Abbreviated or Standard Antiplatelet Therapy After PCI in Diabetic Patients at High Bleeding Risk

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Abbreviated or Standard Antiplatelet Therapy After Percutaneous Coronary Intervention In Patients with Diabetes and High Bleeding Risk: a prespecified analysis from the MASTER DAPT trial

Authors block

**A complete list of the investigators in the Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated Versus Standard DAPT Regimen Trial is provided in the Data Supplement.*

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NONSTANDARD ABBREVIATIONS AND ACRONYMS

MASTER-DAPT, Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated Versus Standard DAPT Regimen

PCI, percutaneous coronary intervention

APT, antiplatelet therapy

SAPT, single antiplatelet therapy

DAPT, dual antiplatelet therapy

OAC, oral anticoagulation

MACCE, major adverse cardiac and cerebral events

NACE, net adverse clinical outcomes

BARC, Bleeding Academic Research Consortium

ABSTRACT

Background. Abbreviated antiplatelet therapy (APT) reduces bleeding without increasing ischemic events in high bleeding risk (HBR) patients. Diabetes mellitus (DM) is associated with higher ischemic risk and its impact on the safety and effectiveness of abbreviated APT in HBR patients undergoing percutaneous coronary intervention remains unknown.

Objectives. To investigate the comparative effectiveness of abbreviated (1-month) vs. standard (≥3-months) APT in HBR patients with and without DM.

Methods. This was a prespecified analysis from the MASTER DAPT trial, which randomized 4,579 HBR patients [1538 (34%) with DM] to abbreviated (n=2295) or standard (n=2284) APT. Co-primary outcomes were net adverse clinical events (NACE; composite of all-cause death, myocardial infarction [MI], stroke, and major bleeding); major adverse cardiac or cerebral events (MACCE; all-cause death, MI, and stroke); and major or clinically relevant nonmajor bleedings (MCB) at 11 months.

Results. Abbreviated APT, as compared with the standard one, was associated with comparable NACE and MACCE among patients with and without diabetes ($P_{interaction}$= 0.47 and 0.59, respectively). MCB were consistently reduced with abbreviated APT in patients with (hazard ratio [HR]: 0.75; 95% confidence interval [CI]: 0.52-1.06) and without diabetes (HR: 0.65; 95% CI: 0.50-0.85; $P_{interaction}$=0.55), with a risk difference of -2.19 and -3.13 percentage points, respectively.

Conclusions. Among diabetic HBR patients, abbreviated APT was associated with similar NACE and MACCE and reduced MCB compared with standard APT, which was comparable to the bleeding benefit observed in patients without DM in terms of relative and absolute risks.

Trial Registration: ClinicalTrials.gov number, NCT03023020.

KEYWORDS: percutaneous coronary intervention, high bleeding risk, dual antiplatelet therapy, diabetes.

CONDENSED ABSTRACT

This prespecified analysis from the MASTER DAPT trial reports the impact of diabetes on ischemic and bleeding outcomes among high bleeding risk (HBR) patients treated with an abbreviated versus standard antiplatelet therapy (APT) regimen. Despite higher risks of major adverse cardiac and cerebral events observed in diabetic patients as compared with nondiabetic counterparts, abbreviated and standard APT resulted in comparable net and major adverse events, with no evidence of heterogeneity of treatment effects at interaction testing. Compared with standard therapy, the effects of abbreviated APT in reducing bleeding was consistent among HBR patients with and without diabetes.

INTRODUCTION

Diabetes mellitus (DM) is a condition with worldwide reach, whose prevalence is projected to markedly increase in the upcoming decades, evolving from 10.5% (536.6 million people) of adult individuals (20-79 years of age) in 2012 to 12.2% (783.2 million) in 2045 (1). The impact of DM on coronary artery disease (CAD) is estimated to be equivalent to 15 years of aging (2). Despite notable advances in pharmacological, interventional, and surgical treatments (3,4), DM remains an independent predictor of ischemic complications following percutaneous and surgical coronary revascularization (5). A number of clinical features associated with DM contribute to the higher risk of adverse events, including advanced and more complex CAD, higher prevalence of multivessel involvement with diffuse and long lesions, left main and bifurcations stenoses, chronic total occlusions, higher grades of coronary calcification and tortuosity, smaller vessel diameters, and greater plaque burden (5). Although DM has been associated with enhanced platelet reactivity and reduced sensitivity to some antiplatelet agents, the translational outlook of these observations remains unclear (6,7). According to current guidelines, the choice and duration of antithrombotic treatment following percutaneous coronary intervention (PCI) should not differ in patients with and without DM (8–11). However, DM is a condition associated with higher ischemic risk and the optimal DAPT duration after PCI for the prevention of ischemic and bleeding complications in high bleeding risk (HBR) patients remains unsettled.

The *Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated Versus Standard DAPT Regimen* (MASTER DAPT) trial randomized HBR patients who underwent the implantation of a biodegradable-polymer sirolimus-eluting stent to abbreviated (one-month) or standard (≥3-months) antiplatelet therapy (APT) (12). In the overall patient population, abbreviated APT was noninferior to treatment continuation for at least two additional months for the occurrence of net and major adverse clinical events and reduced major or clinically relevant nonmajor bleeding (MCB) (12–14). In this prespecified analysis, we sought to investigate whether the treatment effects of abbreviated versus standard APT in unselected HBR patients would be affected by the presence of DM.

METHODS

Study design

The design and the primary results of the MASTER DAPT (ClinicalTrials.gov number, NCT03023020), an investigator-initiated, randomized, open-label, noninferiority trial with sequential superiority testing enrolling an unselected patient population at HBR following implantation of a biodegradable polymer-coated Ultimaster™ (Terumo Corporation, Tokyo, Japan) sirolimus-eluting stent, have been previously reported (12,15). The trial was approved by the institutional review board at each participating site, and all patients gave written informed consent. An independent data safety monitoring board regularly reviewed the conduct of the trial and patient safety. Study organization and participating sites are reported in the **Supplemental material**.

Study population

Patients at HBR who underwent treatment of all coronary lesions requiring revascularization with Ultimaster stent for acute or chronic coronary syndromes and remained events-free (including a new acute coronary syndrome, symptomatic restenosis, stent thrombosis [ST], stroke, or any revascularization resulting in the prolonged use of dual APT [DAPT]) during the first month after index PCI were eligible for trial participation. Patients were considered at HBR if at least one of the following criteria applied: oral anticoagulant (OAC) therapy for at least 12 months, recent (<12 months) non-access site bleeding episode(s) that required medical attention, previous bleeding episode(s) that required hospitalization if the underlying cause had not been definitively treated, age ≥75 years, systemic conditions associated with an increased bleeding risk (e.g., hematological or coagulation disorders), documented anemia, need for chronic treatment with steroids or non-steroidal anti-inflammatory drugs, malignancy (other than skin), stroke at any time or transient ischemic attack (TIA) in the previous 6 months, PRECISE-DAPT score ≥25 (16).

Key exclusion criteria were the implantation of other-than-Ultimaster stent within the previous 6 months or a bioresorbable scaffold at any time before the index procedure or stenting for in-stent restenosis or stent thrombosis. Detailed inclusion and exclusion criteria are presented in the **Supplemental material**. Patients were considered diabetic if they were on diet or on treatment with oral hypoglycemic drugs or insulin.

Randomization and follow-up

Patients were centrally randomized (1:1 ratio) to an open-label abbreviated or standard APT regimen 30 to 44 days after the index procedure. Randomization was concealed using a web-based system; randomization sequences were computer generated, blocked, with randomly selected 10 block sizes of 2, 4, or 6, and were stratified by site, history of acute myocardial infarction (MI) within the past 12 months, and clinical indication for at least 12-month OAC.

Patients randomly allocated to the abbreviated treatment group immediately discontinued DAPT and continued single antiplatelet therapy (SAPT) until study completion, except for those receiving OAC, who continued SAPT up to six months after the index procedure. Patients allocated to the standard treatment group continued DAPT for at least five additional months (i.e., six months after the index procedure) or, for those receiving OAC, for at least two additional months (i.e., three months after the index procedure) followed by SAPT. Antiplatelet and anticoagulant treatments were dosed according to authorizations for use and locally approved regimens. Follow-up visits took place at 60 days, 150 days and at 335 days (for all ±14-day windows) after randomization.

Outcomes

The three ranked co-primary outcomes were 11-month net adverse clinical events (NACE; a composite of death from any cause, MI, stroke, or major bleeding), major adverse cardiac or cerebral events (MACCE; a composite of death from any cause, MI, or stroke), and MCB (a composite of Bleeding Academic Research Consortium [BARC] type 2, 3, or 5 bleeding).

Secondary outcomes included the individual components of the three co-primary outcomes, the composite of cardiovascular death, MI, and stroke, the composite of cardiovascular death, MI, definite or probable ST, cerebrovascular accidents (CVA, the composite of stroke and TIA); and all BARC bleeding events. All events were adjudicated by an independent adjudication committee that was unaware of the treatment allocations. All data were stored at a central database (Department of Clinical Research, University of Bern, Switzerland).

Statistical analysis

The data were analysed according to the intention-to-treat principle. Outcomes were assessed separately for patients with or without diabetes, by calculating hazard ratios (HR) with 95% confidence intervals (CI). For patients with a primary outcome, time-to-event was calculated as the difference between the date of occurrence of the outcome event and the date of randomization plus 1. For patients with incomplete clinical follow-up, time to censoring was defined as the difference between the dates of last known clinical status and randomization plus 1. Kaplan-Meier calculations included all (first) adjudicated outcome events that occurred between randomization and 335 days thereafter according to the randomized treatment assignment, irrespective of the DAPT regimen received at the time of the outcome event. HR and 95% CI were generated for primary and secondary outcomes with the use of Cox proportional hazards regression analysis with censoring at end of study and at the time of death. *P*-values for testing homogeneity of the HR in subgroups of patients were derived in Cox proportional hazards models with the interaction term for treatment group (abbreviated vs standard) and diabetes (yes vs no) tested using one degree of freedom. The 95% CI and *P*-values for interaction were not adjusted for multiplicity and should not be used to infer definitive treatment effects. The analyses were done using Stata release 16.0 (StataCorp LLC, College Station, Texas).

RESULTS

Of the 4,579 patients enrolled in the MASTER DAPT trial from February 28, 2017 through December 5, 2019, 1,538 (34%) patients with and 3,041 (66%) without diabetes were randomized at a median of

34 days post PCI (interquartile range: 32 to 39) to an abbreviated (n=2,295 patients; diabetics: n=754; non-diabetics: n=1541) or a standard (n=2,284 patients; diabetics: n=784; non-diabetics, n=1500) APT. DAPT composition and type of SAPT did not differ among patients with and without DM (**Supplemental Table 1** and **2**). Detailed information on antiplatelet use in diabetic and non-diabetic patients is shown in the **Supplemental Figure 1** and **2**.

Baseline and procedural characteristics

Compared with non-diabetic individuals, patients with DM were younger, had higher body mass index and had more frequently cardiovascular risk factors such and prior atherosclerotic disease, including prior stroke, peripheral arterial, carotid and coronary disease (i.e., prior MI or PCI) (**Supplemental Table 3**). Diabetic patients suffered more frequently from left ventricular and renal dysfunction, hematologic or coagulation disorders, lower hemoglobin and a higher PRECISE DAPT score (27.8±11.4 vs. 26.2±10.7, P<0.001) than nondiabetic patients. (**Supplemental Table 3**).

Angiographic and procedural characteristics were well balanced between the groups, except for less frequent trans-radial access and direct stenting but more frequent intravascular ultrasound use and lesion post-dilatation in DM patients (**Supplemental Table 4**). Baseline and procedural characteristics according to DM and randomized treatment regimen were well balanced between the groups except for a higher prevalence of males and femoral access use in diabetic patients treated with abbreviated compared with standard APT (**Supplemental Tables 5 and 6**). Insulin-dependent diabetes was significantly higher in patients randomly allocated to abbreviated (32.3%) than standard (25.4%) APT (P= 0.003).

Clinical outcomes by diabetes

At 12-month follow-up (**Table 1**), NACE occurred in 130 of 1538 diabetic (8.50%) and in 224 of 3041 non-diabetic (7.39%) (HR, 1.15; 95% CI, 0.93 to 1.43; P= 0.192) patients. The rate of MACCE was higher in diabetic compared with non-diabetic patients (7.06% vs. 5.55%; HR, 1.28, 95% CI, 1.00 to 1.63; P=0.046), whereas MCB occurred in 125 of 1538 diabetic (8.25%) and in 234 of 3041 non-

diabetic (7.79%) (HR, 1.06; 95% CI, 1.06 to 1.32; P=0.602) patients. Definite or probable ST rates were low (≤0.6%) in both groups (**Table 1**). There were no significant differences in the individual components of the co-primary or other secondary outcomes.

Clinical outcomes by diabetes and randomly allocated antiplatelet regimens

Clinical outcomes at 12 months in diabetic and non-diabetic patients stratified by APT are shown in **Figure 1** and **2**. NACE did not differ with abbreviated and standard APT group among diabetic (65 [8.67%] vs 65 patients [8.33%]; HR, 1.04, 95% CI, 0.74 to 1.46; P =0.834) and non-diabetic (107 [6.97%] vs 117 [7.83%]; HR, 0.88, 95% CI, 0.68 to 1.15; P = 0.354) patients, with no heterogeneity at interaction testing (P for interaction = 0.467) (**Table 2**). Similarly, MACCE did not differ with abbreviated and standard APT group among diabetic (55 [7.34%] vs 53 patients [6.79%]; HR, 1.08, 95% CI, 0.74 to 1.58); P = 0.687) or non-diabetic (83 [5.41%] vs 85 patients [5.69%]; HR, 0.95, 95% CI, 0.70 to 1.28; P = 0.726) patients, with no heterogeneity (P for interaction = 0.593) (**Table 2**). MCB was consistently lower with abbreviated APT in diabetic (53 [7.13%] vs 72 patients [9.33%]; HR, 0.75, 95% CI, 0.52 to 1.06; P = 0.105), and non-diabetic patients (95 [6.25%] vs 139 patients [9.37%]; HR, 0.65, 95% CI, 0.50 to 0.85; P =0.001) (P for interaction = 0.553) (**Table 2**). Abbreviated APT was associated with lower CVA rates in diabetic (HR, 0.34, 95% CI, 0.13 to 0.95, P=0.039), owing to numerically lower stroke and TIA, with a consistent trend in non-diabetic patients (HR, 0.68, 95% CI, 0.33 to 1.43, P=0.315, P for interaction: 0.280). The rate of MI was higher in the abbreviated compared with standard APT group in diabetic (HR, 2.01, 95% CI, 1.05 to 3.83; P= 0.034) but not in non-diabetic patients (HR, 0.92; 95% CI, 0.57 to 1.47; P= 0.720), without significant heterogeneity (P for interaction= 0.055). Similarly, there was no clear evidence of heterogeneity of the treatment effects by diabetes for any of the other secondary endpoints (**Supplemental Figure 3**). The rates of definite or probable ST in the diabetic population were similarly low with abbreviated or standard APT (HR, 2.08, 95% CI, 0.52 to 8.30; P=0.301) (**Table 2 and Supplemental Figure 4**). MCB reduction with abbreviated DAPT was mainly driven by lower rates of BARC type 2 bleeding, both in diabetic (HR,

0.68, 95% CI, 0.45 to 1.05, P=0.083, risk difference=-2.04) and non-diabetic patients (HR, 0.64, 95% CI, 0.47 to 0.88, P=0.005; risk difference=-2.35; P for interaction=0.820) **(Table 2).**

Outcomes in diabetic and non-diabetic patients with or without clinical indication for OAC

Among diabetic and non-diabetic patients with clinical indication for OAC (**Figure 3** and **Supplemental Table 7**), NACE, MACCE and MCB did not differ with abbreviated versus standard APT.

Among diabetic and non-diabetic patients without clinical indication for OAC (**Figure 3** and **Supplemental Table 8**), NACE and MACCE did not differ and MCB was consistently reduced in diabetic and non-diabetic patients (HR, 0.51, 95% CI, 0.30 to 0.86, P= 0.012 and HR, 0.57, 95% CI, 0.39 to 0.83, P= 0.003; P for interaction=0.738) with abbreviated versus standard APT regimens.

Additional post-hoc analyses

The treatment effect for MI was consistent across insulin dependency strata in the overall population, or in male and female patients, separately analyzed, with no significant heterogeneity at interaction testing (**Supplemental Figure 5**). The apparent excess of MI in diabetic patients with abbreviated compared with standard APT accrued mainly from males (4.17% *vs.* 1.56%; HR, 2.69; 95% CI, 1.20 to 6.05). No significant heterogeneity of the treatment effect for CVA by sex was detected across DM strata (**Supplemental Figure 6)**. Standard compared with abbreviated APT was associated with a numerical reduction of CVA in diabetic (HR, 0.24; 95% CI, 0.05 to 1.14) and non-diabetic (HR, 0.82; 95% CI, 0.34 to 1.98) male patients.

DISCUSSION

To the best of our knowledge, this is the largest analysis investigating the impact of DM on the comparative efficacy and safety of an abbreviated or standard APT regimens among HBR patients.

Patients with DM incurred a 28% higher MACCE and similar NACE or MCB risks at 1 year after coronary revascularization. There was no evidence of heterogeneity between DM and randomly

allocated APT regimens with respect to the three co-primary outcomes, suggesting that abbreviated APT was consistently associated with similar NACE and MACCE and reduced MCB rates compared with standard APT in both diabetic and non-diabetic patients (**Central Illustration**).

The observation of similar NACE and MACCE rates and a consistent bleeding reduction with abbreviated compared with standard APT in both diabetic and non-diabetic patients suggest that DM does not justify *per se* a more prolonged APT course in HBR patients without ischemic and/or active bleeding events in the first month after PCI. Current guidelines do not clearly recommend a disease-specific attitude for the type and/or duration of antithrombotic treatment after PCI based on DM (8–11,17). However, DM is an ischemic risk equivalent and DAPT duration should be informed by both ischemic and bleeding risks within and beyond the first year after PCI (11,18,19). DM is acknowledged as an ischemic risk enhancer across European Society of Cardiology guidelines on acute (18) and chronic coronary syndrome (20) and may or should justify a second anti-thrombotic agent in patients without or with complex CAD, respectively. However, these recommendations apply to patients without HBR. Therefore, our results concur with current guidelines in supporting a comprehensive bleeding and ischemic risks assessment when deciding upon DAPT duration.

At secondary endpoint analyses, diabetic patients at HBR experienced a nominally significantly higher MI risk with abbreviated compared with standard APT. This apparent excess of MI with abbreviated DAPT was almost entirely driven by events unrelated to ST. On the other hand, CVA rates were also nominally lower with abbreviated compared with standard APT among HBR patients with DM, driven by numerically lower strokes (both ischemic and haemorrhagic events) and TIA. A relevant finding was the absence of clear evidence of heterogeneity between presence of DM and treatment groups for MI or CVA. Hence, our results do not provide evidence that the similar MACCE rates with abbreviated or standard APT in DM patients arises from a trade-off of cardiac and cerebrovascular events.

Other studies investigated the efficacy and safety of abbreviated versus prolonged DAPT in patients with and without diabetes. In an individual patient data meta-analysis of 6 trials, including 11,473 patients, randomised to 6 or 12 month DAPT after drug-eluting stent implantation, the presence of DM

was an independent predictor of major adverse cardiovascular events (MACE) after PCI (21); however, compared with short term DAPT, long term DAPT did not reduce the risk of MACE but increased the risk of bleeding among PCI patients with and without diabetes (21). The results of our study are consistent with those findings and expand their application to a HBR population.

In the DAPT trial, continued thienopyridine beyond 12 months reduced the MACCE rate among non-diabetic (N=6,924; HR, 0.59; 95%, CI 0.46 to 0.74) but not in diabetic (N=3,037; HR, 0.95; 95%, CI 0.72 to 1.25) patients, with significant treatment by DM interaction (P for interaction=0.01) (22).

In the *Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis In Myocardial Infarction 54* (PEGASUS) trial, patients with history of prior MI (1 to 3 years before) and at least 1 additional atherothrombotic risk factor (including DM) were eligible for inclusion (23). Patients with DM had higher rates of ischemic events compared with non-diabetic patients. In this trial, the risk of MACE (the composite of cardiovascular death, MI, or stroke) in the placebo arm was 11.60% among diabetic patients *versus* 7.83% in those without diabetes (adjusted HR, 1.45; 95% CI, 1.22 to 1.73; P < 0.001) (23). The relative risk reduction in MACE for the pooled ticagrelor doses versus placebo was consistent in patients with (n=6,806; HR, 0.84; 95% CI, 0.72 to 0.99; P=0.035) and without DM (n=14,355; HR, 0.84; 95% CI, 0.74 to 0.96; P=0.013), without significant heterogeneity of the treatment effect at interaction testing (P for interaction= 0.99) (23).The absolute risk reduction of MACE with aspirin and ticagrelor compared with aspirin alone was also similar in patients with and without DM, as the risk of bleeding. TIMI major bleeding was significantly increased in diabetic patients treated with ticagrelor (2.56% *versus* 0.98%; HR, 2.56; 95% CI, 1.52 to 4.33; P= 0.0004), at a similar magnitude to what detected in non-diabetic patients (2.39% in pooled ticagrelor *versus* 1.09% in placebo; HR, 2.47; 95% CI, 1.73 to 3.53; P< 0.0001; P for interaction= 0.89) (23). Our results extend these findings to HBR patients and suggest that DM should not be regarded as a treatment modifier for maximizing the net clinical benefit of DAPT in HBR patients.

In the last decade, other studies have also investigated the efficacy and safety of $P2Y_{12}$ inhibitor monotherapy after 1 to 3 months of DAPT in diabetic and non-diabetic patients. A subgroup analysis

of the GLOBAL-LEADERS study showed consistent treatment effects in patients with or without DM of 23-month ticagrelor monotherapy after 1 month DAPT compared with 12-month DAPT followed by aspirin monotherapy (24). Our results are also in line with a sub-analysis from the *Ticagrelor With Aspirin or Alone in High-Risk Patients after Coronary Intervention* (TWILIGHT) trial (25), which demonstrated that, compared with ticagrelor plus aspirin, ticagrelor monotherapy after 3 months of DAPT was associated with a 35% relative risk reduction of 1-year MCB without ischemic harm in diabetic patients. In the TWILIGHT trial, the incidence of MI was comparable between the two groups (3.1% with ticagrelor monotherapy *versus* 4.1% with ticagrelor plus aspirin), albeit much higher than MI rates in our study. The inclusion of unselected HBR patients in our study, the timing of randomization after PCI (at 3 months in TWILIGHT *versus* 1 month in MASTER DAPT) and type of SAPT (ticagrelor monotherapy in TWILIGHT *versus* no protocol mandated SAPT type in MASTER DAPT) may account for these differences. In an individual patient data meta-analysis including 24,096 patients from six trials, $P2Y_{12}$ inhibitor monotherapy (ticagrelor 77%, clopidogrel 22%, prasugrel 1%) compared with 12-month DAPT was associated with lower bleeding and similar death, MI or stroke rates (26). Subgroup analyses demonstrated a reduction in major adverse cardiovascular events with $P2Y_{12}$ inhibitor monotherapy in diabetic (HR, 0.70, 95% CI, 0.63 to 0.99) but not in non-diabetic subjects (HR, 1.00, 95% CI, 0.81 to 1.24) with no significant heterogeneity of treatment effect at interaction testing (P for interaction= 0.10) (26). Therefore, prior evidence concurs with our present finding suggesting that DM, albeit potentially associated with greater risk of fatal or non-fatal composite endpoint, should not *per se* drive the decision-making on DAPT duration.

Study limitations

Some limitations of the present analysis should be acknowledged. First, MASTER DAPT was powered to assess the non-inferiority of NACE and MACCE in the overall study population while no non-inferiority claim is possible when interpreting subgroup-analyses, for which the study is inherently underpowered. Therefore, as all subgroup analyses, these results should be considered hypothesis-generating with respect to the risks and benefits of an abbreviated *versus* standard APT

regimen in HBR diabetic patients who underwent PCI. Second, our trial included HBR patients who underwent biodegradable-polymer sirolimus-eluting stent implantation; consequently, our results may not be generalizable to non-HBR patients or those treated with other stent types. Third, MASTER DAPT randomized patients free of ischemic or bleeding events in the first month after PCI; therefore, our results may not apply to patients suffering an adverse event during this time frame. Forth, in the MASTER DAPT trial, DAPT composition and SAPT type after DAPT discontinuation were left at discretion of treating physician. Finally, these results could not be extended to patients with in-stent restenosis or stent thrombosis who were ineligible for trial participation.

CONCLUSIONS

In this prespecified analysis of the MASTER DAPT trial, HBR patients with DM experienced higher MACCE and similar net adverse and bleeding rates compared with non-diabetic subjects. Among HBR patients with DM, abbreviated APT was associated with similar NACE and MACCE and reduced MCB compared with standard APT. The absolute and relative bleeding benefits of abbreviated APT were comparable in patients with and without DM.

PERSPECTIVES

Competency in Patient Care and Procedural Skills

Diabetic patients at high bleeding risk (HBR) have higher risks of ischemic events and similar bleeding risk than non-diabetic subjects. Among HBR patients undergoing coronary revascularization, an abbreviated dual antiplatelet therapy (DAPT) is associated with comparable major and net adverse clinical events and consistently reduced bleeding compared with treatment continuation for at least two additional months, irrespective of diabetes status.

Translational Outlook

Future studies should investigate the safety and efficacy of shorter than one-month DAPT in HBR patients with diabetes undergoing revascularization in the setting of acute coronary syndromes.

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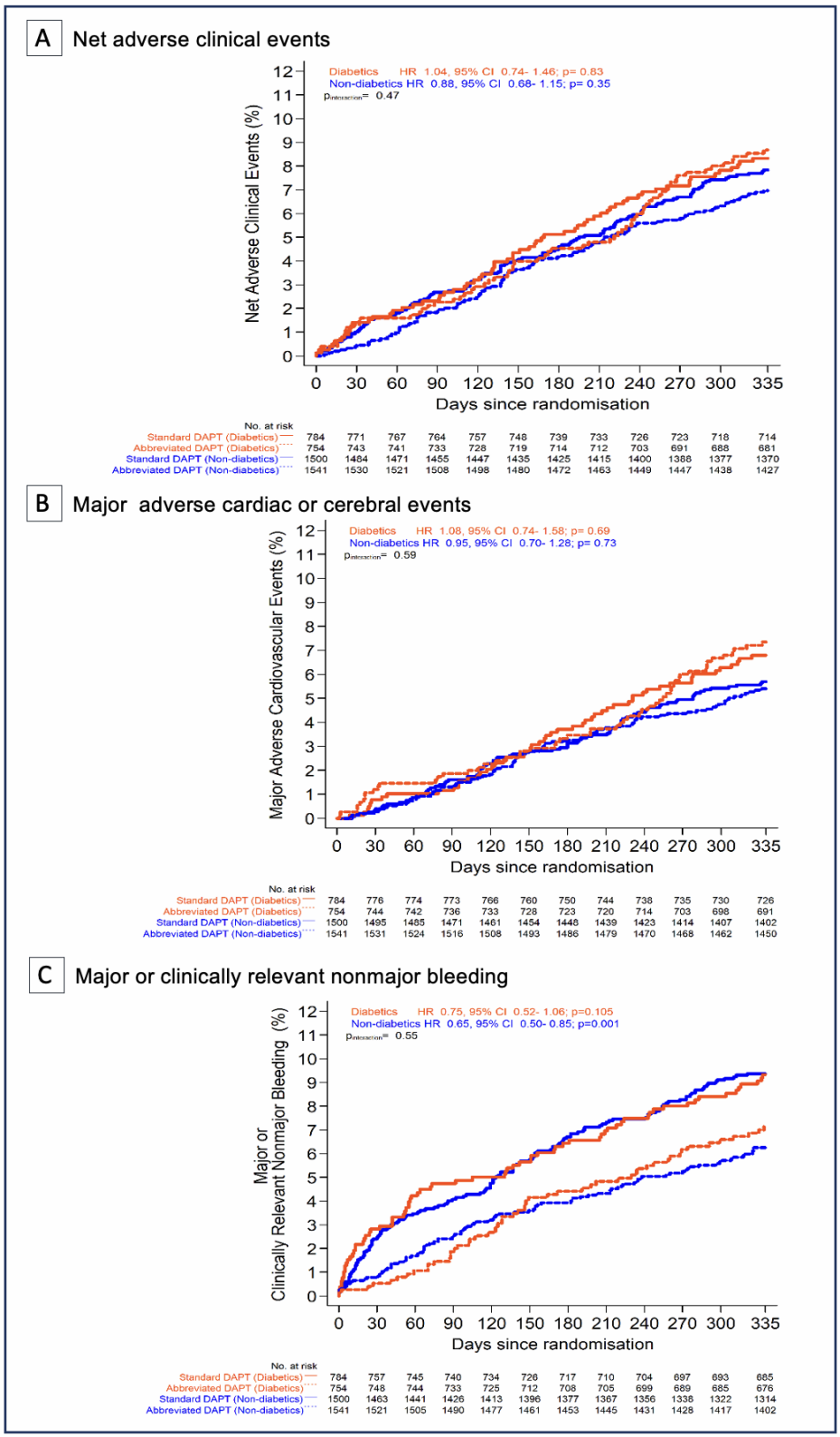
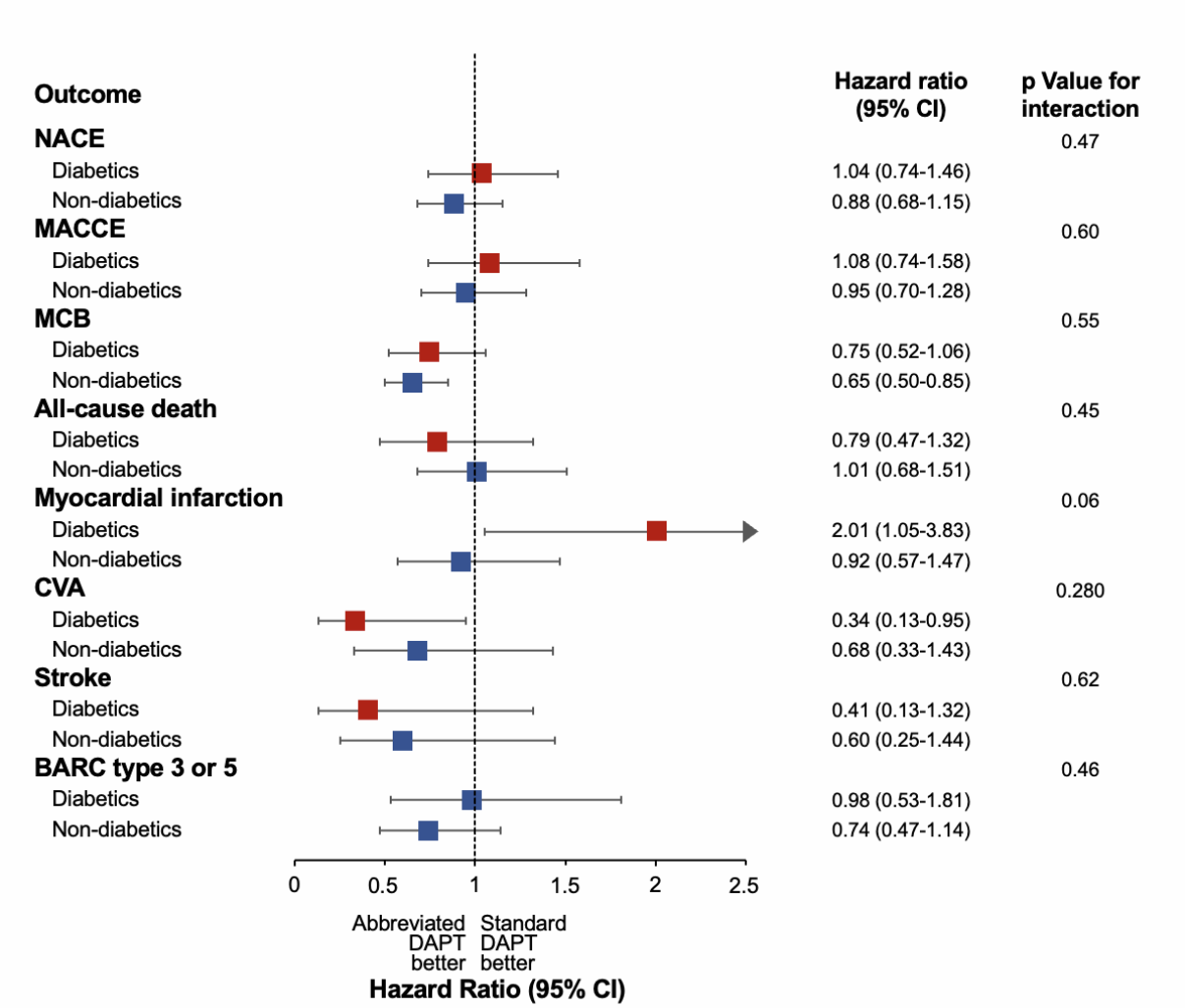
FIGURE LEGENDS

Figure 1. Kaplan Meier curves for NACE (A), MACCE (B) and major or clinically relevant nonmajor bleeding (C).



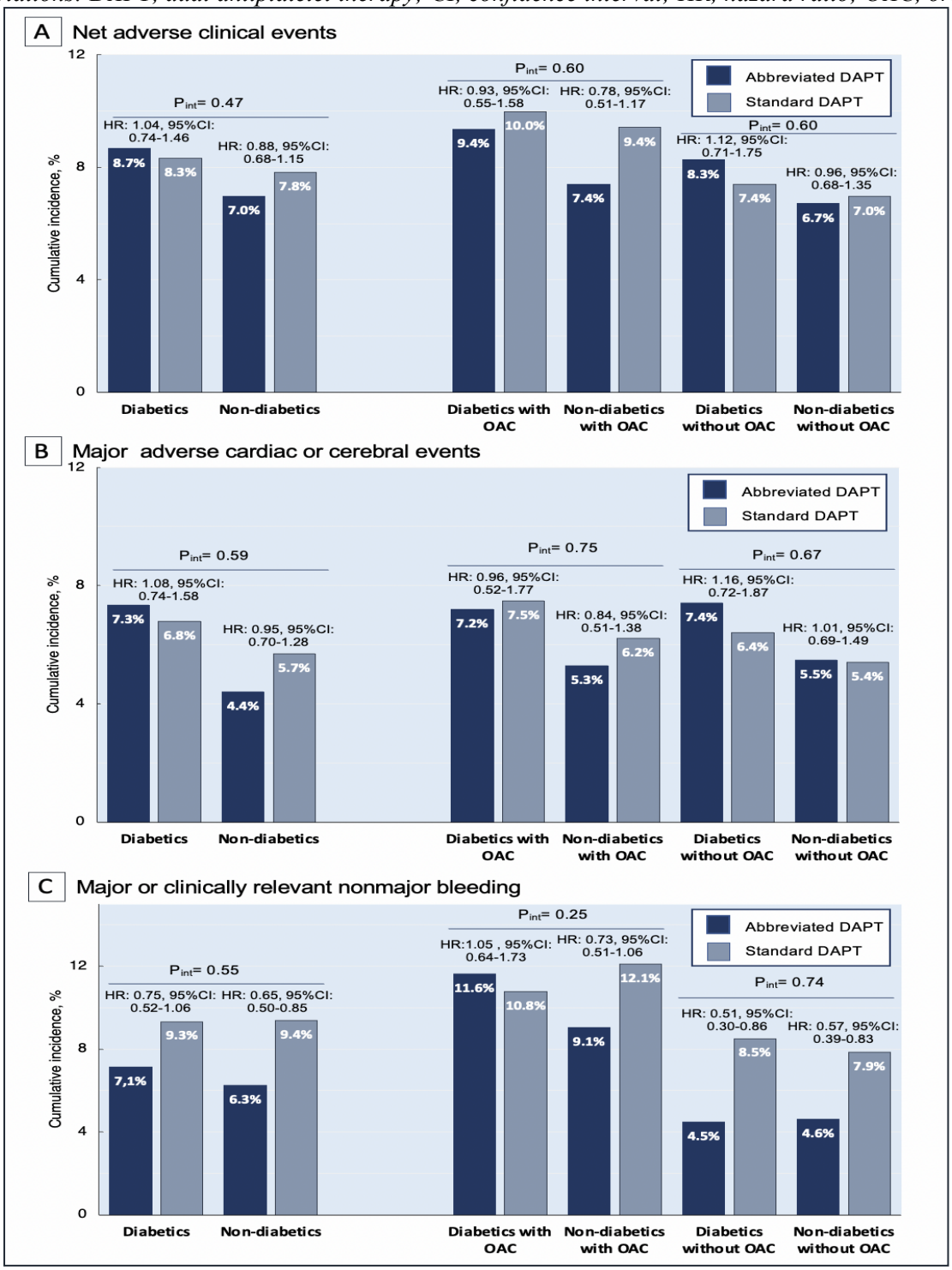
Abbreviations: CI, confidence interval; DAPT, dual antiplatelet therapy; HR, hazard ratio; NACE, net adverse clinical events; MACCE, major adverse cardiac or cerebral events.

Figure 2. Main outcomes of abbreviated versus standard antiplatelet therapy (APT) in diabetic and non-diabetics patients. Abbreviated and standard APT were compared based on diabetes status, with hazard ratios and 95% confidence intervals (CI) for the three coprimary outcomes and their components (all-cause death, myocardial infarction, stroke, Bleeding Academic Research Consortium [BARC] type 3 or 5).

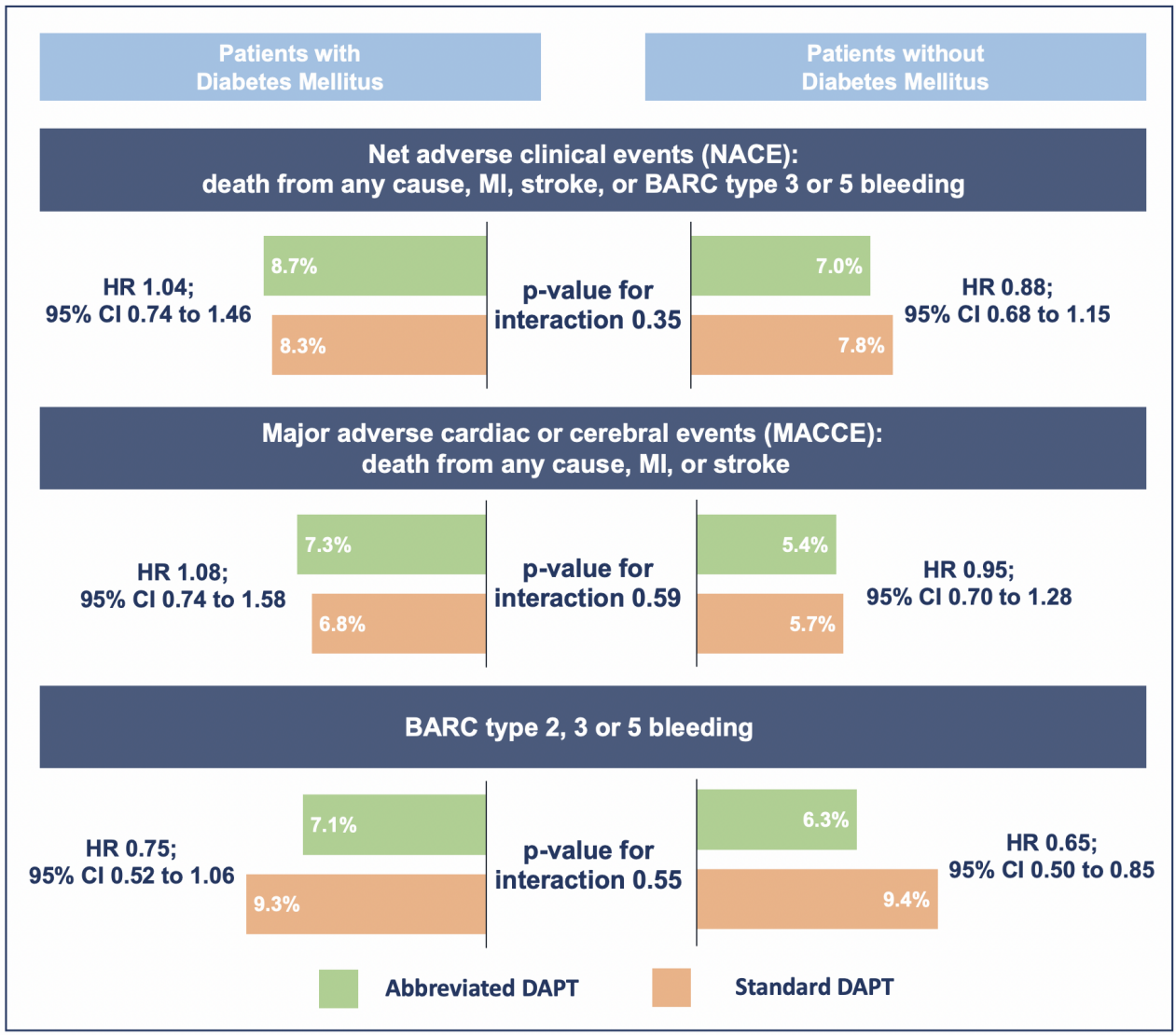


Abbreviations: CVA, cerebrovascular accident; MACCE, major adverse cardiac and cerebral events; MCB, major or clinically relevant non-major bleeding; NACE, net adverse clinical events.

Figure 3. Interaction between diabetes mellitus and DAPT on co-primary efficacy outcomes in the overall cohort and stratified by clinical indication for OAC. The x-axis shows the categories of the patients according to diabetes mellitus and clinical indication for OAC, and the y-axis shows event rates of the co-primary efficacy outcomes: net adverse clinical events (panel A), major adverse cardiac or cerebral events (panel B) and major or clinically relevant nonmajor bleeding (panel C).
Abbreviations: DAPT, dual antiplatelet therapy; CI, confidence interval; HR, hazard ratio; OAC, oral anticoagulation.



CENTRAL ILLUSTRATION. Abbreviated or standard antiplatelet therapy in high bleeding risk patients with and without diabetes mellitus.



Abbreviations: BARC, Bleeding Academic Research Consortium; CI, confidence interval; DAPT, dual antiplatelet therapy; HR, hazard ratio; MI, myocardial infarction.

TABLES.

Table 1. Clinical Outcomes at 11 months after Randomization in diabetic versus non-diabetic patients.

	Diabetics (n=1538)	**Non-diabetics (n=3041)**	**Hazard ratio (95% CI)**	**p-value**
NACE	130 (8.50)	224 (7.39)	1.15 (0.93-1.43)	0.192
MACCE	108 (7.06)	168 (5.55)	1.28 (1.00-1.63)	0.046
MCB	125 (8.25)	234 (7.79)	1.06 (0.85-1.32)	0.602
Death	60 (3.92)	96 (3.17)	1.24 (0.90-1.71)	0.188
Cardiovascular death	34 (2.24)	47 (1.56)	1.44 (0.92-2.23)	0.107
Non-cardiovascular death	19 (1.26)	38 (1.27)	0.99 (0.57-1.72)	0.982
Cerebrovascular Accident	20 (1.32)	29 (0.97)	1.37 (0.78-2.43)	0.273
Stroke¶	14 (0.93)	21 (0.70)	1.33 (0.67-2.61)	0.413
ischemic stroke	12 (0.79)	17 (0.57)	1.40 (0.67-2.94)	0.368
hemorrhagic stroke	2 (0.13)	4 (0.13)	1.00 (0.18-5.43)	0.995
TIA	6 (0.40)	8 (0.27)	1.49 (0.52-4.30)	0.458
Myocardial infarction	41 (2.73)	68 (2.27)	1.20 (0.81-1.76)	0.363
Definite or Probable ST	9 (0.60)	14 (0.47)	1.28 (0.55-2.95)	0.567
Definite ST	7 (0.46)	11 (0.37)	1.26 (0.49-3.26)	0.628
Probable ST	2 (0.13)	3 (0.10)	1.32 (0.22-7.91)	0.760
Bleeding (BARC classification)				

Type 1	48 (3.18)	126 (4.19)	0.75 (0.54-1.04)	0.089
Type 2	87 (5.76)	167 (5.57)	1.03 (0.80-1.34)	0.805
Type 3	37 (2.44)	75 (2.50)	0.98 (0.66-1.45)	0.917
Type 3a	18 (1.19)	38 (1.27)	0.94 (0.54-1.65)	0.827
Type 3b	14 (0.93)	27 (0.90)	1.03 (0.54-1.96)	0.930
Type 3c	5 (0.33)	11 (0.37)	0.90 (0.31-2.60)	0.850
Type 4	0 (0.00)	0 (0.00)		
Type 5	4 (0.27)	6 (0.20)	1.33 (0.37-4.70)	0.662
Type 5a	0 (0.00)	2 (0.07)	0.40 (0.02-8.33)	0.554
Type 5b	4 (0.27)	4 (0.13)	1.99 (0.50-7.95)	0.331
Type 3 or 5	41 (2.71)	81 (2.70)	1.00 (0.69-1.46)	0.980

Abbreviations: BARC, Bleeding Academic Research Consortium; CI, confidence interval; HR, hazard ratio; MACCE, major adverse cardiac and cerebral events; MCB, major or clinically relevant non-major bleeding; NACE, net adverse clinical events; ST, stent thrombosis; TIA, transient ischemic attack.
Nr of first events of each type (Kaplan-Meier failure %). Hazard ratio (95% CI) from Cox's time-to-first event analyses in ITT population. Continuity corrected risk ratios (95% CI) in case of zero events with Fisher's exact test p-value. Interaction p-value testing for modifying effect of Diabetes (yes or no) on the hazard ratio scale.

¶includes undetermined Strokes.

Table 2. Clinical outcomes at 11 months after randomization in diabetic and non-diabetic patients randomized to abbreviated or standard DAPT.

	Diabetics					Non-diabetics					
	Abbreviated DAPT (n=754)	**Standard DAPT (n=784)**	**Hazard ratio (95% CI)**	**p-value**	**Com-Nogue Risk Difference (95% CI)**	**Abbreviated DAPT (n=1541)**	**Standard DAPT (n=1500)**	**Hazard ratio (95% CI)**	**p-value**	**Com-Nogue Risk Difference (95% CI)**	**interaction p-value**
NACE	65 (8.67)	65 (8.33)	1.04 (0.74-1.46)	0.834	0.35 [-2.45 to 3.14]	107 (6.97)	117 (7.83)	0.88 (0.68-1.15)	0.354	-0.87 [-2.73 to 1.00]	0.467
MACCE	55 (7.34)	53 (6.79)	1.08 (0.74-1.58)	0.687	0.55 [-2.02 to 3.12]	83 (5.41)	85 (5.69)	0.95 (0.70-1.28)	0.726	-0.29 [-1.92 to 1.34]	0.593
MCB	53 (7.13)	72 (9.33)	0.75 (0.52-1.06)	0.105	-2.19 [-4.96 to 0.57]	95 (6.25)	139 (9.37)	0.65 (0.50-0.85)	0.001	-3.13 [-5.04 to -1.21]	0.553
Death	26 (3.47)	34 (4.36)	0.79 (0.47-1.32)	0.367	-0.88 [-2.83 to 1.06]	49 (3.19)	47 (3.15)	1.01 (0.68-1.51)	0.948	0.04 [-1.21 to 1.29]	0.453
Cardiovascular death	14 (1.88)	20 (2.59)	0.72 (0.37-1.43)	0.353	-0.71 [-2.20 to 0.78]	23 (1.51)	24 (1.62)	0.93 (0.53-1.65)	0.810	-0.11 [-0.99 to 0.78]	0.577
Non-cardiovascular death	9 (1.22)	10 (1.30)	0.93 (0.38-2.29)	0.875	-0.08 [-1.21 to 1.05]	20 (1.32)	18 (1.22)	1.08 (0.57-2.04)	0.813	0.10 [-0.71 to 0.90]	0.792
Undetermined death	3 (0.41)	4 (0.52)	0.78 (0.17-3.47)	0.741	-0.11 [-0.80 to 0.57]	6 (0.40)	5 (0.34)	1.17 (0.36-3.82)	0.800	0.05 [-0.38 to 0.49]	0.676
Cerebrovascular Accident	5 (0.67)	15 (1.96)	0.34 (0.13-0.95)	0.039	-1.29 [-2.43 to -0.15]	12 (0.80)	17 (1.15)	0.68 (0.33-1.43)	0.315	-0.36 [-1.06 to 0.35]	0.280
Stroke¶	4 (0.53)	10 (1.31)	0.41 (0.13-1.32)	0.136	-0.77 [-1.73 to 0.19]	8 (0.53)	13 (0.88)	0.60 (0.25-1.44)	0.252	-0.35 [-0.95 to 0.25]	0.619
ischemic stroke	4 (0.53)	8 (1.05)	0.52 (0.16-1.72)	0.283	-0.51 [-1.40 to 0.38]	7 (0.46)	10 (0.68)	0.68 (0.26-1.79)	0.434	-0.22 [-0.76 to 0.32]	0.727
hemorrhagic stroke	0 (0.00)	2 (0.26)	0.21 (0.01-4.37)	0.500	-0.26 [-0.63 to 0.10]	1 (0.07)	3 (0.20)	0.32 (0.03-3.11)	0.329	-0.14 [-0.40 to 0.13]	
TIA	1 (0.13)	5 (0.65)	0.21 (0.02-1.77)	0.150	-0.52 [-1.14 to 0.11]	4 (0.27)	4 (0.27)	0.97 (0.24-3.88)	0.966	0.00 [-0.38 to 0.37]	0.235

Myocardial infarction	27 (3.66)	14 (1.83)	2.01 (1.05-3.83)	0.034	1.83 [0.18 to 3.48]	33 (2.18)	35 (2.37)	0.92 (0.57-1.47)	0.720	-0.20 [-1.26 to 0.87]	0.055
Definite or Probable ST	6 (0.81)	3 (0.39)	2.08 (0.52-8.30)	0.301	0.42 [-0.36 to 1.20]	8 (0.53)	6 (0.41)	1.30 (0.45-3.74)	0.629	0.12 [-0.37 to 0.61]	0.599
Definite ST	5 (0.68)	2 (0.26)	2.59 (0.50-13.37)	0.255	0.42 [-0.28 to 1.11]	6 (0.40)	5 (0.34)	1.17 (0.36-3.83)	0.798	0.06 [-0.38 to 0.49]	0.441
Probable ST	1 (0.13)	1 (0.13)	1.04 (0.06-16.58)	0.979	0.01 [-0.36 to 0.37]	2 (0.13)	1 (0.07)	1.95 (0.18-21.46)	0.587	0.06 [-0.16 to 0.29]	0.735
Bleeding (BARC classification)											
Type 1	21 (2.84)	27 (3.51)	0.80 (0.45-1.41)	0.442	-0.67 [-2.44 to 1.10]	44 (2.89)	82 (5.53)	0.52 (0.36-0.74)	0.000	-2.64 [-4.08 to -1.21]	0.203
Type 2	35 (4.72)	52 (6.76)	0.68 (0.45-1.05)	0.083	-2.04 [-4.38 to 0.31]	67 (4.41)	100 (6.76)	0.64 (0.47-0.88)	0.005	-2.35 [-4.00 to -0.71]	0.820
Type 3	19 (2.56)	18 (2.33)	1.09 (0.57-2.07)	0.799	0.23 [-1.32 to 1.79]	34 (2.24)	41 (2.77)	0.80 (0.51-1.26)	0.343	-0.53 [-1.65 to 0.59]	0.451
Type 3a	8 (1.08)	10 (1.29)	0.82 (0.33-2.09)	0.682	-0.20 [-1.29 to 0.88]	18 (1.19)	20 (1.35)	0.87 (0.46-1.65)	0.678	-0.17 [-0.97 to 0.63]	0.917
Type 3b	8 (1.08)	6 (0.78)	1.38 (0.48-3.97)	0.552	0.30 [-0.67 to 1.27]	13 (0.86)	14 (0.95)	0.90 (0.42-1.92)	0.788	-0.09 [-0.77 to 0.59]	0.523
Type 3c	3 (0.40)	2 (0.26)	1.55 (0.26-9.29)	0.630	0.14 [-0.44 to 0.72]	4 (0.27)	7 (0.47)	0.56 (0.16-1.90)	0.348	-0.21 [-0.64 to 0.23]	0.353
Type 4	0 (0.00)	0 (0.00)				0 (0.00)	0 (0.00)				
Type 5	1 (0.14)	3 (0.39)	0.34 (0.04-3.31)	0.356	-0.26 [-0.78 to 0.26]	1 (0.07)	5 (0.34)	0.19 (0.02-1.66)	0.135	-0.27 [-0.60 to 0.05]	0.719
Type 5a	0 (0.00)	0 (0.00)				0 (0.00)	2 (0.14)	0.19 (0.01-3.95)	0.243	-0.14 [-0.32 to 0.05]	1.000
Type 5b	1 (0.14)	3 (0.39)	0.34 (0.04-3.31)	0.356	-0.26 [-0.78 to 0.26]	1 (0.07)	3 (0.20)	0.32 (0.03-3.11)	0.329	-0.14 [-0.40 to 0.13]	0.970
Type 3 or 5	20 (2.70)	21 (2.72)	0.98 (0.53-1.81)	0.952	-0.02 [-1.66 to 1.62]	35 (2.31)	46 (3.11)	0.74 (0.47-1.14)	0.173	-0.80 [-1.96 to 0.36]	0.456

Abbreviations: BARC, Bleeding Academic Research Consortium; CI, confidence interval; HR, hazard ratio; MACCE, major adverse cardiac and cerebral events; MCB, major or clinically relevant non-major bleeding; NACE, net adverse clinical events; ST, stent thrombosis; TIA, transient ischemic attack.

Nr of first events of each type (Kaplan-Meier failure %). Hazard ratio (95% CI) from Cox's time-to-first event analyses in ITT population. Continuity corrected risk ratios (95% CI) in case of zero events with Fisher's exact test p-value. Interaction p-value testing for modifying effect of Diabetes (yes or no) on the hazard ratio scale.

¶includes undetermined Strokes.