620 (37.0%)**	**Non-DM patients N = 4499 (63.0%)**	**p-value**
Clinical Parameters				
Age, years	65.1 ± 10.3	64.8 ± 10.1	65.4 ± 10.5	0.02
Female sex	1698 (23.9%)	618 (23.6%)	1080 (24.0%)	0.69
Nonwhite race	2196 (30.8%)	972 (37.1%)	1224 (27.2%)	<0.001
BMI, kg/m^2	28.6 ± 5.6	29.8 ± 6.0	27.9 ± 5.2	<0.001
Enrolling Region				<0.001
North America	2972 (41.7%)	1186 (45.3%)	1786 (39.7%)	
Europe	2509 (35.2%)	773 (29.5%)	1736 (38.6%)	
Asia	1638 (23.0%)	661 (25.2%)	977 (21.7%)	
Chronic kidney disease	1145 (16.1%)	534 (21.1%)	611 (13.6%)	<0.001
Anemia	1329 (18.7%)	645 (25.6%)	684 (15.2%)	<0.001
Current smoker	1548 (21.8%)	474 (18.1%)	1074 (23.9%)	<0.001
Hypercholesterolemia	4303 (60.4%)	1745 (66.6%)	2558 (56.9%)	<0.001
Hypertension	5154 (72.4%)	2136 (81.5%)	3018 (67.1%)	<0.001
Peripheral arterial disease	489 (6.9%)	221 (8.4%)	268 (6.0%)	<0.001
Previous MI	2040 (28.7%)	767 (29.3%)	1273 (28.3%)	0.38
Previous PCI	2998 (42.1%)	1192 (45.5%)	1806 (40.1%)	<0.001
Previous CABG	710 (10.0%)	330 (12.6%)	380 (8.4%)	<0.001
Previous major bleed	63 (0.9%)	24 (0.9%)	39 (0.9%)	0.83
Indication for PCI				0.12
Stable CAD	2,503 (35.2%)	1006 (38.4%)	1497 (33.3%)	

ACS	4614 (64.8%)	1614 (61.6%)	3000 (66.7%)	
Procedural Parameters				
Multivessel CAD	4466 (62.7%)	1798 (68.6%)	2668 (59.3%)	<0.001
Target vessel				
Left Main	353 (5.0%)	123 (4.7%)	230 (5.1%)	0.43
LAD	4003 (56.2%)	1454 (55.5%)	2549 (56.7%)	0.34
LCX	2297 (32.3%)	889 (33.9%)	1408 (31.3%)	0.02
RCA	2500 (35.1%)	917 (35.0%)	1583 (35.2%)	0.87
Lesion Morphology[†]				
Moderate to severe calcification	987 (13.9%)	409 (15.6%)	578 (12.8%)	0.001
Bifurcation	866 (12.2%)	305 (11.6%)	561 (12.5%)	0.30
Total Occlusion	446 (6.3%)	173 (6.6%)	273 (6.1%)	0.37
Thrombotic	749 (10.5%)	200 (7.6%)	549 (12.2%)	<0.001
Total stent length, mm[‡]	39.9 ± 24.3	39.5 ± 24.0	40.1 ± 24.4	0.37
Minimum stent diameter, mm	2.9 ± 0.5	2.8 ± 0.5	2.9 ± 0.5	<0.001

DM = diabetes mellitus; BMI = body mass index; MI = myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft; CAD = coronary artery disease; ACS = acute coronary syndrome; LAD = left anterior descending; LCX = left circumflex; RCA = right coronary artery

[†]Lesion morphology assessed by operators.

[‡]Stent length calculated by operator.

Supplementary Table 2. Clinical outcomes according to clinical presentation

Variable	ACS DM patients (N = 1614)				Stable CAD DM patients (N = 1006)				Interaction p-value
	Tica + Placebo (N = 810)	Tica + Aspirin (N = 804)	Hazard ratio (95% CI)	p-value	Tica + Placebo (N = 509)	Tica + Aspirin (N = 497)	Hazard ratio (95% CI)	p-value	
	no. of patients (%)				*no. of patients (%)*				
Bleeding outcomes*									
BARC 2, 3 or 5	31 (3.9%)	55 (7.0%)	0.55 (0.35 – 0.85)	0.007	27 (5.4%)	31 (6.3%)	0.84 (0.50 – 1.42)	0.52	0.21
BARC 3 or 5	6 (0.8%)	26 (3.3%)	0.23 (0.09 – 0.55)	0.001	8 (1.6%)	14 (2.8%)	0.56 (0.23 – 1.33)	0.19	0.16
TIMI minor or major	31 (3.9%)	55 (7.0%)	0.55 (0.35 – 0.85)	0.007	27 (5.4%)	31 (6.3%)	0.84 (0.50 – 1.42)	0.52	0.21
GUSTO moderate or severe	3 (0.4%)	20 (2.5%)	0.15 (0.04 – 0.50)	0.002	6 (1.2%)	10 (2.0%)	0.59 (0.21 – 1.61)	0.30	0.09
ISTH major	9 (1.1%)	26 (3.3%)	0.34 (0.16 – 0.73)	0.005	9 (1.8%)	14 (2.8%)	0.63 (0.27 – 1.45)	0.27	0.29
Ischemic outcomes^									
Death, MI or stroke	43 (5.4%)	53 (6.8%)	0.80 (0.54 – 1.20)	0.28	16 (3.2%)	22 (4.5%)	0.71 (0.37 – 1.34)	0.29	0.74
Cardiovascular death, MI or ischemic stroke	43 (5.4%)	49 (6.3%)	0.87 (0.58 – 1.31)	0.50	14 (2.8%)	21 (4.3%)	0.65 (0.33 – 1.27)	0.21	0.47
All-cause death	11 (1.4%)	20 (2.5%)	0.54 (0.26 – 1.13)	0.10	6 (1.2%)	5 (1.0%)	1.17 (0.36 – 3.84)	0.79	0.28
Cardiovascular death	11 (1.4%)	15 (1.9%)	0.72 (0.33 – 1.58)	0.42	4 (0.8%)	4 (0.8%)	0.98 (0.25 – 3.92)	0.98	0.71
MI	31 (3.9%)	36 (4.6%)	0.85 (0.53 – 1.37)	0.51	9 (1.8%)	16 (3.3%)	0.55 (0.24 – 1.23)	0.15	0.36
Ischemic stroke	6 (0.8%)	3 (0.4%)	1.97 (0.49 – 7.89)	0.34	2 (0.4%)	2 (0.4%)	0.98 (0.14 – 6.98)	0.99	0.57
Stent thrombosis (definite/probable)	4 (0.5%)	7 (0.9%)	0.56 (0.16 – 1.92)	0.36	2 (0.4%)	2 (0.4%)	0.98 (0.14 – 6.98)	0.99	0.64

ACS = acute coronary syndrome; CAD = coronary artery disease; DM = diabetes mellitus; Tica = ticagrelor; CI = confidence interval; BARC = Bleeding Academic Research Consortium; TIMI = Thrombolysis in Myocardial Infarction; GUSTO = Global Utilization of Streptokinase and TPA for Occluded Arteries; ISTH = International Society on Thrombosis and Hemostasis; MI = myocardial infarction

*Bleeding outcomes were performed in the intention-to-treat cohort; ^Ischemic outcomes were performed in the per-protocol cohort

The percentages mentioned above represent K-M rates at 12 months after randomization.

Supplementary Table 3. Clinical outcomes according to management of DM

Variable	Insulin dependent DM patients (N = 709)				Non-insulin dependent DM patients (N = 1911)				Interaction p-value
	Tica + Placebo (N = 335)	Tica + Aspirin (N = 374)	Hazard ratio (95% CI)	p-value	Tica + Placebo (N = 984)	Tica + Aspirin (N = 927)	Hazard ratio (95% CI)	p-value	
	no. of patients (%)				*no. of patients (%)*				
Bleeding outcomes*									
BARC 2, 3 or 5	16 (4.9%)	28 (7.6%)	0.62 (0.34 – 1.15)	0.13	42 (4.4%)	58 (6.3%)	0.67 (0.45 – 1.00)	0.051	0.84
BARC 3 or 5	6 (1.8%)	11 (3.0%)	0.61 (0.22 – 1.64)	0.33	8 (0.8%)	29 (3.2%)	0.26 (0.12 – 0.56)	0.001	0.18
TIMI minor or major	16 (4.9%)	28 (7.6%)	0.62 (0.34 – 1.15)	0.13	42 (4.4%)	58 (6.3%)	0.67 (0.45 – 1.00)	0.051	0.84
GUSTO moderate or severe	4 (1.2%)	8 (2.2%)	0.56 (0.17 – 1.84)	0.34	5 (0.5%)	22 (2.4%)	0.21 (0.08 – 0.56)	0.002	0.22
ISTH major	8 (2.4%)	11 (3.0%)	0.81 (0.33 – 2.01)	0.65	20 (1.0%)	29 (3.2%)	0.32 (0.16 – 0.66)	0.002	0.12
Ischemic outcomes^									
Death, MI or stroke	24 (7.3%)	29 (8.0%)	0.92 (0.53 – 1.58)	0.75	35 (3.6%)	46 (5.1%)	0.71 (0.46 – 1.11)	0.13	0.48
Cardiovascular death, MI or ischemic stroke	22 (6.8%)	28 (7.7%)	0.87 (0.50 – 1.52)	0.63	35 (3.6%)	42 (4.6%)	0.78 (0.50 – 1.23)	0.29	0.77
All-cause death	6 (1.8%)	9 (2.5%)	0.74 (0.26 – 2.08)	0.57	11 (1.1%)	16 (1.8%)	0.65 (0.30 – 1.39)	0.26	0.83
Cardiovascular death	4 (1.2%)	8 (2.2%)	0.56 (0.17 – 1.85)	0.34	11 (1.1%)	11 (1.2%)	0.94 (0.41 – 2.17)	0.89	0.48
MI	16 (4.9%)	21 (5.8%)	0.84 (0.44 – 1.62)	0.61	24 (2.5%)	31 (3.4%)	0.73 (0.43 – 1.24)	0.24	0.73
Ischemic stroke	4 (1.3%)	3 (0.8%)	1.48 (0.33 – 6.63)	0.61	4 (0.4%)	2 (0.2%)	1.88 (0.35 – 10.29)	0.46	0.84
Stent thrombosis (definite/probable)	0 (0.0%)	4 (1.1%)	-	-	6 (0.6%)	5 (0.6%)	1.13 (0.34 – 3.70)	0.84	-

DM = diabetes mellitus; Tica = ticagrelor; CI = confidence interval; BARC = Bleeding Academic Research Consortium; TIMI = Thrombolysis in Myocardial Infarction; GUSTO = Global Utilization of Streptokinase and TPA for Occluded Arteries; ISTH = International Society on Thrombosis and Hemostasis; MI = myocardial infarction
*Bleeding outcomes were performed in the intention-to-treat cohort; ^Ischemic outcomes were performed in the per-protocol cohort
The percentages mentioned above represent K-M rates at 12 months after randomization.

Supplementary Table 4. Net adverse clinical events in patients with and without DM at one year after randomization

Variable	DM patients (N = 2620)				Non-DM patients (N = 4499)				Interaction p-value
	Tica + Placebo (N = 1319)	Tica + Aspirin (N = 1301)	Hazard ratio (95% CI)	p-value	Tica + Placebo (N = 2236)	Tica + Aspirin (N = 2263)	Hazard ratio (95% CI)	p-value	
	no. of patients (%)				*no. of patients (%)*				
NACE*	70 (5.4%)	112 (8.7%)	0.61 (0.45 – 0.82)	0.001	93 (4.2%)	84 (3.7%)	1.13 (0.84 – 1.51)	0.43	0.004

DM = diabetes mellitus; Tica = ticagrelor; CI = confidence interval; NACE = net adverse clinical events
NACE is the composite of BARC 3 or 5 bleeding, death, MI or stroke.
*NACE was performed in the intention-to-treat cohort
The percentages mentioned above represent K-M rates at 12 months after randomization.

Supplementary Figure 1. Consort Diagram